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OBESITY AND SEDENTARISM IN THE 21ST CENTURY: WHAT CAN BE DONE AND WHAT MUST BE DONE?

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SUMMARY

OBESITY AND SEDENTARISM IN THE 21ST CENTURY: WHAT CAN BE DONE AND WHAT MUST BE DONE?

Coordinator:
Gregorio Varela-Moreiras

CONSENSUS DOCUMENT AND CONCLUSIONS

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Coordinador:
Gregorio Varela-Moreiras

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CONSENSUS DOCUMENT AND CONCLUSIONS

Obesity and sedentarism in the 21st century: what can be done and what must be done?

COORDINATOR: **GREGORIO VARELA-MOREIRAS**

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Background, justification and goals

At the present time, six out of the seven main risk factors for premature death in Europe (high blood pressure, cholesterol inadequate, Body Mass Index, insufficient intake of fruits and vegetables, physical inactivity, and alcohol abuse) are related with lifestyles, especially with dietary habits, alcohol abuse and physical inactivity and/or sedentarism.

From a public health perspective, the increase in overweight and obesity is of particular concern throughout all of Europe. To approach this issue, both the World Health Organization (WHO) and the European Commission advocate for an integral approach with the implication of all the parties at a European, national, regional, and local level. A good example of this is the recent *Vienna Declaration on Nutrition and Non Transmittable Diseases* that the WHO promulgated after the Ministerial Conference celebrated in Vienna on the 4th and 5th of July of 2013, in the setting of the "Health 2020" Program, in which it was reaffirmed that a multidisciplinary approach is essential.

Obesity is defined as a disease risk factor characterized by an excessive accumulation of fat leading to a body composition with a fat content higher than a standard that is predefined by the height, age, and gender. In the adult population, obesity is typified as the presence of a *Body Mass Index (BMI)* value higher or equal to 30 kg/m^2 (an overweight with values higher than 27), whereas in the pediatric population BMI curves specific for the age and gender are used: if the 95th percentile is exceeded there will be a clinical situation of obesity (being the 85th percentile for overweight).

The pathogenesis of obesity is multifactorial and based on a predisposition mediated by the genetic characteristics of an individual implying a greater personalization of the problem, with the confluence of an excess of energy intake and essentially a decrease in the energy expenditure in relation to an optimal balance between intake and demand. In addition to this thermodynamic expression, in the obese individual

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there are impairments in the balance of the molecular processes and the harmony of the functioning of the different regulatory centers of hunger, appetite, and satiety, located at central (which include attention, cognitive, and reward processes), hypothalamic, and peripheral levels. From the genetic viewpoint, there is no doubt that a considerable progress has been achieved in the scientific knowledge, which is, by instance, manifested by the fact that, nowadays, it is estimated that more than 450 genes, markers and chromosomal regions related with the phenotypes of human obesity are implicated. This Multidisciplinary Forum certainly believes that *individualization* is no more a future challenge but something necessary at present.

Independently of the genetic characteristics, in the process of obesity development determinant exogenous factors converge collaboratively, such as consumption of foods and beverages with high energy density, sedentarism, low intake of fruits and vegetables, weight impairments at birth, lack of breastfeeding, etc., together with a series of conditioning environmental factors such as low sociocultural and/or socioeconomic status, unfavorable environment, and other environmental aspects that directly or indirectly influence on feeding behaviors and on the body physiological response to physical activity.

As risk factors, overweight and obesity clearly induce the occurrence of important comorbidities such as metabolic syndrome, cardiovascular diseases, diabetes, ostheoarticular pathologies, certain kinds of cancers, depression, and impairment of the cognitive function. We may not forget the relationship between overweight/obesity and body image disorders, the difficulty in human relations and socialization, including the daily basic problems associated with walking, sleeping, travelling, the size of the seats, beds, etc.; this problems not only imply a poorer quality of life for the individual but also higher personal, social, and health expenses.

According to the WHO, approximately 1,200 million people have overweight/obesity problems nowadays and approximately the same number of people still suffers from malnourishment. Should this trend of ponderal overload continue, by the year 2040 the whole European population would be overweighed. The *US Centers for Disease Control and Prevention* (CDC) have alerted that the increase in pediatric obesity could make the children of the next generations live shorter than their parents for the first time in History. In Spain, the problem is not deniable according to the data from the *National Health Survey* (NHS, 2013): 27.8% of the Spanish population aged 2-17 years is obese or overweighed, manifesting equally in both genders. In the adult population, obesity already affects 17.0% of the population aged 18 years and over (18.0% in males and 16.0% in females). Since the first *National Health Survey* in 1987, obesity has led an ascending curve in both genders, being more pronounced in males than females. Whereas in 1987 a roughly 7.4% of the population aged 18 years and over had a BMI equal or higher than 30 kg/m^2 (the limit for obesity), in 2012 this percentage was higher than 17%. But more alarming is the fact that 53.7% of the population older than 18 years is overweighed or obese. Obesity is more prevalent with increasing age except in the people older than 74 years. Educational, social, and economical factors are also having a different impact on the Spanish figures: so, obesity increases as the social scale decreases and the educational level is lower. On the other hand, and also a matter of concern, the NHS highlights the prevalence of insufficient weight in females 18-24 years old (12.4%) as compared to 4.1% in males. Regarding the physical activity habits, the NHS shows that four out of ten persons (41.3%) state being sedentary (they do not perform any kind of physical activity during their leisure time): one out of three males (35.9%) and almost one in two females (46.6%). Considering both their main activity and their leisure time, 40.9% of the adults (aged 15-69 years) perform hard to moderate physical activity, being 49.4% in males and 32.4% in females. Not only the physical activity or the obesity data are alarming, but the results also reveal an increase in risk factors and/or chronic pathologies such as high blood pressure, high cholesterol, high plasma triglycerides, low HDL-cholesterol levels, glucose intolerance, and diabetes.

From the health care perspective regarding the management of overweight and obesity, a red flag has been raised many years ago on the limited capacity of nutritional intervention on the patients due to the lack of qualified professionals that may collaborate with dietary and therapeutic education, which translates in low adherence to the therapies; there is another red flag on the lack of effective and safe pharmacological treatments. Besides, among the list of factors that could be improved, poor psychological support is detected for this pathology that includes approximately a 30% rate of eating behavior disorders, as well as shortening of the waiting lists for specific obesity surgery. Of course, the efforts should more intensely be focused on prevention, although it is also true that many aspects of the clinical management are being updated and it is becoming urgent to adopt solutions in this regards at a time when there is some *stagnation* in R&D&I and in the outcomes of pharmacological treatment, particularly regarding the disappointing weight regain approximately two years after the end of treatment for most of the patients, together with higher health care loads at all levels.

The epidemiological evidence supporting the beneficial health effects of the *Mediterranean lifestyle (MLS)* is abundant. Although the evidence is not conclusive, it suggests a clear protective effect of the so-called *Mediterranean Diet* (understood as a true *philosophy of live*) on overweight and obesity and for a higher level of an active life. Our preceding cultural and anthropological substrate favored the acceptance of eating with the family and lifestyle practices, although the current trends have facilitated partially abandoning them.

The rapid social and lifestyle changes that have taken place in the last decades have led to a progressive abandoning of the traditional profile characteristic of the *Mediterranean lifestyle* (MLS) in Spain and other

Mediterranean countries, particularly in younger populations of importance, the MLS considers not only "what I eat" and "what I drink" but also "how do I eat it" and "how do I move", that is to say, the social aspects of the MLS. There have been important changes in other lifestyles, such as the performance of physical activity in our Mediterranean area. With no doubt, technological advances and improvement of the socioeconomic conditions are closely linked to this transformation. Better acclimatization conditions in the houses and workplaces (the so-called *thermal comfort* and its impact on energy expenditure), the mechanization of labor tasks that require less physical effort in most of the cases, the improvement in public transportation, a great increase in the use of private motorized transportation, etc. There have also occurred important changes in the leisure time activities that have notably contributed to increase the time spent on sedentarism and reduce the amount of physical activity. In this sense, it should be reminded that the energy consumed during the physical activity is the component that varies the most in the total energy waste. It includes the energy consumed during voluntary physical activity as well as that consumed involuntarily in other activities and for postural control. The energy cost of physical activity depends on factors such as the body composition, the intensity and duration of the physical exercise, as well as the net efficacy of the work. On the other hand, physical activity usually negatively relates with age and adiposity.

Knowledge on the energy requirements is essential to correctly establish the nutritional recommendations for the different population groups. It is also important to keep in mind that it is not feasible to measure the total energy consumption or the energy waste while resting in all the cases where this information is required. On the other hand, the recommendations on energy intake are mainly based on estimations of the foods consumed, recorded or notified by the individual, factorial methods and balance studies. It is currently believed that these methods do not provide sufficient accurate and objective estimations of the energy consumed by an individual. There is definitively a consensus on the pressing need to develop studies that would allow adequately quantifying the so-called "energy balance" according to the characteristics of the individual of the 21st Century and the several conditioning factors.

The *sedentary lifestyle*, or better said, the *inactive lifestyle* is a common characteristic of the lifestyle of developed societies and is even more pronounced in the Mediterranean countries of Southern Europe. Regarding the pediatric population, situations such as lower level of road and civic safety has made that the percentage of children commuting to schools by foot or by bicycle or playing on the streets, or parks or public spaces is lower. This fact could be included in the so-called "protective kangaroo effect" that many parents adopt preventing their children to play and run on the streets "by their own". Besides, the advances in new technologies make the people engaging more and more in very low energy wasting activities during their leisure time (games console, video games, Internet, etc.).

We should remind that the sedentary behavior is not just lower physical activity, but a set of individual attitudes in which the fact of being *seated and/or laying down* becomes the predominant postural behavior implying a very limited energy waste. On the other hand, sedentary behaviors are present in many places and situations: the workplace, the school environment, transportation, or spare and leisure times. The issue is that a number of studies carried out in the last years have shown that sedentarism or physical inactivity are a risk factor *per se* for the development of many chronic diseases. On the one hand, it has been shown that leading a physically active life implies many health benefits: it decreases the mortality risk from cardiovascular diseases, it prevents and/or delays the development of high blood pressure, it improves the blood lipid profile (it reduces triglycerides and increases HDL-cholesterol), it decreases the risk of suffering from type 2 diabetes, and even certain types of cancers (colon, breast cancer), it improves the body weight control (prevention and treatment of overweight and obesity), it helps optimizing and maintaining the strength and muscle endurance, etc. Moreover, it should also be considered that competition sports represent one of the cultural phenomena interesting most our society. Thanks to basically the mass communication media and private initiatives and sponsoring, many sports events have become big entertainments. In this sense, proper feeding and hydration and mass social entertainments are essential to adapt to the trainings, optimize the physical performance, and accelerate the recovery process. And always keep in mind that a sport will be practiced by anybody liking it, whereas leading an active live is an unavoidable principle for every citizen.

One the other hand, and not less important, the organization of the family and work contributes to spending less time in buying, cooking and consuming the foods, selecting other more readily accessible and cheaper options that require less time to prepare them or that are ready to use. The culinary skills have been declining and the family meals tend to occur during the weekends whereas during the labor days each member of the family unit usually eats at the workplace, the canteen or at some restaurant. Little time is spent for the main meal. So, these social trends lead to new forms of eating, both at home and outside, and to new lifestyle behaviors. This implies a great collective effort to recuperate and/or maintain our dietary habits and lifestyles and also to strengthen the responsibility ("autonomy") at an individual level, which would allow us making the proper choice of our feeding pattern and global lifestyle; at the end, deciding on our quality of life by promoting the education and information at all levels and prioritizing the issues on prevention over treatment, without discrediting the latter.

All of the above has to be considered in our country, with a current situation of economic crisis, with some individual and collective disappointment that implies that the consumers' behaviors have also been affected. The current economic situation, on the one hand, gives

preponderance to the financial criteria on the consumers' individual choices and, on the other hand, renders more difficult public and private investments in the development, implementation and assessment of initiatives for monitoring, implementing preventive strategies, and promoting healthier feeding and physical activity attitudes. Besides, there is little communication and coordination that would favor the synergism between the different efforts made to achieve higher efficiency. We should not forget, of course, the principle recently established by the Health Administrators of the European Union stating that *economic crisis* should not equal *public health crisis.*

Both the WHO and the DG SANCO ("Directorate General for Health & Consumers") of the European Commission, as well as other competent authorities in the fields of public health, scientific, academic, and health provision, agree and share the concern and goal of approaching the issue of weight excess and sedentarism from a multifactorial setting, with the implication of all the parties and sectors with some responsibility. The *Global Strategy on Nutrition and Physical Activity* approved by the WHO in the year 2004 set the standard that triggered in Spain the development of the NAOS Strategy at the national government level. Within this frame, several initiatives have already been developed, mainly at the local and school levels, which is in agreement with the recommendation of the *WHO Vienna Declaration* of the present year. Therefore, the WHO *Global Strategy on Feeding and Physical Activity* and the Spanish *NAOS Strategy*, or the most recent creation of the *Observatory for the Study of Obesity and Nutrition (AESAN)* as well as the *European Union Platform for Nutrition and Physical Activity* are reference frames for the design of prevention and intervention strategies from the strictly public or strictly private settings, as well as mixed models of public and private initiatives. Besides, the *Food and Nutrition Safety Law* passed in Spain, although still not fully developed, together with other laws affecting the Secondary and somehow the Primary Educational levels, endorse the implementation of projects promoting healthy dietary and physical activity habits. In the setting of physical activity and sports, there is a *Registry of Sport Habits in Spain* since 1980, carried out by the *Center for Sociological Studies* (CIS) and the *High Council for Sports (CSD).* Besides, the Spanish Government, in close collaboration with other competent organisms, has reached a consensus with the *Integral Plan*, which is being fully developed and contains specific programs on training of experts in physical activity, sports and health, and aimed at health professionals and physical education and sports professionals. Thus, it may be affirmed that in recent years there is greater awareness on the issue of obesity and physical inactivity and also very diverse community initiatives have been put in place, with heterogeneous results (basically because of the lack of monitoring of the mid-term and long-term impact or insufficient financial support); these results should be analyzed, but with no doubt they represent a considerable progress. So, the acknowledgement and valorization of the experiences performed, the existing capacitation and the available resources represent a motivational substrate that would allow maintaining the different strategies and increasing their efficacy, as well as updating and renovating them. This would require a limited financial effort, given the current circumstances, by seeking synergies. Therefore, a coordinated intervention between the different sectors and parties implicated at a national, autonomic, and local level is paramount, as well as between the different strategies proposed that assess the experiences and the capacitation accumulated.

These strategies should include a broad range of proposed measures aimed at a more correct choice of foods; the regular practice of physical activity; promoting the creation of proactive environments from both the family and the school and the community that would favor the adoption of correct or proper food and physical activity habits by means of consensus and evaluable programs based on the better evidence available and on local studies, with special emphasis on the recovery and preservation of our Immaterial Humanity Patrimony: the *Mediterranean Diet* as a global philosophy of quality of life.

Based on the thoughts and considerations stated above, a *Multidisciplinary Scientific Forum* met with the objective of reviewing and discussing the following *topics* and *questions* with the aim of elaborating the present *Consensus Document and Conclusions:*

- The "main" topics regarding *energy balance* such as diet and physical activity.
- The "other" emergent factors: genetics, chronobiology; sleep; consumption of medicines; energy waste and baseline metabolism; decrease of cigarette smoking; age at first maternity, etc.
- Do we really know the so-called *energy balance* at the present time? Is it necessary to review the Recommended Energy Intakes in Spain? Would it be convenient to establish *Maximum Tolerable Energy Intakes* according to the different age groups?
- Obesity predictors: are the tools and/or biomarkers adequately defined? The power of omics, their strengths and weaknesses.
- Should the excess of sedentarism and physical inactivity also be considered as risk factors? How should be defined and measured? Are there reliable biological markers for the different ages and physiological conditions?
- Overweight and obesity and the excess of sedentarism and physical inactivity at the different life stages and physiological conditions: are indicators and growth curves equally valid in the pediatric and juvenile populations or the BMI (elder people, sportive people vs. adult population)? Is generalized interventionism recommended in the elderly?
- Foods and daily feeding: Do we sufficiently know the composition of our foods? Are there any *cul-*

prits in our feeding and would they be justified from the perspective of scientific knowledge? What is more important, the "quantitative" or the "qualitative" aspects when relating diet and health? Hydration, physical exercise, and body weight control.
- Physical activity, physical exercise and sports today: strengths and weaknesses.
- Common errors and myths about overweight and obesity, and sedentarism/physical inactivity.
- Current challenges in the research of obesity and sedentarism.
- Ethics of prevention and treatment of overweight and obesity and sports practice.

The *main conclusions, recommendations and proposals* reached are presented below and constitute the *"Segovia Consensus Document on Obesity and Sedentarism in the 21st Century: What can be done and what must be done?"*

• The periods of *economic crisis should not and must not imply a public health crisis* regarding the prevention of overweight and obesity and sedentarism and physical inactivity.

• *Health not only means the lack of disease*, but a state of physical, psychological and social wellbeing.

• The *severity of the problem of overweight and obesity* is reaffirmed, although in some aspects some encouraging data are foreseeing, more significantly in the world population and not so easily identified in Spain.

• The *problem of excessive sedentarism and physical inactivity* of the Spanish population is also reaffirmed, and not only in association with overweight and obesity, but also with other disorders, pathologies which evidence and impact are just in their emergent phase.

• *Prevention of overweight and obesity and sedentarism* should be included in the *"services portfolio"* of the Spanish Healthcare System, throughout its different models.

• *We still do not sufficiently know the origin and causes, and sometimes there is a tendency "to believe more than to know"*. They are not only just two factors (feeding and sedentarism); the multifactorial etiology makes that other factors such as hours of sleep, abusive use of some medications, the decrease in cigarette smoking, the global phenomenon of migration/immigration, or the excessive "thermal control", among others, should be analyzed. Unfortunately, in many aspects related to obesity and sedentarism the *unknown or poorly known* surpasses the scientific evidence. A significant example of this is the national integrated survey on nutrition and physical activity, which is considered a fundamental tool to be implemented in the short term. In this sense, there is a clear geographical *asymmetry* regarding the level of instruction, the economic status, the gender, etc., which allows focusing future efforts in the targets derived from these asymmetries, especially during this era of scarce financial resources.

• *The need of carrying out systematic reviews, and when appropriate meta-analyses,* of the studies and programs performed in Spain in recent years on different issues relating to overweight and obesity and/or sedentarism and physical inactivity is proposed.

• It is paramount to *better define which are the barriers to prevention and/or treatment of overweight and obesity and sedentarism and physical inactivity*.

• *We currently have not available a proper nor sufficient therapeutic armamentarium to treat obesity*. The need of counting on effective drugs helping to treat obesity when other types of interventions (diet, physical exercise, dietary behavior habits) are insufficient is confirmed. Generally speaking, pharmacological therapy is seen as an *alternative* and not as the first choice. The drugs currently used or that are about to be marketed seem to be effective in diminishing the cardiovascular risk or progression of diabetes, but they do not seem to adequately cope with the needs of losing weight. Therefore, novel pharmacological targets are needed. This renders prevention more relevant as well as *personalization* as a strategic priority.

• In the case of morbid or extreme obesity, *bariatric surgery* is consolidating as an effective and verified treatment with important therapeutic results within the setting of a multidisciplinary team.

• In the prevention of overweight and obesity and the excess of sedentarism and physical inactivity, the *social aspects* become relevant. This means that the statement of *what you eat and what you drink is important but also how you eat it and how you move* should be promoted trying to recuperate and/or preserve all that pertaining to the socialization of food or shared social life. There exists the unanimous opinion to consider the *family*, in its different structures, as the best model to learn proper and healthy dietary and lifestyle habits. Therefore, policies on prevention should mainly focus on reaching and communicating with the family core, although the institutional canteen (school, university, company, nursing home), is also an adequate frame for action through education.

• Regarding the *family environment*, it is recommended in the first place to avoid the presence of the television in the bedroom of the child / young. In the second place, eating while watching television should be avoided, at the same time that exposing the child-adolescent to inadequate advertisements related with the topics of this Document should be minimized. Besides passive electronic entertainment should not be promoted by public administrations or the community. Finally, and given the already mentioned multifactorial origin of obesity, this *minor* actions will not be successful if main obesogenic factors are not controlled.

• *Special attention should be paid to certain ethnic groups or immigrant populations recently installed in Spain, with a follow-up on feeding transitions.*

• All the actions leading to *social equity* should be promoted so that we may prevent or decrease the fact that the prevalence of overweight and obesity or the

excess of sedentarism and physical inactivity is more pronounced as the educational level decreases and the inequities in the socioeconomic environment increase.

• It is paramount that the *message* given to the population will be that these problems may be prevented and even treated; the professionals implicated being the first believers. We advocate the "yes we can" statement as the fundamental principle to be transmitted individually and collectively.

• *Many errors are recognized in the auto-perception of eating, body weight, and physical activity*, etc.; since nutrition is many times nutrition is individually perceived as "how it works on me" and not based on scientific evidence. This leads to many errors, myths and magic in the topics of nutrition, physical activity and sports. It is proposed to fight more diligently against these errors and myths, from the public administration and the educative, scientific, healthcare, or mass communication media settings.

• There exist a *great number of prevention programs, interventional studies***,** etc., but there is a *lack of coordination and follow-up*, many times due to the dependence on the public administrations and the lack of budgets or the existence of long-term criteria to be achieved succesfully. In this sense, programmed and bound implication of governmental, autonomic and mainly local administrations in obesity prevention is paramount. In agreement with the *WHO Vienna Declaration* of July of 2013, local powers should be prioritized since their managerial range is more efficient and closer to the citizenship and it allows adapting the programs to each population peculiarities. Effective changes require continuous, unified, sustainable, and close actions that cross-sectionally implicate all the community, the family being the core where most of the behaviors related to diet and physical activity reside.

• Similarly, the Administrations should decide if they want and they can have financial models strictly public, or "mixed" public/private models, as occur in countries with similar problems.

• There is a *real need for adopting not only a nationwide consensus but also an international consensus in order to have homogenous criteria for gathering and analyzing the data* from the studies targeting with overweight and obesity and/or sedentarism and physical inactivity.

• Many observational and interventional studies generally lack well defined study samples and the *"obese" and/or "sedentary" individual has usually been considered as one single typology* from both the physiological and pathological perspectives. This methodological bias is no longer acceptable thanks to the ever growing knowledge coming from the *omics* that allows us accurately differentiating the typologies and how to approach them from the prevention and treatment viewpoints. There is a current scientific consensus that "obesity" does not exist as a unitary phenomenon, but that there are several types of "obesities" requiring innovative approaches in prevention and/or treatment, investigating etiological factors and specific biomarkers for each particular condition. Thus, new possibilities for action emerge in the sense of greater individualization of the interventions. This concept of *diversity* should translate to the experimental models and clinical situations, being the starting point for the study of new pharmacological targets by means of studies on genomics, proteomics, etc. In this way, the dilution and excessive homogenization of many studies in this field would be prevented. Finally, the efforts in basic and translational research should be pursued in order to progress in the pharmacological treatment of obesity.

• Regarding *research*, the need for a *multidisciplinary approach* is reinforced, and more specifically we should insist in the development of:

a) New models based on the possibilities that offer the imaging techniques.
b) Identification and validation of new biomarkers of inflammation and metabolic risk associated to the comorbidities of obesity.
c) Epigenetic models that certainly require lots of time for their validation and potential success since many times it seems that much is being demanded from them and in a very short time.
d) New *omics* technologies.
e) New methods to register food consumption and physical activity, as well as other associated factors (i.e chronobiological aspects). The new technologies offer tremendous possibilities in this regards for greater accuracy, both quantitative and qualitative.
f) More intense studies on the bacterial flora ("microbiota")
g) Efforts to link more basic and/or applied research with the so-called "consumer science" in the topics considered in the present document.

• *Diet and food composition and consumption still is a big unknown* in many of its aspects, and even more as it has become more complex in its production, availability, gastronomy, etc. All of this in a consumer's environment with less time and rational capacity for a proper choice of the foods and many times without solid culinary skills, by contrast with what occurred less than one generation ago. In this sense, we should promote the idea of *the individual being "autonomous", promoting individual responsibility*, which is not clearly understood nowadays.

• Knowledge on nutrition of the whole population, assuming the methodological weaknesses still present, is essential to be able to draw a picture of its nutritional status. With regards to the *usual consumption pattern* of the Spanish population, low consumption mainly of grains and their derivatives, greens and vegetables, and legumes are being observed, as compared to the recommendations. By contrast, there is high consumption of fat meats, cold meats, and in the upper limit for simple sugars. This implies an unbalanced caloric profile given that the relative contribution of fats is higher and that of carbohydrates is lower than the percentages recommended. Regarding the fat quality, the contribution of saturated fatty acids to

total energy exceeds the recommendations. Analyzing these data and their evolution from the 1960s, it may be observed that the diet of the Spaniards has been notably modified in the last 40 years, moving away from the traditional model of the Mediterranean Diet (MD). Therefore, all the efforts should be focused on recovering and/or maintaining the characteristics and properties of the MD, always considered together with our lifestyle.

• The *Mediterranean lifestyle,* considered in all its aspects (diet, physical activity, socialization), that is to say as an optimal *philosophy of life*, is the best model for prevention and treatment of overweight and obesity and the excess of sedentarism. Besides, it should be highlighted that it is not only that the density of nutrients and quality of life-associated factors in relation to costs is more favorable to the MD as compared to other kinds of diets, but also that models of adherence to this diet are cost-saving, which is particularly relevant in the current situation of economic crisis.

• The *Mediterranean lifestyle (MLS)* is not just a dietary pattern that has cumulative evidence in the prevention of chronic diseases; it represents a lifestyle as the original Greek term means, "diaita", which also comprises the combination of foods, cultural elements and lifestyle in the process of selecting, processing, and consuming, giving priority to fresh, local and seasonal foods; the culinary activities and social aspects of meals; regular physical activity; resting in the form of a nap; and all the way of living that is part of the cultural inheritance of the Mediterranean countries. These countries share a series of geographical and climatic factors that have favored this common cultural and agro-alimentary frame. However and spite of an acceptable degree of knowledge by a majority of the population on the concept and principles of the MD, there exist big difficulties to follow and adhere to it since many times there is a lack of knowledge, skills and attitudes.

• Monitoring the *MLS pattern* reveals that the *Mediterranean populations*, especially those from the Mediterranean Europe, *are progressively moving away* from it, which menace the adherence to this pattern among the younger populations. Paradoxically the Northern European countries and other regions of the World far away from the Mediterranean area are those that are increasingly and positively adopting several characteristics of the MD. This is a robust example that "positive" intervention policies in public health are a very good tool for the consecution of the short-term and/or mid-term goals.

• It has repeatedly been observed in a number of epidemiological studies that a *good adherence to the MLS pattern* is systematically associated with a significantly lower risk for several chronic diseases (cardiovascular diseases, diabetes, and metabolic syndrome, neurodegenerative pathologies such as Parkinson's disease, Alzheimer's disease or depression, some types of cancers, overweight and obesity, bronchial asthma, etc.), and globally to better nutritional adequacy, longevity and quality of life. Also important in the current and future contexts, the MLS implies low costs and environmental impact and could be included among the most sustainable agro-alimentary systems worldwide. We may add to these unquestionable strengths that, in the Spanish setting, the MLS is adapted to our tastes and customs and there is the possibility of using locally produced foods with a low dependence on foreign markets.

• In Spain, the *agro-alimentary industry* has played an essential role (and still does so) in improving the food offer, food safety, or eradicating situations of general and/or specific malnourishment. However, at the same time, we call for better support and collaboration, essentially and urgently, from the part of the industry related with the food chain, but also from the part of the industry related with entertainment, leisure, physical activity, and sports. This would allow modifying or adapting their products, processes and marketing and advertising strategies to the Dietary Guidelines and Nutritional Goals for the Spanish population, and also fulfilling with the recommendations for leading an active life.

• Many of the so-called functional foods and nutraceutics in the field of body weight control have focused on the target of inhibiting the food intake (by interfering with the feeling of hunger, stimulating satiety, or limiting the bioavailability of certain nutrients), the energy content of the foods (by including less caloric ingredients or substituting fats and sugars), and the body composition and/or energy waste (through stimulation of thermogenesis). The dramatic advance of disciplines such as nutrigenomics o nutrigenetics will certainly allow adopting new strategies for the development of these products, although the outcomes are still scarce and emergent.

• It is essential *to unify the messages in the field of diet, nutrition and physical activity* coming from the different actors (administrations, scientific societies and foundations, professionals), always counting on the collaboration of the mass communication media and the new technologies. We propose the *elaboration of Consensus Guidelines/Recommendations regarding prevention of overweight and obesity and the excess of sedentarism*, with the possibility of association models in view of the scientific knowledge. At the same time, we postulate the importance of better defining the "clusters" in nutrition and physical activity that would allow more specific and effective actions.

• Regarding the *information* on Diet and/or Nutrition, there is no sufficient scientific evidence showing that better information on the foods (composition, nutritional information, etc.) will positively impact on a better choice and adherence to the dietary pattern. The concurrence of new information technologies with more traditional ones seems indispensable given the different skills of the different population groups, and anyhow, it will be necessary to monitor them regarding a real improvement in dietary habits and lifestyles.

• There are *intervention models that have been proved and work well*. When planning and monitoring

interventions in the pediatric and juvenile populations, one should be alert not to increase the prevalence of children with low weight and associated behavior disorders, as it has already been observed in studies conducted in Spain. The population-based obesity prevention projects carried out in Spain, although scarce and many times lacking a follow-up, have described positive results in changes in the eating habits and lifestyles, but also in body composition and biological markers. We are clearly convinced that these prevention systems should be implemented in the long run and be integrated in the socio-occupational dynamics of the collectivities mentioned.

• The so-called *energy balance is not well defined* for the Spanish population and it is essential to approach it with the aim of being able to properly establish the energy requirements for our population and the subsequent Reference Intakes. *Integral studies of all the elements comprised in the energy balance equation* should be done given their interrelationship. Long-term longitudinal studies on the energy balance and body weight/composition are urgently needed. It seems essential to improve the tools for studying the energy intakes and losses of "free living" independent subjects. In this regard, the tools such as databases of the composition of quality foods, especially regarding energy and serving sizes, should be improved.

• *The knowledge for the different age groups on the impact of the different levels of physical activity should be increased*. In the same way, more studies should be carried out in the different population groups and physiological conditions in order to be able to assess the recommendation of the level of physical activity necessary: either moderate, intense or more vigorous. In this sense, the value of the so-called muscle strength should be reinforced as a very useful tool with a clear positive impact at all ages. The important effort done in Spain in the last years regarding the different kinds of sports facilities should not be wasted, even during difficult times as the present one, so that the above mentioned challenges and needs could be met. Sports professionals, in the broadest sense, should increasingly be involved.

• *We should try to answer the following questions*: Is inactivity a "normal" response to an "abnormal" environment? This would imply changing the environment, modifications at the educational level, awareness on the importance of being active giving the highest importance to the expression "to practice what one preaches", at all levels: the administrations, the community, the schools, the families, etc.; Or is it an "abnormal" response to a "normal" environment? This would imply a behavioral change, as well as taking into account the chronobiology of overweight and obesity. *We should consider not only the physical activity performed but also the physical inactivity*. Sedentarism is not necessarily equivalent to physical inactivity, and it is becoming more and more important to assess the different sedentary behaviors, their health impact, and their correlation with the forms of feeding and other lifestyles.

• Independently of the genetic factors, etc., there is sufficient scientific evidence showing that *regular physical activity through sports decreases the percentage of body fat* and decreases the risk factors associated to cardiovascular disease, diabetes, or certain types of cancers. There exists scientific agreement in considering the practice of physical activity as a useful tool for the prevention of obesity, so that spontaneous physical activity, practicing sports, active commuting, etc., should be promoted.

• *Special attention should be paid to projects and organizations that incorporate in the physical activities the greatest number of people* with programs such as "physical exercise for everyone", "physical activity and physical exercise as a leisure activity", "move on", "activate yourself", etc. Therefore, sports organizations represent a unique potential in the promotion of physical activity and healthy living habits, which should be better used in the future.

• *The data on physical activity should be included in health monitoring systems at a national scale*. Besides, physical education professionals, health professionals, trainers, managers of sports and leisure centers, and mass communication media professionals, should have available during their studies, professional training and specialization all the information regarding physical activity, the best way to incorporate it in daily living, the dietary characteristics of the active, moderately active or very active person.

• The active person practicing physical activity, physical exercise or sports should know that in order to provide an adequate daily energy intake and maintain an optimal performance, the caloric expenditure should be considered individually since the amount of energy consumed varies according to the individual's characteristics, the kind of physical activity performed (kind of sport, intensity, duration etc.), and the environmental conditions in which the activity takes place. It is also important to have a proper intake of water, that is to say hydration, as well as macro and micronutrients and other non-nutritive components with a nutritional interest. *We propose to increase the education and information of both the professionals related with physical activity, physical exercise and sports, and the people practicing them as amateurs or professionals.*

• *Health and educational programs prescribing physical exercise and preventing sedentarism should be created and promoted*, as well as assessing this situation in certain risk conditions such as chronic diseases, as well as other related pathologies.

• Leading an *active life* should be associated not only with a better health state but also with *enjoying time and higher sociability*, at all ages, but especially in the pediatric/juvenile population and the elderly. Therefore, intervention programs should consider these principles, strongly giving the message that *it is never late to start leading a more active life*. Similarly, we urge to better promote the investigation that will allow determining more accurately the optimal amount of physical exercise (time, duration, intensity), in combination with the usual sedentary behaviors of our society.

• *Mass communication media and the new technologies* should be used to sensitize the population to be more active and informing on the benefits of leading an active life and practicing physical exercise and the risks of sedentarism and physical inactivity for health and the quality of life in general.

• *Obesity prevention has not been considered as a priority goal in the context of physical activity and sports sciences* until very recently. Therefore, we urgently propose the inclusion of investigators from the sports and educational fields in the multidisciplinary teams that carry out preventive and interventional strategies.

• *The lack of multidisciplinary units* including professionals from the fields of physical education and sports, as well as nutrition and dietetics *is alarming*. A decisive and urgent action is needed to rectify this situation.

• We insist in the need for *promoting investments in infrastructures* for transportation by foot or by bicycle, together with information campaigns aimed at explaining the benefits on health and quality of life.

• *Regular practice of physical activity at school age* is an essential tool for proper integral development of children and adolescents. We must try to increase the performance of physical activity, physical exercise and sports by all the pediatric and juvenile populations as a tool of social cohesion since the habits learnt at childhood usually live on at adulthood.

• *In children, growth and development should be guaranteed, and not only emphasize the energy intake*. Physical activity has to be enjoyable and include the children in decision-making; all of it integrated in the indispensable public health policies. On the other hand, treatment of overweight and obesity through physical exercise is a much more complex topic, it requires some caloric restriction in the adult, and is even more complex in pediatric ages. The approach of this latter situation is more clinical and less related to the school environment. It should be desirable to reach a *consensus at a national level on the reference curves and the cut-off points* for the studies assessing and monitoring the body weight in pediatric populations so that international comparisons could be made.

• *Prevention of diabetes* is essential in order to decrease the incidence of this disease. As compared to the general population, at the time of diagnosis, approximately 50% of the patients have microvascular complications (retinopathy, neuropathy or nephropathy) and twice the risk for macrovascular complications. Obesity is considered as the main modifiable factor, to which approximately half of the new cases may be attributed. We may insist by any means in communicating that even a modest weight loss has a favorable effect on risk and that physical exercise, either combined or not with diet, also contributes to decreasing the risk. Therefore, diabetes should be prevented through different interventions given the fact that:

– Its prevalence is already overwhelming and it is a public health concern.
– There exist markers that allow measuring the progression of the disease.
– "Pre-diabetic" subjects already present cardiovascular risk.
– Once diagnosed, the treatment of diabetes is expensive and difficult.

• Obesity is associated with *greater risk for cardiovascular disease and chronic inflammatory state*; however, many aspects need to be studied in a combined way since they directly impact on the adolescents' health, although not exclusively in this age group. Sedentarism is associated with poorer cardiorespiratory condition, independently of the BMI. Sedentarism is also associated with cardiovascular risk factors in adolescents, especially in those with excessive abdominal adiposity. All of the above implies the need for an action strategy that takes into account all of these factors.

• *Moderate exercise stimulates certain aspects of the immune response* whereas intense physical exercise may lead to unwanted side effects. Once again, the need for personalization of dietary habits and the practice and prescription, if indicated, of physical exercise is reaffirmed.

• *Weight control schedules* should be based on the approximation to the diet, physical activity, and lifestyle, the so-called "theoretical ideal", with a special emphasis on those aspects where the difference with the theoretical ideal is bigger:

– Increasing physical activity.
– Decreasing sedentarism, with a special emphasis on the so-called TICs.
– Promoting breastfeeding and control of the diet and the lifestyle in general of the childbearing mother.
– Improving the dietary pattern through the promotion of consumption of those foods eaten with a frequency below the recommended amount: vegetables, whole grains, fruits, legumes, and fish.
– Being vigilant in the timing and environment of meals, with a special emphasis on breakfast.
– Decreasing the stress at work, family, and the general environment.

• The *NAOS Strategy should keep on integrating and promoting actions* in the most diverse settings, looking for collaborations and synergisms with the different public and private administrations, research centers, universities, and with the different social players implicated in this field. The philosophy of the NAOS Strategy is based on a positive image avoiding stigmatizing and forbidding certain kinds of foods, and stimulating the participation, implication and commitment of all the social and financial players, promoting their proactivity, and trying to promote a coordinated response of all the agents implicated, with the final goal of reverting the obesity trend and, thus, social sedentarism. Therefore, in order to the NAOS Strategy becoming consolidated and definitively recognized, it must face and correct its develop-

mental weaknesses: lacking a budget linked to an action plan; the promotion of physical activity has been less developed; the evaluation and follow-up of the actions have been very limited. However, its inclusion in the *Food and Nutrition Safety Spanish Law* conferred it a legal endorsement and currently it counts with the necessary political endorsement for its development and progression in the coming years, in harmony with the policies of the European institutions (WHO and EU), the very recent Vienna Declaration of the Health Ministers and European Health Administrators (4-5th July of 2013).

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Obesidad y sedentarismo en el siglo XXI: ¿qué se puede y se debe hacer?

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Antecedentes, justificación y objetivos

En la actualidad, seis de los siete principales factores de riesgo de mortalidad prematura en Europa (presión sanguínea, colesterol, Índice de Masa Corporal, ingesta insuficiente de fruta y verdura, inactividad física y abuso del alcohol) están relacionados con los estilos de vida, especialmente con los hábitos alimentarios, el consumo de alcohol y la inactividad física y/o sedentarismo.

En el ámbito de la salud pública es especialmente preocupante el aumento del sobrepeso y la obesidad en toda Europa. Para abordar este problema, tanto la Organización Mundial de la Salud (OMS) como la Comisión Europea abogan por un enfoque integrado, con la implicación de las partes interesadas a nivel europeo, nacional, regional y local. Sirva como magnífico ejemplo la muy reciente *Declaración de Viena sobre Nutrición y Enfermedades No Transmisibles que la OMS* promulgó tras la Conferencia Ministerial celebrada en Viena los pasados 4 y 5 de julio del 2013, en el contexto del programa "Health 2020", en la que se reafirma el imprescindible abordaje multidisciplinar.

La obesidad se define como un factor de riesgo de enfermedades caracterizado por un acúmulo excesivo de grasa, y por tanto conduce a una composición corporal cuyo contenido graso supera un estándar prefijado según altura, edad y sexo. En población adulta se tipifica como obesidad la presencia de un *Índice de Masa Corporal (IMC)* con un valor igual o superior a 30 kg/m^2 (sobrepeso con valores superiores a 27), mientras que en población infantil se utilizan como referencia las curvas de IMC específicas para la edad y el sexo. Si excede el percentil 95 tendremos una situación clínica de obesidad (percentil 85 para el nivel de sobrepeso).

La patogenia de la obesidad se sustenta en un marco multifactorial sobre una predisposición mediada por las características genéticas de la persona, lo que implica cada vez más la necesidad de una personalización del problema, confluyendo un exceso en los aportes de energía, pero fundamentalmente una disminución del gasto energético en relación a lo que supondría un mejor equilibrio entre ingreso y demanda. Junto a esta expresión termodinámica en la persona obesa,

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existen fallos en el equilibrio de los procesos moleculares y en la armonía de funcionamiento de los distintos centros reguladores del hambre, apetito y saciedad, situados a nivel central (abarcando procesos atencionales, cognitivos y de recompensa), hipotalámico y periférico. Desde el punto de vista genético, es indudable que en los últimos años se ha producido un enorme avance en el conocimiento científico, que se manifiesta, por ejemplo, en el hecho de que en la actualidad se estima que están implicados más de 450 genes, marcadores y regiones cromosómicas relacionados con los fenotipos de la obesidad humana; sin duda, la *individualización* entiende este Foro Multidisciplinar que es no ya un reto de futuro, sino necesaria ya en el presente.

Al margen de las características génicas, en el proceso de desarrollo de la obesidad confluyen sin duda colaborativamente factores determinantes exógenos, como son el consumo de alimentos y bebidas de alta densidad energética, sedentarismo, bajo consumo de frutas y verduras, alteraciones del peso al nacimiento, ausencia de lactancia materna, etc., con una serie de condicionantes ambientales como un nivel sociocultural y/o socioeconómico bajo, o entorno desfavorecido, y otros aspectos del entorno que directa o indirectamente influyen sobre las conductas alimentarias, y la respuesta fisiológica del organismo a la actividad física.

El sobrepeso y la obesidad como factores de riesgo inducen claramente la aparición de co-morbilidades importantes, como son el síndrome metabólico, las enfermedades cardiovasculares, la diabetes, las patologías osteoarticulares, algunos tipos de cáncer, depresión y alteración de la función cognitiva. No podemos olvidar tampoco la relación del sobrepeso y la obesidad con trastornos de la imagen corporal, dificultad en las relaciones humanas y en la socialización, incluidos problemas cotidianos básicos vinculados con la deambulación, el sueño, los viajes, el tamaño de los asientos, cama, etc., trastornos que implican, además de una menor calidad de vida del individuo, un elevado coste personal, social y sanitario.

Según la OMS, en la actualidad aproximadamente unos 1.200 millones de personas tienen problemas de sobrepeso/obesidad y, aproximadamente, el mismo número de personas sufren desnutrición. De continuar este proceso de sobrecarga ponderal con la tendencia actual, en el año 2040 la totalidad de la población europea tendría sobrepeso. El *Centro de Control y Prevención de Enfermedades de EEUU* (CDC), ha alertado de que el aumento de la obesidad infantil podría acarrear que en las próximas generaciones, por primera vez en la historia, los hijos podrían vivir menos años que sus padres. En España el problema no es menor, tal como reflejan los datos de la *Encuesta Nacional de Salud* (ENS, 2013): Un 27,8% de la población española que tiene entre 2 y 17 años, padece obesidad o sobrepeso, y se manifiesta de forma similar en ambos sexos. En la población adulta, la obesidad afecta ya al 17,0% de la población de 18 y más años (18,0% de los varones y 16,0% de las mujeres). Desde la primera *Encuesta Nacional de Salud* en 1987, la obesidad sigue una línea ascendente en ambos sexos, más marcada en hombres que en mujeres. Mientras que en 1987 el 7,4% de la población de 18 y más años tenía un IMC igual o superior a 30 kg/m^2 (límite para considerar obesidad), en el año 2012 este porcentaje supera el 17%. Y lo que es más aun alarmante, un 53,7% de la población mayor de 18 años, padece sobrepeso u obesidad. La obesidad es más frecuente a mayor edad, excepto en mayores de 74 años. Los factores educativos, sociales y económicos también están impactando de manera diferente en las cifras españolas: así, la obesidad crece según se desciende en la escala social, y el nivel educativo es menor. Por otro lado, y no menos preocupante, destaca en la mencionada ENS la prevalencia de peso insuficiente en mujeres de 18 a 24 años (12,4%), frente al 4,1% de los varones de su mismo grupo de edad. En relación a los hábitos de actividad física, la propia ENS revela que cuatro de cada diez personas (41,3%) se declara sedentaria (no realiza actividad física alguna en su tiempo libre), uno de cada tres hombres (35,9%) y casi una de cada dos mujeres (46,6%). Considerando tanto la actividad principal como el tiempo libre, el 40,9% de los adultos (de entre 15 y 69 años) realiza actividad física intensa o moderada, 49,4% de los varones y 32,4% de las mujeres. Y no sólo la obesidad o la inactividad física pueden resultar alarmantes, sino que los resultados también revelan un aumento de los factores de riesgo y/o patologías crónicas como: hipertensión arterial, colesterol elevado, triglicéridos plasmáticos elevados, bajos niveles de colesterol HDL, intolerancia a la glucosa, y diabetes.

Desde el ámbito asistencial, dedicado al tratamiento del sobrepeso y la obesidad, se mantiene desde hace años una llamada de atención sobre la escasa capacidad de intervención nutricional sobre los pacientes, por falta de personal cualificado que se encargue de colaborar en la educación alimentaria y terapéutica, lo que repercute en una escasa adherencia a los tratamientos; y sobre la ausencia de tratamientos farmacológicos eficaces y seguros. Además, se detecta un escaso soporte psicológico en una patología que incluye aproximadamente un 30% de alteraciones del comportamiento alimentario entre otros asuntos susceptibles de mejora, entre los que podríamos destacar la reducción de las listas de espera quirúrgicas especificas para la obesidad. Y es que aunque los esfuerzos deberían focalizarse con mayor intensidad en la prevención, no es menos cierto que el abordaje clínico tiene muchos aspectos de actualización, y resulta urgente que se adopten soluciones en este sentido, en un momento de cierto *estancamiento*, tanto en el I+D+i como en la propia eficacia y resultados del tratamiento farmacológico, principalmente en lo que se refiere a la desmotivante recuperación del peso al cabo de aproximadamente dos años, y para la mayoría de los pacientes, además de una mayor presión asistencial a todos los niveles.

Existe abundante evidencia epidemiológica que sostiene los efectos beneficiosos para la salud de un *Estilo de Vida Mediterráneo (EVM)*. Aunque la evidencia no es concluyente, sí se sugiere de manera clara un efecto protector de la llamada *Dieta Mediterránea*, entendida como una auténtica *filosofía de vida*, sobre el sobrepeso y la obesidad y un mayor grado de vida activa. Nuestro sustrato cultural y antropológico precedente favorecería la aceptación de prácticas de consumo alimentario y estilo de vida que resultan familiares a pesar de que las tendencias recientes hayan impulsado su abandono.

Los rápidos cambios sociales y en el modo de vida acontecidos a lo largo de las últimas décadas, se han reflejado en un progresivo abandono del perfil tradicio-

nal característico del *Estilo de Vida Mediterránea* (EVM) en España, y en otros países de la región mediterránea, especialmente en los colectivos de edad más joven, y entendida siempre no sólo en "lo que como" y "lo que bebo", sino también en "cómo lo cómo" y "cómo me muevo", es decir, los aspectos sociales de la EVM. También se han experimentado cambios importantes en otros estilos de vida, como la práctica de actividad física en nuestro ámbito mediterráneo. Sin duda, los avances tecnológicos y la mejora en las condiciones socioeconómicas de vida son factores estrechamente relacionados con esta transformación. Mejores condiciones de aclimatación tanto en las viviendas como en los lugares de trabajo (el denominado *confort térmico* y su impacto en el gasto energético), mecanización de las tareas laborales que requieren menor esfuerzo físico en la mayor parte de los casos, mejora en los transportes públicos, y un aumento enorme en el empleo del transporte motorizado privado, etc. Pero también se han producido cambios importantes en las actividades en el tiempo libre, que de manera definitiva han contribuido a aumentar el tiempo de sedentarismo y a reducir la cantidad de actividad física. En este sentido, debe recordarse que la energía consumida durante la actividad física es el componente más variable del gasto total de energía. Incluye la que se destina al ejercicio físico voluntario, así como la que se utiliza involuntariamente en actividades y control postural. El coste energético de la actividad física depende de factores como la composición corporal, la intensidad y duración del ejercicio físico, así como de la eficacia neta del trabajo. Por otra parte, la actividad física suele guardar una relación inversa, tanto con la edad como con la adiposidad.

El conocimiento de los requerimientos energéticos es esencial para establecer correctamente las recomendaciones nutricionales para los distintos grupos poblacionales. Es importante también recordar que no resulta factible medir el consumo de energía total, o el gasto energético de reposo en todos los casos en los que se requiere información acerca de los requerimientos energéticos de una persona. Por otro lado, el establecimiento de recomendaciones de ingesta energética se ha basado fundamentalmente en estimaciones del consumo de alimentos registrados o notificados por la propia persona, métodos factoriales y estudios de balance. En la actualidad, se cree que estos métodos no proporcionan estimaciones exactas y objetivas del consumo de energía de una persona. En definitiva, existe consenso en la necesidad imperiosa de desarrollar estudios que permitan cuantificar adecuadamente el denominado "balance energético", de acuerdo a las características del individuo del siglo XXI, y los diversos factores que lo pueden condicionar.

El *estilo de vida sedentario,* o mejor dicho, *estilo de vida inactivo* es una característica común del estilo de vida de sociedades desarrolladas, y de manera aún más marcada de los países mediterráneos del sur de Europa. En el caso de la población infantil, situaciones como la menor seguridad vial y ciudadana han hecho que disminuya de forma considerable el porcentaje de éstos que se desplazan a pie o en bicicleta hasta el colegio y que juegan solos en la calle. O acudan a parques, o espacios públicos a practicar juego, ocio, etc. Este aspecto entraría dentro del llamado "efecto canguro protector" que muchos padres adoptan ante sus hijos y que no les permiten correr y jugar en la calle con "libre albedrío". Además, el desarrollo de las nuevas tecnologías hace que cada vez se recurra con más frecuencia a actividades de muy bajo coste energético en el tiempo libre (videoconsolas, videojuegos, internet, etc.). Recordemos que el comportamiento sedentario no es simplemente una menor actividad física, sino que se corresponde con un conjunto de comportamientos individuales en los que el hecho de estar *sentado y/o tumbado* pasa a ser la forma postural predominante, al mismo tiempo que conlleva un gasto energético muy reducido. Por otro lado, los comportamientos sedentarios se presentan en muchos lugares y situaciones, trabajo, entorno escolar, hogar, en el transporte o en el tiempo libre y de ocio. El problema es que numerosos estudios llevados a cabo en los últimos años han demostrado que el sedentarismo o la inactividad física suponen un factor de riesgo "per se" para el desarrollo de múltiples enfermedades crónicas. Por otro lado, se ha comprobado que el llevar una vida físicamente activa produce numerosos beneficios para la salud: disminuye el riesgo de mortalidad por enfermedades cardiovasculares, previene y/o retrasa el desarrollo de hipertensión arterial, mejora el perfil de los lípidos en sangre (reduce los triglicéridos y aumenta el colesterol HDL), disminuye el riesgo de padecer Diabetes de tipo 2, e incluso de sufrir ciertos tipos de cáncer (colon, mama), mejora el control del peso corporal (prevención y tratamiento del sobrepeso y de la obesidad), ayuda a optimizar y mantener la fuerza y la resistencia muscular, etc. Pero también hay que considerar el deporte de competición, que constituye uno de los fenómenos culturales que despierta más interés en la sociedad actual. Gracias fundamentalmente a los medios de comunicación y a la iniciativa e inversión privada, muchos eventos deportivos se han convertido en grandes espectáculos. Y en este contexto, una buena alimentación y una hidratación adecuada, resultan primordiales para adaptarse a los entrenamientos, optimizar el rendimiento físico y acelerar la recuperación. Y siempre conviene recordar que un deporte lo practicará quién le guste, mientras que llevar una vida activa es un principio ineludible por todos los ciudadanos.

Por otro lado, y desde luego no menos importante, la organización de la vida familiar y laboral contribuye a que se dedique cada vez menos tiempo a la compra, preparación y consumo de alimentos, seleccionando las opciones más accesibles y más económicas, y que requieran menos tiempo para su preparación o incluso se presenten listas para su consumo. Se han perdido habilidades culinarias y las comidas familiares tienden a concentrarse en el fin de semana, mientras que los días laborales cada miembro de la unidad familiar realiza el almuerzo con frecuencia en el lugar de estudio, trabajo o en un establecimiento de restauración-hostelería. Se dedica, además, poco tiempo a la comida principal. En definitiva, tendencias sociales que llevan a nuevas formas de comer, tanto en el hogar como fuera del mismo, pero también de comportamiento en general en nuestros estilos de vida, que exigen no sólo un esfuerzo colectivo de recuperación y/o mantenimiento de nuestros hábitos alimentarios y estilos de vida, sino también de reforzar la responsabilidad a nivel individual, de "autonomía", que nos permita hacer una correcta elección de nuestro patrón de alimentación y estilo de vida global, en definitiva, de nuestra calidad de vida, fomentando la educa-

ción e información a todos los niveles, y priorizando los aspectos de prevención sobre los de tratamiento, sin menoscabo de estos últimos.

Todo lo anterior en nuestro país en un entorno actual de crisis económica, de cierto desencanto individual y colectivo, que implica además que las conductas de los consumidores también se han visto afectadas. La actual coyuntura económica, por un lado, favorece el peso del criterio económico en las elecciones individuales de los consumidores y, por otro lado, dificulta las inversiones públicas y privadas en el desarrollo, implementación y evaluación de iniciativas de monitorización y estrategias preventivas y de promoción de hábitos más saludables de alimentación y actividad física. A ello hemos de añadir la escasa comunicación y coordinación que favorezca la sinergia de los diferentes esfuerzos para lograr una mayor eficacia. Y desde luego, sin olvidar el principio establecido recientemente por los propios responsables de Salud de la Unión Europea en el sentido de que *crisis económica* no debería ser igual a *crisis en salud pública*.

Tanto desde la OMS como desde la DG SANCO ("Directorate General for Health & Consumers") de la Comisión Europea y otras autoridades competentes en el ámbito de la salud pública, pero igualmente desde el ámbito científico, académico y asistencial, existe sintonía y se comparte preocupación y objetivo por abordar el problema del exceso de peso y sedentarismo desde un planteamiento multifactorial, con implicación de todos los actores y sectores con alguna responsabilidad. La *Estrategia Global sobre Alimentación y Actividad Física* aprobada por la OMS en el año 2004, marcó una pauta de referencia que impulsó el desarrollo en España de la Estrategia NAOS, a nivel gubernamental estatal. En este marco ya se han puesto en marcha diferentes iniciativas desde el ámbito local y escolar, principalmente, lo que está muy de acuerdo con la recomendación de la *Declaración de Viena OMS* del presente año 2013. Por tanto, la *Estrategia Global sobre Alimentación y Actividad Física* de la OMS y en España la *Estrategia NAOS*, o la muy reciente creación del *Observatorio de la Nutrición y el Estudio de la Obesidad*, así como la *Plataforma de la Unión Europea para la Alimentación y Actividad Física* crean marcos de referencia en el diseño de estrategias de prevención y de intervención, y tanto desde el ámbito estrictamente público, pero también desde modelos mixtos de iniciativa pública y privada, o igualmente desde el ámbito exclusivo privado. Además, la *Ley de Seguridad Alimentaria y Nutrición* aprobada en España, aunque todavía con escaso desarrollo normativo, junto a otras normas que afectan la esfera de la Educación Secundaria, y de manera muy próxima también a la Educación Primaria, favorecen la puesta en marcha de proyectos de promoción de hábitos de alimentación y actividad física saludable. En el ámbito de la actividad física y el deporte, existe un *Registro de los Hábitos Deportivos en España* desde el año1980, por el *Centro de Investigaciones Sociológicas* (CIS) y el *Consejo Superior de Deportes (CSD)*. Pero además, el Gobierno español, en estrecha colaboración con otros organismos competentes ha consensuado el llamado *Plan Integral A+D*, en pleno desarrollo, y desde el que se propone la realización de programas específicos de formación de expertos en actividad física, deporte y salud para profesionales sanitarios y de la educación física y del deporte. En definitiva, se puede afirmar que en los últimos años no sólo se observa una mayor concienciación sobre el problema de la obesidad y la inactividad física, sino que se han puesto en marcha iniciativas comunitarias muy diversas, con resultados muy desiguales (fundamentalmente consecuencia de la falta de monitorización del impacto a medio y largo plazo, o la insuficiente financiación), que deben analizarse, pero que suponen sin duda un avance considerable. En definitiva, el reconocimiento y valorización de las experiencias realizadas, de la capacitación existente y de los recursos disponibles configuran un sustrato de motivación que permitiría, con un limitado esfuerzo económico, en sintonía con las actuales circunstancias, y buscando sinergias, mantener las diferentes estrategias y aumentar su eficacia, al mismo tiempo que se actualizan y renuevan. Es imprescindible, por tanto, una intervención coordinada entre los diferentes sectores y partes implicadas a nivel estatal, autonómico y local y entre las diferentes propuestas estratégicas, valorando las experiencias y capacitación acumulada.

Estas estrategias deben contemplar un amplio abanico de medidas y propuestas, encaminadas a una más correcta elección de la alimentación**,** así como la práctica regular de actividad física; potenciar la creación de entornos proactivos tanto desde la familia como desde el ámbito escolar y comunitario, que favorezcan la adopción de hábitos de alimentación y actividad física correctos o adecuados, mediante programas consensuados y evaluables basados en la mejor evidencia disponible y en estudios locales, poniendo un especial acento en la recuperación y conservación de nuestro Patrimonio Inmaterial de la Humanidad: la *Dieta Mediterránea*, como filosofía global de calidad de vida.

De acuerdo con las anteriores reflexiones y consideraciones, se reunió un *Foro Científico Multidisciplinar*, que tenía como objetivo la revisión y discusión de los siguientes *temas y preguntas*, con el objetivo de elaborar el presente *documento de consenso y conclusiones:*

- Los dos "grandes" en el *balance energético*: alimentación y actividad física.
- Los "otros" factores emergentes: genética; cronobiología; sueño; consumo de fármacos; gasto energético y metabolismo basal; disminución del hábito tabáquico y edad de la madre primeriza, entre otros.
- ¿Conocemos bien el denominado *balance energético* en la actualidad? ¿Es necesaria una revisión de las Ingestas Recomendadas de Energía en nuestro país? ¿Sería conveniente establecer incluso *Ingestas Máximas Tolerables de Energía* de acuerdo a los diferentes grupos de edad?.
- Predictores de la obesidad: ¿están bien definidas las herramientas y/o biomarcadores?: el "poder" de las ómicas, y sus fortalezas y debilidades.
- ¿Debe considerarse el exceso de sedentarismo y de la inactividad física también como factores de riesgo?. ¿Cómo debe definirse y medirse? ¿Hay marcadores biológicos fiables para las diferentes edades y situaciones fisiológicas?
- El sobrepeso y la obesidad y el exceso de sedentarismo y la inactividad física en las diferentes etapas de la vida y situaciones fisiológicas. ¿Sirven por igual los indicadores como las curvas de crecimiento en población infanto/juvenil o el IMC

(personas mayores o deportistas vs. población adulta)?. ¿Es aconsejable el intervencionismo generalizado en la edad avanzada?
- Alimentos y alimentación diaria. ¿Conocemos suficientemente la composición de nuestros alimentos?; ¿Hay *culpables* en nuestra alimentación y estarían justificados desde el punto de vista del conocimiento científico? ¿Qué es más importante, el aspecto "cuantitativo" o el "cualitativo" al relacionar el binomio alimentación y salud?; Hidratación, ejercicio físico y control del peso corporal.
- Actividad física, ejercicio físico y deporte hoy: fortalezas y debilidades.
- Errores y mitos frecuentes acerca del sobrepeso y la obesidad y el sedentarismo y la inactividad física.
- Retos actuales de la investigación en materia de obesidad y sedentarismo.
- Ética en la prevención y tratamiento del sobrepeso y la obesidad y en la práctica deportiva.

A continuación, se recogen las *principales conclusiones, recomendaciones y propuestas* obtenidas, que constituyen el *"Documento de Consenso de Segovia sobre Obesidad y Sedentarismo en el siglo XXI: ¿Qué se puede y se debe hacer?"*.

• Los periodos de *crisis económica* no tienen ni deben significar *crisis en salud pública,* en lo que se pueda referir a la prevención del sobrepeso y la obesidad y el sedentarismo y la inactividad física.

• La *salud no sólo significa ausencia de enfermedad,* sino una situación de bienestar físico, psicológico y social.

• Se reafirma la *gravedad del problema del sobrepeso y de la obesidad,* aunque en algunos aspectos se atisban algunos datos esperanzadores, de manera mucho más significativa en la población mundial, y más difíciles de identificar en España.

• Se reafirma igualmente el *problema del excesivo sedentarismo y de la inactividad física* de la población española, y no sólo en asociación con el sobrepeso y la obesidad, sino con otros desórdenes, patologías cuya evidencia e impacto se encuentran todavía en una fase emergente.

• La *prevención del sobrepeso y la obesidad y del sedentarismo* debería incluirse en la *"cartera de servicios"* del sistema de salud en España, a través de sus diferentes versiones.

• *No conocemos todavía suficientemente bien el origen y las causas, y a veces hay tendencia a "creer" más que a "conocer"*. No son sólo los dos grandes (alimentación y sedentarismo), sino que la etiología multifactorial lleva a que deban analizarse otros factores como horas de sueño, empleo abusivo de ciertos fármacos, la disminución del hábito tabáquico, el fenómeno global de la migración/inmigración, o el excesivo "confort térmico", entre otros. Lamentablemente, es mucho más todavía *lo desconocido o mal conocido*, que la evidencia científica demostrada en muchos aspectos relacionados con la obesidad y el sedentarismo. Como ejemplo significativo, una encuesta nacional integrada de nutrición y actividad física se considera una herramienta imprescindible a poner en marcha a corto plazo. Y en este sentido se denota una clara *asimetría* geográfica en cuanto a grado de instrucción, nivel económico, género, etc., que permite centrar los esfuerzos futuros en las dianas derivadas de las asimetrías, más en los tiempos actuales de escasos recursos económicos.

• Se propone la *necesidad de hacer revisiones sistemáticas y, en su caso metaanálisis,* de los estudios y programas llevados a cabo en España en los últimos años, sobre diferentes aspectos referidos al sobrepeso y la obesidad y/o sedentarismo e inactividad física.

• Resulta imprescindible *definir mejor cuales son las barreras en la prevención y/o tratamiento del sobrepeso y de la obesidad y el sedentarismo y la inactividad física.*

• En la actualidad, *no disponemos de un arsenal terapéutico ni adecuado ni suficiente para tratar el sobrepeso y la obesidad.* Se constata la necesidad de contar con fármacos efectivos, que ayuden al tratamiento de la obesidad cuando otro tipo de intervenciones (dieta, ejercicio físico, hábitos de conducta alimentaria) no resulten suficientes. En definitiva, de forma general, se plantea el tratamiento farmacológico como *alternativa*, y no como primera opción. Los fármacos actualmente en uso, o próximos a su comercialización, parecen ser efectivos en la disminución del riesgo cardiovascular o la progresión de la diabetes, pero no parecen responder adecuadamente a las necesidades de disminución ponderal. Son necesarios, por tanto, dianas farmacológicas novedosas. Ello hace que la prevención adquiera aún más relevancia, así como la *personalización* como estrategia prioritaria.

• En el caso de que se trate de un diagnóstico de obesidad mórbida o extrema, la *cirugía bariátrica* se consolida como un tratamiento eficaz y contrastado, con grandes resultados terapéuticos, en el entorno de un grupo multidisciplinar.

• En la prevención del sobrepeso y la obesidad y el exceso de sedentarismo y la inactividad física, adquieren especial relevancia los *aspectos sociales.* Ello significa que se debe fomentar, por un lado, el hecho de que no *sólo es importante lo que se come y lo que se bebe*, sino también el *cómo se come* y *como nos movemos*, procurando recuperar y/o mantener todo lo relacionado con la socialización de la comida, o la vida activa compartida. Existe la opinión unánime de considerar a la *familia,* en sus diferentes estructuras, como el mejor modelo de aprendizaje para unos hábitos alimentarios y de estilos de vida adecuados y saludables. Por tanto, las políticas de prevención deberían orientarse de manera prioritaria a poder llegar y comunicar con el núcleo familiar, aunque en la actualidad el comedor institucional (escolar, universitario, empresa, geriátrico), constituye igualmente un magnífico marco de actuación a través de la educación.

• En relación con el *entorno familiar,* se recomienda en primer lugar evitar la presencia de televisión en el dormitorio infantil/juvenil. En segundo lugar, se debería evitar comer viendo la televisión, al mismo tiempo que se debería minimizar la exposición del niño-adolescente a los anuncios no adecuados relacionados con las temáticas del presente Documento. Tampoco en las administraciones públicas o desde el ámbito comunitario, se debe incentivar el entretenimiento pasivo electrónico. Finalmente, y dado el ya resaltado origen multifactorial de la

obesidad, estas acciones de carácter *menor* no tendrán éxito si no se logran modificar los factores obesogénicos.

• Se debe prestar *especial atención a ciertas etnias y poblaciones inmigrantes de reciente implantación en España, con un seguimiento de las transiciones alimentarias.*

• Hay que favorecer todas las acciones conducentes a la *equidad social,* que eviten o disminuyan el hecho de que la prevalencia de sobrepeso y la obesidad o el exceso de sedentarismo y la inactividad física, es más grave a medida que disminuye el nivel de educación y aumenta la desigualdad en el entorno socioeconómico.

• Es imprescindible que el *mensaje* que se traslade a la población, y los primeros convencidos deben ser los profesionales implicados, es el del de que estos problemas se puede prevenir y, en su caso, tratar: se aboga por el "sí podemos" como principio fundamental a transmitir a nivel individual y colectivo.

• Se reconocen muchos *errores en la autopercepción sobre alimentación, peso corporal, actividad física,* etc.; en definitiva, la nutrición se percibe en muchas ocasiones a nivel individual más en "cómo me va", y no basándonos en la evidencia científica. Ello lleva a numerosos errores, mitos y magia en las temas de alimentación, actividad física, y deporte. Se propone ser aún más beligerantes para evitar estos errores y mitos, tanto desde las Administraciones públicas, como desde el ámbito educativo, científico, asistencial, o medios de comunicación, en caso de ser necesario.

• Existen *numerosos programas de prevención, estudios de intervención,* etc., pero *falta coordinación y seguimiento,* motivado en muchas ocasiones por la dependencia de las Administraciones, y falta de presupuesto o la no existencia de criterios a largo plazo. En este sentido, resulta imprescindible la implicación programada y vinculada de las Administraciones estatales, autonómicas y fundamentalmente las locales, en la prevención del sobrepeso y la obesidad y del exceso de sedentarismo en exceso. Se deben priorizar los poderes locales, de acuerdo también con la *Declaración de Viena OMS* de Julio 2013, ya que su ámbito de gestión es más eficiente y cercano a la ciudadanía, y permiten adaptar los programas a las peculiaridades de cada población. Los cambios efectivos requieren acciones continuadas y de manera unificada, sostenibles, de proximidad, que impliquen de manera transversal a toda las Comunidad, siendo la familia donde reside la mayor parte de los comportamientos relacionados con la alimentación y la actividad física.

• Igualmente, las Administraciones deberían definir si quieren y pueden disponer de modelos de financiación exclusivamente públicos, o modelos "mixtos" público-privados, como ya está ocurriendo en la mayoría de los países con problemáticas similares al nuestro. En este último caso, las "reglas de juego" deben definirse con claridad.

• Resulta muy *necesario adoptar no solo un consenso a nivel nacional, sino también internacional, para tener criterios homogéneos en la recogida y el análisis de datos* de los estudios que tengan como dianas principales el sobrepeso y la obesidad y/o el sedentarismo y la inactividad física.

• Muchos de los estudios observacionales y también de intervención no suelen tener bien definidas las poblaciones de estudio, y *se ha venido considerando al individuo "obeso" y/o "sedentario" con una tipología de "único",* desde el punto de vista fisiológico o patológico. Este problema metodológico no se sostiene en la actualidad, gracias al conocimiento imparable que nos van deparando las denominadas técnicas *ómicas*, que nos permiten ya de manera muy precisa diferenciar entre las tipologías, y como abordarlas desde el tratamiento, pero también en la prevención. Existe consenso científico actual de que no existe "la obesidad" como un fenómeno unitario, sino distintos tipos de "obesidades", y ello requiere planteamientos innovadores en la prevención y/o tratamiento, investigar factores etiológicos y biomarcadores específicos de cada condición en particular. En definitiva, se abren nuevas posibilidades de actuación en el sentido de una mayor individualización de las intervenciones. Este concepto de *diversidad* debe trasladarse a los modelos experimentales y a las situaciones clínicas, que sirvan como punto de partida para el estudio de nuevas dianas farmacológicas, mediante estudios genómicos, proteómicos, etc. Así, se evitaría la dilución y excesiva homogenización que han acompañado a muchos estudios en este campo. En definitiva, se requiere que para avanzar en el tratamiento farmacológico de la obesidad, se acentúen los esfuerzos en investigación básica y traslacional.

• En materia de *investigación* se reafirma la necesidad del *abordaje multidisciplinar,* y de manera específica se debe insistir en el desarrollo de:

a) Nuevos modelos basados en las posibilidades que nos ofrecen las técnicas de imagen.
b) Identificación y validación de nuevos biomarcadores de inflamación y riesgo metabólico asociados a las comorbilidades de la obesidad
c) Modelos epigenéticos, que ciertamente requieren de un tiempo considerable para su validación y éxito potencial, ya que en muchas ocasiones parece que se les estuviera exigiendo demasiado y en muy poco tiempo.
d) Nuevas tecnologías *ómicas*.
e) Nuevos métodos de registro, tanto de alimentación como de actividad física, y para otros factores asociados (ej. aspectos cronobiológicos). Las nuevas tecnologías abren enormes posibilidades en este sentido, para una mayor precisión tanto cuantitativa como cualitativa.
f) Un mayor estudio de la flora bacteriana ("Microbiota").
g) Procurar cada vez más relacionar la investigación básica y/o aplicada con la denominada "consumer science" en las temáticas objeto del presente documento.

• La *alimentación sigue siendo una gran desconocida* en muchos de sus aspectos, y más cuando se ha hecho más compleja, tanto en los aspectos de producción, oferta alimentaria, gastronomía, etc. Todo ello en un entorno para el consumidor de menos tiempo y capacidad racional para hacer una correcta elección de alimentos y, muy frecuentemente, sin habilidades culinarias sólidas, contrariamente a lo que ocurría hace apenas una generación. Debería promoverse en este sentido *que el individuo sea "autónomo", favoreciendo la responsabilidad individual,* lo que no se percibe con claridad en la actualidad.

• El conocimiento de la alimentación del conjunto de la sociedad, asumiendo las debilidades metodológicas que todavía presenta, es esencial para poder realizar una radiografía de su estado nutricional. Así, en cuanto a la *alimentación habitual* de consumo por parte de los españoles, se vienen observando bajos consumos principalmente, respecto a las recomendaciones, de cereales y derivados, verduras y hortalizas y legumbres. Por el contrario, se observa un elevado consumo de carnes grasas, embutidos y en el límite superior a lo recomendado en azúcares sencillos. Ello implica un perfil calórico desequilibrado, debido a que la contribución porcentual de las grasas es mayor y el de los hidratos de carbono es menor a lo recomendado. En cuanto a las proteínas se encuentran en el límite superior o por encima del valor recomendado. En relación a la calidad de la grasa, el aporte de los ácidos grasos saturados a la energía total supera las recomendaciones. Analizando estos datos, y su evolución desde los años 60 del pasado siglo XX, se observa que la dieta de los españoles se ha modificado notablemente en los últimos 40 años, alejándose en parte del modelo tradicional de la Dieta Mediterránea, por lo que todos los esfuerzos deben orientarse a recuperar y/o mantener las características y propiedades de la DM, considerada siempre con nuestro estilo de vida.

• El *Estilo de Vida Mediterráneo,* considerado en todos sus aspectos (alimentación, actividad física, socialización), en definitiva como un óptimo de *filosofía de vida*, se considera el mejor modelo en la prevención, probablemente también en el tratamiento, del sobrepeso y la obesidad y el excesivo sedentarismo. Además, debe remarcarse que no sólo la densidad de nutrientes y factores asociados de calidad de vida en relación al coste es más favorable para la DM que con otros tipos de dieta, sino que se plantean modelos de adherencia y de seguimiento de la misma a un relativo bajo coste, lo que adquiere especial relevancia en la actual situación de crisis económica.

• El *Estilo de Vida Mediterráneo (EVM)* no es sólo un patrón alimentario que tiene una acumulada evidencia en la prevención de enfermedades crónicas. Representa un estilo de vida, tal y como indica el término griego original: "diaita", que engloba, además de la combinación de alimentos, elementos culturales y de estilo de vida del proceso de selección, procesamiento y consumo, como son la priorización de los alimentos frescos, locales, y estacionales; de las actividades culinarias y de la socialización en las comidas, de la actividad física regular, del descanso en forma de siesta, y toda una manera de vivir que forma parte de la herencia cultural de los países mediterráneos. Los países mediterráneos compartimos una serie de factores geográficos y climáticos que han favorecido este marco cultural y agroalimentario común. Sin embargo, a pesar del conocimiento aceptable por parte de la mayoría de la población del concepto y principios de la DM, existen grandes dificultades para su seguimiento y adherencia, pues muy frecuentemente faltan conocimiento, habilidades y actitudes.

• La monitorización del *patrón de EVM* revela que *las poblaciones mediterráneas,* especialmente las de la Europa Mediterránea, *están progresivamente alejándose,* amenazando la adhesión al patrón, sobre todo entre los más jóvenes. Y sin embargo, paradójicamente, son los países del norte de Europa y otras zonas del mundo alejadas del Mediterráneo las que van adoptando de manera creciente y positiva diversas características de la DM. Lo anterior supone un ejemplo rotundo de que las políticas de intervención en salud pública con carácter "positivo", suponen una magnífica herramienta para la consecución de objetivos incluso a corto y/o medio plazo.

• Numerosos estudios epidemiológicos han observado reiteradamente que una *buena adherencia al patrón de EVM* se asocia sistemáticamente con un riesgo significativamente menor de varias enfermedades crónicas (enfermedades cardiovasculares, diabetes y síndrome metabólico, patologías neuro-degenerativas como el Parkinson, el Alzheimer o la depresión, algunos tipos de cáncer, sobrepeso y obesidad, asma bronquial, etc.), y de forma global con una mayor adecuación nutricional , longevidad y calidad de vida. Igualmente importante en el contexto actual y de futuro, el EVM tiene un bajo coste de recursos e impacto medioambiental y se podría ubicar dentro de los sistemas agroalimentarios más sostenibles del planeta. A estas indudables fortalezas habría que añadir que, en el contexto español, el EVM está adaptado a nuestros gustos y a nuestras costumbres, y a poder utilizar alimentos producidos en nuestro país, ya que la dependencia del mercado exterior es baja.

• La *industria agroalimentaria* en España ha jugado, y lo continúa haciendo en el presente, un papel fundamental tanto en la mejora de la oferta alimentaria, la seguridad alimentaria, o la erradicación de las situaciones de desnutrición general y/o específica, pero al mismo tiempo de este reconocimiento, se solicita más apoyo y colaboración, y fundamentalmente y de manera urgente, con la industria relacionada con el entretenimiento, ocio, actividad física, y deporte. Resulta imprescindible más apoyo y colaboración con la industria relacionada con la cadena alimentaria, pero también con la del entretenimiento, actividad física y ocio, que permita, en su caso, la modificación o adaptación de sus productos, procesos y estrategias de *marketing* y publicidad a las Guías Alimentarias y Objetivos Nutricionales para la población española, pero también para el cumplimiento de las recomendaciones para llevar una vida activa.

• Muchos de los denominados alimentos funcionales y nutracéuticos para el área del control del peso corporal han tenido como diana u objetivo de actuación la inhibición de la ingesta (sobre la sensación de hambre, estimulando la saciedad o limitando la biodisponibilidad de determinados nutrientes), el contenido energético de los alimentos (incluyendo ingredientes menos calóricos o que sustituyan a grasas y azúcares), composición corporal y/o gasto energético (a través de la estimulación de la termogénesis). El enorme progreso de disciplinas como la Nutrigenómica o la Nutrigenética, va a permitir sin duda nuevas estrategias en el desarrollo de estos productos, aunque los resultados son todavía escasos y de carácter emergente.

• Es imprescindible *unificar los mensajes en el ámbito de la alimentación, nutrición y actividad física,* desde los distintos ámbitos implicados (administraciones, sociedades y fundaciones científicas, profesionales), contando siempre con la colaboración de los medios de comunicación y las nuevas tecnologías. Se propone la *elaboración de unas Guías/Recomendacio-*

nes conjuntas en materia de prevención del sobrepeso y la obesidad y el exceso de sedentarismo, planteando modelos de asociación de acuerdo al conocimiento científico. Al mismo tiempo, se postula la importancia de definir mejor los "clusters" en nutrición, pero también en actividad física, que permitirían acciones mucho más específicas y efectivas.

• En cuanto a la *información* en Alimentación y/o Nutrición, no hay evidencia científica suficiente de que una mayor información sobre los alimentos (composición, información nutricional, etc.), impacte positivamente en una más correcta elección y seguimiento del patrón alimentario. La convivencia de nuevas metodologías de comunicación junto a las más tradicionales, parece imprescindible de acuerdo a las capacidades de los diferentes grupos de población y, en cualquier caso, será necesario una monitorización en relación con la mejora real o no de la alimentación, hábitos alimentarios y estilos de vida.

• Hay *modelos de intervención probados que funcionan.* En el planteamiento y seguimiento en el ámbito infanto-juvenil se debe estar muy atento al riesgo de aumentar la prevalencia de niños con bajo peso y trastornos de la conducta asociados, como ya se ha observado en estudios llevados a cabo en España. Los proyectos de prevención de la obesidad a nivel poblacional realizados en España, aunque escasos y carentes en muchas ocasiones de seguimiento, han descrito resultados positivos con cambios en los hábitos alimentarios y estilos de vida, pero también en la propia composición corporal y determinados marcadores biológicos. Existe un claro convencimiento de que estos sistemas de prevención deberían implementarse a largo plazo, e integrarse en la dinámica socio ocupacional de los colectivos relacionados.

• El denominado *balance energético no está bien definido* para la población española, y es imprescindible abordarlo con el fin de poder establecer adecuadamente los requerimientos energéticos para la población española, y las subsecuentes Ingestas de Referencia. Deben realizarse *estudios integrales sobre todos los elementos de la ecuación de balance energético,* debido a la interrelación entre ellos. Se necesitan de manera urgente estudios longitudinales a largo plazo sobre balance energético y peso corporal/composición corporal. Parece imprescindible mejorar las herramientas para el estudio de las entradas y salidas de energía en sujetos de vida independiente "free living". En este último aspecto, habría que mejorar herramientas como las bases de datos de composición de alimentos de calidad, en especial de energía y en los tamaños de las raciones.

• Debe *incrementarse el conocimiento para los diferentes grupos de edad sobre el impacto del diferente grado de actividad física.* Igualmente, se deben llevar a cabo más estudios en los diferentes grupos de población y situaciones fisiológicas para poder determinar si puede ser suficiente la recomendación de realizar actividad física moderada, intensa o se requeriría vigorosa. En el mismo sentido, se debe potenciar el valor de la llamada fuerza muscular como una herramienta muy práctica y de claro impacto positivo, en todas las edades. Para atender a los anteriores retos y necesidades, el importante esfuerzo realizado en España en los últimos años en cuanto a instalaciones deportivas de muy diferente tipo, no debería desaprovecharse incluso en ciclos complicados como el presente, involucrando además de manera creciente a los profesionales del deporte en el sentido más amplio.

• Se debe *tratar de responder a las siguientes preguntas:* ¿Es la inactividad una respuesta "normal" a un entorno "anormal", lo que implicaría cambiar el entorno, modificaciones en el ámbito educativo, concienciación sobre la importancia de ser activo, dando la máxima importancia a la expresión "predicar con el ejemplo", y tanto desde las administraciones, como desde la comunidad, escuela, familia, etc.; o, ¿es una respuesta "anormal" a un entorno "normal"?, que debería llevar en este caso un cambio de conducta, además de tener en cuenta la cronobiología del sobrepeso y de la obesidad. Debe *considerarse no sólo la actividad física que se desarrolla, sino también la inactividad física.* El sedentarismo no tiene porqué ser equivalente a inactividad física, y adquiere especial importancia el valorar los distintos comportamientos sedentarios, su impacto en la salud, y su correlación con las formas de alimentación y otros estilos de vida.

• Independientemente de factores genéticos, familiares, etc., hay evidencia científica suficiente de que la *actividad física deportiva regular disminuye el porcentaje de grasa corporal,* y reduce factores de riesgo asociados a enfermedad cardiovascular, diabetes, o ciertas formas de cáncer. Existe consenso científico en considerar la práctica de actividad física como una herramienta útil para la prevención de la obesidad, por lo que debe promoverse la actividad física espontánea e impulsar la práctica deportiva, de transporte activo, etc.

• Se debe prestar una *atención especial a los proyectos y organizaciones que permiten involucrar en la actividad física al máximo número de personas* con programas como "ejercicio físico para todos", "actividad física y ejercicio físico como ocio", "muévete", "actívate", etc. Es por ello que las organizaciones deportivas representan un potencial único en la promoción de la actividad física y hábitos de vida saludables, lo que debería ser mejor aprovechado en el futuro.

• Los *datos de actividad física se deben incluir en los sistemas de monitorización de la salud a nivel nacional.* Además, la información sobre la necesidad de actividad física, la mejor forma de introducirla en la vida cotidiana, los cambios en el estilo de vida y las características de la alimentación en la persona activa, moderada y muy activa, debe estar disponible para los profesores de educación física, los profesionales de la salud, entrenadores, administradores de centros deportivos y de ocio, y profesionales de los medios de comunicación durante sus estudios, formación profesional y especialización.

• La persona activa y que hace actividad física, ejercicio físico o deporte debe saber que para aportar una adecuada ingesta energética diaria y mantener un óptimo rendimiento, hay que tener en cuenta el gasto calórico de forma individual, ya que la cantidad de energía que se debe consumir difiere según las características propias del sujeto, la actividad física realizada (tipo de deporte, intensidad, duración etc.) y las condiciones ambientales en las que tiene lugar el entrenamiento o la actividad. También es importante que la ingesta de agua, la hidratación en definitiva, así como de macro y micronutrientes y otros componentes no

nutritivos de interés nutricional, sea la adecuada. Se *propone incrementar la formación e información tanto de los profesionales relacionados con la actividad física, ejercicio físico y el deporte, como de los propios practicantes, tanto amateur como profesionales.*

• Se deben *crear e impulsar los programas de salud y educativos de prescripción de ejercicio físico y de prevención del sedentarismo,* y tratar esta situación en determinadas condiciones de riesgo incluso como enfermedad crónica, al igual que las patologías a las que se puede asociar.

• El llevar una *vida activa* debe asociarse no sólo con un mejor estado de salud, sino con el *disfrute del tiempo y una mayor sociabilidad,* a todas las edades, pero de manera especial en la población infanto-juvenil y de edad avanzada. Por ello, los programas de intervención deben considerar estos principios, transmitiendo de manera rotunda que *nunca es demasiado tarde para comenzar a llevar una vida más activa*. Igualmente, se insta a fomentar más investigación que permita determinar de manera precisa la cantidad óptima de ejercicio físico (tiempo, duración, intensidad), y en combinación con los comportamientos sedentarios habituales de nuestra sociedad.

• Hay que utilizar los *medios de comunicación y las nuevas tecnologías* en sensibilizar a la población para que sea más activa, e informar tanto de los beneficios de llevar una vida activa y hacer ejercicio físico, como de los peligros que conlleva el sedentarismo y la inactividad física para la salud y la calidad de vida en general.

• La *prevención de la obesidad no se ha considerado como objetivo prioritario en el contexto de las ciencias de la actividad física y el deporte,* hasta muy recientemente. Es por ello que se propone de manera urgente la inclusión de investigadores del ámbito deportivo, y también del educativo, en los equipos multidisciplinares que deben llevar a cabo las estrategias de prevención e intervención.

• Resulta *alarmante la falta de unidades multidisciplinares* que engloben profesionales de la educación física y deporte, así como de la nutrición y la dietética. Se debe actuar de manera decidida y urgente para corregir la carencia.

• Se insiste en la necesidad de *fomentar las inversiones en infraestructuras* para el transporte a pié y en bicicleta, acompañadas de campañas de información dirigidas a explicar los beneficios para la salud y calidad de vida.

• La *práctica regular de actividad física en la edad escolar* es un instrumento imprescindible para el adecuado desarrollo integral de los niños y adolescentes. Se debe intentar incrementar la realización de actividad física, ejercicio físico y deporte en toda la población infanto-juvenil, como una herramienta de cohesión social, ya que los hábitos aprendidos de niños suelen mantenerse en la edad adulta.

• En los *niños hay que garantizar crecimiento y desarrollo, y no poner énfasis sólo en la ingesta energética*. La actividad física tiene que ser divertida, e incluir a los niños y niñas en la toma de decisiones, todo ello englobado en las imprescindibles políticas de salud pública. Por otro lado, el tratamiento del sobrepeso y la obesidad a través del ejercicio físico, es un tema mucho más complejo, requiere de cierta restricción calórica en el adulto y aún más compleja en la edad infantil. El abordaje en este último caso es más de clínica, y menos del entorno escolar. Sería deseable alcanzar un *consenso a nivel nacional sobre las curvas de referencia y puntos de corte,* en los estudios de evaluación y monitorización del peso corporal en población infantil, que permita establecer las comparaciones necesarias a nivel internacional.

• La *prevención de la diabetes* resulta esencial para disminuir la incidencia de la enfermedad. En el momento de su diagnóstico, aproximadamente el 50% de los pacientes presentan complicaciones microvasculares (retinopatía, neuropatía o nefropatía) y un riesgo doble de complicaciones macrovasculares, en comparación con la población general. Se considera la obesidad como el principal factor modificable, a la que se le atribuyen aproximadamente la mitad de los nuevos casos de diabetes. Debe insistirse por todos los medios disponibles en comunicar que incluso una pérdida modesta de peso tiene un efecto favorable sobre el riesgo, y que el ejercicio físico, en conjunción o no con la alimentación, contribuye igualmente a disminuir el riesgo. Se debería, por tanto, prevenir la diabetes, a través de diferentes intervenciones, dado que:

– La prevalencia es ya enorme, y se trata de un problema de salud pública.
– Existen marcadores, que permiten medir la progresión de la enfermedad.
– Los sujetos "prediabéticos" ya tienen un riesgo cardiovascular alterado.
– El tratamiento de la diabetes, una vez diagnosticada, es caro y difícil.

• La obesidad se asocia con un *mayor riesgo de enfermedad cardiovascular y un estado inflamatorio crónico;* no obstante, son muchos los aspectos que deben ser estudiados de manera conjunta, ya que afectan directamente a la salud de los adolescentes, aunque no a este grupo de edad de manera exclusiva. El sedentarismo se asocia con una peor condición cardiorespiratoria, independientemente del IMC. El sedentarismo también está asociado con factores de riesgo cardiovascular en adolescentes, especialmente en aquellos que presentan una excesiva adiposidad abdominal. Todo lo anterior implica la necesidad de una estrategia de actuación que tenga en cuenta todos estos factores.

• El *ejercicio moderado estimula ciertos aspectos de la respuesta inmune* mientras que el ejercicio intenso puede ocasionar incluso efectos indeseables. Una vez más, se reafirma la necesidad de la personalización no sólo de la alimentación, sino en cuanto a la práctica y prescripción, en su caso, del ejercicio físico.

• Las *pautas de control de peso* deberían basarse en la aproximación de la dieta, actividad física y estilo de vida, al denominado "ideal teórico", con especial énfasis en los aspectos en los que el alejamiento respecto a lo teórico es mayor:

– Aumento de la actividad física
– Disminución del sedentarismo, incidiendo de manera especial en las denominadas TICs.

– Promoción de la lactancia materna y control de la alimentación y estilo de vida en general, en la mujer gestante.
– Mejorar el patrón dietético, a través de la promoción del consumo de los alimentos que se toman en cantidad menor de la recomendada: verduras, cereales integrales, frutas, legumbres, pescado.
– Vigilar el horario y ambiente de las comidas, de manera especial el desayuno.
– Disminuir el estrés laboral, familiar, y ambiental en general.

• La *Estrategia NAOS debe continuar integrando e impulsando acciones* en los más diversos ámbitos, buscando colaboraciones y sinergias con las distintas administraciones públicas y privadas, centros de investigación, universidades, y con los diversos actores sociales que intervienen en este campo. La filosofía de la Estrategia NAOS, que se apoya en una imagen positiva, no estigmatizando ni prohibiendo determinados tipos de alimentos, y estimulando la participación, implicación y compromiso de todos los actores sociales y económicos, fomentando la proactividad de los mismos e intentando promover una respuesta coordinada de todos los agentes implicados, con el objetivo final de invertir la tendencia de la obesidad y por ende, del sedentarismo social. Para ello, es exigible que la propia Estrategia NAOS afronte y corrija debilidades en su desarrollo, y así pueda consolidarse y reconocerse de manera definitiva: no disponer de un presupuesto ligado a un plan de acción; la promoción de la actividad física ha estado menos desarrollada; la evaluación y seguimiento de las acciones ha sido muy limitada. No obstante lo anterior, su inclusión en la *Ley de Seguridad Alimentaria y Nutrición* la dotó de respaldo legal, y actualmente cuenta con el apoyo político necesario para su desarrollo y evolución en los próximos años, en consonancia con las políticas de las instituciones europeas (OMS y UE), en consonancia también con la muy reciente Declaración de Viena de los Ministros y Responsables de Salud a nivel europeo (4-5 julio del 2013).

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The Spanish diet: an update

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Abstract

Background/Aims: **The Food Consumption Survey, conducted for over 20 years by the Spanish Ministry of Agriculture, Food and Environment (MAGRAMA), is the most reliable source of data to evaluate the food consumption and dietary patterns of Spain. The aim of the present article was to review the diet trends in Spain and its evolution. Food availability assessment per capita per day, which allows the calculation of energy and nutrient intake and comparison with the Recommended Nutrient Intakes for the Spanish population is described. In addition, different markers of the quality of the diet have been also evaluated.**

Methods: **The sample consisted of consumption and distribution data, obtained from the nationwide representative Food Consumption Survey for the period 2000-2012. A two-stage sampling method was applied, where in the first stage the units to be sampled were towns or local entities, and in the second stage households which were going to be part of the final sample from those entities were selected. Units consisted of towns or local entities in the national territory. The data allowed the calculation of energy and nutrient intakes, using the Food Composition Tables (Moreiras et al, 2013). The quality of the diet was also evaluated: the adequacy of the diet in meeting the recommended intakes for energy and nutrients; energy profile; dietary fat quality; dietary protein quality; nutrient density; Mediterranean diet adequacy indices. The present data were compared with previous data obtained by our research group in 1964, 1981 and 1991.**

Results: **Using the most recent data, average intake comprised: milk and derivatives (356 g/person/day), fruits (323 g/person/day), vegetables and greens (339 g/person/day), cereals and derivatives (197 g/person/day), meat and meat products (181 g/day), fish (88,6 g/person/day), oils and fats (41,6 g/person/day), sugar and derivatives (25,6 g/person/day), eggs (27,1 g/person/day), legumes (13,9 g/person/day) . There was also a high consumption of non-alcoholic beverages (437 g/person/day) and decreasing for alcoholic beverages (192 g/person/day) compared to previous surveys. In consequence, meat and meat product consumption was higher than the recommendations, whereas for cereals and their derivatives, vegetables and greens, fruit, and legumes and pulses, con-**

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LA DIETA ESPAÑOLA: UNA ACTUALZACIÓN

Resumen

Antecedentes/objetivos: **La Encuesta de Consumo de Alimentos, realizada durante 20 años por el Ministerio de Agricultura, Alimentación y Medio Ambiente (MAGRAMA), es la fuente más fiable de datos para evaluar el consumo de alimentos y patrones dietéticos en España. El objetivo de este artículo fue revisar las tendencias dietéticas en España y su evolución. Se describe la evaluación de la disponibilidad de alimentos per cápita y día, que permite el cálculo de consumo de energía y nutrientes y su comparación con el Consumo Recomendado de Nutrientes para la población española. Además, se han evaluado diferentes marcadores de la calidad de la dieta.**

Métodos: **La muestra consistió en los datos de consumo y distribución, obtenidos de la Encuesta Nacional de Consumo de Alimentos para el período 2000-2012. Se aplicó un método de muestreo en dos etapas en el que, en la primera etapa, las unidades que se muestreaban fueron ciudades y entidades locales y, en la segunda, se seleccionaron los hogares que conformaron la muestra final a partir de las entidades locales. Las unidades consistieron en ciudades o entidades locales del territorio nacional. Los datos permitieron el cálculo de consumo de energía y nutrientes utilizando las tablas de Consumo de Alimentos (Moreiras et al., 2013). También se evaluó la calidad de la dieta: la adecuación de la dieta para alcanzar los consumos de energía y nutrientes recomendados; perfil de energía; calidad de la grasa de la dieta; calidad de la proteína de la dieta; densidad de nutrientes; índices de adecuación de la dieta mediterránea. Los datos actuales se compararon con los datos previos obtenidos por nuestro grupo de investigación en 1964, 1981 y 1991.**

Resultados: **Utilizando los datos más recientes, el consumo promedio comprendía: leche y derivados (356 g/persona/día), frutas (323 g/persona/día), verduras y hortalizas (339 g/persona/día), cereales y derivados (197 g/persona/día), carne y productos cárnicos (181 g/día), pescado (88,6 g/persona/día), aceites y grasas (41,6 g/persona/día), azúcar y derivados (25,6 g/persona/día), huevos (27,1 g/persona/día), legumbres (13,9 g/persona/día) . También un consumo elevado de bebidas no alcohólicas (437 g/persona/día) y un descenso del consumo de bebidas alcohólicas (192 g/persona/día) en comparación con las encuestas previas. En consecuencia, el consumo de carne y productos cárnicos fue superior al recomendado mientras que el consumo de cereales y sus derivados, verduras y hortalizas, fruta y legumbres estaba por debajo de las recomendaciones para la población española (GRUNUMUR, 2004; SENC, 2007). Algunos alimentos mediterráneos de consumo habitual y tradicionales (pan, patatas y**

sumption was below recommendations for the Spanish population (GRUNUMUR, 2004; SENC, 2007). Some staple and *traditional* Mediterranean foods (bread, potatoes and olive oil) showed a dramatic decline when compared to data from Household Budget Surveys in 1964 data. Energy intake showed a marked decline when compared to the 1960's mean consumption, and show marked differences for food groups contributors. Energy profile shows too much coming from lipids vs carbohydrates and slightly higher from proteins.

Conclusion: **Food consumption patterns in Spain and energy and nutrient intakes have changed markedly in the last forty years, differing somewhat at present from the traditional and healthy *Mediterranean Diet*.**

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Key words: *Food consumption survey. Food availability. Dietary intake. Energy profiles. Diet quality. Mediterranean diet.*

aceite de oliva) mostraron un declive notable en comparación con los datos de las Encuestas de Economía Doméstica de 1964. El consumo de energía mostró un marcado declive en comparación con el consumo medio de los años sesenta y mostró marcadas diferencias para los distintos grupos de alimentos contribuyentes. El perfil de energía mostró que una gran parte procedía de los lípidos, frente a los hidratos de carbono y algo superior con respecto a las proteínas.

Conclusión: **Los patrones de consumo de alimentos en España y los consumos de energía y nutrientes han cambiado notablemente en los últimos 40 años, difiriendo algo en la actualidad de la dieta mediterránea tradicional y saludable.**

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Palabras clave: *Encuesta de consumo de alimentos. Disponibilidad de alimentos. Consumo dietético. Perfiles de energía. Calidad de la dieta. Dieta mediterránea.*

Introduction

Spain has undergone dramatic socioeconomic changes since the 1960s, including massive rural-urban migration, but also a generalised incorporation of females into the active work-force added to rapid urbanisation processes in the 1980s, an accelerating factor for dietary change due to factors such as the organization of family life and home meals (Cruz Cantera, 1995). A rapidly increasing number of people use catering services, restaurants and vending machines (Varela Moreiras et al, 2008), both during weekdays and leisure time, which is also a key factor in understanding changes in diet, even though the present economical crisis is deriving more people to eat at home.. In addition, there has been a rapid increase in the immigrant population, which now represents about 8-10% of the total population, although a marked decrease due to economical recession in the country is also observed (Varela Moreiras et al, 2009). These changes in dietary pattern and lifestyle potentially appear to have had negative consequences for both the present and future populations, since overweight and/or obesity affect more than 50% of the adult population and almost 30% of the infant/young population (National Health Survey, 2013).

The Food Consumption Survey (FCS), conducted in Spain since 1987, shows trends in consumption of different food groups and provides data on the place of consumption, i.e. either at home, in institutions, catering, restaurants, etc (Ministry of Agriculture, Food and Environment, 2012). The Spanish Nutrition Foundation (FEN) is in charge of evaluating the dietary trends and nutritional status of the population derived from the FCS. This information is also essential in order to obtain information on the nutritional parameters that allow the identification of the dietary patterns for the Spanish population (Spanish Nutrition Foundation, 2012).

The purpose of the present study was to assess food consumption in the adult population per capita per day (pc/d), at a national level in Spain for the period 2000-2012, allowing the calculation of energy and nutrient intakes and comparison to the Recommended Nutrient Intakes for the Spanish population (Moreiras et al, 2013). Other dietary markers have been also analysed. The evolutionary trends observed in comparison to data obtained through Household Budget Surveys, done in a statistically significant sample of households, conducted by the National Statistical Offices of Spain in the years 1964, 1981 and 1991 are also discussed (Varela et al, 1971; Varela et al, 1991).

Methods

The data sample is about shopping and product entrance into the home obtained from the FCS from 2000 to 2010, and consumption carried out in catering trade and institutions. In order to calculate the contributed the average energy and nutrients intake, has been faced against the needs of men and women aged between 20 and 40 because this age group includes the population segment which the *National Statistical Institute* considered in the year 2006 the largest in Spain.

The most thorough analysis belongs to household. A "household" is considered to be the person or group of people who occupy a family house together or part of it, and consume food and other goods bought from the same budget. Data for the products in the home were registered by a scanner on the same day as product acquisition and for seven consecutive days.

Data from the households have also been considered according to geographical areas; socioeconomic level; size of habitat; number of household members; age of the person responsible for food purchase; profession of the person in charge of purchases; number of children

and age. The location of the study was inland Spain plus the Balearic and Canary Islands.

A two-stage sampling method was carried out for the whole sample studied. In the first stage, the units to be sampled were towns or local entities in the national territory, and in the second stage households that were going to be part of the final sample from those entities were selected.

The obtained data allowed calculation of energy and nutrient intakes, using food composition tables containing over 600 foods, distributed in 15 groups. The data were also compared to the most recent *Recommended Nutrient Intakes* for the Spanish population to evaluate the adequacy of the diet (Moreiras et al, 2013).

In order to evaluate the adherence to the traditional Mediterranean diet, different indicators were used (Bach-Faig et al, 2006). The first one, the so-called "Mediterranean Diet Score (MDS)", is composed of nine variables (Knoops et al, 2006): monounsaturated fatty acids (MUFA)/saturated fatty acids (SFA), alcohol, legumes and pulses, cereals, fruit, vegetables and greens, meat and meat products, dairy products and fish. Each of these variables is given a value of zero or one. Using the MDS, when the consumption of the typical Mediterranean food groups in the Mediterranean diet (vegetables and greens, pulses and legumes, fruit, cereals and fish) is below the median consumption, it scores zero; whereas, if consumption is above the median, the score is one. Food groups which are traditionally not included in the Mediterranean diet score zero when consumed at levels above the median and one when consumption is below the median consumption. Alcohol scores one when consumption is between 10 g/day and 50 g/day for men and between 5 g/day and 25 g/day for women. Altogether, the MDS score would be zero when adherence to the traditional MD was minimum, and nine when it was maximum. The "Healthy Diet Indicator (HDI)" (Huijbregts et al, 1997) is based on World Health Organisation (WHO) guidelines for the prevention of chronic diseases: when consumption is within ranges established in these guides it is scored one (e.g. SFA <10%; polyunsaturated fatty acids (PUFA) 3-7%; carbohydrates 50-70%; fruit, vegetables and greens >400 g/day, etc.), and when it is not within the proposed range it is scored as zero. Here again, the highest theoretical score is "nine".

Results

Analysis of food consumption data for per capita availability based on the food surveys by the Ministry of Agriculture, Food and Environment (MAGRAMA, Spain) panel, over the period of 2000-2012, allows estimation of the average Spanish *daily menu* and the associated distribution of the different food groups as shown in figure 1.

Milk and derivatives consumption was quantitatively one of the most important in the present Spanish diet . However, a significant decrease in the purchase of dairy products is being observed from years 200 (416 g/person/day) and 2012 (359 g/person/day). When comparing the present data with those obtained by Varela et al. in 1991, dairy product intake has increased by approximately 150g/person/day since 1964. Com-

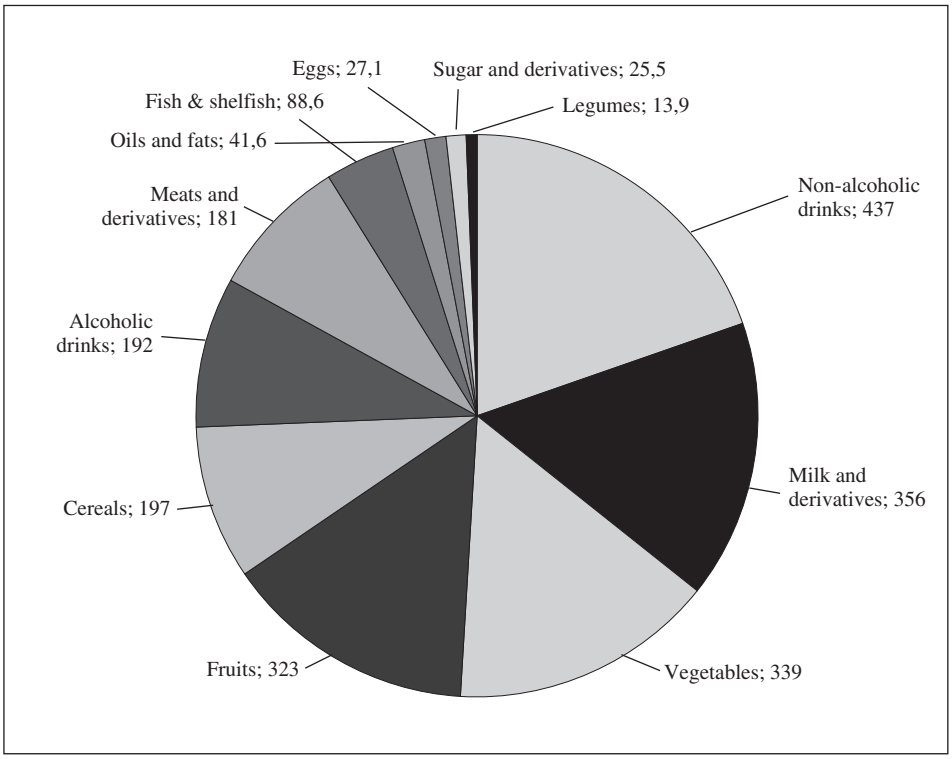

Fig. 1.—Consumption of various foods and food groups in Spain in 2012 (grams/person/day) according to the Food Consumption Survey.

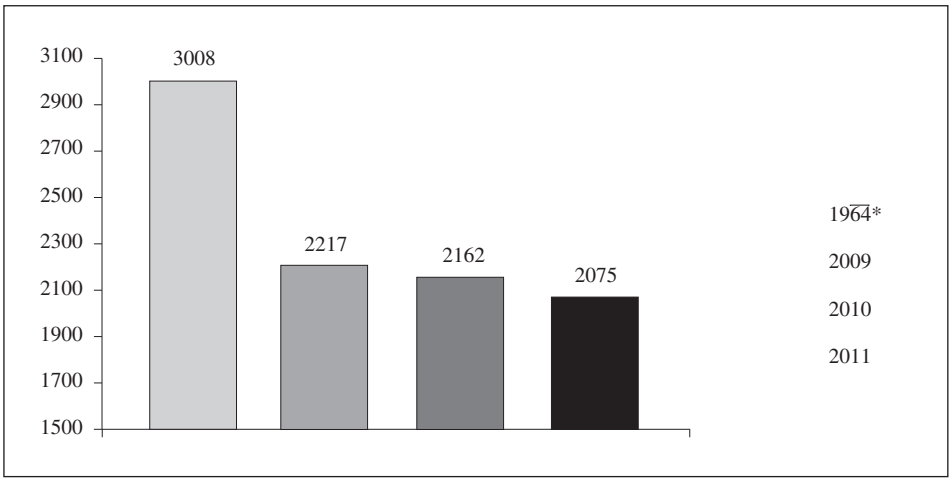

Fig. 2.—Trend in energy intake in Spain (1964-2011), according to the Food Consumption Survey.

pared with other European countries, Finland (507 g/day), Ireland (481 g/day), Sweden (445 g/day), Norway (387 g/ day) and Poland (381 g/day) all reported a higher intake of milk and milk derivatives (DAFNE, 2006).

Eggs consumption has steadily decreased since the year 2000. In that year, 4.3 medium sized eggs per week were consumed, whereas for the year 2012 the mean consumption of medium sized eggs was just 3.5 per week.

Vegetable and greens consumption, including potatoes, remained largely unchanged (a slight increase) from year 2000 to 2012. This was not the case when comparing the results with those obtained in 1964, when more than 450g/day were consumed (Varela et al, 1971). This was mainly due to a steady decrease in potato consumption. In fact, the overall decline for the last forty years has exceeded 200g/person/day. This trend showed a marked tendency of traditional staple foods being increasingly replaced by more processed alternatives. However, consumption of vegetables and greens (without potatoes) was calculated and showed an increase of 220 g/person/day since 1964.

Fruit consumption, including dried fruits, showed an increasing trend from year 2000 (278g/person/day) to year 2012 (305 g/person/day). When compared to 1964 data, fruit consumption has nearly doubled. Within this group, oranges represent by far the most consumed which guarantee a potential high vitamin C intake for the adult population.

The consumption of *legumes and pulses* has decreased (12.9 g/d at present) when compared to the 1991 results (20.2 g/d). However, it seems that there is at present an increase due to a combination of its low price, their culinary possibilities, the nutrient density (source of protein, complex carbohydrates, fiber, vitamins and minerals, but also low in fat). In addition, it has to be remained that this food group plays a key role in the Mediterranean dietary pattern.

Cereals and derivatives consumption has shown a marked decrease over the last forty years (434 g/d in 1964 vs. 218 g/d in 2012). Bread was still the most important food within this group. However, a steadily decline has also been observed (368 g/d in 1964 vs. 139 g/d in 2012).

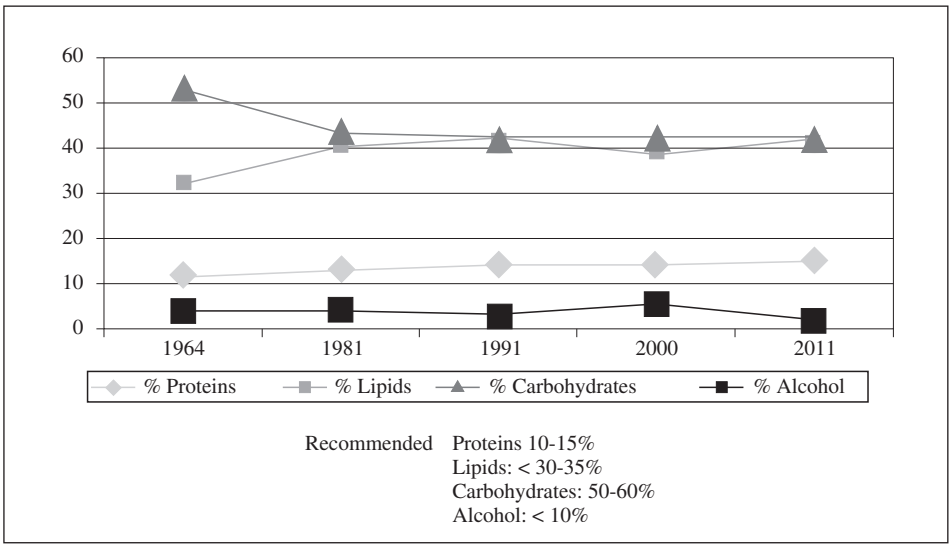

Fig. 3.—Energy profile trends in Spain (1964-2011) vs. recommendations.

White bread is the type of bread for which the most rapid decline has occurred. Rice consumption has also changed, being much lower in 2012 (11.6 g/d) vs. 1964 (26.5 g/d), but also a steady decline is shown very recently (16.7 g/d in year 2000). As for *Oils and fats* consumption, it was 47.2 g/person/day in 2006. However, an overall decrease over the last 40 years has been observed (approximately 20 g/person/day since 1964). The decrease in consumption was more noticeable for olive oil (a fall of over 27 g/person/day). However, more than 90% of the total consumption of oils and fats were still of vegetable origin, mainly olive oil (25.4 g/ person/day in 2012), which represented roughly 60% of the total. Other culinary and spread fats such as butter and margarine only represented a 7% of the total oils and fats consumed.

As for the *meats and derivatives* group, this represents a total of 179 g/person/day, maintained steadily high for over the last twelve years. It should be noticed that the food group has increased by roughly 300% when compared to the 1964 data (77 g/person/day). The mean consumption of *fish and shellfish* was considered high but beneficial (103 g/person/d), according to present national dietary guidelines. There has been a marked increase since 1964 (63g/person/d). Oily fish represented approximately 40% of total fish consumption; this may make a clear contribution to adequate intake of omega-3 fatty acids, although eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) contribution to the total energy intake was markedly below recommended levels (Mataix, 2005).

Alcoholic beverages consumption has undergone a slow decline during recent years (259 g/person/d in year 2000 vs. 208 g/person/d). Within this group, wine as a beverage traditionally included in the Mediterranean diet concept , only represented a 23.5% of the total alcoholic beverages consumption whereas it accounted a 62% of the total consumption in 1991. In the last few years, a gradual substitution of wine with beer has occurred, which represents almost a 70% of the total alcoholic beverage consumption at present. An important additional point is that almost 70% of these beverages were consumed out of home. One of the most striking change has been the enormous increase in *non-alcoholic beverages* consumption, since almost a ten-fold increase was observed since 1964 (46 g/person/d vs.446 g/person/d at present).

Another food group of current importance, for which a marked rise in consumption was noticed, was *precooked foods or ready to eat meals* (23.3 g/person/day for year 2000 vs. 44.2 g/day at present). For this group, unfortunately there were no previous data available for an accurate comparison of the evolution trends.

Adherence to the Recommended Serving Sizes for the Spanish Adult Population

Comparing data from the Spanish FCS with current dietary guidelines for the Spanish population (Dapcich et al, 2007) shows that meat and meat products consumption was clearly above the recommended amount, whereas for cereals and derivatives, vegetables and greens, fruit, and legumes and pulses consumption was lower than that considered to be optimal. Groups for which intakes were closer to the recommendations are milk and derivatives, fish and eggs.

Table I
Trends in energy and macronutrients intake in Spain (2000-2012) in Spain, according to the Food Consumption Survey

	2000	*2003*	*2006*	*2012*
Energy (kcal/d)	2730	2767	2761	2609
Proteins (g/d)	93,3	96,0	93,5	91,0
Lípids (g/d)	120	122	126	127
Carbohydrates (g/d)	284	288	282	259
Fiber (g/d)	18,7	19,1	18,8	18,3

Energy and Nutrient Intake

The mean energy consumption for the Spanish adult population at present is 2609 kcal/person/d, which is clearly lower than in 1964 (3008 kcal/person/d). The trends in energy and macronutients intake from 2000-2012 are shown in table 1.

The food groups contributing the most to energy consumption were cereals and derivatives (24.6%), meats and meat products (14.3%), oils and fats (13.6%) and milk and derivatives (12.5%). By contrast, fish and shellfish (3%), non-alcoholic beverages (2.9%), alcoholic beverages (2.3%) showed a much lower contribution to total energy intake besides the popular perception (table 2).

Table II
Contribution of the food groups to total energy intake in Spain (Food Consumption Survey, 2012)

Food Groups	*% energy*
Cereals	24,6
Meats and derivatives	14,3
Oils and Fats	13,6
Milk and derivatives	12,5
Fish and shelfish	3,0
Non-alcoholic drinks	2,9
Alcoholic drinks	2,3
Sauces and condiments	2,2
Eggs	1,4
Legumes	1,4
Snacks	0,9

Discussion

Several nutrition surveys based on the National Institute of Statistics' Household Budgetary Surveys provide evidence of evolving trends in energy and nutrient intake estimates between 1961 and 1991 (Varela et al, 1971; Varela et al, 1991; Varela et al, 1995; INE, 1985). Since the beginning of the 1990s, a number of Spanish regions have also accomplished randomised population nutrition surveys, including food intake surveys of individuals. These are a valuable source of information from a public health perspective, enabling a more descriptive analysis of the food and nutrition situation of the Spanish population (Aranceta, 1994; Aranceta, 1998). The present study, conducted at national level, updates the food habits and nutritional aspects of importance for the Spanish population. In addition, trends emerging from the other surveys mentioned above were considered.

The Spanish diet may be still considered varied and healthy, although some trends need to be considered negative. Therefore, a more detailed analysis of food consumption patterns at present and evolutionary trends reveals some significant findings. A large proportion of the young adult Spanish population, mainly women, wrongly consider that potatoes and bread are "fattening" foods. However, a recent study (Academia Española de Gastronomía, 2006) confirmed that potatoes are still included among the five most consumed types of food by more than 95% of the population. The decline in egg consumption is probably due to the general concern that eggs are "unhealthy", based on their cholesterol content. Although it is true that eggs contain cholesterol, it must be remembered that the consumption of saturated fatty acids has a higher influence on cholesterol levels than dietary cholesterol.

When compared with other countries, in the pan-European DAFNE study only Greece presented a higher consumption of the vegetables group at 271g/person/day (Naska et al, 2006). From a nutritional point of view, the vegetables and greens group contributed 66% of total carotenoid intake in the diet in 2012. The high fruit consumption is clearly a positive aspect, as this food group will provide antioxidant vitamins and other components, such as pectins, fructose, β-carotenoids and polyphenols, which may be beneficial in helping to prevent chronic degenerative diseases. In 2012 the fruit group contributed over 40 % of the total vitamin C consumed within the diet in Spain, mostly from fresh unprocessed foods. By contrast, legumes and pulses consumption seems to be too low according to the nutritional importance of this group; moreover, this group also provides high quality dietary protein and fibre at relatively low cost that is being skipped. The cereals and derivatives group contributed roughly a 43% of total dietary carbohydrate consumption and approximately 70% of the total starch.

The mean consumption of meat and meat products (181 g/person/day) may be considered to be very high according to the traditional *Mediterranean dietary patterns* and dietary guidelines. Paradoxically, for the DAFNE study Spain showed a higher consumption of meats than Ireland, Norway or the UK, whereas other traditional Mediterranean countries, such as Greece, showed a similar trend to Spain (Naska et al, 2006). Although total fish consumption may be considered high, omega 6/omega 3 fatty acids ratio in the diet in Spain was still not aligned with recommendations (16/1 vs. the recommended 4/1-5/1). In addition, this food group contributed 87% of total dietary vitamin D and 64% of the total vitamin B_{12} consumption. The recommendation is to encourage the maintenance of this valuable characteristic of the Spanish diet.

Adherence to the traditional Mediterranean diet

The food culture of the Spanish society is established within the Mediterranean diet frame, which is considered a healthy eating pattern mainly due to its potential protective role against the most common chronic diseases. It is generally agreed that the main components of the Mediterranean diet include a high intake of plant foods (vegetables, fruits, cereals, legumes, nuts and seeds, and olive oil); a low to moderate intake of dairy products (in the form of cheese or yogurt), low to moderate consumption of poultry and eggs; a moderately high intake of fish & shellfish; low intake of *red* meat and processed meat products, and a moderate intake of wine during meals (Keys A et al, 1986).

At present, there is a high concern that the so-called Mediterranean diet is more a theoretical reference pattern based on the diet that existed in the 60's in some regions on the Mediterranean coast, and that it has been preserved to some extent in just a few Mediterranean locations (Willett et al, 1995). This seems to also be the case for Spain. Paradoxically, Spain is a major producer and exporter of typical Mediterranean products, a factor that amplifies the importance of maintaining a Mediterranean diet pattern.

The percentage contribution of carbohydrates has steadily decreased since 1964. In that year, the energy profile was in line with recommendations. This worsening is linked to the decline in the consumption of the cereals and derivatives, legumes and pulses, and potato groups. However, as expected, cereals and derivatives represented the highest contribution to total carbohydrates, followed by the milk and derivatives food group. In contrast, the percentage of lipids (43%) markedly exceeded the recommendations at the expense of carbohydrates. The main contributors to total dietary lipid consumption were oils and fats (30%); meat and derivatives (28%); milk and derivatives (15%); cereals and derivatives (9%); and fish and fish products (6%). In order to evaluate the dietary fat quality, the lipid profile was calculated (percentage contribution of the three fatty acid classes to the total energy), as well as relationships between PUFA/SFA and (PUFA+MUFA)/

SFA. The SFA and PUFA fractions were well above the recommended levels. A positive aspect that should be maintained was the high proportion of MUFA due to the common occurrence of olive oil in the Spanish diet. In the present study, total omega-3 PUFA consumption was adequate but the percentage contribution of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) to total energy consumption, which is recommended to be between 0.25 and 0.5%, was markedly below recommendations. As far as the omega 6/omega 3 ratio is concerned, the nutritional objectives for the Spanish population indicate that it should be between 5/1 and 4/1 (Mataix, 2005). However, the ratio was found to be deviating markedly towards the omega-6 fraction (16.6/1), which may compromise the potential benefits provided by the omega-3 fatty acids.

The percentage contribution of protein to total energy intake (15%) was unchanged since the survey in 2000 and is above the recommended profile. It is also advisable to decrease the proportion of animal protein in the total protein intake. The mean protein intake at present for the Spanish population was 93.5 g/person/day, the main contributors being: 28% from the meat and derivatives group; 19% from milk and derivatives; 17% from cereals and derivatives and 16% from fish and fish products.

In conclusion**,** social and economic changes have led to important modifications in food patterns in the last few decades, as has also been observed in previous studies (Balanza et al, 2007; García-Closas et al, 2006; Rodríguez-Artalejo et al, 1996). Some changes have had a *potential* positive impact, such as increasing variety in the diet and improved access to food, but are not consistent with an adequate food selection as described for a healthy Mediterranean type of diet. On the other hand, some changes have moved the Spanish diet away from the *traditional Mediterranean Diet pattern* (Moreno et al, 2002). Therefore, strategies that encourage a healthy diet and which also allow the recovery of the traditional characteristics of the Mediterranean Diet are a priority for nutritional policies. This may partly be achieved by an adequate use of new technologies which deal with food production, food conservation, food marketing and food distribution.

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Current mapping of obesity

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Abstract

Obesity is a major risk factor for non-communicable diseases (NCDs), such as diabetes, cardiovascular diseases, and cancers. The worldwide prevalence of obesity has almost doubled between 1980 and 2008. In some regions, such as Europe, the Eastern Mediterranean and the Americas, more than 50% of women are overweight. Tonga, Nauru and the Cook Islands show the highest prevalence of obesity worldwide, above 60% in men and in women. China and the United States are the countries that experienced the largest absolute increase in the number of overweight and obese people between 1980 and 2008, followed by Brazil and Mexico. The regions with the largest increase in the prevalence of female obesity were Central Latin America, Oceania and Southern Latin America. Updated data provide evidence that the progression of the epidemic has effectively slowed for the past ten years in several countries. In low-income countries obesity is generally more prevalent among the better-off, while disadvantaged groups are increasingly affected as countries grow. Many studies have shown an overall socio-economic gradient in obesity in modern industrialized societies. Rates tend to decrease progressively with increasing socio-economic status. Children obesity rates in Spain are amongst the highest in the OECD. One in 3 children aged 13 to 14 are overweight. Overweight in infants and young children is observed in the upper middle-income countries. However, the fastest growth occurs in the group of lower middle-income countries. There is a growing body of evidence for an inverse association between SES and child obesity in developed countries. The prevalence of overweight and obesity is high in all age groups in many countries, but especially worrying in children and adolescents in developed countries and economies in transition.

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Key words: *Overweight. Obesity. Prevalence. Trends. Inequalities.*

MAPPING DE LA OBESIDAD ACTUAL

Resumen

La obesidad es un importante factor de riesgo para las enfermedades crónicas no transmisibles, como la diabetes, las enfermedades cardiovasculares y el cáncer. La prevalencia mundial de obesidad se ha duplicado entre 1980 y 2008. En algunas regiones, como Europa, el Mediterráneo Oriental y América, más del 50% de las mujeres tienen sobrepeso. Tonga, Nauru y las Islas Cook muestran la mayor prevalencia de obesidad en todo el mundo, por encima del 60% tanto en los hombres como en las mujeres. China y Estados Unidos son los países que experimentaron el mayor aumento absoluto en el número de personas con sobrepeso y obesidad entre 1980 y 2008, seguido de Brasil y México. Las regiones con el mayor incremento en la prevalencia de obesidad femenina fueron Centro América, Oceanía y el sur de América Latina. Datos actualizados sugieren que la progresión de la epidemia se ha reducido durante los últimos diez años en varios países. En los países de renta baja la obesidad suele ser más frecuente entre los niveles socioeconómicos más favorecidos, mientras que los grupos desfavorecidos están cada vez más afectados en los países en desarrollo. Muchos estudios han demostrado un gradiente socioeconómico global de la obesidad en las sociedades industrializadas modernas. Las tasas tienden a disminuir progresivamente a medida que aumenta el nivel socio-económico. La prevalencia de obesidad en España se encuentra entre las más altas de la OCDE. Uno de cada 3 niños de 13 a 14 años tiene sobrepeso. El sobrepeso en los lactantes y niños de corta edad se observa en los países de ingresos medios-altos. Sin embargo, el mayor crecimiento se produce en el grupo de países de ingresos medianos bajos. Hay un creciente cuerpo de evidencia de una asociación inversa entre la obesidad SES-infantil en los países desarrollados. La prevalencia del sobrepeso y la obesidad es alta en todos los grupos de edad en muchos países, pero especialmente preocupante en los niños y adolescentes en los países desarrollados y las economías en transición.

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Palabras clave: *Sobrepeso. Obesidad. Prevalencia. Tendencia. Desigualdades.*

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Abbrevations

NCDs: Non Communicable Diseases.
OECD: Organization for Economic Co-operation and Development.
BMI: Body Mass Index.
UK: United Kingdom.
USA: United States of America.
WHO: World Health Organization.
SES: Socio Economical status.
IOTF: International Obesity Task Force.
GIS: Geographic Information System.
BF%: Percentage body fat.
SD: Standard deviation.
OR: Odds Ratio.

Obesity is a major risk factor for non-communicable diseases (NCDs), such as diabetes, cardiovascular diseases, and cancers. In fact, the World Health Organization (WHO) recognizes high blood pressure, tobacco use, high blood glucose, physical inactivity, and overweight and obesity as the leading global risks for mortality in the world, overweight and obesity being responsible for 5% of deaths globally. A high body mass index (BMI) is among the eight risk factors which account for 61% of cardiovascular deaths and over 75% of ischemic heart disease, the leading cause of death worldwide.[1]

In cohort studies an increased risk of all-cause mortality both among participants who had been persistently obese since early adulthood and participants who showed an increase in BMI category from normal to obese, compared with participants with a stable normal BMI category has been reported.[2]

International cohort studies have quantified the associations between high BMI and different diseases in populations worldwide. However additional research is needed into how the duration of being overweight or obese affects risk, and whether the health benefits of prevention of weight gain are similar to those of weight loss.[3] A recent study informed that while relative to normal weight, both obesity (all grades) and grades 2 and 3 obesity were associated with significantly higher all-cause mortality, grade 1 obesity overall was not associated with higher mortality, and overweight was associated with significantly lower all-cause mortality.[4]

Every 15 kg extra in body weight increases the risk of early death approximately 30%. Research conducted in ten European countries shows that obesity doubles the odds of not being able to live a normal active life. Throughout their lives, health care costs for obese people are at least 25% higher than for people of normal weight and increase rapidly with weight gain. Obesity has been estimated to consume between 2-6% of health care costs in many countries, thereby impairing economic productivity and development.[5] Furthermore, it has been argued that increasing BMI is a pandemic that could reverse life-expectancy gains in high-income nations.

In 2008, 35% of adults were overweight. An estimated 2.8 million people die every year worldwide due to overweight. The worldwide prevalence of obesity has almost doubled between 1980 and 2008. In some regions, such as Europe, the Eastern Mediterranean and the Americas, more than 50% of women are overweight.[6]

Prevalence of obesity and trends in adults

BMI

In 2011 Finucane and colleagues[3] estimated worldwide trends in population mean BMI for adults 20 years and older in 199 countries using recent national health examination surveys and other sources collecting measured body weight and height. Results from this study show that between 1980 and 2008 age-standardized mean BMI for men increased in every sub-region considered except for central Africa and south Asia. In high-income countries, male BMI rose most in the USA (1.1 kg/m^2 per decade), followed by the UK (1.0 kg/m^2 per decade) and Australia (0.9 kg/m^2 per decade), and least in Brunei, Switzerland, Italy, and France (0.3-0.4 kg/m^2 per decade). In 2008, age-standardized mean BMI in men was highest in North America (28.4 kg/m^2, 27.9-28.7) and Australasia (27.6 kg/m^2, 27.1-28.1). Japan and Singapore had the lowest male BMI in high-income countries, both less than 24.0 kg/m^2.

Globally, female BMI increased by 0.5 kg/m^2 per decade between 1980 and 2008. The largest rise in female BMI occurred in Oceania (1.8 kg/m^2 per decade), followed by southern and central Latin America (1.3-1.4 kg/m^2 per decade). Female mean BMI trends in central and Eastern Europe and central Asia showed changes less than 0.2 kg/m^2 per decade. The increase in east and south Asia, Asia-Pacific, and Western Europe was also less than 0.4 kg/m^2 per decade. Conversely female BMI increased by about 1.2 kg/m^2 per decade in Australasia and North America. Among high-income countries, women in the USA, New Zealand, and Australia had the greatest gain in BMI (1.2 kg/m^2 per decade), whereas women in Italy and Singapore might have had a modest BMI decrease of 0.1-0.2 kg/m^2 per decade.

Globally, age-standardized mean BMI in 2008 was 23.8 kg/m^2 (23.6-24.0) for men and 24.1 kg/m^2 (23.9-24.4) for women. Male BMI was higher than female in high income subregions, but lower in most low-income and middle-income regions. In 2008, female BMI was highest in North America, North Africa, Southern Africa and Middle East, with mean BMI above 28 kg/m^2, with the highest estimates in Oceania, Nauru (35.0 kg/m^2). Women in the USA had the highest mean BMI of high income countries, followed by New Zealand.

Prevalence of obesity

Based on BMI estimates in the study mentioned above, Stevens and colleagues predicted the preva-

lence of obesity in adults 20 years and older in the same 199 countries in all five continents and trends between 1980 and 2008.[7] Overall, the age-standardized prevalence of obesity nearly doubled from 6.4% in 1980 to 12.0% in 2008. Results of the study highlight that the rise has accelerated in the last decade, when half the estimated trend occurred, between 2000 and 2008. The age-standardized prevalence of overweight increased from 24.6% (22.7-26.7%) to 34.4% (33.2-35.5%) during the same 28-year period. In 2008, female obesity prevalence ranged from 1.4% (0.7-2.2%) in Bangladesh to 70.4% (61.9-78.9%) in Tonga and 74.8% (66.7-82.1%) in Nauru. Male obesity was below 1% in Bangladesh, Democratic Republic of the Congo, and Ethiopia, and was highest in Cook Islands (60.1%, 52.6-67.6%) and Nauru (67.9%, 60.5-75.0%).

Worldwide, age-standardized prevalence of obesity was 9.8% (9.2-10.4) in men and 13.8% (13.1-14.7) in women in 2008, which was nearly twice the 1980 prevalence of 4.8% (4.0-5.7) for men and 7.9% (6.8-9.3) for women. By 2008, the prevalence of overweight among women was over 90% in Cook Islands, Nauru, and Tonga. Male overweight in 2008 was also over 90% in the Cook Islands and Nauru.

According to these estimates, in 2008, female obesity reached up to 70.4% (61.9-78.9%) in Tonga and 74.8% (66.7-82.1%) in Nauru. The prevalence of male obesity was above 60% in Cook Islands (60.1%, 52.6-67.6%) and Nauru (67.9%, 60.5-75%). The countries with the most overweight people were China (241 million) and the United States (158 million). These two countries experienced the largest absolute increase in the number of overweight and obese, followed by Brazil and Mexico.

In 2008, the regions with the highest obesity prevalence were North Africa and Middle East, Central and Southern Latin America, Southern Sub-Saharan Africa, and high-income North America, with prevalence ranging from 27.4% to 31.1%. Western Sub-Saharan Africa which remained a low-obesity region until 2000 experienced a relatively large rise in BMI in the next 8 years.

According to an OECD report age-standardized rates of obesity show significant differences across countries in obesity levels and in trends over time. The analyses carried out for eleven OECD countries (Australia, Austria, Canada, England, France, Hungary, Italy, Korea, Spain, Sweden and the United States) considering self-reported national data collected between 1989 and 2005 (age range 16-65 yr) showed that obesity rates have been increasing in all these countries in men. A similar increase was observed in women in Australia, Austria, Canada, England, France, Hungary, Sweden, and the USA whereas in Italy, Korea and Spain show minimal increases over time. Overweight rates have been increasing in all countries in men except in Canada and France where rates appear to level off. Overweight rates in women show an increasing trend over years except for Italy, Korea, and Spain. Obesity rates in England and the USA are substantially higher than in the other countries, and over five times those observed in Korea.[8]

Projected trends in this report show important differences between Australia, Canada, England and the USA on one hand, and Austria, France, Italy and Spain on the other. A substantial further increase in obesity rates is projected in the former group of countries, with stable or slightly declining rates of overweight. Conversely, obesity rates are projected to grow at a relatively slow pace in Austria, France, Italy and Spain over the next ten years, while overweight rates in the same countries are projected to grow at a faster rate, especially in Korea.[8]

OECD projections suggest that more than two out of three people will be overweight or obese in some OECD countries by 2020.[5] Updated data provide evidence that the progression of the epidemic has effectively slowed for the past ten years in countries such as Korea, Switzerland (obesity rate 7-8%), Italy (obesity rate 8-9%), Hungary (obesity rate 17-18%) and England (obesity rate 22-23%). The latest data show modest increases (2-3%) in obesity over the past decade in countries like Spain and France and larger increases in Ireland, Canada and the United States (4-5%). The prevalence of obesity today varies nearly tenfold among OECD countries, from a low of 4% in Japan and Korea, to 30% or more in the United States and Mexico.

In the USA the prevalence of obesity in 2007-2008 was 32.2% among adult men and 35.5% among adult women. Thus the increases in the prevalence of obesity previously observed do not appear to be continuing at the same rate over the past 10 years, particularly for women and possibly for men.[9]

Table I shows the prevalence of obesity in adults based on measured data in different countries near 2009. Latest figures from the Health Survey for England 2009-11 shows that one quarter of men and women are obese and two thirds of adults are obese or overweight. In the last 20 years, the number of morbidly obese adults (BMI over 40) has more than doubled to over one million people in the UK.

Obesity rates in adults in Spain are higher than the OECD average. Two out of 3 men are overweight and 1 in 6 people are obese in Spain. Considering the most recent data, the OECD updated projections for 2010-2020 point that overweight and obesity rates are expected to grow by 7% during that period in Spain. The prevalence of obesity (self-reported) in population aged 18 yr. and older based on the latest Spanish National Health Survey (2011-2012) is 17% (18% men; 16% women) and overweight 37%. Thus 54% of the population 18 yr. and older is either overweight or obese. According to the same source, obesity rates in 1987 were 7.4%. The upward trend is more pronounced in men than in women.

Higher obesity rates have been estimated based on measured body weight and height in the ENRICA study, a cross-sectional study on a sample aged 18 yr. and older (n = 12.883; data collection 2008-2010): 22.9%

Table I
Prevalence of obesity among adults in different countries based on measured data, 2009 (or nearest year)

	Year	Total	Females	Males
Korea		3,8	4,1	3,6
Japan		3,9	3,5	4,3
OECD			**17,2**	**16,6**
Slovak Republic	2008	16,9	16,7	17,1
Czech Republic	2005	17,0	17,0	18,0
Finland	2007	20,2	21,1	19,3
Luxembourg		22,1	19,0	24,5
Spain	2008-2010	22,9	21,4	24,4
Ireland	2007	23,0	24,0	22,0
United Kingdom		23,0	23,9	22,1
Canada	2008	24,2	23,2	25,2
Australia	2007	24,6	23,6	25,5
Chile		25,1	30,7	19,2
New Zealand	2007	26,5	27,0	26,0
Mexico	2006	30,0	34,5	24,2
United States	2008	33,8	35,5	32,2

Sources: OECD Health Data 2011; national sources for non-OECD countries. Obesity BMI ≥ 30.

for obesity and 39.4% for overweight.[10] Self-reported body weight and height are systematically biased and estimated rates appear to under-estimate obesity compared to individually measured rates. Similar observations have been made regarding self-reported data in the USA (NHIS) and measured data (NHANES), but the time trends projected based on either data are the same.

In Spain previous measured data in the adult population (data collected 1990-2000; (25-65 yr) in the DORICA pooled study estimated a prevalence of obesity 15.5% (13.2% in men; 17.5% in women).[11] This observation suggests a considerable increase over the past 20 years in the country, in line with that referred based on self-reported data.

Gender, age and socioeconomic factors

Gender

A systematic review of studies reporting prevalence of obesity rates based on measured body weight and height in European countries, with data collected 1990-2008 showed that in Europe, the prevalence of obesity in men ranged from 4.0% to 28.3% and in women from 6.2% to 36.5%.[12]

According to the global estimates by Stevens et al, male and female obesity prevalence differed most in Southern Sub-Saharan Africa, where the prevalence of obesity was 18.7% (15.6-21.5%) for men and 36.7% (33.0%-40.2%) for women in 2008. The regions with the largest increase in the prevalence of female obesity were Central Latin America (8.5 percentage points per decade), Oceania (8.2 percentage points per decade), and Southern Latin America. The regions with the largest increase in male obesity were North America (6.9 percentage points per decade) and Australasia. In Western, Central, and Eastern Europe, and in the high-income Asia Pacific countries, the prevalence of obesity increased more among men than women in 41 of 47 countries.[7]

In the USA, the prevalence of obesity is high, exceeding 30% in most age and sex groups except for men aged 20 to 39 years. Among men, age adjusted obesity prevalence was 32.2% and within racial and ethnic groups ranged from 31.9% among non-Hispanic white men to 37.3% among non-Hispanic black men. For women, the age adjusted prevalence was 35.5%, ranging from 33.0% among non-Hispanic white women to 49.6% among non-Hispanic black women.[9]

The prevalence of obesity in Korean males increased during the past 12 years from 25.1% to 35.7%, and the trend for an increase in obesity was significant in all age groups. In contrast, no significant trend over the past 12 years was identified for females. In Korean women aged 30-59 yr the prevalence of obesity decreased significantly but not in women aged 60 yr and older the obesity prevalence increased significantly. A gradually widening gender disparity was observed due to an increase in the prevalence of male obesity and a decrease in the obesity prevalence among young and middle-aged women in Korea.

In Spain both data from the National Health Survey (self-reported) and the DORICA study (measured data) reported higher obesity rates in women than in men. However, in recent years the situation has changed. According to the latest National Health Survey (2011-2012) the prevalence of obesity was 18% in men and 16% in women (fig. 1). The ENRICA study (measured data) reports a prevalence of obesity of 24.4% in men and 21.4% in women, with higher obesity rates in women than men in people aged 65 yr. and older.

Interactions between gender, education and socioeconomic level have been reported. The demographic, educational and socioeconomic changes occurred in the last decades may have played a role in these changes. Gender differences in obesity are important per se, because they may suggest possible pathways through which obesity is generated.

Age

The prevalence of overweight and obesity increase with age in adults up to a certain age. However, the age at which population rates of obesity start to decline varies in different countries, ranging from the late sixties to the late seventies in industrialized countries.

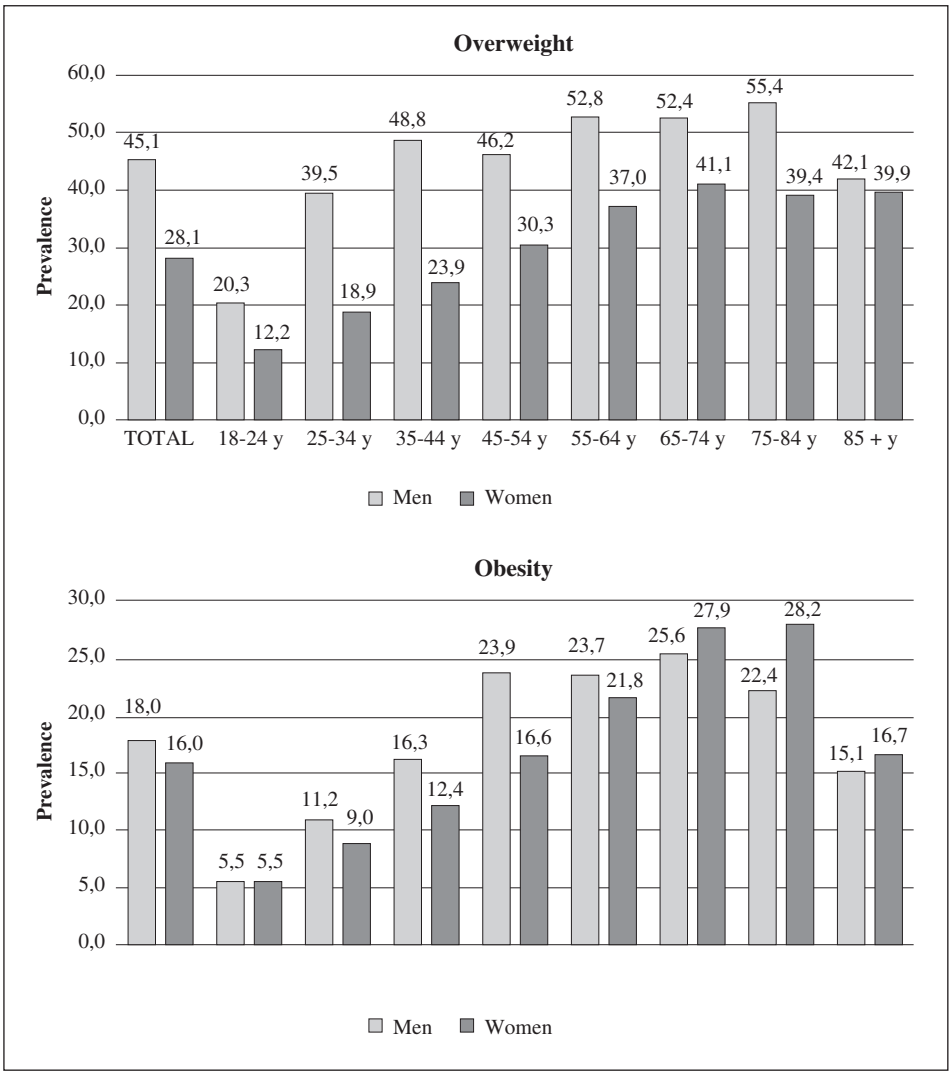

Fig. 1.—Prevalence of overweight and obesity in Spanish adult population by gender (self-reported data). National Health Survey 2011-2012. Overweight BMI ≥ 25 < 30; Obesity BMI ≥ 30.

The analysis conducted by Doak et al in data from WHO European Region taking into account differences related to the aging of the population showed that the 50-64-year-olds had higher prevalence of overweight and obesity as compared to the 25-49-year-olds, a pattern that was similar in every country, by male and female. Age-standardized overweight prevalence was higher among males than females in all countries.[13]

In Spain data for adults aged 60 yr. and older between 2000 and 2010 show that in men the distribution of BMI did not vary in the period, but in women there was a reduction in both mean BMI (from 29.3 to 28.8 kg/m^2) and the prevalence of obesity (from 40.8 to 36.3%). This decline was greatest in women aged 60-69 years.[14]

Socioeconomic and educational level

In low-income countries obesity is generally more prevalent among the better-off, while disadvantaged groups are increasingly affected as countries grow. Many studies have shown an overall socio-economic gradient in obesity in modern industrialized societies. Rates tend to decrease progressively with increasing socio-economic status (SES). The overall socio-economic gradient in obesity observed in many countries is an average of a strong gradient in women and a substantially milder gradient in men. Several reports concluded that socioeconomic status and women's obesity tended to be inversely related in developed populations and directly related in developing populations.

Women in certain ethnic minority groups are substantially more likely to be obese than other women, even after controlling for differences in socioeconomic conditions, but not for men in the same minority groups. In the USA, obesity prevalence among men is generally similar at all income levels, however, among non-Hispanic black and Mexican-American men those with higher income are more likely to be obese than those with low income. Higher income women are less likely to be obese than low income women, but most

obese women are not low income. There is no significant trend between obesity and education among men. Among women, however, there is a trend; those with higher education are less likely to be obese compared with less educated women.[15]

Social disparities in obesity are very large among Spanish women as shown in previous reports[11] and persist according to updated data. Women with poor education in Spain are 3.2 times more likely to be overweight than more educated women. Disparities are substantially smaller in men. The degree of socio-economic inequality has remained virtually unchanged in recent years. In fact, the most recent data available show a low prevalence of obesity among highly educated women aged 18-44 yr. in Spain.

An inverse relationship between household income and BMI has been reported in women in nine European countries, but mixed patterns for men. A later study comparing inequalities in obesity and overweight across 11 OECD countries, including several European countries, Australia, Canada, Korea and USA showed consistently larger education-related inequalities in women than in men, except in Austria. Obesity and overweight tend to be more prevalent in disadvantaged socioeconomic groups, and inequalities are consistently larger in women than in men. In most of the countries a gradient is observed: the lower the education attainment, the higher the likelihood of being obese or overweight. For men, lower education is strongly associated with a higher likelihood of being overweight or obese except in Korea where the gradient seems in the opposite direction. Generally, gradients observed in women are substantially stronger than those observed in men. Considering evolution trends over 15 years, social inequalities in obesity and overweight remain virtually stable with minor variations.[16] In a country such as China with a rapid economic change, urban residents have a much higher prevalence of overweight/obesity than their rural counterparts.

Prevalence of obesity and trends in children

The concern with childhood obesity arises from its association with poor psychological and social outcomes, as well as physical health problems in the short and long term. Among other, obesity in children is linked with low self-esteem, depression, and obese children can suffer from social discrimination. Childhood obesity is associated with a range of physical health problems including type 2 diabetes, liver disease, impaired mobility, asthma, sleep apnea, and risk factors for cardiovascular disease. Most of these health problems arise in later life, although some of them are increasingly being seen in children. In addition, research conducted in different countries indicates that overweight and obese children are at higher risk than normal weight children of becoming overweight and obese adults.[17,18]

Estimates of the prevalence of overweight (including obesity) in OECD and emerging countries among children and youth aged 5-17 years show average rates in OECD countries of 21.4% for girls and 22.9% for boys. One-in-five children are affected by excess body weight across all countries, and in Greece, the United States and Italy the figure is closer to one third. Overweight affects 10% or less of children only in China, Korea and Turkey. In most countries, boys have higher rates of overweight and obesity than do girls. Girls tend to have higher rates in Nordic countries (Sweden, Norway, Denmark), as well as in the United Kingdom, the Netherlands and Australia. The prevalence estimated in Brazil is 21.1% in girls and 23.1% in boys.

Children obesity rates in Spain are amongst the highest in the OECD. One in 3 children aged 13 to 14 are overweight. Using IOTF's cut-offs, the estimated prevalence of obesity based on body measurements in 1998-2000 was 6.3% (7.9% boys; 4.6% girls), while overweight and obesity affected to 24.4% (19). Regarding sociodemographic factors sex, age group, region, size of locality of residence, mother's level of education and familiy SES level were significant predictors for obesity in children and adolescents under 14 yr.

Evolution trends observed in a Spanish region according to the Study of Cuenca in the period 2004-2010 reported that the prevalence of overweight and adiposity has continued to increase among boys but no change in overweight and percentage body fat (BF%) in girls, or in underweight and obesity in either sex.[20]

Comparison of obesity and overweight rates in cross-sectional studies conducted in the same regions and age groups in 1998-2000 (enKid study) and 2009 (PERSEO) suggests an increase in prevalence rates in school children between 1.5 and 4 percentage points in most regions in the country, except for the Canary Islands, where the prevalence of overweight and obesity remains stable at high rates, 21%. According to the ALADINO study based on measured body weight and height the prevalence of obesity in school-aged children is 19.1%, 22% in boys and 16.2% in girls, overweight and obesity add up to 48.3% for boys and 42.1% in girls, similar estimates to those observed in the intervention project PERSEO. In the National Health Survey 2011-2012, based on self/ parent-reported body weight and height, the estimated prevalence of overweight plus obesity was 29% in boys and 26,5% in girls aged 2-17 yr, with higher rates in the 5-9 yr subgroup (fig. 2).

Increasing attention is being given to obesity in children under 5 years of age. The incidence of overweight in infants and young children has increased dramatically in recent decades and is expected to increase further. Although the highest incidence of overweight in infants and young children is observed in the upper middle-income countries, the fastest growth occurs in the group of lower middle-income countries. Cattaneo et al. in a recent review reported prevalence rates of overweight plus obesity at 4 years ranging from 11.8% in Romania (data collected in 2004) to 32.3% in Spain

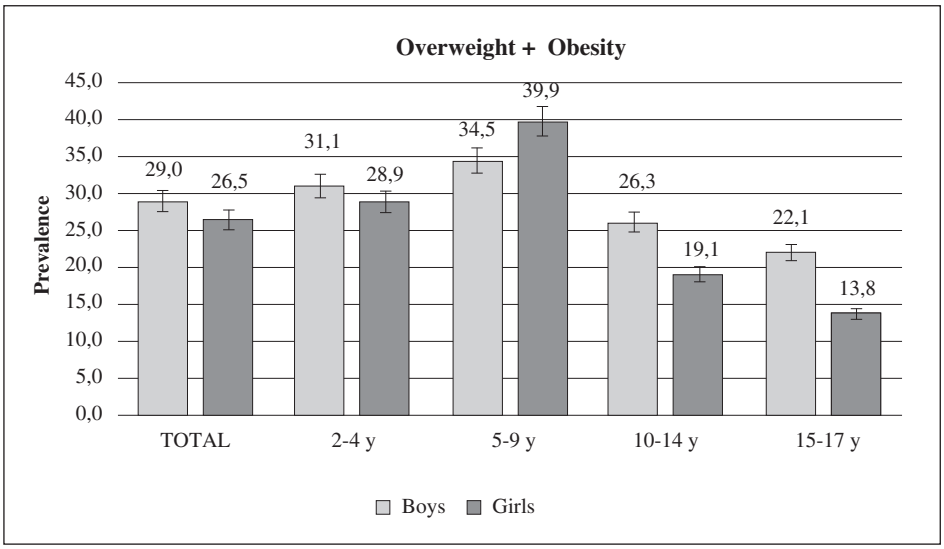

Fig. 2.—Prevalence of overweight plus obesity in Spanish boys and girls (2-17 y). National Health Survey 2011-12. Self /parent reported data. Overweight and obesity defined according to IOTF criteria.

(1998-2000). Countries in the Mediterranean region and the British islands showed higher rates than those in Middle, Northern and Eastern Europe. Reported rates were generally higher in girls than in boys.[21]

However, high quality evidence has emerged from several countries suggesting that the rise in the prevalence has slowed, or even plateaued. New data on child obesity from four OECD countries (England, France, Korea and United States) show that rates evolved according to previous OECD projections or even below those projections, in all four countries. Child obesity rates have effectively remained stable (at 6-8%) over the past 20 years in France. A review including high quality data from nine countries (Australia, China, England, France, Netherlands, New Zealand, Sweden, Switzerland and USA), from 467,294 children aged 2-19 years evidenced that the mean unweighted rate of change in prevalence of overweight and obesity was +0.00 (0.49)% per year across all age×sex groups.[22]

Similar findings were reported by Rokholm et al. supporting an overall levelling off of the epidemic in children and adolescents from Australia, Europe, Japan and the USA. Some evidence for heterogeneity in the obesity trends across socioeconomic status (SES) groups was found. The levelling off was less evident in the lower-SES groups, but no obvious differences between genders were identified. It is worthwhile to keep in mind that previous stable phases have been followed by further increases in the prevalence of obesity.[23] This was the case in England, where childhood obesity and overweight prevalence among school-age children has stabilized in recent years, but children from lower socio-economic strata have not benefited from this trend. In France, the prevalence of overweight in the disadvantaged group increased between 1996 (12.8%) and 2001 (18.9%) and was stable between 2001 and 2006 (18.2%). Thus in France there have been some signs of levelling off but also indications to the contrary, illustrated by a renewed rise in obesity in French children, after ten years of stabilization.[24]

The standardized prevalence of obesity in Chinese children increased rapidly during the past 25 years from 0.2% in 1985 to 8.1% in 2010. The increasing trend was significant in all age subgroups. Although the prevalence of obesity continuously increased in both boys and girls, the changing pace in boys was faster than that in girls. The prevalence of obesity in boys was significantly higher than in girls in all age-specific subgroups from 1991 and after. The gradually expanding gender disparity suggests the prevalence of obesity in boys contribute to a large and growing proportion of obese children.[25]

Socioeconomic inequalities in childhood obesity

There is a growing body of evidence for an inverse association between SES and child obesity in developed countries, with estimated Odds Ratios (OR) ranging from 1.26 to 1.95 for low SES compared to high SES neighbourhoods for varying measures of child obesity. Figure 3 shows the prevalence of obesity in Spanish children and youth (2-17 yr) by family SES level estimated based in the National Health Survey 2011-12.

Knai et al. report on a review including data from 22 European countries that greater inequality in household income is positively associated with both self-reported and measured child overweight prevalence. Several studies from four countries reported on the influence of socioeconomic factors on the distribution of child overweight over time. Although the prevalence of overweight has increased across the population of these countries, the rise has not been as severe among the wealthiest parts of the population, leading to widening social disparities among adults.[26]

Parental weight appears to be the most influential factor driving the childhood obesity epidemic in different countries and is an independent predictor of child obesity across SES groups. Children with at least one obese parent are 3-4 times more likely to also be obese.

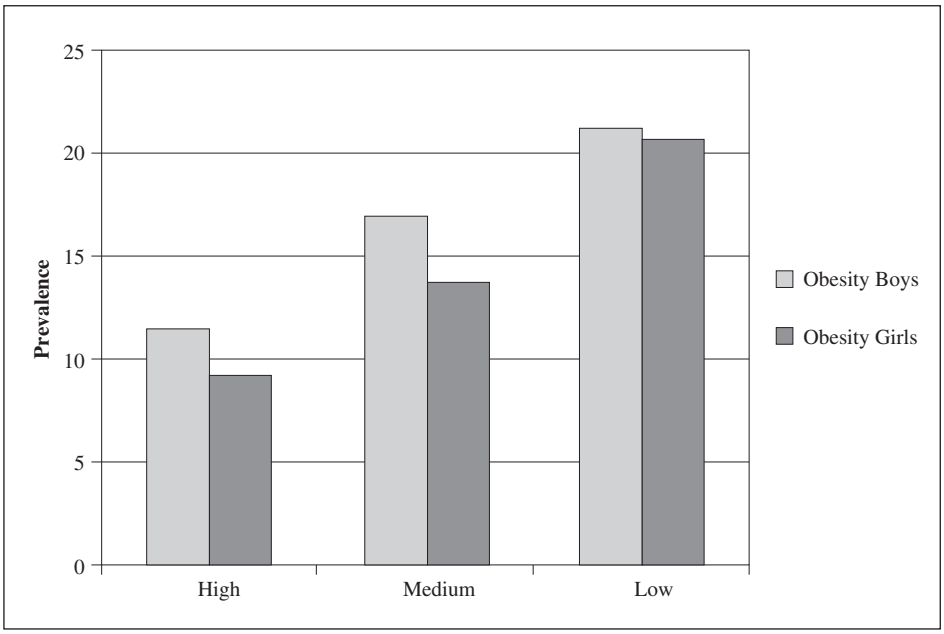

Fig. 3.—Prevalence of obesity in Spanish children and youth (2-17 yr) by family SES level. National Health Survey 2011-12. Self-parent reported data. Obesity defined according to IOTF criteria.

This is partly genetic, but children often share dietary habits and sedentary lifestyles of their parents, influences that have played a major role in the spread of obesity. In fact, the inverse relationship between SES level and obesity is evident in adults in high income countries as well.[5]

The increases in obesity prevalence have been attributed to environmental changes that promote excessive food intake and discourage physical activity. Research also has found that child and adult risk of obesity is related to individual socioeconomic status (SES) factors, such as household income and educational level, as well as race/ ethnicity. The widening social inequality gap in child obesity suggests a particular vulnerability to environmental factors that confer obesity risk among people who face social disadvantage, including lower SES and certain race/ethnicity groups.

Based on information collected using Geographical Information Systems (GIS) to assess the structural aspects of obesity and obesity-related behaviours at the neighbourhood (or larger) level, in adjusted spatial models, child obesity risk has been significantly associated with lower household income, lower home ownership, and for each 10% increase in less educated women, and single parent households, as well as non-white residents. Greves Grow et al. observed in a spatial model that SES/race variables explained approximately 24% of geographic variability in child obesity.[27]

There are a number of plausible neighbourhood contextual factors likely related to SES that may explain how the environmental variables influence diet and physical activity behaviours and create *"obesogenic environments"*. These variables include low walkability, lack of recreation sites for physical activity, lack of grocery stores offering affordable fresh fruits and vegetables, and higher density of fast food outlets. The correlation between geographic area of residence and obesity is of particular interest in identifying the social determinants of obesity, especially factors that may be modifiable in communities most severely affected by obesity.[28]

According to the report *Mapping the childhood obesity epidemic* published in the USA, the community indicators most influential in determining a child's probability of being obese were demographic characteristics, household structure and the education and English language proficiency of the population in the child's community (table II). The conclusions of this report emphasize that communities where childhood obesity is predicted to be highest face disadvantages across

Table II

Socioeconomic inequalities in childhood obesity. Communities where childhood obesity is predicted to be highest are more likely to have:

- Minority residents
- Higher unemployment rates
- Higher proportions of children living in households headed by a non-parent
- Higher proportions of children living in households that are single-parent
- Higher poverty rates
- Lower female labour force participation
- Lower education and income levels

Source: Long S, Hendey L, Pettit K. Mapping the Childhood Obesity Epidemic: A Geographic Profile of the Predicted Risk for Childhood Obesity in Communities Across the United States. The Urban Institute, Dec 2007.

multiple dimensions. These communities are more likely to have minority residents, higher unemployment rates, higher proportions of children living in households headed by a non-parent, higher poverty rates, lower female labour force participation, lower education and income levels, lower home ownership rates.

The plausible neighbourhood contextual factors that may mediate the SES determinants through environmental variables are now increasingly emerging. A review of built environment factors related to obesity among disadvantaged populations, defined by poverty and race/ethnicity, found that important factors are access to healthy foods in supermarkets, places to exercise, and neighbourhood safety. Zick et al. as well as other researchers have found strong association between neighbourhood retail food options and BMI/obesity risk with the magnitude of the effects varying by neighbourhood income.[29] Research conducted by Richardson et al. in the USA concluded that socio-demographic inequities in neighbourhood food resource availability were most pronounced in low-density urban (suburban) areas. In high-density urban areas, higher neighbourhood poverty was associated with greater availability of all food resources.[30]

The conclusions of a social experiment to assess the association of randomly assigned variation in neighbourhood conditions with obesity and diabetes highlighted that the opportunity to move from a neighbourhood with a high level of poverty to one with a lower level of poverty was associated with modest but potentially important reductions in the prevalence of extreme obesity and diabetes.[31]

Research gaps

Despite the efforts devoted in recent years, there is a need for continuing collection of information based at least in measured body weight and height to monitor obesity trends over time in children and adult populations that are comparable across countries. Increased investment in population obesity monitoring would improve the accuracy of forecasts and evaluations.

Increasing attention is being given to obesity in children under 5 years of age. The IOTF reference and the WHO standard yield different results in terms of prevalence of overweight and obesity in children 24-60 months of age in the same population. IOTF curves for girls tend to overestimate overweight and obesity as a result of a problem with the backward tracking of the BMI centiles from 18 years of age. This is probably due to a sex bias at 18 years, because the BMI plateaus earlier in girls than in boys. An additional problem with the WHO cut-offs for overweight and obesity is the transition at 5 years between the standard for children 0-5 years of age and the one for children and adolescents 5-19 years of age. Overweight and obesity are defined with 2SD and 3SD cut-offs in the former, and with 1SD and 2SD cut-offs in the latter, and in the transition between 60 and 61 months of age the prevalence of overweight and obesity will be different depending on whether the first or the second dataset and cut-offs are used. This problem deserves further research.[32]

Over the past few decades, the global emergence of overweight and obesity is confounded by the simultaneous aging of the population. High prevalence for overweight and obesity occur in older adults and hence population aging may contribute independently to the rising prevalence of overweight and obesity in adults. Population aging may differ by country, and over time. Therefore age-adjusted prevalence for overweight and obesity are needed to allow for comparisons of prevalence and trends across countries. Age adjustment is important in documenting emerging overweight and obesity trends, independent of demographic changes. Ideally, nationally representative surveys in countries would be repeated at regular intervals, measure height and weight to objectively estimate overweight and obesity prevalence.[13]

Following the United Nations General Assembly High-Level Meeting on the Prevention and Control of Non-communicable Diseases in September 2011 request to develop targets for key non-communicable disease indicators, WHO drafted the comprehensive global monitoring framework and targets for the prevention and control of non-communicable diseases to be discussed and approved in the context of the Sixty-sixth World Health Assembly in May 2013. The document includes as indicators in relation to obesity monitoring the prevalence of overweight and obesity in adolescents (defined according to the WHO growth reference for school-aged children and adolescents, overweight —one standard deviation body mass index for age and sex and obese— two standard deviations body mass index for age and sex) and age-standardized prevalence of overweight and obesity in persons aged 18+ years (defined as body mass index ≥ 25 kg/m² for overweight and body mass index ≥ 30 kg/m² for obesity.

Conclusions

The prevalence of overweight and obesity is high in all age groups in many countries, but especially worrying in children and adolescents in developed countries and economies in transition. Some evidence suggests a tendency to stabilize the growth rate of the problem. However, this finding should not divert attention from the problem, since in some countries the plateau or decline has been followed by a rebound.

There are significant differences in the prevalence of overweight and obesity among different population groups, with inequalities in disadvantaged

groups in terms of socioeconomic status, education and social environment, which tend to increase even more in the current economic crisis. These differences contribute to increase health inequalities, because this situation adds up to the burden associated with obesity on physical health, psychological and social wellbeing.

In relation to childhood obesity, it would be desirable to reach a consensus on the reference curves and cut-off points used for surveillance and monitoring purposes of excess weight, at least to enable international comparisons.

It is required to develop and implement a monitoring and evaluation system with a set of minimum indicators that allow the collection of comparable high quality information on the evolution of the problem. Based on current evidence available it is necessary to further coordinate and standardized the collection of epidemiological information on anthropometric measurements, weight gain, physical activity and dietary habits in pregnant women during lactation and related to infant weaning and diet diversification.

It would be desirable to identify social environments, geographical areas and population groups whose situation are at increased risk and therefore prevention strategies are necessary and require specific priority attention.

This mapping of the problem is influenced by different interrelated factors framed in distal social level, close social environment such as school, work or community, the family and individual level.

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Etiology of obesity: two "key issues" and other emerging factors

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Abstract

The current obesity epidemic is known to have coincided with profound societal changes involving both physical activity levels and food consumption patterns as well as demographic and cultural changes affecting the conduct of human beings in various ways.

On the other hand, obesity is a complex and multifactorial chronic disease that usually becomes manifest in childhood and adolescence. Its origin is a genetic and environmental interchange, of which environmental or behavioral factors play the most important role, stemming from an imbalance between energy intake and expenditure. Still and all, it is rather simplistic to assume that obesity is only due to excessive consumption and/or deficient physical activity levels. Currently, various lines of investigation have been initiated that evaluate the determinants of obesity, of which nutrigenomics and gut microbiota deserve special attention.

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Key words: *Obesity. Dietary factors. Physical activity. Sedentary behaviors. Gut microbiota.*

ETIOLOGÍA DE LA OBESIDAD: LOS "DOS GRANDES" Y OTROS FACTORES EMERGENTES

Resumen

Se sabe que la epidemia actual de obesidad ha coincidido con un profundo cambio de hábitos de la población, tanto a nivel de actividad física como de patrones alimentarios y que los cambios demográficos y culturales han afectado el comportamiento de los seres humanos en múltiples vías.

Por otra parte, a obesidad es una enfermedad crónica, compleja y multifactorial, que suele iniciarse en la infancia y la adolescencia, y que tiene su origen en una interacción genética y ambiental, siendo más importante la parte ambiental o conductual, que se establece por un desequilibrio entre la ingesta y el gasto energético. Sin embargo, es muy simplista pensar que la obesidad sólo se debe a un consumo excesivo y/o a una actividad física deficiente. En la actualidad hay abiertas diversas vías de investigación en cuanto a los factores causantes de la obesidad, mereciendo especial atención dentro de los mismos la nutrigenómica y la microbiótica.

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Palabras clave: *Obesidad. Factores dietéticos. Actividad física. Comportamientos sedentarios. Microflora intestinal.*

Abbrevations

IOTF: International Obesity Task Force.
WHO: World Health Organization.
BMI: Body Mass Index.
WC: Waist Circumference.
PA: Physical Activity.

Introduction

Obesity is a chronic disease of multifactorial origin that involves genetic as well as environmental determinants. It's characterised by altered body composition having an increased adipose component. In the majority of cases, this augmented level of adipose tissue deposits is accompanied by greater body weight and an increased risk of comorbidities that affect the life expectancy and quality.

Evidence points out that a large percentage of obesity cases involve a clear environmental component linked to sedentary lifestyles and dietary habits that lead to positive energy balance and, as a result, the gradual accumulation of fatty tissue. As for current knowledge on the genetic factors implied in obesity, the principal problem is in the majority of cases it deals with a polygenic pathology. Moreover there is an incomplete understanding of its physiopathology which makes it complex to discern the role of distinct polymorphisms and their interaction with environmental factors.

When applying the analysis of body composition, cases of obesity are defined when percentages of adipose tissue are above 33% in women and over 25% in men. There is increasing emphasis on the distribu-

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tion of abdominal fat and its role in augmenting cardiovascular risk.

The International Obesity Task Force (IOTF) and the World Health Organization (WHO) have declared obesity as the epidemic of the 21st century due to the dimensions acquired within the last few decades, its impact on morbi-mortality, quality of life and related healthcare costs. WHO recognizes the impact obesity has on the development of the most prevalent chronic diseases in our society: type 2 diabetes, cardiovascular diseases, musculoskeletal pathologies and an increasing number of certain cancers.

Increased body volume also provokes the onset of disorders related to body image, self-esteem and social interactions. It generates important direct and indirect economic costs as well as significant increases in social and health services (medical visits, absenteeism, loss of autonomy, special needs, etc). Another obesity-related issue is that once established, it's associated with a large degree of therapeutic failures and the tendency towards relapse, thus making prevention a fundamental pillar in combating obesity.

As such, it is of vital importance to evaluate the current state of obesity determinants-physical activity (PA), dietary intake, environmental and sociocultural factors —so as to establish adequate platforms for its prevention.

Mortality associated with obesity

Diverse epidemiological studies describe a direct relationship between Body Mass Index (BMI) and mortality. The majority of evaluations have demonstrated a J shaped curve in this association. Most studies coincide in cases of increased mortality with BMIs of at least 30. These individuals show a 50% to 100% higher risk of all cause mortality. It's worth noting the result of MgGee's study conducted in 2005.[1] "The Diverse Populations Collaboration" is a meta-analysis of 26 studies conducted in diverse countries that evaluated the relationship between mortality for all causes, coronary disease, cardiovascular disease and cancer and persons with overweight and obesity as compared to normal weight individuals. The analysis included 388,622 subjects with a follow up period varying from 3 to 36 years, and the number of mortalities registered was 60,374. Table I shows the relative risk between obese subjects (BMI ≥ 30 kg/m^2) and normal weight persons (BMI 18,5-25 kg/m^2).

Recently Katherine M. Flegal, of the National Center for Health Statistics in Hyattsville and collaborators published a meta-analysis studying the relationship between obesity and mortality. 97 studies were retained for analysis, providing a combined sample size of more than 2.88 million individuals. They concluded that relative to normal weight, both obesity (all grades) and grades 2 and 3 obesity were associated with significantly higher all-cause mortality. Grade 1 obesity overall was not associated with higher mortality, and overweight was associated with significantly lower all-cause mortality. The use of predefined standard BMI groupings facilitated between-study comparisons.[2] However the methodology of this meta-analysis has raised considerable controversy in the scientific community due to identified errors dealing with the age of the populations included and in the time that passed between their inclusion in the cohort until accounting of mortality for previously existing causes of death, and as such, making it obligatory to interpret the results with caution. Nevertheless, it demonstrates that the role obesity plays in overall mortality is variable, and most likely to a considerable degree, from one country to another. Moreover variability is also secular with the passing of time within the same country, essentially for the same causes of obesity (diet and PA), which can vary from one part of the world to another as time elapses. Obesity's role can also be variable due to the weakness of using BMI as a predictor of mortality.

Tabla I

Relative risk of mortality for all causes and for diverse causes in obese versus normal weight individuals (McGee D and the Diverse Populations Collaboration)[1]

	Relative Risk of Mortality (Odds ratios and 95% confidence intervals)			
Cause of death	*All causes*	*Coronary disease*	*Cardiovascular disease*	*Cancer*
Obese women as compared to normal weight women	1.27 (1.18-1.37)	1.62 (1.45-1.80)	1.52 (1.38-1.69)	1.10 (1.00-1.21)
Obese men as compared to normal weight women	1.20 (1.19-1.28)	1.50 (1.36-1.67)	1.45 (1.32-1.59)	1.05 (0.97-1.13)

Factors associated with obesity

A series of sociodemographic and lifestyle factors have been related to excess body weight.

1. Sociodemographic factors

Age and gender

In almost all studies conducted in adults residing in Spain the prevalence of obesity is higher in the male subgroup and increases as age advances. These differences in distribution according to age and sex have also been documented in Spain by the ENRICA study,[3] the ENKID[4] and in the National Health Study. Weight indexes and obesity prevalence increase with age in both men and women, reaching a maximum at around 60 years of age.

Cultural level

In the majority of epidemiological studies on obesity, an inverse relationship has been observed between cultural level and obesity prevalence, so that at lower educational levels, the prevalence of obesity is more elevated. In children and adolescents, and according to the Enkid study, this was particularly important in girls and for the cultural level of the mother.

Socioeconomic level

The influence of socioeconomic factors is different in developing as compared to more economically advanced countries. In the latter case, generally speaking, obesity prevalence is greater in the most socioeconomically disadvantaged groups. Contrariwise in less developed countries this problem most frequently affects the most well-off socioeconomic groups, particularly those who have incorporated western lifestyles.

Geographic distribution

Geographic differences have been observed in obesity prevalence for distinct Spanish regions, with the highest rates seen in the Autonomous Communities located in the Southeastern part of the country, the Canary Islands as well as in the Northwestern region. Figure 1 shows data from the ENRICA study,[3] which illustrates the age-adjusted prevalence of obesity in general as well as central obesity by Autonomous Community. Figure 2 shows the Enkid study results with important gender and geographical differences.

2. Lifestyle related factors

Sedentary habits

Obesity is more frequent in sedentary persons as compared to those that regularly practice PA. It's been observed that individuals who dedicate more time to sedentary activities and don't regularly do sports more frequently have problems with excess body weight.

Diet

Greater risk of obesity has been estimated for persons having low fruit and vegetable consumption and a high fat intake, especially in saturated fatty acids. In certain countries, habitual alcohol consumption has

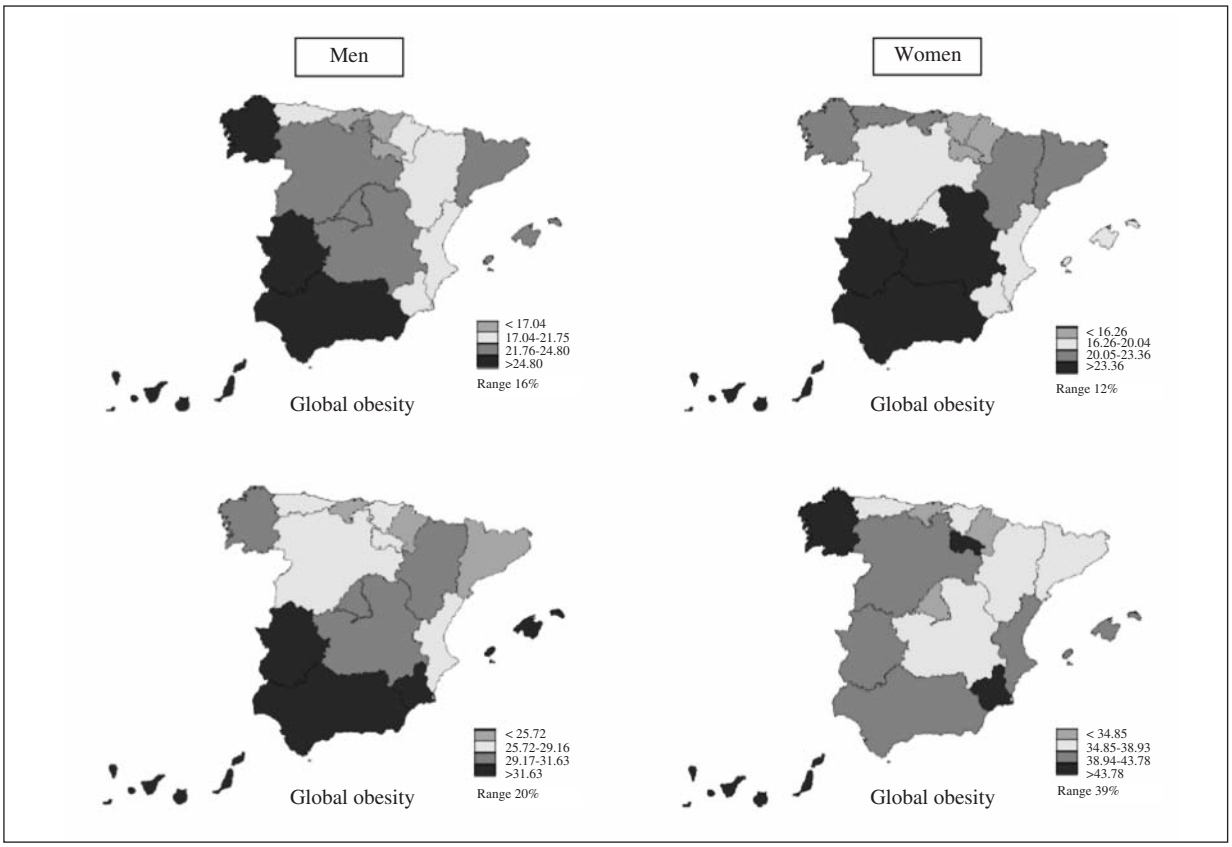

Fig. 1.—Age-adjusted prevalence of general and central obesity by Autonomous Community. ENRICA Study.[3] Source: Gutiérrez-Fisac et al, 2012.[3]

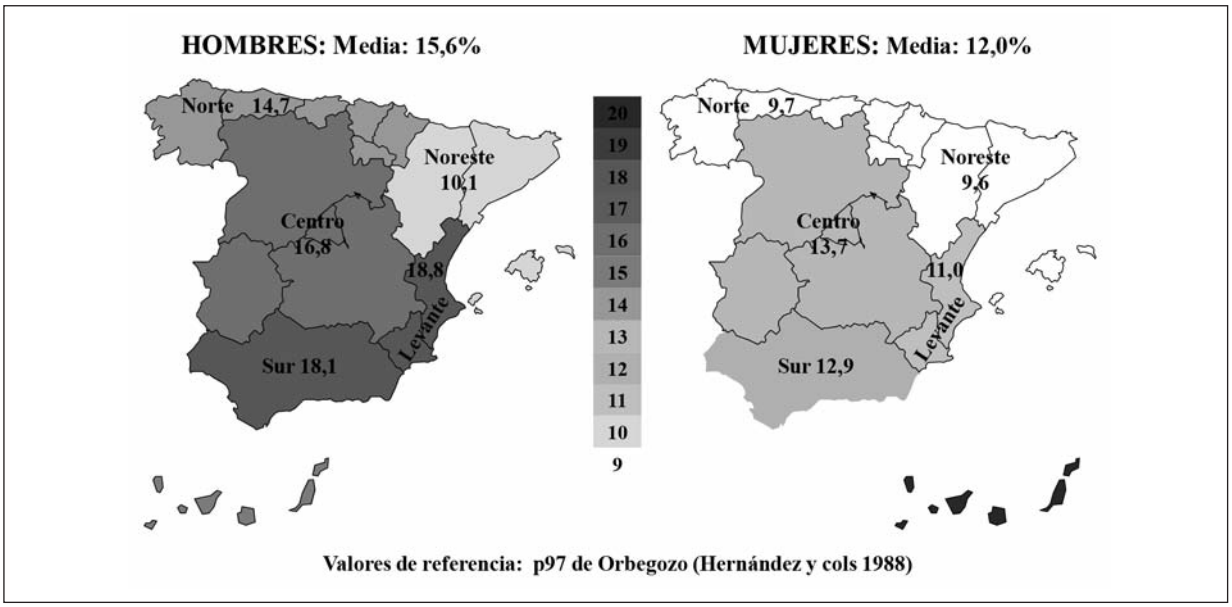

Fig. 2.—Prevalence of obesity in Spanish children and youth, by gender and geographical area. EnKid Study (1998-2000).[4] Source: Serra Majem et al, 2003.[4]

also been associated with excess weight, as well as sugared beverages.

Smoking cessation

Increased BMI has also been associated with persons who have quit smoking. The analysis of results from a subsample of the NHANES III Study demonstrated an average weight gain caused by smoking cessation of 4.4 kg in males and 5 kg in females who had stopped smoking within the last 10 years.[5]

Number of children (parity)

Women who had given birth to a greater number of children were more frequently obese. In general, women tend to increase their usual weight by a certain number of kilograms two years post partum as compared to nulliparous women of the same habitat and age group. En the DORICA study[6] this positive association between parity and excess body weight was also observed.

Etiology of childhood obesity

Multiple studies have shown that obesity in children and adolescents increases the risk of obesity in the future. Its onset in childhood and beyond is clearly predictive for being obese as an adult, even more than other factors such as birthweight and lifestyle variables, and being independent of whether or not parents are obese. Based on data from the EnKid study,[4] conducted in the Spanish population aged 2 to 24 years, the prevalence of obesity in Spanish children and youth (2-24 years old) was estimated to be 13.9%, applying the 97th percentile cutoff based on anthropometric tables published by Hernández et al. The prevalence of overweight and obesity combined (excess body weight) was 26.3% and 12.4% for only obesity. Obesity prevalence was higher in males (15.6%) than in females (12%) and the same trend was observed for overweight. Stratified by age, obesity was highest in the youngest age group (6-13 years old).

Lifecycle stages with increased risk for developing obesity

The prenatal period is one of the three critical moments in the development of childhood obesity in conjunction with the period of adiposity rebound and adolescence. Research analyzing the exposure to hunger during pregnancy or at an early age as well as children of diabetic mothers suggest that excessive or low nutrient intakes during the prenatal and perinatal period play a role in the appearance of obesity in other life stages. In a study conducted at the end of World War II in northern Holland, where food supplies were controlled by Germany from October 1944 to May 1945, the effect that hunger produced on infants born during this period could be observed. In children whose mothers suffered from hunger during the last trimester of pregnancy, at the age of 18 years obesity prevalence was lower. However, an increase in obesity rates were observed in children whose mothers had markedly low intakes during the first two trimesters of pregnancy. It therefore appears that it is in the last trimester of pregnancy and thus of fetal life, when adipocyte replication occurs and adipose tissue increases.

It has been shown that elevated birth weight increases the risk of obesity in later life and that low weight, head circumference and weight for length at birth, accompanied by rapid weight increases in the first years of life, predispose to adults developing more often certain diseases such as obesity, type 2 diabetes, hypertension, hyperlipidemias, metabolic syndrome, coronary disease and arteriosclerosis.

Children born to mothers who smoked during pregnancy and lactation have an increased risk of obesity and type 2 diabetes. The prevalence of obesity in children whose mothers are diabetic is significantly higher than children of the same age born to non or prediabetic mothers, independently of the mother being obese at the time of birth.

Moreover, evidence has also shown the importance of nutrition in the first year of life and its relationship to overweight and obesity in later years. Numerous cross-sectional and cohort studies have confirmed that breastfed children present with lower risk for both overweight and obesity.

A second period of time when obesity becomes manifest is around 5 to 7 years old, otherwise known as adiposity rebound. An inverse relationship exists between the age of adiposity rebound and the risk of increased BMI as well as for obesity occurring in childhood and adulthood. Rebound at an early age (< 5 years) significantly increases posterior obesity risk as compared to children who have adiposity rebound at a later age (> 6 years). Adiposity rebound increasingly occurring at earlier ages could be another factor to keep in mind in rising obesity prevalence.

On the other hand puberty is a period with a tendency towards obesity onset, particularly in females. In this type of pubertal obesity age of menarche is usually earlier than non obese adolescents. Some studies have shown that girls with early menarche (< 11 years) are twice as likely to become obese adults compared to those that mature at a later age (> 14 years). Moreover, females having earlier menarche appear to present with obesity in adolescence that tends to continue on through adulthood. As such, 70% of obese adolescent males normalize their body weight at a later stage as compared to only 20% in obese adolescent females.

Genetic and Family Factors

Family and genetic factors play an important role in the development of obesity. Through the mechanism of thrifty genes, humans have evolved developing the ability to deposit fat and thus utilize it during periods of energy deficit. This ability for depositing fat has possibly turned into a detriment for developed societies in which overabundance and easy access to foods are the norm.

It should always be kept in mind that a strong interaction exists between genetics and the environment. This is because susceptibility towards obesity is mainly determined by genetic factors, but the environment conditions genotype expression. Currently numerous obesity-related chromosomes have been discovered and research is focussing on locating the specific genes involved in the development of this disease.

On the other hand, the role that the family context plays in the development of childhood obesity has been recognized in numerous occasions as being a critical factor. Having one or both parents being overweight constitutes a determinant for developing childhood obesity, increasing the risk of their child becoming obese. This may be a result of genetic and environmental factors that can affect the development of obesity in childhood. For children aged 5 and under, the BMI of their parents is more representative than the children's' actual weights for predicting the development of obesity in the future. Moreover, data obtained from the Framingham study suggest that in reference to childhood obesity, this is not only associated to parental restrictive dieting but also to their uninhibited eating behavior. As such, restrictive and uninhibited parental dietary habits constitute two potentially modifiable factors that may greatly influence the early eating experiences of their offspring.

Nutritional factors[7]

Calorie intake

Diverse studies have evaluated whether obese children had higher calorie intakes than non-obese counterparts. In a review conducted by the authors of the present paper, contradictory results were obtained.[7] Therefore, it remains unclear as to whether obese children consume more calories than non-obese children, making it necessary for further research on this topic. Such studies should analyze the caloric density of the diet in relation to childhood obesity, taking into account important confounding factors of which PA, stage of maturity, basal metabolic rate and parental obesity stand out. Duration of meals has also an impact on caloric intake.

Macronutrient composition

Studies have investigated the possible association between the proportion of energy provided by macronutrients in the diet (proteins, fats and carbohydrates) and the presence of childhood obesity. Only two studies analyzing protein intake and obesity were identified and as such no significant conclusions could be made. With respect to fats and carbohydrates, some studies didn't find any association with greater or lesser intakes and childhood obesity, including its development over time. However, after reviewing published studies, it was observed that a large percentage of them had found that in general, obese as compared to non-obese children consumed a higher percentage of energy coming from fats, and in some cases at the expense of a reduced percentage from carbohydrate intake. Studies that eva-

luated changes in fat consumption and their relationship to changes in BMI in children concluded that an increase in the percentage of fat intake was associated with higher BMIs.

Analyzing the possible reasons that could explain the role of greater fat consumption on the development of childhood obesity, it is worth noting that proportions of fats and carbohydrates in the diet tend to be inversely related. As such, decreasing fat in the diet is usually accompanied by an increase in carbohydrate intake and vice versa. On the other hand, diets high in carbohydrates with low to moderate fat content tend to be low in calories. Moreover, numerous studies have shown that fats have a powerful capacity to destabilize control mechanisms for body weight due to their high energy density. Compared to proteins and carbohydrates, fats provide a greater amount of energy per gram. However, fats are easily stored; in conditions of excess calories, fats are store stored at an energy cost of 3%, in contrast to 28% for carbohydrates and 24% for proteins. Fats are also highly palatable and don't appear to possess homeostatic auto regulation that controls the consumption and oxidation of these substances. Furthermore, the satiating effect is relatively small (in reference to proteins and carbohydrates) compared to the quantity ingested. All the aforementioned reasons could help to explain the possible function fats have in the development of childhood obesity.

Calorie distribution throughout the day

One of the most frequent alterations in the dietary habits of adolescents consists of irregular eating patterns. The studies reviewed that analyzed this variable seem to indicate that childhood obesity is associated with a lower frequency of breakfast consumption. Obese children and adolescents have less desirable breakfast habits than non-obese counterparts. This leads to the question of whether breakfast has bearing on the adequacy of the total diet. Does the possibility exist that an inadequate breakfast contributes to making further inadequate (nutritionally speaking) choices the rest of the day, and in the long term, to increasing obesity risk? Information is scarce on the role of dinner and of its omission on excess body weight.

Physical activity[7]

A variety of studies conducted in children and youth show that PA is inversely related to excess body weight. Sedentary activities such as watching television, videos or playing videogames, etc are conducive to becoming overweight. However, other authors after adjusting for basal expenditure, conclude that obese children expend more energy during PA than non obese children, and some studies show distinct results when stratifying by gender.

As such, in boys a greater level of PA corresponds with higher levels of BMI, whereas in girls, PA is inversely related with body fat. Other studies failed to find associations between anthropometric measurements and PA, after adjusting for lean muscle mass. With respect to longitudinal studies evaluating PA and childhood obesity, some authors concluded that PA did not predict the onset of obesity over time, whereas other associated increased PA in obese children with a greater reduction in BMI.

After reviewing studies addressing this issue, it's possible to suggest that PA plays an important role in maintaining normal weight in children and adolescents and that physical inactivity contributes to maintaining obesity. It's well known that PA in these age groups has decreased in the recent past and that perhaps part of this decline is attributable to fewer chances for realizing physical exercise in daily activities, such as walking to school (due to the use of school transport services) and due to increased television viewing, which has displaced PA in youth. In this respect, it seems that watching television implies not only reducing time available for PA but also increasing calorie intake, as it's frequently accompanied by consuming calorie dense nutrient poor foods. Such consumption is sometimes induced by the large quantity of announcements featuring these types of foods that are shown when children's programmes are emitted. Increasing the opportunity to spontaneously play games may be one of the requirements for children to increase their levels of PA. In this way reducing the time that children dedicate to watching television offers the opportunity for spending more time on PA as well as diminishing the response to food advertisements.

Sleeping patterns

Recent epidemiological studies suggest that short sleep duration may be associated with the development of obesity from childhood to adulthood, and that sleep duration was also inversely associated with BMI and waist circumference (WC) after being controlled for potentially confounding variables.[8] Intervention programs aiming for improving sleeping habits among childhood and adolescents need to consider such potential association of lifestyle variables with sleep duration.

Factors associated with the etiology of obesity in adults

It's common knowledge that the current obesity epidemic has coincided with profound societal changes affecting PA levels as well as dietary habits, and that demographic and cultural changes have affected human conduct in a variety of ways. Moreover, obesity is a complex and multifactorial chronic disease whose onset usually occurs during childhood or adolescence. Its origin is an interaction between genetics and environ-

ment, of which the latter (environmental or behavioral factors) predominates as conduct is what establishes the imbalance between intake and energy expenditure. However it would be very simplistic to think that obesity is only due to excess consumption and/or inadequate PA. Currently, various lines of investigation evaluate emerging determinants of obesity, of which nutrigenomics and gut microbiota deserve special attention.

Dietary factors associated with the prevention of obesity

Dietary habits comprise an essential determinant for health, although their exact contribution in health promotion and disease prevention is difficult to quantify. In the last few decades there has been a significant increase in the amount of scientific evidence that supports a series of associations between diverse dietary factors and chronic diseases, particularly cardiovascular disease, cancer, diabetes, obesity and osteoporosis.

On the other hand, few human rights have been violated so frequently and to such a scale as those that address the right to food and nutrition. According to FAO (Food and Agricultural Organization of the United Nations) estimate, approximately 923 million people worldwide don't have access to sufficient quantities of adequate foods so as to meet their basic nutrition requirements, and this constitutes an unacceptable assault against basic human rights.

The nutrition transition phenomenon also stands out, which occurs in less developed countries and requires them to deal with deficiency diseases in conjunction with the onset of chronic diseases such as obesity, resulting from the rapid incorporation of western dietary habits, among other factors. In general we can state that humans have inadequate dietary habits for three reasons: because they don't know how to, they can't achieve it or they don't want to. Confronting these three obstacles requires different actions:

— *Don't know how*: Nutrition education to provide the right information at the right time
— *Can't do it*: Facilitate economic access, geographic and seasonal availability, eliminating barriers in terms of price, distance or climate. It won't be possible to eliminate certain cultural barriers (religious, etc.)
— *Don't want to*: Health education with the focus of achieving behavior modification, strengthening it, keeping in mind pre-existing motivations, attitudes, influences and beliefs of the population. Resorting to food enrichment and/or nutrient supplementation is an option.

Food and nutrition in the etiopathogenesis of diseases

The evidence associating diet with the onset of given diseases has exponentially increased over the last decade. Although findings have at times been contradictory, improved knowledge of the physiopathology of given diseases along with better designed epidemiological studies have facilitated increasing knowledge of a relationship that is still wrought with gaps in its understanding. Apart from obesity, pathologies with the strongest evidence for diet related factors are: cardiovascular disease, cancer, type 2 diabetes mellitus, osteoporosis, dental caries, anemia deficiencies, immunological disorders, cataracts, neural tube defects and Cognitive decline.

Mediterranean diet and health[9]

The Mediterranean diet is perhaps the healthiest food model in the world, which has been corroborated by numerous nutrition epidemiological and experimental studies which demonstrate that Mediterranean countries have lower morbidity rates for chronic diseases and longer life expectancy.

The traditional Mediterranean diet is characterized by an abundance of plant food such as bread, pasta, vegetables, legumes, fruits and nuts; the use of olive oil as the main source of fat; moderate consumption of fish, seafood, poultry, dairy products and eggs; consumption in small quantities of red meat and; consumption of wine and champagne (cava) usually accompanying meals.

In the last few years scientific evidence has been accumulating regarding the health benefits of the Mediterranean diet. Currently in Spain, two key projects are being conducted. One is the SUN Project[10-12] (Seguimiento Universidad Navarra), a cohort study conducted by the University of Navarra (initiated in 1999 and with a current total of more than 20,000 participants) and the second is the intervention study Predimed (Prevention with the Mediterranean diet).[13-15] Both studies will continue to provide conclusive data on the benefits of this diet which has already demonstrated favorable effects on cardiovascular morbidity, cognitive decline, certain cancers and obesity prevention, among others.

Diet and obesity

Recently the scientific associations, FESNAD (Spanish Federation of Nutrition, Food and Dietetic Associations) and SEEDO (Spanish Association for the Study of Obesity), have published a Consensus Document, about the role of the diet in the prevention of overweight and obesity in adults[16].

The conclusions obtained were classified according to several evidence levels. Subsequently, in agreement with these evidence levels, different degrees of recommendations were established. These recommendations could be potentially useful to design food guides as part of strategies to prevent overweight and obesity. The major weakness of the Document was that most of the evidence was set from studies not conducted in Spain.

The main conclusions and recommendations of the study were:

Dietary factors associated with a lower BMI:

— Diets with higher content of complex carbohydrates (approximately ≥ 50% of the total energy intake) are associated to a lower BMI in healthy adults.
— A high dietary fibre intake in the context of a diet rich in food of vegetable origin is associated to a better control of body weight in healthy adults.
— A high intake of fruit and vegetables is associated with a lower long-term body weight increase in adults.
— A high intake of whole grains is associated with a lower BMI.
— Even though inconsistent results exist, the studies so far performed suggest a possible role of the "Mediterranean" diet in the prevention of overweight and obesity.
— The existing evidence suggests that greater adherence to the "Mediterranean" diet might prevent increases in WC .
— Vegetarian diets are associated, in healthy adults, to a lower BMI.

Dietary factors associated with a higher BMI:

— Dietary patterns of high energy density may lead to body weight increase in adults.
— Some evidence suggests a certain level of association between high ethanol intake and weight gain.
— Frequent intake of sugared beverages is associated with a higher BMI - A high intake of meat and processed meat products might increase weight gain and WC.
— Offering larger portions conditions an increase of the individual's caloric intake.
— The absence of supermarkets with fruit and vegetable availability, or their location at greater distances —in particular from neighborhoods with low socioeconomic levels— are conditioning factors for a higher population mean BMI.
— The habitual intake of "fast food" (over once a week) might contribute to increased energy intake and to weight gain and obesity.

Dietary factors not associated with BMI:

— Fat intake, after adjusting for total energy intake, is not associated to weight gain in healthy adults.
— The intake of olive oil does not seem to be associated with significant body weight gain risk in healthy adults.
— The addition of nuts to the usual diet is not associated with body weight gain.

Moreover, Mozzafarian et al, in 2011,[17] performed prospective investigations involving three separate cohorts that included 120,877 U.S. women and men, who were free of chronic diseases and not obese at baseline, with follow-up periods from 1986 to 2006, 1991 to 2003, and 1986 to 2006.The relationships between changes in lifestyle factors and weight change were evaluated at 4-year intervals, with multivariable adjustments made for age, baseline BMI for each period, and all lifestyle factors simultaneously.

Within each 4-year period, participants gained an average of 3.35 lb (5th to 95th percentile, −4.1 to 12.4). On the basis of increased daily servings of individual dietary components, 4-year weight change was most strongly associated with the intake of potato chips (1.69 lb), potatoes (1.28 lb), sugar-sweetened beverages (1.00 lb), unprocessed red meats (0.95 lb), and processed meats (0.93 lb) and was inversely associated with the intake of vegetables (−0.22 lb), whole grains (−0.37 lb), fruits (−0.49 lb), nuts (−0.57 lb), and yogurt (−0.82 lb).

Other lifestyle factors were also independently associated with weight change ($P < 0.001$), including PA (−1.76 lb across quintiles); alcohol use (0.41 lb per drink per day), smoking (new quitters, 5.17 lb; former smokers, 0.14 lb), sleep (more weight gain with < 6 or > 8 hours of sleep), and television watching (0.31 lb per hour per day). Non similar studies have been published in Spain and other European countries.

Based on the previous studies, it can be deduced that a need exists to identify those foods whose consumption significantly contributes to the onset of obesity in each country, given that calories obtained from the diet have different distributions according to the food habits of each region. Such information is critical for more effectively targeting and implementing effective prevention policies.

Physical activity and prevention of obesity

In order to understand the importance of PA in the onset and/or prevention of obesity, the relationship between intake, energy expenditure and body fat deposit. Following this, the association between the deficit of PA and illness will be analyzed and then the prevalence of sedentary lifestyles and different means of promoting PA at the individual and population level will be presented.

Interrelationships between energy intake, energy expenditure and body fat stores

Obesity is the result of a small and prolonged state of positive energy balance, where total energy intake exceeds total energy expenditure. As Hill pointed out in 2012,[18] understanding the interrelationship between energy intake, energy expenditure and body fat stores

can help us to develop strategies that lead to reducing obesity. The objective of obesity treatment is to reverse this balance and the goal of obesity prevention is to ensure that this balance doesn't become positive.

The messages aimed at the population shouldn't be divided into messages about the importance of eating well in order to prevent obesity and separate messages about the importance of doing PA for the same purpose. Both should go together, as both are components of the same equation, whose result is the deposition of body fat when the equation is positive, loss of body fat when it's negative and maintenance of fat stores when they are balanced. In fact, when referring to weight control, Hill claims that our body functions in a different way when a high level of PA is realized than when at lower levels. The figure 3 illustrates this point.

The idea that energy balance is best regulated at high (but not excessive) levels of have been initiated that PA was first proposed by Mayer and colleagues in the 1950s.[19] They observed that energy intake was better matched to energy expenditure when people were physically active. A healthy body weight is maintained with a high level of PA and a high energy intake. This would be the well-regulated zone in which energy intake and energy expenditure are very sensitive to changes in the other. At low levels of PA, substantial food restriction is needed to maintain a healthy body weight. This would be the unregulated zone in which energy intake and expenditure are only weakly sensitive to changes in each other.

The decline in daily activity that came from industrialization, mechanized transportation, urbanization, and other aspects of technology created the largest decline in activity and created the right conditions under which an increase in food access, availability, and decreased cost could have a major impact on body weight. In effect, the decline in the daily energy expenditure necessary for subsistence prevalent over a century ago was the "permissive" factor that allowed the effect of the changing food environment to become apparent. Furthermore, as PA levels declined, body weight increased, which would have increased total energy expenditure as a result of increases in RMR (resting metabolic rate) and the energy cost of movement. It is not surprising that total energy expenditure has not changed because becoming obese is a way to increase energy expenditure in a sedentary population.

From an energy balance point of view, we are likely to be more successful in preventing excessive weight gain than in treating obesity. The reason is that the energy balance system shows stronger opposition to weight loss than to weight gain. Although large behavior changes are needed to produce and maintain reductions in body weight, small behavior changes may be sufficient to prevent excessive weight gain.

The concept of energy balance combined with an understanding of how the body achieves balance may be a useful framework for developing strategies to reduce obesity rates.

Prevalence of physical activity and sedentary habits

The population increasingly adopts sedentary lifestyles, which of late have been caused by progressive urbanization, the type of urban planning and transport that determine city living as well as new technologies, passive recreation, new work styles, etc. In addition, over the last 40 years, numerous epidemiological studies have demonstrated that being physically inactive leads to important negative health effects.

On a positive note, the promotion of PA provides a great opportunity for obesity prevention. According to WHO, every year at least 1.9 million people die as a result of physical inactivity. In contrast 30 minutes of regular PA 5 days a week reduces the risk of various

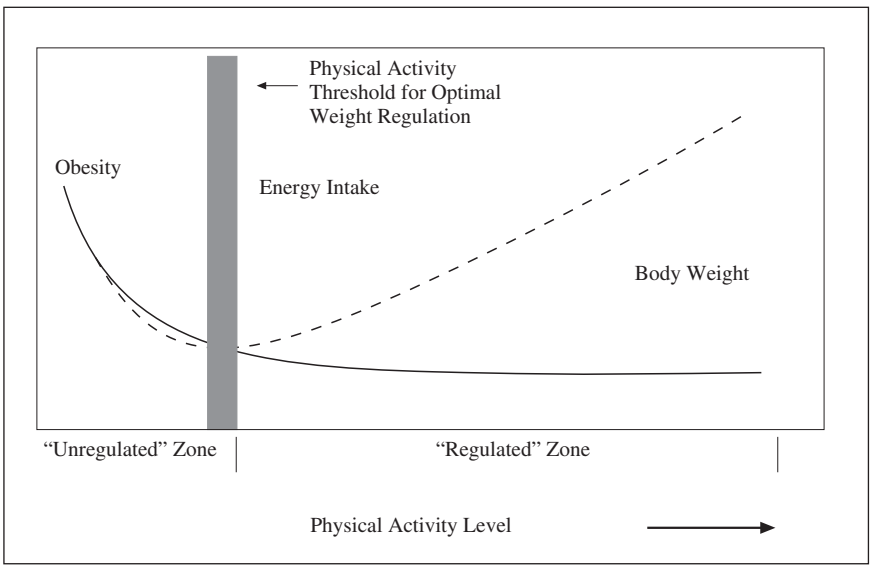

Fig. 3.—Illustration of the hypothesis that energy balance may be easier to achieve at high energy throughput (ie, high energy expenditure). Shown is the concept of a threshold for PA above which people are in the regulated zone of energy balance and below which they are in the unregulated zone. In the regulated zone, energy intake is pulled along to meet high energy needs, and energy intake and expenditure are very sensitive to changes in each other. At low energy throughput, energy intake and expenditure are only weakly sensitive to changes in each other, and maintaining a healthy body weight requires sustained food restriction. Developed based on Mayer et al[19]. Source: Hill JO et al[18].

chronic diseases, making PA a modifiable risk factor for the most common non infectious diseases.

In relation to carrying out PA, it's been observed that although PA in leisure time has remained stable in the last 50 years, technological advances have led to a reduction in energy utilized in household chores, at the worksite and in transport. Moreover, sedentary conduct such as watching television has drastically increased, which translates into an overall decrease in PA. Various sociodemographic groups are especially inclined to being physically inactive, including women, adults from low socioeconomic levels as well as the elderly, people with financial problems and those living alone.

— In *Europe* the Eurobarometer survey conducted in 2009 showed a situation of sedentary lifestyles. The majority of Europeans (60%), don't do any sports (39%) or only rarely do so (21%). As seen in figure 4, Spain has a high ranking of sedentarism as 42% of Spanish citizens never do any kind of sport.

— In *Spain*, the National Health Survey of 2006 showed that 59.6% of the sample exercised in their free time, with a higher percentage in men than in women (63.1% vs 56.3%, respectively).

Relationship between physical activity and health

Analytical epidemiological studies have been increasing the evidence base not only for the protective effect of PA against diverse pathologies, but also that being physically fit reduces the risk of all-cause mortality, independently of the presence of other risk factors and also considerably improves quality of life. In addition, even when increases in the level of PA are only

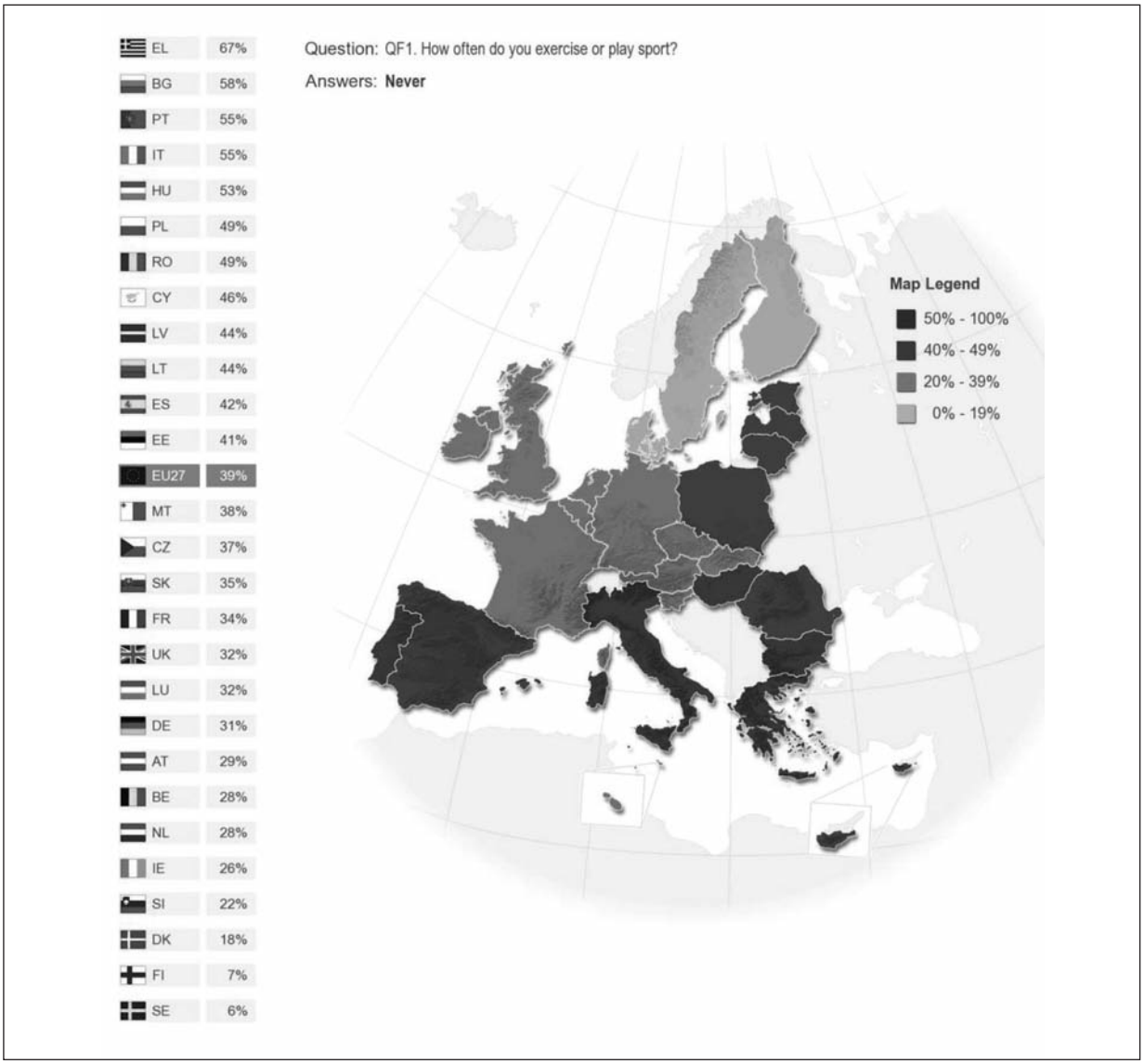

Fig. 4.—Percentage of population that never exercises or play sports in European Union countries. Eurobarometer 2009.

moderate, they confer significant health benefits. Moreover, there is large sector of the population that can benefit from this possibility and thus, considerably increases the potential impact of interventions.

Apart from all-cause mortality and obesity, the main pathologies and processes in which preventive potential exists for adopting a more physically active lifestyle are: Hypertension, Type 2 diabetes mellitus, musculoskeletal diseases, mental health disorders and ischemic heart disease. Although less solid, evidence also exists for a protective effect against the incidence of certain cancers and gallstones.[20-24]

The WHO has designed a global strategy on nutrition, PA and health, which was adopted by the 57th World Health Assembly on 22 May 2004.

In Spain, in order to combat childhood obesity the NAOS (Strategy for Nutrition, Physical Activity and Obesity Prevention) Strategy was established. Apart from striving to improve dietary habits, it also aims to foment the practice of PA, especially during childhood.[25,26] Different Autonomous Communities in Spain have also initiated plans and strategies for fighting against obesity, which include the promotion of PA and healthy eating habits such as the PASEA programme in Galicia, DELTA in the Canary Islands or PAAS in Catalonia.

Gut microbiota and the development of obesity

The human gut harbors a highly diverse microbial ecosystem of approximately 400 different species, which is characterized by high interindividual variability. The intestinal microbiota has recently been suggested to contribute to the development of obesity and the metabolic syndrome. Transplantation of gut microbiota from obese mice to nonobese, germ-free mice resulted in transfer of metabolic syndrome-associated features from the donor to the recipient. Proposed mechanisms for the role of gut microbiota include the provision of additional energy by the conversion of dietary fibre to short-chain fatty acids, effects on gut-hormone production, and increased intestinal permeability causing elevated systemic levels of lipopolysaccharides (LPS). This metabolic endotoxemia is suggested to contribute to low-grade inflammation, a characteristic trait of obesity and the metabolic syndrome. Finally, activation of the endocannabinoid system by LPS and/or high-fat diets is discussed as another causal factor. In conclusion, there is ample evidence for a role of gut microbiota in the development of obesity in rodents. However, the magnitude of its contribution to human obesity is still unknown.[27]

A recently published review has shown that the fact that gut microbiota can be modulated through dietary components highlights the importance of studying how fatty acids, carbohydrates, micronutrients, prebiotics, and probiotics can influence gut microbiota composition and the management of obesity. It is also crucial to study the effect of dietary patterns such as the Mediterranean Diet. Gut microbiota seems to be an important and promising target in the prevention and treatment of obesity and its related metabolic disturbances in future studies and in clinical practice.[28]

Final considerations

Obesity is currently a global public health problem. Obesity in early life increases the risk of long-term energy imbalance, adult obesity and its comorbidities-type 2 diabetes and cardiovascular disease. Since infancy and childhood are critical periods for the adoption of food preferences and PA , prevention strategies must intervene in these early periods to promote healthy habits and reduce risk behaviors.[29,30]

We are witnessing a series of unprecedented scientific, environmental and behavioral changes in the human species, which have brought us many new, and until now unknown, issues that impact upon our health. The obesity epidemic constitutes one of them. Only a global and wide-ranging vision of factors involved in this epidemic will provide us with the necessary tools to introduce adequate and effective preventive measures. Such a vision should address: the idiosyncrasy of distinct populations, their past and present dietary habits, their capacities and attitudes towards PA, their knowledge of nutrition, the interaction between genetics and environment, and a profound knowledge of factors associated with weight gain. Finally, it is essential that interventions include a community based approach combined with a high risk group strategy.

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Genetic susceptibility to obesity and metabolic syndrome in childhood

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Abstract

Obesity is one of the major public health problems worldwide. It is a chronic, complex, and multifactorial-origin disease characterised by body fat excess mainly due to an imbalance between dietary intake and energy expenditure. One of the major complications of obesity is metabolic syndrome, which comprises anthropometrical, clinical, and metabolic dysfunctions that predispose the affected individual to the development of type 2 diabetes mellitus and cardiovascular diseases. It is hypothesised that the variability in the susceptibility to obesity-mediated metabolic complications involves both environmental and genetic factors. Whereas advances in the knowledge of the variations in the human genome have led to the identification of susceptibility genes that contribute to obesity and related disorders, relatively few studies have specifically focused on the interactions between obesity and genetic polymorphisms and the development of metabolic complications. Despite these limited efforts, an increasing amount of evidence suggests that the effects of some gene variants on metabolic traits are modified by or present only in the setting of obesity. Furthermore, some of these loci may have larger effects on metabolic phenotypes in the presence of certain dietary or lifestyle factors. In the present manuscript, we reviewed the genes and their variants that have been evidenced to play a role in obesity-associated metabolic complications through genetic association studies, including candidate gene and genome-wide association approaches in adults and children.

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Key words: *Genes. Gene variants. Metabolic syndrome. Obesity. Single-nucleotide polymorphisms.*

SUSCEPTIBILIDAD GENÉTICA DE OBESIDAD Y SÍNDROME METABÓLICO EN LA INFANCIA

Resumen

La obesidad es uno de los principales problemas de salud pública a nivel mundial. Es una enfermedad crónica, compleja y de origen multifactorial que se caracteriza por el exceso de grasa corporal y se desarrolla, fundamentalmente, debido a un desequilibrio entre la ingesta dietética y el gasto energético. Una de las principales complicaciones de la obesidad es el síndrome metabólico, el cual comprende alteraciones antropométricas, clínicas y metabólicas que predisponen el desarrollo de diabetes *mellitus* tipo 2 y enfermedades cardiovasculares.Existe la hipótesis de que tanto factores ambientales como genéticos participan en la variabilidad a la susceptibilidad de las complicaciones metabólicas mediadas por la obesidad. Mientras que los avances en el conocimiento de las variaciones en el genoma humano, han llevado a la identificación de genes que contribuyen a la susceptibilidad de la obesidad y las enfermedades asociadas, son relativamente pocos los estudios que se han centrado específicamente en la interacción entre la obesidad y polimorfismos genéticos relacionados con el desarrollo de complicaciones metabólicas o directamente con el síndrome metabólico. Además, algunos de estos *loci* pueden tener mayor efecto en los fenotipos metabólicos cuando está modificado por la dieta u otrosfactores ambientales. En este manuscrito se revisan los genes ylas variantes con mayor evidencia de asociación con las complicaciones metabólicasrelacionadas con la obesidad descritas en estudios de asociación genética, incluyendo estudios de genes candidatos y estudios amplios del genoma humano en adultos y niños.

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Palabras clave: *Genes. Obesidad. Polimorfismos de nucleótido simple. Síndrome metabólico. Variantes génicas.*

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Abbreviations

BMI: body mass index.
CVD: cardiovascular disease.
T2DM: type 2 diabetes mellitus.
HDL-c: high-density lipoprotein-cholesterol.
IR: insulin resistance.
MetS: metabolic syndrome.
TAG: triacylglycerol.
VLDL: very-low-density lipoprotein.
GWAS: genome-wide association studies.
BP: blood pressure.
OR: odds ratio.
SNP: single nucleotide polymorphisms.
PPARG: peroxisome proliferator-activated receptor gamma.
TNF-α: tumour necrosis factor alpha.1

Introduction

Obesity, in addition to overweight, is the sixth major cause of disease risk worldwide. It has been estimated that 1 billion adults are currently overweight, and an additional 475 million adults are obese. It has also been estimated that 200 million school-aged children are either overweight or obese worldwide and that 40-50 million of these children are classified as obese.[1] The obesity epidemic, which mainly affected developed countries at the beginning, has extended to developing countries, particularly their urban areas. Childhood obesity has lead to an increase in morbidity and mortality, which in turn result in high financial burdens for health systems.

Childhood obesity is a condition in which excess body fat negatively affects the child's health and/or wellbeing. This disease has been associated with several comorbidities, such as cardiovascular events, hypertension, insulin resistance (IR), dyslipidaemia, metabolic syndrome (MetS), liver steatosis, orthopaedic problems, and sleep apnoea, which can occur in either the short or long term. Different studies have shown an association between childhood obesity and the risk of cardiovascular diseases (CVD) in adulthood,[2] the early development of atherosclerosis, changes in the BMI over time, and the prediction of lipid and lipoprotein concentrations.[3]

Of all of the complications of obesity, a cluster of anthropometric, clinical, and metabolic alterations (low levels of high-density lipoprotein-cholesterol (HDL-c), high triacylglycerols (TAG), high blood pressure (BP), and impaired glucose metabolism) form part of MetS, which predisposes the affected individuals to the development of type 2 diabetes mellitus (T2DM) and CVD.[4]

The mechanisms linking obesity to its metabolic complications are extremely complex and remain hotly debated. It is hypothesised that the variability in the susceptibility to obesity-mediated metabolic complications involves both environmental and genetic factors. Whereas advances in knowledge of the variations in the human genome have led to the identification of susceptibility genes that contribute to obesity and related disorders, relatively few studies have specifically focused on the interactions between obesity and genetic polymorphisms in the development of metabolic complications. Despite these limited efforts, an increasing amount of evidence, particularly related to adipokines and adipose tissue, suggests that the effects of some gene variants on metabolic traits are modified by or present only in the setting of obesity. Furthermore, some of these loci may have larger effects on metabolic phenotypes in the presence of certain dietary or lifestyle factors. In this chapter, we review the small number of genes and their variants that have been evidenced to have a role in obesity-associated metabolic complications.

Definition and prevalence of metabolic syndrome

The MetS diagnosis criteria are very well defined in the adult population (table I).[5] However, despite many attempts, no consensus has yet been reached for the diagnosis of MetS in children and adolescents.[6,7] Many authors, such as those cited in the study by Olza et al[6], have proposed different classifications, but methodological and physiological limitations have complicated the establishment of a definitive definition.[7] The main difficulties in the definition of the criteria are the following:

1. The measure of the adiposity excess with different parameters (body mass index [BMI] or waist circumference).

Table I
The International Diabetes Federation metabolic syndrome definition for adults

For a person to be defined as having metabolic syndrome, they must have central obesity (defined through the waist circumference* with ethnicity specific values) plus any two of the following four factors:

Increased triglycerides	≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
Reduced HDL-c	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
Increased blood pressure	systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
Increased fasting plasma glucose	FPG ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define the presence of the syndrome.

*If the BMI is greater than 30 kg/m², central obesity can be assumed and the waist circumference does not need to be measured. HDL-c, high-density lipoprotein-cholesterol; BP, blood pressure; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; BMI, body mass index. Adapted from ref. 5. For ethnicity-specific waist circumference values, see this reference.

2. The extrapolation of the cut-off values from the adult population.
3. The lack of ethnicity- and sex-specific charts with separate cut-off values for the prepubertal and the pubertal populations.
4. The physiological pubertal changes that temporarily modify the plasma hormones levels have not been taken into account.
5. The measurement of the glucose metabolism dysfunction with a fasting plasma glucose test or an oral glucose tolerance test instead of IR, e.g., homeostatic model of insulin resistance (HOMA-IR).
6. Factors such as physical activity or environmental conditions that have not been taken into account.
7. The lack of inclusion of other biomarkers (e.g., proinflammatory and/or prothrombotic factors) that might contribute to the identification of the syndrome, particularly at the early onset.

Due to the abovementioned problems, it is very difficult to epidemiologically monitor MetS. The prevalence rates depend on the definition used for its classification, but, given that MetS is driven by obesity, the prevalence of the latter will strongly influence the prevalence of MetS[8]. Recently, our group showed that the percentage of MetS in Spanish prepubertal obese children varies from 7.6% to 30.8% in the same population depending on the definition used.[7] In a recent systematic review conducted by Friend et al[9], the prevalence of MetS in a paediatric population was studied (including 85 studies) using the three most used definitions (International Diabetes Federation, National Cholesterol Education Program's Adult Treatment Panel III and World Health Organisation). The results of the review showed that the median prevalence of MetS was 3.3% (range of 0% to 19.2%) in the whole population, 11.9% (range of 2.8% to 29.3%) in the overweight population, and 29.2% (range of 10.0% to 66.0%) in the obese population. These data reinforce the necessity of unifying criteria and establishing a unique definition that encompasses all of the variables involved in the development of the syndrome. In the search of a methodology to overcome this barrier, one promising approach has been the use of the measurements of the MetS components as continuous variables to obtain a sum of the z-scores of each component that can be used to quantify the risk[7]. It has been shown that the use of this cluster would better identify the at-risk paediatric population compared with the use of the most common five components in the definition of this syndrome.

Origin of metabolic syndrome

The aetiology of MetS is not completely clear; however, the evidence indicates that IR, inflammation, and obesity are the three factors that converge to cause all of the metabolic changes that intervene in the development of MetS (fig. 1). Nevertheless, other factors, such as the environment, diet, physical inactivity, genetic predisposition, age, ethnicity, and some drugs, are involved in the development of the syndrome.

Individuals with IR increase their insulin production to force glucose into the peripheral tissues. In fact, each tissue exhibits differential insulin sensitivity, but the liver appears to be where the disorder starts. The increase in the free fatty acid (FFA) flux within the liver, either by *de novo* lipogenesis or by FFA delivery via the portal vein, impairs the hepatic insulin action, which leads to an increase in the hepatic glucose output, the synthesis of proinflammatory cytokines, the TAG syn-

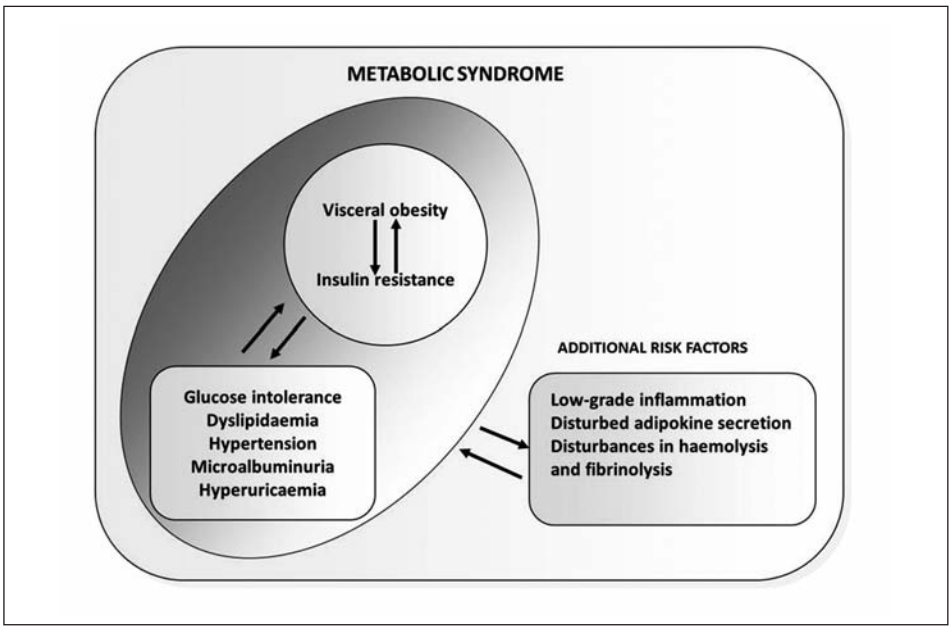

Fig. 1.—Metabolic disorders and inflammation in the metabolic syndrome.

thesis, the intrahepatic lipid deposition, and the ectopic lipid accumulation.[4] The excess TAG is released with apolipoprotein B as VLDL, the HDL-c secretion diminishes, and the number of relatively cholesterol-depleted small dense low-density lipoprotein particles increase. These changes in the lipoprotein metabolism are considered the primary cause for MetS dyslipidemia.[10]

IR in the adipose tissue is also important in the development of MS. The expanded adipose tissue increases lipolysis and releases FFA due to a reduced antilipolytic effect and the loss of inhibition of the hormone-sensitive lipase. The FFAs drain to the liver via the portal vein and increase the hepatic FFA accumulation to create a vicious circle between the liver and the adipose tissue. The changes in the expanding adipose tissue promote the transition to a metabolically dysfunctional phenotype. Whereas the macrophages in lean adipose tissue express markers of M2, the macrophages in obese tissue lead to the recruitment and accumulation of M1 and T cells, which indicates the infiltration of the tissue and the formation of crown-like structures and results in the accumulation of macrophages around dead adipocytes in inflamed adipose tissue.[11] The metabolic dysfunction also stimulates the production of large amounts of pro-inflammatory factors and cytokines as interleukins, leptin, tumour necrosis factor alpha (TNF-α), resistin and plasminogen activator inhibitor-1, that have effects in other tissues such as liver or skeletal muscle but also acts in a paracrine way.[7,11]

The skeletal muscle is an important contributor to the glucose homeostasis, and the liver IR contributes to the disruption of the glucose-fatty acid cycle and the insulin-mediated glucose uptake by skeletal muscle, which facilitates the development of hyperglycaemia. The accumulation of FFAs in the muscle worsens the IR to induce the impairment of insulin signalling.[12]

Evidence for a genetic component

Obesity is a complex trait that stems from a complicated network of contributory components, including genomic and environmental factors, the aggregations of which increase the probability of disease. Sedentary behaviours and high-calorie diets are the major environmental factors that drive the epidemic of obesity. Studies in twins, no twin siblings, and adoptees have shown that genetic components contribute from 40% to 70% to the interindividual variation in common obesity.[13] The influence of both family history and childhood obesity on the obesity risk in young adulthood was assessed by Whitaker et al,[14] who showed that the influence of having one obese parent throughout childhood and adolescence increases an individual's risk of adult obesity by 2.2- to 3.2-fold compared with someone whose parents were not obese. Having two obese parents during childhood and adolescence substantially increases the risk of being an obese adult, with ORs (odds ratios) ranging from 5 to 15.30, compared with someone who had no obese parents, with the exception of parental obesity at the age of 10 to 14 yrs. The influence of obesity during childhood and adolescence on the risk of adult obesity increases steadily with age. Whereas obesity during infancy (1-2 yrs) does not increase one's risk of being an obese adult, an obese child at the age of 10 to 14 yrs has a 22.30-fold increased risk of being an obese adult compared to someone who was not obese as a child. Therefore, without a doubt, the obese phenotype runs prevalently in families, but most of the causative genes are still undiscovered.

Furthermore, the high clustering of components in family and twin studies has implied the importance of a genetic contribution to MetS. In a seminal study of 2,508 male twin pairs, concordance for the clustering of three MetS components (hypertension, diabetes, and obesity) was found in 31.6% of the monozygotic pairs compared with 6.3% of the dizygotic pairs.[15] Similarly, among 236 female twin pairs, the heritability estimates for obesity, insulin/glucose, and dyslipidaemia were found to be 61%, 87%, and 25%, respectively, using a classical non-molecular approach. This finding indicates an important genetic contribution for each of these components.[16] Among 803 individuals from 89 Caribbean-Hispanic families in the Northern Manhattan Family Study, the heritability of MetS itself was found to be 24%, with significant heritability for the lipid/glucose/obesity (44%) and hypertension (20%) components.[17] The marked variability in the heritability between studies might be partly attributable to ethnicity. Based on these demonstrations of heritability for MetS and its components, several investigators have directly examined the genetic determinants for MetS using linkage or association studies.

Genetics of obesity and metabolic syndrome

Hundreds of candidate genes for obesity susceptibility have been identified through a variety of approaches, as revised by Rankinen et al:[18] animal studies, Mendelian syndromes, linkage studies, genetic association studies, and expression studies. Since the mid-1990s, candidate gene studies have aimed to identify obesity-susceptibility genes. Candidate gene studies are hypothesis-driven, and hundreds of genes for which there is some evidence that supports a role in the regulation of the energy balance in animal models or in extreme/monogenic forms of obesity have been tested to determine their association with obesity-related traits.[18] However, consistent associations have been reported for only a handful of these candidate genes. The main reasons for the limited success of the candidate gene approach include the small sample sizes used and thus the low statistical power, the low number of genetic variants tested per gene and thus the incomplete coverage of the common variations, and the limited biological insights that provide the basis for the gene candidacy. The advent of genome-wide association studies (GWAS) in 2005 changed the way and the speed through

which genetic loci are discovered. The completion of the Human Genome Project and the HapMap project, in conjunction with the development of high-throughput genotyping techniques and statistical and computational methods, have enabled large-scale GWAS, in which a large number of genetic variants are tested for association with the trait of interest. To adjust for the vast number of tests performed in GWAS, procedures such as multiple testing correction and replication in independent samples are undertaken to minimise the number of false discoveries. Among the strongest arguments in favour of performing GWASs is the fact that such studies are hypothesis-free, i.e., the whole genome is screened for association to a complex disease or trait without prior hypotheses about which genes or regions are likely to be associated. The results of numerous GWASs performed in recent years have justified this approach because many previously unsuspected regions have been reproducibly associated with numerous complex traits.

Nevertheless, interest remains in the analysis of candidate genes. With GWAS data now available on numerous large cohorts, it has become possible to embed candidate gene studies within GWAS to test the association of a much larger number of candidate genes than previously possible. Recent studies have examined whether those obesity candidate genes are enriched for associations with BMI compared with non-candidate genes using data from a large-scale GWAS. The authors concluded that the candidate genes are more likely to be truly associated than the non-candidate genes, at least in the obesity-susceptibility evidence that supports the enrichment of the association of candidate genes, which suggests that the candidate gene approach retains some value. However, the degree of enrichment is small despite the extensive number of candidate genes and the large sample size. Studies that focus on candidate genes have only slightly increased chances of detecting associations and are likely to miss many true effects in non-candidate genes, at least for obesity-related traits.[19]

Genome-wide association studies of obesity and metabolic syndrome

To date, GWASs have provided robust evidence for a role of some variants, particularly the *FTO*, *MC4R* and *TMEM18* loci, in the development of obesity. The vast majority of these studies have been performed in white Europeans and in adults and have identified 32 loci that reached genome-wide significance. These studies were recently revised.[19,20] Table II reports the genes that have so far been found to be associated with obesity (BMI). The search for genetic factors that specifically influence paediatric obesity-related outcomes has primarily focused on replicated candidate genes in adult studies. In a study performed by Willer et al,[21] the analysis was conducted using a study sample from the Avon Longitudinal Study of Parents and Children (ALSPAC; N = 4,951 with BMI information at age 11) and confirmed significant associations of variants in/near *FTO*, *MC4R*, *TMEM18*, *KCTD15*, and *GNPDA2* with the BMI. Successively, the data were replicated in a cohort of obese children (N = 1,038) from the United Kingdom cohort of the Severe Childhood Onset Obesity Project, and an increased risk of extreme childhood obesity was revealed for the BMI-increasing alleles near *TMEM18*, *GNPDA2*, and *NEGR1*.[22] In the European Youth Heart Study (1,252 children and 790 adolescents), the associations of 15 variants (*NEGR1*, *SEC16B*, *LYPLAL1*, *TMEM18*, *ETV5*, *GNPDA2*, *TFAP2B*, *MSRA*, *BDN*F, *MTCH2*, *BCDIN3D*, *NRXN3*, *SH2B1*, *FTO*, *MC4R*, and *KCTD15*) with BMI were similar to those observed in adults.[23] In a meta-analysis data of 13,071 children and adolescents, significant associations with BMI were found for 9 of 13 variants, and a region near to the *TMEM18* variant had the strongest effect. The effect on the BMI tended to be more pronounced for variants in/near *SEC16*, *TMEM18*, and *KCTD15* in children and adolescents compared with adults.[24]

Several extensive and successful efforts have been made to map variants associated with the components of MetS. Studies using MetS as a binary trait and studies investigating the components using bivariate or multivariate methods have been published in the last few years. However, bivariate methods may be considered somewhat paradoxical because three or more components are used to define the syndrome. Moreover, it should be noted that a number of investigators within the scientific community do not agree that MetS is an entity in itself, but a set of risk factors for cardiometabolic disease that are useful to the biological understanding. Zabaneh and Balding[25] conducted a two-stage GWAS to identify common genetic variations that alter the risk of MetS and related phenotypes in Indian Asian men, who exhibit a high prevalence of these conditions. In stage 1, approximately 317,000 SNPs were genotyped in 2,700 individuals, and 1,500 of these SNPs were selected to be genotyped in an additional 2,300 individuals. No evidence of a common genetic basis for the MetS traits was found in this study. Another approach was used in the study performed by Kraja et al,[26] which grouped seven country-studies from the STAMPEED consortium, comprising 22,161 participants of European ancestry, who underwent bivariate genome-wide association analyses of metabolic traits. The phenotypes for MetS were combined in all possible pairwise combinations, and those individuals who exceeded the thresholds for both traits of a pair were considered affected. Twenty-eight SNPs were associated with MetS or a pair of traits. These variants were located in or near 15 genes that were associated with binary pairwise traits or with MetS *per se* at the genome-wide significance level. All but two of these bivariate associations included a lipid abnormality. The authors suggested that these results show that the genetic effects on lipid levels are more pronounced

Table II

Genetic variants associated with obesity and metabolic syndrome through genome-wide association studies (GWAS)

Nearest gene	*Full gene name*	*SNP*	*Trait*
FTO	Fat mass and obesity associated	rs1558902	BMI*
		rs1121980	BMI*
		rs9939609	BMI*
		rs8050136	BMI*
		rs17817449	BMI*
		rs12149832	BMI*
MC4R	Melanocortin 4 receptor	rs571312	BMI*
		rs12970134	BMI*
TMEM18	Transmembrane protein 18	rs2867125	BMI*
		rs6548238	BMI*
		rs7561317	BMI*
SEC16B	SEC16 homolog B	rs543874	BMI*
		rs574367	BMI
		rs516636	BMI*
BDNF	Brain-derived neurotrophic factor	rs10767664	BMI*
		rs4923461	BMI
		rs6265	BMI*
		rs2030323	BMI
GNPDA2	Glucosamine-6-phosphate deaminase 2	rs10938397	BMI*
SH2B1	SH2B adaptor protein 1	rs7359397	BMI*
		rs7498665	BMI
ETV5	Ets variant 5	rs9816226	BMI*
		rs7647305	BMI
NEGR1	Neuronal growth regulator 1	rs2815752	BMI*
		rs2568958	BMI*
TFAP2B	Transcription factor AP-2 beta (activating enhancer binding protein 2 beta)	rs987237	BMI*
NRXN3	Neurexin	rs10150332	BMI*
FAIM2	Fas apoptotic inhibitory molecule 2	rs7138803	BMI
MTCH2	Mitochondrial carrier 2	rs3817334	BMI
		rs10838738	BMI
KCTD15	Potassium channel tetramerisation domain containing 15	rs29941	BMI*
		rs11084753	BMI
SLC39A8	Solute carrier family 39 (zinc transporter), member 8	rs13107325	BMI

Table II *(cont.)*
Genetic variants associated with obesity and metabolic syndrome through genome-wide association studies (GWAS)

Nearest gene	*Full gene name*	*SNP*	*Trait*
GPRC5B	G protein-coupled receptor, family C, group 5, member B	rs12444979	BMI
PRKD1	Protein kinase D1	rs11847697	BMI
QPCTL	Glutaminyl-peptide cyclotransferase-like	rs2287019	BMI
		rs11671664	BMI
MAP2K5	Mitogen-activated protein kinase 5	rs2241423	BMI
		rs4776970	BMI
LRRN6C	Leucine rich repeat neuronal 6C	rs10968576	BMI
FANCL	Fanconi anaemia, complementation group L	rs887912	BMI
CADM2	Cell adhesion molecule 2	rs13078807	BMI
TMEM160	Transmembrane protein 160	rs3810291	BMI
LRP1B	Low-density lipoprotein receptor-related protein 1B	rs2890652	BMI
MTIF3	Mitochondrial translational initiation factor 3	rs4771122	BMI
TNNI3K	TNNI3-interacting kinase	rs1514175	BMI
ZNF608	Zinc finger protein 608	rs4836133	BMI
PTBP2	Polypyrimidine tract-binding protein 2	rs1555543	BMI
RPL27A	Ribosomal protein L27a	rs4929949	BMI
NUDT3	Nudix (nucleoside diphosphate linked moiety X)-type motif 3	rs206936	BMI
LPL	Lipoprotein lipase	rs295	MetS
CETP	Cholesteryl ester transfer protein, plasma	rs173539	MetS
APOA5	Apolipoprotein A-V	rs2266788	MetS
ZNF259	Zinc finger protein 259	rs2075290	MetS
BUD13	BUD13 homolog (S. Cerevisiae)	rs10790162	MetS
APOC1	Apolipoprotein C-I	rs4420638	MetS
BRAP	BRCA1-associated protein	rs11065987	MetS
PLCG1	Phospholipase C, gamma 1	rs753381	MetS
APOA1/C3/A4/A5	Gene cluster region (SNP rs964184)	rs964184	MetS

* Association observed in children. BMI: body mass index. MetS: metabolic syndrome.

than for other traits. The most influential variants in the correlation among traits were in or near *LPL*, *CETP*, *APOA5*, *ZNF259*, *BUD13*, *TRIB1*, *LOC100129500*, and *LOC100128154*. The genes with variants that influence MetS *per se* included *LPL*, *CETP*, and the APOA-cluster (*APOA5*, *ZNF259*, and *BUD13*), which are known to play an important role in lipid metabolism.[26]

Another approach that combined several components of MetS in a GWAS was published by Avery et al,[27] who used data from 19,486 European Americans and 6,287 African Americans. Six phenotype domains (atherogenic dyslipidemia, vascular dysfunction, vascular inflammation, pro-thrombotic state, central obesity, and elevated plasma glucose), including 19 quantitative traits, were examined and analysed through a principal component analysis. These researchers then applied a multivariate approach that related eight principal components from the six domains. In European

Americans, these researchers identified genome-wide significant SNPs representing 15 loci. Many of these loci were associated with only one trait domain, and five of these associations were consistent with the results obtained with the cohort of African Americans. In addition, several of these associations were already known, e.g., the association of central obesity with *FTO*. However, the study identified three new loci in or near *APOC1*, *BRAP*, and *PLCG1*, which were associated with multiple phenotype domains. The strongest new pleiotropic signal in European Americans was observed for rs4420638, which is located near *APOC1* and was associated with elevated plasma, atherogenic dyslipidemia, vascular inflammation, and central obesity. A recent GWAS on MetS and its component traits in four Finnish cohorts consisting of 2,637 MetS cases and 7,927 controls (all of the individuals in both cohorts were free of diabetes) suggested that genes from the lipid metabolism pathways have a key role in the genetic background of MetS. The lipid locus at the *APOA1/C3/A4/A5* gene cluster region (SNP rs964184) was associated with MetS in all four study samples. Interestingly, the association was further supported by the results from a serum metabolite analysis, in which rs964184 was associated with various VLDL, TAG, and HDL-c metabolites. Most of these metabolites were associated with lipid phenotypes, and none of them were associated with two or more uncorrelated MetS components. A genetic risk score, which was calculated as the number of alleles in a loci associated with individual MetS traits, was strongly associated with the MetS status.[28] Nevertheless, further replication is needed, and, if these pleiotropic loci hold true, these loci may help characterise metabolic deregulation and identify targets for intervention. In addition, to the best of our knowledge, no GWAS has been performed in children; thus, this is mandatory.

Candidate gene association studies of metabolic syndrome

Because glucose metabolism, insulin signalling, adipokines, and inflammation are thought to play crucial roles in MetS pathogenesis, it may be fruitful to examine candidate genes from these areas for MetS. Table III lists the reported candidate genes associated with an increased or decreased risk for MetS. The main findings reported by candidate gene associations studies of the main metabolic pathways involved in MetS are reviewed below.

Glucose metabolism and insulin signalling

The genetic basis of T2DM, glucose homeostasis (fasting plasma glucose and insulin), and indirect measures of IR (HOMA-IR) have been demonstrated by GWAS and meta-analyses of individual case-control studies. More than 50 loci have been found to be associated with the risk of T2DM, and the strongest effect was observed with the rs7903146 in the *TCF7 L2* gene. In a meta-analysis of 21 GWAS cohorts (Meta-Analyses of Glucose and Insulin-related traits Consortium [MAGIC]),[29] robust statistical evidence for the genome-wide association with fasting glucose was observed for SNPs in eight loci (including the candidate genes *ADCY5*, *FADS1*, and *GLIS3*) and SNPs in one locus (with the candidate gene *IGF1*). Expanding upon MAGIC, a joint meta-analysis was conducted to determine whether genes involved in the IR pathways (HOMA-IR) could be discovered by accounting for differences in obesity (BMI) and interactions between the BMI and genetic variants.[30] The discovery of SNPs in six loci (including the candidate genes *COBLL1/GRB14*, *IRS1*, *PPP1R3B*, *PDGFC*, *UHRF1BP1*, and *LYPLAL1*) that were associated with fasting insulin, high TAG levels, and low HDL-c levels suggested a new series of pathways that can be studied to identify genes with contributions to multiple phenotypes.

The associations of genetic variants in insulin signalling have been reported to be associated with MetS. In a recent association study with 1,886 participants from the EPIC-NL cohort, a group of five SNPs were found to be related with IR (*IRS1* rs2943634, *PPARG* rs1801282, *GCKR* rs780094, *GCK* rs1799884, and *IGF1* rs35767), and the *IRS1* SNP was the only one that was significantly associated with MetS and the MetS score. This SNP was also associated with HbA1C, TAG, and HDL-c.[31] Several studies have indicated that *INPPL1* gene polymorphisms may be associated with the MetS and/or T2DM. In a British cohort, three SNPs in the *INPPL1* gene were significantly associated with components of MetS, such as hypertension, obesity, and T2DM, although the findings could not be replicated in French subjects.[32] In a recent cross-sectional study with 1,328 participants with MetS and 1,074 controls without MetS, two SNPs of *INPPL1*, rs2276048 (silent mutation) and rs2276047 (intronic) were found to be associated with MetS in men.[33]

Lipid metabolism

Genes related to lipid metabolism have been described to be strongly associated with MetS. The determinants of the plasma TAG metabolism might be determinants of MetS, and genetic variants have been revised by Joy et al.[34] Apolipoprotein C-III is present in TAG-rich lipoproteins and inhibits lipoprotein lipase, thereby delaying the catabolism of TAG. A case-control study consisting of whites, South Asians, and blacks demonstrated that the *APOC3* promoter polymorphisms –482C > T and –455 T> C were associated with MetS. Among 1,788 Japanese individuals, of whom 1,017 had MetS and 771 were controls, the *APOA5* –1131T > C polymorphism was strongly associated with MetS prevalence, and the C allele was signifi-

Table III

Genetic variants associated with obesity and metabolic syndrome through genome-wide association studies (GWAS)

Nearest gene	*Full gene name*	*Trait*
ADCY5	Adenylate cyclase 5	Increased fasting glucose
ADIPOQ	Adiponectin	Decreased risk of obesity, MetS, and T2DM and high adiponectin
APOA5	Apolipoprotein A-V	Increased TAG and decreased HDL-c
APOC3	Apolipoprotein C-III	Increased TAG and decreased HDL-c
COBLL1/GRB14	Cordon-bleu WH2 repeat protein-like 1 growth factor receptor-bound protein 14	Increased fasting insulin and TAG and decreased HDL-c
FABP4	Fatty acid binding protein 4	Increased HOMA-IR and FABP4 levels in children
FADS1	Fatty acid desaturase 1	Increased fasting glucose
ENPP1	Nucleotide pyrophosphatase/phosphodiesterase-1	Increased fasting insulin and risk of MetS in children
GLIS3	GLIS family zinc finger 3	Increased fasting glucose
IGF1	Insulin-like growth factor 1 (somatomedin C)	Increased fasting glucose
IL6	Interleukin 6	Increased risk of MetS
INPPL1	Inositol polyphosphate phosphatase-like 1	Increased systolic and diastolic blood pressure, obesity, and T2DM
IRS1	Insulin receptor substrate 1	Increased fasting insulin and TAG and decreased HDL-c
INS VNTR	Insulin variable number of tandem repeats	Increased fasting insulin and risk of MetS in children
LPL	Lipoprotein lipase	Decreased fasting HDL-c
LYPLAL1	Lysophospholipase-like 1	Increased fasting insulin and TAG and decreased HDL-c
MCP1	Monocyte chemoattractant protein 1	Increased risk of MetS
PDGFC	Platelet derived growth factor C	Increased fasting insulin and TAG and decreased HDL-c
PLIN4	Perilipin 4	Increased risk of MetS in children and adolescents
PPARG	Peroxisome proliferator-activated receptor gamma	Increased abdominal circumference and TAG and decreased HDL-c
PPP1R3B	Protein phosphatase 1, regulatory subunit 3B	Increased fasting insulin and TAG and decreased HDL-c
RSTN	Resistin	Increased TAG, BMI, and systolic and diastolic blood pressure
SR-BI	Scavenger receptor class B type I	Decreased fasting HDL-c and increased risk of MetS in children
TCF7 L2	Transcription factor 7-like 2	Increased fasting glucose
TNFA	Tumour necrosis factor a	Increased systolic blood pressure and obesity in adults and children
UHRF1BP1	UHRF1-binding protein 1	Increased fasting insulin and TAG and decreased HDL-c
ZFP36	ZFP36 ring finger protein	Increased fasting glucose and LDL-c

TAG: triacylglycerides. HDL-c: high-density lipoprotein-cholesterol. LDL-c: low-density lipoprotein-cholesterol. MetS: metabolic syndrome. T2DM: type 2 diabetes mellitus.

cantly related to increased TAG and decreased HDL-c levels. In contrast, a study of 3,124 white individuals from Germany and Austria did not find an association between the *APOA5* –1131T > C polymorphism and MetS, but did discover that the *APOA5*56C > G variant conferred an increased risk of MetS. These varied results in genetic associations are likely due to ethnic differences. In addition, the *lipoprotein lipase S447X* variant has been associated with MetS in Turkish women. In particular, this study showed that females with the more common SS genotype had a significantly increased likelihood for MetS and low HDL-c levels.

Interestingly, in a recent systematic review, the 56C > G (*APOA5*), –1131T > C (*APOA5*), –482C > T (*APOC3*), and –455T > C (*APOC3*) polymorphisms were more prevalent in subjects with MetS.[31] Thus, genetic variations affecting TAG metabolism might be associated with the composite MetS phenotype.

In addition to genes involved in the TAG metabolism, peroxisome proliferator-activated receptor gamma (PPARG), which is a nuclear receptor involved in glucose and fatty acid metabolism, has been associated with obesity and MetS. The Pro12Ala (rs1801282) polymorphism of the *PPARG* gene has been consistently associated with T2DM. However, although 16 studies have investigated the association between Pro12Ala (rs1801282) and MetS, as discussed in a systematic review,[35] most of these showed no effect. Interestingly, although the 12Pro allele is associated with an increased risk of T2DM and IR independent of BMI, the meta-analysis demonstrates that 12Ala is the risk allele if any effect on MetS exists. The association between C1431T (rs3856806), which is another well-known *PPARG* polymorphism, and MetS has been investigated in six cross-sectional studies, which are included in the same meta-analysis, and no association was found between this SNP and MetS. Although both the 12Ala and the C1431T alleles do not appear to significantly increase the MetS risk, a haplotype containing the same alleles was associated with an increased prevalence of MetS in a cross-sectional study of 1,115 French subjects.[36] Other SNPs in the *PPAR* family of genes have been studied. A study of French-Canadian men revealed no association between the *PPARA* L162 V polymorphism and MetS despite the higher frequency of this polymorphism in men exhibiting increased abdominal circumference, high TAG levels, and low HDL-c levels. The *PPARD* –87T>C polymorphism in French-Canadian men and women conferred protection from the MetS phenotype, and this protection was further enhanced if the carriers consumed less than 34.4% calories from fat, which suggests a gene-environment interaction.[37]

Adipokines

In humans, several polymorphisms in leptin (*LEP*), leptin receptor (*LEPR*), resistin (*RETN*), adiponectin (*ADIPOQ*), adiponectin receptor 1 (*ADIPOR1*), and adiponectin receptor 2 (*ADIPOR2)* have been found to be associated with obesity and MetS phenotypes. A recent metanalysis that included 21 polymorphisms in seven genes that were significantly associated with obesity suggested that only polymorphisms in *ADIPOQ* decreased the risk of obesity, whereas polymorphisms in the *LEP, LEPR*, and *RETN* genes were not related to the development of obesity.[38] Interestingly, some of these genetic variants have been associated with MetS. Among 1,438 Taiwanese individuals, the G allele of the *ADIPOQ* SNPrs1501299 in intron 2 was associated with decreased risk of obesity, MetS, and T2DM.[39] The examination of the –420C>G SNP in the *RSTN* gene revealed that G/G homozygotes had an increased prevalence of MetS and elevated TAG, BMI, and systolic and diastolic BP values compared with the other genotypes. In a follow-up case control study, the *RSTN* –420C > G SNP was associated with an increased MetS prevalence but did not influence the MetS prevalence among individuals at high cardiovascular risk.[40] Recently, 64 tagging SNPs in *ADIPOQ, ADIPOR1*, and *ADIPOR2* were genotyped in two general population cohorts consisting of 2,355 subjects and one cohort of 967 subjects with T2DM. A genetic variation in *ADIPOQ*, but not in its receptors, was associated with altered serum adiponectin. However, genetic variations in *ADIPOQ* and its receptors do not appear to contribute to the risk of IR or MetS.[41]

Inflammation

Proinflammatory cytokines, such as interleukin-6, TNF-α, and monocyte chemoattractant protein-1 (MCP1), are postulated to have a role in the MetS pathogenesis and represent candidate genes. The main finding in adults was revised by Joy et al.[34] Among 6,916 Danes, the AGC/GGG haplotype of three common *IL6* promoter polymorphisms were more common among the adults with MetS compared with the controls without MetS. The examination of the *IL6* –174G > C promoter polymorphism in 571 whites revealed a higher MetS prevalence among those individuals with the CC genotype. Conversely, a population-based sample of 1,630 Germans revealed that none of the seven SNPs of the proinflammatory cytokine *MCP1 g*ene were associated with MetS. In addition, although a meta-analysis of 31 studies revealed that the *TNFA* –308G>A polymorphism conferred a risk of 1.23 for obesity and an increase in the systolic BP of 3.5 mm Hg, the relationship of this polymorphism with MetS was not examined. Zinc finger protein 36 (*ZFP36*), which is involved in TNF-α regulation, has been proposed as a candidate gene for MetS based on its position on the long arm of chromosome 19, which is a region linked with MetS that exhibits significant differential expression (4.6-fold higher) among obese individuals without MetS compared with those with MetS. In the same study, the *ZFP36* rs251864 polymorphism was associated with a lower body weight among women and the T allele was associated with glucose levels in men. Furthermore, the *ZFP36* haplotype was associated with plasma low-density lipoprotein in men and women. Thus, future studies might replicate the *ZFP36* association with MetS.

Association studies of metabolic syndrome in children

Candidate gene association studies that search for factors that specifically influence paediatric obesity

and metabolic-related outcomes are limited and scarce in the scientific literature. The main limit is the sample size, most likely due to the abovementioned difficulty associated with the epidemiological monitoring of MetS depending on the definition used for its classification. Those studies that investigated genes involved in glucose metabolism, insulin signalling, adipokines, and inflammation in at least 100 obese children are briefly summarised below.

The T allele of the rs997509*ENPP1* (nucleotide pyrophosphatase/phosphodiesterase-1) gene has been found to predispose obese children to MetS and IR in 409 obese children compared with 400 lean controls.[42] The insulin variable number of tandem repeats (VNTR) polymorphism located in the insulin gene promoter (*INS VNTR*) has been associated with the insulin levels in obese children and was found predispose 320 obese children to develop the MetS[43] Several genes involved in lipid metabolism have been associated with childhood MetS risk. The rs5888 in the *scavenger receptor class B type I* (*SR-BI*) gene, which plays a role in cholesteryl esters-HDL metabolism, was associated with MetS in 39 children diagnosed with the syndrome compared with 124 children with simple obesity.[44] The presence of selective SNPs in the *FABP4* gene increased HOMA-IR and FABP4 levels in 309 children aged 5-7 years, although the MetS classification was not considered in this study.[45] The minor A allele in *PLIN4* was associated with a higher risk of MetS in 234 obese children and adolescents.[46] In addition, two inflammation genes associated with MetS in adults have also been studied in children. The TNFA –308G > A polymorphism was more common in 124 children with simple obesity; however, it did not appear to be associated with the degree of obesity, insulin resistance, lipid profile, leptin levels, or the incidence of MetS in obese children.[47] The IL6 –174G > C promoter polymorphism did not appear to be associated with obesity or with the incidence of MetS in 124 obese children.[48]

Conclusion

MetS represents a complex phenotypic trait consisting of several clinical factors associated with an increased risk of T2DM and CVD. Genetic studies in adults and children have provided conflicting associations of genes and gene variants rather than consistently reproducible associations and linkages. Nonetheless, the hope remains that understanding the genetic determinants of MetS will lead to early detection of new cases and possible preventive strategies based on the important caveats for genetic studies of complex traits. Thus, although genetics likely plays a crucial role in MetS development, the elucidation of the exact genes involved has been hindered by the lack of a consistent MetS definition, the varying combination of phenotypes even within a single definition, ethnic disparities, and gender influences. Furthermore, the lifestyle determinants for MetS development should not be ignored, and these determinants are also likely under genetic control. In short, MetS development represents an intricate interaction between genetic susceptibilities and environmental influences, and genetic studies increase our appreciation of this complexity.

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Associated factors of obesity in Spanish representative samples

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Abstract

Given the dramatic increase in the prevalence of obesity and the serious health and economic consequences, the scientific community, health professionals and health agencies are looking for the best strategies to prevent/fight this trend.

In order to plan the most appropriate intervention measures the first step is to identify the associated factors of obesity. This paper presents the results of research conducted/coordinated by our research team and promoted by the Spanish Food Safety Agency (AESAN), in the last five years. These studies were focussed on representative samples of the Spanish population, paying attention to the condition of overweight/obesity and their associated factors.

The first study, FANPE ("Fuentes alimentarias de nutrientes de la población española") (2009), was centered in 418 adults (18-60 years) from 15 provinces (30 sampling points). Its aim was to analyze the dietary sources of nutrients, paying particular attention to sodium. This research showed that the risk of overweight/obesity increases with age, in people who have follow weight control diets, in ex-smokers, married people and those who slept less than 8.5 hours per day, while the risk is lower in women, people who make sport and those with an University degree. It was also found that overweight people had higher sodium intake and urine excretion. Therefore, and having in mind that 88.2% of the subjects took more than 2 g/day of sodium (the maximum recommended), it is advised to lower the sodium intake not only from the health point of view but also as a probably strategy against obesity.

The study ALADINO (Estudio de Alimentación, Actividad física, Desarrollo Infantil y Obesidad- Study of the Diet, Physical Activity, Child Development and Obesity) (2010-2011) was focused on 7659 children (6-9 years) from 19 autonomous communities. We founded a higher percentage of overweight/obesity in boys than in girls, and a significant increase in the figures from the age of 7. Being overweight is more evident in offspring of parents with low educational level or low income, or if parents are smokers (especially when both parents smoke). The problem increases in those children who skip breakfast, have

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FACTORES ASOCIADOS AL PADECIMIENTO DE OBESIDAD EN MUESTRAS REPRESENTATIVAS DE LA POBLACIÓN ESPAÑOLA

Resumen

Ante el espectacular incremento en la prevalencia de obesidad y dadas las graves consecuencias sanitarias y económicas que conlleva, la comunidad científica, los profesionales y organismos sanitarios están buscando las mejores estrategias para prevenir/combatir la tendencia.

Para tomar medidas el primer paso es conocer los factores asociados al padecimiento de obesidad, para planificar las medidas de intervención más adecuadas. El presente trabajo presenta resultados de investigaciones realizadas/coordinadas por nuestro equipo investigador, en los últimos 5 años y promovidas por la Agencia Española de Seguridad Alimentaria (AESAN), en los que se presta atención al padecimiento de sobrepeso/obesidad y a los factores asociados, analizando muestras representativas de la población española.

Por una parte, se presentan datos de 418 adultos (18-60 años) estudiados en 2009 en 15 provincias (30 puntos de muestreo) para analizar las "Fuentes alimentarias de nutrientes de la población española" (FANPE) con especial atención al sodio, esta investigación puso de relieve que el riesgo de padecer sobrepeso/obesidad incrementa con la edad, en las personas que han realizado dietas de control de peso, exfumadores, personas casadas y en aquellas que dormían menos de 8.5 horas diarias. Mientras que el riesgo es menor en mujeres, personas que realizan algún deporte y en aquellas con estudios universitarios. También se constató que las personas con exceso de peso tenían mayor ingesta y excreción de sodio por orina. Por ello, teniendo en cuenta que un 88,2% de los sujetos estudiados tomaba más de los 2 g/día de sodio (límite máximo aconsejado) se considera conveniente reducir la ingesta de sodio, desde el punto de vista sanitario y probablemente también como estrategia en la lucha contra la obesidad.

En población infantil los datos del Estudio de Alimentación, Actividad física, Desarrollo Infantil y Obesidad (ALADINO) (2010-2011) estudiando 7.659 niños (6-9 años) de 19 CCAA, ponen de relieve un mayor padecimiento de sobrepeso/obesidad en varones, con incremento notable del problema a partir de los 7 años. También se constata que el exceso de peso es más evidente en descendientes de padres con escaso nivel de estudios y/o bajos ingresos, entre niños que no desayunan, en aquellos que comen en casa en comparación con los que comen en el colegio, cuando las instalaciones deportivas están lejos del domicilio del niño, o cuando los escolares disponen de ordenador personal, videoconsola o TV en su habitación, cuando

lunch at home (compared with having this meal at school), in those with sports facilities far from their home, those who have a personal computer, video game or TV in their room, or those who sleep less than 8 hours per day.

All these factors, either by themselves or because they influence eating habits and/or activity patterns, are associated with a higher risk of being overweight, so it must be monitored and modified in a more favourable direction, within the health policies of each country, as part of strategies to halt the rise in obesity condition.

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Key words: *Obesity. Overweight. Risk factors. Spanish children. Spanish adults.*

duermen menos de 8 h/día o los padres son fumadores (especialmente si fuman ambos).

Todas estas influencias, por si mismas o por condicionar los hábitos alimentarios y/o pautas de actividad del individuo se asocian con un mayor riesgo de presentar exceso de peso, por lo que deben ser vigiladas y modificadas en una dirección más favorable, dentro de las políticas sanitarias de cada país, como parte de las estrategias encaminadas a frenar el incremento en el padecimiento de obesidad.

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Palabras clave: *Obesidad. Sobrepeso. Factores de riesgo. Niños españoles. Adultos españoles.*

Abbreviations

FANPE: "*Fuentes alimentarias de nutrientes de la población española*"-Food Sources of Nutrients in Spanish Diet.

ALADINO: *"Alimentación, Actividad física, Desarrollo Infantil y Obesidad"* -Study of the Diet, Physical Activity, Child Development and Obesity.

AESAN: Spanish Agency for Food Safety and Nutrition.

BMI: Body mass index.

%BF: Percentage body fat.

NW: normal weight.

OW: Overweight.

OB: Obese.

WHO: World Health Organization.

25(OH)D: 25-hydroxyvitamin D.

Na: Sodium.

NS: Non smoking parents.

1S: One smoking parent.

2S: Both smoking parents.

Introduction

Given the dramatic increase in the prevalence of obesity[1,2] and the serious health and economic consequences,[3-6] scientists, health professionals and health agencies are looking for the best strategies to prevent/fight this trend.

In order to plan the most appropriate intervention measures the first step is to identify the associated factors of obesity. Obesity is a multifactorial disease result of an interaction between genetic and environmental factors.[1,4,5,7] But the environmental factors are those that most contribute to explain the increase in obesity in recent years (up to 60-70%),[1] having in mind that the genetic basis of the population may not have changed so quickly.[4,7,8]

Given the health impact of overweight,[3-6] it is important to take measures to fight this problem. It is important to identify the associated factors with a higher risk of obesity in order to take some concrete steps that can be especially useful for a particular population groups. Therefore, analyzing the prevalence of overweight (OW) and obesity (OB) and their associated factors, in representative samples of the Spanish population, is of great interest and the subject of this study.

Studies in adults (FANPE)

The FANPE study ("*Fuentes Alimentarias de Nutrientes en la Población Española*") was driven by the Spanish Agency for Food Safety and Nutrition (AESAN) and performed in a representative sample of Spanish adults, with the aim of analyze the food sources of nutrients in the Spanish population, paying special attention to the food sources of sodium.[9]

A total of 418 adults aged 18 to 60 years (196 male and 222 female) volunteered to take part in this study. Participants were selected from 15 Spanish provinces in order to represent the Spanish population. Within each province, some participants were selected from the province capital and another sample from a semi-urban or urban village. In total, 30 town/villages were selected to be part in the study. Fieldwork was conducted between January and September 2009.

Food intake was determined using the 24 h recall method on two consecutive days.[10] Participants were asked about the food consumed on the preceding day (where appropriate the brands of these foods were also recorded), and on the size of the servings consumed (approximate weights or household measures: cups, bowls, plates, etc.). In addition, they indicated whether these weights or sizes corresponded to raw or cooked food, with or without bone, with or without skin, etc. The energy and nutrient intakes were then calculated using food composition tables.[11] DIAL software (Alce Ingeniería, 2004) was used to process all data.[12] Sanitary and socioeconomic data were recorded and all subjects completed a questionnaire on their usual physical activity.[13]

Some anthropometric measures were taken: weight, height, skinfolds, and waist and hip circumferences. All data were collected following norms set out by the WHO.[14] The body mass index was calculated (BMI = weight [kg]/height [m]^2). Percentage body fat (%BF) was determined by electrical bioimpedance.[15] Subjects

Table I
FANPE Study. Weight data of the study sample. Differences regarding sex. (%)[18]

	Total n = 418	*Men n = 196*	*Women n = 222*
Normal weight (%)	52.2 (218)	39.8 (78)	63.1 (140)
Overweight (OW) (%)	34.2 (143)	43.9 (86)	25.7 (57)
Obesity (OB) (%)	13.6 (57)	16.7 (32)	11.3 (25)
Whit weight excess (OW + OB) (%)	47.8 (200)	60.3 (118)	37.0 (82)
Excess of body fat (%)[#]	70.2 (293)	73.7 (143)	67.1 (147)
Central obesity[†] (%)	22.2 (93)	18.6 (36)	25.3 (56)
Waist/height ≥ 0,5 (%)	54.7 (227)	65.5 (127)	45.3 (100)

[#] > 20% in males and > 30% in females. ***p < 0,001. [†] Waist circumference ≥ 102 cm in males and ≥ 88 cm in females.

were classified following the WHO classification as normal weight (NW) (BMI < 25 kg/m^2), overweight (OW) (BMI ≥ 25 kg/m^2 and BMI < 30 kg/m^2) and obese (OB) (BMI ≥ 30 kg/m^2).[14,16] A 24-h urine sample was taken and volume, sodium, potassium and creatinine concentration were determined.[17]

Table I resumes anthropometric data. 34.2% and 13.6% of the subjects were OW and OB respectively. That means that 47.8% of the population have an excess of weight (including OW and OB).[18] 22.2% of adults have central obesity (defined by waist circumference ≥ 102 cm in men and ≥ 88 cm in women), and 54.7% have a waist/height ratio ≥ 0.5. Body composition data are more worrisome, since 70.2% of those studied have a fat excess[18]

The risk of OW/OB was higher with increasing age [OR = 5.96 (3.20-11.13), p = 0], in people who had followed weight control diets in the past [OR = 3.28 (1.98- 5.43), P < 0.001], in former smokers [OR = 2.22 (1.23-4.00), p = 0.008], in married people [OR = 1.64 (1.02-2.64), p = 0.041] and in those who slept less 8.5 hours per day [OR = 1.62 (1.05-2.52), p = 0.030][7] (fig. 1).

Furthermore, the risk was lower in women [OR = 0.34 (0.22-0.51), p = 0], in people who practiced a sport [OR = 0.55 (0.35 to 0.85), p = 0.008], and those with a university degree [OR = 0.53 (0.28-1.02), p = 0.050]. There was no association between OW/OB and the place of residence (rural/urban), stress, pregnancy or the number of children[7] (fig. 1).

When we considered dietary data, it has been observed that individuals with NW had higher intakes of calcium and dairy products compared with those with OW and OB.[19] There was also an inverse correlation between calcium intake and waist circumference (r = –0.096), waist/height ratio (r = –0.105) and waist/hip ratio (r = –0.100)[20].

Previous studies have shown a relationship between vitamin D status and weight contol[21]. In an intervention study in overweight women who were following a hypocaloric diet during 6 weeks, those with better vitamin D status (25-hydroxyvitamin D (25(OH)D) serum level ≥ 50 nmol/l) loosed more body fat (–1.7 (SD 1.8) kg) than those with lower serum levels (–0.5 (SD 0.8) kg) and with the same caloric restriction. Therefore, a better vitamin D status aided the loss of body fat over the experimental period (OR 0.462; CI 0.271, 0.785; P < 0.001). This study highlighted that women with a better vitamin D status respond more positively to hypocaloric diets and lose more body fat; and this was especially clear among the subjects who had a greater vitamin D supply during the experimental period.[21]

Assuming that all urinary sodium (Na) (168.0 (SD 78.6) mmol/d) comes from the diet, the mean dietary salt intake was 9.8 (SD 4.6) g/d, and 88.2% of the subjects had

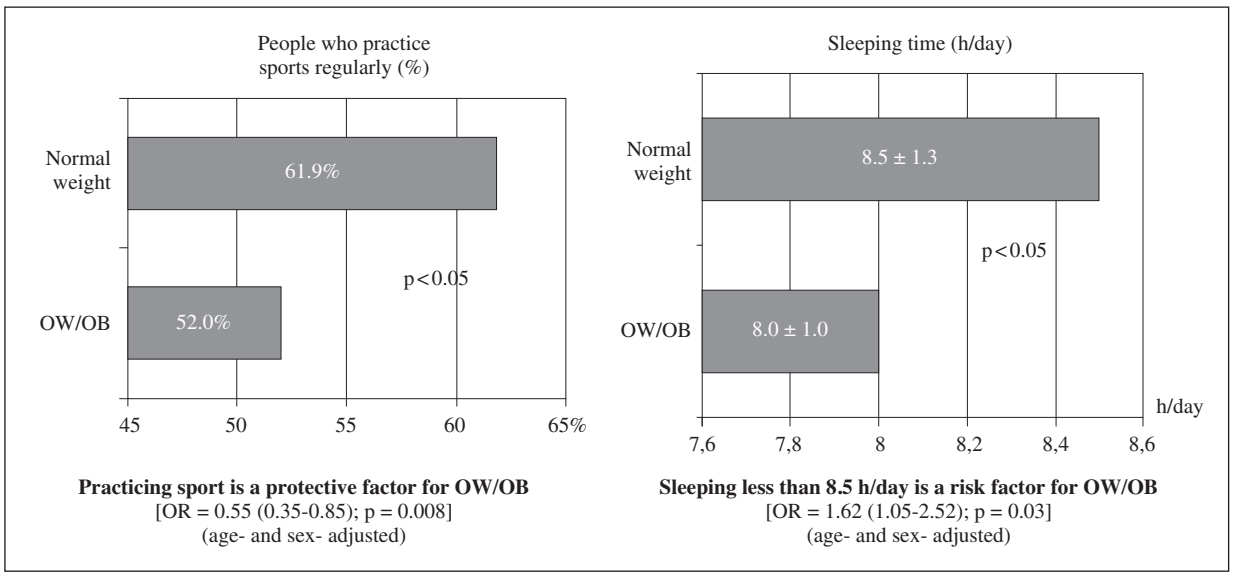

Fig. 1.—Associated factors of overweight/obesity (OW/OB) in Spanish adults.[7] Rodríguez-Rodríguez et al. (2011).[7]

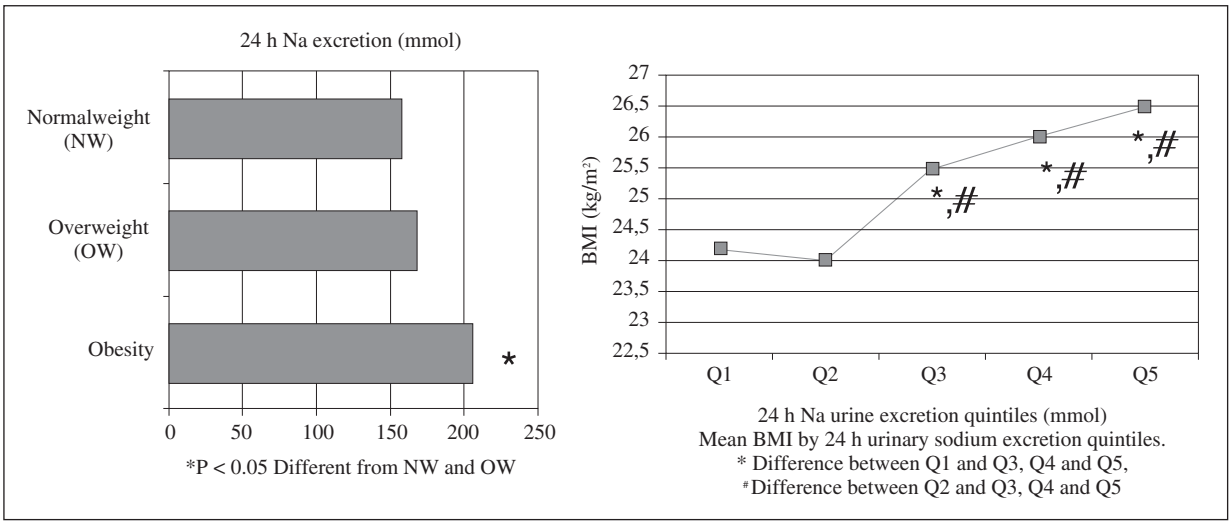

Fig. 2.—Relationship between sodium intake and Body Mass Index (BMI) in Spanish adults.[16] Ortega et al. (2011).[16]

salt intakes above the recommended 5 g/day (85 mmol of Na/day).[22] Logistic regression analysis, adjusted for sex, age and BMI, showed that being male (OR 3.678, 95% CI 2.336, 5.791) and increasing BMI (OR 1.069, 95% CI 1.009, 1.132) ($p<0.001$) were associated with excreting >200 mmol/d urinary Na. Na excretion was higher in those with overweight/obesity (179.8 (SD 81.9) mmol/d) compared with normal weight subjects (158.3 (SD 74.6) mmol/d) ($P<0.001$) (fig. 2). Having in mind that the higher sodium intake is associated with higher BMI, the study highlights the importance of reducing Na intake, not only from the health point of view but also in the obesity control.[16]

Some of the observed associated factors of overweight/obesity can be easily modified: sleeping 8.5 h / day or more, being more active, avoiding an insufficient supply of some nutrients such as calcium and vitamin D and reducing the sodium intake. All of these are changes that can be helpful in weight management and the fight against overweight/obesity.

Studies in children (ALADINO)

ALADINO study was focused on anthropometric and obesity risk factors in childhood (ALADINO = Estudio de Alimentación, Actividad física, Desarrollo Infantil y Obesidad- Study of the Diet, Physical Activity, Child Development and Obesity). This was a cross-sectional study of Spanish schoolchildren performed under the auspices of the *Agencia Española de Seguridad Alimentaria y Nutrición* (AESAN; Spanish Agency for Food Safety and Nutrition). The study was conducted between October 2010 and May 2011[23] in 7659 children (3841 boys and 3818 girls) aged 6 to 9 years from 19 autonomous communities in 144 primary schools. Sample size and sampling points were established by AESAN in order to study a representative sample of Spanish schoolchildren.

ALADINO study was performed in the frame of the Childhood Obesity Surveillance Initiative (COSI) which is promoted by the European Office of the WHO. 17 member states participate in COSI and collect data from children aged 6-9 years using the same methodology and questionnaires.[24] Three questionnaires were originally designed by OMS in English and then translated and adapted to the Spanish population. The first was designed to record the child anthropometric data and completed by trained interviewers. The second one was filled out by parents and designed for recording dietary habits, activity patterns, and sanitary and socioeconomic data. The third one was filled out by the principal of each school who recorded information about school environment.

Each child's body weight and height were recorded, and then BMI was calculated as weight (kg)/height^2 (m^2). All anthropometric measurements were made at the schools in the morning and following norms set out by the World Health Organization[14]. In the present paper we present the prevalence of overweight and obesity by sex and age group using the reference tables for Spanish children[25]. Overweight and obesity are defined by the 85th and 97th percentiles respectively (table II).

The study ALADINO showed a higher percentage of overweight/obesity in boys, and a significant increase in this problem from the age of 7 (table II). It was also found that being overweight was more evident in offspring of parents with lower educational level or lower income. For NW children, 58.5% of mothers and 59.4% of fathers had a university degree, while in the OB group only 14.6% and 14.7% of mothers and fathers respectively reached the same educational level

Being OW/OB was more frequent in children who skipped breakfast (table III). Other studies have found that the higher breakfast quality the higher quality of the whole diet and the better weight control[26,27]. The problem is great in those children who have lunch at home (compared with having this meal at school), and in those with sports facilities far from their home (table III).

Table II
Prevalence of overweight[1] and obesity[2] in Spanish children, by sex and age (ALADINO Study)

	Total	*Boys*	*Girls*
Total (n)	7659	3841	3818
Overweight (%)	14.0	14.1	13.8
Obesity (%)	16.8	19.3	14.2*
With weight excess (%)	30.8	33.4	28.0*
6 years (n)	1822	902	920
Overweight (%)	11.1	10.5	11.7
Obesity (%)	11.5	14	8.9*
With weight excess (%)	22.6	24.5	20.6
7 years (n)	2204	1106	1098
Overweight (%)	13.2	12.1	14.3
Obesity (%)	15.8	18.7	12.8*
With weight excess (%)	29.0	30.8	27.1*
8 years (n)	2126	1081	1045
Overweight (%)	14.9	15.8	14.0
Obesity (%)	18.0	20.2	15.6*
With weight excess (%)	32.9	36.0	29.6*
9 years (n)	1507	752	755
Overweight (%)	16.5	17.6	15.2*
Obesity (%)	21.5	23.6	19.2*
With weight excess (%)	38.0	41.2	34.4*

[1] Overweight was defined as BMI ≥ P85 and < P97. [2] Obesity was defined by BMI ≥ P97. * $p < 0.05$ Significant differences regarding sex.

Sleep duration (reported by parents) was also related to weight control in ALADINO study. NW children slept more hours (9.92 ± 0.70 h/day) than OW (9.84 ± 0.70 h/day) and OB children (9.76 + 0.78 h/day) (differences significant among all groups). Sleep duration was negatively correlated with weight ($r = –0.179$, $p < 0.001$), BMI ($r = –0.130$, $p < 0.001$) and waist circumference ($r = –0.139$, $p < 0.001$). Children who slept less than 8 h/day were more likely to be overweight (OR = 1.67, CI = 1.09-2.55) and to be obese (OR = 2.26, CI = 1.59-3.20), comparing with those who slept more than 10 h/day[28] (fig. 3).

Parents were also questioned about their smoking habits. 54.7% of children were offspring of non smoking parents (NS), while 29.8% of children had one smoking parent (1S) and 15.6% had both smoking parents (2S). 2S children had higher BMI (18.3 ± 3.3 kg/m^2) than NS children (17.8 ± 2.8 kg/m^2, $p < 0.05$). 16.4% NS children were obese versus 19.2% in 1S group and 22.8% in 2S ($p < 0.05$ in all cases). These figures highlight that the smoking habits of parents are associated with the prevalence of obesity in their offspring. This could be explained by the worst dietary habits and lifestyle of the offspring of smokers, especially when both parents were smokers. NS children declared a higher consumption of fruits, vegetables, cheeses, eggs, breakfast cereals and bread, and lower of legumes, soft drinks, milkshakes, snacks, sweets, pastries and ready-to-eat and fast-foods than children with at least one smoking parent ($p < 0.05$ in all cases). A higher percentage of NS children participated in extracurricular sports activities, and spent less time watching television. It is probably that smokers were less concerned about health and nutrition issues, so they could be adversely influencing on the health of their offspring[29].

The dietary habits of the studied children were found far from those ideal, but more so in those children with overweight/obesity, who declared a lower consumption of vegetables, whole milk, meat, fish, sweets and pastries, white bread, pasta and breakfast cereals, and consumed more often diet soda, low fat or skim milk, and bread. No associations were observed between the

Table III
Dietary and lifestyle habits in Spanish children (ALADINO Study). Differences regarding weight

	Normal weight	*Overweight*	*Obese*
¿Did you have breakfast this morning? (Answered by children):			
– Yes (%)	96.9	97.0	95.8
– No (%)	3.1	3.0	4.2
Weekly breakfast frequency (answered by family):			
– All / almost all days of the week (%):	97.7	97.2	96.5*
– Never /less than 3 days/week (%):	2.3	2.8	3.5 *
Where do the children usually have lunch Turing labouring days? (answered by family):			
– At home (%):	52.1	57.6*	59.5*
– At school (%):	47.9	42.4*	40.5 *
Distance between home and sport facilities (answered by family):			
-Less than 1 km (%)	64.8	64.3	60.2*
-More than 1 km (%)	35.2	35.7	39.8 *

* $p<0.05$ regarding normal weight.

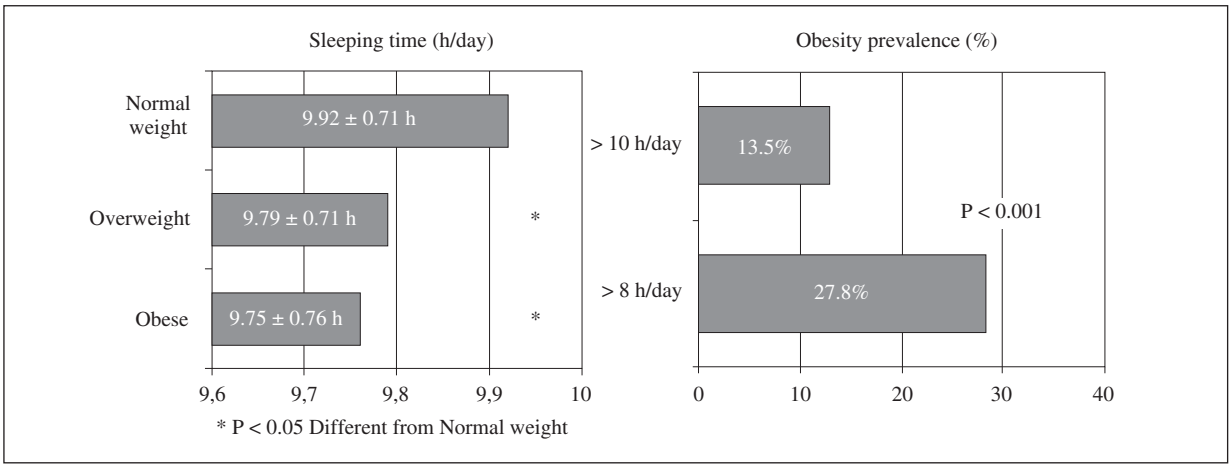

Fig. 3.—Sleeping time in Spanish children. Differences regarding weight status.[28] Villalobos et al (2013).[28]

consumption of fresh fruit and natural fruit juices, vegetables, sugared soft drinks, milkshakes, eggs, cheese, yogurt, snacks or fast food and being overweight/obese.[30]

Other studies have shown associations with different factors. For example, Kipping et al.[5] suggest that modifiable risk factors for childhood obesity are maternal gestational diabetes, high levels of television viewing, low levels of physical activity; parents' inactivity, and high consumption of dietary fat, carbohydrate, and sweetened drinks. Some of these relationships are consistent with those observed in our Spanish population, while other aspects are different.

The results observed in our research on representative samples of the Spanish population in recent years highlight the high prevalence of overweight/obesity in both adult and children, and also point to several factors associated with the problem, which may be subject to future interventions.

The factors that favour obesity in particular populations should be analyzed and monitored in the future, in order to take specific measures and modify them in a more favourable direction.

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Predictors of obesity: the "power" of the omics

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Abstract

During the entire 20th Century, nutrition research experienced and amazing interest and development fueled by the initial success on the fields of malnutrition and the discovery of vitamins and other essential nutrients. During the second part of the Century, it was realized that most common diseases (i.e., cardiovascular diseases, cancer and obesity) had a strong nutritional component. However, from the public health perspective as well as from the point of view of the individual recommendations, current recommendations for healthy nutrition resemble those provided over one hundred years ago. Therefore, modern nutritional research has a great potential of still contributing to improved health for future generations, assuming that the new developments in research and technologies are applied to nutritional problems. Nutrition research must embrace state of the art epidemiology, objective food assessment tools, genomics, epigenomics, transcriptomics, proteomics, metabolomics, metagenomics, advanced biostatistics, imaging, challenge tests, and integration of all data by bioinformatics, under the umbrella of molecular nutrition research. The ultimate goals of future nutritional research are to understand the detailed mechanisms of action for how nutrients/foods interact with the body and with the individual genomes to further the advance of nutrigenomics, thereby providing new tools for disease prevention and treatment.

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Key words: *Nutrigenomics. Metabolomics. Epigenomics. Chronobiology. Obesity.*

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PREDICTORES DE OBESIDAD: EL "PODER" DE LAS OMICAS

Resumen

Durante todo el siglo XX, la investigación en nutrición experimentó un notable interés y desarrollo alentados por el éxito inicial en los campos de la malnutrición y el descubrimiento de las vitaminas y otros nutrientes esenciales. Durante la segunda parte del siglo, se constató que las enfermedades más frecuentes (es decir, las enfermedades cardiovasculares, el cáncer y la obesidad) poseían un fuerte componente nutricional. Sin embargo, desde la perspectiva de la salud pública, así como desde el punto de vista de las recomendaciones individuales, las recomendaciones actuales para una nutrición saludable se parecen a aquellas proporcionadas hace más de 100 años. Por lo tanto, la investigación moderna en nutrición tiene un gran potencial para seguir contribuyendo a mejorar la salud de las generaciones futuras, asumiendo que los nuevos desarrollos en la investigación y las tecnologías se apliquen a los problemas nutricionales. La nutrición en investigación debe incorporar la epidemiología puntera, las herramientas objetivas de evaluación alimentaria, la genómica, la epigenómica, la transcriptómica, la proteómica, la metabolómica, la metagenómica, la bioestadística avanzada, las imagenología, las pruebas de provocación y la integración de todos los datos con la bioinformática bajo el paraguas de la investigación en nutrición molecular. Los objetivos últimos del futuro de la investigación en nutrición deben comprender los mecanismos de acción precisos de cómo interaccionan los nutrientes/alimentos con el organismo y con los genes individuales para avanzar en la nutrigenómica, proporcionando así nuevas herramientas para la prevención y el tratamiento de la enfermedad.

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Palabras clave: *Nutrigenómica. Metabolómica. Epigenómica. Cronobiología. Obesidad.*

Abbreviations

3-UTR (3'-untranslated region).
Apolipoprotein A2 (APOA2).
Cardiovascular diseases (CVD).
Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE).
Endothelial nitric oxide synthase (eNOS).
Genome-wide association studies (GWAS).
High carbohydrate diets (HCD).
High-fat diets (HFD).
Insulin-like growth factors (IGF).
Lipid storage droplet (LSD).
Lyso-phosphatidylcholine (lysoPC).
Metabolic syndrome (MetS).
microRNAs (miRs).
miR recognition element (MRE) seed sites (MRESS).
Nutrigenomics Organization (NuGO).
Partial least-squares-discriminant analysis (PLS-DA).
Perilipin 1 (PLIN1).
Perilipin 4 (PLIN4).
Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α).
Proopiomelanocortin (POMC).
Retinoid X receptor-α (RXRA).
Single nucleotide polymorphisms (SNP).
Suprachiasmatic nucleus (SCN).
Type 2 diabetes (T2D).
United States Department of Agriculture (USDA).

Introduction

Obesity and cardiovascular diseases (CVD) are two dramatic public health burdens that share common underlying mechanisms and afflict most industrialized countries and both are largely influenced by lifestyle, including dietary intake. General recommendations for most CVD —and obesity— related dietary factors are available, but these diseases affect individuals and at-risk subsets (i.e., minorities, elderly) of the population differently. Some of this variability is explained by genetic variation, and in this regard the genetics of CVD, CVD risk factors (e.g. hypertension, dyslipidemia, and diabetes), obesity, or CVD-related phenotypes (e.g., carotid intima media thickness, endothelial function, oxidative stress, and fat distribution) have been explored by several studies, but results are inconsistent and heritability only partially explained. Part of that inconsistency and unexplained heritability could be attributable to complex gene-environment and particularly to gene-diet interactions.[1]

While most environmental factors are discretionary and transitory (e.g. smoking and exercise), nourishment is a necessary, lifelong and universal environmental factor. Gene-diet interactions reflect the fact that genetic variations can predispose individuals to disease while diet can decrease or exacerbate this risk. Nutrigenetics is an emerging discipline that studies the different physiological responses to diet depending on the genotype(s) of each individual. From a nutrition research standpoint, gene-diet interactions likely explain some of the inconsistencies of the diet-disease associations reported in different populations. From a genetic research standpoint, a meaningful gene-diet interaction can neutralize genetic effects (resulting in a null genetic effect). From a public health standpoint, it is critical to distinguish between genetic susceptibility, diet impact, and gene-diet interactions, and to be able to quantify their relative importance as risk factors for morbidity and mortality in an aging population. The proportion of the excess incidence of disease risk that can be reduced by altering the environmental (i.e., dietary) agent can then be estimated and acted upon. A similar discourse applies to the effects, associations and interactions with physical activity. Therefore, nutrigenetics could reveal risks and benefits of specific diets or dietary components to the individual and thus assist the development of personalized dietary recommendations instead of generalized ones. By contributing to the definition of optimal dietary and behavioral (i.e., physical activity and biorhythms) recommendations aimed at preventing disease and promoting optimal health and aging, nutrigenetics offers substantial and prudent direction in the translation of nutrition research into public health recommendations. Accordingly, "personalized nutrition" or "individualized nutrition" approaches are being developed within the USDA (e.g., mypyramid.gov) and already are proposed elsewhere (e.g., Nutrigenomics Organization (NuGO)).

The challenge of accurate and objective dietary assessment

To be effective, the optimal development of evidence-based personalized nutritional guidance for prevention of obesity and other metabolic disorders hinges on an adequate assessment of food intake, nutrient availability, activity, and efficacy. However, assessment of dietary intake has known limitations, including the difficulty of recalling complex food intake patterns over long periods of time. Therefore, the subjective nature of self-reported dietary intake assessment methods presents numerous challenges to obtaining accurate dietary intake and nutritional status. This limitation can be overcome by novel "omic-based" approaches, which can objectively assess dietary consumption (or exposure) without bias of self-reported dietary intake errors.[2] Diet and nutrient biomarkers should provide objective measures of dietary intake and nutritional status, as well as an integrated measure of intake, absorption and metabolism. Thus, the search for an unbiased biomarker of dietary intake and nutritional status is an important aspect of nutritional epidemiology. This also applies to other key environmental factors. Thus, biomarkers of physical fitness are also desired and the need for such developments was addre-

Table I
Methods in Nutritional "omics"

Omics	*Technology*	*Measures*
Genomics	Microarrays Next generation sequencing	SNPs mutations
Epigenomics	Microarrays Sequencing	DNA Methylation Histone modification microRNAs
Metabolomics	Nuclear magnetic resonance Liquid chromatography Gas liquid chromatography Mass spectrometry	Metabolites
Proteomics	Protein microarrays Electrophoresis Mass spectrometry	Proteins and protein modifications
Transcriptomics	Microarrays RNA sequencing	mRNA levels
Metagenomics	Sequencing	Microbe species
Bioinformatics	Mathematical models Statistical methods Data mining Network analysis	Data integration and interpretation

ssed by the Institute of Medicine, which recognized the lack of such tools as a knowledge gap requiring future research. In this context, the application of "omics" techniques, especially metabolomics, represents a promising and needed approach to identify new biomarkers in nutrition assessment, through an integrative application of new technologies in human nutritional research.

Changing the nutritional landscape: the power of omics

Nutrigenetics

The concept of nutrigenetics was already introduced above; however, given the pivotal role that this approach will have on the future of nutrition research and practice, we provide in this section a more detailed description as well as some relevant examples. Nutrigenetics refers to the role of DNA sequence variation in the responses to nutrients, whereas nutrigenomics is the study of the role of nutrients in gene expression. This research is predicated on the assumption that there are individual differences in responsiveness to acute or repeated exposures to a given nutrient or combination of nutrients. Throughout human history, diet has affected the expression of genes, resulting in phenotypes that are able to successfully respond to environmental challenges and that allow better exploitation of food resources. These adaptations have been key to human growth and development. Technological advances have made it possible to investigate not only specific genes but also to explore in unbiased designs the whole genome-wide complement of DNA sequence variants or transcriptome. These advances provide an opportunity to establish the foundation for incorporating biological individuality into dietary recommendations, with significant therapeutic potential.

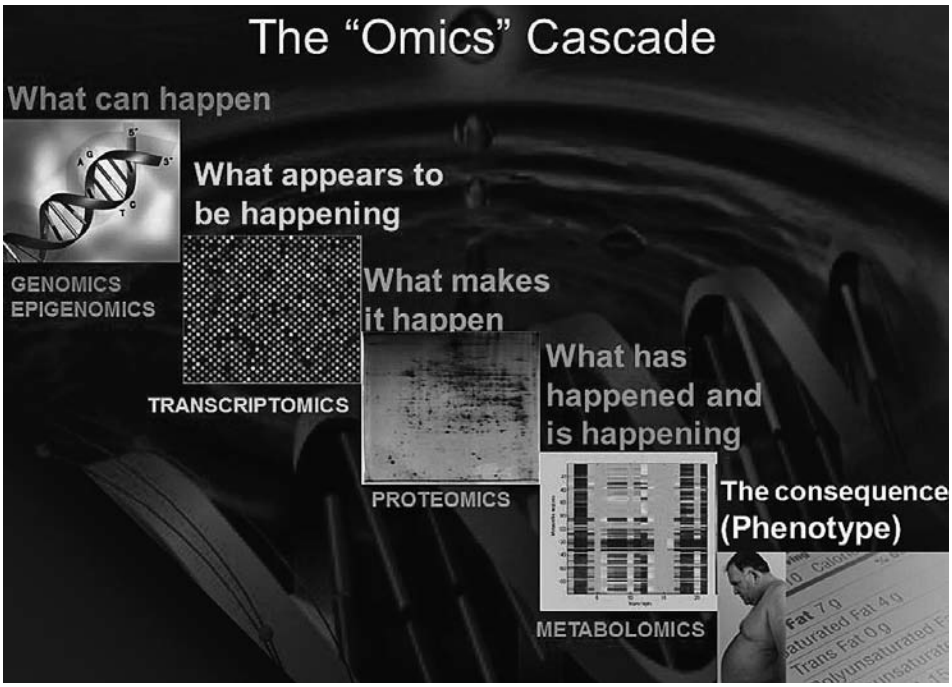

Fig. 1.— Omics cascade showing the specific omic and the biological information provided.

The importance of the genome in nutrition research is self-evident when we consider the multiple processes involved in nutrient handling which need the coordinated working of multiple genes bearing variants that may alter the response to diet. However, the progress of nutrigenetics has been hampered by technological and study design limitations that restricted the number of single nucleotide polymorphisms (SNP) that were examined in past nutrigenetic studies. As part of our research aimed to investigate whether genetic variants found on genes expressed in the adipocyte were associated with obesity risk in human populations and modulated by dietary factors, we have been investigating the perilipin family of genes. Perilipin 1 (PLIN1) is the major protein surrounding lipid droplets in adipocytes and regulates adipocyte metabolism by modulating the activity of enzymes that digest and release the fat in the adipocyte. We have previously identified numerous relationships between PLIN1 gene variants and measures of obesity[3]. In the work described next, we focus on research examining whether dietary macronutrients (e.g. carbohydrates and fats) modulated the associations PLIN1 genetic variants with obesity.[4] For this purpose, we studied a population-based sample of Caribbean-origin Hispanics living in the Boston area and with a high prevalence of obesity and related ailments. In these subjects we found a significant interaction between complex carbohydrate intake and a specific PLIN1 gene variant for waist circumference. When we divided the population into those with low (< 144 grams/day) and high (>/= 144 grams/day) complex carbohydrate intake, we found significantly different effects across PLIN1 genotypes. When complex carbohydrate intake was low, waist circumference was larger in carriers of the PLIN1 polymorphism. Conversely, when complex carbohydrate intake was high, waist and hip circumferences were less in carriers of the polymorphism. These interactions were not found for simple sugars or total carbohydrates. Therefore, we have identified a significant gene-diet interaction associated with obesity at the PLIN1 gene. In subjects with higher complex carbohydrate intake, the gene variant was protective against obesity, whereas in subjects with lower carbohydrate intake, the gene variant was associated with increased obesity. These interactions may be relevant to dietary management of obesity.

A major challenge in the area of gene-diet interactions is the replication of significant findings across different populations. Along these lines, we investigated the role of a functional genetic variant, known as APOA2-265T > C, in the regulation of food intake and body weight. Three independent populations in the United States were examined: the Framingham Offspring Study (1454 whites), the Genetics of Lipid Lowering Drugs and Diet Network Study (1078 whites), and Boston-Puerto Rican Centers on Population Health and Health Disparities Study (930 Hispanics of Caribbean origin)[5]. The results of this study show that people carrying the genetic variant at the APOA2 gene developed obesity only in the presence of a high saturated fat diet. This was true for the three populations and this is the first time that such replication was achieved across populations in research involving gene and diet interactions. This finding will contribute to the identification of individuals susceptible to diet-induced obesity. Moreover, it will guide the implementation of tailored dietary recommendations to specifically quench their increased predisposition to obesity and cardiovascular diseases.

Regardless of the research perspective, be it nutrition research, public health, or personalized diets, a crucial need for robust scientific evidence in support of nutrigenetics remains elusive. Only recently with the advent of genome-wide association studies (GWAS) and huge meta-analysis, we can start examining the interactions between millions of SNPs, dietary factors and the phenotypic trait of interest (i.e., obesity). So far, the number of nutrigenetic studies relying on systematically designed approaches applied to large enough populations has been limited and CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) represents one of the most successful and promising efforts. Although replicating gene-diet interactions is a key step to augment scientific evidence, such interactions must be approached from a more biologically functional angle, integrating higher level interactions that include, genomic and nutritional information, epigenetics, microbiota, and behavioral factors[6] such as physical activity and chronotype. Current gaps in nutrigenomics research may lead to a suboptimal science and partial and fragmented results that delay translation of this science for the benefit of the public. Therefore, in order to move the field forward we need to go beyond genomics and to include in the equation other major "omics". Here we will briefly describe the progress reported around the most promising omics in nutrition research, these being epigenomics and metabolomics.

Epigenomics and Obesity

As stated above, fixed genomic variation explains only a small proportion of the risk of adiposity and epigenetics and epigenomics may help us to understand some of the current gaps in knowledge. Epigenetics refers to the study of mitotically and/or meiotically hereditable changes in gene expression that occur without changes in the DNA sequence. The difference between genetics and epigenetics can be compared to the difference between having all the letters of a text (the DNA sequence) and knowing how to space and punctuate them to provide meaningful sentences (epigenetic modifications). Epigenomics refers to the study of the complete set of epigenetic modifications in a cell or a tissue at a given time. It was Barker and Osmond, using epidemiological observations, who described some of the first links between the impact of environment on fetal development and the subsequent associations with age-related diseases

such as CVD. Results from other studies, such as those coming from the Dutch famine cohort, showed similar findings and provided more mechanistic evidence about the processes involved uncovering connections between epigenetics and environmental factors such as dietary intake.[7]

Work on the three main epigenetic marks and mechanisms (DNA methylation; chromatin organization by histone modifications; and noncoding RNAs) affecting obesity is growing fast and some of the progress is presented here. First, in relation to DNA methylation, this is a major epigenetic mark that involves the addition of a methyl group to a cytosine positioned next to a guanine nucleotide (CpGs) usually in regions with a high presence of CpG dinucleotides. Methylation usually results in the repression of gene expression. Most of the evidence linking epigenetics with obesity has relied on animal studies. In animal models, maternal diet alters offspring body composition, accompanied by epigenetic changes in metabolic control genes.[8]

In humans, and as reviewed by Norheim et al.[6] twin studies have shown that DNA methylation profiles were more divergent in older twins than in infant twin pairs, suggesting that environmental factors may influence the epigenome. Diet-induced weight loss for 8 weeks in obese men altered DNA methylation in peripheral blood mononuclear cells of specific genes. Changes in DNA-methylation levels among humans with metabolic diseases were associated with alterations in expression of genes involved in mitochondrial function, including PGC-1 . Reduced PGC-1 activity is linked with the pathogenesis of metabolic diseases as it increases metabolic and cardiovascular risk and precedes the development of Type 2 diabetes (T2D). Interestingly, whereas palmitate and oleate can acutely induce methylation of the PGC-1α promoter, exercise induces hypomethylation of PGC-1α in skeletal muscle. The hypomethylation of the PGC-1α promoter in response to exercise was paralleled with an increase in PGC-1α mRNA content.

Interestingly, the relation between maternal nutrition, methylation and offspring obesity has been shown quite convincingly in humans by Godfrey et al.[9] revealing some exciting and promising findings. These investigators used Sequenom MassARRAY to measure the methylation status of 68 CpGs 5' from five candidate genes in umbilical cord tissue DNA from healthy neonates. They related methylation status to maternal diet during pregnancy to child's adiposity at age 9 years. The initial findings revealed that retinoid X receptor-α (RXRA) and endothelial nitric oxide synthase (eNOS) methylation had independent associations with sex-adjusted childhood fat mass ($P = 0.009$ and $P < 0.001$, respectively) and %fat mass ($P = 0.023$ and $P = 0.002$, respectively). Regression analyses including sex and neonatal epigenetic marks explained >25% of the variance in childhood adiposity. Higher methylation of RXRA, but not of eNOS was associated with lower maternal carbohydrate intake in early pregnancy, previously linked with higher neonatal adiposity in this population. These investigators sought replication in a second independent cohort, where they found that cord eNOS methylation showed no association with adiposity, but RXRA methylation showed similar associations with fat mass and %fat mass (both $P = 0.002$). Therefore, these findings support the notion, previously suggested by the Barker hypothesis, that a substantial component of metabolic disease risk has a prenatal developmental basis. Moreover, in addition to genetic testing, perinatal epigenetic analysis may have utility in identifying individual vulnerability to later obesity and metabolic disease.

In relation to histone modifications, the second epigenetic mechanism or mark, it is important to underscore that DNA in cells is packaged as chromatin in a "beads on a string" configuration. The fundamental unit of chromatin is the nucleosome, which consists of 146 bp of DNA wrapped around a histone octamer (made up of two copies of four core histones: H2A, H2B, H3, H4). The N-terminal histone is subjected to a variety of post-translational modifications that include acetylation, methylation, phosphorylation and ubiquination. Gene activation correlates with the hyperacetylation of histones H3 and H4, whereas hypoacetylation correlates with inactive chromatin[8]. The relation between this epigenetic mark and obesity has been less studied, bit some promising findings, in animal models, are already supporting the importance of this epigenetic mechanism in relation to obesity. This is the case of the work by Masuyama and Hiramatsu[10] who investigated in a mouse model the potential epigenetic mechanisms linking a maternal high-fat diet exposure in utero with metabolic syndrome in the offspring. For this purpose, they examined whether the offspring from dams exposed to a high-fat diet during pregnancy (OH mice) exhibited hypertension, insulin resistance, and hyperlipidemia along with epigenetic changes in the expression of adipocytokine, such as leptin and adiponectin. OH mice were significantly heavier than the offspring of dams exposed to a control diet during pregnancy (OC mice). OH mice exhibited higher blood pressure and worse glucose tolerance than the OC mice at 24 wk. Total triglyceride and leptin levels were significantly higher and the adiponectin level was significantly lower in OH compared with OC mice at 12 wk of age. This was associated with changes in leptin and adiponectin expression in white adipose tissue. There were lower acetylation and higher methylation levels of histone H3 at lysine 9 of the promoter of adiponectin in adipose tissues of OH mice at 2 wk of age as well as at 12 and 24 wk of age compared with OC mice. In contrast, methylation of histone 4 at lysine 20 in the leptin promoter was significantly higher in OH compared with OC mice. Thus, exposure to a high-fat diet in utero might cause a metabolic syndrome-like phenomenon through epigenetic modifications of adipocytokine, adiponectin, and leptin gene expression. The fact that these changes were observed in adipose tissue under-

scores the difficulty to carry similar studies in human and the need to rely on experimental models to advance our mechanistic knowledge.

Finally, another important and novel aspect relates to the study of noncoding RNAs or microRNAs (miRs) which are often classified to be part of epigenetics. miRs are small non-coding RNA molecules derived from hairpin precursors, usually between 20 and 30 nucleotides in length. They normally bind to the 3-UTR (3'-untranslated region) of their target mRNA through imperfect base pairing, leading to translation inhibition and/or mRNA degradation. Over 1000 miRs have been found in the human genome, and it has been estimated that they could regulate 74-92% of all protein encoding mRNAs. Considering the complex level of gene expression regulation conferred by miRs, it comes as no surprise that miRs are involved in processes associated with obesity, such as adipocyte differentiation, insulin action and fat metabolism.[6,8]

Our own work provides interesting connections between miRs, genetics, obesity and dietary modulation. This is the case of PLIN4, a member of the PAT family of lipid storage droplet (LSD) proteins.[11] We investigated the associations between seven SNPs at human PLIN4 with obesity related phenotypes. Samples consisted of subjects from two populations of European ancestry. We demonstrated association of one the SNPs (rs8887) with anthropometrics. Meta-analysis demonstrated significant interactions between the rs8887 minor allele with PUFA n3 modulating anthropometrics. rs884164 showed interaction with both n3 and n6 PUFA modulating anthropometric and lipid phenotypes. In silico analysis of the PLIN4 3'UTR sequence surrounding the rs8887 minor A allele predicted a seed site for the human miR-522, suggesting a functional mechanism. Our data showed that a PLIN4 3'UTR luciferase reporter carrying the A allele of rs8887 was reduced in response to miR-522 mimics compared to the G allele. These results suggest variation at the PLIN4 locus, and its interaction with PUFA as a modulator of obesity related phenotypes, acts in part through creation of a miR-522 regulatory site. This is the first example of a genetic variant that creates a miRNA binding site that influences obesity-related traits through a gene-diet interaction. Although further research is necessary, the findings suggest that miRNA activity is a possible target for dietary-based weight-loss therapies for obesity. Therefore we conducted a genome-wide survey for SNPs altering microRNA seed sites identifies functional candidates in GWAS. We focused on functional variants related with the binding of microRNAs (miR), we utilized SNP data, including newly released 1000 Genomes Project data to perform a genome-wide scan of SNPs that abrogate or create miR recognition element (MRE) seed sites (MRESS). We identified 2723 SNPs disrupting, and 22295 SNPs creating MRESSs. We determined that 87 of these MRESS SNPs were listed in GWAS association studies, or in strong LD with a GWAS SNP, and may represent the functional variants of identified GWAS SNPs. Furthermore, 39 of these have evidence of co-expression of target mRNA and the predicted miR.[12] We also gathered previously published eQTL data supporting a functional role for four of these SNPs shown to associate with disease phenotypes. The potential of miRNA-based therapeutics targeting obesity is high and might lead to breakthroughs in the treatment of obesity.

Metabolomics

Another "omic" that is being deeply investigated in relation to obesity is Metabolomics, which refers to the types and concentrations of all metabolites in a biological sample. Biological metabolites are specific products of genomic, transcriptomic and proteomic processes of the host or external organisms. The characteristics and concentrations of all small molecules, provide a potential for measuring flux through all important biological pathways, and thereby allow detailed understanding of how metabolites interact with tissue components of functional importance[6]. Moreover, as indicated above, metabolomics can also be used to identify biomarkers for intake of specific nutrients and health. For example it has recently been shown in an meta-analysis that blood concentrations of carotenoids, a biomarkers for fruit and vegetable intake, are more strongly associated with reduced breast cancer risk than are carotenoids assessed by dietary questionnaires.[6]

Ideally, metabolomics should have the ability to provide a detailed snapshot of biological processes at any particular point in time. In nutritional research, such an approach may provide an opportunity to identify changes in metabolic pathways induced by nutrients or other life-style factors, to explore relationships between environmental factors, health and disease, and to discover novel biomarkers.[6] However, due to the diverse chemical nature of low-molecular metabolites, including lipids, amino acids, peptides, nucleic acids, organic acids, vitamins, thiols and carbohydrates, the global, untargeted analysis represent a tough challenge. Although development of analytical platforms enables separation, detection, characterization and quantification of a large number of metabolites from only minor amounts of biological samples, targeted metabolomics are most often used.

Targeted analysis, where a pre-defined set of metabolites are monitored, may be used for assessment of single nutrients or metabolites, determination of subsets of metabolites, including lipids, inflammatory markers or oxidative damage.[6] The profiling of lipids has developed into its own field of lipidomics, and as adversely altered lipid metabolism is an underlying factor in a number of human chronic diseases, lipidomics has become an important tool to identify potential novel therapeutic targets.[6]

Although metabolomics gain increased interest in nutrition research, there are still some major limiting

factors. In untargeted metabolomics, there are many unidentified metabolites. The high number of unknown signals makes it often difficult to extract meaningful information. Thus, there is a great need for publically available databases for the identification of metabolites.[6] Furthermore, the use of pattern-recognition techniques is crucial for exploring novel molecules that may serve as biomarkers. Moreover, the data sets based on metabolomics are usually huge and multi-dimensional. The metabolomics data should be compiled along with data on transcriptomics and proteomics, supporting more extensive use of bioinformatics including multivariate analyses.[6]

In the specific case of obesity, there is a great interest in applying metabolomics to examine alterations in the metabolic profile according to weight gain/obesity and identify metabolomic signatures.[13] Using targeted serum metabolomics of 163 metabolites, 12 of them were found significantly related to obesity. Among those, glycine, glutamine and glycero-phosphatidylcholine 42:0 (PCaa 42:0) serum concentrations were higher, whereas PCaa 32:0, PCaa 32:1, and PCaa 40:5 were decreased in obese compared with lean individuals. Likewise, using obese and lean mice fed on high fat or normal diets it was found that liver and serum metabolites analyzed using MS with partial least-squares-discriminant analysis (PLS-DA) of were able to clearly discriminate between obese and lean groups and major metabolites contributing to the discrimination were assigned as lipid metabolites, lipid metabolism intermediates, amino acids, acidic compounds, monosaccharides and serotonin. A high-fat diet increased lipid metabolites, but decreased lipid metabolism intermediates, indicating that abnormal lipid and energy metabolism induced by a high-fat diet resulted in fat accumulation via decreased b-oxidation. It revealed that the levels of many metabolites, including serotonin, betaine, pipecolic acid and uric acid, were positively or negatively related to obesity-associated diseases. These metabolites can be used to better understand obesity and related diseases induced by a hyperlipidic diet. The differences in metabolomic profiling were also investigated between overweight/obese and normal-weight men.[14] Three lyso-phosphatidylcholine (lysoPC) were identified as potential plasma markers and confirmed eight known metabolites for overweight/obesity men. Especially, overweight/obese subjects showed higher levels of lysoPC C14:0 and lysoPC C18:0 and lower levels of lysoPC C18:1 than lean subjects. Results confirmed abnormal metabolism of two branched-chain amino acids, two aromatic amino acids, and fatty acid synthesis and oxidation in overweight/obese men. Furthermore, the level changes of these metabolites can be used to assess the risk of obesity and the therapeutic effect of obesity management.

The growing problem of obesity at younger ages has attracted also the interest of metabolomics as investigation of serum metabolite concentrations in obese children might give new insights into biological mechanisms associated with childhood obesity. In this regard, serum samples of obese children were analyzed using a MS-based metabolomics approach targeting 163 metabolites.[15] Fourteen altered metabolites were significantly altered in obese children. The identified metabolite markers are indicative of oxidative stress and of changes in sphingomyelin metabolism, in b-oxidation, and in pathways associated with energy expenditure and might be considered as potential biomarkers on the biological mechanisms behind obesity. High-fat diets (HFD) and high carbohydrate diets (HCD)-induced obesity through different pathways, but the metabolic differences between these diets are not fully understood. In summary, metabolomics approaches have the potential to bring new tools to fight obesity. Among other things, it has the potential to generate novel non-invasive diagnostic tests, based on biomarkers of metabolic dysregulation, which are simple and cost-effective.

Metabolic flexibility, chronobiology and obesity

Some of the health disparities reported above relate to the impaired adaptation of an ancestral genome to a new environment, similar to what in the sociological field is known as lack of acculturation. The fact is both, in the short term (i.e., day to day variation in food intake or physical activity) and over the long term (i.e., human migrations) we are exposed to a constantly changing environment to which our physiology has to adapt. This adaptive capacity requires a metabolic flexibility that is key to maintaining overall homeostasis and thus, to a healthy life in old age. An individual's capacity to respond to environmental challenges has a strong genetic component, and our long-term translational objective aims to uncover the optimal environment (i.e., diet, physical activity, biorhythms) that will maintain sufficient metabolic flexibility for an individual's genetic architecture. In this regard, the circadian clock governs a large array of such physiological functions that maintain our metabolic flexibility, and current studies suggest that interruption of the circadian system may contribute to metabolic syndrome (MetS) and obesity-related complications.[16] Moreover, metabolic processes are aligned with the periodic environmental changes and behavioral cycles, such as the sleep/wake and fasting/feeding cycles. Thus, a precise estimation of an individual's internal body time may be a key component to facilitate metabolic homeostasis. Relative to dietary intervention, the timing of food intake may contribute to weight gain and metabolic disease because energy homeostasis and circadian rhythms are molecularly and physiologically interconnected.[16] Consequently, altering the timing of food intake can alleviate or exacerbate diet-induced obesity.

The role of this circadian system, including such central components as CLOCK, BMAL1, PER2 and CRY1/CRY2, in human obesity has been demonstrated by clock genes variants in association with obesity and

metabolomic outcomes.[17-19] Moreover, although the circadian systems are controlled by the master pacemaker located in the suprachiasmatic nucleus (SCN), other endogenous oscillators are found essentially in every cell in the body, and mounting evidence suggests that these local oscillators regulate critical functions in most organs. In this regard, our observation that the basal expression of clock genes in human adipose tissue is associated with abdominal fat content and cardiovascular risk factors is significant.[20-24]

Recently, miRs (microRNAs) have emerged as significant players in circadian clock timing, thus implicating clock-controlled miRs and/or miRs controlling clock genes as contributors to disorders related to the circadian system. Hence, miRs present novel therapeutic targets for disorders of the circadian clock. Examples include miRs both regulated by the circadian system and regulating circadian period length and clock resetting,[25] miRs that show rhythmic fluctuations in circulating levels, and miRs under circadian control with roles in hepatic lipid metabolism. Chronodisruption, a dysregulation of the finely tuned central/peripheral synchrony, impairs the response to time-based signals, and the resulting disruption in peripheral clocks (e.g., skeletal muscle, adipose) impairs homeostasis for energy, glucose, and immunity leading to obesity, MetS and systemic inflammation. Therefore, understanding of chronodisruption, its molecular basis, its responsiveness to timing and quality of the diet, and potential therapies provides an exciting entry point for unraveling and ameliorating the diseases of unhealthy aging. To this end, we have been emphasizing obesity and its effects on age-related diseases; however, another hallmark of unhealthy aging is sarcopenia, in which skeletal muscle loss is accompanied by muscle weakness and adipose accumulation. We propose that chronodisruption may medicate sarcopenia. Suggestively, chronodisrupted animals exhibit a premature aging phenotype, complete with sarcopenia, systemic inflammation, and circadian behavioral disturbance and loss of the characteristically rhythmic gene expression patterns in peripheral circadian targets. Although chronodisruption appears to mediate unhealthy aging, mechanistic understanding of central-peripheral clock cross-talk and its dysregulation is limited, especially in humans. Equally critical, but unidentified, are remedies that will rescue the chronodisrupted phenotype. Light and feeding regimes synchronize and reset the clocks to some extent, but the role of physical activity remains unexplored. Through its targeting of peripheral clocks in relevant tissues (i.e., muscle and adipose), the feedback provided by physical activity potentiates strengthening of homeostatic circadian regulation.

Building networks

In the pursuit of health, considerable effort has been placed in defining and cataloging diseases and we have made significant advances. However, the ability to precisely define health has met with less success. "Optimal health", from a metabolic and physiological point of view, can be defined as an organism's ability to maintain or regain homeostasis in an ever-changing environment, and especially in response to a wide range of stressors ("buffering capacity"). For an organism to remain stable (healthy) even in the presence of unpredictable changes, it must be able to adjust molecular parameters within cells and organs to match the situation. This can be achieved by appropriate changes in protein functions, either by direct modifications or indirectly via gene expression. Thus, the organism is in fact continuously changing its phenotype (defined as the observable properties of an organism as produced by the interaction of the genotype and the environment). The efficiency and timeliness of these phenotypic adjustments to new situations will determine its health and healthy aging. The individual's capacity to adapt in time and location to alterations in external conditions is called "phenotypic flexibility".

As indicated above, nutrition plays a key role in promoting health and healthy aging. In mammals, downregulation of the activity of several nutrient-sensing pathways (e.g. insulin/IGF-1/mTOR) induced by dietary restriction, mutations or chemical inhibitors promotes an increase in health status, lifespan, and preservation of biological functions in more "youthful-like" states. Dietary restricted animals are also more metabolically flexible and resistant to many types of stresses (e.g. surgery, radiation, acute inflammation, exposure to heat, and oxidative stress) as compared to those fed ad-libitum. A prime feature of phenotypic flexibility is that alterations in the availability of the different energy substrates and metabolites can be resolved by the various metabolic compartments involved (plasma, muscle cell, adipocyte, liver) in a time- and magnitude-dependent manner. Phenotypic flexibility thus is a 3-dimensional (time, location and extent) measure for all processes underlying metabolic adaptation. "Metabolic flexibility" is one of the important aspects of phenotypic flexibility and refers to "the capacity of the organism to adapt fuel oxidation to fuel availability." Most tissues undergo rapid changes in the flow of nutrients and metabolites between the fasting and fed states. Major regulators in this rapid adaptation to catabolic and anabolic states are insulin and insulin-like growth factors (IGF) with reciprocal changes in circulating levels of glucagon and catecholamines and glucocorticoids.

Building upon metabolic flexibility and its foundation in numerous inter-related processes, we view obesity and its complications (e.g., CVD and T2D) as multifaceted, involving numerous organs, cell types, biological pathways as well as genetic variation, metabolite levels, circadian status and gene expression activity. Thus, in a manner that takes its cues from cancer genomics, we need to implement state of the art computational biology tools to uncover high-level interactions between genetic, epigenetic and environmental factors responsible for maintaining the balance between health and

disease. Current and future research needs to capitalize on the use of data generated using high-throughput omic techniques (genomics, epigenomics, transcriptomics, and metabolomics), both in ongoing studies of free-living ethnically diverse populations and in the metabolic ward (intervention studies). The primary focus of this effort is to identify new genomic, epigenomic and metabolomic biomarkers to apply individually or in concert as indicators of metabolic health as well as for early detection of metabolic disruption. These indicators will act as predictors of the health consequences derived from an individual's interaction with environmental challenges with special emphasis on cardiovascular health and obesity prevention especially in an aging population. We need to build interaction networks of relevant phenotypes, aging and nutrition in which diet, health/disease biomarkers, genetic variants, biological processes and gene activity are linked in a manner that permits the generation of new, testable hypotheses.

However, these networks will not be complete without the inclusion of the microbiota, an emerging player in obesity. The human gastrointestinal tract is estimated to host up to 10^{14} microorganisms, tenfold the number of human cells, predominately composed of bacteria. Together they make up the gut microbiota, which during normal circumstances live in a commensal or mutualistic relationship with their host. Although humans can live with a bacteria-free intestine the microbes are crucial for human health. For example, the gut microbiota metabolizes indigestible carbohydrates to valuable short-chain FAs; synthesize certain vitamins; degrade oxalates and is essential in recirculation of bile acids.[6]

Traditional *in vitro* cultivation has limited the research on gastrointestinal bacteria because their normal growth environment is complex and difficult to imitate. Thus, the introduction of gene-sequencing has markedly extended the knowledge about their species diversity. Between 500 and 1000 different species occupy a single human gut, whereas the total microbiome in humans include between 10,000 and 40,000 species. However, the majority of microbes within the digestive tract appear to include less than 100 different species.

Development of next-generation sequencing have permitted mapping of the microbial metagenome in humans and 3.3 million non-redundant microbial genes have been annotated with 536,000 prevalent unique genes detected in each individual. Among these are genes involved in the biosynthesis of short-chain fatty acids, amino acids and certain vitamins, which all are molecules suggested to be provided by bacteria to humans.[6]

How nutritional habits interfere with the intestinal microbiota is far from understood. It was traditionally believed that the microbe composition was relatively unchangeable, but DNA sequence analyses have challenged this view. Studies have clearly shown that the composition of gut microbiota adapt during changes from breast milk to solid food and when altering the composition of ingested macromolecules.[26] In terms of obesity, certain bacteria, specifically the archaeon Methanobrevibacter smithii, have enhanced ability to metabolize dietary substrate, thereby increasing host energy intake and weight gain. With weight loss, there is a decrease in the ratio of Firmicutes to Bacteroidetes phyla and the research in this area is booming to identify approaches with pre-, probiotics or more novel approaches, to tilt the balance of the gut microbiota towards a less obesogenic mix.

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Do we really know the composition of our foods?

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Abstract

We are currently witnessing important changes in the feeding patterns of the world population, especially in developing countries. These changes are leading to higher incidence of overweight, obesity, and non-communicable chronic diseases. These changes are influenced by a series of factors regarding the food, the individual, and the environment, which determine the selection of foods to buy and consume.

The knowledge of our foods, such as their composition and the technological and cooking processes, among others, is important given their impact on the nutritional status and health. One of the key steps in the decision of what foods we incorporate to our diet is the time spent for shopping. Therefore, it would be important to develop standardized and computerized systems for food classification that connected to databases of foods composition could bring real time information about nutrients and energy content, as well as other food components. The most developed system so far is LanguaL ("Langua aLimentaria"). We should also be knowledgeable on how cooking modifies not only the orosensorial properties but also the nutritional and health aspects of foods. Nowadays it is almost essential to also be informed about the foods we consume out of our homes, such as in collective canteens or restaurants given the work and school timetables, as well as leisure time.

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Key words: *Food composition. Food choices. Food transition.*

¿CONOCEMOS LA COMPOSICIÓN DE NUESTROS ALIMENTOS?

Resumen

En la actualidad estamos asistiendo a cambios importantes en los patrones alimentarios de la población mundial, especialmente en los países en desarrollo. Estos cambios están conduciendo a una mayor incidencia de sobrepeso y obesidad y de enfermedades crónicas no comunicables. Estos cambios vienen influenciados por una serie de factores del alimento, el individuo y el medio que determinan la elección de los alimentos a comprar y consumir.

El conocimiento de nuestros alimentos, como su composición y los procesos tecnológicos y culinarios a los que se han sometido entre otros, es importante por sus repercusiones en el estado nutricional y en la salud. Uno de los momentos claves en la decisión de que alimentos incorporar a nuestra dieta es el momento de comprarlos. es importante que se desarrollen sistemas estandarizados de clasificación de alimentos que conectados a bases de datos de composición puedan, a través de sistemas informatizados, aportar información en tiempo real acerca del contenido en nutrientes y energía y de otros componentes alimentarios. El sistema más desarrollado es LanguaL ("Langua aLimentaria"). También debemos conocerlos cuando los cocinamos ya que se modifican no solo en sus propiedades orosensoriales sino en sus aportes nutricionales y aspectos de salud. En la actualidad también se hace casi imprescindible la información sobre los alimentos que consumimos fuera del hogar, en comedores colectivos o restaurantes, debido a los horarios laborales y escolares y al ocio.

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Palabras clave: *Composición de los alimentos. Elección de alimentos. Transición alimentaria.*

The food offer

The first definition of the Spanish Royal Academy of Language for the foods that comprise our usual diet is: "*The set of things that humans and animals eat and drink to survive*". The second definition states: "*Each one of the substances that a living body eats or receives for its nutrition*".[1]

Today the range of foods offered to the consumer is notably higher than that existing only 30 years ago. Nowadays, we usually buy the foods that we consume in big supermarkets and exceptionally in local neighborhood grocery stores. If we stand by the line of for example dairy products at a supermarket, we may observe that there exist several types of milks: whole milk, semi-skimmed milk, skimmed milk, vitamins-enri-

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ched, calcium-enriched, with isoflavones, etc., and other dairy products in which the fat content has been substituted: milk with omega-3, milk with olive oil, milk with omega-3 and nuts. Regarding yogurts, there is a similar situation: there are multiple variants considering the probiotic used, the fat content, the presence of foods of other origins such as fruits, grains, etc., the addition of other nutrients or different bioactive components (phytosterols, isoflavones, fiber, etc.). A similar situation occurs when we enter the area of products derived from cereals, an example of this being the different breads offered: brown bread, bread with nuts, olives, tomato, onion, garlic and oil, rye bread, soy bread, etc. All this makes the consumer be hesitant when he has to choose a food to take part of his daily diet. By contrast, the offer is much reduced at local grocery stores where there only are the basic foods that, by the way, are those more often consumed and that we can buy almost everywhere.

The other issue to consider of the current food offer is the increasing presence of highly processed foods that take part of our daily diet. For instance, we may buy easy-to-cook fish and vegetables packs ready to fry (snacks, delicatessens, sticks, etc.), bars with grains, nuts, or fruits, or industrial bakery products (laces, donuts, muffins, *ensaimada*, croissants, *napolitana*, *caña*, etc.). Also pre-cooked foods are being offered more and more at the supermarkets, the so-called "ready-to-cook" and "ready-to-eat" products of fourth and fifth generation.

Changes in the feeding pattern

Since the last decade of the 20th Century and the first of the 21st, we are unquestionably witnessing important changes in the feeding patterns worldwide, not only in developed countries but also, and most especially, in developing ones. Some people speak about the globalization of feeding. It is expected that these changes may be more pronounced in the next 20 years.

The main conditioning factors implicated in the future changes of the feeding patterns are:[2]

— The slowing down in the population growth, as has been published by the United Nations in 2003.[3] This fact would determine greater availability of foods for the population, meaning an increase in the available energy of about 300 Kcal/person/day.
— An increase in the urbanization of the population. It is thought that the population increase will be in urban areas in the following years. This situation implies important feeding changes derived from a higher participation of women in the working population. As a consequence, home cooking of the foods, which is labor intensive, would be relegated with greater presence of pre-cooked foods ready to be consumed and fast foods and snacks out of the main meals. Urbanization also implies important changes and convergences in big areas of the planet. Urbanization facilitates the commerce between countries. All this makes that traditional diets will progressively be changed by others with higher amounts of processed foods, rich in sugar, fat and energy.

  Besides, increasing urbanization has led to a significant increase in sedentarism, with a reduction in the energy waste that has been calculated in 10-15%.[4]
— Globalization in food distribution and the emergence of supermarkets and big shopping areas worldwide, especially in developing countries. Transportation and preservation methods. The easiness of transporting food products all over the world has significantly contributed to these changes in world feeding habits. This transportation easiness is not only based in more effective and frequent aerial, sea, and terrestrial transportations, but also in the parallel development of preservation methods of foods so that they can reach the consumers in the best preservation conditions, both organoleptic and of food safety. Not too long ago, it was not easy to have a fresh tomato in January, unless it was a canned food. Today, we have tomatoes in wintertime, tropical fruits in countries with an almost polar climate, etc.
— We should also highlight that supermarkets offer more varied, safe and cheaper products to the population, which determines important changes in the feeding patterns, for instance, higher consumption of dairy products and derivatives, but also of non-healthy snacks and platforms for chains of fast food and junk food restaurants.

  This has led to a uniformity of the diet of the populations from different countries, which was based before more fresh products, the so called seasonal and local products. In this regard, it is important to highlight the immigration phenomenon and its consequences in the introduction of foods from the countries of origin. It is not only the introduction of foods in the grocery stores but also the opening of restaurants offering the gastronomy of those countries to the immigrants and also to the population of the host country. Today we may find in every city a Chinese, Thai, Japanese, Mexican, Arab restaurant, etc.
— The rapid increase of the population money income, although with important regional differences, has increased, and will still do so, the buying power for the general population, especially in urban areas. This fact is determined by the lower population increase mentioned above, which changes the population structure. Thus, the segment of active population increases and the expenses in education and pensions decrease. Unquestionably this changes the access to foods and consequently the dietary pattern.
— The elderly population has also an impact on the dietary pattern. In this scenario, the parents and

grandparents focus their attention on the little number of descendants, for example as in China with only one child, which has increased and will increase, from a feeding perspective, pediatric overweight and obesity.

— Mass media. Today communications are one of the tools that have more developed. In audiovisual media particularly, although also in the advertisement spaces, magazines, and even in the opinion columns of the paper media, it is talked about foods, new foods, new feeding trends, foods for all, functional foods, foods for losing weight, for better sleeping, for getting energy, for getting rid of stress, etc. This mass media "bombarding" that reaches many millions, makes the consumers assimilate this messages and, at first by curiosity, and then by orosensorial or hedonic reasons,they incorporate these new foods in their usual diet. This phenomenon is worldwide.

— The work and school timetables have determined that at least one (lunch) and sometimes two (breakfast and lunch) of the daily meals are done out of the house, either at the workplace, the school, or at a restaurant. Again, this situation affects the feeding pattern of the population since part of it is determined externally by the menus offered by the catering service or the restaurant.

— Social networks and leisure also condition the dietary pattern. Currently almost all social events are celebrated around a table, in a broad sense: cocktails, receptions, etc. The role played by the big characters of cooking and popular chefs is also important. Today every paper publication, television or radio station allocates part of their programming to cooking, gastronomy, etc. This fact, together with food advertisements, has an unquestionable impact on the consumers' attitudes towards foods regarding foods choice and cooking techniques.

What does the consumer look for when he buys food?

One of the determinant factors of the feeding pattern of the people is the selection of the foods they are going to eat. Every day we make several decisions regarding the food: where to eat, what to eat, with whom, and when. In this sense, it is important to analyze what are the main reasons influencing a consumer to buy and/or consume a food.

The determinant factors in food choice are complex and are related with: 1) the food; 2) the person making the choice; and 3) the current physical and social environments.[5]

1) As regards with the food, the choice is determined by the orosensorial properties including the sight, the taste, the smell (the flavor as an integrated perception), and the texture with the inter-individual differences there exist.

   Satiety also has an influence, being determined by the orosensorial properties, which also determines the diversity of foods in our usual diet. The size of the servings also has an influence. This is what happens when we eat at a free buffet with a great diversity of foods with different sensorial properties and with high palatability as compared to a traditional meal of an individual menu.

   The existence of taste preferences and aversions, which are conditioned by previous experiences with post-intake consequences of particular foods on our body, also have an influence.

   We should also think about that the previous hunger or satiety state determines the orosensorial conditioning factors of the available foods. We should also include in this context the social experiences with food, such as the social environment and the family.

2) The determinant factor related with the individual may be classified in intra-personal and inter-personal, being related with the perceptions, feelings, and expectations towards the food.

   Regarding the intra-personal factors, the people want that their foods to the tasty, easy to eat, cheap, nutritive, and familiar. When buying and eating a food, the consumers value the taste, the easiness to get it and eat it, the price, the quality, the freshness the nutritional value, or the family preferences. The ranking is different in the different countries. In the USA the first factor is the taste whereas in Europe it is the quality and/or the food freshness. In all this process the environmental stimuli (diseases of known people related with the consumption of foods), the relations between different foods (between healthy properties, palatability, and cultural expectations), the knowledge on foods and feeding and nutrition (daily servings of fruits and vegetables that have to be consumed or the foods composition) take relevance. Also, the social and cultural rules.

   Regarding the inter-personal conditioning factors, the family, the workmates, and the social interactions.

   In Spain, a study performed by the Ministry of Agriculture, Food and Environment (MAGRAMA) showed that the consumer looks in foods for quality, convenience, pleasure, time, and health. From this information, the food choice is based on quality but mainly organoleptic more than nutritional value. This same study shows that what determines most food buying is the proximity of the grocery store (54.8%), the quality (54.0%) and the economic issue (prices) (35.3%). It may be observed that the nutritional issues are not among the reasons considered for buying a food, at least explicitly, although within the term quality the nutritional quality may

be implied although hedonic quality comes in the first place most frequently.[6]

3) Social and environmental determinant factors should be taken into account when explaining the choice of foods to be consumed.

Regarding the physical environment built by mankind, the availability and accessibility to foods are one of the choice factors. Today there are more than 50,000 foods or feeding products easy to handle, cook, and eat at a supermarket, and this figure increases year by year. Therefore, the availability and accessibility to foods is impressive. On the other hand, the type of facility in which we get our food influences our choice. The amount and quality of the foods we select are determined by the offer of small grocery stores versus the big supermarkets, the physical location of the first ones close to homes versus the second ones, generally located at the outskirts of the cities needing transportation, and the prices in ones and the others. The determinant factors for food choice of meals outside the home should also be considered and depend on the presence of canteens at the place (workplace, school, residence, etc.) and the establishments that offer meals close to the worksites. At last, this physical environment determines physical activity patterns —sedentarism, of special importance in relation to the feeding patterns and non-communicable chronic diseases.

The social structures and the cultural environment are also important conditioning factors in food choice. The social relationships, including the family, may lead to dietary patterns different from those that we would have in the case we eat alone. The cultural issues in a broad sense also determine the food choice in our diet, even in the current multi-ethnic societies.

Finally, other determinant factors in food choice include economic factors (prices, incomes, the family structure, education, etc.) as well as information factors, especially advertising.

Why should we know the foods we consume?

The knowledge of food composition is important because of its repercussion on the nutritional status and thus health. Today, it is a fact that obesity has reached pandemic proportions and diet-related chronic diseases are still increasing, being the main cause of morbidity and mortality worldwide. On the other hand, as mentioned above, there are more than 50,000 foods at a supermarket and we have to choose which ones are going to be part of our diet. Besides, the daily pace and the work and school timetables make the meals out of home being more frequent. All this makes important to know the content of nutrients and other bioactive components in the foods we will eat.

This knowledge is specially important for those individuals that have food intolerances and allergies, hypertension, cardiovascular risk factors, diabetics, those with a tendency to constipation or with gout, the stringent vegetarians or vegans, etc. All of them need to know the qualitative and quantitative composition of the different nutrients and other food components that may precipitate and/or aggravate an illness or prevent it. The general population should also know the foods with the aim of preventing different diseases that today we know are related with our feeding pattern.

Although it may seem paradoxical, the nutritional and food safety information has increased in the last decades thanks to the labeling legislation, which is more and more advanced and comprehensive. The labels may be as simple as those showed at the fish shops, in which only the location of fishing or breeding, the commercial name, the production method, and the presentation are indicated. There are however other so complex that it will be difficult for the average consumer to find out the real composition, and therefore to deduce the properties of the food he is going to get and consume.

On the other hand, the messages and statements on nutritional and health issues have been regulated by national and supranational administrations to protect, as far as possible, the consumer from receiving messages without scientific exactness that induce consumption and create false nutritional and health expectations. However, we still do not know or correctly interpret, at least from a nutritional viewpoint, the information provided on foods.

To know them when buying them[7]

The key step in choosing a food to consume is when we buy it at the supermarket or at the local grocery store. However, as mentioned above, the consumer is more hesitant when he is faced to big amounts of foods and processed products of which he has little information about their ingredients and the technological processes to which they have been submitted.

In this regards, there are important initiatives aimed at the consumer knowing in real time, that is to say, at the time of buying the food, its composition, which can be useful in case of food allergies and intolerances and in other pathological conditions.

Within this purpose some food classification and description systems have been developed, which allow us unequivocally to identify the foods. The LanguaL ("***Langu****a* ***aL****imentaria*")[8] system is an automated method that describes, captures, and recovers the data on food composition. This multilingual and thesaurus-based system has been developed since the late 70's although it is still under development, using a classification by differente aspects. Each food is described by a set of standard and controlled terms chosen from the aspects that characterize the nutritional quality and the hygiene of

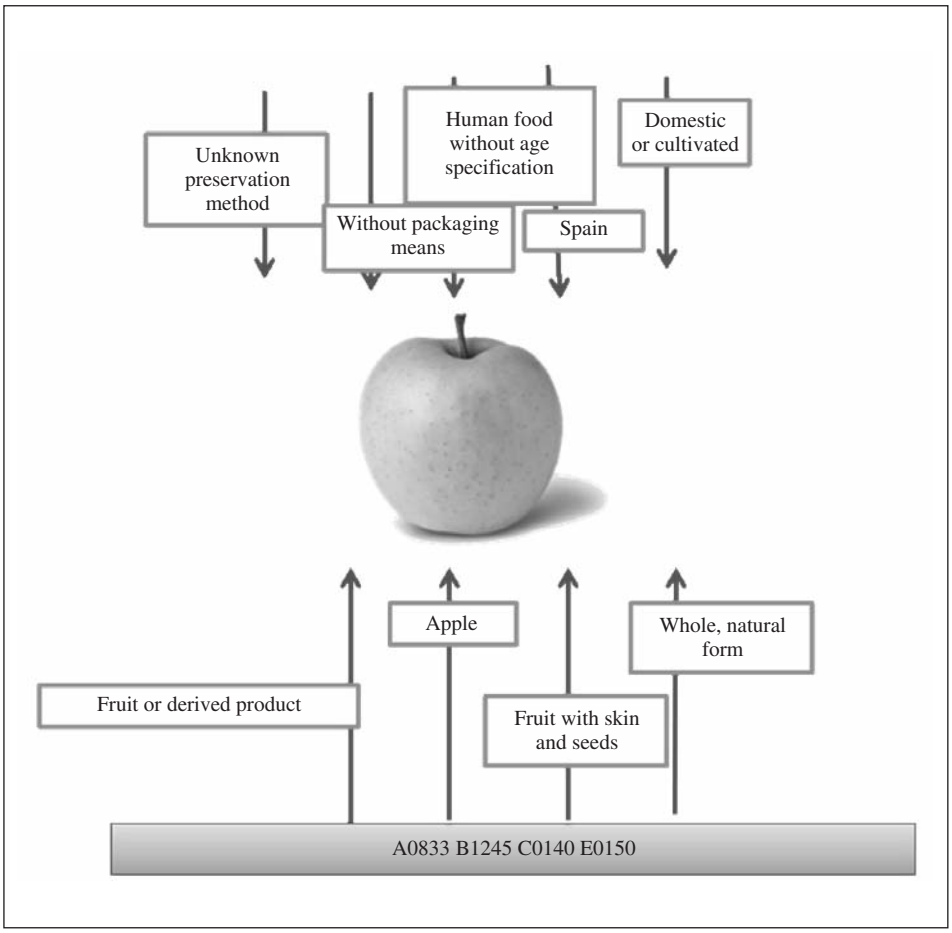

Fig. 1.—Description with the LanguaL system of a food (apple). The LanguaL code of the different aspects are included.

a particular food. These aspects include descriptors informing us about the origin, the cooking and preserving methods, the technological treatments, and the geographical origin. The classification of a natural food, such as an apple, using the LanguaL system is described in figure 1, and figure 2 includes the aspects that comprise this system. Currently the thesaurus is in several languages (Czechoslovakian, Danish, English, French, German, Italian, Portuguese, Spanish and Hungarian) and the foods indexed at present are more than 30,000. This makes possible to consult in real time the nutrient composition of any food at different European food composition databases through the tool EuroFIR AISBL (*eSearch Prototype facility*) (http://www. eurofir.net/) and the USDA (Department of Agriculture of the United States) database.

A. Product type [A0361]
B. Food source [B1564]
C. Part of plant or animal [C0116]
E. Physical state, shape or form [E0113]
F. Extent of heat treatment [F0011]
G. Cooking method [G0002]
H. Treatment applied [H0111]
J. Preservation method [J0107]
K. Packing medium [K0020]
M. Container or wrapping [M0100]
N. Food contact surface [N0010]
P. Consumer group/dietary use/label claim [P0032]
R. Geographic places and regions [R0010]
Z. Adjunct characteristics of food [Z0005]

Fig. 2.—Items that comprise the LanguaL Thesaurus.

On the other hand, it is necessary to consult the Food Composition databases to know the nutrients and other dietary components e.g. (bioactive components) contained in foods. In this sense, in the last five years an important work focused on harmonization of the Food Composition databases in Europe (NoE *European Food Information Resource*) and the World (INFOOD, FAO) has been made. In this European network in which participate stakeholders from more than 23 European countries, the fundamentals of the structure of the database have been put in place. This database includes documentation on all the components of the foods regarding their origin, analytical method for each component, food sampling, etc., and quality assessment of every available data. This is important because it allows us having the possibility to know the composition of foods from other countries (e.g. French cheese, Dutch butter, Norwegian salmon, etc.) when we buy them at the supermarket by accessing all of these databases that bring us the information with the same format as the

national database. Also, this standardized information allows carrying out pan-European studies of nutritional assessment.

In coincidence with the work of the EuroFIR network, the Spanish Database of Food Composition (BEDCA. http://www.bedca.net/)[9] has been developed in our country. In this database the foods and data on food composition information from different databases existing in Spain have been indexed in LanguaL, standardized, compiled and documented (fig. 3). BEDCA, which originated from a network from the recent Ministry of Science and Innovation (MICINN), is financed and coordinated by the Spanish Agency on Food Safety and Nutrition (AESAN), being the BEDCA Boar who is in charge of its maintenance and update.

These tools are necessary to develop an information system in real time on food composition. Some European initiatives have implemented a system that uses the last generation mobile phones (*smartphones*) and the bar codes of the marketed foods to readily know their composition.[10] The bar codes include information that links through the smartphone to the database and the nutritional composition or the qualitative composition of potential allergenic foods are sent back to the phone.

Another hot topic is the recent introduction in the market of functional foods, ecological or "organic" foods, new foods, etc. We should be cautious with this kind of foods that are even presented on specific shelves at the supermarkets. We should not forget that many of the foods that we eat in our diet are functional foods. Blue fishes, whole meal bread, fruits and yogurts, for example, are as functional as other foods that have been enriched, modified, added with another nutritional or bioactive component. In this regard, we ought to know about these natural foods and incorporate them to our diets since they are cheaper and they bring us the same benefit than more processed foods. This does not mean that functional foods may not be necessary, it just means that they have been designed for people that do not have a varied and balanced diet, and that through these foods they may be able to balance their diet.

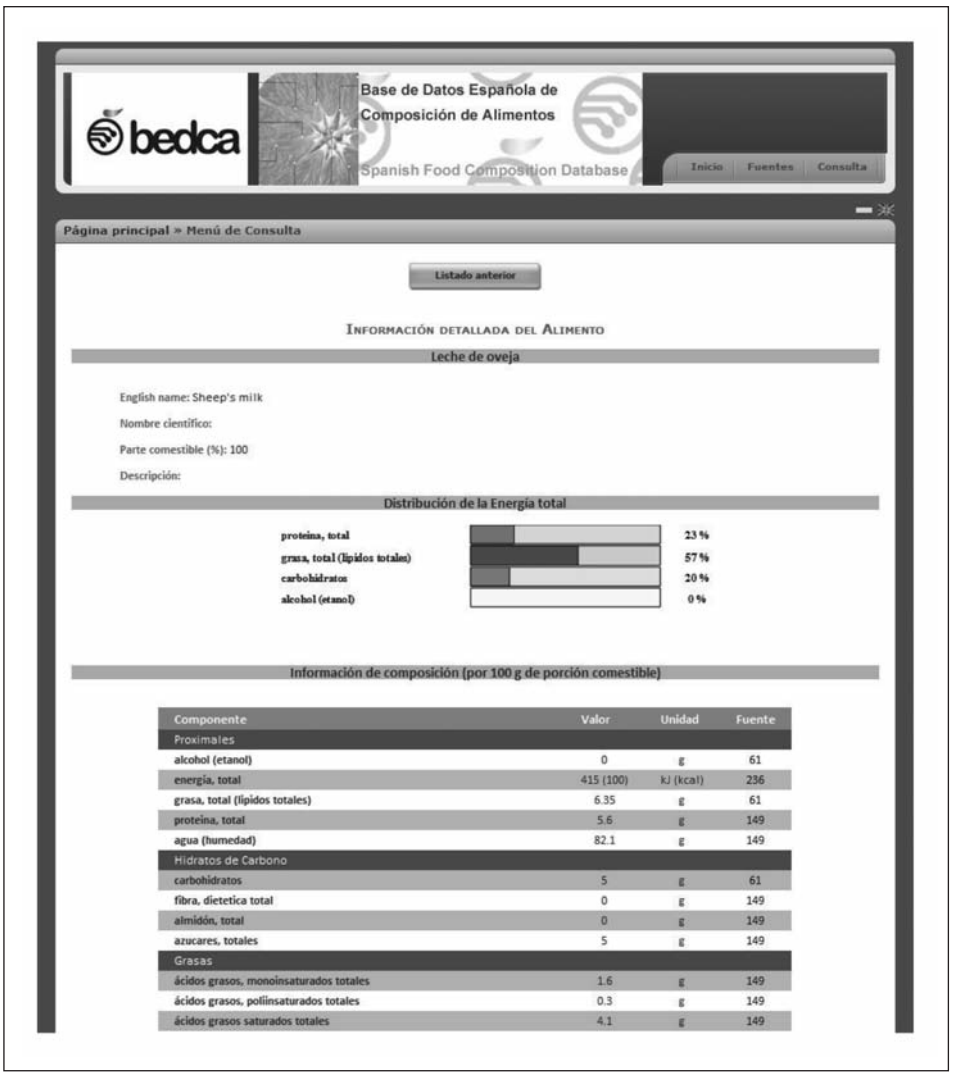

Fig. 3.—Example of the BEDCA webpage (http: //www.bedca.net).

To know them when cooking them[7]

Culinary processing of foods gives rise to changes in the taste, texture and color of foods (organoleptic changes) that may lead to higher palatability (the individual response to the sensorial properties of foods); it also produces changes in the nutritional properties, especially in energy and micronutrients (minerals and vitamins).

When we a food is prepared under different culinary techniques, two main changes may occur:

— Weight changes of the cooked food as opposed to the raw food "weight performance". Some foods weigh more and other less after being cooked. Those gaining weight do so by incorporating water (boiled pasta, for instance) or fat (fried foods in general); those losing weight do so by dehydration (baked breads) or fat losing (grilled meats).[11]

— Loss of different nutrients due to the cooking method "nutrients retention". Nutrients retention, that is to say, the nutrient loss by culinary processing is essentially produced by two factors: heat, which gives rise to loss of nutrients and bioactive components (for instance, heat-related loss of vitamin A), loss in the cooking water of minerals and other water soluble components (e.g., loss of minerals in the water thrown away after boiling vegetables).[10]

These changes in weight and in nutritional intake can be calculated according to weight performance[12] and nutrient retention[13] tables.

An especial important case is that of the influence on the composition and the nutritional value of the deep frying technique used in Spain. It is usually perceived that fried foods are less healthy than those cooked on the pan, boiled, or baked, especially when they are related with body weight reducing diets. This statement is not always true. The issue with frying implies knowing how to do it correctly. In the first place, choosing the type of oil is essential. Oils with high content in polyunsaturated fatty acids and low content in antioxidant components, such as sunflower seed or soy, are bad oils for frying since they decay rapidly by heating them at high temperatures giving rise to undesirable substances (fatty acid polymers, oxidation products, etc.) and, on the other hand, by creating a thinner crust they penetrate more in the food, increasing thus its caloric content. By contrast, virgin olive oil has higher content in monounsaturated fatty acids and phenolic compounds, decays more slowly and thus supports a higher number of frying cycles, creates a more resistant crust so that it does not penetrate into the food and therefore the final caloric content is not much increased as compared to the food raw or cooked by other technique not including oil. Besides, the foods will also incorporate bioactive components from oil, especially phenolic compounds, which are potent antioxidants.[14]

To know them when eating outside[7]

Due to work, school, or leisure, we eat more and more outside. This implies that we do not know the foods that are served in the places where we eat, either the workplace canteen, the school canteen, or the restaurant. The foods served at these places, especially the restaurants, are usually more elaborated, using mixed foods and culinary techniques that are not frequent in our usual diet, and using the technological resources (thickeners, foaming agents, etc.) that generate more sophisticated textures, colors, and presentations. Indeed, in many cases it is not easy to recognize the component of a particular dish unless it is written on the menu; examples of this may be the deconstructed Spanish omelet, tomato popcorns, or an olive oil semolina.[15]

Another important factor in our diet when eating out is the size of the servings. Several studies have shown that the size of the servings chosen by the cooker is due to conditioning factors other than the nutritional ones. The factors determining the size of the servings of the dishes in restaurants ranked by influence order are: a more attractive presentation of the food on the plate, the price of the dish, the consumer's expectations, competition with other restaurants, and also, although less importantly, the caloric content of the foods included.

If we compare the serving size of the foods included in the menu of a restaurant with those recommended by the dietary guidelines for a given population, in almost all the cases the serving size of a restaurant is bigger. This tendency to increase the serving size is clearly observed with the dishes served by fast chains. For instance, French fries and hamburgers potion sizes of a well-known chain of fast food has increased from 30 to 90 grams of meat since the beginning of the business in the fifties until today. It occurs something similar with non-alcoholic beverages that have increased their normal serving size from 200 mL to 350 mL.[16,17]

Finally, it is important to highlight that most of the consumers ignore the content in calories, saturated fats, and salt of the foods listed on the menu. This lack of information can be solved by the incorporation of important nutritional information on the menu. Some attempts have been done in this sense although the results are not very much promising so far.[18]

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Errors and myths in feeding and nutrition: Impact on the problems of obesity

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Abstract

The increase in obesity prevalence cannot be explained by a sudden and generalized change in human genome. It is certainly due to the modification of lifestyle habits and especially of the diet, as well as a lack of physical activity and sedentary living. Changes in the feeding pattern and the subsequent unbalance in the caloric profile of the diet may have had great importance in the occurrence of obesity.

The social pressure in relation to the body image, the desire to have a slim body, and the fear to gain weight present in the current society have given way to the proliferation of myths and errors regarding pretentiously weight-losing foods and the appearance of miracle diets and dietary complements with magic results on weight loss. Weight-losing foods such as grapefruit, pineapple, apple, cucumber, wholemeal bread or drinking water while fasting are among the most popular and with less scientific evidence errors and myths. On the other hand, miracle diets cause more harm than good and their success is based on weight loss, but not fat loss, since they initially induce dehydration and a decrease in the muscle mass. The intervention study described here shows, once again, that when someone takes a hypocaloric diet he/she will lose weight and that the supplements tried with a satiating, lipolytic and supposedly weight-losing effect do not modify the weight loss produced by the hypocaloric diet.

The main therapeutic tools available to fight against obesity are dietary therapy, which is a must in the program, education and behaviour modification, increased physical activity, to fight against sedendarism, and some pharmacological therapy available. The best solution to all these problems that have a great repercussion on the society surely is the development of wide and prolonged informational and educational campaigns in the field of nutrition.

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Key words: *Obesity. Errors. Myths. Miracle diets. Miracle products.*

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ERRORES Y MITOS EN ALIMENTACIÓN Y NUTRICIÓN: IMPACTO EN LA PROBLEMÁTICA DE LA OBESIDAD

Resumen

El aumento de la prevalencia de obesidad no podría ser explicada por un cambio repentino y generalizado en el genoma de la población. Sin duda, se debe a la modificación de los hábitos de vida y, especialmente, de la alimentación, así como a la falta de actividad física y a la vida sedentaria. Los cambios en el modelo de alimentación y el consecuente desequilibrio en el perfil calórico de la dieta pueden haber tenido gran importancia en la aparición de la obesidad.

La presión social en relación con la imagen corporal, el deseo de poseer cuerpos estilizados y el miedo a engordar presentes en la sociedad actual, han dado lugar a la proliferación de mitos y errores sobre alimentos supuestamente adelgazantes, a la aparición de dietas milagrosas y de complementos dietéticos con resultados mágicos sobre la pérdida de peso. Entre los errores y mitos más extendidos y con menor evidencia científica se incluyen alimentos que supuestamente adelgazan, como pomelo, piña, manzana, pepino, pan integral, o beber agua en ayunas. Por otro lado, las dietas milagrosas provocan más perjuicios que beneficios, su éxito radica en la pérdida de peso, que no de grasa, pues inicialmente producen deshidratación y disminución de la masa muscular. El estudio de intervención descrito en este capítulo, demuestra, una vez más, que cuando un individuo ingiere una dieta hipocalórica pierde peso, y que los suplementos con efectos saciantes y lipolíticos ensayados, supuestamente adelgazantes, no modifican la pérdida de peso producida por la dieta hipocalórica.

Las principales herramientas terapéuticas de las que se dispone para luchar contra la obesidad son el tratamiento dietético, base irrenunciable de la terapia, la educación y modificación de la conducta, el incremento de la actividad física, la lucha contra el sedentarismo y la escasísima terapia farmacológica disponible. La mejor solución frente a todos estos problemas, de una gran repercusión para la sociedad, es sin duda el desarrollo de amplias y duraderas campañas de información y formación en el campo de la nutrición.

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Palabras clave: *Obesidad. Errores. Mitos. Dietas milagrosas. Productos milagro.*

Abbreviations

BMI: Body mass index.
FDA: Food and Drug Administration.

Introduction

The obesity epidemics taking place in the modern, developed and reach world in the last decades cannot be explained as the consequence of a sudden and generalised change in the genome of the population, since it would be scientifically impossible that this change would occur in such a short time. The increase in obesity prevalence must be the consequence of modifications in environmental factors, such as lifestyle habits and feeding models, the decrease in physical activity, and the ever increasing sedentarism, although the predisposition to overweight and obesity may vary considerably among individuals (genetic factors).

The occurrence of this epidemic in some developing countries is especially alarming since not all the favourable circumstances that took place in the modern world occur there. All this would one make think that the changes in the feeding model may have repercussion more important than the one thought, and that it would be a big error not to consider these changes appropriately.

The humankind is evolutionarily better adapted to face excessive intake of energy than the lack of it, even if the first one is very important. The organism can store the energy in excess very easily. As a consequence of this evolutionary process, in order to control the weight, our system is more effective fighting against weight loss than preventing excessive gain. All the factors cited generate an obesogenic environment that is favoured by the extraordinary offer of foods, not only in their amounts but also in their variability and palatability.

The main therapeutic tools available to fight against obesity are dietary therapy, which is a must in the program, education and behaviour modification, increased physical activity, to fight against sedendarism, and some pharmacological therapy available.

The social pressure in relation to the body image, the desire to have a slim body, and the fear to gain weight present in the current society have given way to the proliferation of myths and errors regarding pretentiously weight-losing foods and to the appearance of miracle diets and dietary complements with magic outcomes on weight loss.[1-5]

Errors and myths

Figure 1 shows the changes in the dietary pattern that have occurred in Spain in the last 60 years regarding the caloric profile of the diet. In the period between 1964 and 1990, there was a change in the energy distribution brought by each group of macronutrients: there was an increase in the proportion of energy provided by proteins from 12% to 14%; also for fats, from 32% to 42%, and logically a decrease in that provided by carbohydrates, from 53% to 42%. This nutrients proportion has remained unchanged until today, with very little modifications. By contrast, total energy intake has not varied much in that same period and even a decreasing trend has been observed.[6-9]

We do not know what impact this change has on the increase in overweight/obesity since no direct studies have been performed and we only count on epidemiological studies. When the nutrients do not reach the internal milieu in determined proportions, it is metabolically difficult, sometimes impossible, to obtain energy from them. Therefore, if not used, they will be stored in the only way that our organism can and knows how to do it, that is to say, in the form of triglycerides by accumulating fat in the adipose tissue. It is important to keep in mind that when the glycaemia is compromised, it is impossible to use fatty acids as an energy substrate and, therefore, they will accumulate. This situation may be occurring since the proportion of carbohydrates has been reduced and that of lipids has increased. These circumstances would justify the concomitant increase in the incidence of cardiovascular diseases, which have become the main cause of death in Spain.[10]

As a consequence of the epidemic of overweight and obesity that is occurring lately, there has been a prolife-

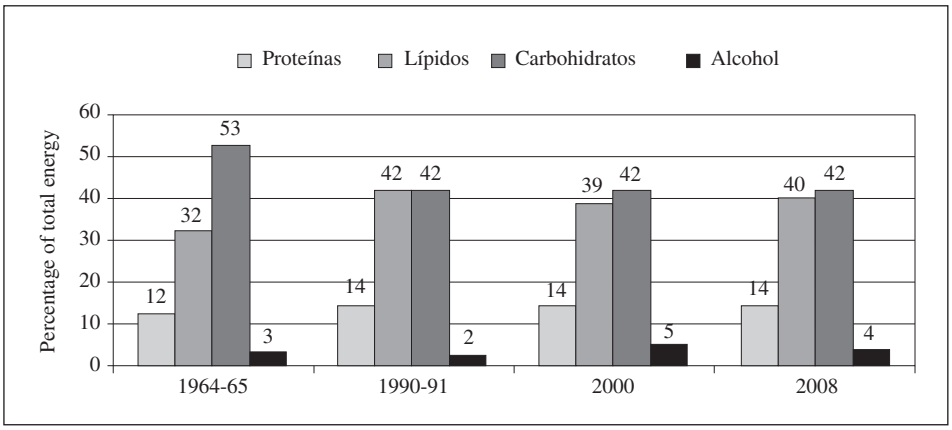

Fig. 1.—Evolution of the caloric profile of the Spanish diet in the last fifty years.

ration of supposedly weight-losing foods, giving way to a series of errors and myths about this topic.[11-14] Some of the most popular ones have been selected.

"Bananas make you gain weight" or *"bananas and milk make you losing weight"*.

If the banana makes you gain weight, the banana consumed with milk will make you gain even more weight since the caloric intake increases.

"Margarine has fewer calories than butter"

All the fats provide 9 kcal/g, so that margarine and butter will provide the calories according to the amount of fat they contain.

"Cheese, even if it contains fat, is excellent for a weight-losing diet because it contains a whole amount of proteins."

The nutritional composition varies widely from one cheese to another, so that it is practically impossible to establish average values that would be representative for all of them. Generally speaking, we would say that for each 100 calories, 25 would come from proteins and the remaining 75 from fat. Once again, this would be a false believe.

"Drinking water during the meals makes you gain weight and while fasting it makes you lose weight."

On the first place, water has no energy, and secondly, it lacks the capacity of dissolving the fat. Therefore, it would be impossible for it to have these effects, independently of when it is consumed (before, during or after the meal, or when fasting). Drinking water just before the meal would be justified due to the mild satiating effect that it produces, although this effect is very weak.

"White bread makes you gain weight and wholemeal bread makes you lose weight".

Bread, either white or wholemeal, is a necessary food in a balanced diet given its high content in complex carbohydrates, and the energy provision is similar for both types of breads. It is not a particular food what makes you gain or lose weight, but the intake of a diet with a caloric intake higher than the individual needs.

"Light foods do not make you gain weight, they even make you lose weight"

According to the European Union regulations, a food termed *"light"* must have a caloric value per weight unit lower than 30% compared to the equivalent food or the reference food, but in no case it means that it does not contain energy. This misunderstanding makes that these foods are being consumed without any limit or control, forgetting that they are not weight-losing.

"Some fruits such as pineapple or grapefruit make you lose weight because they dissolve the fat"

It is no estrange to get about with people that attribute magical properties to certain foods, such as dissolving the body fat.

"Cucumbers and apples have negative calories because they need more energy than the ones they contain in order to be chewed and digested"

Certain foods, such as the apple, have been attributed negative energy contents by arguing that more energy is wasted to eat them than the energy they contain. One argument against would be that, considering that it would be necessary to chew for approximately 3 minutes to consume 1 kcal, and that an average apple contains some 80 kcal, it would be necessary to chew for 240 minutes for the apple to have negative calories. Of course it is rather difficult to imagine someone being able to chew an apple for at least 4 hours.

"If you sweeten your beverages with honey instead of sugar, you save calories"

In some diets for losing weight, this sweetener has been recommended instead of sugar because it supposedly has a lower caloric content. It is well known that the caloric content of 1 gram of sugars is always 4 kcal. Besides, honey has been attributed some healing properties, which may be related to some unknown substance, with an also unknown function, and with no recommendation about the amount to be consumed. Its composition is rather simple: 70% of sugars, and the remaining is mostly water.

"When we eat less, the stomach shrinks"

Another common error in the weigh-losing regimes is to think that the stomach shrinks when the food intake is reduced for a certain time. This belief is not true, as it is not true that the size of the hand or the eye decreases when reducing the food intake.

Recently, some other beliefs related with obesity, nutrition, and feeding, have appeared and diffused among the people, being accepted. These beliefs, which have been qualified as myths since there is no scientific evidence demonstrating their veracity[15], and are described next:

— "Little but sustained changes in the diet or the physical activity have a big impact on long-term weight loss".
— "The individual that considers losing weight has to set realistic goals because he/she could otherwise become frustrated and lose less weight".
— "Losing too much weight abruptly is linked to worse outcomes in the long-term than doing it gradually".
— "To start a good weight loss program, there should be a good initial predisposition in order to warrant a successful intervention".
— "The physical education classes as we know them today are key factors for the prevention of paediatric obesity".
— "Breastfeeding protects the children against obesity".

— "During sexual intercourse, 100-300 kcal are burnt".

Weight-losing substances: Miracle products

In the last decades, there has been a proliferation of a considerable number of weight-losing substances in the health care area that are advertised in a very striking way, such as "fat devouring molecules", "it dissolves fat", "natural substances", "plant-derived", "calories-burning", "fat-absorbing", and of course, as harmless without any contraindication.[1-3]

Generally the products or dietary complements used to lose weight lack the effects they claim in the advertisements. In the best scenario, they have an indirect action by making psychologically easier to follow a hypocaloric diet and thus losing weight. Besides, they usually do not have the unwanted effects of pharmacological treatments, although they not always lack of secondary effects. Table I shows some examples of weight-losing complements.

In order to assess the effects of some of these weight-losing substances, Lydia Fernández, Mª Dolores García-Prieto and Salvador Zamora carried out an interventional study, which results are in the process of publication. The experimental design was as follows:

Table I
Supplements with supposed weight-losing effects

Supplements	*Components*
Peripheral satiating agents	Chitosan Fucus Spirulina *Garcinia gamboia*
Diuretics	Horse tail Bermuda grass Dandelion
Laxatives	alder buckthorn Rhubarb
Tranquilizers	Valerian Linden blossom
Lipolytics	Green tea Chromium picolinate
Digestive	Bitter fennel Pineapple
Stimulants of the central nervous system	Guarana Kola nut
Circulation invigorating agents	Crataegus oxyacantha Horse chesnut

A sample of 69 individuals with overweight or obesity was selected (58 women and 11 men), with a mean age of 35.4 years (15-64 years) that participated for 6 months in a weight-losing program aiming at achieving their healthy weight according to their gender, age and height, maintaining it through time, as well as incorporating healthy dietary and lifestyle habits.

The population was divided in two homogenous groups and both groups received a balanced and hypocaloric diet (1,500 kcal/day), according to the recommendations on energy and nutrients for the Spanish population.[16] The dietary preferences and the buying power of the participants were taking into account. One of the groups additionally received a weight-losing supplement made of a mixture of satiating agents (chitosan, *Fucus*, Spirulina and *Garcinia gamboia*) and lipolytic agents (green tea and chromium picolinate).

In the group receiving the balanced and hypocaloric diet (without supplements), 54.5% of the participants achieved the 6-month goal of weight loss, approximately 9.0 kilos, with a concomitant reduction of the body mass index (BMI) and the waist circumference, being in all the cases statistically significant (fig. 2).

In the group receiving the hypocaloric diet and the mentioned supplement (satiating and lipolytic agents), 57.4% of the participants achieved the 6-month goal of weight loss, approximately 9.3 kilos. Similarly, the BMI and the waist circumference were reduced in a statistically significant way (fig. 2).

No statistically significant differences were observed between both groups. The supplements used to lose weight did not exert any effect in this sense, independently that they could have been of some psychological help for some participants by following more easily the proposed diet. However, the few differences between both groups in the number of individuals achieving the goal do not support an effect.

In conclusion, the results of this study show, once again, that when an individual eats a hypocaloric diet he/she will lose weight and that the supplements tested in this study, which are supposedly intended to lose weight, have not modify the weight loss produced by the hypocaloric diet. For none of the substances tried there are experimental evidences showing that they may act by decreasing the volume or the amount of adipose tissue. That does not exclude the importance that these substances may have to achieve the goals of weight loss as a psychological help by increasing the motivation or the adherence to the diet.

Miracle diets

In the current society, the increasing interest in feeding and nutrition and their relationship with health has given way to the proliferation of very diverse dietary regimens promising to work some sort of miracle in the organism (health, beauty, youth, good mood, etc.), although their scientific base is scarce or null. In most

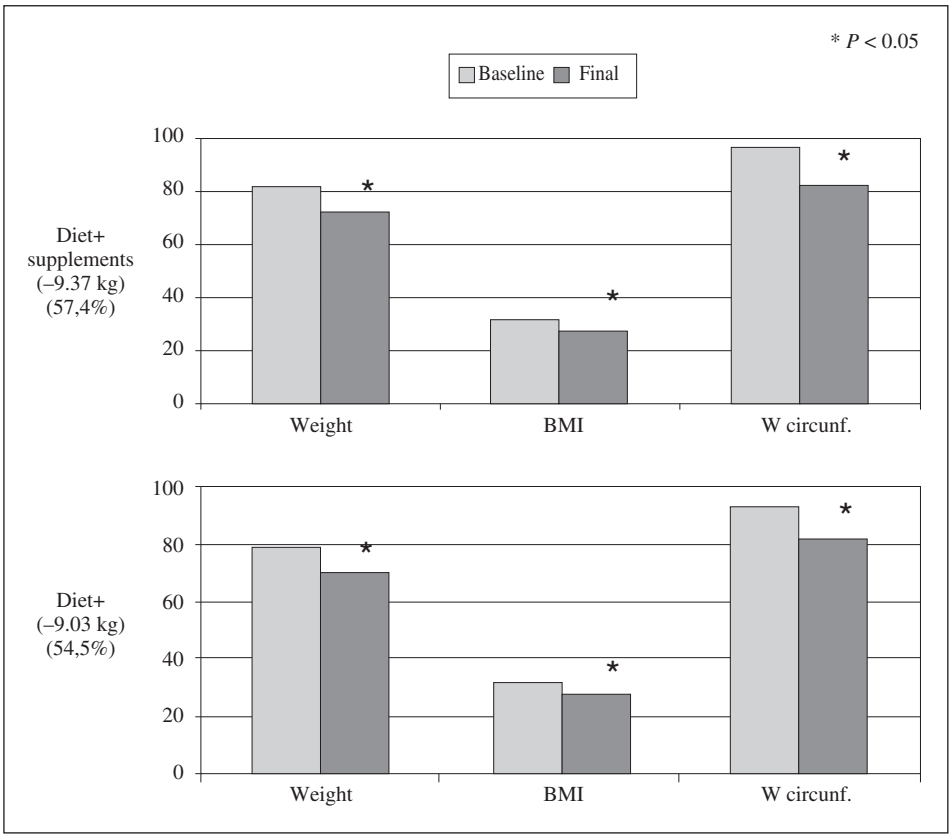

Fig. 2.—Effect of the weight-losing program on weight, body mass index (BMI), and waist circumference in both groups of participants (diet and Diet + Supplements).

of the cases, these dietary models, named as "miraculous diets", or "miracle diets", hide commercial interests or interests in the promotion of "popular people". Some of these fraudulent recommendations, some of them harmless while others clearly harmful, have widely diffused and represent today a serious health problem in the developed world. One additional problem that implies the use of these diets is they favour a rapid gain of the lost weight (rebound or "yo-yo" effect).[2-5,17-18]

From Dr. Hays' theories of the dissociation of acid and basic foods in the thirties until today, Science has considerably progressed. Today we know that the enzymes work equally either the foods are consumed as differentiated groups or simultaneously. Even though, different types of dissociated diets constitute one of the weigh-losing therapies more currently used.[19]

Besides being false, these theories induce to abandon such healthy habits as eating fruit for dessert, eat a dish of lentils with rice, or having ham and bread as an evening snack (these habits are even recommendable in weight-losing diets). Besides, these theories are against the digestive physiology: the stomach emptying is not immediate, it occurs very slowly and depends on several factors:[20]

In the first place, the size of the particle: the ingested food does not leave the stomach until it reaches a size small enough to be attacked by the digestive enzymes. For this reason, the liquids get out of the stomach relatively quickly, with some exceptions, such as milk that has to be coagulated in order to suffer the clorhydropepsic digestion in the stomach for the digestive process taking place adequately in the duodenum.

In the second place, another important factor conditioning the gastric emptying is the pH at the duodenal side of the pylorus. Until this side does not become alkaline due to bicarbonate of the pancreatic secretion, the sphincter does not open. At this time, a wave of highly acid digested product abandons the pyloric antrum, reaches the duodenum, and the pH of the duodenal side of the pylorus becomes acid closing again the sphincter, and so on, so that the process lasts for several hours. Therefore, it does not matter to take the fruit at the beginning or at the end of the meal; what matters is to consume fruits, and doing so when one likes it most.

According to the Spanish Agency on Food Safety and Nutrition (AESAN),[18] a "miracle diet" can be recognized when one of the following effects is claimed:

— Rapid weight loss, more than 5 kg per month.
— They are easy to follow.
— They are completely safe, with no health risks.

Some examples of diets that offer miraculous weight losses without an apparent effort are:[3]

— Hyperprotein diets, such as the one attributed to the Dukan Clinic[21,22] or the peach diet.
— Hyperfat diets, such as Dr. Atkins'.[23,24]

— Dissociated diets, such as Montignac's.[19]
— Excluding diets.
— Psychological diets.
— The anti-diet.
— The Rafaela Carrá's diet.

There are some diets to lose weight that have no fundamentals at all and a null scientific base, such as:[17]

— Mono-diets, that is to say, diets based on the use of a single food, generally for one day in the week, among which we may find the banana diet, the grapefruit diet, the chicken diet, the rice diet, etc.
— Liquid diets, such as the milk diet, the beer diet, the juice diet, etc.
— The calendar diet in which every day of the month one must eat those foods starting by a particular letter.
— There are others related with the hours, for example, "all that we eat before 8 a.m. will not make us gain weight". It may be a good decoy for a sleepyhead to get up early, but it will not cheat our body.
— The diet of the "Ps" (potatoes, pasta, and bread (*pan* in Spanish)) recommends that these foods get excluded from the diet.
— The colours diet. It states that each colour has its own vibratory energy and it will vibrate with different parts of the body; hence, each organ of the body has a particular colour with which it relates. Each day the foods with a particular colour have to be eaten.

Given the fact that to talk about each particular diet would be difficult, we expose a brief summary of the most popular and frequently used ones, comparing their caloric profile with that of a balanced diet. As it may be observed in table II, the main characteristic of this type of diets is that the energy coming from carbohydrates has been dramatically reduced, increasing then the one coming from the other nutrients.

In the so called hyperprotein diets, most of the energy comes from this macronutrient and very little from lipids. In the case of the Dukan diet,[21, 22] there are some variants, always hyperproteic and hypoglycidic, and even dangerously hypocaloric with less than 1,000 kcal/day, and thus frequently unbalanced in micronutrients.

Table II
Energy content and caloric profile of the different kinds of diets

Diets	*Sugars (%)*	*Proteins (%)*	*Fats (%)*	*Energy (kcal/day)*
Balanced	55-60	10-12	25-35	
Hyperprotein	30-35	50-55 (80)	10-15	750
Dukan	19	40 (87)	41	880
	23	37 (117)	38	1262
	32	33 (124)	33	1500
Dissociated	10-15	25-30	50-60	Unlimited
Atkins	4	12-23	63-94	Unlimited

Hyperfat diets, the essential model being Dr. Atkins' diet, are practically voided of sugars and overtly hyperfatty, with reasonable or slightly higher amounts of proteins as compared to a balanced diet. Their main attraction is that the individual can eat all what he/she wants but carbohydrates, which are forbidden.[23, 24]

Finally, dissociated diets are basically hypoglycidic, hyperproteic (up to twice the energy coming from this macronutrient) and strongly hyperfat diets. They are a mix of all the above, the best propaganda for their use being the lack of restriction in energy intake: you can lose weight while eating all the calories you want.

The diets with no intake limitation, such as the dissociated and hyperfat diets, are based on a deceptive decoy. They are diets difficult to follow in the long term because they produce weariness, loss of the appetite, with a satiating feeling possibly due to the satiating power of proteins.

In general, the molecular bases and the mechanisms of action of all these miracle diets reside in halting the anabolic routes and trigger the catabolic paths to inhibit lipogenesis and stimulate lipolysis. However, this is not so easy or so specific. Normally all the anabolic processes will be impaired and, thus, not only the lipid metabolism will be impaired but also the water and saline metabolism, giving way to water and electrolytes losses. In all these cases, the aim is to generate a not too severe hypoglycaemia, to halt the action of insulin, and to start up the processes regulated by catabolic hormones (fig. 3).

When insulin release is stopped by hypoglycaemia, the big anabolic hormone is stopped, the synthesis of triglycerides is compromised, and thus fat accumulation is prevented. But not only this occurs, sugar-increasing hormones are released to maintain the glycaemia, which is a priority to ensure that glucose reaches the brain no matter the price, even by producing glucose from amino acids through the gluconeogenesis.

Under these circumstances, the energy comes exclusively from the amino acids, but in the absence of glucose, the oxidation of this substrate to produce energy is incomplete and ketonic acids (acetoacetic and β-hydroxibutiric) are produced instead of CO_2 and water.

As a whole, these processes lead to pH decrease in the internal milieu, originating a metabolic acidosis with the production of important amounts of ketonic compounds, putting in danger the physiology and even the survival of the organism. There have been reports of people dying from the use of this kind of diets. The levels of plasma lipids are notably increased, leading to impairments in coagulation and platelets aggregability.

It is usual that some people praise a particular method because of the extremely good result achieved: an astonishing and very rapid weight loss. Almost always

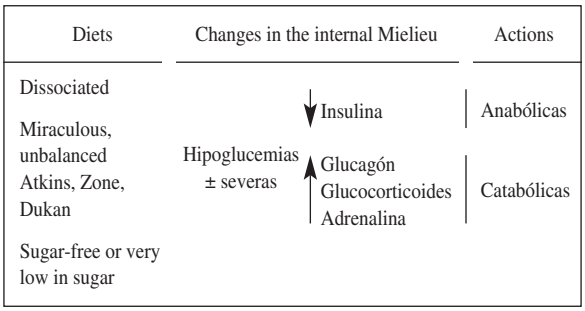

Fig. 3.—Mechanisms of action of the different "miracle" diets.

the results are deceptive, or false. In general, rapid reductions in the body weight are due to important losses of water and electrolytes, through the sweat and urine, but not to fat loss. The main goal for losing weight is to reduce the amount of fat, any other thing is a fraud, or even a danger. Commercially speaking, this kind of diets may be very interesting since the patient, or better said, the client, comes back again and again to the office, feeling guilty; that is to say, in the best conditions to be fooled once again.

Final thinking

To end up this chapter, we would like to refer, in the first place, to one of the conclusions of the White House Conference (1969) on Feeding, Nutrition and Health, stating:[1]

"It is likely that in the field of population health, there is no other area so affected by fraud and misleading information than nutrition. The consumer gets trapped with many and coarse imitations that cheat him big amounts of money, besides redounding against his health".

As it can be seen, the current problems regarding the myths, errors and frauds in the use of products to lose weight and miracle diets were already present more than 40 years ago.

On the other hand, the Food and Drug Administration (FDA) has received a series of complaints related with the use of this kind of products or miracle diets including: nausea, vomiting, diarrhoea (liquid preparations), constipation (dry preparations), faints, muscle cramps, weakness or fatigue, irritability, intolerance to cold, decreased libido, amenorrhea, hair loss, skin dryness, cardiac arrhythmia, recurrent gout, dehydration and hypokalaemia. The FDA commissioners have proposed the following label to be attached to protein supplements: "Protein diets with very low calories may cause serious diseases or death. Not to be used to lose weight or maintain the weight without medical supervision. Do not use for any purpose without medical advice if under any other medication. Not to be used in children, pregnant or breastfeeding women".

The severity of the lesions and deaths due to the use of hyperproteic diets extremely low in calories is unclear. However, it is evident that there is a need of careful studies focused on the geographical influence, concurrent pathologies, age and other factors.

Sometimes, the warnings in this sense seem to be intentionally vague. For example, when it is indicated: "do not use or do not recommend for long-term use", what duration are we talking about? One week, one month, one year? Is it the same for everybody? Young, adults, the elderly?

Finally, in our opinion, one of the big problems with the use of inappropriate feeding models is that, even when things are very badly done, they almost never have a consequence in the short term, so people think that there is nothing to worry about. And when something happens, it is already late. For example, it is difficult to relate the occurrence of osteoporosis or renal disease in the adulthood with a cause that might have been a nutritional defect during adolescence.

The best solution to all these problems and with a big social repercussion certainly to develop extensive and long term informational and educational campaigns on nutrition for the citizen.

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Sedentarism, active lifestyle and sport: impact on health and obesity prevention

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Abstract

The benefits of regular physical activity have been known since ancient Greek. But in the last Century the scientific knowledge around this topic has progressed enormously, starting with the early studies of JN Morris and RS Paffenberger, who demonstrated that physical activity at work reduced incidence of cardiovascular disease and mortality. In the Harvard alumni study, the lowest risk was associated with a weekly output of 1000 to 2000 kcal performing vigorous activities. Further studies in all age groups have supported these findings and have added that even moderate levels of physical activity provide considerable benefits to health, including lower prevalence of overweight and obesity at all ages. Metabolic fat oxidation rate is highest at exercise intensities between 45 and 65% of VO_2max. This means that people must be active regularly and force physiological mechanisms at certain intensities. All this body of evidence has contributed to current WHO physical activity recommendations of 150 min/week of moderate to vigorous physical activity (MVPA) in adults and elderly, and 60 min/day of MVPA in children and adolescents, with additional strength training, apart from adopting an active lifestyle.

In the last 50 years, occupational physical activity has been reduced for about 120 kcal/day, and sedentarism has emerged as an additional risk factor to physical inactivity. Even if less than 60 min of TV time in adults have been related to lower average BMI, there is still a need for research to determine the appropriate dose of exercise in combination with sedentary behaviours and other activities in the context of our modern lifestyle in order to prevent obesity at all ages. As public health measures have failed to stop the obesity epidemic in the last 3 decades, there is clearly a need to change the paradigm. The inclusion of sport scientists, physical education teachers and other professionals in the multidisciplinary team which should be responsible for drawing the road map to prevent the increase of the obesity epidemic effectively is a "must" from our point of view.

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SEDENTARISMO, VIDA ACTIVA Y DEPORTE: IMPACTO SOBRE LA SALUD Y PREVENCIÓN DE LA OBESIDAD

Resumen

Los beneficios de la práctica regular de actividad física se conocen desde la antigua Grecia. En el siglo XX, el avance del conocimiento científico fue enorme, empezando con los estudios de JN Morris y RS Paffenberger, que demostraron que la actividad física en el trabajo reducía la incidencia de morbilidad y mortalidad por enfermedad cardiovascular. En el estudio de los ex alumnos de Harvard, el menor riesgo se asoció a gastos semanales de 1000 a 2000 kcal realizando actividades vigorosas. Estudios posteriores en todos los grupos de edad han verificado estos resultados. Además, se ha observado que incluso actividades a intensidades moderadas aportan beneficios importantes para la salud, incluyendo una menor prevalencia de sobrepeso y obesidad a todas las edades. La tasa metabólica de oxidación de las grasas es máxima a intensidades entre el 45 y el 65% del VO_2max, que se alcanzan únicamente con entrenamientos mantenidos en el tiempo, con en fin de forzar los mecanismos fisiológicos a determinadas intensidades. Toda esta evidencia científica llevó a la OMS a formular sus recomendaciones de 150 min/semana de actividad física de moderada a vigorosa (MVPA) en adultos y mayores, y de 60 min/día de MVPA en niños y adolescentes, además de entrenamiento de la fuerza y en el contexto de un estilo de vida activo.

En los últimos 50 años, la actividad física laboral se ha reducido en unas 120 kcal/día, y el sedentarismo surge como un factor de riesgo adicional a la inactividad física. Aunque se han relacionado tiempos de menos 60 min de TV en adultos con menor tasa de IMC, aun es necesario profundizar en la dosis apropiada de ejercicio físico en combinación con comportamientos sedentarios en el contexto de nuestro estilo de vida moderno para prevenir la obesidad a todas las edades. Consideramos necesario un cambio de paradigma, ya que las medidas de Salud Pública no han conseguido frenar el progreso de la epidemia de la obesidad en las últimas 3 décadas. La inclusión de los científicos y profesionales del deporte, de los profesores de educación física en el equipo multidisciplinar que debería ser el responsable de trazar las líneas maestras para prevenir y frenar la epidemia de la obesidad de forma efectiva es algo imprescindible desde nuestro punto de vista.

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Palabras clave: *Condición física. Salud. Actividad física. Obesidad. Prevención.*

Abbreviations

AVENA: Alimentación y valoración del estado nutricional en adolescentes.

EXERNET: Red de investigación en ejercicio físico y salud para poblaciones especiales.

EYHS: European Youth Heart Study.

HBSC Study: Health and behaviour in school-aged children.

HELENA: Healthy Lifestyle in Europe by Nutrition in Adolescence.

MVPA: Moderate to vigorous physical activity.

NHANES: National health and Nutrition Examination Survey.

PRONAF: Programas de nutrición y actividad física para el tratamiento de la obesidad.

Introduction

The human being is meant to move. Our ancestors had to move to hunt animals, gather fruit or cultivate their fields. Since the industrial revolution, human movement has been reduced constantly and sedentarism has increased progressively. It has been estimated that in the 1960's, around half of the jobs in private industry in the U.S. required at least moderate intensity physical activity, in contrast to less than 20% of the jobs currently.[1] A worrying trend as inactivity is accompanied by a tendency towards dysfunction, and in some cases increased morbidity as lack of movement produces progressive atrophy and physical weakness in the whole organism. At the end of the 1950s and beginning of the 1960s, Kraus and Raab[2] had already introduced the term hypokinetic to refer to a series of changes associated with physical activity and those diseases which could be provoked or worsened as a consequence of physical inactivity.

Modern technology and the development of motor-based transport systems, of machines which take over former high-energy demanding activities both at home and at the workplace, as well as in commuting, have reduced the intensity of, and time spent in, physical activity in our daily living,[1] turning us into a "*Homo sedentarius*". In fact, sedentary behaviour has begun to be used to describe prolonged sitting (*sedēre* in Latin = to sit), instead of the absence of physical activity. The word "sedentary" has begun to be applied to people who spend most of the day sitting down.[3] There is a rapidly expanding body of evidence suggesting that time spent in sedentary behaviours is associated adversely with health risks and can be a factor which is independent of the protective action of physical activity.[3]

Energy balance, which has been considered fundamental for avoiding overweight and obesity, has puzzled scientists for a long time. In the 16th century, Sanctorio in Padua built a scale for himself in order to understand weight maintenance in adulthood.[4] It was in the late 18th Century with the studies of Lavoisier and his colleagues that science started to understand heat production, oxygen consumption and energy output; and at the end of the 19th and beginning of the 20th Century interest grew regarding the physiological and biochemical adaptations to training[4]. In the last five decades, daily energy output due to the reduction in occupational physical activity has been estimated to have decreased among US men and women by 140 and 124 kcal, respectively[1], probably affecting energy balance.

Physical activity and cardiovascular health

The belief that people who are physically active in their daily life both because of their occupation and through their recreation, exercise and sports activities have a lower level of morbidity and mortality are not new ideas, and can be traced back to the writings of different authors in ancient Greece or Rome.[4] However, for a long time these ideas have come up against the scepticism of health professionals. A change in mentality was brought about as a result of a series of important epidemiological studies.

The famous articles by J.N. Morris and colleagues published in 1953 examined the incidence of coronary heart disease among the bus drivers who spent more than 90% of their working hours sitting down, and bus conductors, who spent their working days going up and down the stairs on the famous London double-decker buses. They found a lower incidence of coronary heart disease among the conductors and postulated that "physically active" work provided a certain amount of protection against sudden death due to cardiac problems as a first manifestation of disease. Further data obtained from post office employees, comparing those who had to deliver the post by walking or by riding a bicycle with those working at the post office that carried out more sedentary work like sorting letters, confirmed the protective effect of physical activity.[5]

In this line of epidemiological research, R.S. Paffenbarger and colleagues[6] published the results of their research studying the stevedores at the San Francisco port. The researchers found out that in the group of the most active stevedores, who expended an additional 4,200 kJ/week (1,000 kcal/week) cardiovascular mortality was clearly lower than in the less active workers.

Other epidemiological studies from the same research group which have been critical for confirming the relationship of exercise and cardiovascular health and mortality were the college alumni of the University of Harvard studies, initiated by Paffenberger. After a follow-up of 6 to 10 years, it was concluded that there was an inverse relationship between the levels of physical activity and the risk of suffering coronary heart disease. After 12 to 16 years, the researchers showed that an extra energy expenditure of 8,400 kJ/week (2,000/kcal/week), was associated with a decrease of 28% in all cause mortality, and that the decrease was even more with regard to cardio-respiratory problems.

Specifically in the cohort of alumni from Harvard[6,7] it was demonstrated that those subjects who performed regular physical activity of certain intensity reduced to half the risk of suffering from coronary heart disease compared to sedentary ones. The lowest risk was associated with a weekly energy output of between 4,200 and 8,400 kJ/week (1000 to 2000 kcal) despite the fact that 8,400 kJ/week seems to be a critical point for men. There were benefits with 4,200kJ for women and a dose-response for the levels of exercise training showing a lower risk with a higher energy output and additional benefits with vigorous activities.[6] Older men should expend at least 4200 kJ/week in total physical activity to potentially reduce their risk for CHD in a statistically significant way (about 20%); however, when expending 2,100 to 4,100 kJ/week, a value slightly lower than the one recommended by the Surgeon General, a 10% reduction was observed. This reduction was not statistically significant but can have an important practical value.[7] Interesting findings of the abovementioned studies were that the benefits of regular and vigorous physical activity seemed to be irrespective of body composition; in other words, they also applied to obese subjects. Some exercise is better than none, while more is better than some[6], and cardiovascular adaptations to training have a positive influence on the many pathophysiological conditions associated with obesity, and better fitness facilitates the tasks of daily living.[7]

More recently, the work of S.N. Blair and others has confirmed these findings in relation to a lower all cause mortality underlining the fact that even moderate levels of physical activity, and an improved fitness level used as a more objective marker of physical activity, provide considerable benefits for health in general[8]. And while the benefits may be more dramatic in a sedentary 45 year-old like Dr Paffenberger himself, benefits can be derived regardless of age as shown in 80-year-olds who can improve the quality of their life significantly,[6] something possible in even older people.[9]

Physical activity, obesity and health

Obesity (BMI > 30, high body fat) as a risk factor for health has recently been the focus of research, due to the increase in its prevalence in all age groups in developed, and currently also, in developing countries. Age-adjusted prevalence of obesity in the U.S. has shifted from 10%-15% in the 1960s up to 35% in 2008. Over the last 50 years in the U.S. there have been progressive decreases in the percentage of individuals employed in occupations that require moderate intensity physical activity. It has been estimated that daily occupation-related energy expenditure has decreased by more than 100 kcal per day, and that this reduction in energy expenditure could account for a significant portion of the increase in mean U.S. body weight for women and men in the U.S.[1] The estimation of this reduction of 100 kcal/day or even more would have been adequately compensated for by meeting the 2008 U.S. Department of Health and Human Services Federal Physical Activities Recommendation of 150 minutes per week of moderate intensity or 75 minutes per week of vigorous intensity activity or the 2010 WHO Global recommendations on physical activity for health[10] (table I).

If data on children and adolescents are taken separately, prevalence of overweight has shifted from around 4% in the 1960s up to 20% in 2008.[11] As age-adjusted prevalence of overweight has been quite stable since the 1970s (around 28% for women and 40% for men), prevalence of overweight and obesity together is currently around 64% for women and 72% for men in the U.S.[11] Currently, data seem to indicate that prevalence is starting to plateau in both children and adults[11].

Trends in Europe have been less consistent. In Spain, prevalence of overweight and obesity has increased steadily.[12] Median total body fat of 14-y old boys was 7.5% in 1985 and 14% in 1995 and mean waist circumference increased significantly from 72.75 ± 6.78 cm in 1995 to 77.90 ± 11.89 cm in 2002. Currently, prevalence data are tending to stabilize.[13] In Europe, prevalence in children and adolescents varies from less than 10% in some of the Nordic countries up to more than 25% in the Mediterranean countries and the UK.[12] In the analysis performed by Church et al.[1], increases of obesity rates in the US adults over the last 5 decades have been related to the decrease in occupation-related physical activity. Interestingly, estimated increase in body weight (since 1960) by means of the energy balance model closely matches measured body weight of the National Health and Nutrition Examination Surveys (NHANES) data form 2003-2006.

There is quite a huge amount of supporting evidence that trained people have less body fat percentage at all ages than non-trained people.[11] In the study by Kohrt et al.,[11] healthy older endurance-trained men and women had similar body fat percentages (17% and 25%) to healthy young sedentary subjects (18 and 24%, respectively). For comparison, it is interesting to indicate that older sedentary males and females had 28% and 38% body fat, respectively. In the EXERNET study, a representative study of Spanish elderly performed on non-institutionalized subjects of both sexes, those who walked regularly had a lower prevalence of overweight and obesity than the sedentary ones.[14]

European adolescents from the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study who performed more than 60 minutes of moderate to vigorous physical activity (MVPA) had less total and abdominal fat (%) than their less active counterparts.[15] In the Spanish cohort of the European Youth Hearth Study (EYHS) the risk of developing overweight/obesity was nearly 4-fold in children who practiced less than 60 minutes of MVPA per day than their more active counterparts.[16]

Exercise intensity has also been proposed as a main factor influencing stem cell differentiation.[17] Based on animal studies it has been hypothesised that vigorous

Table I

Physical activity recommendations by age group. Adapted from WHO 2010[10]

Age Group	*Physical activity recommendation*	*Additional comments*
5-17 years	• Children and youth aged 5–17 should accumulate at least 60 minutes of moderate- to vigorous-intensity physical activity daily. • Amounts of physical activity greater than 60 minutes provide additional health benefits. • Most of the daily physical activity should be aerobic. Vigorous-intensity activities should be incorporated, including those that strengthen muscle and bone*, at least 3 times per week.	For this age group, bone-loading activities can be performed as part of playing games, running, turning or jumping. In order to improve cardiorespiratory and muscular fitness, bone health, and cardiovascular and metabolic health biomarkers.
18-74 years	• Adults aged 18–64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity. • Aerobic activity should be performed in bouts of at least 10 minutes duration. • For additional health benefits, adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week, or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate- and vigorous-intensity activity. • Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week.	For this age group, physical activity includes leisure time physical activity (for example: walking, dancing, gardening, hiking, swimming), transportation (e.g. walking or cycling), occupational (i.e. work), household chores, play, games, sports or planned exercise, in the context of daily, family, and community activities. In order to improve cardiorespiratory and muscular fitness, bone health, reduce the risk of NCDs and depression.
> 65 years	• Older adults should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity. • Aerobic activity should be performed in bouts of at least 10 minutes duration. • For additional health benefits, older adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week, or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate- and vigorous-intensity activity. • Older adults, with poor mobility, should perform physical activity to enhance balance and prevent falls on 3 or more days per week. • Muscle-strengthening activities, involving major muscle groups, should be done on 2 or more days a week. • When older adults cannot do the recommended amounts of physical activity due to health conditions, they should be as physically active as their abilities and conditions allow.	For this age group, physical activity includes leisure time physical activity (for example: walking, dancing, gardening, hiking, swimming), transportation (e.g. walking or cycling), occupational (if the individual is still engaged in work), household chores, play, games, sports or planned exercise, in the context of daily, family, and community activities. In order to improve cardiorespiratory and muscular fitness, bone and functional health, reduce the risk of NCDs, depression and cognitive decline.

physical activity produces a sufficient mechanical stimulation of the tissues in order that stem cells are turned preferably into fat-free mass cells. In contrast, the absence of moderate-intensity physical activity or an excessive energy intake favours stem cells turning into fat mass cells.[17] There are two periods during growth in which noticeable increases in adipocytes occur: infancy and adolescence which are viewed as "critical" for the enlargement of the adipose tissue and in turn for development or prevention of obesity during growth. The above-mentioned theory could be "crucial" to apply in these periods in which it is also important to provoke a higher accretion of bone mass, one of the aspects considered in the theory that is important for growth. Professor Claude Bouchard had already proposed in 1990 that physical fitness is the main determinant of health in the broad sense as defined by WHO.

Regarding metabolic risk, cardio-respiratory fitness has been defined as a powerful marker of health at all ages.[19] Healthy children aged 9 and 10 years from the EYHS study and adolescents aged 13 to 18 years from the AVENA study with high cardio-respiratory fitness (classified in quartiles) had a significantly and progressively better metabolic profile (index based on fasting triglycerides, LDL-cholesterol, HDL-cholesterol and glucose concentrations) than those with lower cardio-respiratory fitness.[20] But even in overweight subjects, cardio-respiratory fitness can make the difference. Separating the adolescents from the AVENA study according to their body composition, those overweight adolescents with high

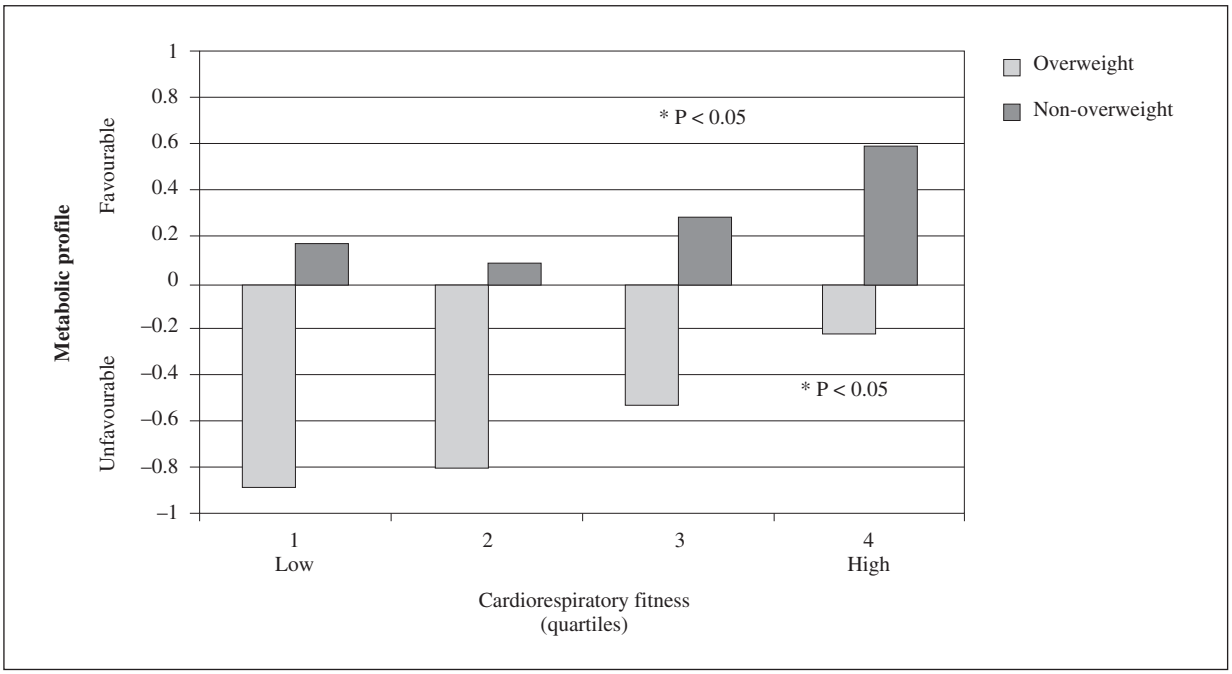

Fig. 1.—Relationship between cardiorespiratory fitness, body composition and metabolic risk in Spanish adolescents from the AVENA study. Modified from[19]. Footnote: *Association between metabolic profile (computed with age- gender specific standardized values of triglycerides, low density lipoprotein cholesterol, high density lipoprotein cholesterol and fasting glycaemia) and cardiorespiratory fitness quartiles in non-overweight and overweight Spanish adolescents. The higher is the metabolic profile the healthier. Weight categories were constructed following the International Obesity Task Force-proposed gender- and age-adjusted body mass index cutoff points. Data shown as mean and standard error of the mean. *P for trend in both overweight and non-overweight categories.*

respiratory fitness had the same metabolic profile as the normal weighted adolescents with low cardio-respiratory fitness[19] (fig. 1). The cardio-metabolic effects of exercise in overweight and obese children (boys and girls) aged 9.4 years have been confirmed in the randomized control trial mentioned below,[21] and appear to be able to be generalized regardless of race (black and white), of pre-diabetes or a family history of diabetes.

Trying to get a deeper understanding of the dose-response of exercise in overweight and obese children, a randomized control trial over 13 weeks was performed in sedentary children in Georgia (U.S.).[21] Children had to perform 20 or 40 minutes of aerobic training daily after school and were compared to a control group. General and visceral body fat, among other variables, was reduced significantly in a dose-response gradient. The increment of benefit between the control and low-dose exercise conditions was larger than the additional benefits observed between the low- and the high-dose exercise and both groups showed similar effects on insulin resistance. As has been observed in several studies, the lower the baseline physical activity status, the greater will be the health benefit associated with a given increase in physical activity (fig. 2).

Several studies have proposed that muscular strength influences cardio-metabolic health independently and reduces the risk of metabolic syndrome in addition to cardio-respiratory fitness.[22] As we get older, both VO_2max and strength diminish. Regular exercise can at least slow down this process. Both the percentage of body fat and total body fat are more similar among trained young and old people than among the un-trained. Studies indicate that trained older people have a similar fat mass to young un-trained people, and one that is much lower than older un-trained people.

Regular daily physical activity contributes to energy balance in several ways. There is no doubt about that every activity the human body performs is linked to energy output. The higher the intensity and duration, the more energy is spent. Additionally, adaptations to training, i.e. increases in muscle mass, in capillaries, etc, also contribute to raising the basal metabolic rate; and after exercise, oxygen consumption (and consequently energy output) remains high for a while until the body has again reached homeostasis.[23]

Adipose tissue increases with age and obesity itself has been proposed as a barrier for being physically active. In a recent prospective study performed on middle-aged women, both mean weekly physical activity and MVPA measured by accelerometry decreased significantly more in obese women over a 20-month period than in non-obese women.[24] Low levels of growth hormone have been linked to obesity.[23] Growth hormone is one of the hormones involved in FFA metabolism during exercise.

Several studies have shown that at all ages, boys are more active than girls,[18] which tracks also into adulthood, adult men being more active than adult women in

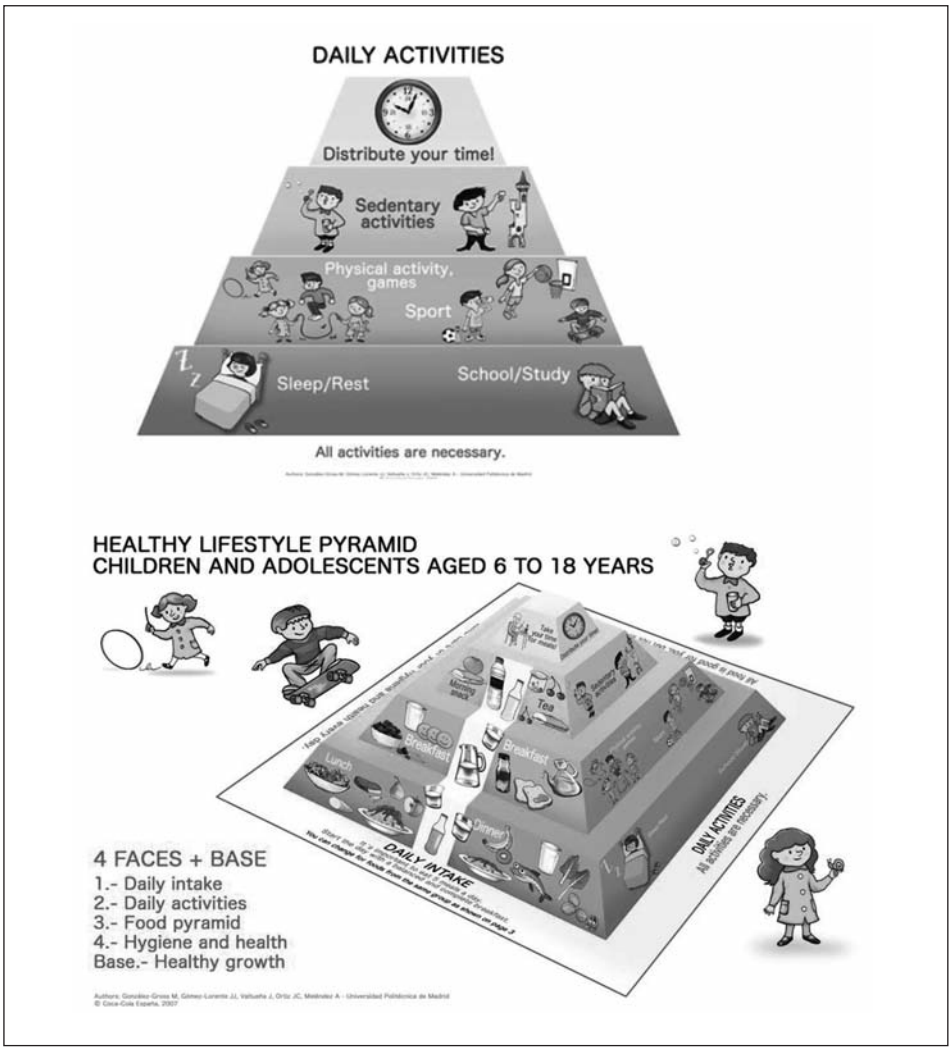

Fig. 2.—The importance of the daily Schedule including physical activity within a healthy lifestyle for children and adolescents.[18]

all WHO Regions.[10] In accordance, cardiorespiratory fitness and strength values are higher in boys than in girls, with more homogenous fitness levels among girls than boys.[22] In Europe, data from the HELENA study have revealed that 61% of the adolescent boys and 57% of the girls presented a healthy cardio-respiratory fitness (CRF) level,[22] a similar prevalence as found for U.S. adolescents. There is consistency among the studies that with increasing age there is a tendency in both sexes to abandon physical activities and sports (i.e. HBSC Study, AVENA study, HELENA Study). According to the "Study of sport habits among school-age children in Spain",[25] the main cause of not practicing physical activity is lack of time, a cause which increases with increasing age (10% at ages 6-7 up to 32% at ages 16-18). It is essential to educate children in learning how to distribute their time in order that MVPA is included in their daily schedule,[18] as it is specifically indicated in the Healthy Lifestyle Pyramid for children and adolescents (fig. 3). Additionally, some other factors have been identified in relationship to physical activity in youth. A physically active mother (i.e. AVENA study) positively influences both boys and girls. Lower physical activity among female friends and perceived lack of safety in the neighbourhood represents a negative influence among the girls.[26]

In relationship to relative risk reduction of coronary heart disease, currently the evidence suggests that any type of physical activity contributes to reducing the risk, but that a high level of physical fitness reduces the relative risk even more.[23]

In relation to body fat reduction, both strength and aerobic exercise have been demonstrated to be effective, though aerobic exercise has a much higher impact on body fat and body fat distribution.[27]

In relation to the improvement of blood lipid profiles and glucose metabolism, both types of exercise have demonstrated similar efficacy[27] (table II).

Substrate utilization during exercise

The human body functions in accordance with the laws of thermodynamics. If total food calories consu-

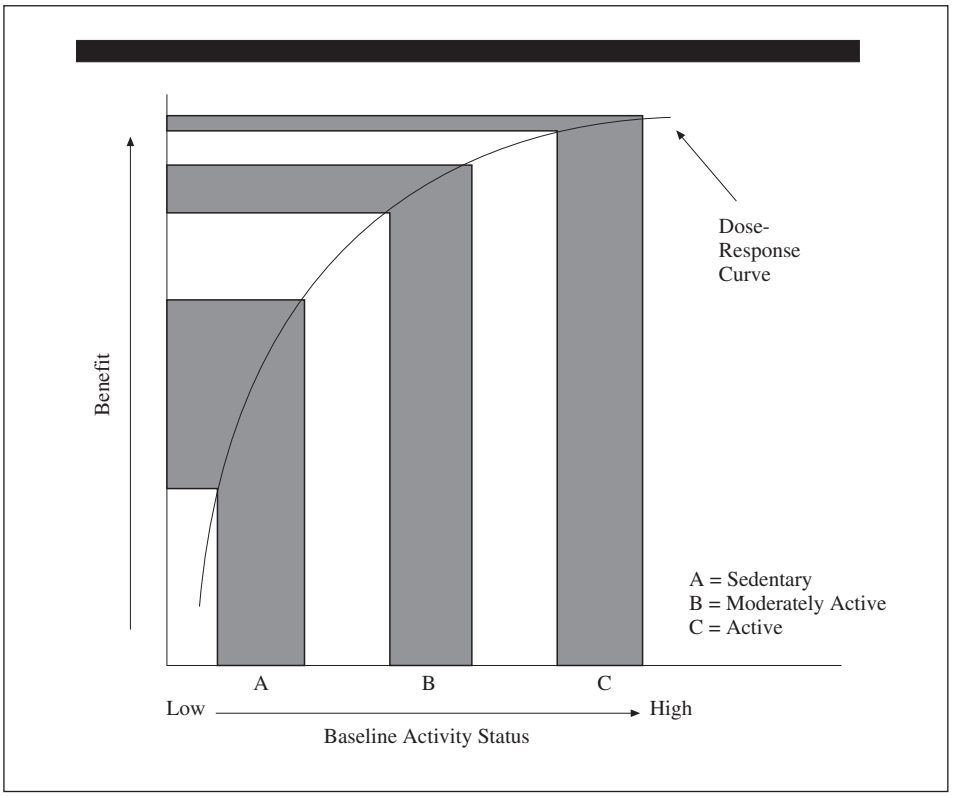

Fig. 3.—The dose-response curse represents the best estimate of the relationship between physical activity (dose) and health benefit (response). The lower the baseline physical activity status, the greater will be the health benefit associated with a given increase in physical activity (arrows A, B, and C).

med exceed daily energy expenditure, excess calories accumulate and are stored as fat in the adipose tissue.[23] In this situation, there are three ways to recover the energy balance: increasing physical activity, decreasing food intake or a combination of the two.

The energy expenditure for an activity depends on its intensity and duration. Greater intensity will demand greater energy expenditure per unit of time, and longer duration greater total energy expenditure. These aspects should be taken into account when a certain amount of energy expenditure is required. Brooks and Mercier[28] pointed out that the crossover point is the power output at which energy from carbohydrate derived fuels predominates over energy from lipids, with further increases in power eliciting a relative increment in carbohydrate utilization and a decrement in lipid oxidation. During rest and mild- to moderate intensity exercise, lipids predominate as energy sources, especially in an endurance-trained state. Exercise at low intensities (about 45% of VO2 max) is accomplished with lipids as the main substrate. In contrast, in hard intensity exercise (about 75% of VO2 max) carbohydrates become the predominant substrate. Lipids also become the predominant substrate during recovery from exercise that results in glycogen depletion.[28]

There is a consensus that in endurance trained athletes fat oxidation rate is the highest in those activities performed at intensities around 65% of VO_2 max.[11] This intensity corresponds to a value of approximately 70-75% of maximal heart rate, a value commonly recommended in exercise prescriptions for programmes to improve cardiovascular fitness, but this intensity is difficult to reach or to maintain for overweight or obese untrained people. This was recently confirmed in the PRONAF study, in which untrained overweight and obese adult subjects followed a supervised training protocol of 22 weeks. At the end of the study, even after losing weight and body fat and improving their fitness status, they were not able to perform at the target intensity of 65%VO_2max.[27]

There is a belief that to increase the use of fats as the energy source, exercise intensity should be moderate or low because the higher the exercise intensity the greater the body's reliance on carbohydrates as an energy source,[11] but to reach a determined energy expenditure for maintaining or losing body weight, untrained, overweight or obese people, should emphasize exercise duration and progress to higher intensity exercise increasing the energy expenditure which will also bring them additional cardiovascular benefits.

Sedentary or Sitting time as a risk factor for health

The relationship between physical activity and sedentary behaviour is still not clear in adults according to the systematic review by Rhodes et al.[29]. There seems to be some evidence for a negative association between TV viewing and general screen viewing with physical activity, but no relationship is apparent for computer use or general screen behaviour. Few studies

Table II
Effects of aerobic training and strength training on selected health parameter

Variable	*Aerobic exercise*	*Resistance exercise*
Bone mineral density	↑↑	↑↑
Body composition		
% body fat	↓↓	↓
Fat free mass	↔	↑↑
Strength	↔	↑↑↑
Glucose metabolism		
Insulin response to glucose challenge	↓↓	↓↓
Basal insulin levels	↓	↓
Insulin sensitivity	↑↑	↑↑
Blood lipid levels		
HDL-cholesterol	↑	↑↔
LDL-cholesterol	↓	↓↔
Heart rate at rest	↓↓	↔
Stroke volume	↑↑	↔
Blood pressure at rest		
Systolic	↓↔	↔
Diastolic	↓↔	↓↔
VO2 max	↑↑↑	↑↑
Endurance performance	↑↑↑	↑↑
Basal Metabolic rate	↑	↑↑

Footnote: The Arrows indicate the change produced by training. ↑ = increase; ↓ = decrease; ↔ = little or no change. The more arrows, the greater the effect. Modified from 11.

have analysed the combined influence of sedentary behaviour and physical activity on obesity. In a recent study on adults from the NHANES, low MVPA was consistently associated with a higher risk of obesity, regardless of TV time or total sedentary behaviour.[30] Interestingly, small differences in daily MVPA (5-10 minutes) were associated with relatively large differences in the risk of obesity. Another study found that the strength of the association between certain types of sedentary behaviour and BMI was influenced by the time spent performing physical activity. More than 60 minutes of MVPA and less than 60 minutes of TV time per day resulted in lower average BMI than the same TV time but less than 60 minutes of MVPA.[31] As data are still scarce and even contradictory when analysing the same subjects,[30,32] the combined effect of sedentary behaviour (and here differentiating between several ones like TV time, reading, learning, etc) and physical activity (here also differentiating between MVPA, active transportation, etc.) deserves further study.

Currently, many common forms of behaviour in our daily life involve sitting, for example, driving a car, working at a desk, eating a meal at a table, playing video games, watching TV, listening to music, etc, and they can occupy a large part of our day, a tendency which is predicted to increase further in the near future.[29] Sedentarism has begun to be studied as an independent risk factor in the last decade. A recent study performed on 222,497 adults in Australia, concluded that prolonged sitting is a risk factor for all-cause mortality even for people who engage in the recommended 150 min/week of physical activity, suggesting that what happens in the remaining 6500 minutes of the week one is awake is important for health.[33] Shorter sitting time and physical activity are independently protective against all-cause mortality not just for healthy individuals but also for those with cardiovascular disease, diabetes, overweight and obesity. In contrast, sitting periods of 4 to less than 8 hours/day, 8 to less than 11 hours/day, and 11 or more hours/day, increased the mortality hazard ratios (1.02, 1.15, 1.4, respectively) after an average follow-up period of 2.8 years. The association between sitting time and all-cause mortality appeared consistent across the sexes, age groups, body mass index categories, and physical activity levels and across healthy participants compared with subjects with pre-existing cardiovascular disease or diabetes mellitus.[33]

General practitioners participating in the health care system should be involved in a population-based intervention to increase physical activity in the population.[34] But the percentage of primary care physicians who include physical activity together with nutrition in a combined lifestyle guidance to their patients is low, and therefore we are possibly missing additional opportunities for obesity prevention.[35] Other settings such as schools, workplaces and sports clubs have been proposed for increasing physical activity in all age groups by providing optimal conditions for each subpopulation.[34] These authors also express the urgent need of a coordinated population-based intervention program for improved health and reduced health expenses through increased physical activity in the entire population, which should be implemented at the national and international level.

Conclusions and future prospects

There is scientific evidence that regular physical activity reduces total mortality risk, mortality risk from cardiovascular disease and other causes (independently of weight loss). Physically active people have a lower body fat percentage than inactive people, at all ages and in both sexes. Overweight people who have a good fitness level have better cardio-metabolic health than non-fit overweight people and similar to lean but unfit people. Physical activity and physical fitness seem to exert synergic but independent effects on health-related parameters. Sedentarism and hours of physical inactivity

seem to act as independent risk factors for health. Aerobic exercise should be complemented with strength training in both sexes and all age groups. An active life is fun and helps in socialization. Several studies have shown that it is never too late to start doing physical activity; this means that intervention programmes should focus on people of all ages, including the elderly. Gender aspects should also be taken into account.

There is still a need for research to determine the appropriate dose of exercise (time, duration and intensity) in combination with sedentary behaviours and other physical activities (i.e. transport) in the context of our modern lifestyle in order to prevent obesity at all ages. As has been mentioned above, obesity prevention has not been a target issue of sport sciences until quite recently. As public health measures have failed to stop the obesity epidemic in both developed and developing countries in the last 3 decades, there is clearly a need to change the paradigm. The inclusion of sport scientists, physical education teachers and other professionals in the multidisciplinary team which should be responsible for drawing the road map to prevent the increase of the obesity epidemic effectively is a "must" from our point of view.

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Obesity and sedentarism in children and adolescents: What should be bone?

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Abstract

Paediatric overweight continues to be a public health problem, and the etiology of obesity is multifactorial and complex. Dietary patterns, physical activity (PA) and sedentary behaviors are acknowledged as major behavioural determinants of obesity. New technologies and electronic based activities have produced a decrease in PA levels, and an increase in sedentary activities in children and adolescents. Potential mechanisms that explain the association between TV viewing and childhood obesity are: displacement of PA, unhealthy food preferences produced by food advertisements, a higher energy intake by automatic eating and overconsumption caused by distraction. Interventions aimed to reduce time in sedentary behaviours are in children generally positive. However, their benefits on adiposity markers are small. Thus, if global and macro-level *obesogenic* factors are not changed substantially, the interventions oriented to prevent obesity will produce small benefits.

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Key words: *Obesity. Sedentary behaviour. Children. Adolescent.*

OBESIDAD Y SEDENTARISMO EN NIÑOS Y ADOLESCENTES: ¿QUÉ DEBERÍA HACERSE?

Resumen

El sobrepeso en población en edad pediátrica continúa siendo uno de los problemas de salud pública. La alimentación, actividad física y las conductas sedentarias son los mayores determinantes de la obesidad. Las nuevas tecnologías y las actividades basadas en la electrónica han producido un descenso en los niveles de actividad física y un aumento de las actividades sedentarias en niños y adolescentes. Diversos mecanismos se han sugerido para explicar la asociación entre ver la televisión y la obesidad: desplazamiento de actividad física, los efectos de la publicidad de alimentos, el aumento de la ingesta energética en ausencia de hambre (automáticamente), y el aumento de la ingesta producida por la distracción. Intervenciones orientadas a reducir el comportamiento sedentario en niños y adolescentes han mostrado ser exitosas. Sin embargo, su impacto sobre marcadores de adiposidad es pequeño. Por lo tanto, si los factores obesogénicos que dependen de escalas a nivel global y macro no son cambiados substancialmente, los beneficios de las intervenciones para prevenir la obesidad serán muy modestos.

Nutr Hosp 2013; 28 (Supl. 5):99-104

Palabras clave: *Obesidad. Conductas sedentarias. Niños. Adolescentes.*

Abbreviations

HELENA: Healthy Lifestyle in Europe by Nutrition in Adolescence.
PA: Physical Activity.
TV: Television.

Introduction

Paediatric overweight continues to be a major and growing public health problem, although stability or a levelling off in the prevalence of obesity has been observed among children and adolescents in several parts of the world.[1] A multi-factorial approach to obesity prevention requires changes in multiple factors contributing to energy imbalance. Dietary patterns, physical activity (PA) and sedentary behaviours are acknowledged as major behavioural determinants of obesity.[2-4]

In the last decades developed countries have suffered a deep change in the traditional way of life. Labour saving technologies and electronic based recreational activities have produced a marked decrease in children PA levels. In addition, sedentary activities are increasing, and involve all activities involving low levels of moderate-vigorous physical activity, including television (TV) and computer use, school work, reading, playing or listening music. The most prevalent form of sedentary behaviour is time spent in front of a screen, which includes television, videos, computer and video games. The American Academy of Pediatrics recommends that children limit their total media time to no

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more than 1-2 h a day;[5] while more restrictive limits are applied to pre-school children for instance in Australia, recommending less than 1 hour per day of sitting and watching TV and the use of other electronic media.[6] There is a huge variation on the prevalence on excessive sedentary time between countries. Children and adolescents spent on average 1.8 to 2.8 hours of TV per day, depending on age and gender.[7] For instance, in several European countries 61% of children aged between 11 to 15 years watched TV more than 2 hours/ day. In adolescents from the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study, the proportion of adolescents watching TV during weekend days, more than 2 hours/day was 58% in males and 53% in females.[8]

The aim of this study is to review the current literature regarding sedentary behaviours and their relation with obesity in children and adolescents.

Sedentary behaviours and obesity

Most of scientific community agree that the growth in worldwide prevalence of obesity during the last decades is due to profound changes in our (traditional) lifestyle. That is, today people are more sedentary (in transportation, jobs and leisure time). Furthermore, many countries are losing their traditional (healthy) diets by others rich in animal products, refined grains and sugar.

Several studies have showed the relationship between an increase of several sedentary behaviours, for instance television viewing or screen time, and weight gain.[4,9] In addition, a novel risk factor for weight gain in adolescents is TV availability in the bedroom. Those adolescent males who reported having a TV in the bedroom had higher risk of having higher body mass index, high waist circumference and body fat,[10] and to have a TV in the adolescent's bedroom increased the risk of having central obesity.[11] Moreover screen-viewing behaviour (TV viewing, playing computer games and using the internet) has been associated with higher consumption of energy dense foods (i.e. sweetened-beverages and savoury snacks) and lower consumption of healthy foods (i.e. fruits).[12] In the same line, an inverse association between several indicators of sedentary behaviours and healthy dietary patterns, and a positive association with snacking patterns has been observed in other young-age population groups.[13] On the other hand, we[14] and others[15] have observed that adolescents who spent long time playing with videogames were more likely of having cardiovascular risk factors. Interventions aimed at reducing screen time have been a focus of childhood obesity prevention and treatment, however the evaluation of their effectiveness need to be taking into account in order to develop successful prevention programs.

Currently, most children and adolescents spend the majority of their leisure time in sedentary behaviours. This is of concern for children's health because In 1985, Dietz and Gortmaker found a positive association between hours of TV viewing and obesity in children and adolescents.[16] Since then, multitudes of studies in different countries have found similar associations. In fact, we reviewed studies (cross-sectional, longitudinal and intervention) focused in the relationship between obesity markers and sedentary behaviours.[4] We concluded that there was enough evidence for the *obesogenic* effect of TV viewing, especially in children. More recent reviews support our findings. In children, a moderate evidence was observed between TV viewing and obesity.[17] In contrast, in adolescents insufficient evidence was found for a longitudinal positive relationship between TV viewing and body mass index or more specific indicators of fat mass.[18] For videogames and computer use more studies are needed, but not positive associations were found.[4] Several mechanisms can explain the *obesogenic* effect of TV viewing. Here, we briefly discuss the four main mechanisms.

Mechanisms linking TV viewing with obesity

Obesity has a multifactorial origin. TV viewing may promote a positive energy balance by different ways (fig. 1):

TV viewing and physical activity

One explanation is that TV viewing displaces time spent in physical activity. Some study supports this

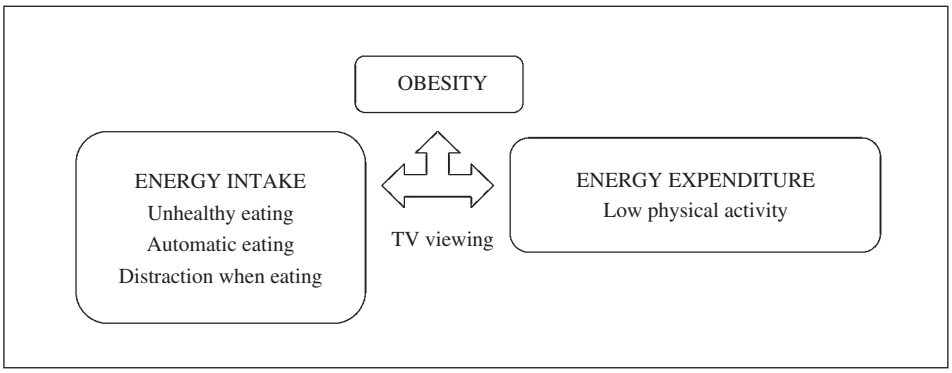


Fig. 1.—Potential mechanisms by which TV viewing may lead to obesity.

mechanism. Children spending more time watching television (>120 minutes/day) at age six were less active and had higher body mass indices at ages eight and ten.[19] However, in a cross-sectional study conducted in children and adolescents, TV viewing and physical activity were not associated.[20] Interestingly, in the latter study eating meals while watching TV was positively associated with obesity. Recently, we found that even adjusting for vigorous physical activity, a TV set in the bedroom was associated with abdominal obesity in European adolescents.[11] These findings indicate that TV viewing may favour a positive energy balance for mechanisms beyond the physical activity level.

TV viewing and unhealthy food advertisements

Currently, food industry makes use of different channels (internet, toys, games, sponsoring, and school material) to advertise their food and drinks to children and their parents. However, in children TV advertisements are the most effective and most heavily used marketing instrument.[21] Unfortunately, food companies have traditionally used TV adds to promote the consumption of caloric dense and highly palatable products.[22] In theory, the more food advertisements children see, the more primed they are to want to eat or drink the advertised food. Remarkably, it has been estimated in some studies that children are exposed to 25,000 TV ads per year. About 20% of them, are related with food/drink products.

Automatic eating while watching TV

This mechanism is based on the assumption that part of the human behaviours are automatic, cued by environmental stimuli, resulting in actions unaccompanied by conscious reflection. For instance, in laboratory studies children exposed to food adds ate automatically even in the absence of hunger.[23] Remarkably, the type of food advertised was not available for the concurrent consumption. Therefore, the overconsumption attributed to TV viewing can be explained by unconscious actions. Today food companies are replacing TV advertising with more subtle marketing strategies. Advertisers methodically place food products into programs, movies, musical videos. Product placements can be shown by direct visual or auditory signals but also indirectly (product is part of the background, but attention is not paid to the product). In summary, food placements can lead to obesity by increasing (automatically) the energy intake and favouring the less direct advertised food product.

Distraction while watching TV

In some countries is common to eat while watching TV. This distraction can lead to "mindless eating," or a lack of attention paid to the amount of consumed food. In laboratory studies, children consumed significantly more food when watching a continuous TV program than when they watched a repeated segment of a TV program.[24] Similarly, individuals who viewed TV while consuming a meal were less accurate in estimating the amount of food they had consumed than those who consumed the meal without TV.[25]

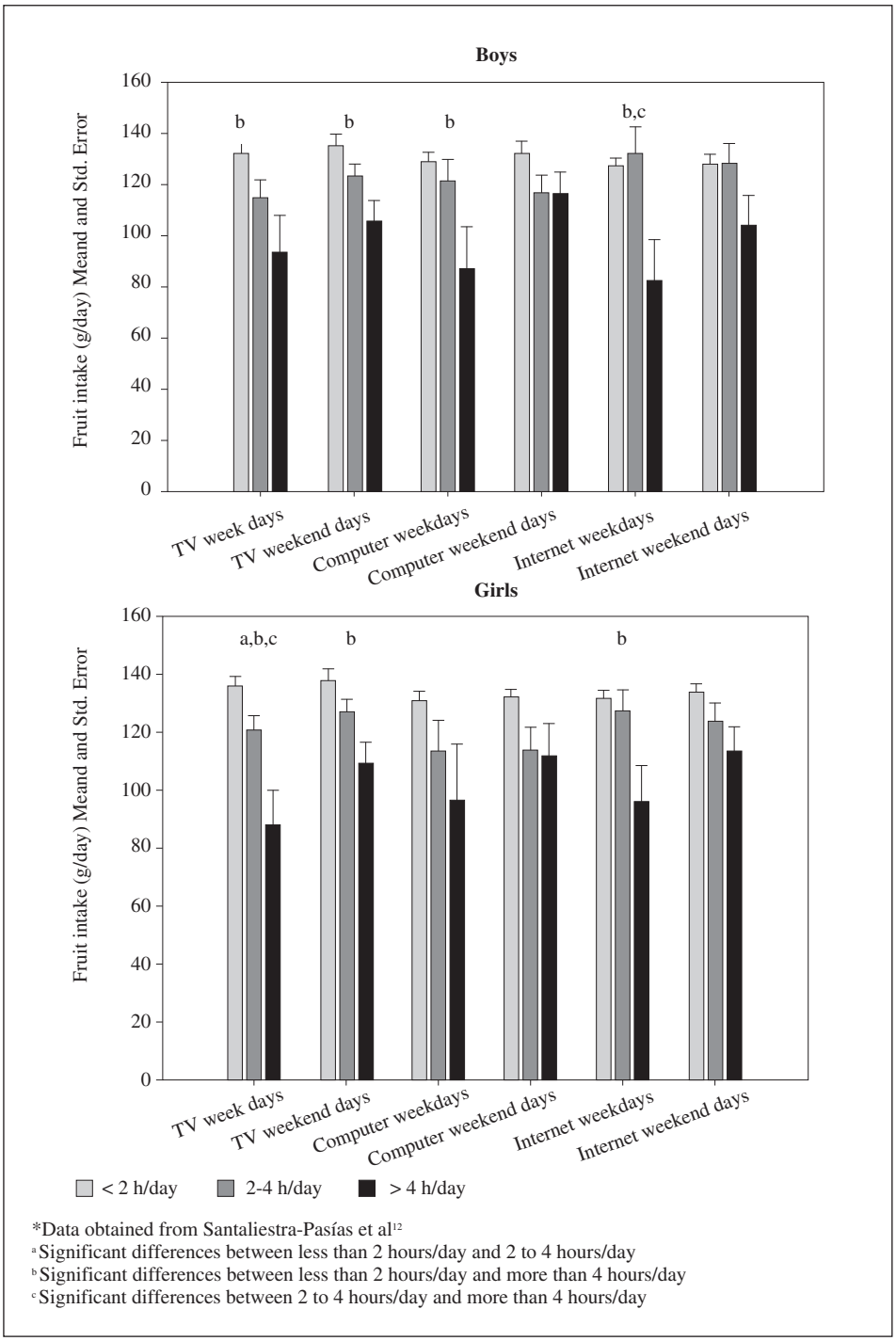
Food habits and sedentary behaviours

Several studies have been reported that those children who spent more time watching TV were more likely to consume sweets and drinks, and less likely to consume fruits and vegetables daily.[26] In addition, adolescents were more likely to consume energy-dense foods and drink products while watching TV.[27] Also, the amount of sugar sweetened beverages and snacks increased significantly when the adolescents spent more time in several sedentary behaviours like TV viewing, playing computer games and using the internet.[12] In the same population group, the amount of fruits consumed decreased when they spent more hours in these activities (figs. 2 y 3).

Interventions aiming to decrease sedentary behaviours

A huge variation of interventions has been published linking several sedentary behaviours and obesity. Several systematic reviews and meta-analysis have been recently published regarding the effectiveness of interventions aiming to decrease sedentary behaviours.[28,29] In a review, 13 trials with children aged between 3.9 to 11.7 years;[29] whereas another included both children and adolescents resulting in 34 intervention studies.[28] Effective interventions on reducing TV viewing have been described in pre-schoolers and young children, showing significantly decreases on time spent in this sedentary behaviour when comparing the intervention group versus the control one (24.4% reduction versus 11.8% increase; and 42.7% reduction versus 6.5% reduction, respectively).[30,31] In the same line, the results in the whole group are consistent with these results, reported that intervention on sedentary behaviours decreased significantly the time that children spent on it.[28] The intervention group compared with the control group showed a difference in mean change in screen time of –3.72 hours/week (95% CI –7.23 to –0.20 h/week) in children younger than 6 years; however no statistical significances were found in children and adolescents older than 6 years (–0.19 IC 95% –3.12 to 2.75).

Wahi et al did not showed enough evidence about the effectiveness of interventions aimed to reduce screen time in children to reduce body mass index (–0.10 (95% CI –0.28 to 0.09)).[29] Nevertheless, in the preschool age group significant reductions in the effect associations of screen time reductions and reducing BMI were obser-



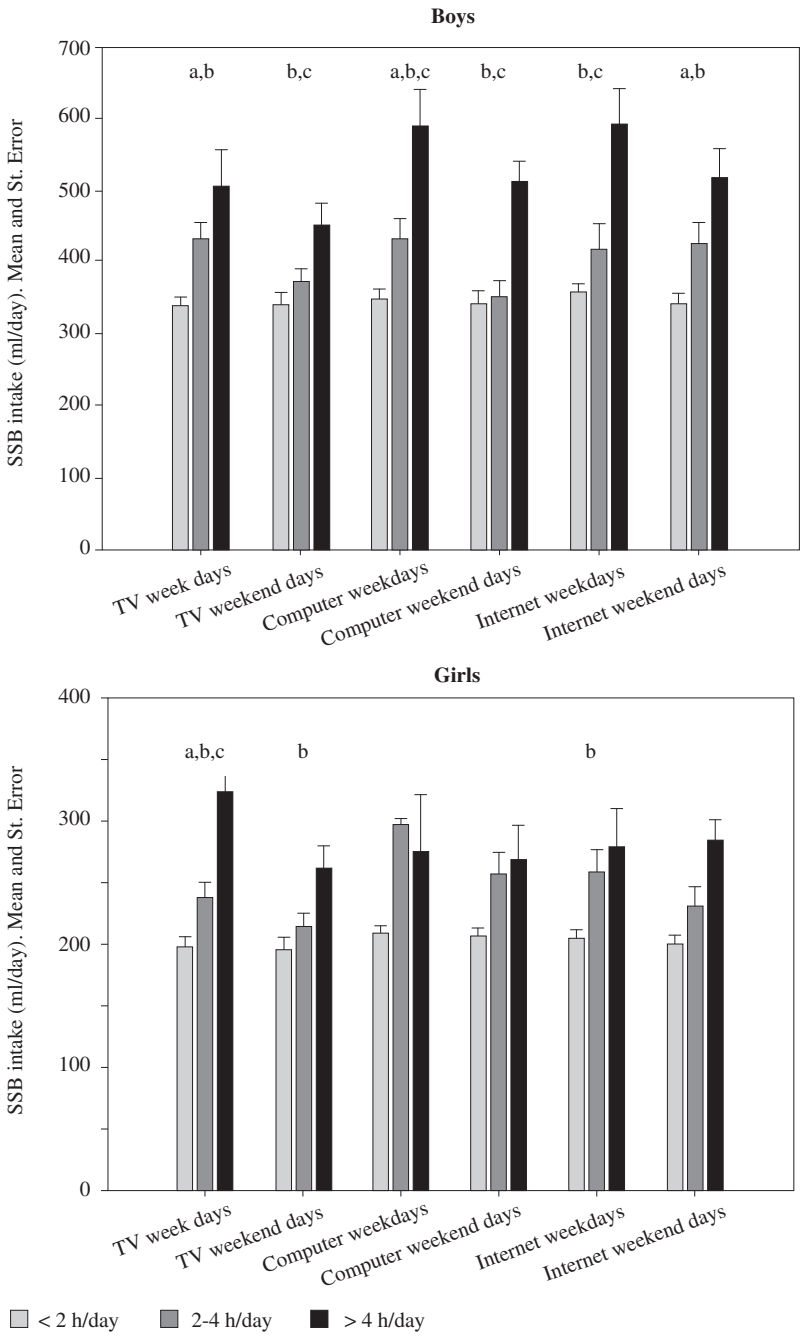
*Data obtained from Santaliestra-Pasías et al[12]
[a] Significant differences between less than 2 hours/day and 2 to 4 hours/day
[b] Significant differences between less than 2 hours/day and more than 4 hours/day
[c] Significant differences between 2 to 4 hours/day and more than 4 hours/day

Fig. 2.—Fruit intake according to sedentary behaviours in European adolescents by sex.*

ved.[29] In addition, when the meta-analysis of interventions includes only young children, the results indicate that interventions performed in school- and general population settings can help prevent excessive sedentary behaviour and unfavourable health outcomes.[28] Van Grieken et al. showed that for sedentary behaviours the post-intervention mean difference was -17.95 minutes/day (95% CI –26.61 to –9.28) and for BMI, the post-intervention group mean difference was –0.25kg/m^2 (95% CI –0.40 to –0.09).

Conclusion

The etiology of obesity is multifactorial and complex. The evidence of different *obesogenic* factors is stronger in some ages than others (Example: TV viewing is strongly associated with obesity in childhood but less consistently during adolescence). Currently, the prevalence of sedentary behaviours related with screen time is high,[12,32] therefore interventions to decrease time spent in sedentary behaviours may help to reduce



*Data obtained from Santaliestra-Pasías et al[12]
[a] Significant differences between less than 2 hours/day and 2 to 4 hours/day
[b] Significant differences between less than 2 hours/day and more than 4 hours/day
[c] Significant differences between 2 to 4 hours/day and more than 4 hours/day

*Fig. 3.—Sugar sweetened beverages intake according to sedentary behaviors in European adolescents by sex**

the prevalence of obesity. The current evidence says that decreasing and breaking sedentary behaviours may be important for achieving a better population health. In order to obtain a benefit in terms of body composition indicators, it is highly recommended to focus on preschool population. Some practical recommendations can be made based on several observational and laboratory studies but the value of these recommendations should be tested by intervention studies. First, parents should be aware of how different lifestyles impact theirs children's health in order to promote healthy behaviours. Regarding the familiar environment, it seems recommendable to lay

TV sets outside children/adolescent's bedroom. Second, preferentially children should not eat while watching TV. Third, families should minimize the amount of time that children are exposed to food advertisements. Fourth, governments (i.e. by taxes) and communities (promoting competing sport-games activities) should not incentive passive electronic entertainment. Finally, given the multifactorial origin of obesity, (micro-level) prevention strategies can result unsuccessful if global and macro-levels *obesogenic* factors are not altered substantially.

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Successful intervention models for obesity prevention: The role of healthy life styles

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Abstract

Children obesity is considered a serious public health problem around the world. In Spain, the prevalence of overweight/obesity is reaching alarming figures, exceeding 35% of the children. Several hypotheses suggest that the energy balance model does not fit very well when analyzing the causes of the current obesity epidemic and, although genetics seems to explain up to 30% of the likelihood to become obese in infancy, has been suggested that genetics might be influenced by environment factors including vigorous physical activity (PA). Some recent systematic reviews indicate that there is enough evidence about the effectiveness of interventions to prevent obesity in children 6-12 years old; however, the heterogeneity of the effect, and the potential selection, information and publication biases that undermine the validity of these studies, thus their results should be interpreted with caution. In Spain, an extracurricular PA program of leisure-time (MOVI) has evidenced some effectiveness on reducing the adiposity and on improving the lipid profile in schoolchildren. To overcome some weakness of MOVI program, a second edition of this study was designed. The objectives of this review are twofold: 1) to analyze latest data of the obesity epidemic in Spain; and 2) to describe the main features of MOVI-2 program, and overall of the successful interventions to prevent children obesity.

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Key words: *Obesity. Interventions. Children. School. MOVI program.*

MODELOS EXITOSOS DE INTERVENCIÓN PARA LA PREVENCIÓN DE LA OBESIDAD: EL PAPEL DE LOS ESTILOS DE VIDA SALUDABLES

Resumen

La obesidad infantil continúa siendo un serio problema de salud pública en todo el mundo. Las cifras actuales en España son alarmantes, y se sitúan en torno al 35,4%. Hay varias hipótesis que apuntan a que el modelo de balance energético como causa de la obesidad infantil no se sostiene. Y aunque las razones genéticas parecen explicar hasta el 30% de la probabilidad de llegar a ser obeso, se ha sugerido que esta herencia podría ser influenciable por factores ambientales entre los que se encuentra la actividad física (AF) vigorosa. Aunque las últimas revisiones señalan que existe evidencia suficiente sobre la efectividad de las intervenciones para prevenir la obesidad en niños de 6-12 años, la heterogeneidad del efecto encontrado en los resultados y la posibilidad de sesgos de diseño y de publicación de los estudios hacen que los resultados deban interpretarse con cautela. En España la intervención MOVI, un programa extraescolar de AF de carácter recreativo, ha conseguido disminuir la adiposidad, y mejorar el perfil lipídico. Para superar potenciales limitaciones de la primera intervención, se diseñó una segunda edición. Los objetivos de esta revisión fueron: 1) analizar los últimos datos de la epidemia de la obesidad infantil en España; y 2) describir las principales características del programa MOVI-2, y en general de las intervenciones que han sido efectivas para prevenir la obesidad en niños.

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Palabras clave: *Obesidad. Intervenciones. Niños. Escuela. Programa MOVI.*

Introduction

Children obesity remains a serious public health problem around the world[1]. In Spain, current prevalence rates range from 35% to 42%.[2,3] Although recent studies have shown a leveling-off or even a decline in the prevalence of overweight/obesity in children in different countries of the world,[4,5] in the period 2004-2010 prevalence of overweight in boys aged 8-11 years from Cuenca, Spain, increased from 21.6% to 28.0% and the percentage of body fat from 22.6% to 24.0%. In girls, however, the trend seems to have stabilized.[2]

In parallel to the growing trend in the overweight prevalence, during the last decade of the 20th century underweight prevalence was increasing in Spain, from

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2.7% in 1992 to 9.2% in 2004 in children 9-10 years,[6] and in other European countries[7]. Fortunately, latest estimations reported in Spanish children show that from 2004 to 2010 the underweight prevalence has not increased, and stands at around 8.5%.[2]

Therefore, the population approach for addressing the prevention of overweight, as in other public health problems, we should to be into account the classic good practice Latin axiom *primum non nocere,* so that it might be that interventions whose effectiveness on reducing overweight is controversial have also an undesirable effect increasing the proportion of underweight children.

Determinants of the obesity epidemic in Spanish children

At the individual level, body fat accumulation results from an imbalance between energy intake and energy expenditure. If intake exceeds expenditure the excess of energy will be stored as fat. On the other hand, it has been estimated that genetics susceptibility explains about the 30% of the likelihood of child will develop obesity,[8] although this is a polygenic inheritance strongly influenced by the interaction genes, environment and lifestyle.[9]

However, at the population level non-genetic factors are the responsible for the frequency of obesity, including epigenetic,[10] eating behavior patterns at an early age, activity/inactivity patterns, and other psychological, social and environmental factors.[9] Nowadays, the relative importance of energy expenditure and intake in the development of the current obesity epidemic is a debatable issue. A recent review of studies addressing this question in different regions of the world[11] concluded that in view of the great variability in the study designs, in the exposure and outcome measures used, and the wide population range in which the studies were based, the estimation of the importance of each one of these two factors, intake and energy expenditure, was not possible in children and teens.

In Spanish children, however, there are some considerations that worth to examine, and that leading us to suspect a greater importance of the decreasing of energy expenditure as determinant of the current obesity epidemic. First, data from both the AVENA study[12] and the enKid study[13] support the association between overweight and TV hours in Spanish children and adolescents. Furthermore, baseline measurement of an intervention study not yet published by our group,[14] show that children who are overweight or obese consume on average less calories/day than children with normal weight, and these normal weight children less than thinness children. After a first view of these data might be argued that children with overweight/ obesity do less daily physical activity than less normal weigh children, but when we controlled in multivariate models for cardiorespiratory fitness levels, a variable closely related to physical activity levels, these differences in energy intake by weight categories remain unchanged. These results are in accordance with that reported from other studies,[15,16] and support the new hypothesis proposed by Gutin suggesting that vigorous physical activity at early ages would have a pivotal role in the of stem cells differentiation in bone and muscle tissues through stimulation by mechanical influences such as physical activity[17]. If this theory were consolidated would have important implications in determine which is the best age range for implement preventive interventions, and which is the most appropriate type of activity for it.

There are several hypotheses that do not support the energy balance model for explaining the childhood obesity epidemic, and even though no one doubt of the importance of genetics on predicting obesity, it has been suggested that genetics could be very strongly influenced by environmental factors including vigorous physical activity.[18,19]

Efectividad de las intervenciones preventivas sobre obesidad infantil

A Cochrane systematic review aimed to evaluate the effectiveness of interventions for preventing obesity in children and adolescent concluded that there is enough evidence on the effectiveness of interventions to prevent obesity in children aged 6-12 years, although should be considered that the heterogeneity of the effect found in the studies, as well as the risk of design and publication biases, and therefore this results should be interpreted with caution. Furthermore this review concludes by recommending for future studies: 1) analyze the long-term results, 2) assess how those interventions that are effective can be maintained over time in a sustainable manner, 3) include economic evaluations, 4) potential damage reporting (i.e. eight reduction in thinner children, reduction of essential nutrients, etc.), 5) subgroup analysis by gender, location, race or socioeconomic status, 6) describe in detail the activities carried out in the intervention (to facilitate their applicability and transferability to other populations), and finally, 7) to focus on children 0-5 years.[20]

A recent meta-analysis whose objective was to assess the efficacy of intervention programs on the body mass index (BMI) of children and adolescents, as well as explore the possible differences between the school and after-school intervention programs showed school or after school interventions had a similar effect.[21] Considering that in Spanish context seems very complicated to propose legislative changes aimed to include interventions to tackle children obesity in the schools curricula, the implementation of interventions at recess or after school seems to be more feasible.

The conclusions of a review that examines the systematic reviews and meta-analysis aimed to evaluate the effectiveness of programs addressing the prevention and control of childhood obesity indicates that information about the barriers and challenges encountered

when designing and implementing interventions in real life situations will provide important information on feasibility and sustainability, and identify if failure or modest success of the intervention was due to a problem with the intervention's development, content or implementation.[22]

Most of the systematic reviews emphasize on the importance of taking into account the theoretical models of behavior's changes in which the intervention is based.[23] The usefulness of these models in in the development of intervention strategies that affect multiple areas has been proven in several studies.[24,25] One of the most commonly used is the socio-ecological model.[26,27] This model distinguishes several levels on influence on behavior usually depicted as a graph with concentric circles (fig. 1). At the central level are represented the biological/genetic, physiological and sociocultural influences that make-up the individual's identity. In the second circle are placed personal relationships, the environment close to the children; this micro-system consisted of relationships with parents, teachers, sibling, and friends. A third level of influence it's known as exosystem, and includes physical and social environments that influence children's behavior, but without interacting (neighborhood and its built environment, media, location of the school, working conditions of parents, etc.). Finally, the macro-system (fourth level) influences the child's behavior; this macro-system includes traditions, social, culture, laws, history, etc., of the country where the child growths.

This paper review the characteristics of the most promising interventions.

Results

Table I shows characteristics of 12 effective school-based interventions on prevention obesity in children (6-12 years). All studies were randomized controlled trials, implemented in school area, and included as outcome BMI or prevalence of overweigh/obesity.

Six studies were conducted in the United States, one in South America, one in Australia and four in different countries of the European Union (Spain, Switzerland, Germany and Sweden). Most of the studies were done in school (with modifications into curriculum),[28-36] two studies were done in after school schedule (FitKid and MOVI),[37-40] and one was done jointly in school and after school (STOPP).[41] The duration of follow-up ranged from 3 months to four years; of these 12 studies, 2 studies had a follow-up period of 3 months, 5 studies between 8 months and one and a half year, and 6 studies more than one and a half year (two, three o four years). Seven of the interventions included increase in phys-

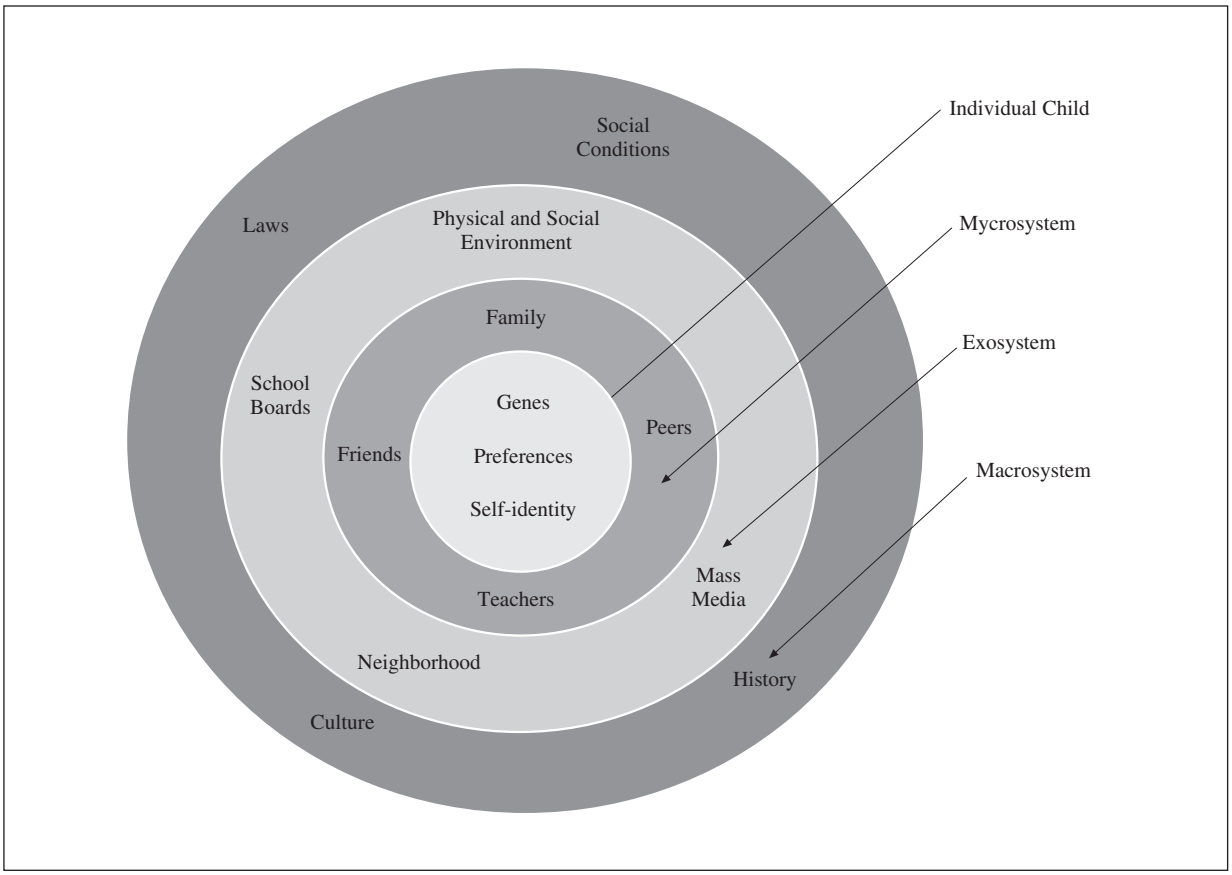

Fig. 1.—Ecological Model. Adapted from Bronfenbrenner's Ecological Model describing the environmental influences on a child.[27]

Table I *(Cont.)*
Characteristics of effective school-based interventions on prevention obesity in children (6-12 years)

Authors/year/ country/ name of program	*Setting/ Duration (month or years)*	*Sample sizes/ age (years)/ gender*	*Theory/Intervention*	*Outcome measures*	*Results*
Interventions based on increase PA and reduce sedentary time					
Flores R, 1995 *California*, USA **Dance for Health**[28]	School 3 months	At baseline: 81 At follow up: 49 10-13 Only girls	*NA* School based aerobic dance replaced usual PE class and education in health	– BMI – Attitude to PA	– Reduction BMI – No changes in the attitude to PA
Robinson TN, 1999 *California*, USA[29]	School 3 months	At baseline: 192 At follow up: 192 8-9 Boys and girls	*NA* Reducing time TV, videotape and video game. The intervention consisted of 18 lessons lasting 30' into the-standard curriculum	– BMI – TST – WC – TV time	– Reductions BMI and all other measures of body fat – Reductions reported TV time
Yin, Z. et al, 2005; Gutin B, et al, 2008 *Georgia*, USA **The Medical College of Georgia Fitkid Project** [37,38]	After-School 3 years	At baseline: 601 At 3 years follow up: 316 8-9 Boys and girls	*Environmental change* 2 hour after-school sessions, 5 days/week on school days. The programme included: • 40 min of academic enrichment activities, during which healthy snacks were provided. • 80 min of moderate-to-vigorous PA (40 min vigorous) including activities to improve sports skills, aerobic fitness, strength, and flexibility.	– % body fat – Bone density – Fat mass – Fat-free mass – BMI – WC – Fitness – CV risk factors	**1st year:** – Reduction % body fat – Increasing bone density – No differences fat mass and fat-free soft tissue between groups post-intervention – Increasing fitness **3 year:** – Reduction body fat during school months – Significant group by time interaction in favour of intervention participants in bone density and fat-free soft tissue – No differences between groups post intervention in fat mass – Increasing fitness – No difference in BMI, WC and CV risk factors
Salmon J, et al, 2008 Melbourne, *Australia* **Switch-play**[30]	School 1 year	At baseline: 295 At follow up: 268 10-11 Boys and girls	*Social cognitive theory and behavioral choice theory* Three intervention groups: • Behaviour Modification (BM) group: In addition to the usual PE and sports classes, 19 lessons (40-50 min each) were delivered in classroom by one qualified PE teacher for 1 school year • Fundamental Motor Skills (FMS) group: In addition to the usual PE and sports classes, 19 lessons (40-50 min each) were delivered either in the indoor or outdoor PA facilities at each school for 1 school year • BM/FMS group: children in this group received both BM and FMS lessons	– BMI – Overweight/ Obesity – Objectively assessed PA	– Reduction in BMI post-intervention in the BM/FMS – On average, those in the BM/FMS group were over 60% less likely to be overweight or obese – Compared with controls, FMS group children recorded higher levels and greater enjoyment of PA; and BM children recorded higher levels of PA across all four time points

Table I *(Cont.)*
Characteristics of effective school-based interventions on prevention obesity in children (6-12 years)

Authors/year/ country/ name of program	*Setting/ Duration (month or years)*	*Sample sizes/ age (years)/ gender*	*Theory/Intervention*	*Outcome measures*	*Results*
Martínez-Vizcaíno V, et al, 2008; Salcedo-Aguilar F, et al, 2010) *Cuenca, Spain* **MOVI programme**[39,40]	After-School 2 years	At baseline: 1119 At 2 years follow up: 921 9-10 Boys and girls	*NA*. Non-competitive recreational PA programme consisted of 3 × 90-min sessions per week for 24 weeks. These were held after school. 90-min session included 15 min of stretching, 60 min of aerobic resistance and 15 min of muscular strength/resistance exercise.	– BMI – TST – % body fat – CV risk factor	**1 year:** – Reduction in TST. – Reduction in % body fat in girls. – Intervention children had lower apolipoprotein B levels and higher apolipoprotein A-1 levels. **2 year:** – Intervention girls reduced the frequency of overweight. – Intervention was associated with an increase in the % of body fat in boys – Children in the IG had lower total cholesterol level and apolipoprotein B level.
Donnelly JE, et al, 2009 *Northeast Kansas, USA* **PAAC**[31]	School 3 years	At baseline: 1527 At follow up: 1490 7-9 Boys and girls	*Environmental model*. Programme promoted 90 min/week of moderate-to-vigorous physically active academic lessons delivered to children intermittently throughout school day. This is in addition to the existing 60 min/week PE which would result in a total of 150 min of PA/week.	– BMI – Objectively assessed PA (sub-sample only)	– Schools with ≥ 75min of PAAC/week showed significantly less increase in BMI at 3 years compared to schools with < 75min. – Children in PAAC schools had greater levels of PA during the school day and on weekends.
Kriemler S, et al, 2010 *Aargau and Baselland, Switzerland* **KISS**[32]	School 9 months	At baseline: 502 At follow up: 498 6-12 Boys and girls	*Socio-ecological model*. Multi-component PA programme that included structuring the three existing PE lessons each week and adding two additional lessons a week, daily short activity breaks, and PA homework.	– Skin folds – Fitness – Objectively assessed PA – Quality of life – BMI – CV risk factor	– Children showed more negative changes in the z score of the sum of four skin folds. – Z scores for aerobic fitness increased more favorably, as did those for moderate-vigorous PA in school, all day moderate-vigorous PA, and total PA in school. – Z scores for overall daily PA and physical quality of life as well as psychological quality of life did not change. – Children showed smaller increases or larger reductions in BMI and in most CV risk factors.
Interventions based on PA and Diet combined					
Gortmaker SL, et al, 1999 *Massachusetts, USA* **Planet Health (33)**	School 18 months	At baseline: 1560 At follow up: 1295 11-12 Boys and girls	*Social cognitive theory*. 32 classroom sessions taught by regular teachers to reduce time spent in front of the TV, increase PA, reduce intake of fat and increase the intake of fruit and greens.	– BMI – Skin folds. – Diet – PA	– Lower prevalence of overweight in girls. – Both boys and girls in the IG decreased time spent with TV. – Girls in the IG eat more fruit and green and had reduced their total energy intake.

Table I

Characteristics of effective school-based interventions on prevention obesity in children (6-12 years)

Authors/year/ country/ name of program	*Setting/ Duration (month or years)*	*Sample sizes/ age (years)/ gender*	*Theory/Intervention*	*Outcome measures*	*Results*
Muller MJ, et al., 2001 Kiel, Germany **KOPS**[34]	School 8 months	At baseline: 322 At follow up: 272 5-7 Boys and girls	*NA.* 8 hour course of nutrition education including "active" breaks was given by a skilled nutritionist and a trained teacher. The course included the following messages: "eat fruit and vegetables each day", 'reduce intake of high fat foods', keep active at least 1 hour each day', "decrease TV consumption to less than 1 hour per day". In addition a family-based intervention plus a structured sports programme (twice a week) were offered to families with overweight or obese children and to families with normal weight children but obese parents.	– BMI – Skin folds and % fat. – Knowledge on diet – PA – Intake of fruit and greens and food with a low fat percent.	– The IG had a lower prevalence of obesity measured by Skin folds – No difference regarding BMI – Increase in nutrition knowledge, daily PA and decrease in TV time
Kain J, et al., 2004 *Santiago, Curico and Casablanca, Chile* **Healthy schools**[35]	School 1 year	At baseline: 3577 At follow up: 3086 7-11 Boys and girls	*NA.* School-based multi-component intervention aimed to change adiposity and PA levels, delivered by a nutritionist and a PE teacher. Nutrition education was available for children and parents supported by healthier food kiosks. Sessions included 90 minutes additional PA weekly for 3rd to 8th grade for 6 months and 15minutes of activity in recess per day, for last 3 months.	– BMI – Skin folds – WC – Fitness	– No difference regarding BMI and skin folds – Lower waist circumference – Increasing fitness
Coleman K J, et al., 2005 Texas, USA El Paso Catch[36]	School 4 years	At baseline: 896 At follow up: 744 8-9 Boys and girls	*NA.* Intervention schools: received money ($3500 in first year, $2500 in second year, $1500 for third year and $1000 for fourth year) for purchasing equipment and paying substitutes so that PE teachers and food service staff could attend training, and for promotion of CATCH programme at each school.	– BMI – Waist-to-hip ratio – Fitness	– Lower increase of BMI – No difference in fitness
Marcus C, et al., 2009 *Sweden* **STOPP**[41]	School and After school 4 years	At baseline: 3135 At follow up: 2838 6-10 Boys and girls	*NA.* Intervention was designed to change the school environment to promote healthy eating and PA during school and in after school care. Including: 1. 30 minutes of daily PA time was added to the curriculum. 2. The teachers were instructed to encourage the children to increase the intake of vegetables during the school lunch. 3. Intervention schools were encouraged to eliminate sweets, sweet buns and ice cream in association with festivities.	– Prevalence over-weight/obese – Objectively asse-ssed PA – Eating habits	– Prevalence of overweight/obesity decreased in IG com-pared with an increase in CG – No difference in PA – Differences between children in intervention and control schools were found for high-fat dairy products, sweetened cereals and sweet products

ical activity levels or reduce sedentary time, and the rest combined increase in physical activity levels or reduce sedentary time and diet. It is noteworthy that none study exclusively focused on diet was identified. Five of them were designed from the perspective of theoretical models of behavior change (FitKid, Switch-play, PAAC, KISS and Planet Health).

Participants' characteristics

One study included girls only (Dance for Health) and the rest included both girls and boys, although only two of these reported sex specific results (MOVI and Planet Health). The mean age at baseline varied from 6 to 12 years (median 9.5 years). One study involved a participants group with overweight/obese (KOPS), and the rest involved children recruited from all body mass index categories.

Types of outcome measures

Five studies reported BMI or prevalence of overweigh/obesity and seven studies reported furthermore BMI or prevalence of overweigh/obesity of at least one measure of adiposity. Three of them measured cardiovascular risk factors (FitKid, MOVI and KISS); four, objectively physical activity (KISS, Switch-play, PAAC and STOPP); four, fitness (FitKid, KISS, Healthy school, El Paso Catch); three, physical activity related behaviours (Dance for Health, Planet Health, KOPS) and three, diet-related behaviours (Planet Health, KOPS, STOPP). Only one study included results on quality of life (KISS).

Effectiveness of the interventions in Spanish settings

The MOVI interventions in schoolchildren

Two interventions focused on the promotion of physical activity in the school setting have been tested in the last years by our group. The distinguishing characteristics of MOVI interventions are the following: 1) in children in 4th and 5th of Primary School (age ranged 9-11 years); 2) recreational, non-competitive, leisure time physical activity; 3) open to all the children, and suitable for everyone, regardless of their body composition or motor skills; and 4) takes place outside school hours but in the school sports facilities (see www.movidavida.org).

This intervention, in its first edition (three sessions per week, each one of 90 minutes of moderate and vigorous intensity physical activity, lasting two school years) showed moderate effect in reducing adiposity and improving the lipid profile, but did not significantly improve overall cardiometabolic risk because of did not reduce insulin levels.[39,40] Our working hypothesis was that another intervention increasing the intensity of the program, putting more emphasis on the development of muscle strength, and including a weekend session on Saturday morning because we suspected that in the first edition compensating behaviors during weekend might be responsible of mitigate the effects of the intervention; therefore we implemented a 2nd edition of MOVI including two after school 90 minute sessions on school days and a 150-minute session on Saturday morning, during a school year) hypothesizing that this new intervention could be more effective on reducing obesity, but also remain acceptable to parents and school authorities. In addition, the MOVI-2 intervention,[14] included as objectives to produce behavioral changes in children and parents similarly to other effective previous interventions (CATCH, M-SPAM).

The main objective of MOVI-2 was to evaluate the effectiveness of an intervention that essentially consisted of implementing a standardized leisure time physical activity program aimed to reduce overweight/obesity and other cardiovascular risk factors, and lasting one academic year. As secondary objectives we plan to evaluate the impact of MOVI-2 on other health-related variables: physical fitness, duration and quality of sleep, health-related quality of life, and academic performance. Among the most notable results of this cluster randomized clinical trial, in preliminary analysis, worth noting a decrease in body fat, an increase in lean mass, and a decreased in insulin levels.

The experience of these two consecutive interventions makes us feel able to provide some recommendations for future interventions to tackle against childhood obesity in the Spanish context:

1) Because of the magnitude and consequences of childhood obesity not only at this moment but also in the future, it is a priority testing the effectiveness of interventions for controlling this epidemic in Spain; otherwise we would expect an increase in morbidity/ mortality and other cardiovascular diseases in the coming years.
2) The most appropriate interventions in Spanish children to prevent obesity should be based on the promotion of physical activity so that: a) it has been repeatedly reported low levels of physical fitness in Spanish schoolchildren, particularly from data of the AVENA study;[12] b) unpublished data from our group indicate that the caloric intake of overweight children is not greater than in normal weight or underweight children; c) a exclusively diet based intervention may not be free of risk for thinness children; and d) an intervention to promote physical activity based on playground games could improve other health-related aspects such as quality of life, academic performance, time and quality of sleep, etc.
3) Although it is generally accepted that BMI is the most useful and practicable indicator of excess of adiposity on clinical and population based studies, it should taken into account that BMI does

not distinguish between fat and lean body mass. Therefore, it seems advisable include in population interventions focused on promoting physical activity in children as the main outcome, in addition to BMI, an indicator of body fat such as skinfold thickness or body fat measured by bioimpedance,[22] so that physical activity might reduce fat while increasing muscle mass, and as consequence the weight/height ratio would remain unchanged.[17,39]

4) Early infancy is probably the best opportunity to intervene, so that is considered the best age to establish perdurable healthy behaviors. Furthermore, it is known that the risk of obesity in adulthood is much higher when early adiposity rebound occurs.[42]
5) Consistent evidence indicate that genes explain up to 30% of the likelihood of becoming obese; however epigenetic hypothesis support that genetic expression could be influenced by environmental factors, and vigorous physical activity is one of the most influential factor.[18,19]
6) The school environment is considered the most suitable setting for carrying out physical activity interventions on children because of: it is possible targeting to large segments of the youth population, students spend a considerable amount of day in school, most of schools provide health education (physical activity and nutritional habits) and, finally, the school environment provides a powerful social network of teacher and peers.[22]
7) The design of the interventions should be based on theoretical models of behavior change. A main limitation for most of obesity interventions in children is that the lack of theoretical underpinning on behavioral change models threats the perdurability over time of the effect.

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Chronobiology and obesity

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Abstract

Chronobiology is a word derived from three Greek stems: *kronos* for time, *bios* for life and *logos* for study. From microarrays studies, now it is accepted that 10-30% of the human genome is under the control of circadian molecular clocks. This implies that most behavioral, physiological and biochemical variables display circadian rhythms in their expression. In its simplest form, circadian clocks are composed of a set of proteins that generate self-sustained circadian oscillations. The molecular clock comprises two transcription factors, CLOCK and BMAL1, whereas PERs and CRYs are responsible for the negative limb. One of the most important questions related to the circadian system and obesity, was to elucidate if adipose tissue displayed circadian rhythmicity or whether it had an internal peripheral clock. Our group of research has provided an overall view of the internal temporal order of circadian rhythms in human adipose tissue.

A new concept related to illness is Chronodisruption (CD). It is defined as a relevant disturbance of the internal temporal order of physiological and behavioral circadian rhythms. In our modern society, CD may be common in several conditions such as jet lag, shift work, light at night, or social jet lag. In addition clock gene polymorphisms and aging may have also chronodisruptive effects. Our group has also demonstrated that Obesity and CD are also highly interconnected. With the help of chronobiology we can reach a new view of obesity considering not only "what" are the factors involved in obesity, but also "when" these factors are produced.

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Key words: *Chronobiology. Obesity. Chronodisruption. Epigenetics. Human adipose tissue.*

CRONOBIOLOGÍA Y OBESIDAD

Resumen

Cronobiología es una palabra de origen griego: *kronos* significa tiempo, *bios*, vida y *logos*, estudio. A partir de los estudios de microarrays, se acepta en la actualidad que del 10 al 30% del genoma humano queda bajo el control de relojes moleculares circadianos. Este implica que la expresión de la mayor parte de las variables de la conducta, psicológicas y bioquímicas muestran ritmos circadianos. En su forma más sencilla, los relojes circadianos están compuestos por un conjunto de proteínas que generan oscilaciones circadianas auto-mantenidas. El reloj molecular comprende dos factores de trascripción, CLOCK y BMAL1, mientras que los PERs y los CRYs son responsables de la fracción negativa. Una de las preguntas más importantes relacionadas con el sistema circadiano y la obesidad fue dilucidar si el tejido adiposo mostraba un ritmo circadiano o si poseía un reloj periférico interno. Nuestro grupo de investigación proporcionó una visión de conjunto del orden temporal interno de los ritmos circadianos del tejido adiposo humano.

Un nuevo concepto relacionado con la enfermedad es el de cronodisrupción (CD). Se define como una alteración relevante del orden temporal interno de los ritmos circadianos fisiológicos y conductuales. En nuestra sociedad moderna, la CD podría ser frecuente en diversos trastornos como el *jet lag*, el trabajo a turnos, la luz nocturna o el *jet lag* social. Además, los polimorfismos de los genes horarios y el envejecimiento también podrían tener efectos de cronodisrupción. Nuestro grupo también ha demostrado que la obesidad y la CD están muy interconectadas. Con la ayuda de la cronobiología podemos llegar a un nuevo enfoque de la obesidad, considerando no solamente "cuáles" son los factores implicados en la obesidad, sino también "cuándo" se producen estos factores.

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Palabras clave: *Cronobiología. Obesidad. Cronodisrupción. Epigenética. Tejido adiposo humano.*

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Abbreviations

AT: adipose tissue.
BMI: body mass index.
LEP: leptin.
LEPR: leptin receptor.
V: visceral.
S: subcutaneous.
MetS: Metabolic Syndrome.
SCN: suprachiasmatic nucleus.
CLOCK: circadian locomotor output cycles kaput).
BMAL1: brain- and muscle- ANRT-like protein.
PER: period.
CRY: cryptocrome.
REV-ERBα: reverse erythroblastosis virus α.
RORα: retinoic acid receptor-related orphan receptor α.
ADIPOQ: adiponectin.
RHT: retino-hypothalamic tract.
CCG: clock-controlled genes.
CD: Chronodisruption.

Introduction

Chronobiology is a word derived from three Greek stems: *kronos* for time, *bios* for life and *logos* for study, which is a relatively new science which was first discovered in the eighteenth century. It came out with Linnaeus, who designed a beautiful "floral clock" that represented the hours of the day depending on the time that flowers open their petals.[1] It is a scientific field which studies the timing processes (the biological rhythms) which occur in the living organisms at their different levels of organization. *Circadian rhythms* are those biological rhythms whose frequency is close to a day (period between >20 and <28 h) such as the rhythms of secretion of some hormones (cortisol, melatonin, etc.). *Ultradian rhythms* refer to those rhythms whose frequency is higher than one cycle per day (period less than 20 h) such as breathing, heart beats, intestinal movements, etc. while, *infradian rhythms* are those whose frequency is lower than one cycle per day (period more than 28 h) such as the circalunar rhythms or the menstrual cycle in humans. All these types or rhythms characterize the biological function in different animal species including humans.

Circadian control of glucose metabolism has also been recognized from studies demonstrating variation in glucose tolerance and insulin action across the day. In humans, it has been repeatedly shown that glucose tolerance is impaired in the afternoon and evening compared with the morning hours. This situation has been ascribed to the impaired insulin sensitivity of the peripheral tissues and to a relative decrease in insulin secretion during the evening hours.[2]

How molecular clocks coordinate metabolism

From microarrays studies, now it is accepted that 10-30% of the human genome is under the control of circadian molecular clocks.[3] This implies that most behavioral, physiological and biochemical variables display circadian rhythms in their expression. The rhythms of cortisol, growth hormone, leptin, and melatonin are some examples.[4] However, together with the existence of circadian rhythmicity it has been demonstrated the importance of the maintenance of an adequate internal temporal order between different variables. According to this, the peaks and troughs of every variable have to be finely tuned by the circadian system to keep a health status as occurred in a music orchestra when plays a classical music. As occurred in a symphony orchestra, the circadian orchestra is hierarchically organized, being its conductor, the suprachiasmatic nucleus (SCN) of hypothalamus.

Circadian rhythms, under artificially constant environmental condition, run with a period slightly different from 24 h. However, under natural conditions, the SCN is reset every day by light-dark alternance through the retino-hypothalamic tract (RHT).[5] Each of its neurons acts as an individual oscillator based on clock gene feedback loop, composed by positive (*CLOCK* and *BMAL1*) and negative limbs (*PER* and *CRY*). Although the photic input is the main SCN entraining signal, other periodical cues such as feeding time and scheduled exercise can also entrain the mammalian circadian system.[6,7] Furthermore, outputs pathways are responsible for the coordination of circadian rhythm between different functions and most peripheral tissues and organs. These are the result of humoral mediators such as prokineticin-2, which is able to generate the rhythm of locomotor activity,[8] and neural outputs, such as the rhythmic change in the parasympathetic/sympathetic balance,[9] or the pineal release of melatonin during darkness.[10]

The biological clock at a molecular level

In its simplest form, circadian clocks are composed of a set of proteins that generate self-sustained circadian oscillations through positive and negative transcriptional/translational feedback loops. Although the whole picture of the clock model is continuously evolving, the positive limb of the molecular clock comprises two transcription factors, CLOCK and BMAL1, whereas PERs and CRYs are responsible for the negative limb. In addition to these core clock genes, other genes of SCN neurons, which are not components of the circadian mechanisms, but whose expression is regulated by clock genes, oscillate with a periodicity close to 24 h. They are the so-called clock-controlled genes (CCG) or circadian output genes (fig. 1).[11,12] These genes orchestrated by the SCN in due time, are necessary for creating and sustaining rhythms of 24 h. In addition, posttransla-

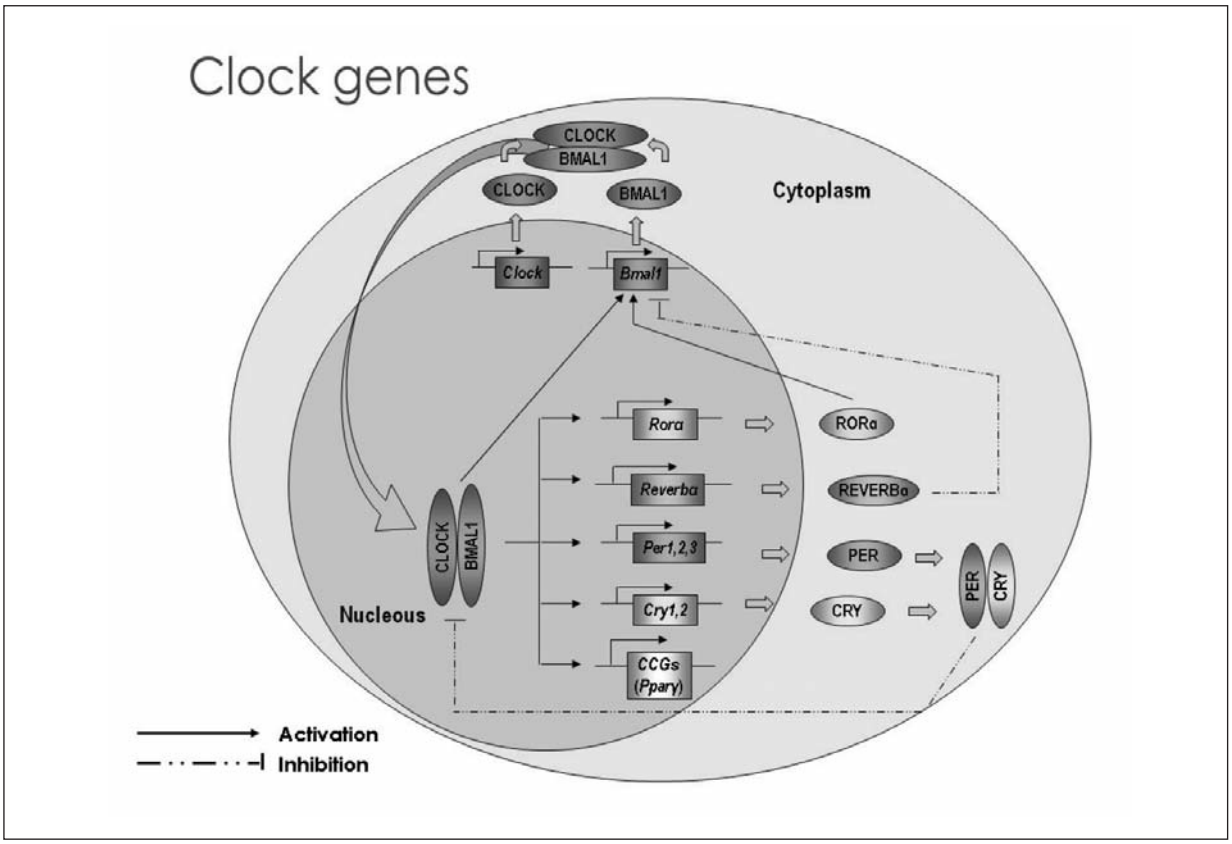

Fig. 1.—Molecular machinery of circadian clock. The core of the circadian clock is composed of two basic helix–loop–helix transcription factors, CLOCK *and* BMAL1*, which act as positive limb in the feedback loop. The heterodimer CLOCK-BMAL1 binds in the promoter of some target genes, driving the transcription of several repressor encoding genes: three period genes* (PER1, PER2 *and* PER3), *two cryptocrome* (CRY1 *and* CRY2) *and the transcription factor* REV-ERBα *gene, and one promoting gene,* RORα. *In addition, the product of* PPARα *gene, one of the clock controlled gene regulated by the circadian oscillator (CCG), induces* BMAL1 *and* REV-ERBα *transcription. PER and CRY proteins dimerize and are then translocated into the nucleus counteracting the positive effect of CLOCK-BMAL1 and thereby inhibit their own transcription. In addition,* BMAL1 *rhythm is also regulated by rhythmical changes in RORE occupancy by* REV-ERBα *(activating) and* RORα *(inhibiting).*

tional mechanisms such as protein phosphorylation, affect stabilization, degradation, and subcellular localization of clock proteins, thus contributing to the molecular clockwork.[13,14] However, one of the most interesting outcomes in the chronobiological field has been the discovery of different peripheral clocks in many tissues and organs such as liver, oral mucosa, heart and kidneys among other.[15]

Chronodisruption: causes and consequences

Circadian disruption or Chronodisruption (CD) is defined as a relevant disturbance of the internal temporal order of physiological and behavioral circadian rhythms. It is also a breakdown of the normal phase relationship between the internal circadian rhythms and 24-h environmental cycles. In our modern society, CD may be common in several conditions such as jet lag, shift work, light at night, or social jet lag.[16] In addition clock gene polymorphisms and aging may have also chronodisruptive effects.

Thus, CD can be induced by factors related to the following: 1) Impairment of the inputs to the circadian pacemaker: low contrast between day and night synchronizing agents (continuous light, frequent snacking, low levels of physical exercise, etc.); exposure to zeitgebers of different periods or unusual phasing (i.e., light at night, nocturnal feeding, nocturnal physical exercise) or by frequent shifts in the time provided by zeitgebers (i.e., jet lag, shift work). 2) Circadian oscillators: the uncoupling between different subpopulations of oscillators inside the SCN caused by aging or clock gene alterations and the uncoupling between central pacemaker and peripheral oscillators also result in chronodisruption. 3) Outputs: the suppression of nocturnal melatonin and the loss of cortisol rhythm are also chronodisrupters.

Clinical and epidemiological studies have shown that certain situations such as shift work, eat during night-time, exposure to bright light or sleep deprivation are contributing to CD and this situation is related to the increasing risk of developing certain diseases and with the impairment of preexisting pathologies such as

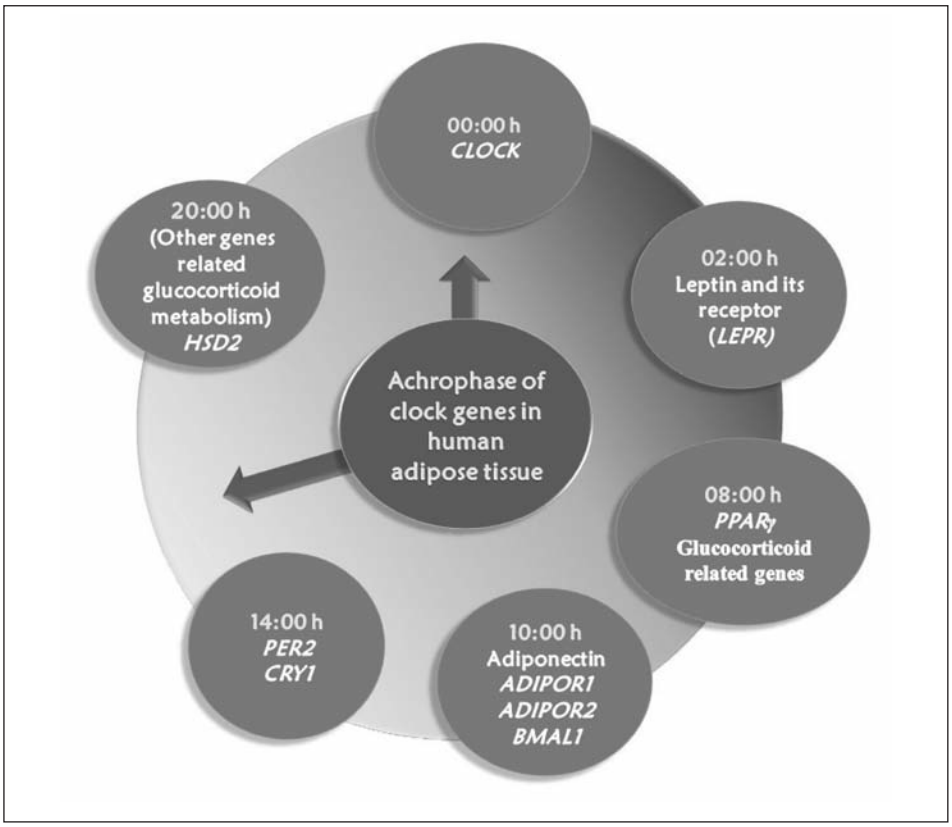

Fig. 2.—Rhythmic expression of genes studied: (leptin and its receptor (LEPR)*, adiponectin and its receptors* (ADIPOR1 *and* ADIPOR2)*, clock genes* (PER2, BMAL1, *and* CRY1) *and glucocorticoid metabolism-related genes* (PPARg, GR, HSD1, HSD2, *and* 5aR) *in human subcutaneous and visceral adipose tissue. Adipose depots were isolated at 6-h intervals over the course of the day from adipose tissue cultures (time at 0, 6, 12, and 18 h). Results are presented relative to the lowest basal relative expression for each gene. Data of relative expression are represented as arbitrary units (AU). Data are reported as means.*

such as cancer, obesity, metabolic syndrome, insomnia, cognitive and affective disorders and premature ageing.

Interesting results have arisen from studies relating sleep duration and metabolic risk. The time we sleep has declined by 1.5 h over the past century, accompanied by an important increase in obesity. Moreover, a third of adults sleep less than six hours a night.[17] Different causes could explain the association between sleep loss and obesity. Studies with adults have shown associations between inadequate sleep and alterations in leptin and/or ghrelin indicative of increased appetite.[18,19] Moreover, short sleep duration could lead to weight gain and obesity by increasing the time available to eat and has also been theorized to decrease energy expenditure by increased fatigue as well as changes in thermoregulation which could explain obesity.

Adipose tissue changes during the day

One of the most important questions related to the circadian system and obesity, was to elucidate if adipose tissue displayed circadian rhythmicity or whether it had an internal peripheral clock. Analysis of murine adipose tissue revealed robust 24h rhythms of clock gene expression. The relative phasing of genes in adipose tissue is consistent with SCN rhythms and the molecular model of the circadian clock.[20,21] Moreover, use of microarrays suggests that up of 20% of the murine and the human adipose transcriptome is expressed according to diurnal rhythm].[21,23]

Therefore, a recent study performed by our group of research has provided an overall view of the internal temporal order of circadian rhythms in human adipose tissue represented in a phase map.[24] The data included various genes implicated in metabolic processes such as energy intake and expenditure, insulin resistance, adipocyte differentiation, dyslipidemia, and body fat distribution, and indicated that circadian rhythmicity of the genes studied followed a predictable physiological pattern, particularly for subcutaneous depot. As expected, leptin, a peripherally synthesized hormone which acts as an anorexigenic hormone in the brain, showed its achrophase (maximum expression) during the night (at 02:00 hours). The expression of adiponectin (*ADIPOQ*) achieved its zenith (maximum) during the morning (at 10:00 hours) which could be implicated in the maximal withdrawal of fatty acids, and the improvement in glucose tolerance and that time.[25] *PPARγ* could be also related to *ADIPOQ* circadian pattern. In fact, the high expression of *PPARγ* and glucocorticoides related genes during the morning (08:00 hours), located at the beginning of the of the daily activity, is consistent with results obtained in nocturnal mammals[26] and could be influencing the further increase in *ADIPOQ* expression and the increase in insulin sensitivity during this time of the day. Moreover, our investigation group has demon-

strated that these clock also changes with different factors including sex,[27] menopause,[28] stress[29] and obesity.[30,31]

The time is important

Time of food

Many factors have been recognized to influence the success of a dietary intervention in obesity.[32-41] Indeed, obesity is a heterogeneous condition and individual responses to standardized protocols targeting weight loss are highly variable.[2] In real life settings such as obesity treatment programs, physiological and psychological factors, some of which may carry a strong genetic influence, interact with environmental factors in a complex manner.[3-5] Recent studies link energy regulation to the circadian clock at the behavioural, physiological, and molecular levels,[6-9] emphasizing that the timing of food intake itself may play a significant role in weight regulation.[10]

In this regards, our group of investigation has performed the first prospective longitudinal study showing that timing of food intake relates with weigh loss effectiveness in humans. In 420 overweight/obese patients undergoing a 20-week weight-loss diet, those who ate their main meal late (after 15:00 h) lost significantly less weight than early eaters (before 15:00 h).[42] The current findings may help in the development of novel therapeutic strategies incorporating not only the caloric intake and macronutrient distribution —as is classically done— but also the timing of food.

Chronobiology and Genetic aspects

From the genetic epidemiology point of view, the study of single nucleotide polymorphisms (SNPs) is contributing to the identification of the genetic background of chronotypes (morningness or eveningness), sleep alterations, or seasonal mood disorders. All these advances have allowed researchers to find the relevant link which exists between chronobiology and obesity.

Genetic polymorphisms in human clock genes have been associated with increased incidence of obesity in epidemiological studies. Different authors are currently investigating the role of clock gene variants and their predicted haplotypes in human obesity and MetS alterations.[43-45] From studies of our own group and others we deduce that *CLOCK* gene SNPs rs3749474, rs4580704 and rs1801260 (3111T>C) polymorphisms, are particularly interesting, since they seem to be associated with BMI, energy intake and different obesity-related variables.[46,47] Moreover, different psychological traits have been related to *CLOCK* 3111T>C SNP.[48,49] The association with psychological illnesses is related to the fact that minor allele carriers of *CLOCK* 3111TC display sleep disorders and eveningness,[34] characteristics that, in addition, make these subjects susceptible to obesity. Moreover a recent study shows the association of the *CLOCK* 3111T/C SNP with obesity and weight loss. In this work, C genetic variants in *CLOCK* 3111T/C display a less robust circadian rhythm than TT and a delayed acrophase, which characterizes "evening-type" subjects.[50] We also found different effects across *CLOCK* 3111T/C genotypes for saturated fatty acid intake (% of energy) and the deleterious effect of gene variants on waist circumference was only found with high saturated fatty acid intakes.[44]

Epigenetics, Chronobiology and Obesity

Epigenetic research shows that we are not predetermined by our genome. What we eat, how much we sleep, if we exercise or even how we use our mind may change our epigenome, and our fate. Moreover, these changes are not restrained to us but can pass down to our children or even to our grant children. In other words, epigenetics does not change the DNA but decides how much or whether some genes are expressed in different cells in our bodies.

The molecular basis of epigenetics is complex. It involves modifications of the activation of certain genes, but not the core DNA structure. One way that gene expression is regulated is by the remodeling of chromatin (the complex of DNA and histones). Chromatin proteins associated with DNA may be activated or silenced. Histones can change how tightly or loosely the DNA wraps around them by modifying their amino acids. If the amino acids that are in the chain are changed, the shape of the histone sphere might be modified.

A second way of chromatin remodeling is the addition of methyl groups to the DNA, mostly at CpG sites, which are regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide. "CpG" is shorthand for "—C—phosphate—G—", that is, cytosine and guanine separated by only one phosphate. Methylation converts cytosine to 5-methylcytosine. Some areas of the genome are methylated more heavily than others, and highly methylated areas tend to be less transcriptionally active.

In 2011, it was demonstrated for the first time that the methylation of mRNA had a critical role in human energy homeostasis. Obesity associated FTO gene was shown to be able to demethylate N6-methyladenosine in RNA. This opened the related field of RNA epigenetics and its relation to obesity.

Despite this conceptual knowledge, data about the connection between this circadian epigenome and obesity are still scarce. Nevertheless, recently our group has demonstrated an association between the methylation status of CpG sites located in clock genes (*CLOCK*, *BMAL1* and *PER2*) with obesity, Metabolic Syndrome and weight loss.[31] Our research unveils new epigenetic mechanisms involving clock genes that may contribute to better obesity prevention, as well as better prediction of successful weight reduction. Of note, these new data

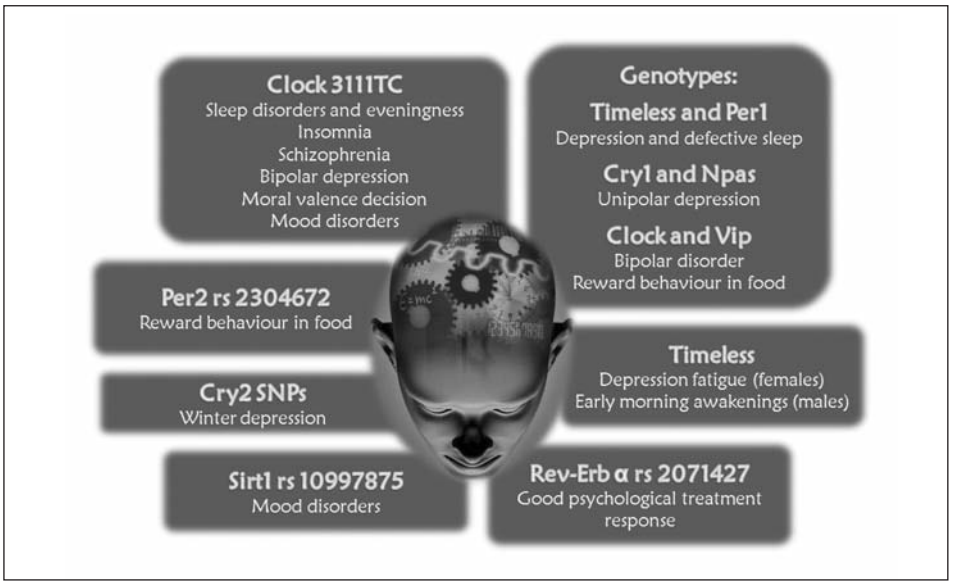

Fig. 3.—Main genetic variants related to psychological traits.

related to DNA methylation are consistent with previous results related to *CLOCK* genetic variants, which demonstrated that sleep reduction, changes in ghrelin values, alterations of eating behaviors and evening preference are all connecting genetics, chronodisruption and obesity.[34] These results support the hypothesis that the influence of the clock genes may be extended to a broad range of variables linked with human behavior and metabolism. Moreover, our data pave the way to the study of epigenetic mechanisms in the regulation of circadian rhythms in relation to obesity and weight loss.

Genetic, Chronotype, and Psychological Traits: Towards a deepest approach on their connections

Initially, the emphasis of chronobiology genetics was placed on the study of the association between chronotype and different psychological illnesses such as depression, anxiety, or bipolar disorder. Other mood features that have been associated with clock genes are stress, seasonality, and personality traits related to the chronotype such as the morningness/eveningness profile.

Taking into account that obesity is related to behavior and also with personality traits, and considering that the chronotype is behind some of these relationships, an obvious step was to link these psychological-related SNPs with obesity-related traits. Proof of this hypothesis is the case of CLOCK and PER2 SNPs that were firstly associated with mood disorders and then to obesity and Metabolic Syndrome (MetS) (fig. 3).

Conclusion

The study of circadian rhythms of the individual is of great use in medicine today. The development of this new science is being vertiginous and its applications in the prevention of certain diseases such as cancer or obesity could be innumerable. Still further studies are needed to reach decisive conclusions.

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Update on pharmacology of obesity: Benefts and risks

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Abstract

The prevalence of obesity in Western countries has increased at a much greater pace than the development of new efficient and safe drugs, beyond mere lifestyle changes, for the treatment of overweight. Numerous different types of drugs which had been used in the past for the treatment of obesity have currently been withdrawn due to undesirable long-term side effects. The only available drug in Europe is orlistat, which serves only as an aid for the treatment of obesity. In the USA, however, a few central adrenergic-mediators, for instance, diethylpropion and phentermine, have been available for decades to treat obesity during a short-term period (less than 12 weeks). The Food and Drug Administration (FDA) has recently approved lorcaserin and the combination phentermine/topiramate for the treatment of obesity. The first one is a selective serotonin 2C receptor agonist that works by decreasing food intake with few side effects. Its outcomes on weight are modest, but may be helpful in certain selected patients. The phentermine/topiramate combination has proved to be highly effective, achieving a 10% reduction in weight in the majority of patients, although attention must be drawn to the possible development of side effects in both the short and the long-term follow-up. Further investigation regarding the mechanisms involved in weight balance will anticipate the development of new expectations for the treatment of obesity in the near future.

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Key words: *Obesity. Pharmacology. Pharmacotherapy. Phentermine topiramate. Lorcaserine.*

FARMACOLOGÍA DE LA OBESIDAD AL DÍA: BENEFICIOS Y RIESGOS

Resumen

El incremento de la prevalencia de obesidad en los países occidentales no ha sido paralela al desarrollo de nuevos fármacos eficaces y seguros a largo plazo para el tratamiento del exceso de peso más allá de los cambios en el estilo de vida. La larga lista de fármacos que se han utilizado para el tratamiento de la obesidad han tenido que ser retirados por efectos secundarios indeseables para la salud a largo plazo. En Europa solo contamos con orlistat, como único fármaco coadyuvante para el tratamiento de la obesidad, mientras que en EEUU hace décadas disponen de unos pocos fármacos adrenérgicos de acción central (como Dietilpropion o Phentermine) para un tratamiento a corto plazo (inferior a 12 semanas). Recientemente, la Food and Drug Administration (FDA), acaba de aprobar la lorcaserina y la combinación de Phentermine y topiramate. Lorcaserine es un agonista específico del receptor serotoninérgico 2c, con actividad anorexígena y pocos efectos secundarios. Sus efectos sobre el peso son moderados, pero pueden ser de utilidad en algunos pacientes seleccionados. La combinación de phentermine y topiramate es muy eficaz alcanzando un 10% de pérdida de peso en una mayoría de pacientes, aunque debemos estar atentos acerca de sus potenciales efectos secundarios a corto y largo plazo. La profundización en la investigación de los mecanismos implicados en la regulación del peso corporal conllevará nuevas expectativas de tratamientos para la obesidad en un futuro próximo.

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Palabras clave: *Fármacos obesidad. Combinación topiramato-fentermina. Lorcaserina.*

The historical progress of drug therapy for obesity has been discouraging, since no drug has achieved a long-term favorable benefit-risk ratio. Beginning with the first thyroid hormone extracts that were used in the late 19th century, continuing with amphetamines and other sympathetic-activator drugs, and the most recent sibutramine and rimonabant, both with central and peripheral action, side effects have repeatedly outweighed benefits, forcing international regulatory agencies to subsequently proceed to their withdrawal[1] (table I). With the exception of orlistat, which is still available for the long term treatment of obesity (> 12 months), only a few adrenergic drugs are accessible exclusively in the USA for the short-term treatment of obesity, i.e., < 12 weeks (table II).

Undoubtedly, obesity entails a major healthcare problem which affects 24% of adult Spanish population[2] and for which no real effective methods are available for its management. Conventional approaches based on

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Table I
Anorexigenic drugs used in the past for obesity and reasons for their withdrawal

Drug	*Year*	*Reason for withdrawal (year)*
Dinitrofenol	1930s	Risk of neuropathy and cataracts
Anphetamines	1936	Dependency and abuse, potential cardiovascular adverse effects
Aminorex	1965	Pulmonary hypertension (1968)
Mazindol	1970	Discontinued 1993- (Australia)
Fenfluramine	1963 Europe 1973 US	Valvular heart disease. Pulmonary hypertension (1997)
Dexfenfluramine	1985 Europe 1996 US	Valvular heart disease. Pulmonary hypertension (1997)
Sibutramine	1997 US 2001 Europe	Cardiovascular disease (2010)
Rimonabant	2006 Europe	Severe psychiatric disorders (2009)

lifestyle interventions reach, at the most, 5-10% weight loss at 6-12 months' follow-up, but adherence to treatments is scarce, and weight recovery is commonly observed in the long-term.[3]

The search for a drug with the best benefit-risk ratio should include the achievement of at least a 10-20% weight loss, which would imply an intermediate effect between the modest outcomes of lifestyle interventions (5-10%) and those of the simplest bariatric surgery technique (20-30%). For this reason, the FDA considers that a suitable drug for the treatment of obesity should comply with the following characteristics: a) a significantly different weight loss (> 5%) in comparison to placebo after one year of treatment and b) that the number of individuals reaching > 5% weight loss is at least 35% in comparison to placebo, with differences being statistically significant. In any case, drug treatment for obesity would be indicated in those with a body mass index (BMI) ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with obesity-associated major comorbidities.

Commercially available drugs for the treatment of obesity

In Europe, the only available drug for the treatment of obesity is orlistat. The other ones which have been already approved by the FDA in the USA are still under evaluation by the European Medicines Agency (EMA).

Orlistat

Orlistat is a gastric and pancreatic lipase inhibitor, which was first introduced in the market in 1998. Its mechanism of action is related to inhibition of fat absorption to approximately 30% of intake.[4] This action entails the development of its well-known side effects, such as flatulence, increased bowel habit, voluminous stools and steatorrhea, which may occur in up to 15-20% of patients; but these have not frequently been a reason for discontinuation of treatment. Orlistat 120 mg TID achieves a 3% higher weight loss than placebo and contributes to a decrease of obesity-associated metabolic comorbidities. Further sub-analysis demonstrated that 26% of those receiving orlistat lost > 10% of total body weight, whilst 30% of this group lost > 5%, in comparison to 14% and 19% in the placebo group, respectively. The XENDOS (Xenical in the prevention of diabetes in obese subjects) study, a four-year double-blind placebo-controlled trial of 3305 non-diabetic obese patients, showed that orlistat reduced the risk of developing type 2 diabetes by 37.3% compared to placebo (lifestyle modification).[5]

Orlistat is the only currently available drug whose technical data sheet includes obesity as an indication of use. However, 32 alerts of severe hepatic failure, together with some cases of pancreatitis and renal oxalate calculi, have decreased its popularity.

Table II
Drugs approved by the FDA for weight loss

Generic names	*Trademark names*	*Usual doses*
Long-term treatment of obesity (> 12 months)		
Orlistat	Xenical	120 mg, 3 times a day
Sympathomimetic drugs approved for short-term treatment of obesity (< 12 weeks)		
Diethylpropion		
Tablets	Tenuate	25 mg, TID
Extended release	Tenuate 75 mg	Once daily
Phentermine HCl		
Capsules	Phentridol Teramine Adipex-P	15-37,5 mg QD
Tablets	Tetramine Adipex-P	
Extended release	Lonamin	15 or 30 mg/day, QD
Benzphetamine	Didrex	25 to 150 mg/day, in single or divided doses
Phendimetrazine		
Capsules, extended release	Adipost Bontril Melfial Prelu-2 X-trozine	105 mg/day, in the morning
Tablets	Bontril Obezine	35 mg, 2–3 times a day

Drugs that have been used to treat obesity, but that are not approved by regulatory agencies for this purpose

Bupropion

Bupropion, which inhibits the reuptake of norepinephrine and dopamine, is approved for the treatment of depression and smoking cessation. These neurotransmitters are involved as well in the regulation of food intake.[6] In a study in which 327 obese subjects were randomized to placebo, bupropion 300 mg/d, or bupropion 400 mg/d, at 24 weeks, body weight was reduced by 5.0%, 7.2%, and 10.1%, respectively. The trial was extended to week 48, and weight loss in the bupropion 300-mg and 400-mg groups was 6.2% and 7.2% of the initial body weight, respectively,[7] but the final dropout rate was 41%. The pharmaceutical company did not consider its commercialization for the treatment of obesity due to its central side effects, for instance, mouth dryness, insomnia, anxiety and palpitations, and due to the high discontinuation rate.

Combination of Bupropion and Naltrexone

Bupropion stimulates hypothalamic pro-opiomelanocortin (POMC) neurons that release alpha-melanocyte stimulating hormone (-MSH) which, in turn, binds to melanocortin-4 receptors, and thus, favors an anorexigenic action. When α-MSH is released, POMC neurons simultaneously release β-endorphin, an endogenous agonist of the mu-opioid receptor. Binding of β-endorphin to μ-opioid receptors on POMC neurons mediates a negative feedback loop on POMC neurons leading to a decrease in the release of α-MSH. Blocking this inhibitory feedback loop with naltrexone is thought to facilitate a more potent and longer-lasting activation of POMC neurons, thereby amplifying its effects on energy balance. As a result, co-administration of bupropion and naltrexone produces a substantially greater effect on the POMC neurons, suggesting that the drugs act synergistically.

Bupropion was combined with naltrexone in its sustained release form (Contrave™). Several phase III trials, grouped under the Contrave Obesity Research (COR), have been conducted in both diabetic and non-diabetic patients: COR-I, COR-II, COR-BMOD and COR-Diabetes.[8-10] The naltrexone/bupropion patients lost significantly more weight (5.0% versus 1.5%, $p < 0.001$) at 56 weeks, with 45% of patients achieving ≥5% body weight loss, compared to 19% with placebo. This combination resulted in significant improvements in depressive symptoms in addition to weight loss, as well as in a satisfactory recovery of eating-control in overweight and obese women with major depression. This drug combination has generally been well tolerated in most patients; nausea was the most frequently reported adverse event, which was associated to higher naltrexone doses.

The FDA advisory panel voted 13 to 7 in favor of approval of this combination in December 2010; however, the FDA declined to approve the drug in February 2011, claiming that cardiovascular safety should be proved in a specific large-scale long-term trial, before it could be reconsidered for evaluation. This was an unexpected decision by the FDA, given that bupropion, which is the drug potentially associated with an increased cardiovascular risk, is already available and used by millions of Americans for the treatment of mild depression or smoking cessation.[3]

Bupropion plus zonisamide

The combination of bupropion with the antiepileptic agent zonisamide has been evaluated in phase II trials. Zonisamide's mechanism of action has not been fully characterized; however, it has demonstrated a biphasic dopamine and serotoninergic activity. A 24-week RCT of bupropion 300 mg combined with zonisamide 400 mg achieved a greater weight loss (9.2%) than either drug alone (bupropion 6.6%, zonisamide 3.6%) or placebo (0.4%). Weight loss with zonisamide and bupropion appeared to be greater than that observed with the bupropion/naltrexone combination over the same period of treatment.[11,12]

Topiramate

Topiramate is an anticonvulsant drug that was approved for use in certain types of epilepsy and for the treatment of migraine headache. Its mechanism of action is not fully understood, although several hypotheses are considered, such as blockage of voltage-activated sodium channels, inhibition of high-voltage-activated calcium channels, glutamate-receptor antagonism (an orexigenic agent), inhibition of carbonic anhydrase, enhancing of gamma-aminobutiric acid (GABA)-evoked currents and inhibition of kainite-evoked currents.[13]

It proved to reduce food intake, but was not further developed clinically because of side effects occurring at doses selected for trials. In a 6-month, placebo-controlled, dose-ranging study, 385 obese subjects were randomized to four topiramate doses: 64, 96, 192, or 384 mg/d, or placebo. The key to improve drug tolerance was that these doses were gradually increased over 12 weeks and were tapered down in a similar way at the end of the trial. Weight loss from baseline to 24 weeks was –5.0%, –4.8%, –6.3%, –6.3%, and –2.6% in the five groups, respectively.[14] The most frequently reported adverse events were paresthesias (an effect due to inhibition of carbonic anhydrase), somnolence, and concentration, memory, and attention difficulties. A metanalysis of ten randomized clinical trials (3320 individuals) were recently analyzed. Patients treated with topiramate lost an average of 5.34 kg (95% confidence interval [95%CI] –6.12 to –4.56) of additional weight as compared with placebo. In the evaluation of

trials using topiramate 96-200 mg day, the weight loss was higher in trials with >28 weeks of duration (–6.58 kg [95%CI –7.48 to –5.68]) than in trials with <28 weeks (–4.11 kg [95%CI –4.92 to –3.30]).[15] The authors concluded that topiramate might be a useful adjunctive therapeutic tool in the treatment of obesity as long as proper warnings about side effects are considered.

Drugs under clinical investigation

Cetilistat

Like orlistat, cetilistat is a gastrointestinal and pancreatic lipase inhibitor that reduces fat absorption. In a 12-week phase-II double-blinded RCT (n = 447), cetilistat, in combination with a hypocaloric diet, produced significantly greater weight loss than placebo, with a dose-related response for 60, 120 and 240 mg TID.[16] In a multicenter, randomized, double-blind study (n = 869) to determine the efficacy and safety of cetilistat (40, 80, or 120 mg TID) and orlistat (120 mg TID) in comparison to placebo, in obese patients with type 2 diabetes on metformin, for 12 weeks, similar reductions in body weight were observed in patients receiving cetilistat 80 or 120 mg TID or 120 mg TID orlistat; these reductions were significant vs. placebo (3.85 kg, 4.32 kg, and 3.78 kg, respectively; $p < 0.001$).[17]

The results are comparable to those of orlistat, with approximately 30% of the treated patients experiencing >5% weight loss compared to 19% in the placebo group. The adverse side effects of cetilistat were similar to those reported with orlistat, although such events were less frequent, suggesting a better tolerability and therefore precluding good compliance.[16,17]

Tesofensine

Tesofensine is another novel pharmacological agent which inhibits the uptake of presynaptic noradrenaline, dopamine, and serotonin. Patients receiving this drug for the treatment of Alzheimer's and Parkinson's diseases reported weight loss.[18] Further evidence was demonstrated in a 24-week phase IIb randomized dose-dependent tesofensine trial in 203 obese individuals, with 79% of completers.[19] Weight loss was dose-dependent with 4.5% weight loss (0.25 mg), 9.2% (0.5 mg), and 10.6% (1.0 mg) and was greater than placebo ($p < .0001$). The drug was well tolerated, with mild symptoms appearing due to its central effects: mouth dryness, constipation, insomnia, anxiety and a significant increase in heart rate (7.4 beats/min), with no associated changes in blood pressure.[19]

Glucagon-Like Peptide-1 (GLP1) Analogues: Liraglutide, Exenatide

Liraglutide and exenatide are glucagon-like peptide-1 receptor analogues (GLP-1R) which were developed and approved for the treatment of type 2 diabetes. In a systematic review and metanalysis of 25 trials, GLP-1R agonist groups achieved a greater weight loss than control groups (weighted mean difference –2.9 kg, 95% confidence interval –3.6 to –2.2; 6411 participants).[20] GLP-1R agonists had additional beneficial effects on systolic and diastolic blood pressure, plasma concentrations of cholesterol, and glycemic control. GLP-1R agonists were associated with nausea, diarrhea and vomiting, but not with hypoglycemia. In a head-to-head comparison, liraglutide 1.2 mg and exenatide produced similar amounts of weight loss (3.24 kg with liraglutide vs 2.87 kg with exenatide); although with both treatments 17% of patients achieved a > 5% weight loss, with liraglutide 1.8 mg/d, this rate increased to 24% of patients.[21]

A recent 20-week multicenter European dose-ranging RCT of liraglutide (1.2, 1.8 mg, 2.4 mg, 3.0 mg) in comparison with orlistat (120 mg) treatment in 564 non-diabetic obese patients, demonstrated a mean weight loss of 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg, respectively, compared with 2.8 kg in the placebo-treated group and 4.1 kg in the orlistat-treated group.[22] Higher doses of liraglutide (3.0 mg) demonstrated significantly greater mean weight loss than placebo or orlistat. A total of 76% achieved at least a 5% weight loss compared with 30% in the placebo group, and 44 % in orlistat group. Liraglutide reduced blood pressure at all doses, and reduced the prevalence of prediabetes (84–96% reduction) with 1.8–3.0 mg per day. Nausea and vomiting occurred more frequently in individuals on liraglutide than in those with placebo; yet adverse events were mainly transient and rarely led to discontinuation of treatment[22].

Drugs approved by FDA advisory panels

The US FDA has recently approved 2 new drugs for the treatment of obesity: Lorcaserin and a combination of Phentermine plus Topiramate.

Lorcaserin (Belviq™)

Lorcaserin is a selective serotonin subtype 2C receptor agonist on hypothalamic pro-opiomelancortin neurons, which leads to reduced caloric intake and increased satiety. It is similar in its mechanism of action to fenfluramine and dexfenfluramine, except for that it is specific for the 2C subtype serotonin receptor, which is not found in the heart or heart valves (these two are linked to serotonin subtypes 5A or 5B receptors). The result is thought to be a compound effect of a desirable increased satiety and an inhibition of hunger, with no heart valve damage.

The tolerability and efficacy of lorcaserin for the treatment of obesity have been evaluated in 3 large RCT, placebo-controlled, double-blind studies, which

provided the basis for FDA approval in June 27, 2012. In the BLOSSOM (Behavioral Modification and Lorcaserin Second Study for Obesity Management) trial,[23] 4008 obese or overweight patients with obesity-related comorbid conditions were randomized to receive either lorcaserin 10 mg QD (n = 801), lorcaserin 10 mg BID (n = 1602), or placebo (n = 1601) for 52 weeks. A total of 2224 (55.5%) completed the 1-year trial. Absolute weight loss was 5.8 kg, 4.7 kg, and 2.9 kg for lorcaserin BID, lorcaserin QD, and placebo, respectively. More subjects receiving lorcaserin BID (47.2%) and lorcaserin QD (40.2%) lost at least 5% body weight at 1 year than placebo (25%), with differences being statistically significant. On the other hand, although systolic and diastolic blood pressure and heart rate decreased in all groups, differences were not statistically significant in this case.

The BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management) study[24] evaluated 3182 patients for up to 2 years with similar results (–5.8 kg for lorcaserin, compared with –2.2 kg for placebo). On the other hand, the BLOOM-DM (Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus) study[25] evaluated the safety and efficacy of lorcaserin in 604 patients with type 2 diabetes, with glycosylated hemoglobin (HbA1c) of 7-10%, and treated with either metformin, sulfonylurea, or both. Absolute weight loss was approximately 5 kg for lorcaserin and 1.6 kg for placebo. The study found that 45 % on lorcaserin QD and 16 % on placebo achieved at least a 5% weight loss. Approximately half of the patients in the lorcaserin treatment arm achieved an HbA1c level < 7%, almost twice the rate in the placebo group. It is not clear at this time, however, whether lorcaserin has effects on glycemic control that are independent of weight loss.

On the basis of the results of these studies, lorcaserin was approved at a dose of 10 mg BID in patients with BMI ≥ 30 kg/m^2, or BMI ≥ 27 kg/m^2 and at least one weight-related comorbidity, such as hypertension, type 2 diabetes, or dyslipidemia, in addition to a reduced-calorie diet and an increased physical activity. This therapy should be assessed at week 12 and if there is a < 5% decrease in weight, use of the drug should be discontinued because it is unlikely that the patient will achieve and sustain an adequate weight loss with continued treatment[26].

The most common adverse events with lorcaserin include headache, dizziness, nausea, constipation, fatigue, and mouth dryness. Although lorcaserin meets FDA weight loss criteria, the efficacy is modest, but the risk profile is also low. Lorcaserin treatment demonstrates an approximate average of 3 kg weight loss in a patient weighing 100 kg, or a reduction of 1.2 kg/m^2 in BMI, where the basal mean BMI is 36.1 kg/m^2. It is prudent to identify potential "responder patients", who will benefit from treatment, and differentiate them from other patients in which efficacy will not be likely, especially considering the fact that the estimated cost is approximately US$ 1500 per year or US$ 265 for each kilogram lost.[26,27]

Combination of phentermine and topiramate (Qsymia ™, Qsiva ™)

The drug combination of phentermine and topiramate (PHEN/TPM) was also recently approved by the FDA. Phentermine is a central noradrenergic drug that was commercialized in 1956 as monotherapy (15-30 mg/d) to induce a decreased appetite and favor weight loss in obese patients, but only for short-term use (< 12 weeks). Topiramate monotherapy (200-400 mg/d) was approved in 1996 for the treatment of partial seizures and in 2004 for migraine prophylaxis. The combination of PHEN/TPM allows a lower dose of both phentermine and controlled-release topiramate, and thus provides a more acceptable side-effects profile. The tolerance and safety of this drug combination are being evaluated in several phase III trials, comparing different dosages PHEM/TPM: low-dose (3.75/23 mg), mid-dose (7.5/46 mg), and high-dose (15/92 mg).

The EQUIP trial (Controlled-Release Phentermine/Topiramate in Severely Obese Adults: A Randomized Controlled Trial)[28] included people aged 18 to 70 years with a BMI of ≥ 35 kg/m^2 who were randomized to PHEN/TPM 15 mg/92 mg (n = 512), PHEN/TPM 3.75 mg/23 mg (n = 241), or placebo (n = 514) for 52 weeks. The percentage of weight loss with high-dose was 10.9% (–12.6 kg), compared with 5.1% (–6 kg) in the low-dose and 1.6 % (–1.8 kg) for placebo ($p < 0.001$ for both doses compared with placebo).

The CONQUER (Effects of Low-Dose, Controlled-Release, Phentermine Plus Topiramate Combination on Weight and Associated Comorbidities in Overweight and Obese Adults) trial[29] (n = 2487) compared full-dose and mid-dose PHEN/TPM with placebo for 56 weeks, including obese and overweight adults (BMI, 27-45 kg/m^2) who had 2 or more weight-related comorbidities. This trial was followed by the SEQUEL study, an extension for 1 additional year.[30] At the end of the CONQUER study, the percentage weight loss was 9.8% (10.2 kg) for high-dose, 7.8% (8.1 kg) with mid-dose, and 1.2% (1.8 kg) for placebo ($p < 0.001$ for both doses vs placebo). Approximately 70%, 62% and 21%, reached at least 5% weight loss, respectively. Weight loss was maintained during the second year of treatment in completers (SEQUEL study), resulting in 10.5% (10.9 kg) in PHEN/TPM 15/92 mg, 9.3% (9.6 kg) in PHEN/TPM 7.5/46 mg, and 1.8% (2.1 kg) in the placebo group ($p < 0.001$ for both dosages vs placebo). Nearly 80% of participants receiving the top-dose attained 5% weight loss compared to 75% receiving mid-dose and 30% receiving placebo ($p < 0.001$ for both doses compared with placebo). The combination of PHE/TPM achieves a high rate of adherence to treatment, similar to that obtained with orlistat, but with a clearly better efficacy (table III).

Table III
Summary of weight loss effects and dropout rates of drugs available for obesity treatment. Results at one-year follow-up (intention to treat analysis)

Drug	*Weight loss with drug*	*Weight loss with placebo*	*≥ 5 % weight loss*	*Dropouts*
Orlistat				
Metanalysis[4]	–6.5%	–3.6%	45%	30%
Lorcaserin				
BLOOM and BLOSSOM[23,24]	–5.8%	–2.5%	47%	45%
BLOOM-DM[25]	-4.5%	–1.5%	38%	50%
PHE/TPM[20]				
15 mg/92 mg	–9.8%	–1.2%	70%	30%
7.5 mg/46 mg	–7.8%	–1.2%	62%	30%

PHE/TPM: Combination of phentermine and topiramate.

Following the outcomes of the results of these studies, PHEN/TPM was approved for the treatment of obesity in patients with a BMI ≥ 30 kg/m^2 or a BMI ≥ 27 kg/m^2 with at least one weight-related comorbidity, such as hypertension, type 2 diabetes mellitus, or dyslipidemia, in addition to a reduced calorie diet and increased physical activity. Drug combination PHEN/ TPX therapy is started at 3.75 mg/23 mg, taken QD in the morning and, after 14 days it can be increased to 7.5 mg/ 46 mg. If at 12 weeks follow-up at least 3% weight loss has not been obtained, the drug may be discontinued or the dose may be increased to 11.25 mg/69 mg for another 14-day trial, followed by a final dosage increase to 15 mg/92 mg. Weight loss should be evaluated after a period of 12 weeks, and if 5% weight loss is not achieved, therapy should be withdrawn. Annual estimated cost is approximately US$ 2200 (US$ 180 per each kilogram lost).[26]

The most common adverse drug reactions include paraesthesias, dizziness, dysgeusia, insomnia, constipation, and mouth dryness. Potential safety concerns include depression, anxiety, cognitive-related complaints (memory and attention), cardiovascular risk with a small increase of heart rate, reduced bicarbonate levels, which could exacerbate metabolic acidosis, and teratogenicity.[3]

The combination of PHEN/TPM received a vote of 20 to 2 in favor at the February 2012 FDA Advisory Panel and was FDA approved on July 2012. However, on October 18th 2012, the Committee for Medicinal Products for Human Use (CHMP), from the European Medicines Agency, adopted a negative opinion and rejected marketing authorization for the medicinal product Qsiva, intended for the treatment of obesity. The CHMP remarked that main studies anticipated concerns regarding certain adverse effects related to cardiovascular risk, as well as in the psychiatric and cognitive fields; the Committee perceived that there was a high probability that, if approved, the drug would not be used strictly and exclusively for the intended patients. The applicant did propose specific measures to reduce this risk, but they were considered to be of difficult implementation in clinical practice. Therefore, the CHMP concluded that the benefits of Qsiva did not outweigh its risks and recommended that it were refused for marketing authorization.

Conclusions

Overweight and obesity are constant queries demanded in every day clinical practice, and attention to these issues should not be disregarded, since their associated comorbidities entail a significant increased morbidity and mortality. Lifestyle interventions and bariatric surgery for selected patients are the only two approaches currently available. Obesity-targeted drug therapies used in the past have deemed unreliable and the reality is that we are actually back at the starting point: the possibility of obtaining an ideal long-term effective and safe drug is still out of reach. The improvement of knowledge regarding physiopathology and mechanisms involved in food intake regulation and weight balance will surely help the development of specific therapies which will be available in the near future.

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Public health and the prevention of obesity: Failure or success?

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Abstract

In recent decades, obesity has become a major public health problem in developed societies and economies in transition. Rapid social changes that have occurred since the mid 20th century prompted major changes in eating habits and lifestyles, with the gradual abandonment of traditional dietary patterns and culinary techniques, significant decrease in physical activity and increased sedentary time, giving as result in an imbalance in the energy balance. Obesity is a risk factor for many chronic diseases. There is evidence that childhood obesity influences adult health condition. Additionally, obesity in children affects their physical, emotional and social wellbeing. According to some estimates the cost of obesity may represent up to 12% of health cost in some countries. Many actions have been developed since around the year 2000 WHO alerted about the problem. The analysis of the factors involved in the origin of the problem have led to recognize the importance of creating supportive environments for healthier food choices and physical activity to be the easiest and accessible options in common everyday environments, such as schools, workplace or community environment. Evidence is long available that the most effective interventions to prevent childhood obesity should consider multiple strategies and last longer. Today it is also recognized the importance of implementing policies that encourage supportive friendly environments for physical activity and help decisions to opt for healthy eating habits.

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Key words: *Obesity. Children. Prevention. Food habits. Physical activity. Policy.*

SALUD PÚBLICA Y PREVENCIÓN DE LA OBESIDAD: ¿ÉXITO O FRACASO?

Resumen

En las últimas décadas la obesidad se ha convertido en un importante problema de salud pública en las sociedades desarrolladas y economías en transición. Los rápidos cambios sociales acontecidos desde mediados del siglo 20 impulsaron importantes transformaciones en los hábitos alimentarios y estilos de vida, con el progresivo abandono de los modelos alimentarios y técnicas culinarias tradicionales, importante disminución de la actividad física y aumento del tiempo de sedentarismo, dando como resultado un desequilibrio en el balance energético. La obesidad es un factor de riesgo asociado para muchas enfermedades crónicas. En los niños además de condicionar su salud como adultos, afecta su salud física, emocional y social durante la niñez. Según algunas estimaciones el coste de la obesidad puede representar hasta el 12% del gasto sanitario en algunos países. Se han desarrollado muchas acciones desde que en torno al año 2000 la OMS alertara sobre el problema. El análisis de los factores implicados en el origen del problema han llevado a reconocer la importancia de crear ambientes favorables para que las opciones alimentarias y de actividad física más saludables sean las más fáciles y asequibles en las actividades y entornos cotidianos más habituales, como colegios, medio laboral, entorno comunitario. Desde hace tiempo se dispone de evidencia de que las intervenciones más efectivas para la prevención de la obesidad infantil deben contemplar múltiples estrategias y prolongarse en el tiempo. Hoy además reconocemos la importancia de poner en marcha políticas que favorezcan entornos amables que estimulen la práctica de actividad física, favorezcan decisiones que permitan configurar hábitos alimentarios más saludables.

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Palabras clave: *Obesidad. Niños. Prevención. Alimentación. Actividad física. Políticas.*

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Introduction

According to WHO, overweight and obesity is the fifth risk factor for mortality in the world. About 2.8 million deaths yearly are associated to obesity in the world. Furthermore, 44% of the burden for diabetes, 23% for ischemic heart disease and between 7% and 41% for certain types of cancer are attributable to excess body weight.

In Spain the prevalence of overweight and obesity has steadily increased in the last decades. Data from studies based on individually measured body weight and body height on random population samples from different age groups show that the prevalence of obesity around the year 2000 was higher in boys than girls in childhood and adolescence up to 25 years. From this age onwards, particularly from 45 years the prevalence of obesity rises with age in women and rates are clearly above those in men. The prevalence of obesity rises with age in men from 45 years as well, although more slowly.[1]

Among the school age population, data estimated in the PERSEO project in 2009 in the Autonomous Regions involved show a significant increase in the prevalence of obesity between 6 and 12 years in Andalusia, Murcia, Extremadura and Galicia compared to previous data measured between 1998 and 2000, regions which already showed high rates then. However, the prevalence of obesity has considerably increased in the same age group in regions such as Castilla-Leon with moderate-low prevalence rates in 2000. The Canary Islands showed the highest rate in 2000 and the prevalence is still high, but has not increased. These figures are consistent with estimates in the Aladino study in a national sample of the same age group in 2010.

In the international context, the prevalence of obesity in Spain in adults is slightly below average estimates for OECD countries. Prevalence of excess body weight in Spanish children and adolescents, however, is clearly above the average estimates for OECD countries for this age group, 22.9% for girls and 32% for boys aged 5-17 years, according to data published by IASO.[2]

In Western Australia body mass index is the leading risk factor for disease, above tobacco. If estimated projections become true most, adults in the world will be overweight or obese by the year 2030. A systematic review including studies from 25 countries analysed obesity trends since 1999. Results show a steady increase in the problem. This trend can be observed both in European and in Asian countries. In America, evolution trends of obesity rates is associated with race and ethnicity; thus obesity has increased in non-Hispanic American blacks and Mexican women, while the trend is changing in other population groups.[4] Figure 1 shows standardized rates of overweight (including obesity) and projected trends according as estimated by the OECD.

Despite the prevalence of obesity in adults is increasing in most countries in the world,[5] some studies suggest decline is starting in children, as shown in a review including data from 9 European countries, North America, Asia and Oceania[6] maybe a result of Public Health interventions.

Body Mass Index (BMI), health indicators and health costs

Different analyses on the impact of low BMI and high BMI on disease and survival have been conducted.

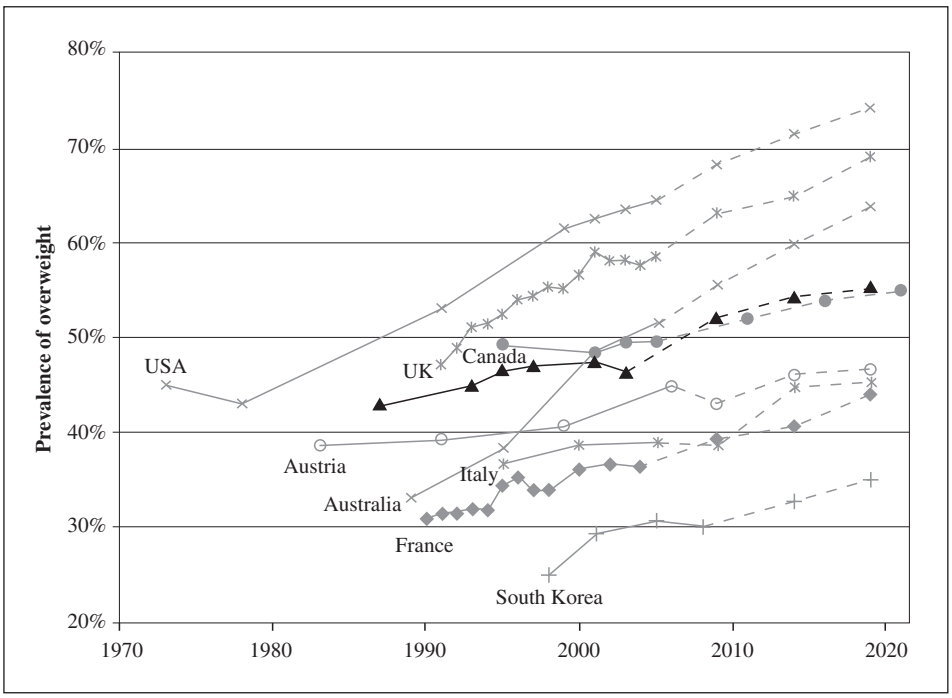

Fig. 1.—Standardized rates of overweight (including obesity) and projected trends. Source: OECD, 2012.

According to the analysis based on the "Prospective Studies Collaboration",[7] including data from 57 studies from Western Europe and USA (n = 894.576), mean age: 46 years; 61% males and BMI: 25 kg/m^2, BMI is a strong predictor of overall mortality. In this study each 5 kg/m^2 higher BMI was on average associated with about 30% higher overall mortality, 40% for vascular mortality, 60-120% for diabetic, renal, and hepatic mortality, 10% for neoplastic mortality and 20% for respiratory. The authors concluded that mortality was lowest at BMI about 22.5-25 kg/m^2. The progressive excess mortality above this range is due mainly to vascular disease. At 30-35 kg/m^2, median survival is reduced by 2-4 years; at 40-45 kg/m^2, it is reduced by 8-10 years, comparable with the effects of smoking. The excess mortality below 22·5 kg/m^2 is due mainly to smoking-related diseases, but is not fully explained[7].

A recent meta-analysis of reported hazard ratios of all-cause mortality for overweight and obesity relative to normal weight in the general population included 97 studies providing a combined sample size of more than 2.88 million individuals and more than 270 000 deaths. Relative to normal weight, both obesity (all grades) and grades 2 and 3 obesity were associated with significantly higher all-cause mortality. Grade 1 obesity overall was not associated with higher mortality, and overweight was associated with significantly lower all-cause mortality, suggesting that the main contribution to excess mortality in obesity comes from higher levels of BMI, equal or above 35.[8]

Regarding health care costs attributable to overweight and obesity, the Bernard Krief Institute published a report in 1999 about the cost of obesity in Spain and estimated the health expenditure associated to obesity to account up to 7% of total health care costs in the country. These estimates could likely add up to 9% to date considering pharmaceutical treatments used without a prescription, herbal remedies, especial dietetic products and private consultants and clinics. Table I summarizes the impact of childhood obesity on physical, emotional and social health.

Obesity and overweight have been shown to increase the rate of several common adverse medical conditions, resulting in economic costs of $300 billion per year in the United States and Canada. These costs result from an increased need for medical care and the loss of

Table I
Impact of childhood obesity on health

Physical Health	
Impaired glucose tolerance	Hyperinsulinemia: OR: 12.1
Type 2 diabetes	In the USA, ↑ 10 times diabetes prevalence in children (1982-1994)
Metabolic syndrome	Present in 30% of obese children (USA)
Hypertension	Almost 60% of children with hypertension are obese TAS: OR 4.5; TAD: OR 2.4
Dyslipemia	↑ LDL: OR 3.0; ↓ HDL: OR 3.4; ↑ TGC: OR 7.1 58% of obese children has 1 cardiovascular risk factor; 25% ≥ 2 RF
Hepatic steatosis	>10% of obese children
Cholelithiasis	Approx. 50% of cases are associated with adolescent obesity. ↑ 75% (1979-1999)
Sleep Apnea	↑ 175% (1979-1999)
Asthma	40% of hospital admissions are associated with obesity
Menstrual disorders	30% of women with polycystic ovary syndrome are obese
Orthopedic disorders	Flat feet, genu valgum, Blount disease, (two thirds of cases occur in obese),...
Emotional Health	low self-esteem
	Negative body image
	Depression
Social Health	Stigmatization
	Negative stereotypes
	Bullying
	Marginalization and isolation

Sources: Dietz WH. Pediatrics, 1998; Reilly JJ et al. *Arch Dis Child*, 2003; NAS. *Preventing childhood obesity*, 2005; Wang G; Dietz WH. *Pediatrics*, 2002.

economic productivity resulting from excess mortality and disability. It has been reported that more than one quarter of America's health care costs are related to obesity and that health care costs of obese workers are up to 21 percent higher than non-obese workers.[9] A systematic review of costs associated with obesity or intervention programs in Canada between 1990 and 2011 referred that direct costs accounted for 37.2% to 54.5% of total annual costs and between 2.2% and 12.0% of Canada's total health expenditures were attributable to obesity.

The costs of obesity in American children has been estimated to account for 9% of health care costs, and a considerable increase has been reported compared to estimates a decade ago (1-6%). Preventive interventions for childhood obesity are estimated to account for 5% of health care costs.[10-12] In addition to that, disturbances related to emotional and social health caused by obesity in children and adolescents should be considered as well.

Actions to control obesity

Awareness about the obesity situation has improved, at least in terms of the number of policy programs, guidelines and strategic plans. Since the WHO published the obesity report in 2000, defined obesity as an epidemic and one of the more relevant public health problems, a lot of efforts have been invested in the design of effective strategies to combat excess body weight and reverse trends.

In 2004 WHO published the Global Strategy on Diet and physical activity for health after a long development process. The initiative engaged all member states to take action and adopt national strategic plans and local actions in line with the agreed strategy.[13]

Additional documents in the same direction have been prepared by expert committees and agreed by member states from different international organizations. Some examples to mention include the European Charter on counteracting obesity published in the context of the WHO European Ministerial Conference on counteracting obesity, diet and physical activity for health, held in Istanbul (Turkey), 15-17 November 2006; the Commission of the European Communities White Paper on a Strategy for Europe on Nutrition, Overweight and Obesity related health issues, 2007[14] or the report Obesity and the economics of prevention: fit not fat, carried out jointly by the OECD and the World Health Organization and discussed by Health Ministers at a meeting held in Paris in October 2010.[15]

In September 2011 the United Nations general Assembly held a high-level meeting on non-communicable disease prevention and control in New York. The General Assembly adopted by consensus the resolution titled "Political Declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases". The Action Plan for implementation of the European Strategy for the Prevention and Control of Non-communicable Diseases 2012-2016 consider priority interventions the reduction of trans fatty acids and salt intake as well as the promotion of healthier food habits by means of fiscal policies,[16] and the WHO Action Plan 2008-2013 for the implementation of the world strategy for the prevention and control of non-communicable diseases.

The Ecological Model: Policies, environments and behaviours

To design strategies to counteract obesity it is important to consider the origins of the problem. Since the middle of the 20th century and particularly in the last third of the last century rapid sociological changes took place with great impact in life styles and the organization of everyday life in many countries: urbanization processes and progressively abandonment of rural areas, women incorporation into the work force which brought changes in family life with an impact in family meals, the time devoted to the acquisition of food, food preparation and consumption or even the way foods and beverages are consumed; changes in the systems of food production and distribution with a huge growth in the industries related to this sector; transformation in the marketing and publicity strategies as well as the means used; improvements in wellbeing and welfare society, among other considerations.

All these modifications influenced life styles of children, adolescents and adults driving to changes in food habits, a considerable reduction in usual physical activity in a high proportion of the population and an increase in the time devoted to sedentary activities. At the same time, traditional food patterns, cooking styles and traditional recipes have been gradually replaced by food preparations requiring short time to be ready and increasing consumption of either in part or just ready to eat foods and beverages as well as more frequent consumption of foods away from home, in commercial restaurants, canteens, school meals, workplaces or institutions.[17]

This analysis of the current situation implies the recognition that food consumption patterns and individual physical activity are significantly influenced by the environment in which we live, by the supply of food and drinks available in the environments in which we develop daily activities —study, work, leisure—, by the possibility of access to safe and friendly environments to practice physical activity, walking, etc.. In this context we are also influenced by the social groups with which we interact, closer groups which are more relevant such as the family, the school or the group of friends; other social influences are more distal as fashions, trends or the community in which we live.

From this point of view, the Ecological Model of behavior change has been accepted. The model recognizes the interaction between the environment and the

different behaviors as a theoretical model of reference for planning strategies for the prevention of obesity. In fact, the WHO recognizes that to support people in the process of making choices, so that in relation to eating and physical activity the healthier option is also easy to access and simple, it is essential to create favorable environments in the areas in which normal daily activities are performed, the community where we live, where we study, where we work or where we enjoy leisure time and rest. Policies, norms, regulations and social agreements at different levels are essential to create healthier environments. In this framework the different social groups interact and finally, individuals make choices and take decisions based on their personal motivations, attitudes, information and beliefs.[18]

Initiatives to improve nutrition and prevent obesity and its complications in different countries

With this approach different strategies have been tested in different countries. Incentives to encourage healthy behaviors, such as reducing taxes for families participating in sports (Canada) and use of financial disincentives to discourage unhealthy behaviors, such as quotas for each employee that exceeds the acceptable limit of waist circumference (Japan). Initiatives to increase the variety and quality of food supply have also been launched, such as fruits and vegetables in socioeconomically disadvantaged environments or in isolated and distant areas (UK, USA), regulation of access to food and beverages high in fat, sugar or salt in schools (France, Spain, USA, etc.), regulations to influence consumers purchasing decisions of food and drink, such as changes in food labeling as the multiple traffic light (UK), or the Healthy Choices symbol (The Netherlands), control and regulation of food and beverage advertising by self-regulatory codes and other measures (Spain, UK, etc..), creating communities that support healthy eating and physical activity, with initiatives such as the EPODE program in France and other countries; Shape-UP Sommerville in the U.S. and other community interventions implemented in the U.S. and in Australia.[19-21]

In other cases, as some U.S. states have been proposed regulations governing minimal time devoted to physical activity at school. Other interventions have regulated care to people with overweight or eating behavior disorders, or even regulating the systematic collection of information on weight and height in certain conditions for surveillance purposes, for example in France aimed at school population. Table II shows policy approaches for obesity prevention implemented in different countries.

Overall policies are aimed at promoting changes in the environment so as to generate spaces (time and place), safe and friendly routes to encourage the practice of physical activity and facilitate the provision of food and beverages that enable the practice of healthy eating habits as the most easy and accessible option. Some of these interventions have promoted changes in the menus offered in school canteens or in the repertoire of foods and beverages offered at the outlets inside school buildings or sports or leisure centers for children and youth. Other initiatives have regulated the nutrition information on food labels so that it is easier to understand to consumers and help them to make informed choices of food and beverages in line with healthy eating patterns, for example quantitative advice and graphics as the multiple traffic light or symbols like the healthy choices logo or the green lock[22] In some countries fiscal policies have suggested either to add taxes to certain foods and drinks high in energy density or reducing others, such as fruits and vegetables to encourage their consumption.[23].

Moreover, policies should also be directed at promoting individual behavior change towards the adoption and practice of healthier eating habits and physical activity from local environments.[17,19,21]

In this sense, both the Global Strategy on Diet, Physical Activity and Health (DPAS) and PAHO include the following among the key interventions to reduce the burden of obesity and chronic diseases through dietary changes: promoting and protecting exclusive breastfeeding until six months of age, increasing the availability, accessibility and consumption of plain water, reduce the consumption of sugar and fat in drinks, reduce consumption and the amount of added sugar in foods, reduce saturated fat intake and eliminate the consumption and production of industrial trans fats, increase the consumption of vegetables and fruits, increase consumption of whole grains and fiber in the diet, reducing sodium intake, reduce portion sizes in restaurants and outlets selling prepared foods and processed foods, increase nutrition for health literacy and increase the capacity of responsible decision-making about a healthy diet in the population.

Strategy for Nutrition, Physical Activity and Obesity Prevention (EsNAOS)

Following the commitments made with the approval of the DPAS, in 2005 Spain adopted the Strategy for Nutrition, Physical Activity and Obesity Prevention (EsNAOS),[24] an ambitious strategic plan that marked the lines of action in subsequent years , which considered the implementation of measures such as nutrition education programs, improving the food supply in school canteens; limiting the availability of energy-dense products in vending machines located in the school environment, promotion of school sport activities, control of food and beverage advertising aimed at children; adequacy of the nutritional composition of products mainly in the content of salt and trans fats and the development of protocols for primary care. All these lines of action focus on actions in three main areas. In the family and community environment through infor-

Table II
Policy approaches for obesity prevention implemented in different countries

Policy	*Description*	*Country*
Incentives to motivate healthy behaviours; Financial disincentives to discourage certain less healthy behaviours	Tax reduction for families participating in sports	Canada
	Added fees in companies contribution to national insurance for each employee exceeding the acceptable limit for waist circumference	Japan
Requirements to improve food quality, food diversity and availability	An initiative was issued in New York city to increase permits for sale of fruit on sidewalks in neighbourhoods with high rates of poverty	USA
Restricting access to unhealthy foods	Elimination of sugary drinks in schools	France, USA
Regulations focused on influencing consumer choice	The voluntary traffic light system in highly visible image on the front of food packages	UK, Australia
Regulation of marketing and advertising	NAOS Strategy. Self-regulation of advertising codes. Development of dietary guidelines for families, schools and businesses	Spain
Creating communities that support healthy lifestyles	EPODE. Community intervention to prevent childhood obesity, based on 4 pillars: 1) Political support at the highest level, 2) a solid scientific basis, 3) social marketing and 4) multi-stakeholder participation. Program "Shape-Up Somerville". Initiative by Tufts University and the City of Somerville in Massachusetts to promote physical activity and healthy eating	France European Unión USA
Stipulation of minimum requirement of physical activity (work places) and physical education (school setting)	Norms in Connecticut and Kentucky in the US to regulate a minimum daily physical activity in school children	USA
Mandates for health care coverage of overweight and obesity by insurance companies	Law requiring social work and health insurance companies to provide coverage for eating disorders such as obesity, bulimia and anorexia. Anti-discrimination Act of obesity in Georgia, requires insurers to cover treatment for morbid obesity in their insured	Argentina USA
Mandates to generate resources for government use	Law determining the measurement and reporting of body weight and height in schools	France

mation campaigns, creation of working groups at regional and municipal levels and collaboration with entertainment companies and toy manufacturers and advertisers.

At school level the NAOS Strategy includes three main lines of action: nutrition education through the school curriculum, specific workshops and promoting teacher training in this area; regulation and supervision of food supply and operation of school canteens and regulation of the supply of food and beverages through vending machines located in schools. It also focuses on physical activity in schools.

In all lines of action specifically the strategy considers participation, meeting spaces and negotiation with key stakeholders: federation of parents associations, business associations of affected sectors: food and beverage manufacturers, catering, vending, commercial distribution, as well as the scientific and professional associations concerned.

NAOS strategy considers especially the industrial sectors involved through the establishment of agreements with the Spanish Federation of Food and Drink Industries (FIAB) and commercial distribution companies: ANGED or ASEDAS. Results of these collaboration agreements was the adoption and implementation of the code of self-regulation of food and beverage advertising aimed at children PAOS, supporting the design and implementation of dissemination of the Strategy; Trade policies in the products of "own brand" or Development of advertising and promotion of food under the NAOS Strategy. In July 2011, the Parliament approved Law 17/2011, of 5 July, Food Security and Nutrition and a few months later was published a consensus document on food in schools.

Intervention studies conducted in Spain

Apart from PERSEO Project,[25] statewide, different intervention proposals have emerged aimed at the prevention of obesity. The study of Cuenca and the Four Provinces study investigated the association of adiposity on cardiovascular risk factors in childhood and youth. These studies were used as starting point for the implementation of a research project aimed at evaluating the effectiveness of an intervention to promote leisure-time physical activity in order to prevent overweight/ obesity and other cardiovascular risk factors in schoolchildren. The results after two years of implementation of the

project in 10 schools in Cuenca were encouraging with a 6% reduction in the prevalence of obesity in girls and 2% in boys and a substantial improvement in the lipid profile.

Thao-Salud is inspired EPODE, a program started in France in 2004. This initiative was launched based on the experience carried out in two northern cities of France, Fleurbaix and Laventie in 1992. These experiences revealed that the actions in schools and in the city have a positive impact and may slow the progression of the prevalence of obesity and overweight in children. EPODE Program ("Ensemble Prévenons l'Obésité Des Enfants") started in 10 pilot French cities lead by the French communication agency. Thao-Child Health began in 2007 in five pilot municipalities. This is a program to promote healthy habits at the municipal level. The program is targeted to school children of 3-12 years involving all local actors in contact with the children. Since 2010, it has begun to develop a specific program for children 0-3 years.[26]

The project strategy includes a first step of information and awareness campaigns aimed at local stakeholders through communication strategies. In a second phase begins intervention in schools. It provides a component for secondary prevention aimed at health professionals and families with overweight children.

"Kids in Motion" is a structured program aimed at modifying eating habits, lifestyles and emotional aspects in obese children (6-12 years) and their families. The results show a decrease in BMI, an increase in the quality of the Mediterranean diet, and less anxiety. Ability was observed for long-term follow-up in 59% of the population.

Almost all the Autonomous Communities are developing activities or projects of nutritional epidemiology and prevention of obesity.

PERSEO project

The PERSEO project has been based on the development of a community intervention program focused on the school environment with involvement of students, teachers, families and community environment, with the overall objective to promote better eating habits and adequate physical activity in the school population. PERSEO seeks to achieve a school and family environment conducive to the practice of healthier eating habits and physical activity in Primary school children, promoting increased consumption of fruits and vegetables, reducing fat intake, increasing levels of physical activity and reduce sedentary time both at school and in the home environment.[25]

The proposed intervention in the project consists of 10 teaching units with classroom activities (change knowledge, attitudes, habits, skills, preferences), creates occasions at school that favor increased availability and access to a healthy food supply, limited access to high caloric and low nutrient density food and drink (cafeteria, recess fruit, alternative parties). PERSEO promotes physical activity by suggestions for more active recess. It includes working with families and involvement of Parents Associations (AMPAs) in the project. Specific educational materials including teachers guides, activity books for students, educational materials for families, educational materials for persons responsible for school meals and includes collaboration of health centers next to participating schools.

Aspects such as sustainability, intergenerational and intercultural dialogue, and recognition to local products, culture and culinary tradition were taken into account in the design of the contents and promoted. Dynamics were proposed based in active learning experiences. This is a proposal for continued and progressive intervention in the 6 years of Primary school, with a required minimum intensity of 20 activities per school year.

In relation to the financial budget available it was decided that the first phase of the project would be developed in the Autonomous Communities with higher prevalence of obesity, with reference to the study enKid. In this PERSEO area were included Andalucía, Canarias, Castilla-Leon, Extremadura, Galicia, Murcia and the autonomous cities of Ceuta and Melilla.

A prospective study was designed for evaluation of the project, with an intervention group (34 schools) and a control group (33 schools), with assessments at baseline, after the first year and after two years of intervention. The participating schools delivered Primary education (First to -4th grade primary school at the beginning) from six autonomous regions, Ceuta and Melilla.

The study protocol contemplated individual anthropometric measurements, a validated assessment questionnaire of dietary habits and physical activity of schoolchildren and others about the habits of the families, and determinants of these behaviors. Information was also collected on the school environment, school policies, nutrition education and physical activity at school and in particular, on food intake in the cafeteria. Information was collected using the same protocol at all sites at the beginning of the project, at the end of the first school year of intervention and after two years.

We recruited 13,767 children aged between 6 and 11 years, enrolled between 1st and 4th year of primary education in 67 schools, with the active collaboration of 640 teachers. The average rate of permits for students: 95% and the response rate in the first phase of the project PERSEO: 88.35% (n = 11,677) completed both phases the 80.37% (n = 10,623). Between 2000 and 2010 the prevalence of obesity in the Perseo region has increased an average of 2%.

It has been observed a protective effect of the intervention on the risk of obesity, the greater the higher the degree of implementation and program fidelity. The results of the intervention show significant progress in improving lifestyles in students/participants in the project belonging to the intervention group in relation to the control schools.

Evidence of the PERSEO project's positive results in all aspects suggest the need to maintain over time the dynamic

and content of the intervention in the school setting, facing the challenge of engaging families in helping to develop healthier eating habits and physical activity behaviors in school and exploring teaching methods that achieve maximum efficiency in collaboration with all professionals and workers involved in the school community and health professionals in the area of reference.

Estimating the potential impact of reducing obesity in the medium term

García Goñi,[27] expert in health economics has analyzed in depth the estimation of the potential impact on the prevalence of obesity in the medium term according to three levels of action: 1) A first level that would trigger health information programs, food safety, prevention strategies and promotion of physical activity. A potential reduction level of 10-15% is estimated for this section. 2) A second level with coercive measures, regulation and intervention on the food industry and stakeholders. Expected impact: 15:33%; 3) Economic measures to change consumer behavior in particular reducing the price of healthy food items, ban of XXL portions or commissioning additional special taxes to certain products as have been launched in Denmark, France, Hungary and some cities USA. Potential reduction: 30-55%.

Cost effectiveness of interventions

Some authors have conducted the cost-effectiveness analysis of different interventions for the prevention of

Table III
Cost-effectiveness for selected interventions to prevent obesity

Intervention	*Target population*	*Cost-effectiveness*
Unhealthy food and beverage tax (10%)	Adults	Cost-saving
Front-of-pack traffic light nutrition labelling	Adults	Cost-saving
Reduction of advertising of junk food and beverages to children	Children (0-14 years)	Cost-saving
School-based education programme to reduce television viewing	Primary schoolchildren (8-10 years)	Cost-saving
Multi-faceted school-based programme including nutrition and physical activity	Primary schoolchildren (6 years)	Cost-saving
School-based education programme to reduce sugar-sweetened drink consumption	Primary schoolchildren (7–11 years)	Cost-saving
MOVI, After school physical activity intervention	Primary schoolchildren (10-11 years)	Intervention cost: 125.469,75 € Cost per child 269,83 €
PERSEO Multi-faceted school-based programme including nutrition and physical activity	Primary schoolchildren (6-11 years)	Cost per child 16 €
Family-based targeted programme for obese children	Obese children (10-11 years)	Cost-saving
Multi-faceted targeted school-based programme	Overweight/obese primary schoolchildren (7-10 years)	Cost-saving
Gastric banding-adolescents	Severely obese adolescents (14-19 years)	Intervention cost: 101,644,702 € Net cost per DALY saved: 3,440 €
Family-based GP-mediated programme	Overweight/moderately obese children (5–9 years)	Intervention cost: 4,926,000€ Net cost per DALY saved: 3,675 €
Multi-faceted school-based programme without an active physical activity component	Primary schoolchildren (6 years)	Intervention cost: 40,036,500 €) Net cost per DALY saved: 16,650 €
Active After Schools Communities Program	Primary schoolchildren (5-11 years)	Intervention cost: 31,507,800 € Net cost per DALY saved: 64,100 €
TravelSMART schools	Primary schoolchildren (10-11 years)	Intervention cost: 10,242,380 € Net cost per DALY saved: 91,475 €
Walking School Bus	Primary schoolchildren (5-7 years)	Intervention cost: 31,501,600 € Net cost per DALY saved: 594,168 €

Source: Modified from Gortmaker et al. *Lancet* 2011; 378: 838-47.

obesity and have also taken into account the available evidence on the effectiveness of each intervention. Vost et al. in Australia concluded in their study that it is possible to get great impacts on the health of the population (>100,000 DALYs) only with some interventions that reach large proportions of the population as taxes or legislative measures to restrict the content of salt in staples like bread; Evidence for these interventions is classified as "probable".[28]

In relation to obesity in particular have been identified as cost-effective interventions in addition to the tax measures, reduction of television advertising and the use of nutritional labeling graphical information such as the multiple traffic light. Also some community interventions to change eating habits and physical activity, but its effects depend on maintaining their public funding over time.[29] Table III shows information related to cost-effectiveness for selected interventions to prevent obesity.

According to an OECD report[2] the implementation of a universal strategy for the prevention of obesity each year would prevent 155,000 deaths from chronic diseases in the countries involved in this organization. These measures would have an annual per capita cost very acceptable: USD 12 per capita in Mexico; 19 USD per capita in Japan and England or 32 USD in Canada. In Spain the Perseo study estimated a cost of 21 USD per capita. This cost does not account for the indirect impact on families, teachers and other professionals in the education community and the health system (2008-2011).

Measuring the effectiveness of such interventions can be difficult because they cannot always be measured by controlled trials and it is necessary to use other approaches. Moreover, when assessing the effectiveness of interventions on the prevalence of obesity in the population is important to note that although perhaps not capable of achieving the target prevalence raised, slowing the projected trend may be an indicator of success and can have a major impact on the health system.[30]

Conclusions

Despite the implementation of various initiatives of community intervention the prevalence of obesity continues to rise in Spain in all age groups except in the female group belonging to high socioeconomic status.

The initiatives with the school population target group obtained significant improvements or in some cases modest changes in obesity indicators. These programs (including those with modest results) should be continued in time as part of the teaching, demanding greater involvement of the school community.

The improvement in eating habits should be accompanied by an increase in physical activity energy expenditure.

Children with overweight and obesity require distinct patterns of physical activity... Even with regard to the subject area of physical education.

We need to continue encouraging preventive strategies and self-management by means of programs and initiatives with families, food companies, health administration, public administration, education sector, and mass media, local and regional governments.

Treatment of obesity requires multidisciplinary teams in place in all levels of health care, in both the public and private sectors.

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Obesity and Diabetes

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Abstract

Type 2 diabetes mellitus is characterized by hyperglycemia, insulin resistance, and relative impairment in insulin secretion and its possible long term complications. Its pathogenesis is poorly understood, but both genetic and environmental factors, such as obesity and aging, play a key role. "Diabesity" is a new term which refers to diabetes occurring in the context of obesity. In this article, we will discuss the epidemiology and impact of diabetes and obesity and will also outline the components of the metabolic syndrome and the studies that demonstrate that screening and prevention are possible in an attempt to control this epidemic.

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Key words: *Metabolic syndrome. Type 2 diabetes. Insulin resistance. Obesity.*

OBESIDAD Y DIABETES

Resumen

La diabetes tipo 2 se caracteriza por hiperglucemia, resistencia a la insulina y una relativa alteración en la secreción de insulina y por la posibilidad de complicaciones a largo plazo. Su patogénesis no está clara pero influyen tanto factores genéticos como ambientales, tales como la obesidad y el envejecimiento. Se ha acuñando un nuevo término, la "diabesidad" para definir la diabetes que se produce en el contexto de la obesidad. En este artículo se discuten la epidemiología y el impacto de la diabetes y obesidad, y también se describen los componentes del síndrome metabólico y los estudios que demuestran que el screening y la prevención son posibles, en un intento de controlar esta epidemia.

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Palabras clave: *Síndrome metabólico. Diabetes tipo 2. Resistencia insulínica. Obesidad.*

Abbrevations

MetS: Metabolic syndrome.
DM: diabetes mellitus.
IR: insulin resistance.
BMI: body mass index.
CVD: cardiovascular disease.
ESRD: end-stage renal disease.
IL: Interleuquin.
TNF: tumor necrosis factor.
HT: Arterial Hypertension.
NO: nitric oxide.
CRP: C reactive protein.
WHO: World Health Organization.

Introduction

Type 2 diabetes mellitus (DM) has become a highly prevalent disease all over the world and it has been recognized as a worldwide epidemic. The prevalence of both type 2 DM and obesity has increased worldwide during the last century, not only in developed countries, but also in developing countries, sometimes coexisting with undernutrition. Furthermore, the global prevalence of diabetes in 2010 was 280 million people worldwide (around 6.2% of the world's total population), and it has been predicted that in 2030 the prevalence will reach more than 7.5% of the world's total population, paralleling the aging and body mass index (BMI) of the population, thus confirming the relationship between obesity and diabetes. During the last 25 years, the prevalence of diabetes has doubled in the USA and multiplied by three to five times in Asian countries.[1] Epidemiological data in Spain has shown a diabetes prevalence of between 5,5-18%, and a glucose intolerance prevalence of between 7,2-18%, depending on geographical location.

Diabesity

Obesity induces insulin resistance and involves a plethora of molecules that predispose individuals to an inflammatory state and metabolic complications. Insulin resistance is determined by genetic factors and also environmental factors as hyper-energetic and saturated and trans-fat high diet, obesity, aging and sedentarism.

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Diabesity is a new term referring to diabetes occurring in obese persons. A direct relationship between BMI and diabetes has been demonstrated. The pathogenesis has been demonstrated to be a resistance to insulin action in peripheral tissues. Insulin resistance can be defined as a state in which greater than normal amounts of insulin are required to produce a normal biological response. Insulin acts through coupling to a membrane cell receptor, a tetrameric protein with 2 identical alfa sub-units and other 2 identical beta sub-units. Alfa sub-units are extracellular and after insulin coupling translate the signal to both intracellular beta sub-units, which have tyrosine kinase activity, and are auto-phosphorilated, with a subsequent increase of their catalytic tyrosine kinase activity. Then, endogenous protein substrates are phospforilated and activate a cascade of intracellular signals, which in last term induce migration of glucose transporters (Glut-4) from intracellular pools to the cellular surface, to facilitate glucose entry into the cell. So, insulin resistance is due to an impairment in one or more of these steps of this process in the target-tissue, which induces compensating hyperinsulinemia to maintain normoglycemia. But along the years, pancreas gets exhausted and plasmatic glucose levels start to increase. Once glucose has increased, hyperglycemia has a toxic effect over islet cells (glucotoxicity) and has been demonstrated to impair the kinase function of insulin receptor ("down-regulation").

An important consequence of insulin resistance is the increase of free fatty acids, which in turn, impairs even more the insulin resistance (lipotoxicity). Even more, insulin resistance on hepatic, muscular and adipose tissue is associated with overproduction of proinflamatory citoquines, as interleuquin-6 (IL-6) and tumor necrosis factor (TNF), and a relative decrease of antinflamatory citoquines, as adiponectin. All these factors contribute to a chronic inflammatory status.

The health impact of type 2 DM is due to its long-term complications including cardiovascular diseases (CVD), stroke, peripheral vascular diseases, retinopathy, nephropathy, neuropathy. In Western countries, diabetes is the main cause of blindness and end-stage renal disease (ESRD), accounting for 40-50% of incident ESRD cases, and it doubles the possibility of CVD. It has been anticipated that due to increasing rates of childhood obesity in the USA, we may see the first generation which will be less healthy and have a shorter life expectancy than their parents, because of diabetic complications. Even more, diabetic patients had a significantly lower health-related quality of life in contrast to those without diabetes. The economic burden of diabesity is noteworthy, and it has a real impact on the world economy, as reflected by the consumption of about 14-15% of a country's total health expenditure,[2] because of diabetic complications, with management of macrovascular disease being the largest and earliest.[3] Even more, the burden of diabetes on the world economy has been increasing during the last decades, reaching at least $376 billion in 2010. Therefore, improving glycemic control of diabetes, or even better, avoiding diabetes by staying thin and fit, will prevent complications, and will reduce these high costs.

Metabolic Syndrome (MetS)

The rising prevalence of abdominal overweight and obesity has also a direct correlation with increasing prevalence of hypertension, dyslipidaemia. In 1998, Dr. Reaven defined metabolic syndrome (MetS), also known as X syndrome, as a conglomerate of coronary risk factors. It is characterized by the clustering of abdominal obesity, impaired glucose tolerance, elevated triglyceride levels, reduced high-density lipoprotein (HDL) cholesterol levels, and hypertension, often accompanied by a proinflammatory status that predisposes to CVD. Persons with MetS are at increased risk of type 2 DM and CVD. The waist perimeter can be used as an indirect, but effective marker of intraabdominal fat content, as it has been demonstrated to significantly correlate with it, quantified by radiological techniques. Over the years, several classifications for the MetS have been proposed by experts. The major definitions used are the WHO, National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III),[4] National Heart, Lung and Blood Institute/American Heart Association[5] and International Diabetes Federation (IDF)[6]. These definitions differ somewhat in terms of the prerequisite components and the cut-off levels used for each component. WHO, IDF and NECP ATPIII and criteria for Identification of the Metabolic Syndrome are shown in Tables I, II and III, respectively. These last criteria have been widely accepted by its easy clinical applicability.

Other components of the MetS

Arterial Hypertension (HT) is often associated with obesity and increases the risk of CVD, even with minor

Table I
WHO Criteria for Identification of the Metabolic Syndrome

At least 1 of the following:

- Type 2 Diabetes
- Abnormal glucose tolerance
- Insulin Resistance

At least 2 of the following:

- Hypertension (≥ 140/90 mm Hg)
- Obesity (IMC ≥ 30)
- Dislipemia:
  - TG ≥ 150 mg/dl.
  - c-HDL < 35 mg/dl (men)
- < 40 mg/dl (women)
- Microalbuminuria ≥ 20 g/min

Table II
Criteria for Identification of the Metabolic Syndrome
Central obesity

- Waist circumference
  - 94 cm (men)
  - Abnormal glucose tolerance

And two more of teh following:

- Hypertrigliceridemia*: TG ≥ 150 mg/dl
- Low HDL-cholesterol*:
  - < 40 mg/dl (men)
  - < 50 mg/dl (women)
- HT* (≥ 130/85 mm Hg)
- Fasting blood glucose*: ≥ 100 mg/dl

* Or being under treatment.

elevations. Its prevalence is about 20-30% in general population, but if treated patients are included, it reaches about 44% of middle age adults. Insulin resistance decreases renal clearance of uric acid, so hyperuricemia can coexist. A proinflamatory status is underlying in the MetS, due to the overproduction of proinflamatory citoquines, as interleuquin-6 (IL-6), resistin, C reactive protein (CRP) and TNF, and a relative decrease of antinflamatory citoquines, as adiponectin, produced by adipose tissue. Plaquetar hyperagregability and hypercoagulation are also components of the metabolic syndrome, and predispose to a protrombotic status. Abnormalities in endothelial and vascular smooth muscle cell function, as well as a propensity to thrombosis, contribute to atherosclerosis and its complications. In normal endothelial cells, biologically active substances are synthesized and released to maintain vascular homeostasis, ensuring adequate blood flow and nutrient delivery while preventing thrombosis.[7] One of these molecules synthesized by the endothelial cell is nitric oxide (NO) that causes vasodilation. In addition, NO protects the blood vessel from injury and atherosclerosis, by mediating molecular signals that prevent platelet and leukocyte interaction with the vascular wall and inhibit vascular smooth muscle cell proliferation. Endothelial dysfunction, as represented by impaired endothelium-dependent, NO-mediated relaxation, occurs in diabetes. Microalbuminuria is an early marker of endothelial dysfunction. Non-alcoholic fatty liver disease is the hepatic expression of metabolic syndrome, which comprises a spectrum of clinical and histological events ranging from simple and benign fatty liver to steatohepatitis, which is characterized by the abnormal activation of pathways leading to an aggressive inflammatory condition. Insulin resistance plays a key role and arises from multiple defects in the liver, adipose tissues, and muscle signaling, which leads to a failure to suppress hepatic gluconeogenesis and glycogenolysis, thereby enhancing fat accumulation in the hepatocytes via increased lipolysis and increased hepatic synthesis of triglycerides.

Table III
APT III Criteria for diagnosis of the Metabolic Syndrome

- Abdominal obesity:
  - Waist circumference
    - 102 cm (men)
    - 88 cm (women)
- Hipertrigliceridemia:
  - TG ≥ 150 mg/dl.
- Low HDL-cholesterol:
  - < 40 mg/dl (men)
  - < 50 mg/dl (women)
- Hypertension (≥ 130/85 mm Hg)
- Fasting glucose:
  - ≥ 110 mg/dl

Diagnosis of the metabolic syndrome is made when 3 or more of the risk determinants shown above are present.

MetS prevalence is also growing at an alarming rate, and has also been defined as pandemic.[8] In a compilation of observational studies conducted on European countries, it was reported that non-diabetic subjects under 40 years of age had an MS prevalence of 14-41 %, depending on the age range[9]. In the USA, a prevalence of 21.8% was found, which ranged from 6.7% (in 20 to 29-year olds) to 43.5% (in 60 to 69-year olds).[10] Although less frequent than in Western countries, obesity and MetS are also major health problems in Asian populations. The prevalence of MetS in Japan was estimated at 25.3% for men and 10.6% for women. Results from different cross-sectional studies conducted in countries with emerging economies have reported that the prevalence of MS in these countries is also high. The general prevalence of MS in Latin-American countries was 24.9 %, and was slightly more frequent in women than in men.[11] Globally, MetS affects 24% of all adults over 20 years of age, and the figure raises to 42% over 60 years of age.

Clinical importance of metabolic syndrome

MetS has been criticized because of the different definitions proposed. Since the WHO criteria in 1999, when insulin resistance was primordial, to NCEP ATP III, that priories abdominal obesity, or International Diabetes Federation (IDF) criteria in 2005. It has also been said that the criteria are incomplete and the etiology is not clearly understood. In some of the definitions, type 2 diabetic patients are not included. Even more, a specific treatment of MetS does not exist, but every one of the components must be treated separately. Even more, the cardiovascular risk of persons diagnosed is not higher than the associated to the risk factors. In this context, Dr. Reaven published in 2005 an article titled "Metabolic Syndrome: Requestiem in Pace".[12] Nonetheless, the presence of a MetS is associ-

ated to 3.5 times higher mortality cardiovascular risk. And it is also doubtless that MetS has a clinical value, to implement an aggressive dietary treatment, and to treat the coexistent risk factors. The diagnosis of MetS amplifies the importance of obesity, hypertension or glucose and lipid alterations. As an example, hypertension is possible to be more severe, non dipper, and refractory to treatment, with microalbuminuria and more endothelial dysfunction. Anyways, no one can deny the good job of Gerald Reaven describing the unified concept of MetS, which has been translated to a big impulse, opening new ways to the basic, clinic, pharmacologic and epidemiologic research. This new concept has changed our knowledge about metabolic diseases and CVD.

But MetS detection is important because it allows for easy identification of patients who are at risk of developing atherosclerosis, type 2 diabetes mellitus and/or associated co-morbidities and who are subject to a higher mortality risk from these causes.[13] Even more, individuals who are genetically predisposed to insulin resistance may forestall or even prevent the development of diabetes by staying thin and physically active. In addition, the concept of MetS facilitates the understanding of the underlying physiopathological relationships between its different components. This understanding may also be helpful for epidemiological and clinical studies associated with the treatment and/or prevention of CVD.

Diabetes prevention

In spite of new diabetes treatments, including sophisticated devices and continuous infusion pumps, obtaining an adequate metabolic control is a difficult challenge. Therefore, the goal would be to prevent diabetes. Although insulin resistance and type 2 diabetes have a genetic component, they can also be influenced by environmental factors. Weight reduction can substantially improve glycemic control in patients with type 2 diabetes, but there is also some evidence that weight loss can improve insulin resistance and prevent progression from IGT to type 2 diabetes.

Healthy lifestyle has been reported to reduce the incidence of new cases of type 2 diabetes in a subgroup of patients with impaired Glucose Tolerance (IGT), who have a high risk of developing diabetes.[14] In The Malmo Prospective Study, performed in Sweden, a program of diet plus regular exercise improved glucose tolerance in the active group, who had a lower rate of progression to type 2 diabetes (11 versus 29%).[15] The Finnish Diabetes Prevention Study, patients with impaired glucose tolerance (mean age 55 years, mean BMI 33.2) assigned to a weight-reduction and exercise program[16] lost 3.5 kg (vs 0.8 kg in the control group) and the cumulative incidence of diabetes was significantly lower in the intervention group (11 versus 23%). Similar results were obtained in the Diabetes Prevention Program (DPP).[17] In this study, 3,234 obese (average BMI 34 kg/m^2) subjects, with high risk for diabetes due to impaired glucose tolerance, were randomly assigned to one of the following groups: 1) Intensive lifestyle changes through a low-fat diet and exercise for 150 minutes per week. 2) Treatment with metformin plus information on diet and exercise, 3) Control group with placebo plus information on diet and exercise. The diet and exercise group lost an average 7 percent of weight in the first year, most of which was sustained through the duration of the study. After 3 years, fewer patients in this group developed diabetes (14% versus 22% and 29% in the metformin and placebo groups, respectively). After 2.8 years follow-up, 58% reduction in metformin group was observed. Improvements in insulin sensitivity and insulin secretion, greatest in the intensive lifestyle intervention group, and somewhat lower in the metformin group, correlated directly with decreased risk of diabetes.[18]

Lifestyle intervention may also be effective in individuals without impaired glucose tolerance in the MRFIT.[19] In this large primary prevention trial, an intervention (advice on diet, exercise, giving up smoking, and intensive blood pressure treatment) in men at high risk for coronary heart disease was associated with a lower risk of type 2 diabetes in the nonsmokers.

But, although effectiveness of lifestyle intervention has been clearly demonstrated, the dietary and exercise changes may be difficult to implement in the real world. Long term compliance with dietary interventions has been poor, and new, less expensive strategies must be found to achieve long-term weight loss. The "real-world" implementation of lifestyle interventions is a challenge. The Good Ageing in Lahti Region (GOAL) Lifestyle Implementation Trial[20] was designed for the primary health care setting in Finland, with lifestyle and risk reduction objectives derived from the major diabetes prevention efficacy trials. A total of 352 middle-aged participants with elevated type 2 diabetes risk were recruited. The intervention included six group counseling sessions, delivered by nurses. At baseline, mean BMI was 32 kg/m^2, and 25% of the participants had impaired glucose tolerance. After 12 months, 20% of participants achieved at least four of five key lifestyle outcomes. Therefore, this trial demonstrates that lifestyle counseling can be effective and is feasible in real-world settings for individuals with elevated risk of type 2 diabetes.

Challenges and opportunities

Prevention of diabetes is crucial to lowering diabetes incidence, and thus minimizing the health burden. At the time of diagnosis, 50% of patients have microvascular complications (retinopathy, neuropathy or nephropathy) and twice the risk of macrovascular complications compared to the general population. Obesity is the most important modifiable factor, accounting for

more than half of new diabetes' cases.[21] Even modest weight loss has a favorable effect in preventing the appearance of diabetes. Also, physical exercise with or without diet contributes to a healthier lifestyle, and is important for lowering risk.[22] The best way to contain this epidemic is to screen for early detection, prevention and management of obesity, especially in younger individuals, before the development of type 2 DM. In table IV the American Diabetes Association recommendations for type 2 DM screening[23] are shown. Risk factors include family history, hypertension, obesity, sedentary lifestyle, smoking and hyperlipidaemia. Screening should be done for high risk individuals using fasting plasma glucose (FPG). An FPG <126 mg/dL (7.0 mmol/L) in an individual with a high suspicion for diabetes should be followed by a OGTT to confirm diabetes.

In 2010 the American Heart Association (AHA) announced its new Strategic Impact Goals: "by 2020, to improve the cardiovascular health of all Americans by 20% while reducing deaths from cardiovascular diseases and stroke by 20%".[24] The novel aspect of the 2020 goals is the promotion of "cardiovascular health", a new, positive approach to prevention of CVD, including smoking status, BMI, dietary content, participation in physical activity, and levels of blood pressure, blood glucose, and total cholesterol. Hopefully, these goals will imply a decrease in obesity, type 2 DM, and MetS.

Table IV
Recommendations for Screening for Pre-Diabetes and Diabetes

Testing should be considered in all adults who are overweight (BMI > 25 kg/m^2) and have additional risk factors:

- Physical inactivity
- First-degree relative with diabetes
- Members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- Women who delivered a baby weighing > 4 kg or were diagnosed with gestational diabetes mellitus
- Hypertension (>140/90 mmHg or on therapy for hypertension)
- Women with polycystic ovary syndrome
- HDL cholesterol level < 35 mg/dl and/or a triglyceride level > 250 mg/dl
- A1C ≥ 5.7%, impaired glucose tolerance or impaired fasting glucose on previous testing
- other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans polycystic ovarian syndrome)
- History of cardiovascular disease

In the absence of the above criteria, testing for pre-diabetes and diabetes should begin at the age of 45 years. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status

Conclusion

Diabesity and MetS have become a worldwide epidemic with a significant health and economic burden affecting both developed and developing countries. It seems possible to reduce the burden of diabetes. Clinical trials have convincingly shown that lifestyle modification is the most effective tool in the prevention or delay of type 2 diabetes. For overweight and obese patients, a modest weight-loss goal of 5-10% can substantially reduce diabetes risk. Moderate-intensity physical activity such as brisk walking for at least 150 minutes per week also plays an important role in reducing diabetes risk, even in the absence of weight loss. Therefore, prevention of diabetes should be a priority, and successful implementation of these proven strategies should be the focus of our efforts. We have a lot to do.

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Challenges in obesity research

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Abstract

Obesity is the main nutritional problem and one of the most important health problems in developed societies. Central to the challenge of obesity prevention and management is a thoroughly understanding of its determinants. Multiple socio-cultural, socio-economic, behavioural and biological factors —often interrelated and many of them still unknown or poorly understood— can contribute to the establishment and perpetuation of obese phenotypes. Here, we address current research challenges regarding basic aspects of obesity and emerging science for its control, including brown adipose tissue thermogenesis and browning of white fat as possible therapeutic targets for obesity, the influence of the microbioma, and genetics, epigenetics, nutrigenomics and nutrigenetics of obesity. We also highlight hot topics in relation to food and lifestyle as determinants of obesity, including the brain mechanisms underlying environmental motivation to eat, the biological control of spontaneous physical activity, the possible role of concrete foods and food components, and the importance of early life nutrition and environment. Challenges regarding the connections of obesity with other alterations and pathologies are also briefly addressed, as well as social and economical challenges in relation to healthy food production and lifestyle for the prevention of obesity, and technological challenges in obesity research and management. The objective is to give a panoramic of advances accomplished and still ahead relevant to the different stakeholders engaged in understanding and combating obesity.

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Key words: *Obesity. Research challenges. Body weigth.*

RETOS DE INVESTIGACIÓN EN OBESIDAD

Resumen

La obesidad es el principal problema nutricional y uno de los principales problemas de salud en las sociedades desarrolladas. Conocer y entender los determinantes de la obesidad es clave para conseguir prevenirla y controlarla. Múltiples factores sociales, económicos, culturales, conductuales y biológicos —a menudo interrelacionados y muchos todavía desconocidos o mal conocidos— pueden contribuir al establecimiento y mantenimiento de fenotipos obesos. Aquí destacamos retos en relación con aspectos básicos de la obesidad y ciencia emergente para su control: la termogénesis en el tejido adiposo marrón y el "pardeamiento" *(browning)* de la grasa blanca como posibles dianas anti-obesidad, la infuencia del microbioma, y la genética, epigenética, nutrigenómica y nutrigenética de la obesidad. También destacamos temas abiertos en relación con la alimentación y el estilo de vida como determinantes de la obesidad, incluyendo los mecanismos neuronales que subyacen a la motivación a la ingesta por claves ambientales, el control biológico de la actividad física espontánea, el posible papel de alimentos y componentes concretos de alimentos, y la importancia de la alimentación y el ambiente en etapas tempranas de la vida. Nos referimos asimismo a los retos en relación con la conexión de la obesidad con otras alteraciones y patologías, los retos sociales y económicos en relación con el estilo de vida y la producción de alimentos saludables para la prevención de la obesidad, y los retos tecnológicos en la investigación y tratamiento de la obesidad.

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Palabras clave: *Obesidad. Retos de investigación. Peso corporal.*

Abbrevations

BAT: brown adipose tissue.
BMI: body mass index.
BRITE: brown-in-white.
GWAS: genome-wide association studies.
SNP: single nucleotide polymorphism.
UCP1: uncoupling protein 1.
WAT: white adipose tissue.

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Introduction

Obesity is the main nutritional problem and one of the most important health problems in developed societies. In fact, combating obesity constitutes a primary health objective, since many alterations and pathologies related to diet and lifestyle associate with obesity,

and strategies and treatments for obesity control have proved quite inefficient to date. The issue is complicated, most probably, by the fact that we are dealing with a set of "obesities", rather than with a single condition, since the aetiology of obesity can be very diverse.

Main challenges in relation to obesity relate to key aspects including its causes and mechanisms, the physiological processes affected, and possible treatments and preventive measures, and the definition of the main objectives to face for progress in these areas in upcoming years (fig. 1). These objectives can be grouped in 6 main blocks, which are very much interrelated and include many collateral aspects:

1) Basic aspects of obesity and the strategies for its control.
2) Food and lifestyle as determinants of body weight and its alterations.
3) The connections between obesities and associated clinical alterations and pathologies.
4) Social challenges in relation to environment, lifestyle and the prevention of obesity .
5) Economical and business challenges in relation to healthy food production and the improvement of diet.
6) Technological challenges in obesity research and management.

Here, we will try to define main challenges and research objectives in each of these blocks, with special focus on specific aspects that are being studied in our research group.

Basic aspects of obesity (causes, mechanisms, biochemical processes involved) and emerging science for its control

Central to the challenge of obesity prevention and management is a thoroughly understanding of its causes. Obesity can be most simply defined as the presence of excess body fat as adipose tissue and it is ultimately caused by chronic energy imbalance whereby energy intake exceeds energy expenditure. However, multiple endogenous and exogenous factors, i.e., a variety of socio-economic, socio-cultural, behavioral and biological factors —often interrelated and many still unknown or poorly understood— can contribute to the establishment and perpetuation of obese phenotypes reflecting this imbalance.

Biochemically speaking, the level of fat reserves in mammals depends on the interplay between several interconnected processes, including the control of feeding behaviour, energy expenditure, partitioning of nutrients among tissues and anabolic *versus* catabolic

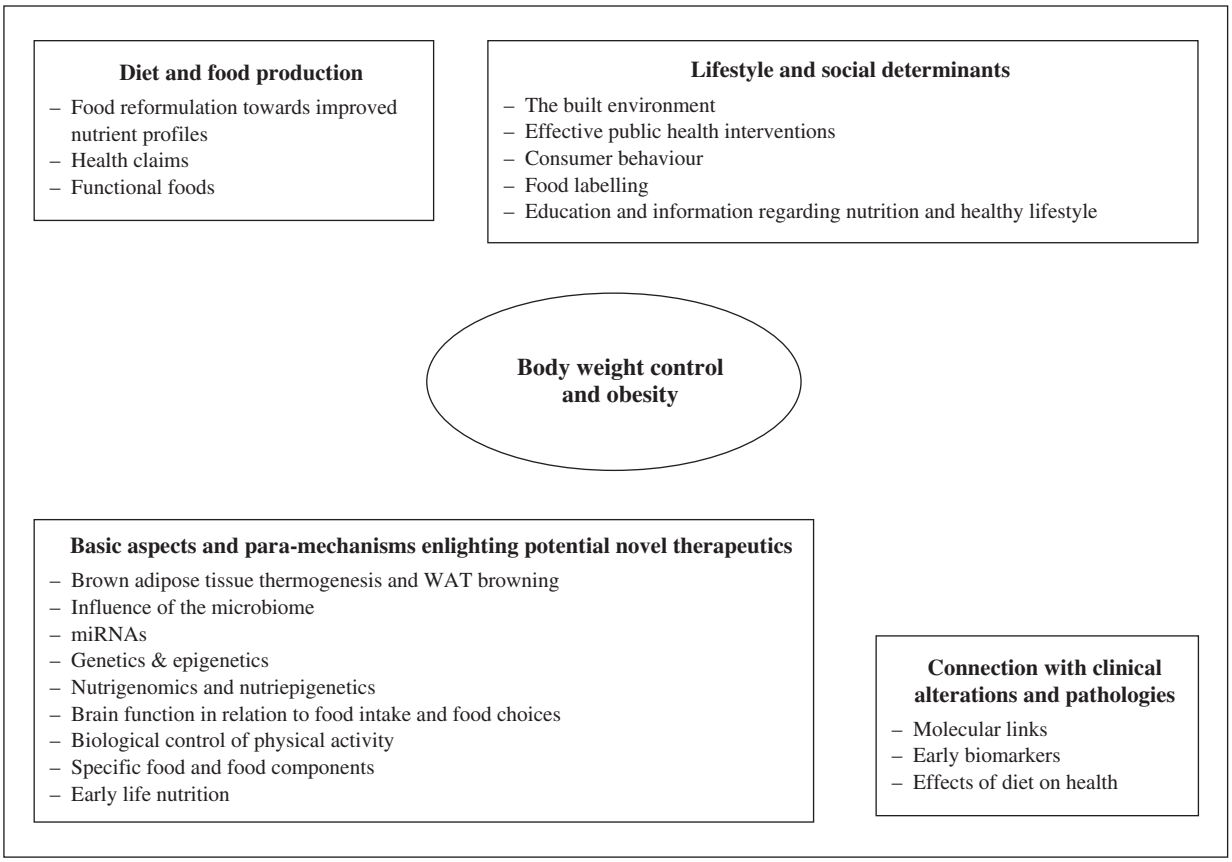

Fig. 1.—Key issues and challenges in the control of body weight and obesity.

pathways, and on-going processes within fat depots determining adipocyte number (e.g., preadipocyte proliferation, adipocyte differentiation, adipocyte apoptosis).[1] Each of these processes involves many signals, receptors, signal transduction cascades and downstream targets including metabolic enzymes, transport proteins, and additional regulatory factors. Alterations in key molecular elements of this complex system can favour a positive energy balance leading to obesity, as can subtle alterations in several "minor" elements, when presenting in a concerted way. These alterations can be inherited or acquired as a consequence of environmental expositions, particularly early life experience as part of developmental programming. Importantly, once identified, processes determining body fat and key molecular elements in them constitute new potential therapeutic targets for obesity management.

Brown adipose tissue thermogenesis and browning of white fat as therapeutic targets for obesity

The role of uncoupling protein 1 (UCP1)-mediated brown adipose tissue (BAT) thermogenesis in the regulation of energy balance and maintenance of body weight is well known in rodents. In adult humans, BAT has long been believed to be absent or negligible, but recent studies using fluorodeoxyglucose-positron emission tomography in combination with computed tomography demonstrated the existence of metabolically active BAT in healthy adult humans.[2] Intriguingly, functional and active BAT is inversely correlated with age and body mass index (BMI) in humans. Furthermore, in addition to purported regulatory roles of BAT in energy expenditure and body fat content, thermogenic BAT is a major site for lipid breakdown and glucose uptake, and there is recent evidence from animal studies that BAT controls blood triglyceride clearance[3] as well glucose homeostasis and insulin sensitivity.[4] These and other findings have suggested that BAT may be involved in the etiology of diabetes mellitus and dyslipidemias, independently of and/or secondly to obesity.

Another phenomenon long known for which there is a renewed interest nowadays is WAT-to-BAT remodelling or *browning* of white fat, which implies stimulating catabolic versus anabolic lipid metabolism and, eventually, UCP1 expression and function in fat depots traditionally considered white adipose tissue (WAT). Brown-like adipocytes —called "BRITE" (from brown-in-white) or "beige"— can be induced in WAT depots of rodents in response to appropriate stimuli. The origin of these cells, i.e. whether they result from trans-differentiation of pre-existing white adipocytes or from the recruitment of different resident precursor cells, is controversial. Regardless of this, available data from animal studies indicate that WAT browning can confer protection from obesity and related diseases and be induced by a variety of physiological, pharmacological and nutritional agents, as well as in response to certain targeted genetic manipulations[5]. Molecular mechanisms involved in WAT browning and their control constitute an active area of research. From these studies, synthetic chemicals and humoral factors able to induce BAT activation and/or WAT browning (many factors have proven to do both in animal models) can be designed/implemented. Alternatively, the possibility is envisaged to engineer synthetic brown adipocytes and BRITE cells *ex vivo* for autologous transplantation.[6]

Many research questions and challenges remain open in this area, among them: Does BAT function significantly impact energy balance and human obesity? What are the bases for the differences in BAT amount found among humans? What are the causes for the observed age-related decline in BAT activity in humans? What are the pathways linking BAT function to systemic insulin sensitivity and pancreatic beta cell function? What is the physiological significance if any of WAT browning in animals or humans? Is BAT activity or WAT browning activatable by dietary factors in a meaningful way? To what extent are pathways and factors involved in BAT development and WAT browning identified in animal research conserved in humans? What is the molecular signature of brown adipocyte and BRITE progenitor cell populations (this knowledge is a pre-requisite for cell-based therapies for the treatment of obesity and diabetes)? In addition, potential counterregulatory mechanisms (e.g., increased appetite) and side-effects (e.g. exaggerated heat production; ectopic body fat deposition) associated with anti-diabesity strategies based on activation of BAT or WAT browning should be rigorously considered. These are open questions that are being addressed by running projects such as the EU-funded DIABAT (http://www.diabat.org/).

Influence of the microbioma

Interest has surged in the last years regarding the possible role of the intestinal microbiota as potential novel contributors to the increased prevalence of obesity, metabolic syndrome, and type 2 diabetes. Mechanisms by which the gut microbiome may influence metabolism and energy homeostasis include regulation of energy uptake from diet, interaction with signalling molecules involved in host metabolism, modification of gut permeability, release of gut hormones, and low-grade, chronic inflammation, the latter being a hallmark of obesity-related diseases.[7] For instance, changes in the composition and metabolic function of the gut microbiota in obese individuals have been described which appear to enable the "obese microbiota" to extract more energy from the diet.[8] Additionally, various host pathways, mainly emanating from epithelial cells, have been characterized in the last years that might mediate the effects of microbiota on metabolism, including Fiaf, Ampk, Gpr41, Gpr43, Glp2, and the endocannabinoid system, among others.[9]

Recent advances in microbial DNA sequencing technologies have enabled the application of whole-genome sequencing technologies for metagenomic DNA analysis of complex ecosystems such as the human gut. Dietary factors and caloric intake appear to affect the composition of the gut microbiome, which also appears to be shaped by genetics and other environmental factors.[9] However, this research is still in its infancy. Additionally, most findings in the field of microbiome and obesity are based on rodent studies, and the relevance to human biology requires further investigation. Challenges are to gain a proper understanding of genetic and environmental influences on the microbiota and of the consequences of structural and functional changes within the microbiota on metabo-inflammatory diseases. It will also be important to reveal potential long-term consequences of antibiotic therapies at various ages of life, which could contribute to some forms of iatrogenic obesity.[9]

Genetics of obesity

Most cases of human obesity —aside from rare cases of monogenic obesity— are thought to be complex, i.e. to depend on genetic variation at several susceptibility loci (each entailing usually only a modest effect *per se*), with a variable contribution from environmental factors such as diet and physical activity.

The field of the genetics of obesity was dominated till 2006 by candidate gene studies examining the association of concrete polymorphisms (usually single nucleotide polymorphisms, SNPs) in one or a few *candidate* genes with obesity and/or obesity-related phenotypes such as BMI or percent body fat as continuous traits.[10] Candidate genes are those with higher prior probability for phenotypic involvement on the basis of different criteria including biology, pharmacology, transgenic and knockout murine models relevant to obesity, and positional information, among others. These studies resulted in the suggestion of numerous *obesity* genes (at least 127), related for instance to the central regulation of energy balance, adipogenesis, lipid turnover, adaptive thermogenesis, and signaling by insulin and other extracellular signals impinging on energy metabolism.[11] However, none of these genes or combinations could be firmly validated, usually due to inadequate statistical power of the studies and insufficient biological and genomic knowledge. Since 2006, genome-wide association studies (GWAS) have been implemented which allow scanning the entire genome for common disease-associating SNPs in a hypothesis-free manner in large cohorts of familial-unrelated people, and are ideally suited to detect common (frequent) variants with small effect sizes. These unbiased, powerful studies have allowed the identification of about 40 loci related to human obesity, among which the fat mass and obesity associated gene (FTO) is the most replicated and the one showing the highest statistical significance.[12]

Complete understanding of identified associations in either candidate gene or GWA studies is often hampered by lack of data on the specific functional significance of the polymorphism(s) under investigation. Functional assessment remains a challenge in many instances, especially for variants located in non-coding areas of the genome including intronic or intergenic regions, which could either be linkage disequilibrium markers of the causal variants or true causal variants influencing for instance gene function or transcript regulation. The vast majority of obesity susceptibility variants identified in GWAS lie in non-coding regions.[12]

Additional challenges come from the fact that the contribution of a given SNP to obesity/adiposity can be modulated by the presence of other SNPs in the same gene or other genes. Therefore, the influence of haplotypes (comprising specific combinations of genetic polymorphisms in a single allele) and gene-gene (epistatic) interactions need to be considered. Epistatic interactions relevant for obesity development are largely unknown and yet to be analysed and mapped in a systematic way, using appropriate tools.

Importantly, despite the advances in the genetics of obesity, the combined effect of all loci identified so far account for only about 2-4% of the total heritability of common forms of obesity (estimated to be between 40-70%).[12] These numbers confirm the complex nature of obesity and the challenge to identify additional factors that may unravel some of the missing or hidden heritability of obesity. Such factors may include interactions between multiple genes and environmental factors (see the heading on Nutrigenomics below)[12] and the contribution of other types of variants not covered by current GWAS design, including low-frequency and rare variants, copy number variations and epigenetic modifications.[12] The latter may also be part of the mechanisms by which the environment could induce biological changes with lasting effects on obesity-related parameters (see next).

Epigenetics of obesity

Epigenetics refer to mitotically heritable modifications that regulate gene activity and/or expression rather than its DNA sequence.[13] Epigenetic marks are tissue specific and include, though are not limited to, DNA methylation and histone modifications. Epigenetic marks can be programmed already in the intrauterine environment and can be modulated by environmental influences including diet, besides genetic influences.[14] The epigenome is thus seen as a malleable interface between the environment and the genome. Changes in the epigenome at critical developmental stages can be shaped by the environment and have long-lasting effects affecting health and susceptibility to disease in later life, including obesity and metabolic syndrome.[10]

To what extent epigenetic modifications contribute to the above findings and to the total heritability of com-

mon forms of obesity is presently unknown. However, several lines of evidence suggest their contribution. At least one "obesity gene" codes for an enzyme involved in the control of epigenetic marks (the FTO locus, encoding a DNA-demethylase enzyme[15]), while genetic disruption of one of such enzymes (the histone H3k9-specific demethylase Jhdma2a) has been shown to result in obesity and hyperlipidemia in mice.[16] Many "obesity genes" critical to energy balance are regulated by epigenetic mechanisms depending on nutritional clues. Examples are the MC4R gene, which has reduced methylation in the brain following long-term exposure to a high fat diet in mice;[17] the POMC gene, whose promoter methylation in the hypothalamus is sensitive to early overfeeding[18] and, more specifically, to early leptin administration;[19] the leptin gene, whose promoter methylation in adipose tissue is modified by a high-fat diet;[20] and the PGC1a gene, whose promoter methylation in human umbilical cord and human muscle has been related, respectively, to maternal pregestational BMI[21] and to high-fat overfeeding in a birth-weight-dependent manner[22]. Finally, methylation at five candidate gene promoters at birth has been shown to be associated with child's later adiposity in humans[23].

Challenges regarding epigenetics of obesity include the translation of animal results to humans while dealing with the great tissue specificity of epigenetics marks (relevant tissue samples may be inaccessible, such as brain samples) and the integration of genetic and epigenetic information, for instance, linking the causally unexplained GWAS association signals with epigenetics and even further, at a large- scale genome —wide level.

miRNAs and obesity

MicroRNAs are endogenous small non-coding RNAs involved in the post-transcriptional regulation of gene expression by binding to complementary sequences often located in the 3' untranslated region of target mRNAs, leading to their translation repression or degradation. miRNas have been widely implicated in the fine-tuning of many physiological processes, including the pathogenesis of type 2 diabetes and obesity.[24] Microarray studies have highlighted an altered profile of miRNA expression in insulin target tissues in diabetic and obese models. Emerging evidences suggest that miRNAs play significant roles in insulin production, secretion and actions, as well as in diverse aspects of glucose homeostasis and lipid metabolism. They are also involved in many functional aspects of adipocyte differentiation and potentially contribute to the pathogenesis of obesity and its related medical complications. The identification of tissue-specific miRNAs implicated in type 2 diabetes and obesity might be useful for the future development of effective strategies for early diagnosis and therapeutic intervention of obesity-related medical complications.

Nutrigenomics and nutrigenetics of obesity

Nutrigenomics studies the links and interrelationships among diet, genetic makeup, and physiological responses, at a genome-wide level and in a systematic manner. From a nutrigenomics perspective, particular nutrients, non-nutritive food components, or nutritional regimes are dietary signals that are detected by cellular sensor systems that influence gene and protein expression and, subsequently, metabolite production.[25] Nutrigenomics attempts to study these "dietary signatures" in specific cells, tissues and organisms to understand how these signals influence homeostasis and thus, regulate health and the progress of diet-related chronic diseases, such as obesity and metabolic diseases. Features of such signatures are being investigated as biomarkers of early disruption of homeostasis, of interest in the context of public health strategies (disease prevention) as well as a basis for the substantiation of novel health claims made on food. This is the focus of a large collaborative EU funded project currently under development, BIOCLAIMS (http://bioclaims.uib.es/).

Nutrigenomics is very relevant for understanding obesity as well as the links of obesity with associated diseases. Dietary chemicals interact with the biochemical processes involved in the control of body fat (hunger and satiety, intestinal nutrient absorption, BAT thermogenesis and WAT browning, fat oxidation, lipogenesis), as well as with inflammation and stress pathways. Furthermore, specific food chemicals have been shown to ameliorate obesity in animals by molecularly defined mechanisms.[5,26,27] This knowledge has led to the proposal of nutritional strategies (functional foods or nutraceuticals) for weight management based on selected traditional foods (containing functional ingredients) or novel foods, although current knowledge in this area is based largely on animal and cell studies, with limited evidence from well designed, human intervention studies. The latter remain a challenge for most "anti-obesity" foods/compounds proposed so far (ethical considerations might be a limiting factor for such studies).

Nutrigenomics core concepts also imply that the individual genetic background can influence nutrient status, metabolic response to nutrients/diets and predisposition to diet-related diseases. This is at the foundations of Nutrigenetics, which has many implications in the field of obesity. Not everyone becomes overweight or obese in an obesogenic environment, suggesting that there are genetic or acquired factors interacting with actual environmental factors to predispose some individuals to obesity. Gene-environment interaction can also influence the outcome of weight-loss programs and weight-management strategies in overweight and obese subjects.[28,29] Not only SNPs in obesity-related genes may play a role; "metabotypes", i.e., an individual's distinct metabolic response to a specific intervention (e.g., calorie restriction), alone or in combination with genotypes, may also be a good predictor of personal outcomes.[30]

Ultimately, Nutrigenetics has the potential to provide, at least in part, the rationale for personalized dietary recommendations based on the individual's genetic constitution and biochemical individuality, to prevent and manage obesity and other diet-related diseases with maximal efficacy, and from an early stage. However, many challenges persist. Adequate statistical power is extremely hard to achieve in gene x environment interaction analysis, and better tools for the comprehensive and reliable capture of diet and other environmental exposures in timely and economically feasible approximations that can be effectively used in large-scale genetic epidemiological studies such as GWAS are needed.[12] Furthermore, the large majority of Nutrigenetics studies published so far have examined interactions in a simple scenario, in which single (or a few) dietary component and single (or a few) genetic polymorphism is/are analyzed in relation to well-defined single health outcomes/traits. Each individual possesses potentially hundreds of "at-risk" gene variants and consumes a highly-complex diet. Understanding gene x diet interactions and their relationship with health in general (or a range of relevant health outcomes) at a genome-wide level remains a big challenge, requiring strong investment, post-genomic approaches and adequate mathematical and bioinformatic tools.

Food and lifestyle as determinants of body weight control and its alterations

The increased availability and accessibility of palatable, energy dense foods and the reduced requirement for physical exertion during working and domestic life are usually seen as the two most critical factors underlying the obesity pandemic. However, food intake and physical activity behaviors might not always be a matter of conscious choice, and understanding causal pathways for them remains a challenge in obesity research. These aspects, together with the possible contribution to the current obesity pandemics of concrete food components, diet at critical developmental periods, and lifestyle factors other than total daily energy intake and physical activity are briefly addressed next.

Environmental and psychological factors as determinants of food intake

The brain plays a central role in the control of food intake and energy balance by coordinating on-going information about the quality and quantity of calories being consumed (mainly via satiation signals), the levels of fuels already in the plasma (via direct sensing by specialized cells in the brain and elsewhere), and the amount of energy present in the various storage depots (via adiposity signals, such as insulin and leptin).[31] However, factors unrelated to energy balance such as where and when food might be available, relevant aspects of the social situation, memory for key relevant information from past experiences (learned cues), and hedonic factors, among others, also control appetite and eating and are computed by the brain. One fundamental question in obesity research is to decipher the brain mechanisms underlying environmental (non-physiological) motivation to eat, and how these mechanisms are integrated with the physiological regulatory control of food intake.[32]

Limited investigations in obese subjects show that obesity is associated with alterations in neural and behavioural mechanisms of food reward and parallels have been drawn between drug and food addiction.[33] Internal mechanisms may favor neurophysiologic responses to food cues that result in overconsumption in a context of food abundance and food salience (through marketing and advertising).[34] This investigation is, however still in its infancy. It is unclear, for instance, whether genetic and other pre-existing differences in reward functions cause obesity, or if the obese state secondarily changes reward mechanisms, perhaps to contribute to accelerate/ perpetuate obesity, or both.

How is spontaneous physical activity determined?

Many environmental cues may play a role in determining voluntary exercise and spontaneous physical activity —defined as to include all energy expended due to activity, exclusive of volitional exercise and also called non-exercise activity thermogenesis— in the individual. These cues interact with a biological control of these activities, which remains poorly understood (reviewed in[35]). An important role of dopamine, in addition to other neural signalling networks (e.g. the endocannabinoid system), in the control of voluntary exercise has been proposed. Other reports point to a key role for orexins in the control of spontaneous physical activity. Brain reward centers are involved in both types of physical activities and eating behaviours, likely leading to complex interactions. Moreover, like eating, voluntary exercise can be addictive. Genes are being identified whose sequence variants have been associated with either the level of physical activity or indicators of sedentarism.[35,36] Future studies should explore the neurobiology, endocrinology and genetics of physical activity and sedentary behaviour by examining key brain areas, neurotransmitters and hormones involved in motivation, reward and/or the regulation of energy balance, as well as in the intertwined control of physical activity and eating.[35, 37]

Is there a role for specific foods or food components?

It has been speculated that not only overall excess energy intake but also excess of particular nutrients/foods may play a role in the aetiology of obesity. In particular, a role for fructose and fructose-derived sweeteners

(sucrose, high-fructose corn syrup in beverages) has been proposed, although the issue remains controversial.[38,39] Increasing intake of the omega 6 fatty acid linoleic acid has also been associated to obesity in both humans and rodents, through mechanisms that appear to include proadipogeneic effects,[40] and an elevation of the endocannabinoid tone (which is overall anabolic, increasing food intake, and causing increased lipogenesis and fat storage in adipose tissue and liver).[41] The specific role for leptin[42] and other nutrients in breast milk protecting from the development of overweight and obesity later on in life have been described (see next).

Early life nutrition and obesity in adult life

Epidemiological studies in humans and controlled intervention studies in animals have shown that nutrition in early periods of life programs a number of metabolic and physiological functions throughout life.[43] In this sense, gestation and lactation are disclosed as critical periods. Continuous food restriction during these stages, for instance, may lead to permanent adaptations with lasting effects on offspring metabolic mechanisms; they may alter the propensity to different chronic diseases, such as obesity and other features of the metabolic syndrome. However, the different outcomes of these adaptations on later health appear to depend on factors such as the type, duration, period and severity of the exposure to energy restriction conditions, and they are, at least in part, gender specific. A better understanding of the factors and mechanisms involved in metabolic programming, and their effects, may contribute significantly to the prevention of obesity.[43]

Mechanisms involved in developmental programming of obesity may include epigenetic changes (see previous section) and effects on the development of anatomical structures crucial to the control of energy balance and storage, such as regulatory brain centers[44] and the adipose depots themselves[45]. Many studies have addressed the role of calorie restriction, total energy intake and diet macronutrient composition during gestation or lactation in this programming.[43] Studies dealing with the impact of concrete nutrients and signals on the metabolic programming of obesity are less represented. Important effects in this sense have been confirmed experimentally for leptin,[42] nutrients known to participate in methyl transfer epigenetic reactions,[46] leucine,[47] vitamin A,[48] and maternal dietary fats.[40,49] A challenge in this area is the translation of results to humans in studies of sufficient duration so as to catch medium and long-term effects.

The discovery of the new role of leptin intake during lactation as an essential nutrient during this period appears paradigmatic, as it deals on a protein which is present in breast milk but not in infant formula, and whose lack during lactation may be responsible for a number of obesities. The impact of the changes from breast-fed to formula fed needs further assessment.

Evidence for the essential role of leptin during the suckling period has been obtained from both animal and human studies. Firstly, studies in rats have shown that the intake of physiological doses of leptin during the suckling period prevents the animals from overweight and obesity and other metabolic alterations associated with feeding a high-fat diet during adulthood.[42,50,51] In addition, leptin treatment during lactation has lasting effects on the expression of the hypothalamic factors involved in the control of food intake, particularly POMC, leptin receptor and suppressor of cytokine signaling 3 (SOCS3).[42] Thus, leptin appears important during the lactation period in both regulating neonate food intake and affecting the developmental events involved in the control of energy balance in adulthood.[52] In addition, leptin during the suckling period has also been shown to program a better response of the adipose tissue under high fat diet conditions, by preventing the decrease of leptin receptor in internal depots and increasing the oxidative capacity of this tissue.[51] Therefore, leptin may exert regulatory effects, not only at a central level, but also peripherally. Interestingly, indirect evidence of the role of breast milk leptin during lactation in humans has also been obtained[53-55] and intervention studies should be performed to allow the inclusion of leptin in infant formulae to prevent a number of potential obesities.

Other lifestyle factors and a variety of incidents or circumstances impacting along life

Other factors related to environment and lifestyle that have been related to the obesity pandemics and deserve further study include increasing maternal age, sleep debt, reduction in variability of ambient temperatures, and increased presence in the environment and the food chain of "obesogen" chemicals such as endocrine disruptors, which appear to have estrogenic or other hormonal effects and could be especially active on the developing embryos.[56]

In addition, there are a variety of factors or circumstances (fever, different illness, injuries, infections, emotional periods, hormonal alterations, alterations of biological rhythms, etc.) that can conceivably alter the homeostasis of important control systems in the body leading to changes in the predisposition to obesity, through mechanisms that currently are out of our knowledge.

The connections between obesities and associated clinical alterations and pathologies

Many alterations and pathologies related to diet and lifestyle associate with obesity, including insulin resistance, diabetes, hypertension, dyslipidemias, cardiovascular disease and non-alcoholic fatty liver disease, which together are hallmarks of the metabolic syndrome, but also osteoarthritis of weight and non-weight

bearing joints,[55] several types of cancer,[56] neurodegenerative and autoimmnune diseases such as Alzheimer's disease[57], and others. Biological mechanisms underlying the relationship between obesity and these alterations/pathologies begin to be understood, with inflammatory, oxidative and endoplasmic reticulum stress in critical tissues including the adipose and key humoral mediators playing in general a prominent role. The main challenge is to get further insight into the molecular and cellular mechanisms linking obesity to these different forms of stress, and the later to pathologies, with the aim of understanding the system and developing therapeutics.

Social challenges in relation to environment, lifestyle and the prevention of obesity

Improving communication on food habits and different aspects of lifestyle is a key issue. The efficacy of public health messages to individuals to inform their lifestyle choices should be complemented, and thus enhanced, by environmental changes that facilitate healthy options. Education and information campaigns are an important mechanism for improving consumer understanding of food information.

The ultimate goal is to shape the physical and social-cultural food environment and improve education to facilitate people in making healthy food and lifestyle choices for effectively combating obesity and other diet-related diseases.[57] Many things can be done, and are being done around the world in this sense: architectural and urban design policies; legislative measures (e.g., taxes to certain foods, control of vending machines at schools); control on aggressive advertisement, especially to children; governmental educational campaigns to promote a healthy body weight; promotion of breastfeeding and of healthy pre(pregnancy) foetal and infant nutrition; school nutrition and physical education policies; interventions at the family, school, community, and population level, etc… The challenge is to understand the most effective ways to accomplish the goal. Studies on how individual, social, economic, cultural, gender and environmental factors affect dietary and physical activity behaviours are needed to help designing successful initiatives. Tools for evaluating the impact of institutional campaigns, legislative measures and interventions undertaken are also required.

Food labelling, in particular, has been the target of some interesting developments in Europe. The Commission White Paper of 30 May 2007 on a Strategy for Europe on Nutrition, Overweight and Obesity related health issues noted that nutrition labelling is one important method of informing consumers about the composition of foods and of helping them to make an informed choice. Knowledge of the basic principles of nutrition and appropriate nutrition information on foods would contribute significantly towards enabling the consumer to make such an informed choice. Considerable progress in Europe has been attained with the Regulation (EU) Nº 1169/2011, which will be largely in force in December 2014.

However, there are many other factors that can influence psychological and behavioural responses of the consumers. Key aspects related with the communication to the consumers of the "health-promoting" properties of foods have been addressed in recent EU legislation (see next section). However, the impact of communication on other aspects (cosmetics, biomedical devices, tools, etc.) needs further attention.

Scientists have a responsibility to provide the evidence base, on which to build policy and practice, but a range of other stakeholders, including governments, manufacturers and retailers, employers, schools, health professionals and parents, must each recognise their role and responsibilities. Effective communication between all parties is essential to build a national framework that facilitates the necessary changes in lifestyle.[58]

Economical and business challenges in relation to healthy food production and the improvement of diet

The food industry is faced with the challenge of producing tasty foods that are consistent with health status and lifestyle, and which meet consumer preferences, and to do it in a cost-effective and sustainable way.[57] This requires research and investment to develop reformulated food products with improved nutritional or nutrient profile, as well as functional food products with optimised levels of bioactive components. Incentives for such investment might be needed coming from outside the market, including protection of exploitation rights when novel food developments and claims are achieved.

Many functional foods and nutraceuticals for body weight control have been proposed which target food intake (by inhibiting hunger, stimulating satiety or limiting the bioavailability of nutrients), caloric content of foods (by including less caloric or less digestible substances substituting for sugars or fat), body composition or non-conscious energy expenditure (by stimulating thermogenesis). With the progress in Nutrigenomics and Nutrigenetics (see corresponding section above), new developments in the functional foods arena are envisaged shaped to specific groups of consumers. However, so far supportive human studies are scarce and, when available, the weight loss observed is small and should be considered mostly as a measure to prevent weight gain, or as co-adjuvant in more strict regimens. Properly designed human intervention studies and knowledge on the mechanism of action of food bioactives is required in order to support evidence based health claims.

The impact of the implementation in Europe of the Regulation (EC) No 1924/2006 that harmonises the provisions that relate to nutrition and health claims and

establishes rules governing the authorisation of health claims made on foods may be important in the following years. According to the Regulation, health claims should only be authorised for use in the Community after the European Food Safety Authority (EFSA) has carried out a scientific assessment of the highest possible standard. Moreover, article 21 of this Regulation protects the investments to obtain scientific data and other information required to substantiate a claim by stating that they may not be used for the benefit of a subsequent applicant for a period of five years from the date of authorisation, unless the subsequent applicant has agreed with the prior applicant that such data and information may be used. This clearly promotes R&D investments in the food sector. Among the health claims specified in this legislation are those related with overweight/obesity: *"health claims describing or referring to slimming or weight-control or a reduction in the sense of hunger or an increase in the sense of satiety or to the reduction of the available energy from the diet"*.

Regulation (EC) No 1924/2006 includes the provision that only those foods having an "appropriate nutrient profile" will be allowed to bear health claims. This provision – that would affect mainly the composition of saturated fat, salt and simple sugars— has not been implemented yet, due to its huge economic impact and related controversy. However, it is already producing deep changes in the food sector in Europe by stimulating food reformulation, which is also the subject of other initiatives over the world.

Technological challenges in obesity research and management

Genome-wide understanding of the genetics, epigenetics and nutrigenomics of obesity and the influence of microbiome largely depends on advances in mathematical modelling, bioinformatics and computational analysis, enabling interpretation and data meaning from high throughput analysis of genomes, metagenomes, transcriptomes, proteomes and metabolomes and the comparison between them in systems biology approaches. In parallel, there is also a need for better, feasible tools to capture and quantify diet and the "exposome", for use in large scale genetic epidemiological studies of obesity, such as GWAS, and devices enabling the control of energy expenditure in humans under free living conditions. The development of imaging technologies in relation to hunger, satiety, food preferences, taste perception and heat production applicable to human studies is also seen as a challenge in obesity research, as well as the development of novel non-invasive or micro-invasive techniques for tissue composition analysis and the provision of tissue biopsies for omics studies.

Technological solutions to obesity may include new drugs that do not have the side-effects and limited efficacy of current treatments. However, the relatively high costs, possible risks and lack of societal acceptability mean the use of medicines alone is not a long-term sustainable solution. Other technology to support healthy behaviours is envisaged, such as devices to monitor and provide feedback on energy intake and energy expenditure, along with biomarkers of health and functional status.

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