Executive summary

The International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) convened a Working Group meeting in Lyon in December 2015 to review the evidence regarding energy balance and obesity and to consider the following scientific questions:

- Are the drivers of the obesity epidemic related only to energy excess and/or do specific foods or nutrients play a major role in this epidemic?
- What are the factors that modulate these associations?
- Which types of data and/or studies will further improve our understanding?

This IARC Working Group Report provides summaries of the evidence from the literature as well as the Working Group's conclusions and recommendations to tackle the global epidemic of obesity.

A summary of the topics addressed and the conclusions and recommendations of the Working Group has been published in *Cancer Causes & Control* [1].

Prevalence of overweight and obesity

Obesity is now well recognized as a disease in its own right, one that is largely preventable through changes in lifestyle, especially diet. Obesity is also a major risk factor associated with increased morbidity and mortality from many noncommunicable diseases (NCDs). Obesity has increasingly been considered to be a life-course condition, with its roots being established during pregnancy and with an intergenerational cycle, overlapping with the secular trend.

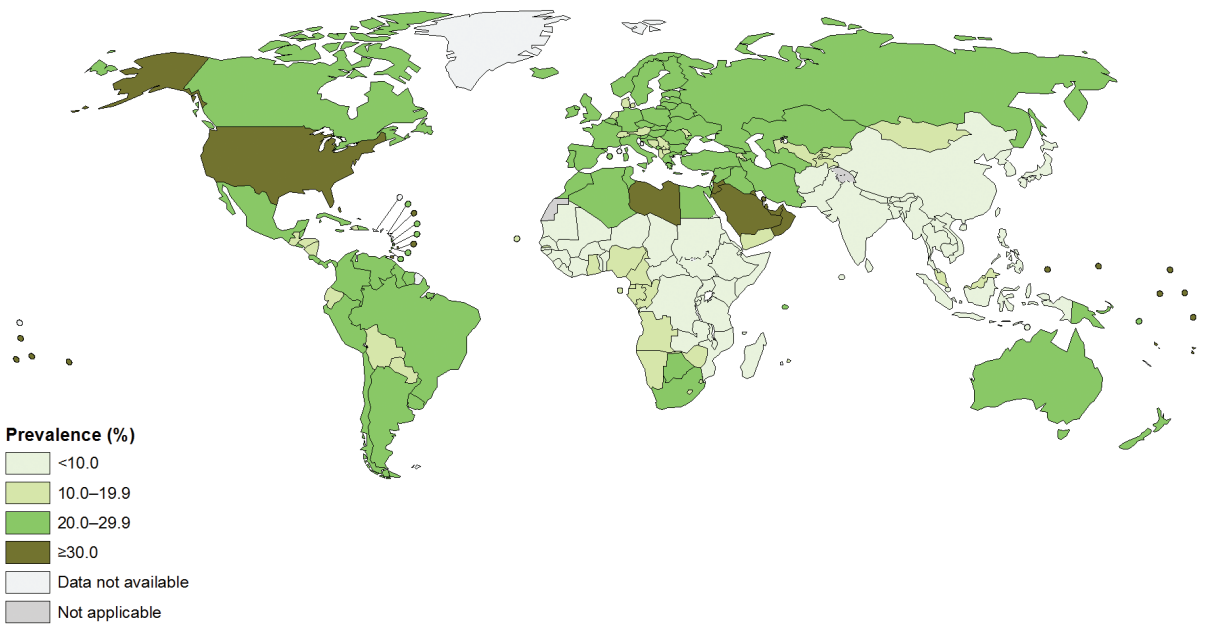
Obesity rates have been constantly increasing during the past 30 years. The worldwide prevalence of obesity in adults nearly doubled between 1980 and 2014 [2]. In 2014 there were 41 million overweight children younger than 5 years in the world, about 10 million more than there were in 1990. In 2014, almost half of all overweight children younger than 5 years lived in Asia, and one quarter lived in Africa. The number of overweight children in lower-middle-income countries has more than doubled since 1990, from 7.5 million to 15.5 million [3].

In 2014, 39% of adults aged 18 years and older (38% of men and 40% of women) were overweight. The prevalence of obesity in high-income countries (HICs) and upper-middle-income countries is more than double that in low-income countries (Fig. 1), and an increasing number of countries are affected.

The double burden of malnutrition

The double burden of malnutrition is the coexistence of undernutrition (including macronutrient and micronutrient deficiencies) and overnutrition in the same population across the life-course. In most regions, undernutrition and overnutrition coexist in the same country, in the same community, or even in the same household.

Fig. 1. The prevalence of obesity (body mass index ≥ 30 kg/m^2) in adults aged 18 years and older, for both sexes, in 2014 (age-standardized estimates). Source: WHO Global Health Observatory.



Although the prevalence of stunting and wasting in preschool children in low- and middle-income countries (LMICs) has declined, the rapid rise in rates of overweight/obesity in both children and adults is striking. The hidden hunger index indicates persistent problems. Hot spots and severe problems have been found in most countries in sub-Saharan Africa and South Asia and in some countries in South-East Asia.

Rapid economic development and urbanization in LMICs have resulted in rapidly changing dietary patterns. Increasingly, there is a shift away from traditional plant-based diets to less-nutrient-dense diets with consumption of highly processed foods and sugar-sweetened beverages, with a simultaneous reduction in physical activity levels across all ages. For many LMICs, government policy does not address these drivers of the double burden of malnutrition. Hence, many LMICs face a triple burden of malnutrition, with persistence of undernutrition, micronutrient deficiencies, and overnutrition, and the resulting rapidly increasing rates of obesity and related NCDs, including cancer.

The nutrition transition in LMICs provides an important opportunity to study the rapid changes in dietary patterns and physical activity levels, and to fill the gaps in our knowledge about whether these factors can explain the increases in cancer risk observed across different populations, so that programmes and policies can be strategically designed.

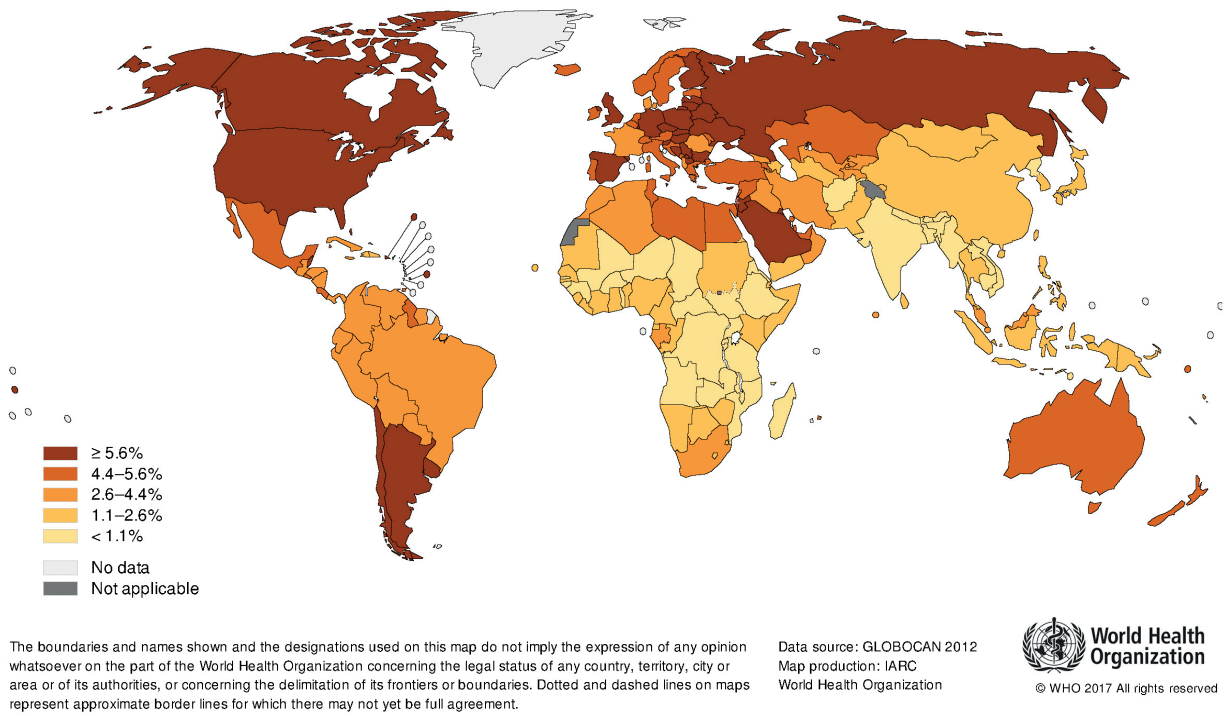
Obesity and cancer

The increase in the global burden of cancer may be explained partly by demographic changes; however, changes in lifestyle factors and globalization related to diet (increased consumption of highly processed foods and sugar-sweetened beverages) and increases in sedentary behaviour are also increasingly being recognized as major contributors to the rising prevalence of obesity and the increasing cancer burden.

The World Cancer Research Fund (WCRF) has reviewed the evidence linking diet, physical activity, body composition, and cancer worldwide in a systematic way [4]. From the WCRF review, there is convincing evidence for the role of obesity as a causal factor for several types of cancer, including cancers of the colorectum, endometrium, kidney, oesophagus, postmenopausal breast, gallbladder, and pancreas, and advanced prostate cancer.

A recent evaluation of the global cancer burden linked to obesity estimated that 481 000 or 3.6% of all new cancer cases in adults in 2012 were attributable to high body mass index (BMI) [5]. Cancers of the corpus uteri, postmenopausal breast, and colon accounted for

Fig. 2. The percentage of all cancer cases (at all anatomical sites) attributable to excess body mass index (BMI), for both sexes, in 2012. Source: Arnold et al. (2015) [31].



63.6% of cancers attributable to high BMI (about 10% of all cancers). Although the attributable burden was larger in HICs, high BMI appears to play a substantial role in Latin America, the Middle East and North Africa, and South Africa (Fig. 2). Furthermore, taking into account both current population mean BMI and the BMI changes over time, a larger increase in the population attributable fraction was observed in the Middle East and North Africa and in Latin America and the Caribbean, pointing to the importance of the cumulative effects of overweight and obesity in cancer etiology. Because there is a time lag between the development of obesity and the appearance of related comorbidity, it can be expected that the burden of obesity-related disease will increase markedly and will continue to do so for some time.

Recent progress in elucidating the mechanisms underlying the obesity–cancer link suggests that obesity exerts pleomorphic effects on pathways related to tumour development and progression. Therefore, there are multiple opportunities for primary, secondary, and tertiary prevention of obesity-related cancers. It is now known that obesity can affect each of the well-established hallmarks of cancer, but obesity-associated perturbations in systemic metabolism and inflammation, and the interactions of these perturbations with cancer cell energetics, are emerging as the primary drivers of obesity-associated cancer development and progression.

Interventions to prevent and control the rise in the prevalence of obesity are needed in order to control the rapid increase in the burden of NCDs, including cancer.

Energy intake and energy expenditure

Energy balance is the result of equilibrium between energy intake and energy expenditure. When energy intake exceeds energy expenditure, the excess energy is deposited as body tissue [6]. Such positive energy balance is a normal feature of growth during childhood, and of pregnancy, when accumulation of body tissue is physiological. During adulthood, the maintenance of stable body weight depends on the energy derived from food and drink (energy intake) being equal to the total energy expenditure over time.

Total energy expenditure is the sum of the basal metabolic rate, the energy expended in physical activity, and the energy expended in digestion of foods and absorption and assimilation of nutrients (diet-induced thermogenesis). The main determinant of the basal metabolic rate is the mass of lean tissue, and the main modifiable determinant of energy expenditure is physical activity. For weight loss, total energy expenditure must exceed energy intake, and for weight gain, energy intake must exceed energy expenditure [7].

Recommended levels of physical activity are about 30–60 minutes per day of moderate to vigorous activity [8, 9]. There is increasing evidence that time spent at very low activity levels (sedentary time) is important in energy balance and risk of NCDs, including cancer and cardiovascular disease, independent of the amount of moderate to vigorous activity [10–12].

Measuring dietary intake and energy expenditure is a challenge in epidemiology. In particular, assessment of energy intake sometimes has considerable measurement errors and may be subject to selection biases, such as the tendency of overweight and obese people to underestimate their intake. Although some objective measures exist for assessing energy expenditure or physical activity, such tools are not available for energy intake. Thus, assessment of energy balance by calculating the difference between intake and expenditure is not practically useful.

Over time the best marker of positive or negative energy balance is *change in body weight*. However, because change in body weight cannot distinguish between loss or gain of lean or fat mass, in the absence of specific measures of body composition, interpretation of weight change in an individual rests on assumptions about the nature of tissues lost or gained, i.e. the relative proportions of lean and fat tissue [13]. However, for most people, weight gain during adulthood is driven largely by gain in fat mass, and therefore change in body weight is a highly useful measure of medium- to long-term energy balance.

Measurement of adiposity

Several measures of overweight and obesity have been used in epidemiological studies. However, it is important to be aware that such measures are imperfect markers of the internal physiological processes that are the actual correlates of cancer development.

BMI (defined as the quotient between weight in kilograms and height in metres squared) is the most commonly used marker of body composition in epidemiological studies, because of the simplicity of assessment and the high precision and accuracy. However, it does not differentiate between lean and adipose tissue or take into account fat distribution, which varies across individuals, among ethnicities, and throughout the lifespan. Waist circumference and waist–hip ratio are useful tools to identify abdominal obesity but cannot clearly differentiate between visceral and subcutaneous fat compartments [14, 15].

Other measures that can be used in medium- or large-scale studies include skin-fold thickness and bioelectrical impedance analysis. More direct measures of body composition are available, such as air displacement plethysmography, underwater weighing (hydrodensitometry), dual-energy X-ray absorptiometry, ultrasonography, computed tomography, and magnetic resonance imaging [16, 17]. Although these methods are highly reproducible and valid [18], because of high costs and lack of portability, their use is limited to small-scale studies that require a high level of accuracy. Their use in large-scale epidemiological studies tends to be as reference methods [19].

Determinants of obesity

Factors that influence energy balance can be considered as relating to the host (i.e. people), the environment (i.e. the set of external factors to which people are exposed), and the vector (i.e. foods and drinks). These factors interact in a complex way to influence eating and drinking patterns as well as activity behaviours. Although these factors are experienced at the individual level as the acceptability, availability, and affordability of foods, drinks, and activity behaviours, their roots lie in policies and actions that determine the environment, which may be local, national, or international [20]. Such factors include food and drink prices (and relative prices) in relation to people's economic status, cultural and socioeconomic factors, availability of foods, different levels of food processing, advertising and marketing of foods and drinks, and the type and amount of options for eating meals outside the home, as well as the impact of the urban environment on the likelihood of people adopting active behaviours during everyday life.

For any individual, constitutional factors – genetic and/or arising from early-life exposures – can determine the degree of susceptibility to obesity [21, 22]. Apart from these largely non-modifiable factors, other characteristics may influence energy balance – in particular, the amount of energy expended in physical activity. Increasing energy expenditure might be expected not to influence energy balance, because of appetite control mechanisms that feed back and tend to maintain balance. However, there is evidence that at the low levels of activity characteristic of many HICs and increasingly of LMICs, this feedback operates imperfectly and does not suppress appetite to the low levels necessary to maintain energy balance [23].

Many factors relating to the foods and drinks consumed have been shown to influence the amount consumed or energy balance over the short to medium term, such as energy density and portion size [24, 25]. Long-term (> 1 year) experimental data on prevention of weight gain suggest that the change in body fatness that occurs when intake is modified appears to be mediated

via *changes in energy intakes* and that intake of naturally occurring fat does not have a significant impact on obesity [26]. In weight-loss trials, low-carbohydrate interventions led to significantly greater weight loss than did low-fat interventions [27]. Other aspects of diet quality, such as the degree of processing, have important effects on long-term weight gain [28, 29], presumably mediated primarily by influencing satiety and energy intake.

In addition, dietary habits and the physiology of the host influence the intestinal microbiota, and dysbiosis (an imbalanced microbiota) has been linked to obesity [30].

Childhood obesity is an important contributor to adult obesity, diabetes, and NCDs. The trends in childhood obesity rates and the large variations in the rates and trends between countries provide useful insights into the drivers of the epidemic. Multiple biological, behavioural, family, and societal factors affect a child's risk of developing obesity. Because children are different from adults, special efforts are needed to help them develop healthy eating patterns and physical activity behaviours and maintain an optimal body weight. Although genetic factors play a role in affecting individuals' susceptibility to developing obesity, environmental factors should be the key targets of intervention efforts to fight the epidemic, because they are modifiable.

A major challenge is to capture life-course exposure and identify windows of susceptibility. The growth patterns of infants and children can be altered by early exposure to poor diet, increased consumption of sugar-sweetened beverages, physical inactivity, tobacco smoke, and other environmental exposures, and these factors may result in altered metabolism, obesity, and a high risk of chronic diseases in adulthood. However, adolescents are an understudied group and merit further attention.

Further work on birth cohorts or other prospective studies in LMICs is likely to provide additional insights into developmental causes of obesity and NCDs. Although prospective studies are an important area of research, as are nutrition surveillance, intervention, and implementation research, resources and expanded research capacity are of the highest priority. Input from local research communities, health ministries, and policy-makers and appropriate funding or resource assignment are critical for the success of new efforts in LMICs.

Conclusions and recommendations

The global epidemic of obesity and the double burden of malnutrition are both related to poor diet quality, and therefore improvement in diet quality can address both of these challenges.

The benefits of a healthy diet in terms of adiposity are likely mediated by effects of diet quality on *energy intake*, which is *the main driver of weight gain*. Energy balance is best assessed by changes in body weight or in fat mass. Measures of energy intake and expenditure are not precise enough to capture small differences that are of individual and public health importance. The quality of the diet may exert its effect on energy balance through *complex hormonal and neural pathways* that influence *satiety* and possibly also through *other mechanisms*.

Dietary patterns characterized by higher intakes of fruits and vegetables, legumes, whole grains, nuts and seeds, and *unsaturated fat*, and lower intakes of refined starch, red meat, saturated and trans-fatty acids, and sugar-sweetened foods and beverages, consistent with a traditional Mediterranean diet and other measures of diet quality, can contribute to long-term weight control. Limiting consumption of sugar-sweetened beverages has a particularly important role in weight control. Specifically concerning weight-loss trials, the available evidence does not support the role of reducing the percentage of energy from fat on weight loss. However, the reductions in fat may not have been low enough to observe an effect in these trials. As a matter of general principle, the effects of single macronutrients cannot be adequately captured without specifying replacement or comparison sources of energy.

Genetic factors cannot explain the global epidemic of obesity. It is possible that factors such as genetics, epigenetics, and the microbiota can influence individual responses to diet and physical activity. Very few gene–diet interactions have been established. Understanding the mechanisms underlying the relationship of adiposity to cancer may offer the possibility of identifying targets for prevention or treatment independent of adiposity.

Short-term studies have not provided clear evidence of the benefit of physical activity for weight control, but meta-analyses of longer-term trials indicate a modest benefit for weight loss and weight maintenance. The combination of aerobic and resistance training seems to be optimal. Long-term epidemiological studies also support a mild benefit of physical activity on body weight. This includes benefits of walking and bicycle riding, which can be incorporated into daily life and be sustainable for the whole population. Physical activity has important health benefits independent of its effects on regulating body weight. In addition, long-term epidemiological studies show that sedentary behaviour (in particular television viewing) is related to increased risk of obesity, suggesting that limiting sedentary time has potential for preventing weight gain.

The major drivers of the obesity epidemic are the *food environment*,

marketing of unhealthy foods, and *urbanization*, and probably *reduction in physical activity levels*. Existing evidence on the relationships of diet, physical activity, and socioeconomic and cultural factors to body weight is largely from HICs. There is an important lack of data on diet, physical activity, and adiposity in most parts of the world, and this information needs to be collected in a standardized manner. In most settings, 24-hour recalls will be the most suitable method for dietary surveillance. Attention should be paid to data in subgroups, because mean values may obscure important disparities. The in utero and early childhood environment has important implications for lifetime adiposity, and early life offers an important window of opportunity for intervention. Observational data on determinants of body weight and intervention trials across the life-course to improve body weight are also required. To accomplish these goals, resources are needed to build capacity and to conduct translational research.

Gaining control of the obesity epidemic will require the engagement of many sectors, including education, health care, the media, worksites, agriculture, the food industry, urban planning, transportation, parks and recreation, and governments from local to national. Thus, there is an opportunity for all individuals to participate in this effort, whether at home or in establishing high-level policy. Evidence is now available that intensive multisectoral efforts can stop and partially reverse the rise in the prevalence of obesity, in particular among children.

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