

REVIEW

Obesity and sexual dysfunction, male and female

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Obesity has become a worldwide public health problem of epidemic proportions, as it may decrease life expectancy by 7 years at the age of 40 years: excess bodyweight is now the sixth most important risk factor contributing to the overall burden of disease worldwide. Overweight and obesity may increase the risk of erectile dysfunction (ED) by 30–90% as compared with normal weight subjects. On the other hand, subjects with ED tend to be heavier and with a greater waist than subjects without ED, and also are more likely to be hypertensive and hypercholesterolemic. The metabolic syndrome, characterized by a clustering of risk factors associated with insulin resistance and abdominal obesity, associates with ED. Moreover, women with the metabolic syndrome have an increased prevalence of sexual dysfunctions as compared with matched control women. Lifestyle changes aimed at reducing body weight and increasing physical activity induce amelioration of both erectile and endothelial functions in obese men. Moreover, preliminary evidence suggests that a Mediterranean-style diet might be effective in ameliorating sexual function in women with the metabolic syndrome. Lifestyle changes, mainly focussing on regular physical activity and a healthy diet, are effective and safe ways to reduce cardiovascular diseases and premature mortality in all population groups; they may also prevent and treat sexual dysfunctions in both sexes.

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Obesity has become nowadays a common condition and a worldwide public health problem of epidemic proportions.¹ World Health Organization describes obesity as one of the most visible, yet most neglected, public-health problem that threatens to overwhelm both more and less developed countries.² The problems of overweight and obesity have achieved global recognition only during the past decade, in contrast to underweight, malnutrition and infectious diseases, which have always dominated thinking. The International Obesity Task Force estimates that at present 1.1 billion adults are overweight, including 312 million who are obese. These estimates are conservative, however, as with the new Asian criteria of overweight at a lower cutoff of 23 kg/m² for body mass index (BMI), the number is even higher, reaching 1.7 billion people.³ For the first time, the number of overweight

individuals in the world is equivalent to the number of underweight.

Obesity has been shown to decrease life expectancy by 7 years at the age of 40 years.⁴ Although there has been a trend over the last half century showing a general decline in the age-adjusted death rates of heart disease and stroke, the increasing epidemic of obesity, followed closely by type II diabetes, will likely slow the decline and reverse the trend.⁵ The increase in risk of death with each unit increase in BMI declines progressively with age but remains substantial until the age-group of 75 years and older. Intentional weight loss in obese individuals seems to prolong life and reduce risks: diabetes-related mortality was reduced by 30–40% with moderate weight loss (less than 10% of initial body weight);⁶ moreover, people with type II diabetes who lost 10 kg in the first year after diagnosis gained a further 4 years of life.⁷

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Metabolic consequences of obesity

In addition to being an independent risk factor for cardiovascular diseases, obesity also increases the incidence of other risk factors, notably diabetes,

dyslipidemia, hypertension and the prothrombotic state.⁸ The risks of diabetes, hypertension and dyslipidemia increase from BMI of about 21 kg/m², thereby reducing life expectancy and increasing the health and societal economic burden; excess body weight is now the sixth most important risk factor contributing to the overall burden of disease worldwide.⁹

The risk of hypertension is up to five times higher among obese people than among those of normal weight,¹⁰ whereas more than 85% of hypertension arises in individuals with BMI values above 25 kg/m².¹¹ The increase in blood pressure with excess weight is presumably linked to the release from adipocytes of angiotensinogen, the precursor of the well-known hypertensive molecule angiotensin, an increase in blood volume associated with the greater body mass and a rise in blood viscosity. Diets conducive to weight gain independently amplify blood pressure, as saturated fats and hypercholesterolemia induce a rise in systolic and diastolic blood pressure.¹²

Dyslipidemia progressively develops as BMI increases from 21 kg/m², with a rise in proatheromatous, dense, small-particle-sized low-density lipoprotein. With low high-density lipoprotein concentrations, as well as high concentrations of triglycerides, coronary heart disease risk increases.¹³ This particular dyslipidemia occurring in the obese people, especially in association with visceral obesity and insulin resistance, is also known as atherogenic dyslipidemia.

Overweight, obesity and weight gain have been shown to be major risk factors for the development of type II diabetes regardless of age and sex. In the Nurses' Health Study involving about 85 000 US women free of diagnosed diabetes at baseline, a strong relation between overall obesity and the risk of incident diabetes was observed during the 16 years of follow-up:¹⁴ the relative risk of diabetes was amplified by 7.6 times for overweight, 20.1 times for obese and 39 times for severely obese (BMI > 35 kg/m²) women compared with lean women (BMI < 23 kg/m²). Similar results were noted in men.¹⁵

Obesity and erectile dysfunction

Epidemiological studies suggest that modifiable health behaviors are associated with a reduced risk for erectile dysfunction (ED). In the Health Professionals Follow-up Study,¹⁶ several modifiable lifestyle factors, including leanness, were associated with maintenance of good erectile function. For instance, men with a BMI (calculated as weight in kilograms divided by the square of height in meters) higher than 28.7 are likely to carry a 30% higher risk for ED than those with a normal BMI (25 or lower). Data from other surveys also indicate a higher prevalence of impotence in obese men.^{17,18} For

instance, the 9-year follow-up Massachusetts Male Aging Study¹⁹ and the 25-year follow-up Rancho Bernardo Study²⁰ reported that body weight was an independent risk factor for ED, with a risk exceeding 90% of controls (odds ratio between 1.93 and 1.96, respectively). In general, subjects with ED tend to be heavier and with a greater waist than subjects without ED, and also are more likely to be hypertensive and hypercholesterolemic.²¹

Although the relation between obesity and ED may not be readily apparent, a growing body of evidence implicates central adiposity as key regulator of inflammation and endothelial functions.²² Insulin resistance, endothelial dysfunction and subclinical inflammation have been all demonstrated in the obese population and may contribute to increased cardiovascular risk in the population.²³ Vascular endothelium plays a pivotal role in pathogenesis of numerous thrombotic and inflammatory disorders. Endothelial dysfunction is a predictor of future coronary events and may be detected clinically by determining the plasma levels of circulating soluble markers.²⁴ According to a raising popular view, subjects with ED seem to have a vascular mechanism similar to that seen in atherosclerosis²⁵ and therefore a diagnosis of ED may be seen as a sentinel event that should prompt investigation for coronary heart disease in asymptomatic men.²⁶

We evaluated associations between erectile function, endothelial function and markers of systemic vascular inflammation in 80 obese men, aged 35–55 years, divided into two equal groups according to the presence/absence of ED.²⁷ Compared with non-obese age-matched men, obese men had impaired indices of endothelial function and higher circulating concentrations of the proinflammatory cytokines interleukin-6, interleukin-8, interleukin-18, as well as C-reactive protein (CRP). Endothelial function showed a greater impairment in impotent obese men as compared with potent obese men, whereas circulating C-reactive protein levels were significantly higher in obese men with ED. The association between International Index of Erectile Dysfunction (IIEF) score and indices of endothelial dysfunction supports the presence of a possible common vascular pathway underlying both conditions in obese men. A defective nitric oxide activity, linked to reduced nitric oxide availability, could provide a unifying explanation for this association.

Endothelial microparticles and ED

Microparticles are small membrane vesicles that are released from cells upon activation or during apoptosis.²⁸ The majority of *in vivo* microparticles in blood are derived from platelets, whereas microparticles from erythrocytes, granulocytes, monocytes, lymphocytes and endothelial cells usually

circulate at lower numbers. Because of their pro-coagulant properties and capability to affect the endothelium functions, microparticles have been subjected to increasing attention during last years. An increase in endothelial microparticle (EMP) levels has been demonstrated in patients with cardiovascular disease, such as acute coronary syndromes, diabetes, hypertension and hypertriglyceridemia.^{29–33} Microparticles can also influence endothelial functions: microparticles from patients with acute coronary syndromes directly impaired endothelium-dependent vasodilatation in rat aorta-rings, presumably by inhibition of the nitric oxide-mediated signal transduction.^{34,35} Although microparticles are elevated in condition of endothelial cell loss, as a consequence of inflammatory processes and the associated vascular damage, they may play a direct role in atherogenesis, also considering that EMPs can directly activate and stimulate cells to produce inflammatory mediators such as cytokines.³⁶

Thirty overweight and obese diabetic men with ED and 20 age-matched control subjects without ED were assessed for circulating microparticles and endothelial dysfunction.³⁷ Compared with non-diabetic subjects, diabetic men presented significantly higher numbers of EMPs ($P=0.001$), and reduced endothelial-dependent vasodilation ($P=0.01$), with a significant inverse correlation between the number of circulating EMP and the IIEF score ($r=-0.457$, $P=0.01$). Multivariate analysis correcting for age, anthropometric indices, glucose and lipid parameters, FMD and PMP identified EMP as the only independent predictor for IIEF score ($P=0.03$). The results demonstrate that circulating endothelial-derived microparticles are higher in impotent diabetic men as compared with age-matched non-diabetic potent men, and also negatively correlated with the severity of ED (Figure 1). As in multivariate analysis EMPs remained the only independent predictor of IIEF, it seems likely that EMP may represent a link between diabetes and ED.

The metabolic syndrome and ED

The metabolic syndrome, characterized by a clustering of risk factors associated with insulin resistance and abdominal obesity, is associated with an increased risk of coronary heart disease and cardiovascular disease mortality. The prevalence of this condition in developed and developing countries continues to increase. The initial report documenting the prevalence of the metabolic syndrome based on US adults surveyed in 1988–1994 showed approximately one-fourth of US adults or 47 million to have this condition,³⁸ whereas more recent estimates from 1999 to 2002 place the US adult prevalence between 34 and 40% in men and

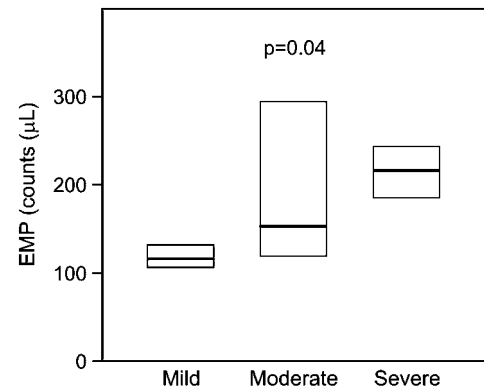


Figure 1 Relationship between EMPs and severity (mild: IIEF between 16 and 21; moderate: IIEF between 10 and 15; severe: IIEF <10) of ED in a sample of 30 overweight type II diabetic patients with ED. Each bar represents median and interquartile range. Adapted from Esposito *et al.*³⁷ ED, erectile dysfunction; EMP, endothelial microparticle.

between 35 and 38% in women, depending on the definition used to define the syndrome.³⁹

Common features are central obesity, insulin resistance, hypertension and dyslipidemia. Patients with the metabolic syndrome also are at increased risk for type II diabetes. The ATP-III guideline also suggests a working definition of the metabolic syndrome that includes the presence of at least three of the following characteristics: abdominal obesity, elevated triglycerides, reduced levels of high-density lipoprotein cholesterol, high blood pressure and high fasting glucose.⁴⁰ In particular, the cutoff values are the following: waist circumference >102 cm in men and >88 cm in women; triglycerides >150 mg per 100 ml; high-density lipoprotein-cholesterol <40 mg per 100 ml in men and <50 mg per 100 ml in women; blood pressure >130/85 mm Hg; and fasting glucose >110 mg per 100 ml.

As four of the five components of the metabolic syndrome are risk factors for ED, we postulated an association between ED and the metabolic syndrome, and tested the hypothesis that ED was more prevalent in men with the metabolic syndrome.⁴¹ In uncontrolled prospective studies, 43% of men presenting with ED met the US National Cholesterol Education Program criteria for metabolic syndrome;⁴² 29% of men presenting with sexual dysfunction had metabolic syndrome: 96% had ED, 40% hypoactive sexual desire, 23% premature ejaculation and 5% delayed ejaculation.⁴³ In a case-control study,⁴¹ compared with age- and weight-matched control subjects ($n=50$), patients with the metabolic syndrome ($n=100$) had increased prevalence of ED (26.7 vs 13%, $P=0.03$); moreover, there was an increase in ED prevalence (IIEF <21), as the number of components of the metabolic syndrome increased, suggesting that the cumulative burden of cardiovascular risk may be central to the pathogenesis of ED.

Hypogonadism and the metabolic syndrome

Hypogonadism in men has been associated with increased risk of metabolic syndrome,^{44–46} cardiovascular disease⁴⁷ and sexual dysfunction. Metabolic syndrome is associated with endothelial dysfunction, penile vascular compromise and the autonomic neuropathy of diabetes, which underlie ED in men.⁴⁸ An uncontrolled prospective study of men for the assessment of sexual dysfunction reported that the presence of hypogonadism in men with metabolic syndrome was associated with worse sexual dysfunction and anxiety than in men with metabolic syndrome but without hypogonadism.⁴³ For example, in 864 men (mean age 52 years) participating in two lipid treatment studies,⁴⁹ testosterone decreased with increasing BMI ($P < 0.0001$). Mean baseline total serum testosterone levels in obese and severely obese aging men with the metabolic syndrome were around 150 and 300 ng per 100 ml, respectively, less than that in aging, lean men with no metabolic syndrome. Based on these analyses, the presence of diabetes or fasting serum glucose greater than 110 mg per 100 ml, BMI 30 kg/m² or greater, and triglycerides 150 mg per 100 ml or greater each appeared to have a clinically relevant association with low serum testosterone. Aging men with obesity and the metabolic syndrome have a significant decrease in total serum testosterone levels compared to aging, metabolically healthy men.

Obesity, metabolic syndrome and female sexual function

Female sexual dysfunction (FSD) is characterized by disturbances in the psychophysiological changes associated with the sexual response cycle in women, including disorders of sexual desire, arousal, orgasm and pain.⁵⁰ Sexual difficulties in women appear to be widespread in society, influenced by both health-related and psychosocial factors, and are associated with impaired quality of life and interpersonal relationships.⁵¹ Older data reveal that up to 76% of women had some type of sexual dysfunction.⁵² Data from the National Health and Social Life Survey (NHSL), a study of adult sexual behavior, showed that 43% of women in the United States had at least one of sexual problem, in relation with age, marital status, education, race or ethnicity.⁵³ These figures have recently been confirmed by the results of GSSAB (Global Study of Sexual Attitudes and Behaviors), an international survey of various aspects of sex and relationships among adults aged 40–80 years.⁵⁴ However, well-designed, random-sample, community-based epidemiological studies are limited and hampered by low response rate, the

use of different tools to assess FSD and the underlying complexity of female sexuality.

Both overweight and obesity have been identified as risk factors for sexual dysfunction in men,⁵⁵ but the relationship between female sexual function and amount of body fat is still obscure.^{56,57} The discrepancy that still exists among the few reports may mainly be due to the different instruments used to assess sexual function in women. The FSFI (female sexual function index) is a brief, validated 19 items self-report instrument proposed to decode information on specific sexual dysfunction symptoms.⁵⁸ This clinical tool has the advantage of being standardized, easy to administer and score, and provides normal values in general and pathological populations.⁵⁹

Previous evidence linking FSD to obesity is very scanty. In 171 postmenopausal women, Kirchengast *et al.*⁵⁶ reported that body weight and BMI were significantly related to the degree of reduced sexual interest. In 59 healthy women aged 19–40 years, Brody⁵⁷ found that hip size was negatively associated with a lower frequency of penile–vaginal intercourse. However, both studies focused upon single aspects of women sexuality, and used different tools for investigating sexual function. Also for diabetes mellitus, which represents an important causes of ED in men,⁶⁰ the data about the prevalence of FSD are controversial.^{61–63}

We found⁶⁴ a negative relationship between body weight and sexual function in 52 women with abnormal values of FSFI (score ≤ 23) (Figure 2). We also showed that obesity affects several aspects of sexual function in otherwise healthy women with FSD, including arousal, lubrication, satisfaction and orgasm, but not desire and pain. Central fat distribution, as evaluated by the waist-to-hip ratio,

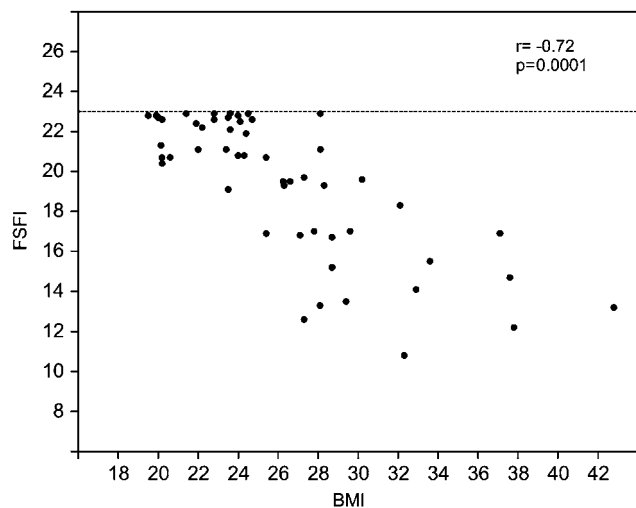


Figure 2 Relationship between female sexual function and BMI in a sample of 52 women with abnormal (≤ 23) value of FSFI. Adapted from Esposito *et al.*⁶⁴ BMI, body mass index; FSFI, female sexual function index.

showed no correlation with FSFI score or with any individual sexual domains, suggesting that the amount of fat is more important than its distribution. Interestingly enough, desire was the only domain showing a positive yet not significant relation with BMI, supporting the hypothesis that the domains of women's sexual function (desire, arousal, lubrication and orgasm) may not represent a linear progression.⁶⁵ The lack of relation between BMI and FSFI in women without FSD ($r=0.2$, $P=0.09$) seems to suggest that obesity may be an important factor once FSD is manifested, but prospective studies are needed to answer this question. At present, we can only speculate that the increasing number of circulating factors produced by the fat cell may probably play a role,⁶⁶ although specifically addressed studies are needed.

In a preliminary observation, we showed that women with the metabolic syndrome have an increased prevalence of sexual dysfunctions as compared with matched control women, although the association remained not easily explained.⁶⁷ Compared with the control group, women with the metabolic syndrome had reduced mean full FSFI score (23.9 ± 5.4 vs 29.9 ± 4.8 , $P < 0.001$). We considered the functional results to be good when the FSFI score was 30 or more, intermediate between 23 and 29, and poor below 23. The percentages of women falling within these three categories of FSFI score were for control women 77, 21 and 2%, respectively, and for women with the MS 55, 36 and 9%, respectively ($P < 0.01$). Individual analysis of the different domains demonstrated that women with the metabolic syndrome reported significantly lower arousal, orgasm and lubrication scores ($P < 0.01$) in comparison with controls (Figure 3). Satisfaction rate was 3.5 ± 1.1 in patients and 4.7 ± 1.2 in controls ($P < 0.001$). There was a decrease in full FSFI score as the number of components of the metabolic syndrome increased (three components, $N=65$: 24 ± 3.8 ; four components, $N=23$: 19 ± 3.1

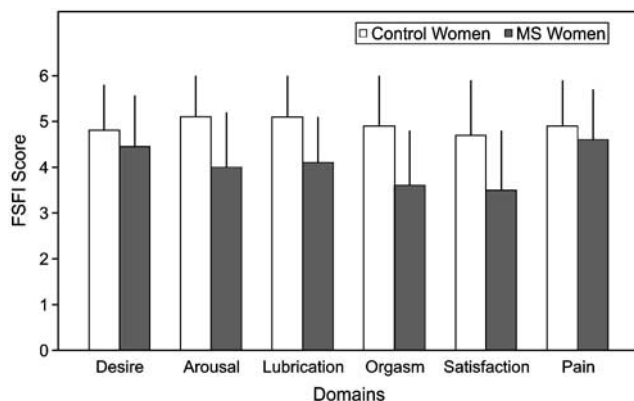


Figure 3 Individual domains of female sexual function in women with the metabolic syndrome (SM) and in control women. Adapted from Esposito *et al.*⁶⁷

and five components, $N=12$: 16 ± 2.7 , $P < .01$). Women with the metabolic syndrome have an increased prevalence of sexual dysfunctions as compared with matched control women; however, the inverse relation between the FSFI score and the numbers of components of the syndrome is intriguing but at present not easily explained.

Lifestyle and sexual function

Erectile and endothelial dysfunction may have some shared pathways, through a defect in nitric oxide activity, which may be inhibited through age-, disease- and behavior-related pathways. Intervention on modifiable health behaviors, especially reducing body weight and increasing physical activity, may in theory be a safe strategy to reduce the risk of both erectile and endothelial dysfunction. In the Massachusetts Male Aging Study, for example, Derby *et al.*⁶⁸ found that men who were overweight at baseline were at an increased risk of developing ED regardless of whether they lost weight during the follow-up records. Moreover, epidemiological evidence suggests that physical activity is associated with a 30% lower risk of ED.¹⁶ A more recent assessment of the association between physical activity and ED comes from a meta-analysis of population-based studies demonstrating the existence of a simple dose-response relationship, with higher physical activity conferring lower risks. The adjusted reduction of the risk of having ED was 58% for high activity and 37% for moderate activity, as compared with men with low physical activity.⁶⁹

We hypothesized that lifestyle changes aimed at reducing body weight and increasing physical activity would induce amelioration of erectile and endothelial functions in obese men. We conducted a randomized controlled trial involving 110 obese men with ED.⁷⁰ Men assigned to the intervention group were entered in an intensive weight loss program, involving personalized dietary counseling and exercise advice and regular meetings with a nutritionist and personal trainer. Men assigned to the control group received general guidance on weight loss at each visit. After 2 years, men randomized to the intervention had lost significantly more weight, increased their physical activity, experienced favorable changes in physiologic measures of endothelial dysfunction and had significant improvement in their ED score compared with men in the control group. In particular, erectile function score was improved from 13.9 to 17 ($P < 0.001$) after the intervention: 17 men in the intervention group and 3 men in the control group reported having IIEF score 22 or more (that is returned to normal). Multivariate analysis found that physical activity, BMI and C-reactive protein independently

predicted IIEF score and almost explained 68% of the variance.

This study provided evidence that sustained lifestyle changes can partially ameliorate erectile function in obese men. Additionally, men in the intervention program showed improvement in the number of surrogate traditional and novel cardiovascular risk factors, which were better than those seen in control men. Although the findings may not be totally generalizable to primary care clinics as the intervention was very intensive and involved many contacts with the study team, this should not detract from the potential importance of the findings for the public health, in the light of the mounting evidence that sustained lifestyle modifications have profound impact on diseases.

We tested the effect of a Mediterranean-style diet on sexual function in women with the metabolic syndrome (unpublished data). Thirty-one women with a diagnosis of FSD and metabolic syndrome were assigned to the Mediterranean-style diet and 28 to a standard control diet. After 2 years, women on the Mediterranean diet consumed more fruits, vegetables, nuts, whole grain and olive oil as compared with men on the control diet. FSFI improved in the intervention group, from a mean basal value of 19.7 ± 3.1 to a mean post-treatment value of 26.1 ± 4.1 ($P = 0.01$), and remained stable in the control group. No single sexual domain (desire, arousal, lubrication, orgasm, satisfaction, pain) was significantly ameliorated by the dietary treatment, suggesting that the whole female sexuality may find benefit from lifestyle changes. A Mediterranean-style diet might be effective in ameliorating sexual function in women with the metabolic syndrome.

Conclusions

Dietary energy restriction and increasing physical activity still represent the cornerstone of prevention and therapy of obesity. Regular exercise can reduce body weight and fat mass without dietary caloric restriction in overweight individuals. An increase in total energy expenditure appears to be the most important determinant of successful exercise-induced weight loss. The best long-term results may be achieved when physical activity produces an energy expenditure of at least 2500 kcal per week. The optimal approach in weight reduction programs appears to be a combination of regular physical activity and caloric restriction. A minimum of 60 min but most likely 80–90 min of moderate-intensity physical activity per day may be needed to avoid or limit weight regain in formerly overweight or obese individuals. Sustained lifestyle changes, including regular moderate-intensity physical activity, a healthy diet and avoiding unhealthy weight gain are effective and safe ways to reduce

cardiovascular diseases and premature mortality in all population groups,^{71–73} and to prevent and treat ED.

As overweight and obesity represent important risk factors for the development of type II diabetes, which is one main cause of ED, it is fundamental to avoid or limit those nutritional factors that have been associated with the risk of type II diabetes in epidemiological studies. A pattern characterized by higher intake of fruits and vegetables (prudent pattern) was associated with a reduced risk of type II diabetes, whereas a pattern characterized by higher intake of foods typical of Western diets, including processed meat, French fry, sugar-sweetened beverages, food with high glycemic load, was associated with an increased risk.^{74,75} To combat the epidemic of overweight at a population level, it is important to develop strategies to increase habitual physical activity and to prevent overweight and obesity in collaboration with communities, families, schools, work sites, health-care professionals, media and policymakers.

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