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## INVITED REVIEW

Sexual Function

# Lifestyle modifications and erectile dysfunction: what can be expected?

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Erectile dysfunction (ED) is a common medical disorder whose prevalence is increasing worldwide. Modifiable risk factors for ED include smoking, lack of physical activity, wrong diets, overweight or obesity, metabolic syndrome, and excessive alcohol consumption. Quite interestingly, all these metabolic conditions are strongly associated with a pro-inflammatory state that results in endothelial dysfunction by decreasing the availability of nitric oxide (NO), which is the driving force of the blood genital flow. Lifestyle and nutrition have been recognized as central factors influencing both vascular NO production, testosterone levels, and erectile function. Moreover, it has also been suggested that lifestyle habits that decrease low-grade clinical inflammation may have a role in the improvement of erectile function. In clinical trials, lifestyle modifications were effective in ameliorating ED or restoring absent ED in people with obesity or metabolic syndrome. Therefore, promotion of healthful lifestyles would yield great benefits in reducing the burden of sexual dysfunction. Efforts, in order to implement educative strategies for healthy lifestyle, should be addressed.

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## INTRODUCTION

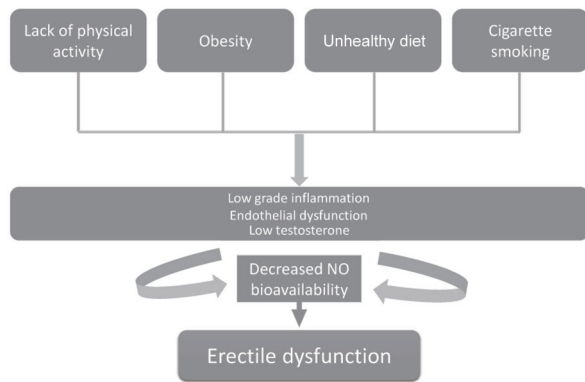
Erectile dysfunction (ED) is a common medical disorder which decreases quality of life in men.<sup>1,2</sup> It has been estimated that the worldwide prevalence of ED will be 322 million cases by the year 2025. Risk factor categories associated with ED include general health status of the individual, the presence of diabetes mellitus, and of cardiovascular disease (CVD), concurrence of other genitourinary disease, psychiatric/psychological disorders, and sociodemographic conditions.<sup>3</sup> Several cross-sectional and longitudinal studies showed an association between ED and most of the cardiovascular risk factors, such as diabetes, smoking, hypertension, hyperlipidemia, metabolic syndrome.<sup>4</sup> Moreover, ED is a marker of increased risk of CVD, and all-cause mortality.<sup>5–7</sup>

Cardiovascular diseases are the main cause of mortality in both sexes worldwide.<sup>8,9</sup> behavioral modifications that occurred in the last decades have led to the spreading of unhealthy lifestyles, which are believed to be one main cause of the burden of noncommunicable diseases worldwide.<sup>10</sup> Consequently, there has been a dramatic increase in the incidence of both type 2 diabetes mellitus and obesity, both in the Westernized and the developing countries. The increasing prevalence of obesity has brought about the rising prevalence of metabolic syndrome, a cluster of risk factors for CVD and type 2 diabetes mellitus, occurring together more often than could be attributed to chance alone. On the basis of the most recent epidemiological analysis using the National Cholesterol Education Program/Adult Treatment Panel III guidelines for cut-off values, slightly more than one-third of adults in the United States could be characterized as having the metabolic syndrome.<sup>11</sup> Quite interestingly, all these metabolic conditions are

strongly associated with a pro-inflammatory state that results in endothelial dysfunction and decrease in the availability and activity of nitric oxide (NO). As NO is the driving force of the genital blood flow, it has been hypothesized and demonstrated that most cardiovascular risk factors are associated with ED in men.<sup>12</sup> Moreover, an inverse association between obesity and low-testosterone levels has been established in healthy men; the prevalence of low-testosterone levels in obesity may vary from 20% to 64% depending on the population and on whether total or free testosterone is used to make a diagnosis.<sup>13</sup> A higher prevalence of hypogonadotropic hypogonadism has been described in patients with type 2 diabetes mellitus<sup>14</sup> and referred to metabolic disorders causing hypothalamic-pituitary-gonadal axis regulation.<sup>15</sup> Testosterone regulates nearly every component of erectile function, and also modulates the timing of the erectile process, which occurs as a function of sexual desire, coordinating penile erection with sex.

Lifestyle and nutrition have been recognized as central factors influencing both vascular NO production and erectile function. Moreover, it has also been suggested that lifestyle habits that decrease low-grade clinical inflammation may have a role in reducing the burden of sexual dysfunction.<sup>16</sup> Both basic and clinical studies have shown that targeting several lifestyle factors commonly associated with ED, such as smoking, alcohol consumption, obesity, and limited physical activity can have significant effects on improvement of erectile function as well as testosterone levels (**Figure 1**).<sup>17–22</sup> Therefore, there may be a role for lifestyle measures to prevent progression or even enhance the regression in the earliest manifestations of ED.<sup>23</sup> In this review, a comprehensive literary search was carried out in order to discuss the effects of lifestyle intervention strategies on erectile function, focusing

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**Figure 1:** Behavioral risk factors and principal mechanisms involved in erectile dysfunction.

on the potential mechanisms involved in increasing vascular NO production. We searched PubMed for papers published in English between 1990 and March 2014, using the key words “ED” and “lifestyle changes” “physical activity,” “weight loss,” “diet,” “alcohol,” “smoking,” we mainly focused on publications in the past 5 years. Other relevant articles identified by review of the reference lists of selected articles were also included.

## EPIDEMIOLOGY AND RISK FACTORS

Erectile dysfunction is a frequent sexual problem that increases with age. According to a recent analysis of published works on the prevalence of sexual dysfunction by the International Consultation Committee for sexual medicine on definitions/epidemiology/risk factors for sexual dysfunction,<sup>3</sup> the prevalence of ED was 1%–10% in men younger than 40 years, 2%–9% among men between 40 and 49 years, and it increased to 20%–40% among men between 60 and 69 years, reaching the highest rate in men older than 70 years (50%–100%). Modifiable risk factors for ED include smoking, lack of physical activity, obesity, excessive alcohol consumption, recreational drug use.<sup>24</sup> In the Health Professional’s Follow-up Study<sup>25</sup> several lifestyle factors, including physical activity and leanness, were associated with maintenance of good erectile function. On the other hand, diabetes mellitus is the most common risk factor for ED, as diabetic men showed a three-fold probability of having ED than men without diabetes.<sup>26</sup> Moreover, both cross-sectional and longitudinal studies have linked the development of ED to CVD, hypertension, hyperlipidemia, and metabolic syndrome,<sup>27–29</sup> all of which are largely preventable with an intervention strategy based on lifestyle changes.

## EFFECTS OF LIFESTYLE CHANGES ON ERECTILE DYSFUNCTION

The association of modifiable behavioral factors with ED, primarily among men free of comorbidities, represents the rationale for intervention strategies addressed to prevent and potentially improve erectile function in patients with ED. As NO is a key factor for vascular health and ED is strongly associated with CVD, maximal attention should have to be paid on measures known to increase vascular NO production.

### Physical activity

The only meta-analysis regarding exercise and ED showed that moderate and high physical activities were associated with a lower risk of ED, with odds ratios at 0.63 (95% confidence interval (CI): 0.43–0.93) and 0.42 (95% CI: 0.22–0.82), respectively.<sup>30</sup> Several prospective

investigations indicate that the physical activity has a beneficial effect on prevention and/or improvements of ED.<sup>31–33</sup>

In hypertensive patients with ED, an 8-week exercise training for the duration of 45–60 min day<sup>-1</sup>, improved ED compared with controls who remained sedentary during the same period.<sup>34</sup> A recent study evaluated the effect of a standard protocol of aerobic physical activity (150 min week<sup>-1</sup>) on quality of ED in middle-aged patients with arterial ED.<sup>35</sup> After 3 months, compared with controls, patients in the intervention group showed a significantly higher International Index of Erectile Function 5 (IIEF-5) score associated with a reduction of apoptotic circulating endothelial progenitor cells (EPCs) and endothelial microparticles. In a randomized, open-label study,<sup>36</sup> a total of 60 patients with ED were randomized to receive phosphodiesterase type 5 inhibitor (PDE5i) alone or PDE5i plus regular ( $\geq 3$  h week<sup>-1</sup>), aerobic, nonagonistic physical activity. After 3 months, IIEF restoration of ED occurred in 77.8% (intervention group) versus 39.3% (control) ( $P < 0.004$ ). Moreover, physical activity was the only independent variable for normal erection ( $P = 0.010$ ), higher sexual satisfaction ( $P = 0.022$ ) and normal total IIEF-15 score ( $P = 0.023$ ), suggesting that lifestyle changes may significantly increase the benefits of medical ED therapy.

The mechanisms by which physical activity ameliorates ED include improved cardiovascular fitness and endothelial dysfunction,<sup>37</sup> increase in endothelial-derived NO,<sup>38</sup> decrease in oxidative stress,<sup>20</sup> and increase in regenerative EPCs.<sup>39</sup> Moreover, physical exercise showed beneficial effects on self-esteem and mental health,<sup>40</sup> with a positive impact on psychological issues associated with sexual dysfunction.

### Weight loss

Both cross-sectional and prospective epidemiologic studies suggest that overweight, obesity and metabolic syndrome are associated with an increased risk of ED.<sup>41</sup> In particular, the largest population from the Health Professionals Follow-up Study in the United States, including 31 724 men free of ED at baseline, showed a 40% increased risk of developing ED with obesity.<sup>25</sup> Prospective studies<sup>31,42,43</sup> of variable duration from 5 to 25 years of follow-up reported that overweight or obese men had an increased probability (70%–96% higher) of developing ED compared with normal weight men.

Both short- and long-term weight-loss studies including only caloric modifications or restrictions demonstrated improvement of ED. In a study examining the effect of weight loss on quality of life among 37 men and women, after a follow-up of 28 days, the weight loss program seemed to have been beneficial on sexual life among men.<sup>44</sup> Khoo *et al.*<sup>22</sup> compared the effects of 8 weeks of a low-calorie diet (LCD) using meal replacements (KicStart) on insulin sensitivity, plasma testosterone levels, erectile function (IIEF-5), and sexual desire as measured by the Sexual Desire Inventory (SDI) in abdominally obese men with uncomplicated diabetes ( $n = 519$ ) or without type 2 diabetes mellitus ( $n = 525$ ) with a control group of nondiabetic men ( $n = 526$ ) with similar body mass index (BMI) and waist circumference (WC). Weight loss of 10% was significantly associated with increased insulin sensitivity, plasma testosterone levels, and IIEF-5 and SDI scores in diabetic as well as nondiabetic men. The same group investigated the effects of diet-induced weight loss on sexual and endothelial function, lower urinary tract symptoms, and inflammatory markers in obese diabetic men.<sup>45</sup> Over 8 weeks, 31 abdominally obese type 2 diabetic men received either a meal replacement-based LCD  $\sim 1000$  kcal day<sup>-1</sup> ( $n = 19$ ) or low-fat, high-protein (HP), reduced-carbohydrate diet ( $n = 12$ ). Subjects continued on, or were switched to, the HP diet for another 44 weeks. Compared with patients with HP, men with LCD lost more

weight (5% vs 10%). Moreover, both diets significantly improved plasma glucose, low-density lipoprotein, sex hormone-binding globulin, IIEF-5, SDI, and endothelial function (increased flow-mediated dilatation, reduced soluble E-selectin). At 52 weeks, reductions in weight, WC, and C-reactive protein were maintained, and IIEF-5, and SDI scores improved further. Similar results were obtained with bariatric surgery-induced weight loss. In a randomized controlled trial,<sup>46</sup> surgery-induced weight loss increased erectile function quality measured by IIEF-5, with increased total testosterone, free testosterone, follicle-stimulating hormone, and reduced prolactin levels. Moreover, significant improvements in all domains of the Brief Sexual Function Inventory, including erectile function, were also demonstrated in a 2 years study of bariatric surgery-induced weight loss.<sup>47</sup>

Increased visceral adiposity and related risk factors are associated with a pro-inflammatory state that results in a decrease in the availability and activity of NO; the reduced testosterone levels associated with obesity and the metabolic syndrome may worsen both insulin resistance and endothelial function, thereby contributing to ED.<sup>48</sup> Moreover, body weight loss, obtained either by lifestyle or bariatric intervention, is associated with a decline in estrogen levels and a rise in gonadotropins and testosterone, which is greater in those who lose more body weight.<sup>49</sup>

### Dietary factors

Dietary patterns with high content of whole grain foods and legumes and vegetables and fruits, and that limit red meat, full-fat dairy products, and food and beverages high in added sugars are associated with a reduced risk of ED.<sup>50</sup> The greater adherence to a Mediterranean-style diet, in particular, has been associated with a lower prevalence of ED in both diabetic and nondiabetic men.<sup>51,52</sup>

Only few studies assessed the role or the effect of diet on ED. Esposito *et al.*<sup>53</sup> studied 65 men with the metabolic syndrome and ED; 35 out of them were assigned to the intervention diet and 30 to the control diet. Subjects in the intervention group were advised to consume at least 250–300 g of fruits, 125–150 g of vegetables, and 25–50 g of nuts per day; in addition, they were encouraged to consume 400 g of whole grains daily (legumes, rice, maize, and wheat) and to increase the consumption of olive oil. After 2 years, men on the Mediterranean diet consumed more fruits, vegetables, nuts, whole grain, and olive oil when compared with men on the control diet. IIEF score increased up to 22 in 13 and 2 men in the intervention group and control group, respectively ( $P = 0.015$ ).

A substantial body of knowledge demonstrates that the abundant consumption of vegetables, fruit, and whole grain, and the dietary patterns rich in these foods produced a markedly lower risk of coronary disease.<sup>54</sup> The beneficial effect of the Mediterranean diet on atherosclerosis in general, and ED in particular can be mediated through multiple biological pathways, including a reduction of oxidative stress and subclinical inflammation, amelioration of endothelial dysfunction and insulin sensitivity,<sup>55,56</sup> which in turn may increase NO release in the penis arteries.

### Overall lifestyle changes

Lifestyle changes, such as increased physical activity, healthy diet, and reduced caloric intake, have been associated with the amelioration of erectile function in the general male population. Esposito *et al.*<sup>16</sup> conducted a randomized controlled trial involving 110 obese men with ED. 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. The dietary advice was tailored to each man on the basis of food records collected on three nonconsecutive days which had to be done

the week before the meeting with a nutritionist. Men in the control group were given general oral and written information about healthy food choices and exercise at baseline and subsequent bimonthly visits, but no specific individualized programs were offered to them. After 2 years, men randomized to the intervention 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. The same group used their database of subjects participating in randomized controlled trials to evaluate whether improvements in erectile function were related to success in achieving lifestyle changes.<sup>20</sup> After ranking men according to their success in achieving the goals of intervention (weight loss, low intake of saturated fat, high consumption of monounsaturated fat and fiber, and moderate physical activity), a strong correlation was observed between the success score and the restoration of erectile function. Moreover, at the 2 years examination point, the number of men without ED was significantly higher in the group randomized to intensive lifestyle changes compared with that of men in the control group. Wing *et al.*<sup>57</sup> evaluated 1 year changes in erectile function in 306 overweight men with type 2 diabetes mellitus participating in the Look Action for Health in Diabetes trial; from baseline to 1 year, 8% of men assigned to an intensive lifestyle intervention reported a worsening of erectile function compared to 22% of the control participants. Moreover, the overall IIEF score improved from 17.3 to 18.6 ( $P = 0.04$  and  $P = 0.06$ , after adjusting for baseline differences) in the intervention group.

The suggested mechanisms by which weight loss, healthy diet, and physical exercise can improve erectile function include the amelioration of endothelial dysfunction, insulin-resistance, and low-grade inflammatory state associated with diabetes and metabolic diseases – all of which are risk factors for ED.<sup>58</sup> The resulting improved inflammatory status may help contribute to reduce the burden of sexual dysfunction in men.

### Smoking

Both the direct use of tobacco and second-hand exposure seem a consolidated risk factor for ED.<sup>59,60</sup> A recent meta-analysis of four prospective cohort studies and four case-control studies involving 28 586 participants showed that compared with nonsmokers, the overall odd ratio of ED in prospective cohort studies was 1.51 (95% CI: 1.34–1.71) for current smokers, and 1.29 (95% CI: 1.07–1.47) for former smokers.<sup>61</sup>

Harte and Meston<sup>62</sup> investigated the association between smoking cessation and indices of physiological and subjective sexual health in men: smoking cessation significantly enhanced both physiological and self-reported indices of sexual health in long-term male smokers, irrespective of baseline erectile impairment. In a prospective study, Pourmand *et al.*<sup>63</sup> reported a beneficial effect on erectile function in men who ceased smoking. After 1 year the ED status improved in  $\geq 25\%$  of ex-smokers but in none of the current smokers; moreover, men who stopped smoking continued to have a significantly better ED status with long-term follow-up.

### Alcohol

The moderate consumption of alcohol may exert a protective effect on ED in both the general population and in diabetic men.<sup>25,64</sup> In a recent study aimed at describing the incidence or remission and bio-psychosocial predictors of ED in 810 randomly selected Australian men aged 35–80, low-alcohol consumption was predictor of ED.<sup>65</sup> The data from a population-based cross-sectional study of men's health to assess the association between usual alcohol consumption and ED

in Australia revealed that among current drinkers ( $n = 51\,374$ ), the odds were lowest for consumption between 1 and 20 standard drinks per week.<sup>19</sup> On further adjustment for CVD or cigarette smoking, age-adjusted odds of ED were reduced by 25%–30% among alcohol drinkers. In general, the overall findings are suggestive of alcohol consumption of a moderate quantity conferring the highest protection.<sup>66</sup> The beneficial effects of alcohol on erectile function may be due, in part, to the long-term benefits of alcohol on high-density lipoprotein cholesterol and other variables that increase the bioavailability of NO.

#### Experimental findings involving lifestyle modifications

Corroborating findings in the clinical studies, several experimental studies demonstrate beneficial effects of lifestyle-related factors (exercise, calories restriction, dietary factors, alcohol, smoking) on erectile function in animal models of ED. The most frequently reported models of ED used rodents as the predominant animal for investigating erectile function. Experimental animal models of ED include traumatic, metabolic (diabetes, hypercholesterolemia/lipidemia, and castration) and other organic models (smoking, hypertension, and chronic renal failure).<sup>67</sup> In male Sprague–Dawley rats, both erectile function and coronary artery erectile function (CAEF) were blunted in Western diet-fed rats who remained sedentary, but were preserved in those who started physical exercise (aerobic treadmill running) throughout the dietary intervention, suggesting that exercise training may be a practical strategy of preventing diet-induced ED.<sup>68</sup> A recent study in the same experimental model of rats demonstrated that the caloric restriction preserved both visceral adipose tissue (VAT) accumulation and erectile function; moreover, analysis of body composition showed that enhanced erectile response in calories-restricted rats was well correlated with the lower levels of VAT, indicating that the beneficial effect on erectile function may depend on decrease in adipose tissue.<sup>69</sup> Hannan *et al.*<sup>70</sup> showed that a combination of exercise and calories restriction may, in part, attenuated the age-related decline in apomorphine-induced erectile function in both normotensive and hypertensive rats, with an inverse correlation between the number of pharmacologically-induced erections and body weight. The role of dietary anti-oxidants on erectile function was investigated in a study of Zhang *et al.*<sup>71</sup> rabbits with atherosclerosis-induced ED by balloon de-endothelialization of the iliac arteries were assigned to assumption of pomegranate extract as dietary anti-oxidant or tap water as placebo. Compared with rabbits receiving placebo, those who assumed pomegranate underwent improvement of intracavernosal blood flow, erectile activity, smooth-muscle relaxation and decrease in oxidative products, suggesting that dietary anti-oxidants may have an effect on molecular and ultra-structural alteration involved on ED. Ethanol may impair the endothelial function of corpus cavernosum producing endothelial damage, as it abolishes the endothelium-dependent relaxations induced by acetylcholine in mice.<sup>72</sup> Finally, chronic

exposure to smoking decreases significantly both testosterone levels and the filling rate of corpora cavernosa in mice, when compared with a control group who was not exposed.<sup>73</sup>

#### WHICH ROLE FOR LIFESTYLE CHANGES IN ERECTILE DYSFUNCTION?

Erectile dysfunction is associated with smoking, excessive alcohol intake, physical inactivity, abdominal obesity, metabolic syndrome, diabetes, hypertension, and decreased anti-oxidant defenses, all of which reduce NO availability. Moreover, there has been increasing recognition of the many physiological causes of ED and of the potential for therapy to improve patient's quality of life, self-esteem, and ability to maintain intimate relationships.<sup>74</sup> Although epidemiological evidence seems to support a role for lifestyle factors, limited data are available suggesting that the treatment of underlying risk factors and coexisting illnesses – for example with diet, exercise, stress reduction, and smoking cessation – may improve ED.<sup>24</sup> It has been demonstrated that lifestyle-based intervention strategies improve endothelial function, NO bio-availability, and testosterone levels, producing benefits on erectile function.<sup>12,16,49</sup> The major limitation remains the paucity of intervention studies that have assessed the role of lifestyle changes on ED. Moreover, the studies reviewed are mainly limited to the exiguity of the study samples. However, the European Association of Urology recently stated that “lifestyle changes and risk factors modification must precede or accompany ED treatment” and classified the Level of Evidence as 1b with a Grade A.<sup>75</sup>

None of the many available treatment options offers a complete response in all patients. Thus, as with many other medical diseases, prevention maybe the most effective approach to alleviate the consequences of ED. Despite the increasing evidence that unhealthy lifestyles lead to metabolic diseases, including sexual dysfunction, the majority of adults fail to meet physical activity and nutritional guidelines.<sup>76</sup> In particular, it is recommended that adults accumulate 30 min of moderate-intensity aerobic physical activity on most days of the week. Moreover, a weight loss of 5%–10% in overweight or obese nondiabetic or diabetic men can result in effective improvement in erectile function in a short period. The lack of food-based recommendations and actual dietary practice of the population could be an additional limitation. However, dietary pattern which is high in fruit, vegetables, nuts, whole grains, and fish but low in red and processed meat and refined grains are more represented in subjects without ED. Mediterranean diet has been proposed as a healthy dietary pattern based on evidence that greater adherence to this diet is associated with lower all-cause and disease-specific survival. In clinical trials, Mediterranean diet was more effective than a control diet in ameliorating ED or restoring absent ED in people with obesity or metabolic syndrome, so that the adoption of a Mediterranean diet may be associated with an improvement of ED.

**Table 1: Suggested recommendations on lifestyle changes to be observed in order to prevent/treat erectile dysfunction**

Risk factor	Strategy	Recommendation	Level of evidence
Sedentary lifestyle	Physical activity	30 min at least per day or 150 min week <sup>-1</sup> of moderate intensity aerobic activity	A*
Overweight/obesity	Weight loss	5%–10% of weight reduction	A*
Unhealthy diet	Improvement of diet quality	Increase in consumption of fruit and vegetables, whole grains and legumes; limit red meat and processed food; reduction of saturated fat to <10% calories, increase in intake of monounsaturated and polyunsaturated fatty acids; abolishment of added sugars-beverages	A*
Alcohol abuse	Avoid excessive alcohol consumption	1–2 drinks maximum per day	B
Cigarette smoking	Educate on current cessation options	Smoking cessation	B*

A: evidence from intervention studies; B: evidence from prospective cohort studies or case-control studies. \*Few studies with small number

## CONCLUSIONS

Improvement of sexual (erectile) function in men should be added to the growing list of clinical benefits brought about by healthy lifestyles in human beings. Current recommendation that patients should observe to avoid or alleviate ED include increasing physical exercise, reducing weight (5%–10% or achieving a BMI  $\leq$  30 kg m<sup>-2</sup>), stopping smoking (Table 1).<sup>77</sup> When comorbidities, such as diabetes or hypertension, are present lifestyle modifications may be important in preventing or reducing sexual dysfunction.<sup>4</sup> From this point of view, promotion of healthful lifestyles for primary prevention among individuals at all ages would yield great benefits and reduce the burden of noncommunicable diseases, including sexual dysfunction. Efforts, in order to implement educative strategies for healthy lifestyle, have to be addressed.

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