Diet and exercise in the management of obstructive sleep apnoea and cardiovascular disease risk

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ABSTRACT   Obstructive sleep apnoea (OSA) is associated with increased cardiovascular disease (CVD) morbidity and mortality. It is accepted that OSA and obesity commonly coexist. The American Academy of Sleep Medicine recommends dietary-induced weight loss and exercise as lifestyle treatment options for OSA. However, most clinical trials upon which this recommendation is based have focused on establishing the effectiveness of calorie-restricted, often low-fat diets for improving OSA severity, whereas less attention has been given to the means through which weight loss is achieved (*e.g.* altered dietary quality) or whether diet or exercise mediates the associations between reduced weight, improved OSA severity and the CVD substrate. The current evidence suggests that the benefits of a low-carbohydrate or Mediterranean diet in overweight and obese individuals go beyond the recognised benefits of weight reduction. In addition, exercise has an independent protective effect on vascular health, which may counter the increased oxidative stress, inflammation and sympathetic activation that occur in OSA patients. This review aims to expand our understanding of the effects of diet and exercise on OSA and associated CVD complications, and sets the stage for continued research designed to explore optimal lifestyle strategies for reducing the CVD burden in OSA patients.

Introduction

Obstructive sleep apnoea (OSA) is characterised by repeated episodes of extrathoracic upper airway obstruction or reductions in breath amplitude that result in intra-arterial hypoxaemia and hypercapnia and transient arousals from sleep, leading to fragmented sleep [1]. The prevalence of OSA among

middle-aged adults is estimated to be 24% in males and 9% in females, with 7% of the general population estimated to have moderate to severe OSA [2]. Moreover, OSA is increasingly being recognised as a cause of cardiovascular mortality [3].

Obesity, in particular central obesity [4], is the strongest predictor of OSA [5] and weight loss has long been recognised as an effective OSA treatment [6]. The American Academy of Sleep Medicine recommends weight loss through lifestyle modification (*e.g.* dietary change and exercise) as behavioural treatment options for improving the apnoea–hypopnoea index (AHI) in obese patients with OSA [7]. This recommendation has been bolstered by data from several large randomised controlled trials demonstrating that significant reductions in apnoea and hypopnoea indices with lifestyle programmes (*e.g.* dietary-induced weight loss, behavioural counselling and increased physical activity) are observed among overweight patients with mild OSA [8], obese OSA patients with diabetes [9] and moderate to severe OSA patients undergoing continuous positive airway pressure treatment (CPAP) [10]. Importantly, these favourable improvements in OSA severity are associated with the degree of weight loss and can be sustained for 1–3 years after the interventions have ended [11–13], despite a 30–50% weight regain.

The optimist is likely to embrace these findings as definitive evidence supporting weight reduction through lifestyle change as a primary treatment modality for OSA. We are certainly encouraged by these observations and refer readers to a review by TUOMILEHTO *et al.* [14] which discusses the potential clinical significance of weight loss programmes in all OSA patients. Still, our optimism is tempered when we consider that most dietary lifestyle studies in OSA have employed calorie-restricted diets with low-fat content (<30% of calories from fat) to induce weight loss [15]. Thus, the therapeutic potential of alternative dietary approaches that focus on other characteristics of the diet and not on fat restriction (*e.g.* low-carbohydrate [16] and Mediterranean [17] diets) to treat OSA and its cardiovascular complications has largely been ignored. Furthermore, although a bidirectional association appears to exist between obesity and OSA, behaviour-induced weight loss studies are designed to establish the effectiveness of lifestyle interventions (*i.e.* independent variables) in improving OSA severity (*i.e.* dependent variables). In contrast, less attention has focused on examining the effect of OSA on diet and weight loss as mediators of cardiovascular disease [18]. Finally, while physical activity is generally regarded as a critical component of lifestyle programmes [19], we suspect that most clinicians view exercise as a means to establish a "negative energy balance" [20] and, in turn, facilitate weight loss. Unfortunately, this presumption fails to appreciate that exercise has a direct impact on OSA severity [21] and cardiovascular health [22], regardless of body weight changes. Accordingly, the purpose of this review is to address these points and set the stage to continue to refine lifestyle therapies to reduce cardiovascular disease (CVD) risk in obese patients with and without OSA in the long term, specifically with regard to lifestyle programmes that include dietary, exercise or weight loss recommendations.

Biological pathways linking OSA and CVD

Epidemiological [23] and prospective studies [24, 25] clearly support a causative link between OSA and various manifestations of CVD. The multiple pathways through which OSA sets up the CVD substrate are
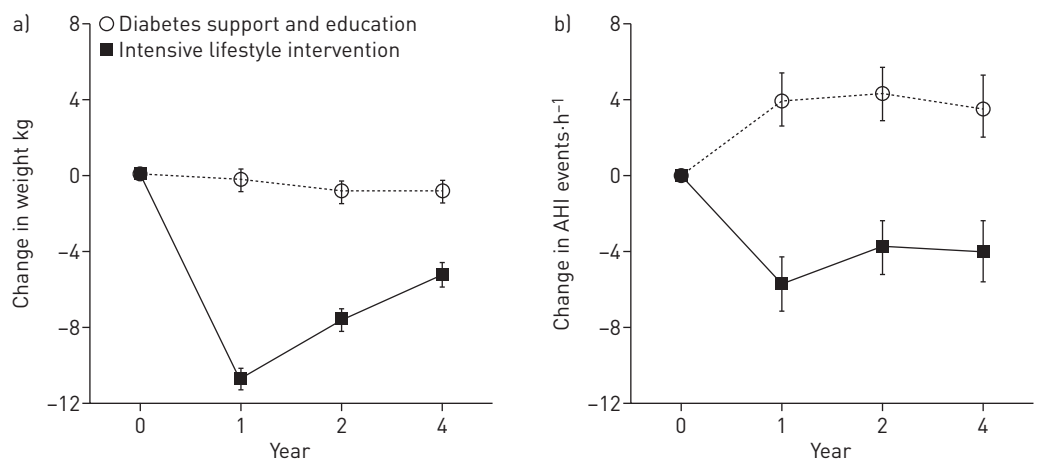

FIGURE 1 Estimated mean±SE changes in a) body weight and b) apnoea–hypopnea index (AHI) from baseline at years 1, 2 and 4 in obese patients with diabetes given diabetes support and education or a lifestyle intervention comprising dietary-induced weight loss and promotion of physical activity. Reproduced and modified from [12] with permission.

incredibly complex and have been reviewed elsewhere [26]. We provide a brief discussion of these pathways in order to highlight the potential targets for treatment.

Sleep fragmentation occurs with obstructive apnoea and may induce severe intermittent hypoxaemia and carbon dioxide retention during sleep. As a result, the normal structured autonomic and haemodynamic response to sleep is disrupted. Repetitive apnoeas are accompanied by sympathetic activation and consequent vasoconstriction due to the combined influence of hypercapnia and hypoxia [27]. Patients with sleep apnoea have high levels of nerve activity during wakefulness and sleep, with blood pressure increasing markedly toward the end of apnoea events [28].

Apart from these acute haemodynamic effects, OSA-induced hypoxia may promote the production of oxidative stress, which, in turn, adversely affects endothelial regulation through nitric oxide-mediating pathways [29]. Nitric oxide plays an important role in vascular homeostasis by inhibiting inflammation, cellular proliferation and thrombosis. Thus, the downregulation of nitric oxide bioavailability in OSA may predispose patients to atherosclerosis. Indeed, the literature shows that endothelial dysfunction is a major consequence of OSA [30].

OSA and obesity

It is well accepted that conditions that comprise metabolic syndrome commonly coexist with OSA. Of these metabolic factors, obesity is perhaps the strongest predictor of OSA. 40–60% of obese individuals are believed to suffer OSA [31]. Yet, KUNA et al. [12] showed in obese patients with diabetes that the improvement in AHI achieved after a 1-year weight loss intervention persisted at 4 years despite significant weight regain (figure 1). These data indicate a complex relationship between weight change and OSA severity.

OSA susceptibility is determined by the extent to which the upper airway is prone to collapse during sleep. Pharyngeal collapsibility is a consequence of elevations in critical closing pressure (P_{crit}). Mechanical and neural factors that regulate pharyngeal collapsibility both determine P_{crit} [32]. Obesity is associated with adipose deposition in peripharyngeal fat pads, which increase surrounding tissue pressure (i.e. mechanical load) leading to pharyngeal collapsibility during sleep [33]. Thus, greater risk of OSA is observed in adults who exhibit a predominantly central fat deposition pattern around the neck, trunk and abdominal viscera [2]. Moreover, pro-inflammatory cytokines are secreted from adipose tissue [34], and it has been theorised that their collective activity may depress neuromuscular control of the upper airway [35]. Furthermore, these cytokines induce the production of reactive oxygen species, thereby impairing the force-generating capacity of skeletal muscle and adversely affecting upper airway function by contributing to upper airway neuropathy [36]. Finally, obesity induces a leptin-resistant state. Leptin regulates appetite and metabolism
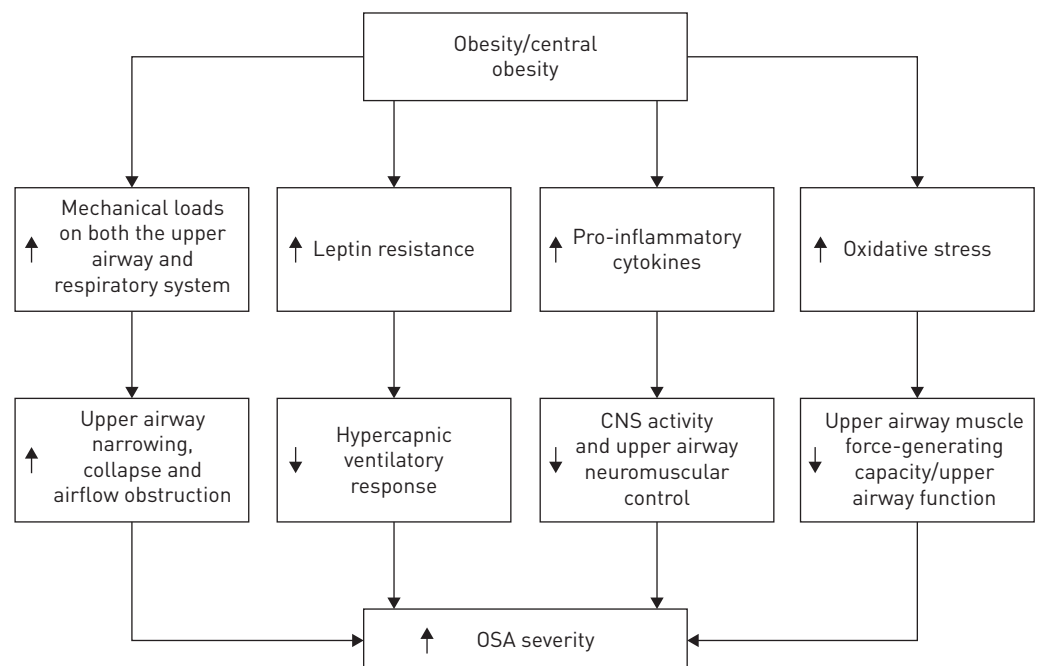

FIGURE 2 Schematic diagram indicating the possible mechanisms linking obesity/central obesity with obstructive sleep apnoea (OSA) development. CNS: central nervous system.

[37, 38], but also acts as a powerful neurohumoral ventilator stimulant [39]. A relative deficiency in central nervous system leptin levels, due to an impaired transport across the blood–brain barrier (*i.e.* leptin resistance) may induce disruption of the central respiratory control mechanisms and impaired hypercapnic ventilatory response, especially during sleep [39] (figure 2).

This evidence indicates a "two-hit" [40], rather than simple weight-load pathogenesis of OSA. Indeed, decreases in P_{crit} during sleep, which have been observed following controlled weight loss studies [41] may be attributable to reduced mechanical loads as well as improvement in pharyngeal neuromuscular controls. However, to date, the focus of nearly every lifestyle weight loss intervention in OSA has been on the induction of a negative energy balance, and P_{crit} changes are not commonly assessed. While this approach might facilitate a reduction in mechanical load, it may not be the most effective approach for optimising improvements in neuromuscular controls.

The role of diet in weight regulation

Calorie-restricted diets are based on the premise that in order to facilitate weight loss, fewer calories must be consumed than expended. This assumes that energy intake and energy expenditure do not influence one another and macronutrient composition is irrelevant to weight loss. However, the central nervous system controls weight maintenance by integrating specific environmental stimuli with peripheral signals to regulate appetite and energy expenditure [42]. Glucose and free fatty acids, along with leptin, insulin, ghrelin and cholecystokinin are among the many hormones and nutrients that influence weight maintenance. Caloric restriction results in compensatory changes that trigger increased hunger and, in turn, increased food intake in an attempt to restore fat mass to a homeostatic set point. In addition, caloric restriction is associated with a compensatory reduction in energy expenditure that prevents weight loss in the long term [42].

Accordingly, it is interesting to consider an alternative model of obesity, in which chronic overeating and sedentary behaviour are the consequences rather than the causes of weight gain. In this model, LUDWIG and FRIEDMAN [20] suggest that various genetic and lifestyle factors (*e.g.* dietary quality and inadequate sleep) promote a disproportionate anabolic state that favours storage rather than oxidation of ingested calories. Attempts to lose weight by creating a caloric deficit, whether through the conscious restriction of dietary calories or through increasing calories expended (*i.e.* physical activity or exercise) would exacerbate the problem of fuel availability. Instead, dietary factors, such as low intake of refined sugar, high levels of monounsaturated fatty acids, high omega-3 and low trans-fatty acid intake and adequate protein have been postulated to decrease anabolic drive, thus leading to weight loss. Traditionally, the medical establishment has endorsed a diet low in total fat content (<30% of total calories) as a means to avoid CVD [43]. Yet, data derived from several large clinical studies, including the Framingham study [44], the Women's Health Initiative [45] and most recently the Look AHEAD study [46] have failed to demonstrate link between dietary and total fat with increased risk for CVD. In contrast, while plasma saturated fatty acids are associated with increased risk for CVD, their presence in plasma is more dependent on dietary carbohydrates than dietary fat [47]. While there is much ground to cover with regard to re-educating the public on healthy nutritional practices, we consider the 2015 dietary guidelines [48], which discourages the consumption of "low-fat" or "non-fat" products with high amounts of refined grains and added sugars to be a step in the right direction. In the following paragraphs, we discuss alternative dietary approaches and how these approaches may be most effective for obese individuals with OSA, in whom the CVD burden is accelerated.

Diet as a treatment for OSA
Lower-carbohydrate diets
Effects on OSA pathology

There is strong evidence supporting the efficacy of lower-carbohydrate diets in promoting weight loss [49]. Low-carbohydrate diets can take several forms, ranging from moderate carbohydrate intake (26–45% of total energy from carbohydrates) to very low-carbohydrate ketogenic diet (20–50 g·day^{-1} or <10% of a 2000 kcal·day^{-1} diet). While there is no limitation on dietary saturated fat consumption, this is not a necessary component of a low-carbohydrate diet. Moreover, vegetables with a low glycaemic load that are rich in fibre make up the foundation of a well formulated low-carbohydrate diet. Thus, it is possible, although perhaps challenging, to be a vegetarian who follows a low-carbohydrate approach. In the A TO Z trial [16], overweight or obese females with the lowest carbohydrate intake (roughly 20–50 g·day^{-1}) lost more weight at 1 year than those who followed traditional low-fat, calorie-restricted diets. Similarly, SHAI *et al.* [50] found that among moderately obese subjects who completed a 2-year dietary intervention, those following a low-carbohydrate diet lost more weight compared to a low-fat, calorie-restricted diet group. Moreover, meta-analyses reveal an overall change in abdominal circumference of −5.74 cm (95% CI −6.07−−5.41 cm) among individuals following a low-carbohydrate diet (<6–24 months in duration) [51] and that the decrease of body weight or body fat mass in low-carbohydrate diets, especially very

low-carbohydrate diets, were higher than in control diets (*e.g.* higher in carbohydrates) [52]. Based on these data alone, lower-carbohydrate diets have a greater potential to reduce mechanical loads directly (*i.e.* greater weight loss), compared to calorie-restricted low-fat diets.

Why lower-carbohydrate diets are so effective for weight loss is debatable, although the theory with the most supporting evidence is that diets very low in carbohydrate appear to affect appetite control hormones and produce ketones that may have a direct appetite suppressant effect [53]. Interestingly, leptin levels are lower, which seems somewhat paradoxical given that leptin limits further energy intake and supports energy expenditure [54] *via* a negative feedback loop. Yet, during ketosis, lower levels may reflect improved central sensitivity to leptin. Thus, we hypothesise the dietary induced ketosis may also counter the mechanical loading placed on the upper airway by enhancing the activity of neuromuscular controllers that keep the airway patent (*e.g.* neurohumoral actions of leptin). Moreover, we speculate that upper airway neuromuscular control in the obese OSA patient might be enhanced to the greatest degree in very low-carbohydrate diets, since carbohydrate restriction results in a considerably greater reduction in pro-inflammatory cytokines and adhesion molecules, compared to low-fat diet [47]. Further evidence is needed to support these theories.

Effects on cardiovascular risk

Attributing the success of low-carbohydrate diets for weight loss solely to appetite suppression underestimates the potential metabolic effects of this dietary approach. Weight loss may have parallel rather than direct causative effects on the cardiometabolic risk profile of OSA patients. For instance, diabetes is characterised by hyperglycaemia, and the restriction of dietary carbohydrate has the largest impact on decreasing blood glucose levels [55]. In other words, dietary carbohydrate is the primary stimulus for insulin secretion, and metabolic disease states such as obesity and diabetes that are associated with OSA [56] may be the consequence of hyperinsulinaemia, since insulin inhibits lipolysis and increases lipid uptake by increasing lipoprotein lipase. In diabetes, insulin fails to reduce hepatic glucose production, but hyperglycaemia is exacerbated by dietary ingestion of carbohydrates (see figure 1 in [57]).

A reduction in fasting glucose among type 2 diabetes patients is observed after 10 weeks of following a carbohydrate-restricted diet (~30% of total calories) despite maintaining initial body weight [58]. In addition, WESTMAN *et al.* [59] randomised obese volunteers with type 2 diabetes to either a low-carbohydrate ketogenic diet (LCKD) (<20 g of carbohydrate) or a low-glycaemic reduced calorie diet (LGID) (500 kcal·day^{-1} deficit from weight maintenance levels). In 24 weeks they found greater improvements in haemoglobin A_{1c}, body weight and high-density lipoprotein cholesterol among the LCKD group compared to the LGID group. Essentially, all LCKD group participants had an elimination or reduction in medication and the change in haemoglobin A_{1c} was not associated with the change in weight. Similarly, DASHTI *et al.* [60] compared the effect of a 56-week ketogenic diet in obese subjects with high blood glucose levels (>6.1 mmol·L^{-1}) to those with normal blood glucose levels. They found continued improvement in blood glucose levels and blood lipids along with weight loss in both groups, although changes in total cholesterol, triglycerides and glucose were more significant in subjects with high blood glucose levels compared to those with normal blood glucose levels. In addition, low-carbohydrate diets have a more favourable effect on alternative indicators of cardiovascular risk in overweight subjects, including postprandial lipaemia, low-density lipoprotein particle distribution [61] and vascular function [62].

The clinical significance of these findings is underscored by data from the Sleep AHEAD cohort indicating that ~86% of obese patients with diabetes have OSA [63]. Given the apparent improvement that carbohydrate restriction has on biomarkers of CVD risk in obese diabetes patients, we postulate that a diet lower in carbohydrate would have tremendous therapeutic potential in the large majority of OSA patients. The magnitude of reduced calories from carbohydrates needed to induce the most favourable changes may ultimately depend on individual levels of carbohydrate tolerance and OSA severity.

Mediterranean diet
Effects on OSA pathology

The term "Mediterranean diet" refers to dietary patterns found in olive-growing areas of the Mediterranean region. Although some heterogeneity in traditional patterns of food consumption exists in these countries, there are many common features, including the abundant use of olive oil as the main culinary source of fat, plentiful consumption of plant-based foods (*e.g.* nuts, vegetables, fruits, cereals, grains and legumes), consumption of fresh and varied fruits as the typical dessert, frequent consumption of fish and other seafood, moderate wine consumption with meals, limited meat (mainly poultry, instead of beef or pork) or processed meat intake and low-to-moderate consumption of dairy products [64]. Compared to a low-fat diet, the Mediterranean diet (50% carbohydrate) has been found to be as effective in promoting weight loss as a lower-carbohydrate (40% carbohydrate) nonrestricted-calorie diet among

moderately obese subjects without diabetes during a 2-year follow-up [50]. Longer (median 4.8 years of follow-up) beneficial effects of a moderate-carbohydrate (40%), high-fat (40%) calorie-restricted Mediterranean diet on weight and waist circumference compared to a low-fat diet have been demonstrated among individuals who had type 2 diabetes or three or more cardiovascular risk factors [65]. Therefore, a Mediterranean diet seems a promising approach to reduce mechanical loads and thus improve OSA severity, compared to a low-fat, calorie-restricted diet.

We are the first to investigate the effect of the Mediterranean diet compared with that of a diet low in fat (both were calorie restricted) on obese patients with moderate to severe OSA [17]. All patients were using CPAP and received counselling to increase physical activity levels. Patients in the Mediterranean diet group showed a greater improvement in AHI during rapid eye movement sleep at 6 months. This may have been related to greater reduction in mechanical load, considering waist circumference decreased to a greater degree in the Mediterranean diet group. Indeed, an *ad libitum*-isocaloric high-monounsaturated fatty acid diet *versus* a low-fat carbohydrate-enriched diet prevents central fat redistribution [66] in insulin-resistant obese subjects, suggesting that the Mediterranean diet could exert beneficial effects on abdominal fat in obese OSA patients. Besides this, the Mediterranean diet is characterised by abundant plant foods (fruits, vegetables, nonrefined cereals, nuts, seeds, wine and olive oil) and molecules with antioxidant and anti-inflammatory properties, such as omega-3 fatty acids, oleic acid, folic acid, vitamins B_6, B_{12}, C and E, phenolic compounds and fibre, which, when consumed in combination may have synergistic effects [67]. These molecules may exert their beneficial effects in patients with OSA by combating inflammation and oxidative stress and possibly improving upper airway neuromuscular control and upper airway muscle force-generating capacity (figure 3).

Effects on cardiovascular risk

The extent to which a Mediterranean diet might improve OSA-associated CVD risks is unknown. However, it has gained significant attention as a way to prevent CVD in adults at high risk. The PREDIMED trial [68] tested the efficacy of two energy-unrestricted Mediterranean diets (one supplemented with extra-virgin olive oil and another with nuts), compared with a low-fat diet in primary prevention of CVD. After a median 4.8-year follow-up both Mediterranean diets resulted in a relative risk reduction of ∼30% of major CVD events. Whether this dietary pattern might prevent CVD complications of OSA *via* an improvement of OSA conditions *per se* or other pathways requires further investigation.

OSA as moderator of weight loss and cardiovascular risk

While dietary-induced weight loss is known to be effective for treating OSA, whether underlying OSA attenuates dietary-induced weight loss is less clear. BOREL *et al.* [18] addressed this question in a group of males with visceral adiposity who underwent a weight loss intervention that included nutritional counselling (500 kcal daily energy deficit) and moderate physical activity promotion (160 min·week^{-1}). All participants underwent at-home sleep monitoring. After the 1-year intervention, males with OSA at
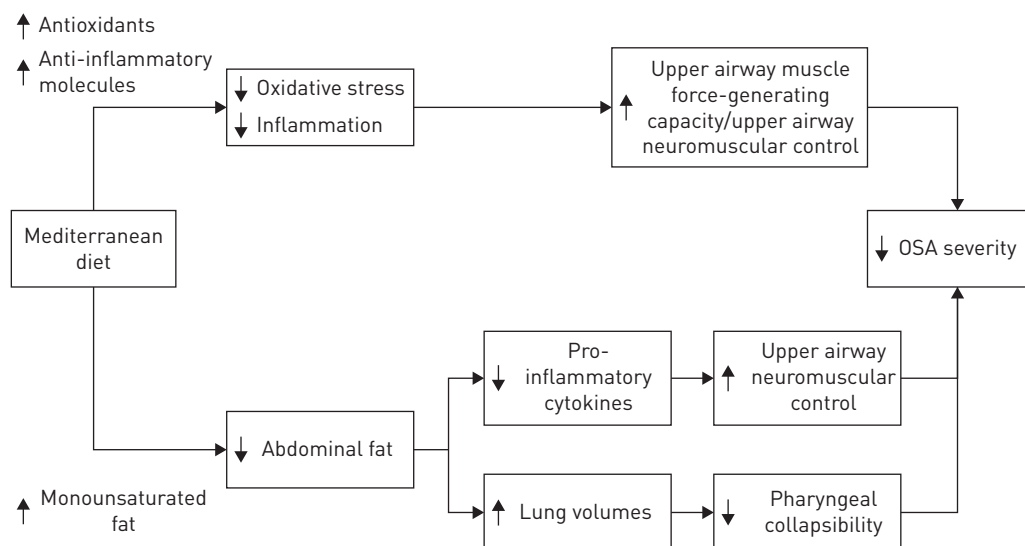

FIGURE 3 Schematic diagram indicating the possible mechanisms through which the Mediterranean diet may improve the severity of obstructive sleep apnoea (OSA), independent of weight loss.

baseline (oxygen desaturation index (ODI) $\geqslant$10 events·h^{-1}) had smaller reductions in waist circumference, total fat mass and triglycerides, and attenuated improvement in high-density lipoprotein cholesterol compared to males without OSA (ODI <10 events·h^{-1}). Higher ODI at baseline was associated with lower reductions in fat mass and waist circumference as well as smaller improvement in glucose clearance.

There is speculation that resistance to weight loss is caused by frequent arousals from sleep or disruptions in sleep quality. While the explanation for this is not well understood, addressing possible mechanisms could have implications for therapeutic approaches. Accordingly, SPIEGEL et al. [69] assigned 12 young males to 2 days of sleep restriction and 2 days of sleep extension while controlling calories ingested and the levels of physical activity. When the participants spent 4 h in bed, mean leptin levels across the following day were 18% lower and ghrelin levels were 28% higher compared to spending 10 h in bed. The decrease and increase in leptin and ghrelin, respectively, could be due to increased sympathetic nervous system activity or cardiac sympathovagal balance from sleep loss [70, 71], a critical point for the current discussion, given that these are major features characterising OSA. In addition, the subjects self-reported increased hunger and appetite during the sleep-restricted protocol. Indeed, sleep restriction appears to increase signalling to reward and pleasure centres of the brain that enhance hedonic perception of food, which would drive motivation for food seeking and consumption [72]. The obvious implication of these findings is that inadequate sleep resulting from OSA could promote excess eating, thereby impairing weight loss. We emphasise that these participants had an increased appetite for food with high carbohydrate content, including "sweets, salty snacks and starchy food", but there was no information related to diet prior to undergoing these sleep protocols.

In addition to the potential impact of disrupted sleep on appetite hormones, PUNJABI and POLOTSKY [73] gathered data showing that OSA is associated with altered glucose metabolism, which may disrupt weight loss. Indeed, increased AHI in overweight males is related to worsening insulin resistance, regardless of the degree of obesity [31]. STAMATAKIS and PUNJABI [74] found that following 2 nights of experimentally fragmented sleep, healthy volunteers exhibited decreased insulin sensitivity. In addition, sleep fragmentation increased sympathetic nervous activity during sleep and wakefulness and increased cortisol levels. Substantial evidence indicates that increased sympathetic nervous system activity promotes insulin resistance [75], while a rise in cortisol levels can decrease insulin sensitivity, enhance hepatic gluconeogenesis and inhibit insulin secretion [76]. Sleep restriction relative to normal sleep results in increased free fatty acid levels and is correlated to a reduction in insulin sensitivity [77]. These changes would facilitate increased synthesis of triglycerides, the generation of triglyceride-rich lipoproteins [78] and fat accumulation in the liver. A vicious cycle would ensue, in which a fatty liver increases the delivery of fat to all tissues via increased export of very low-density lipoprotein [55].

Whether sleep disruption or increased sleep fragmentation is the mechanism through which OSA might impair weight loss, each is in line with the theory proposed by LUDWIG and FRIEDMAN [20] of a disproportionate anabolic state that favours storage rather than oxidation of ingested calories, reinforcing the need for treatment. However, KAJASTE et al. [79] found that adding CPAP treatment to a cognitive behavioural weight reduction programme did not augment weight loss over 6 months among obese males with OSA at baseline. In the APPLES study [80], a randomised, double blinded, two-arm, sham-controlled study of CPAP, the use of CPAP led to weight gain. A subgroup analysis of this clinical trial [81] revealed that CPAP use did not substantially change dietary or physical activity habits. By no means do these data suggest against primary treatment of OSA. What they do suggest is that additional interventions are needed to facilitate weight loss. We emphasise that the APPLES trial did not include a dietary intervention and the diet employed by KAJASTE et al. was calorie restricted with high carbohydrate levels (65% of total calories). To this end, a major shortcoming of previous work is the failure by investigators to appreciate the benefits of low carbohydrates and its potential interaction with CPAP treatment.

There is evidence that OSA may impair metabolic improvements among males who change dietary and exercise habits [18]. Addressing this last point is especially important in light of the decision taken by the National Institutes of Health in 2012 to halt the Look AHEAD trial on the basis of futility [19]. The Look AHEAD study was undertaken to assess the long-term effects of intensive lifestyle intervention, consisting of dietary modification, exercise and education versus diabetes support and education in 5000 overweight and obese individuals with type 2 diabetes. At a median follow-up of almost 10 years, there was no significant difference in CVD morbidity and mortality was noted between the groups at 10 years [46]. This "negative" result has raised questions about contemporary paradigms of preventive cardiology, some of which were the focus of a recent commentary by DESPRÉS and POIRIER [82]. Noticeably absent from current discussions has been the consideration of the possible role of underlying OSA in moderating the associations between altering dietary habits, increased exercise and improved cardiovascular risk profiles. Considering that 86% of Sleep AHEAD (an ancillary study of Look AHEAD) participants had established OSA [63], the lack of apparent benefit in the larger trial might be explained by the high likelihood that

most individuals had underlying OSA at baseline, and despite measurable changes in OSA severity, fitness and weight, a majority still had underlying OSA at 10 years of follow-up.

Exercise as treatment for OSA
Effects of exercise on OSA pathology
Evidence from epidemiological research suggests that individuals who are physically active have a reduced risk of OSA compared to individuals who are less active [83, 84]. In the Wisconsin Sleep Cohort study [85], adults underwent overnight sleep studies every 4 years and completed exercise surveys at baseline and at a 10-year follow-up. Independent of confounders such as body mass index, hours of exercise were associated with a reduced incidence of mild and moderate OSA, while a decrease in exercise duration was associated with worsening OSA. In addition, experimental studies suggest improvements in severity of sleep apnoea with exercise alone [15]. For instance, KLINE et al. [21] randomised 43 patients with OSA of moderate severity to four sessions of exercise training per week for 12 weeks or a stretching control. Compared with a stretching control, exercise resulted in a reduction in AHI of ~7 events·h^{-1} of sleep as well as significant changes in oxygen saturation and stage N3 sleep. These improvements were observed independent of weight loss, suggesting other possible mechanisms of improvement in OSA with exercise.

One hypothesis is that moderate exercise reduces fluid accumulation in the legs and nocturnal rostral fluid shift. Fluid redistributed to the neck upon lying down at night may lead to increased tissue pressure surrounding the upper airway, reducing its size and increasing its collapsibility [86]. In a 4-week-long study consisting of 30 min of walking for 5 days per week, MENDELSON et al. [87] found a 34% reduction in AHI among OSA patients with coronary artery disease. Exercisers experienced a significantly greater reduction in evening leg fluid volume (20%) while the overnight change in upper airway cross-sectional area increased from −0.20 cm^2 to 0.09 cm^2. No changes in physical fitness or body weight were observed, indicating that the reduction in AHI in those with OSA was due to the reduction in overnight fluid shift from the legs to the neck and the consequent dilation of the upper airway.

Another compelling theory for why exercise might reduce sleep apnoea severity is that it appears to have a profound effect on central adiposity. Studies [88, 89] have shown that exercise training without weight loss can achieve significant reductions in central adiposity. In particular, 6 months of exercise training was associated with reductions in total abdominal fat of 12% and abdominal visceral fat of 18% despite a total body weight loss of only 2.2 kg among older adults with hypertension. Importantly, the positive change in central adiposity was the strongest predictor of improvements in markers of the metabolic syndrome [90].

These studies highlight the fact that moderate exercise can lead to favourable modifications in body composition, specifically by reducing abdominal obesity. As described, exercise may be necessary for abdominal visceral fat loss [89, 90], which may have major implications for the obese OSA patient.

Effects of exercise on cardiovascular outcomes
Perhaps equally important, and critical to the current discussion is the impact of increased physical activity and exercise and consequent improved fitness on cardiovascular health. An abundance of data demonstrate a reduced risk of both CVD morbidity and mortality with increasing levels of physical activity [91] and peak exercise capacity [92, 93]. Importantly, we [94] and others [95] have demonstrated improvements in exercise capacity in OSA patients using lifestyle programmes including exercise.

Cardioprotective benefit of exercise
The precise mechanisms through which physical activity or fitness reduces the risk of all-cause and CVD mortality remains incompletely understood. However, in a prospective sample of 27 055 females the risk of CVD over 10 years decreased linearly with higher levels of self-reported physical activity, while haemoglobin A$_{1c}$, traditional lipids, novel lipids and homocysteine explained just 59% of this reduction, thereby implying that the degree of risk reduction associated with physical activity cannot be entirely attributed to improvements in traditional risk factors. Others have hypothesised that this apparent "risk factor gap" [96] can be partly filled by the independent effect of exercise on vascular endothelial function [97]. HAMBRECHT et al. [98] found that 4 weeks of cycle exercise enhanced both conduit and resistance artery endothelium-dependent vasodilator function in coronary artery disease patients. Additionally, endothelial nitric oxide synthase (eNOS) mRNA and shear stress-related eNOS phosphorylation improved with training, indicating that episodic increases in arterial shear stress is the likely mechanism responsible for enhanced nitric oxide bioactivity and, in turn, endothelial function. Moreover, aerobic training appears to reduce arterial stiffness in obese adults with below-median values in systolic blood pressure [99]. Thus, it appears that some of the beneficial effects of exercise on cardiovascular health may be associated with vascular conditioning that results in enhanced endothelium-dependent function. However, we speculate whether exercise can be an effective countermeasure to protect against the nightly insults imparted on the
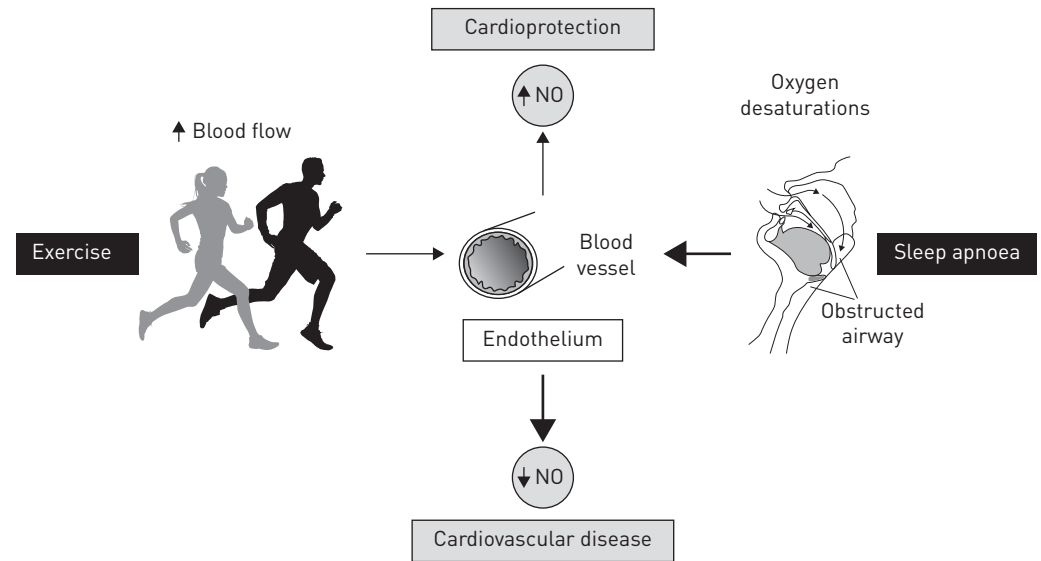
FIGURE 4 Exercise confers cardioprotection through improved vascular function. Obstructive sleep apnoea is characterised by oxyhaemoglobin desaturations and sympathetic activation, which result in cardiovascular morbidity and mortality. The thin arrows imply that exercise may not confer cardioprotection in the presence of disturbed sleep. NO: nitric oxide bioavailability.

vascular wall, as are believed to occur with OSA. The effectiveness of exercise on reducing cardiovascular risk may ultimately depend on the severity of OSA as well as the intensity of exercise programming (figure 4). Currently, there are few data to demonstrate whether vascular function in OSA patients is amenable to modification using current guidelines [100].

Effects of exercise on cardiovascular risk in OSA

None of the above-mentioned OSA exercise studies assessed cardiometabolic parameters or markers of vascular structure and function commonly associated with OSA. We [94] recently reported that following a 12-week intervention that included exercise and dietary-induced weight loss, older males and females with OSA had reduced AHI and improvements in nightly desaturations as well as reductions in body fat and increased fitness. Uniquely, we found in addition that positive changes in arterial distensibility (a marker of vessel wall damage) was related to reduced severity of nightly desaturations, suggesting that improvements in vascular structure and function occurring with lifestyle change may be influenced more by the severity of OSA rather than body weight or degree of adiposity. This implies in addition that vascular impairments in many patients with OSA may not be caused by physical inactivity. Only one exercise study [101] assessed forearm blood flow (FBF) heart failure patients with and without OSA. 4 months of aerobic exercise lessened the severity of OSA and increased FBF in both groups. Among the potential mechanisms underlying this peripheral vascular adaptation is an enhancement in endothelium function. However, these data were collected in heart failure patients, and the cardiovascular risk improvement with exercise in otherwise healthy obese adults with OSA remains a novel aspect of exercise treatment to be investigated.

Conclusion

Lifestyle changes and weight loss are cornerstones of OSA therapy. Few studies have examined the role of changes in diet quality or exercise in this disease. Since there is a complex, rather than simple weight-load pathogenesis of OSA, it would be interesting to consider how altering dietary quality might affect OSA severity beyond simply facilitating weight loss. The effectiveness of different diets in OSA patients beyond the potential reductions on upper airway mechanical loads needs to be explored. Investigating the role of unrestricted low-carbohydrate and Mediterranean diets in upper airway neuromuscular control and taking into account the confounding effect of weight change could be an approach.

Future studies should identify the optimal exercise programme, characterised by type, frequency and intensity of exercise, length of programme, duration of individual supervised sessions and number of sessions per week for OSA treatment. These studies should focus not only on a single mechanism responsible for improvements in OSA following exercise training, but on several possible mechanisms.

While diets and exercise will no doubt have major implications for CVD morbidity, concomitant use of CPAP to treat underlying OSA may result in more beneficial cardioprotective outcomes, and this can be explored in patients undergoing CPAP treatment in comparison to patients not undergoing CPAP treatment.

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