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SYSTEMATIC REVIEW

Assessing the impact of diet, exercise and the combination of the two as a treatment for OSA: A systematic review and meta-analysis

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ABSTRACT

This study aimed to provide an updated systematic review and meta-analysis of randomized controlled trials (RCT) investigating the effectiveness of lifestyle interventions on weight loss and the impact on the severity of obstructive sleep apnoea (OSA). A systematic search of five databases between 1980 and May 2018 was used to identify all RCT which employed a lifestyle intervention (i.e. diet-only, exercise-only or combination of the two) aiming to reduce the severity of OSA (assessed using the apnoea–hypopnoea index (AHI)). Random-effects meta-analyses followed by meta-regression were conducted. Ten RCT involving 702 participants (Intervention group: n = 354; Control group: n = 348) were assessed in two meta-analyses. The weighted mean difference in AHI (−8.09 events/h, 95% CI: −11.94 to −4.25) and body mass index (BMI, −2.41 kg/m^2, 95% CI: −4.09 to −0.73) both significantly favoured lifestyle interventions over control arms. Subgroup analyses demonstrated that all interventions were associated with reductions in the AHI, but only the diet-only interventions were associated with a significant reduction in BMI. No association was found between the reduction in AHI or BMI and the length of the intervention, or with baseline AHI and BMI levels. All lifestyle interventions investigated appear effective for improving OSA severity and should be an essential component of treatment for OSA. Future research should be directed towards identifying subgroups likely to reap greater treatment benefits as well as other therapeutic benefits provided by these interventions.

Key words: diet, exercise, meta-analysis, obstructive sleep apnoea, randomized controlled trial.

INTRODUCTION

Obstructive sleep apnoea (OSA) is a common sleep disorder and is associated with a wide range of adverse health consequences, including cardiovascular disease, metabolic disorders and cognitive impairment.[1,2] Obesity, which is the strongest risk factor for OSA, is a growing epidemic and is one of the western world's leading healthcare concerns. Available data indicate that the prevalence of OSA is as high as 40% in obese men (body mass index (BMI) > 30 kg/m^2)[3] and up to 90% in morbidly obese individuals (BMI > 40 kg/m^2).[4,5] Importantly, as the prevalence of obesity continues to rise, so too does the number of individuals developing OSA. Large epidemiological studies have reported a striking dose response association between obesity and OSA.[6] For example, the Wisconsin Sleep Cohort found that 10% weight gain led to a sixfold increase in the odds of developing moderate–severe OSA, independent of confounding factors such as age and baseline body habitus measures.[7] As such, weight loss is often recommended as a means of managing both OSA (either alone or in combination with common OSA treatments such as continuous positive airway pressure (CPAP)) and the many complications associated with obesity.

In 2013, a systematic review and meta-analyses of randomized controlled trials (RCT) assessed the impact that lifestyle interventions such as diet (four studies) and exercise (two studies) or the combination of the two (one study) had on losing weight and reducing OSA severity.[8] The findings from these analyses demonstrated that exercise alone modestly reduced the

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apnoea–hypopnoea index (AHI), and patients appeared to gain a small additional benefit when exercise was combined with a diet intervention. Interestingly, only the diet and exercise combined intervention was associated with a significant reduction in BMI. However, the small number of RCT included in this analysis and the high level of heterogeneity between the trials limited the ability to make comparisons between intervention subgroups.

Notably, there have now been an additional four RCT[9–12] published since 2013. We therefore aimed to perform an updated systematic review and meta-analysis of RCT comparing lifestyle interventions to a control condition in adult OSA patients. More specifically, we aimed to determine the impact these lifestyle interventions had on both the severity of OSA (assessed using the AHI) and BMI. A secondary aim was to also investigate the influence of intervention type (i.e. diet, exercise and the combination of the two), and whether the change in AHI is related to the change in BMI using a combination of both subgroup analyses and meta-regression techniques.

METHODS

The present systematic review and meta-analysis was performed in line with recommendations from the Cochrane Collaboration and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13]

Data sources

A systematic review was conducted in May 2018 through searching five databases including CINAHL, Cochrane, Embase, OVID Medline and Scopus (see Appendix S1, Supplementary Information, for complete search descriptions). All searches were limited to human studies published in English and were limited to publications since 1980. For Scopus, we used the search string: TITLE-ABS-KEY ((diet* OR food* OR eating* OR beverage* OR nutrition* OR exercis* OR 'physical* activ*' OR fitness* OR sport*) AND ('sleep apnoea' OR 'sleep apnoea')) AND PUBYEAR >1979 AND (LIMIT-TO (LANGUAGE, 'English')).

Study selection

To be eligible for inclusion, we required that the studies were performed in adults (i.e. aged over 18 years) and diagnosed with OSA (AHI ≥ 5 events/h). The intervention was specified as either a diet or exercise/physical activity intervention, or combination of the two. Diet interventions were defined as any diet programme with a clearly reported energy restriction plan. Physical activity/exercise interventions were defined as any programme that clearly specified a time and intensity for the intervention. Our primary outcome measure was the severity of OSA as measured by the AHI, thus any paper that did not report a post-intervention AHI was excluded. A secondary outcome of interest was BMI. All RCT that met the inclusion criteria were eligible for review (1980–May 2018). Cohort studies, case studies, literature reviews, meta-analysis, narrative reviews, as well as commentaries, letters, conference abstracts and protocols were excluded and cross-reviewed for exclusion by several reviewers (C.B., B.A.E., D.M.O. and GSH). Additional exclusion criteria included interventions in heart failure and/or coronary artery disease patients, exercises for the upper airway (i.e. oropharyngeal exercise), no moderate-vigorous physical activity component (i.e. inspiratory muscle training), weight loss as a result of bariatric surgery or pharmaceutical interventions, diet and/or exercise modifications 'suggested' to participants but no defined prescription, follow-up studies (original research studies and data sets only) and control group receiving OSA treatment, that is CPAP (unless both groups being treated concurrently). Studies in which the control group were also being prescribed some form of diet/exercise intervention were further excluded (see Table S1 in Supplementary Information for list of excluded RCTs).

Database search results were screened for duplicates using EndNote (Version 7.0.2, Thomson Reuters, Eagan, Minnesota, USA 2013). Once duplicates were removed, titles and abstracts of studies were screened for eligibility using Covidence software (Covidence systematic review software, Veritas Health Innovation, Melbourne, VIC, Australia). All studies that comprised the relevant populations, interventions and outcomes were included. The full text of the included papers was then reviewed to further exclude papers that did not meet the inclusion criteria. Finally, articles' reference lists from already-included studies were also searched but no additional studies meeting inclusion were found.

Data extraction and assessment of risk of bias

Data were extracted according to the National Health and Medical Research Council (NHMRC) Data Extraction form for RCT and cohort studies.[14] Data extraction of each eligible study was performed independently by two reviewers (C.B. and L.G.), and then the extracted data was cross-checked by a third reviewer (B.A.E. or G.S.H.) and any disagreements were discussed and resolved. Three independent reviewers (C.B., Z.E.D. and L.G.) reviewed the risk of bias of individual studies using Cochrane's risk of bias tool.[15] Risk of publication bias was examined using visual inspection of funnel plots and Egger's test for asymmetry in the funnel plot.

Synthesis of results and statistical analysis

Two meta-analyses were conducted to examine the effect of the interventions (i.e. diet or physical activity/exercise alone or in combination) on the primary (AHI) and secondary (BMI) outcomes. Inclusion in the meta-analysis was based on whether authors reported mean post-intervention or mean within-group change (pre vs post) and SD of the AHI for both intervention and control groups.

Random-effects meta-analyses were undertaken (Review Manager Version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A weighted mean difference analysis was undertaken

for each of the outcome measures examined. Following receipt of information from authors, we obtained consensus on reporting the within-group change scores across all studies which was therefore used as our primary analyses. In total, complete change data were provided for 10 studies for the AHI outcome and 9 studies for the BMI outcome. As a sensitivity analyses, we also conducted an analysis where the post-intervention scores were used preferentially (Appendix S1, Supplementary Information). Subgroup meta-analyses were performed based on the type of intervention applied (i.e. diet, exercise or combination of the two). Statistical heterogeneity was assessed using the Cochran's Q and I^2 statistics. Meta-regression analyses were carried out using STATA (Version 14, StataCorp College Station, TX, USA, 2015) using a random-effects model.[16] Meta-regression analyses were used to identify whether the study characteristics of length of intervention and baseline AHI and BMI values explained variation in each meta-analysis dependent variable. We also examined whether between-study differences in changes in BMI explained variation in between-study variation in AHI to examine a potential mechanism of action.

RESULTS

Studies included in meta-analyses

The summary of the search results is depicted in Figure 1. A total of 4996 publications were identified in the initial search, of which 11 were suitable to include in the systematic review; however, one study was further excluded as the data were not obtained from the authors.[17] Thus, a total of 10 studies were included in the final systematic review and meta-analyses. The pre- and post-intervention values from all 10 eligible studies are presented in Table 1. All studies were assessed using the Cochrane risk of bias tool[15] which is outlined in Figure 2.

Overall, the 10 RCT included in the meta-analyses recruited a total of 702 participants (Intervention group: n = 354; Control group: n = 348), who underwent lifestyle intervention programmes including diet (n = 4 studies[11,19,20,23]), exercise (n = 4 studies[9,10,21,22]) and a combination of the two (n = 2 studies[12,18]). The diet-only RCT typically employed very low-calorie diets (VLCD; ~600–800 kcal/day) of between 9 and 52 weeks in duration, the exercise-only RCT consisted of supervised aerobic and/or resistance exercises between 4 and 12 weeks in duration (≥3 times/week) and the combined diet and exercise interventions aimed to reduce caloric intake undertake between 60 and 175 min of aerobic exercise per week (see Table 2 for more details). Three of the included RCT[9,12,19] utilized CPAP therapy in combination with lifestyle intervention (one from each category), whereas the remaining studies excluded participants receiving current treatment for OSA. The age of the participants in the studies ranged from 18 to 80 years, with mean baseline AHI ranging from 9.0 to 43.4 events/h (overall mean: 27.1 events/h) and mean baseline BMI ranging from 28.0 to 36.8 kg/m^2 (overall mean: 32.4 kg/m^2). The timeframe of the intervention varied from 1 month to 1 year (12 (4–43) weeks, median (interquartile range)). Two of the included studies were conducted in Brazil, two in the United States and two in Finland, while the remainder were conducted in China, France, Sweden and Turkey.

Impact of lifestyle interventions on OSA severity

A meta-analysis was conducted to assess the differences in mean AHI changes between intervention and control groups, and results are outlined in a forest plot (Fig. 3). This meta-analysis included 10 RCT with a total of 702 participants, grouped into three subgroups of diet (four RCT, 217 participants), exercise (four RCT, 117 participants) and combined intervention (two RCT, 368 participants).

When using the change in AHI data, the pooled mean change in AHI was −8.09 events/h (−11.94 to −4.25). Total heterogeneity between all studies was high (I^2 = 78%, Cochran's Q P-value < 0.001). Subgroup analyses detected considerable heterogeneity within subtypes of lifestyle intervention (I^2 ranged between 22% and 89% within subgroups). A significant reduction in AHI was observed in all three types of interventions, with each reducing the AHI by ~8.1 events/h. Referencing the post-trial AHI values (where available) had minimal impact on the pooled mean change in AHI (Fig. S1A, Supplementary Information).

Impact of lifestyle interventions on BMI

A second meta-analysis was conducted to explore the impact of various components of the lifestyle interventions on mean changes in BMI between intervention and control groups. One of the 10 studies included in the AHI analysis did not report the post-BMI data.[9] As such, only nine RCT were included in the BMI meta-analysis. In total, this meta-analysis included 670 participants again grouped into three subgroups: diet intervention (four RCT, 217 participants), exercise intervention (three RCT, 85 participants) and combined (two RCT, 368 participants). When using the change in BMI data, the pooled effect demonstrated that lifestyle interventions were associated with a reduction in BMI (Fig. 4). The pooled mean reduction in BMI was −2.41 kg/m^2 (−4.09 to −0.73). However, the heterogeneity between these study results was high (I^2 = 98%, Cochran's Q P-value < 0.001). Heterogeneity was similarly high within subtypes of lifestyle interventions (I^2 ranged between 42% and 96% within subgroups). A significant reduction in BMI was observed in both the diet-only and combined diet and exercise subgroup analyses, but not for the exercise-only analysis. These results were unchanged when preferencing the post-trial BMI values where available (Fig. S1B, Supplementary Information).

Investigation of heterogeneity

To investigate the source of the high levels of heterogeneity in both the BMI and AHI meta-analyses, meta-regression was conducted (see Appendix S2, Supplementary Information, for complete meta-regression analyses). The effect of the (i) intervention length, as

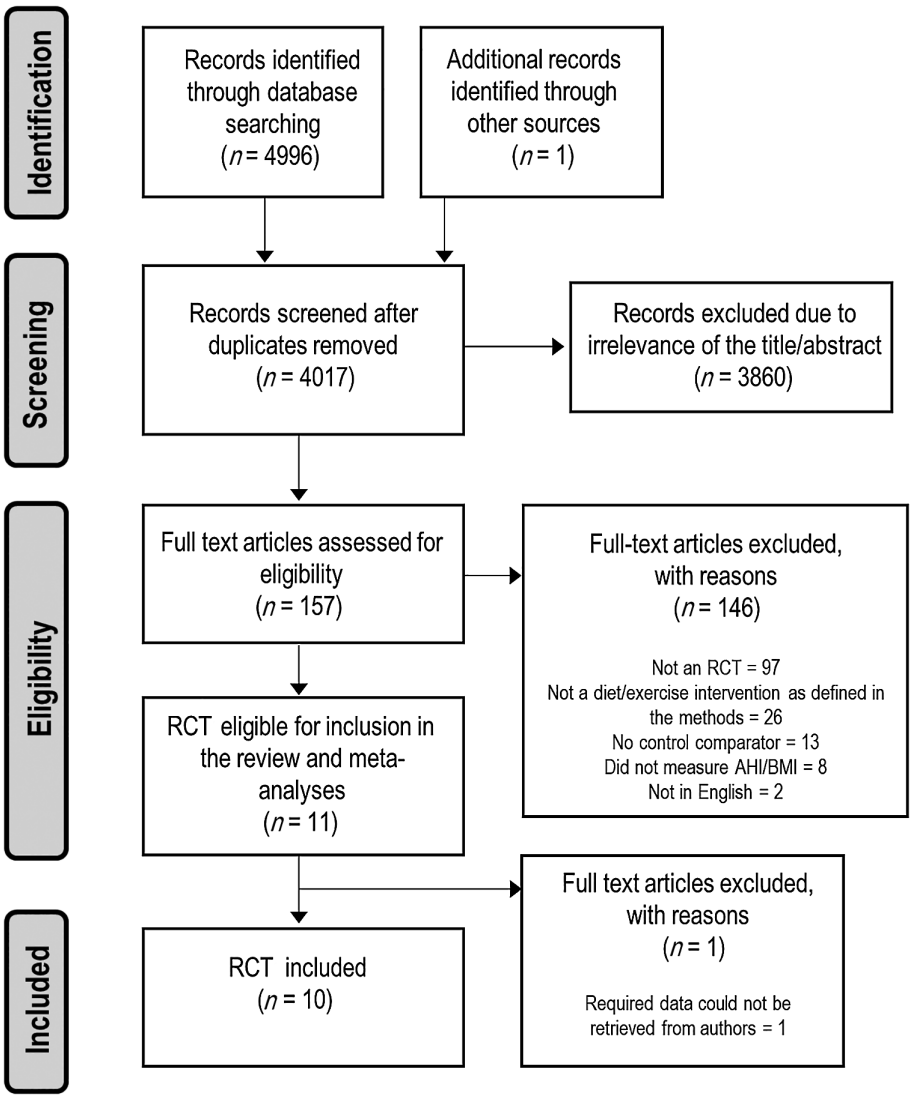

Figure 1 Flow chart of study selection. AHI, apnoea–hypopnoea index; BMI, body mass index; RCT, randomized controlled trial.

well as (ii) baseline AHI and (iii) baseline BMI, on the change in BMI and AHI was investigated in all studies. No significant correlation was observed in any of the investigated potential cofactors and changes in outcomes (i.e. change in AHI and BMI). A meta-regression to assess whether variation in BMI results across studies explained variation in AHI results did not identify a significant association.

Publication bias assessment

The effect of the potential publication bias in the findings was assessed separately for each outcome. The results of the Egger's test for both diurnal AHI and BMI were non-significant (all $P > 0.05$). However, both sets of funnel plots (Fig. S2, Supplementary Information) demonstrated that multiple studies laid outside the pseudo 95% confidence limits, although for BMI this was in a way where the largest study reported the more extreme effect size. For AHI, larger studies were on both sides of the mean indicating heterogeneity more than a systematic publication bias in this area.

DISCUSSION

The major findings of this meta-analyses are that all lifestyle interventions (diet, exercise or the combination of the two) result in a reduction in OSA severity (as measured by the AHI) by a similar magnitude. However, only diet interventions demonstrated a significant reduction in BMI. Interestingly, neither baseline BMI, AHI nor the length of the intervention was associated with changes in AHI or BMI following the interventions. Taken together, our findings suggest that the relationship between OSA and obesity is non-linear and complex.

Sources of heterogeneity and predictors of response

The findings in this review are similar with that of previous systematic reviews and meta-analyses[8,24–26] in that lifestyle interventions generally are effective in reducing the severity of OSA. Furthermore, similar to previous analyses, there was a high level of heterogeneity

Table 1 Summary of pre- and post-intervention weight, BMI and AHI outcomes

Study	Sex	Drop-out rate (%)	Group	Age (years)	Pre-weight (kg)	Post-weight (kg)	Weight standard mean change (SD)	Pre-BMI (kg/m^2)	Post-BMI (kg/m^2)	BMI standard mean change (SD)	Pre-AHI (events/h)	Post-AHI (events/h)	AHI standard mean change (SD)
Ackel-D'Elia *et al.* (2012)[9]	M	32	A	48.4 (9.2)	81.0 (10.0)	—	—	28.0 (3.1)	—	—	40.5 (22.9)	35.0 (19.6)	−5.5 (15.3)†
			B	49.5 (7.7)	84.4 (9.7)	—	—	28.5 (2.2)	—	—	42.3 (21.6)	34.7 (23.5)	−7.6 (16.4)†
Desplan *et al.* (2014)[10]	M/F	11	A	—	85.0 (17.2)†	82.6 (16.4)†	−2.3 (1.7)†	29.9 (3.4)	29.1 (3.1)b	−0.8 (0.6)†b	40.6 (19.4)	28.0 (19.3)b	−12.6 (9.6)†b
			B	—	89.1 (11.6)†	89.1 (10.8)†	0.0 (2.0)†	31.3 (2.5)	31.3 (2.2)	0.0 (0.7)†	39.8 (19.2)	45.4 (22.5)	5.5 (13.8)†
Fernandes *et al.* (2015)[11]	M/F	28	A	39.1 (10.8)	100.1 (13.5)	94.5 (11.9)c	−5.57 (6.0)c	34.6 (2.7)	32.7 (2.8)c	−1.9 (2.0)c	26.7 (64.4)	19.5 (26.6)a	−7.2 (9.3)a
			B	44.1 (6.2)	99.7 (14.2)	100.2 (16.3)	0.4 (3.8)	35.9 (2.9)	36.0 (3.4)	0.1 (1.4)	16.9 (8.6)	17.0 (11.0)	0.1 (5.9)
Foster *et al.* (2009)[18]	M/F	17	A	61.2 (6.6)	102.9 (19.6)	—	−10.8 (7.8)c	36.8 (5.8)	32.6 (5.6)c	−3.8 (3.4)c	22.9 (18.0)	18.3 (15.3)c	−5.4 (16.8)c
			B	61.3 (6.4)	102.0 (17.1)	—	0.6 (8.3)	36.5 (5.7)	36.1 (5.5)	0.2 (3.5)	23.5 (15.0)	28.3 (20.7)c	4.2 (16.5)c
Johansson *et al.* (2009)[19]	M	3	A	47.5 (7.5)	113.4 (14.8)	—	−18.7 (4.1)c	34.4 (2.9)	—	−5.7 (1.1)c	37.0 (17)	12.0 (7.0)	−25.0 (17.0)c
			B	49.9 (7.1)	111.7 (13.7)	—	1.1 (1.9)	34.8 (2.9)	—	0.3 (0.6)	37.0 (14)	35.0 (14.0)	−2.0 (11.0)
Kemppainen *et al.* (2008)[20]	M/F	0	A	51.0 (8.3)	103.0 (14)	—	—	33.0 (3.3)	—	−5.4 (1.5)c	11.0 (3.6)	—	−3.2 (9.2)
			B	49.0 (8.9)	94.0 (12)	—	—	32.0 (3.1)	—	−0.5 (1.5)	9.0 (2.7)	—	−1.3 (5.5)
Kline *et al.* (2011)[21]	M/F	12	A	47.6 (6.8)	105.6 (15.5)	104.7 (16.1)†	−0.9 (3.3)†	35.5 (6.2)	35.2 (6.4)†	−0.3 (1.1)†	32.2 (29.1)	24.6 (22.9)a	−7.6 (13.0)a
			B	45.9 (8.8)	99.3 (20.0)	98.7 (20.0)†	−0.6 (1.9)†	33.6 (5.6)	33.5 (6.0)†	−0.2 (0.6)†	24.4 (22.4)	28.9 (25.6)	4.5 (9.6)
Ng *et al.* (2015)[12]	M/F	21	A	51.4 (9.1)	83.7 (15.4)†	78.8 (16.3)†	—	30.2 (3.9)	28.4 (4.2)c	−1.7 (1.7)†c	43.4 (20)	35.3 (21.7)c	−8.1 (15.5)†c
			B	52.0 (9.3)	83.3 (12.2)†	81.4 (11.9)†	—	30.5 (4.2)	29.9 (4.2)c	−0.7 (1.3)†c	42.5 (20)	39.6 (19.5)	−2.8 (16.5)†
Sengul *et al.* (2011)[22]	M	20	A	54.4 (6.6)	86.4 (8.0)	84.7 (9.1)	−1.7 (3.9)†	29.8 (2.7)	29.2 (3.1)	−0.6 (1.4)†	15.2 (5.4)	11.01 (5.3)a	−4.2 (4.4)†a
			B	48.0 (7.5)	88.5 (16.2)	88.1 (16.8)	−0.4 (4.0)†	28.4 (5.4)	28.3 (5.5)	−0.1 (1.3)†	17.9 (6.4)	17.4 (11.2)	−0.6 (8.9)†
Tuomilehto *et al.* (2009)[23]	M/F	11	A	51.8 (9.0)	101.2 (11.9)	—	−10.7 (6.5)c	33.4 (2.8)	—	−3.5 (2.1)c	10.0 (3.0)	—	−4.0 (5.6)a
			B	50.9 (8.6)	92.3 (11.3)	—	−2.4 (5.6)	31.4 (2.7)	—	−0.8 (2.0)	9.3 (3.0)	—	0.3 (8.0)

a, <0.05; b, <0.01; c, <0.001 (statistically significant difference between pre- and post- intervention measures).
Data presented as mean (SD).
†Data provided by authors.
—, Value not reported; A, intervention group; AHI, apnoea–hypopnoea index; B, control group; BMI, body mass index; M, male; F, female.

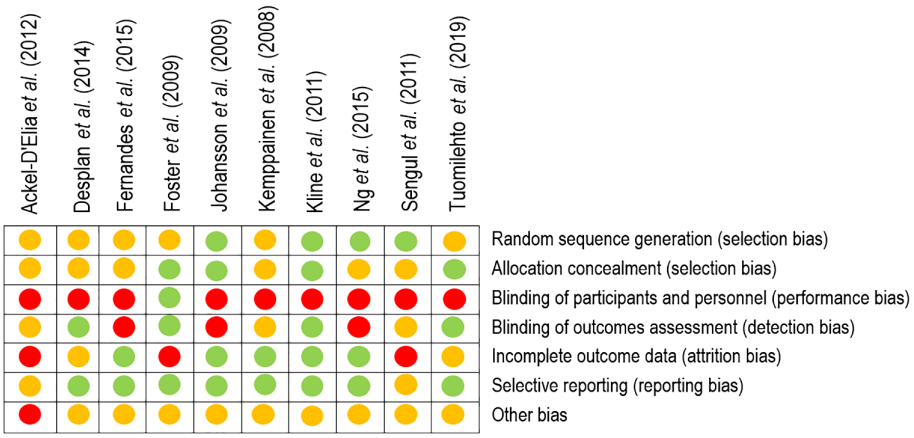

Figure 2 Risk of bias summary. Review of authors' judgements about each risk of bias item for each included study. ●, Low risk of bias; ●, high risk of bias; ●, unclear risk of bias in each respective aspect of study design.

observed between studies (both overall and at the subgroup level) in both analyses. Importantly, exploring the factors potentially responsible for this high level of heterogeneity through meta-regression revealed no correlation between the reduction in AHI and BMI. This finding is similar to the results of a previous meta-analysis by Araghi *et al.*,[8] who also failed to find a significant correlation between reduction in AHI and BMI. Interestingly, Araghi *et al.*[8] reported a positive correlation between baseline AHI and AHI reduction ($r = -0.41$, $P = 0.001$) regardless of the type of intervention introduced, which is in contrast with our analysis showing no significant correlation between these two parameters. Such disparities may be due to the difference in baseline AHI among the participants included in the current and previous meta-analysis,[8] as they included patients with more severe OSA (AHI ranged from 10 to 66.5 events/h, whereas ours ranged from 9 to 43.4 events/h), or may have been biased by the fact that before and after studies were lumped in with the RCT for their analyses. Other potential factors contributing to the high level of heterogeneity in the present analysis may be the degree of caloric restriction (in the diet interventions) or the compliance to the interventions; however, these were not able to be assessed with the available data.

The fact that neither baseline AHI nor BMI predicted the reduction in AHI suggests that a complex interaction likely exists between the obesity and OSA. Previous studies have demonstrated that in the ~40% of patients in whom weight loss resolves their OSA (either due to lifestyle-intervention programmes or weight loss surgery), its resolution cannot be predicted by their starting weight or post-intervention weight loss.[19,27,28] Given that OSA pathogenesis is now recognized to have a combination of anatomical and non-anatomical (e.g. neuromuscular responsiveness and ventilatory control sensitivity) causes, perhaps a better understanding of these traits and how they are modulated by obesity may help the field develop more robust predictors of treatment success, particularly predicting the amount of weight loss required to achieve OSA resolution.

Improvement in OSA with diet interventions

Our results indicate that diet-only interventions reduced BMI by the greatest amount (~4 kg/m^2), there was minimal, non-significant reduction with exercise-only interventions (−0.5 kg/m^2) and there was a strong trend for the combined interventions to reduce BMI by 2 kg/m^2. Notably, despite these variable reductions in BMI between intervention subgroups, they were all associated with similar reductions in AHI. One potential reason explaining why diet-only interventions demonstrated the greatest reductions in BMI is that they typically applied VLCD, compared to the combined intervention studies in which more modest reductions in daily caloric intake were employed. While VLCD interventions often provide rapid and dramatic weight loss, a key concern is the ability to maintain this long-term weight loss, as there is often weight regain after discontinuing the diet.[29,30] As such, in order to achieve long-term benefits and avoid weight regain, lifestyle alterations via behaviour modification programmes are highly recommended.[30]

Improvement in OSA with exercise interventions independent of changes in BMI

Interestingly, the four exercise-only interventions showed that despite no improvement in BMI, there was a significant reduction in AHI. Notably, these findings are similar to several previous meta-analyses conducted in either RCT[8] or a combination of RCT and observational trials[26,31] that also included oropharyngeal exercises as the intervention (excluded from the present meta-analyses). What could explain the improvement in AHI following exercise if BMI remains unchanged? There is no definitive answer to this question, although a number of potential mechanisms have been proposed. First, a reduction in subcutaneous fat surrounding the upper airway would be expected to reduce the tissue pressure surrounding the airway and therefore its propensity towards collapse. Indeed, Karlsen *et al.*[17] demonstrated that high-intensity interval training was associated with a reduction in total body fat (by 2%) despite no change in BMI. Second, increased levels of physical activity are known to improve venous blood flow and reduce leg oedema, which may result in a reduction in the amount of rostral fluid shift surrounding the upper airway thereby attenuating airway collapse during sleep.[32,33] Finally, exercise alone may improve the strength/function of

Table 2 Descriptive characteristics of included studies

Study	*n* (A/B)	Population characteristics	Country	Intervention length	Intervention
(E) Ackel-D'Elia *et al*. (2012)[9]	A: 13 B: 19	Men aged 25–65 years, BMI <35 kg/m^2, moderate–severe OSA (AHI > 15 events/h), ESS >9. Exclusion: history of regular physical activity, previous treatment for OSA, previously diagnosed chronic diseases, alcohol, drug abuse and/or sedative use	Brazil	8 weeks	A: 1 Month sleep hygiene, 2 months CPAP and exercise in forms of walking and running (3 times/week, supervised), 1 week wash-out B: 1 Month sleep hygiene, 2 months CPAP only, 1 week wash-out
(E) Desplan *et al*. (2014)[10]	A: 11 B: 11	Adults aged 35–70 years, moderate–severe OSA (recent diagnosis <1 month, untreated, AHI > 15 events/h), sedentary (Voomips activity score < 9) Exclusion: BMI≥40 kg/m^2, regular use of hypnotic medications, unstable CVD, no history of CPAP treatment	France	4 weeks	A: 4-Week inpatient rehabilitation programme including 24 supervised exercise sessions (2-h session per day; 6 sessions per week) B: 4-Week outpatient standard health education programme twice weekly
(D) Fernandes *et al*. (2015)[11]	A: 11 B: 10	Obese adults (grade I or II), aged 20–55 years, AHI ≥5 events/h. Exclusion: smoking, use of dietary supplements/medications that could affect weight, metabolic profile and/or blood pressure, use of α-adrenergic-blocking agents or pacemakers, recent changes in body weight, diet or exercise regime. Exclusion also included a comprehensive list of medical illnesses such as diabetes, kidney disease, angina pectoris, etc. Pregnant or lactating women were further excluded	Brazil	16 weeks	A: ERG formulated to a 3347·2 kJ/day (800 kcal/day) reduction in baseline total daily energy expenditure. At weeks 4, 8 and 12, the total energy value of the diet was adjusted according to the participant's body weight B: No treatment during the trial; however, patients were prescribed the intervention upon conclusion of the trial as reimbursement
(D + E) Foster *et al*. (2009)[18]	A: 125 B: 139	Adults aged 45–76 years, BMI ≥ 25 kg/m^2, physician-verified T2DM, haemoglobin A1C < 11%, blood pressure < 160 mm Hg systolic and <100 mm Hg diastolic, diagnosed or newly diagnosed but untreated OSA (mild/moderate/severe) (AHI > 5 events/h). Exclusion: previous surgical or current medical treatment for OSA	USA	52 weeks	A: Behavioural weight loss programme prescribed with portion controlled diet (1200–1500 kcal/day if patients weighed <113.6 kg or 1500–1800 kcal/day if the patients weighed >113.6 kg), liquid and bar meal replacements for the first 4 months and 175 min/week of moderate-intensity exercise B: Diabetes support and education consisting of three annual group sessions focused on diet, physical activity and social support (as relating to T2DM)
(D) Johansson *et al*. (2009)[19]	A: 30 B: 33	Men aged 30–65 years, BMI between 30 and 40 kg/m^2, moderate–severe OSA (AHI ≥15 events/h), treated with CPAP. Exclusion: T1/T2DM, current use of a weight loss drug, previous bariatric surgery or recent angina pectoris/atrial fibrillation	Sweden	9 weeks	A: Liquid VLCD (2.3 MJ/day liquid energy) for 7 weeks, followed by 2 weeks of gradual re-introduction of solid food, reaching 6.3 MJ/day at week 9. Clinical examinations were conducted at weeks 1,3,5,7 and 9 including a 1-h group session to

Table 2 Continued

Study	*n* (A/B)	Population characteristics	Country	Intervention length	Intervention
					build support and provide motivation B: Usual diet during the 9-week period. Patients in the control group were offered the intervention programme post-trial to prevent drop-outs
(D) Kemppainen *et al.* (2008)[20]	A: 26 B: 26	Adults aged 18–65 years, BMI between 28 and 40 kg/m^2, mild OSA (AHI 5–15 events/h). No exclusions listed	Finland	12 weeks	A: Supervised, individual lifestyle intervention by a clinical nutritionist including weight reduction counselling at 2, 4, 6, 8 and 10 weeks and consuming a VLCD for 3 months with a recommended increase in daily physical activity B: A single dietary and exercise counselling session by the study nurse and physician
(E) Kline *et al.* (2011)[21]	A: 27 B: 16	Adults aged 18–55 years, BMI ≥ 25 kg/m^2, sedentary (self-reported exercise <2 days/week), moderate–severe untreated OSA (AHI ≥15 events/h). Exclusion: too active/current weight loss, known or suspected cardiovascular, pulmonary or metabolic disease, uncontrolled hypertension (>159/99 mm Hg), pregnancy or inability to exercise due to orthopaedic or musculoskeletal problems	USA	12 weeks	A: Moderate-intensity aerobic exercise (4 days/week; weeks 1–4 gradual increase from 50 min/week to 150 min/week from week 5–12) plus resistance training (1–2 days/week) B: Low- intensity stretching (2 days/week)
(D + E) Ng *et al.* (2015)[12]	A: 61 B: 43	Adults aged 30–80 years, BMI > 25 kg/m2, AHI > 15 events/h. Exclusion: severe sleepiness that might constitute risk to themselves or others, unstable medical disease, coexisting sleep disorders, history of previous surgery to upper airway (except those for nasal problems) or previous surgical treatment of OSA, pregnant women	China	52 weeks	A: Dietitian-led lifestyle modification programme for 12 months. A caloric reduction of 10–20% in daily energy intake from the patient's usual diet was prescribed, which was adjusted with subsequent changes in body weight (targeted BMI 23 kg/m^2). Patients were encouraged to see an exercise instructor at least once during the programme and perform 30 min of aerobic exercise two to three times a week B: Subjects in the control group received simple lifestyle advice from a clinician at baseline and at 6 months
(E) Sengul *et al.* (2011)[22]	A: 10 B: 10	Men, typically healthy, aged 40–65 years with OSA symptoms (snoring, breathing cessations, and daytime sleepiness) and PSG evidence (AHI, sleep efficiency percentage, minimum saturation percentage and total sleep time). Exclusion: medical conditions	Turkey	12 weeks	A: Breathing exercise (15–30 min) and aerobic exercises (45–60 min) 3 times/week. Training programme began at low-moderate intensity over the first 1–2 weeks and progressed to a moderate intensity programme. Exercises targeted

Table 2 Continued

Study	*n* (A/B)	Population characteristics	Country	Intervention length	Intervention
		that may affect ability to exercise, that is angina pectoris, congestive heart failure, cardiomyopathy, emphysema, lung cancer, etc. Any serious medical psychological/neurological problems			at submaximal intensity at 60–70% of maximal oxygen consumption supervised by a physiotherapist B: Not advised any information and/or exercise except for routine clinical treatment and proposals
(D) Tuomilehto *et al*. (2009)[23]	A: 40 B: 41	Adults aged 18–65 years, BMI between 28 and 40 kg/m^2, mild OSA (AHI 5–15 events/h). Exclusion: treated for OSA, pregnant, chronic kidney, thyroid or liver disease	Finland	52 weeks	A: Intervention group provided with VLCD of 600–800 kcal/day for 12 weeks (also permitted calorie-free drinks and vegetables). Subjects were recommended to increase their overall level of daily physical activity. Post VLCD, patients continued sessions with a nutritionist for the rest of the trial B: General oral and written information about diet and exercise was given at baseline, 3-month and 1-year visits by the study nurse and physician; however, no specific individualized programmes were offered

All studies are RCT—parallel (Level II) as per the NHMRC evidence table.[14]

A, intervention group; AHI, apnoea–hypopnoea index (presented as events/h); B, control group; BMI, body mass index (presented as kg/m^2); CPAP, continuous positive airway pressure; CVD, cardiovascular disease; (D), diet only intervention; (D + E), diet and exercise intervention; (E), exercise only intervention; ERG, energy restriction group; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnoea; PSG, polysomnographic; RCT, randomized controlled trial; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; VLCD, very low-calorie diet.

the various upper airway muscles responsible for opening the upper airway.[34] Future physiological studies will likely be needed in order to determine the various mechanisms by which exercise alone improves OSA independent of changes in weight.

Lifestyle interventions and OSA resolution

Despite all interventions reducing the AHI by similar amounts, rarely was this reduction enough to resolve OSA at the group level; the pooled mean baseline and post-intervention AHI in the present analyses were 27.9 ± 4.0 and 23.8 ± 3.9 events/h, respectively (data missing from two studies[20,23]). Of the 3/10 studies that reported cure rates (defined as an AHI < 5events/h) following the lifestyle intervention, success varied dramatically (13.6–61%).[18,19,23] Such variation may be related to the severity of the patients' OSA upon entry into the trial (with the highest cure rate being observed in those that started with mild OSA) as well as the multifactorial nature of OSA pathogenesis (see above) and how these factors/traits are modulated by weight loss/gain.

While the proportion of individuals that have their OSA resolved with lifestyle interventions may be small, there are still likely to be a number of improvements in other patient-centred outcomes. For instance, a recent network meta-analysis[25] comparing the efficacy of CPAP, oral appliances and lifestyle interventions suggested that while CPAP is the most effective at reducing the AHI, exercise training was associated with the greatest improvement in subjective sleepiness, and diet interventions showed reductions in subjective sleepiness that were comparable to those observed with CPAP.

Methodological considerations

There are several limitations in this meta-analysis. First, despite contacting authors to collect unpublished data, we were not able to obtain data from one eligible RCT[17] which might have altered the conclusions drawn. However, the authors report that the AHI was reduced by 8 events/h in the intervention group and there was no significant between-group changes in BMI, which is near identical to the findings from the present meta-

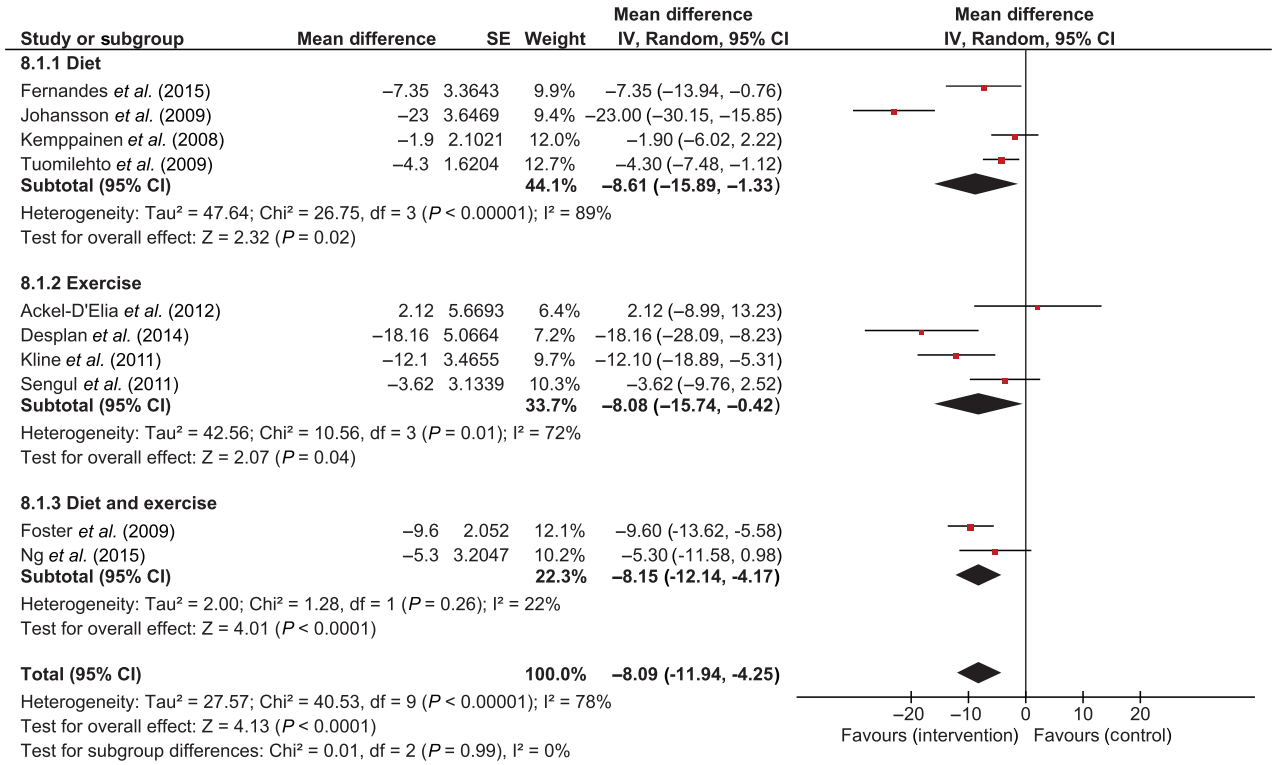

Figure 3 Forest plot comparing the effects of lifestyle interventions and control on the apnoea–hypopnoea index (AHI). For each study, the square represents the mean difference in AHI between the particular lifestyle intervention (i.e. diet, exercise or the combination of the two) and control arms and the width of the line represents 95% CI; a line crossing the 0 events/h (vertical line) indicates no significant difference at α = 0.05. The diamonds summarize the pooled effect by intervention, the apex represents the overall mean difference in AHI between conditions and the width represents 95% CI. IV, inverse variance method; random, random-effects model.

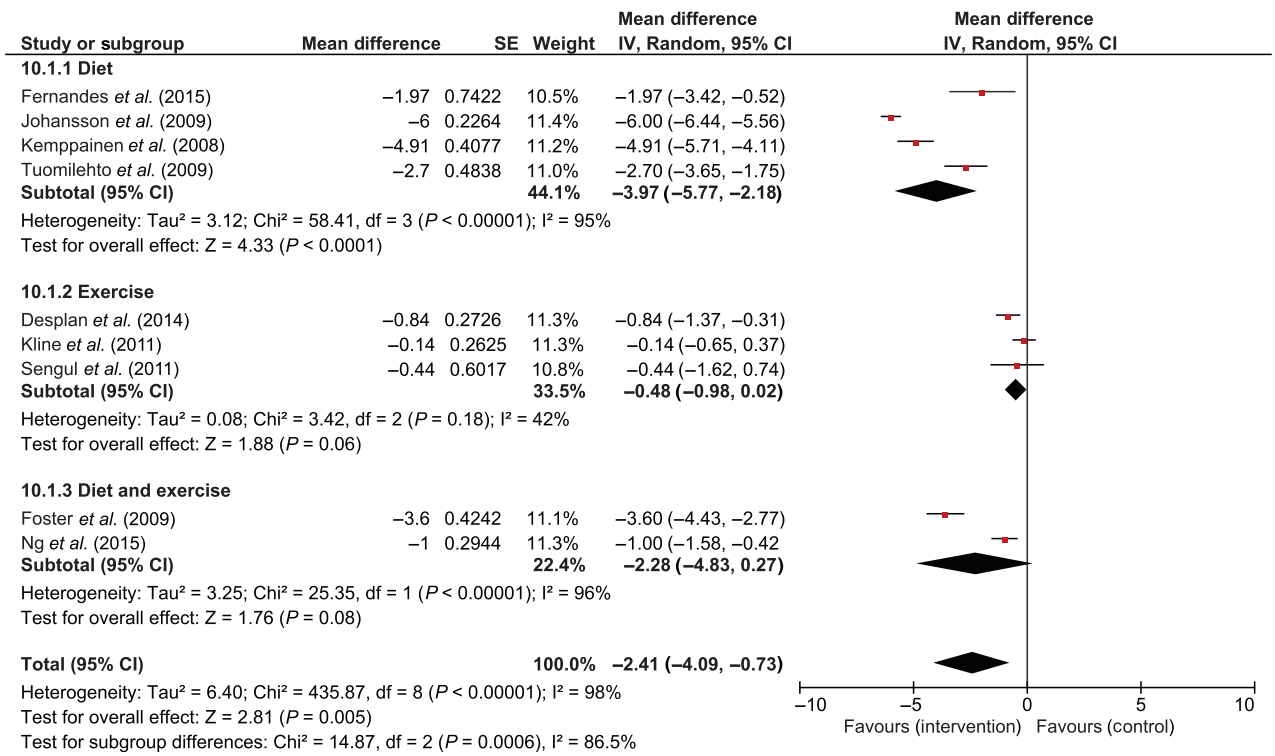

Figure 4 Forest plot comparing the effects of lifestyle interventions and control on the body mass index. IV, inverse variance method; random, random-effects model.

analysis (exercise-only subgroup). Second, 3 of the 10 included RCT[9,12,19] utilized CPAP therapy in combination with lifestyle intervention. Note that a recent meta-analysis of RCT demonstrated that the treatment of CPAP is associated with small, yet significant increases in weight/BMI.[35] Although likely underpowered, sub-analyses of these groups showed that there was no difference between the reduction in AHI and BMI between those studies in which CPAP was utilized in addition to the lifestyle intervention. It is therefore reassuring to see that patients on CPAP can still successfully lose weight and improve their underlying OSA when undertaking a lifestyle intervention. Third, there was a small number of combined intervention studies (i.e. diet and exercise), which may have led to a type 2 error in our meta-analysis. Fourth, an intention-to-treat analysis (ITT) was used in only five of the included studies[12,18–21] which may have partly biased the results. Studies which used ITT analysed all participants who were randomized in the study regardless of their compliance with the treatment, which delivers a more realistic estimate of the clinical effectiveness of a treatment.[36]

In conclusion, lifestyle interventions, regardless of type, are effective in reducing the severity of OSA despite the variable impact they have on BMI. While such interventions often improve OSA severity, when employed alone they should not be expected to resolve OSA in the majority of patients; however, they may have important improvements in a number of patient-related symptoms and cardiometabolic risk factors. Therefore, clinicians should always encourage patients to undertake lifestyle intervention, whether it be dietary, exercise or both, as an adjunct to their primary OSA therapy.

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Abbreviations: AHI, apnoea–hypopnoea index; CPAP, continuous positive airway pressure; ITT, intention-to-treat; OSA, obstructive sleep apnoea; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus; VLCD, very low-calorie diet.

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Appendix S1 Methods.
Appendix S2 Investigations of heterogeneity.
Table S1 Additional randomized controlled trials that were excluded from our analysis.
Figure S1 Forest plots comparing the effects of various lifestyle intervention and control on OSA severity (assessed using the apnoea–hypopnoea index) and body mass index referencing the post-intervention data.
Figure S2 Funnel plots of the SE of the weighted mean difference in the apnoea–hypopnoea index and body mass index for assessment of publication bias.

