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Positive airway pressure therapy and all-cause and cardiovascular mortality in people with obstructive sleep apnoea: a systematic review and meta-analysis of randomised controlled trials and confounder-adjusted, non-randomised controlled studies

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AVB, J-LP, PAC, and AM designed and supervised the study. SHM, BS, SRB, and KCW did the literature search and set up the database. LW and CK did the statistical analyses. AM drafted the first version of the Article. AVB, J-LP, PAC, AW, FL, FHSK, TK, DAJ, RH, and C-HL commented on the data and its interpretation and critically revised the content. All authors contributed to review and revision of the Article and approved the final manuscript. AVB and AM accessed and verified the underlying data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing

All data generated or analysed in this study are included in the appendix.

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Summary

Background—Data regarding the effect of positive airway pressure (PAP) therapy for obstructive sleep apnoea (OSA) on all-cause mortality are inconsistent. We aimed to conduct a systematic review and meta-analysis to test the hypothesis that PAP therapy is associated with reduced all-cause and cardiovascular mortality in people with OSA.

Methods—For this systematic review and meta-analysis, we searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials, from database inception to Aug 22, 2023 (updated Sept 9, 2024), with no language or geographical restrictions. Reference lists of eligible studies and recent conference abstracts (2022–23) were also reviewed. We included outpatient studies (randomised controlled trials [RCTs] or confounder-adjusted, non-randomised controlled studies [NRCSs]) assessing the incidence of all-cause mortality, cardiovascular mortality, or both in adults (aged ≥18 years) with OSA who were treated versus not treated with PAP; other study types and studies that evaluated only PAP adherence were excluded. Abstracts of all retrieved publications were independently screened by two of three researchers (BS, SRB, and KCW), with disagreements resolved by adjudication from another researcher (SHM). The AutoLit feature of the Nested Knowledge platform was used for the review and data-extraction phases. We analysed each log-transformed hazard ratio (HR) and SE using a linear random-effects model to estimate overall HRs and 95% CIs. To evaluate the risk of bias, we used the Cochrane Risk of Bias tool for RCTs and the Newcastle–Ottawa Scale for NRCSs. This study was registered with PROSPERO, CRD42023456627.

Findings—Of 5484 records identified by our search, 435 were assessed for eligibility and 30 studies were included in the systematic review and meta-analysis (ten RCTs and 20 NRCSs). These studies included 1 175 615 participants, of whom 905 224 (77%) were male and 270 391 (23%) were female (SE 1.9), with a mean age of 59.5 (SE 1.4) years and a mean follow-up of 5.1 (0.5) years. The risk of bias was low to moderate. The risk of all-cause mortality (HR 0.63, 95% CI 0.56–0.72; p<0.0001) and cardiovascular mortality (0.45, 0.29–0.72; p<0.0001) was significantly lower in the PAP group than in the no-PAP group, and the clinically relevant benefit of PAP therapy increased with use.

Interpretation—Our results are consistent with a potentially beneficial effect of PAP therapy on all-cause and cardiovascular mortality in patients with OSA. Patients should be made aware of this effect of their treatment, which could result in greater acceptance of treatment initiation and greater adherence, leading to a higher likelihood of improved outcomes.

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Introduction

Obstructive sleep apnoea (OSA) has been estimated to affect up to 1 billion people aged 30–69 years worldwide.[1] The condition is defined by the repetitive occurrence of pharyngeal collapse during sleep, leading to intermittent hypoxaemia, which results in catecholamine surges and sleep fragmentation.[2] OSA has major health consequences, including neurocognitive and cardiometabolic sequelae.[3–5] Observational study data and a meta-analysis of observational studies suggest that OSA is associated with increased incidence of mortality and major cardiovascular and cerebrovascular events.[6–8]

Positive airway pressure (PAP) is an effective treatment for OSA and is the recommended first-line treatment.[9,10] PAP therapy reduces the apnoea–hypopnoea index and symptom burden, such as excessive daytime sleepiness, and improves quality of life;[11] however, currently available data from randomised controlled trials (RCTs) are inconsistent regarding the effect of PAP therapy for OSA on all-cause mortality and major cardiovascular and cerebrovascular events. In addition, a report prepared for the Agency for Healthcare Research and Quality stated that the standard of available evidence (up to March, 2021) was low and that PAP did not appear to affect all-cause mortality or cardiovascular outcomes.[12]

Reasons for the discrepancy between the observed major clinical benefits of PAP and the equivocal results from RCTs are speculative. Some research clinicians have argued that clinic-based patients enrolled in non-randomised studies differ considerably from those participating in RCTs. For example, individuals with severe OSA—including those with profound sleepiness—could be at higher cardiovascular risk than those in whom the condition is less severe, but were often excluded from RCTs on ethical grounds.[8] Additionally, many of the reported studies could be underpowered for detecting differences in event (eg, mortality) rates, providing a sound rationale for pooled data analyses and larger clinical trials.

Previous meta-analyses have had notable limitations. For instance, the study by Feng and colleagues[13] primarily included RCTs and a few observational studies, resulting in

a smaller sample size (13 832 participants) than in larger, real-world cohorts. Yang and colleagues[14] focused specifically on patients with OSA and coronary artery disease, limiting the generalisability of their findings to OSA populations more generally. Furthermore, Fu and colleagues[15] included patients with heart failure and central sleep apnoea treated with adaptive servo-ventilation, potentially confounding the results owing to the distinct pathophysiology and treatment responses in these populations.

We aimed to conduct a systematic review and meta-analysis of existing RCTs and confounder-adjusted, non-randomised controlled studies (NRCSs) to test the hypothesis that PAP is effective in reducing both all-cause and cardiovascular mortality in patients with OSA.

Methods

Search strategy and selection criteria

For this systematic review and meta-analysis, we searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials, from database inception to Aug 22, 2023 (updated Sept 9, 2024), with no geographical or language restrictions and using advanced search methods such as wildcard truncation. Lists of search terms for PubMed (p 25), Embase (pp 25–26), and the Cochrane Register (p 26) are available in the appendix. Literature reviews and reference lists of eligible studies were manually searched to identify additional studies that might have been eligible. We also reviewed conference abstracts from major sleep and respiratory conferences—the American Thoracic Society International Conference, SLEEP (Associated Professional Sleep Societies), the European Respiratory Society Congress, the Sleep Europe Congress (European Sleep Research Society), and the World Sleep Congress (World Sleep Society)—held in 2022 and 2023 and, where relevant, authors of conference abstracts were contacted to identify completed studies that had not yet been published in full.

Identified records were combined and duplicates removed using AutoLit in Nested Knowledge (Nested Knowledge; St Paul, MN, USA); this software platform was used for the review and data extraction phases. Abstracts of all publications were independently screened by two of three researchers (BS, SRB, and KCW) to identify those to be advanced to full-text review; disagreements were resolved by adjudication from another researcher (SHM). Articles that assessed PAP therapy for sleep apnoea and had a follow-up duration of at least 12 months underwent full review, as did abstracts with insufficient detail to ascertain whether study criteria were met. Full reviews were done independently by two of three researchers (BS, SRB, and KCW), with adjudication by another researcher (SHM) in the case of any disagreements. Where necessary, study authors were contacted to obtain the information needed to reach a decision. Google Translate, review by a native-language speaker, or both were used for publications not written in English.

Studies were eligible if they were blinded, placebo-controlled RCTs or NRCSs that adjusted for confounding bias using techniques such as regression or propensity score matching; enrolled adult outpatients (aged ≥18 years) with a diagnosis of OSA; included an intervention group receiving PAP therapy (continuous PAP, automatically titrating CPAP,

or bilevel PAP without a back-up rate) for at least 1 h/night and a control group who were untreated, sham-treated, used PAP for less than 1 h/night, or tried PAP for any duration but discontinued use (the no-PAP group); and had all-cause mortality, cardiovascular mortality, or both as an endpoint.

We excluded preclinical studies, meta-analyses, systematic literature reviews, other reviews, editorials, consensus statements, guidelines or protocols, case–control studies, case reports or case series, cross-sectional studies, crossover studies, and studies with a pre–post design. Studies were also excluded if any participants were pregnant or had central sleep apnoea, obesity hypoventilation syndrome, or neuromuscular diseases at baseline or if the studies compared only low versus high PAP adherence, evaluated features designed to improve comfort or PAP adherence, or evaluated PAP titration methods. A full list of excluded studies with reasons is provided in the appendix (pp 26–40).

This study adhered to PRISMA-P[16] and PRISMA 2020 guidelines and the protocol was registered in PROSPERO (CRD42023456627); the full protocol can be found in the appendix (pp 2–15). The study did not require any ethics committee approval or informed consent because of its non-experimental design.

Study quality assessment

Two of three independent researchers (BS, SRB, and KCW) individually reviewed articles to determine bias; another researcher (SHM) resolved grading conflicts until consensus was reached.

The Cochrane Risk of Bias tool[17] was used to assess RCTs (appendix pp 16–23). This tool examines study methodology by assessing potential bias arising from five domains: the randomisation process, deviations from the intended intervention, missing outcome data, the measurement of outcomes, and the selection of reported results. Judgements about risk of bias in each domain were categorised as low risk, some concerns, or high risk. The overall bias judgement was determined by combining assessments across the five domains.

The quality of NRCSs was assessed using the Newcastle–Ottawa Scale (appendix p 24).[18] Each study was judged on three criteria: selection of study groups (four items), comparability of groups (one item), and ascertainment of the outcome of interest (three items). A study can be awarded a maximum of one star for each item within the selection and outcome categories, whereas a maximum of two stars can be given for comparability. The total score is obtained by adding the number of stars (to a maximum of nine), with higher scores indicating better study quality. Funnel plots were constructed, then analysed using Begg’s test and Egger’s test, to assess potential publication bias.

Data analysis

Outcomes of interest were all-cause mortality and cardiovascular mortality in the PAP group versus the no-PAP group. We also conducted subgroup analyses in which RCTs and NRCSs were assessed separately.

We compared differences in patient populations between RCTs and NRCSs—in terms of demographics, comorbidities, PAP adherence, and follow-up duration—using mixed-effects models, which account for within-study correlations. The exception was follow-up duration, for which we compared differences using a two-sample *t*-test because, for most studies, the within-study variability for this attribute was zero or missing. Normality was assessed with residual plots. The mean and SE of demographic variables for RCTs and NRCSs were estimated in the mixed-effects models. Meta-analysis model fit statistics are shown in the appendix (p 40).

In general, an intention-to-treat (ITT) principle was used for data analysis. In two RCTs[19,20] and two NRCSs,[21,22] results for two different subpopulations were presented (appendix pp 43–45). Our primary analysis conservatively used the least compliant subgroups of each of these studies, specifically the ITT rather than the compliant population in the RCTs and the non-compliant rather than the compliant population for the NRCSs. The results for the more compliant subgroups of these studies were included in the adherence analyses.

All NRCSs used statistical techniques to adjust for potential confounders. Most studies adjusted for age, sex, and baseline comorbidities. The covariates used for confounder adjustment are presented for each NRCS in the appendix (p 41).

The log-transformed hazard ratio (HR) from each study and its SE were analysed in a linear random-effects model to estimate an overall HR and 95% CI. Study was treated as a random effect (normally distributed). A model with a moderator of study type (RCT or NRCS) was also run; this model has study type as a fixed effect and study as a random effect. When only the 95% CI for the HR was reported, this value was converted to an SE by dividing the difference in the log-transformed confidence limits by two times the 97.5th percentile of the standard normal distribution.

All HR values are presented using the control group as the reference group. In studies presenting the treatment group as the reference, the HR and associated 95% CI values were inverted for analysis. For studies in which HR values were presented across multiple subgroups that did not present the desired comparison of PAP versus no PAP, the desired HR was calculated as a contrast of subgroup HR values (eg, if the HRs of group 1 *vs* group 0 [HR_{10}] and group 2 *vs* group 0 [HR_{20}] were presented and the desired HR was group 1 *vs* group 2, this value was calculated as HR_{10}/HR_{20}).

In RCTs or propensity-matched NRCSs in which HR values were not estimated and only mortality rates were reported, the HR was estimated using the odds ratio (OR). When the proportional hazards assumption holds and the follow-up time is not long, the HR can be estimated with the OR.[23] For studies with no deaths in one or both of the PAP and no-PAP groups, a factor of 0.5 was added to each cell of the OR calculation, which yields an estimate that performs well in terms of bias and mean-squared error.[24]

Because a single study[25] contributed approximately 75% of the total sample size, we conducted a sensitivity analysis in which it was excluded to investigate the influence of this study on the HR estimates.

For mortality analyses, we conducted a stepwise, multivariate meta-analysis regression selection with predictor variables (study type, mean age, proportion of male participants, mean BMI, and follow-up duration). Specifically, the meta-analysis model was run with fixed study type and each demographic variable (one at a time); these results are presented in the appendix (p 42). In addition, we did a secondary multivariate meta-analysis regression analysis using studies that reported average PAP adherence to establish whether this variable had an influence on the effect size of PAP therapy on all-cause mortality and cardiovascular mortality. This model used log-transformed HRs as the dependent variable, study type as a fixed effect, study as a random effect, and average PAP adherence as a linear fixed effect. The linearity of PAP adherence was assessed with residual plots.

All statistical analyses were conducted using R software (version 4.4.0); for meta-analyses we used the metafor package[26] and CIs for ORs were calculated in the epitools package.[27]

Role of the funding source

Representatives of ResMed, the study sponsor, were involved in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

5484 records were identified from PubMed (n=1609), Embase (n=3243), the Cochrane Central Register of Controlled Trials (n=536), and conference presentations or reference lists of relevant articles (n=96); of these, 4670 were screened, 435 were assessed for eligibility, and 30 studies (ten RCTs and 20 NRCSs) were included in the systematic review and meta-analysis (figure 1). These studies included 1 175 615 participants, of whom 905 224 (77%) were male and 270 391 (23%) were female (SE 1.9), with a mean age of 59.5 (SE 1.4) years. Of these 30 studies, ten RCTs[19,20,28–35] (5685 participants; appendix p 43) and 17 NRCSs[21,22,25,36–49] (1 166 471 participants; appendix pp 44–45) were included in the all-cause mortality analysis and six RCTs[19,20,28,33–35] (5223 participants; appendix p 46) and five NRCSs[7,36,42,50,51] (20 559 participants; appendix p 47) were included in the cardiovascular mortality analysis; the mean follow-up duration for all studies was 5.1 (SE 0.5) years. In the all-cause mortality analysis, the mean age of participants was 61.7 (SE 2.3) years in the RCTs and 59.6 (1.8) years in the NRCSs, there were 4474 male participants and 1023 female participants in RCTs and 862 338 male participants and 302 040 female participants in NRCSs, and the corresponding mean proportion of male participants was 81.4% (18.6% female; SE 2.9) in the RCTs and 74.1% (25.9% female; 2.1) in the NRCSs (table 1). In the cardiovascular mortality analysis, the mean age of participants was 60.8 (2.8) years in the RCTs and 55.2 (2.8) years in the NRCSs, there were 4097 male participants and 938 female participants in RCTs and 15 960 male participants and 4599 female participants in NRCSs, and the corresponding mean proportion of male participants was 81.4% (18.6% female; 4.8) in RCTs and 77.6% (22.4% female; 4.7) in NRCSs (table 2).

Participants in the all-cause mortality analysis were most likely to be White males and had a mean BMI that indicated overweight or obesity (table 1). Sex, race, BMI, and the baseline apnoea–hypopnoea index did not differ significantly between participants in the RCTs and the NRCSs included in the all-cause mortality analysis; however, mean follow-up

duration was significantly longer, proportion of males significantly lower, and mean PAP adherence significantly higher in NRCSs than in RCTs (table 1). Characteristics of the cardiovascular mortality analysis population were similar to those of the all-cause mortality analysis population: the mean duration of follow-up was significantly longer and PAP adherence was significantly higher in NRCSs than in RCTs (table 2).

Four of the RCTs[19,28,32,34] had a low risk of bias, three[20,29,35] had some concerns regarding bias, and three[30,31,33] were at high risk of bias (appendix p 48). Of a maximum score on the Newcastle–Ottawa Scale of 9, six of the NRCSs[25,42,44,45,47,51] had a score of 7, seven[7,22,36,38,39,41,48] had a score of 6, four[21,40,49,50] had a score of 5, two[37,46] had a score of 4, and one[43] had a score of 3 (appendix p 49).

In Begg's rank correlation test, the estimated value of Kendall's tau rank correlation coefficient was −0.322 (p=0.018), indicating potential publication bias. However, the regression test for funnel-plot asymmetry was not significant (Z=−1.258; p=0.21) overall but was significant when study type was included as a moderator (Z=−2.513; p=0.012; appendix p 50). Analysing data separately by study type showed no funnel-plot asymmetry for RCTs (Z=−0.309; p=0.76) or for NRCSs (Z=−1.202; p=0.23; appendix p 51).

The overall all-cause mortality risk was significantly lower in the PAP group than in the no-PAP group (HR 0.63, 95% CI 0.56–0.72; p<0.0001; figure 2). Data from only NRCSs also showed a significantly lower risk of all-cause mortality in the PAP group than in the no-PAP group (0.60, 0.52–0.70; p<0.0001), whereas the risk reduction based on only RCT data did not reach significance (0.87, 0.65–1.16; p=0.35; figure 2). In stepwise multivariate regression, only study type was retained in the model, and this factor had a modest influence on mortality effect size (p=0.072).

In a sensitivity analysis that excluded the largest study,[25] the overall all-cause mortality risk was similar to that in the primary analysis (HR 0.64, 95% CI 0.56–0.74; p<0.0001). The analysis of only NRCSs also yielded similar results (0.60, 0.51–0.71; p<0.0001).

Eight RCTs[19,20,28,30–34] and four NRCSs[21,22,45,47] with data for all-cause mortality reported the average PAP adherence of the participants. In a mixed-effects model with repeated measures to account for studies that reported results for multiple subgroups, neither study type (p=0.095) nor PAP adherence (p=0.19) was a significant moderator of the treatment effect of PAP versus no PAP. However, treatment effects tended to be smaller in RCTs than in NRCSs and greater in studies in which PAP adherence was higher (appendix p 52). The magnitude of the reduction in all-cause mortality risk with PAP versus no PAP increased as the duration of PAP therapy use increased (table 3).

Overall cardiovascular mortality risk was significantly lower in the PAP group than in the no-PAP group (HR 0.45, 95% CI 0.29–0.72; p<0.0001; figure 3). Combined data from only NRCSs also showed significantly lower cardiovascular mortality risk in the PAP group than in the no-PAP group (0.35, 0.21–0.58; p<0.0001), whereas risk reduction based on RCT data only did not reach significance (0.87, 0.53–1.41; p=0.57; figure 3). Comparing RCTs and NRCSs did not yield a significant difference in treatment effects (p=0.059).

Five RCTs[19,20,28,33,34] and three NRCSs[7,50,51] with data for cardiovascular mortality risk reported the average PAP adherence of the participants. In a mixed-effects model with repeated measures, study type was a significant moderator (p=0.020), with lower HR values for NRCSs than for RCTs. PAP adherence was not a significant moderator (p=0.96), but treatment effects tended to be greater in studies in which PAP adherence was higher (appendix p 53). As with all-cause mortality risk, the magnitude of reduction in cardiovascular mortality risk with PAP versus no PAP increased as the duration of PAP use increased (table 3).

To address the concern of sparse data bias for the overall mortality analysis, we conducted a sensitivity analysis that excluded the study, by Ou and colleagues,[43] with a very small HR; no effect of this study on the overall estimate of the HR was found. For the cardiovascular mortality analysis, we did a similar sensitivity analysis in which the study by Parra and colleagues,[33] which also had a small HR, was excluded. In this sensitivity analysis, the overall HR increased slightly to 0.46 (95% CI 0.28–0.75).

Discussion

This study is, to our knowledge, the largest meta-analysis of the effect of PAP therapy on mortality and has several important findings. First, the aggregated RCT and NRCS data showed an association between the use of PAP therapy and lower all-cause mortality. The HR values for all-cause mortality were in favour of PAP for both RCTs and NRCSs, although overall significance was driven by NRCS data, as has been noted previously.[12] We also saw numerically greater reductions in all-cause mortality risk with PAP versus no PAP as nightly PAP use increased. Second, our assessment of the risk of bias was rigorous. The observed asymmetry was most likely due to true heterogeneity in NRCS data, meaning that the likelihood of the overall result being driven by study design bias is low. Finally, we also found an association between PAP use and lower cardiovascular mortality risk, based on aggregated data from both RCTs and NRCSs. These data add to available evidence showing that OSA is a major modifiable risk factor for both all-cause death and cardiovascular death, and update and extend the results of previous meta-analyses.[15,52]

Several factors are relevant when considering the differences in findings based on data from RCTs and NRCSs. The duration of follow-up was generally longer in NRCSs than in RCTs, meaning that hard clinical outcomes such as all-cause death were more likely to be identified in NRCSs. Nevertheless, the direction of the effect was similar in RCTs and NRCSs. The fact that differences between the PAP and no-PAP groups reached significance with data from NRCSs but not with data from RCTs could relate to a lack of statistical power in the RCT data (ie, a smaller number of events occurring during follow-up, with a total number of deaths in RCTs of 192 *vs* 139 430 in NRCSs) rather than a lack of benefit of PAP therapy. We calculated that a single RCT would need to include 23 785 participants to achieve 80% power for showing a significant effect of PAP on all-cause mortality based on a HR value of 0.87 and an event rate of 3.34% (the values from RCTs included in this analysis).

The possibility of a healthy-user effect is well recognised,[53,54] whereby individuals who are adherent to PAP therapy might have better outcomes than those who are non-adherent. For

example, a 2010 study by Platt and colleagues[55] showed that statin use was more common in people with OSA who used their PAP therapy than in those who were non-adherent. Conversely, a more recent study, by Sterling and colleagues in 2022,[56] did not find any evidence for the influence of a healthy-user effect (based on statin adherence) on PAP device use in the first year of therapy. Individuals with good PAP adherence in the NRCSs might have better education and health literacy than those who were non-adherent, but the healthy-user effect could still occur in RCTs given that randomly assigned patients might or might not be adherent to their assigned therapy. We also appreciate that randomisation allows for balancing of known and unknown confounders between groups, which is less feasible in non-randomised studies.

We acknowledge other potential issues and considerations regarding the literature included in our meta-analysis. The first is selection bias, which can occur if study participants are not representative of the general population. For example, as is common,[57,58] individuals with low socioeconomic status and those from racially minoritised groups were not well represented in most studies. These populations could include people without good access to health care, who are unlikely to be adequately represented in the included studies. In addition, these populations might have higher rates of untreated sleep apnoea and have a lower average life expectancy than those represented in the studies, high lighting the importance of understanding the benefits of PAP therapy in these settings. Another potential issue is participation bias, which can occur when individuals who lack trust in the health-care system refuse to participate in a trial. One of the benefits of a meta-analysis compared with individual trials is that data from a large number of countries and health-care systems are pooled, which maximises the generalisability of the results. However, the possibility of these types of bias still exists with respect to our overall findings.

Why RCTs of PAP therapy have not found any benefit regarding the risk of death and major cardiovascular and cerebrovascular events has been the topic of considerable discussion,[59] and several potential explanations have been proposed.[10] First, as we have mentioned, these studies could have been underpowered, highlighting a need for larger studies and meta-analyses. Poor PAP adherence could also contribute to a lack of power in some studies.[19,34] One meta-analysis of individual patient data showed a robust benefit of PAP with respect to lower risk of recurrent major cardiovascular and cerebrovascular events in individuals who had good adherence (device use ≥4 h/night).[60] Second, OSA has marked phenotypic and endotypic variability, and only a subset of individuals with OSA are at increased risk of cardiovascular events.[25,61] In particular, some of the RCTs to date have included people with mild OSA, those with minimal daytime sleepiness, or both, and such individuals might be least likely to obtain cardiovascular benefits during PAP therapy. In addition, participants enrolled in the RCTs had already had a cardiovascular event and might therefore be too late in the disease course for PAP to have a significant effect. Conversely, observational studies have included individuals without overt cardiovascular disease, in whom PAP might have a greater effect. Another issue is that individuals with more severe OSA, daytime sleepiness, or both might be less likely to be excluded from NRCSs than from RCTs, supporting the suggestion that the lack of these individuals in many RCTs is one factor driving the lack of benefit of PAP therapy in individual studies and the smaller effect size for RCT data in our meta-analysis.

The duration of follow-up in RCTs might have been inadequate to detect the full cardiovascular and mortality benefits of PAP therapy in people with OSA. Therefore, future studies investigating the effects of PAP therapy on cardiovascular and mortality endpoints should focus specifically on the subsets of people with OSA who are at high cardiovascular risk at baseline based on known risk markers (eg, hypoxic burden,[62] delta heart rate,[63] and pulse wave amplitude drops[64]) and should include a sufficient follow-up duration to enable the number of outcome events detected to provide adequate statistical power.

Our study has several key strengths, including the large sample size and comprehensive assessment of bias in included studies. However, several limitations also need to be acknowledged. Our analyses relied on published literature and, therefore, the findings can be generalised only to populations and health-care settings that match those applicable to the trials providing the source data. For example, we are not aware of major publications or adequate representation from much of the world, especially Africa and southeast Asia. Therefore, we would encourage further study of the global burden of OSA and its optimal treatment in a diverse range of locations and populations. Another limitation is that, owing to our study design, important details for many of the individuals and cohorts included in the meta-analysis are missing. For example, medical history and demographic data, sleep studies, objective PAP device data, and information about symptoms are incomplete or absent for some participants, emphasising the need for further mechanistic and individualised research. Although we have included only NRCSs that controlled for potential confounders using statistical adjustments such as propensity score matching or regression analysis, some confounding factors still might not have been accounted for in some studies. Most studies used a Cox proportional hazards model, which enables a combined analysis of studies with varying follow-up periods. However, this model necessitates the assumption of proportional hazards across all timepoints. HR values could vary over time for several reasons, including selection bias of period-specific HR values. This assumption was investigated in some studies through Schoenfeld residuals and found to be reasonable.

A potential limitation in this analysis is the sparse data bias;[65] however, given the results of our sensitivity analyses, we believe this limitation is not substantial. Finally, we recognise the issue of competing risks and deaths; eg, cancer mortality could be protective against cardiovascular death. However, we doubt that competing risk would have a major effect on cardiovascular mortality or any effect on all-cause mortality.

Despite these limitations, we believe that our findings are robust, but await further high-quality trial data about the effect of PAP therapy on all-cause mortality and cardiovascular mortality. In addition, we believe that our findings are highly clinically relevant given that the reduction in all-cause mortality risk with PAP therapy for OSA (HR 0.63, 95% CI 0.56–0.72; $p<0.0001$) exceeds that reported in a systematic review and meta-analyses of statin use (0.72, 0.66−0.76).[66]

In conclusion, the findings of this systematic review and meta-analysis support the benefits of PAP therapy with respect to all-cause mortality and cardiovascular mortality across a range of populations with OSA. Physicians and their patients need to be aware of our

findings to understand the magnitude of benefit that can be obtained from PAP therapy and to help with informed decision making in health care. Future research should explore causal pathways for the reported associations between PAP therapy and reductions in all-cause and cardiovascular mortality, methods to achieve health equity, and variables that might contribute to or influence the observed benefits of PAP therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of interests

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References

1. Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med 2019; 7: 687–98. [PubMed: 31300334]
2. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet 2014; 383: 736–47. [PubMed: 23910433]
3. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial. Lancet 2002; 359: 204–10. [PubMed: 11812555]
4. Jenkinson C, Davies RJ, Mullins R, Stradling JR. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. Lancet 1999; 353: 2100–05. [PubMed: 10382693]
5. Punjabi NM, Caffo BS, Goodwin JL, et al. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med 2009; 6: e1000132.
6. Heilbrunn ES, Ssentongo P, Chinchilli VM, Oh J, Ssentongo AE. Sudden death in individuals with obstructive sleep apnoea: a systematic review and meta-analysis. BMJ Open Respir Res 2021; 8: e000656.
7. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea–hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005; 365: 1046–53. [PubMed: 15781100]

8. Reynor A, McArdle N, Shenoy B, et al. Continuous positive airway pressure and adverse cardiovascular events in obstructive sleep apnea: are participants of randomized trials representative of sleep clinic patients? Sleep 2022; 45: zsab264.
9. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet 1981; 1: 862–65. [PubMed: 6112294]
10. Patil SP, Billings ME, Bourjeily G, et al. Long-term health outcomes for patients with obstructive sleep apnea: placing the Agency for Healthcare Research and Quality report in context—a multisociety commentary. J Clin Sleep Med 2024; 20: 135–49. [PubMed: 37904571]
11. Gay P, Weaver T, Loube D, Iber C, et al. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults. Sleep 2006; 29: 381–401. [PubMed: 16553025]
12. Balk EM, Adam GP, Cao W, et al. Long-term health outcomes in obstructive sleep apnea: a systematic review of comparative studies evaluating positive airway pressure and the validity of breathing measures as surrogate outcomes. Technology Assessment Program (project ID SLPT0919) for the Agency for Healthcare Resarch and Quality Dec 1, 2022. https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/sleep-apnea/sleep-apnea-report.pdf (accessed Sept 4, 2024).
13. Feng G, Zhuge P, Zhang Z, Ma J. The impact of continuous positive airway pressure therapy on cardiovascular events in patients with obstructive sleep apnoea: an updated systematic review and meta-analysis. Sleep Breath 2024; 28: 2095–105. [PubMed: 39083193]
14. Yang D, Li L, Dong J, Yang W, Liu Z. Effects of continuous positive airway pressure on cardiac events and metabolic components in patients with moderate to severe obstructive sleep apnea and coronary artery disease: a meta-analysis. J Clin Sleep Med 2023; 19: 2015–25. [PubMed: 37497624]
15. Fu Y, Xia Y, Yi H, Xu H, Guan J, Yin S. Meta-analysis of all-cause and cardiovascular mortality in obstructive sleep apnea with or without continuous positive airway pressure treatment. Sleep Breath 2017; 21: 181–89. [PubMed: 27502205]
16. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015; 350: g7647. [PubMed: 25555855]
17. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898. [PubMed: 31462531]
18. Wells GA, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed Aug 5, 2024).
19. McEvoy RD, Antic NA, Heeley E, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med 2016; 375: 919–31. [PubMed: 27571048]
20. Sánchez-de-la-Torre M, Sánchez-de-la-Torre A, Bertran S, et al. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. Lancet Respir Med 2020; 8: 359–67. [PubMed: 31839558]
21. Campos-Rodriguez F, Peña-Griñan N, Reyes-Nuñez N, et al. Mortality in obstructive sleep apnea–hypopnea patients treated with positive airway pressure. Chest 2005; 128: 624–33. [PubMed: 16100147]
22. Palm A, Midgren B, Theorell-Haglöw J, et al. Factors influencing adherence to continuous positive airway pressure treatment in obstructive sleep apnea and mortality associated with treatment failure—a national registry-based cohort study. Sleep Med 2018; 51: 85–91. [PubMed: 30103074]
23. Stare J, Maucort-Boulch D. Odds ratio, hazard ratio and relative risk. Adv Method Stat 2016; 13: 59–67.
24. Haldane JB. The estimation and significance of the logarithm of a ratio of frequencies. Ann Hum Genet 1956; 20: 309–11. [PubMed: 13314400]
25. Mazzotti DR, Waitman LR, Miller J, et al. Positive airway pressure, mortality, and cardiovascular risk in older adults with sleep apnea. JAMA Netw Open 2024; 7: e2432468.
26. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010; 36: 1–48.

27. Aragon T. Package ‘epitools’: epidemiology tools. Oct 13, 2022. https://cran.r-project.org/web/packages/epitools/epitools.pdf (accessed April 3, 2024).
28. Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA 2012; 307: 2161–68. [PubMed: 22618923]
29. Bernasconi C, Ott SR, Fanfulla F, et al. SAS CARE 2—a randomized study of CPAP in patients with obstructive sleep disordered breathing following ischemic stroke or transient ischemic attack. Sleep Med X 2020; 2: 100027.
30. Gupta A, Shukla G, Afsar M, et al. Role of positive airway pressure therapy for obstructive sleep apnea in patients with stroke: a randomized controlled trial. J Clin Sleep Med 2018; 14: 511–21. [PubMed: 29609704]
31. Huang Z, Liu Z, Luo Q, et al. Long-term effects of continuous positive airway pressure on blood pressure and prognosis in hypertensive patients with coronary heart disease and obstructive sleep apnea: a randomized controlled trial. Am J Hypertens 2015; 28: 300–06. [PubMed: 25125635]
32. McMillan A, Bratton DJ, Faria R, et al. Continuous positive airway pressure in older people with obstructive sleep apnoea syndrome (PREDICT): a 12-month, multicentre, randomised trial. Lancet Respir Med 2014; 2: 804–12. [PubMed: 25172769]
33. Parra O, Sánchez-Armengol Á, Capote F, et al. Efficacy of continuous positive airway pressure treatment on 5-year survival in patients with ischaemic stroke and obstructive sleep apnea: a randomized controlled trial. J Sleep Res 2015; 24: 47–53. [PubMed: 25040553]
34. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICCADSA randomized controlled trial. Am J Respir Crit Care Med 2016; 194: 613–20. [PubMed: 26914592]
35. Turnbull CD, Craig SE, Kohler M, Nicoll D, Stradling J. Cardiovascular event rates in the MOSAIC trial: 2-year follow-up data. Thorax 2014; 69: 950. [PubMed: 24508706]
36. de Batlle J, Gracia-Lavedán E, Escarrabill J, et al. Effect of CPAP treatment on cardiovascular outcomes. Arch Bronconeumol 2024; 60: 627–33. [PubMed: 38876919]
37. Holmqvist F, Guan N, Zhu Z, et al. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation—results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Am Heart J 2015; 169: 647–54.e2. [PubMed: 25965712]
38. Ioachimescu OC, Janocko NJ, Ciavatta MM, Howard M, Warnock MV. Obstructive Lung Disease and Obstructive Sleep Apnea (OLDOSA) cohort study: 10-year assessment. J Clin Sleep Med 2020; 16: 267–77. [PubMed: 31992433]
39. Jennum P, Tønnesen P, Ibsen R, Kjellberg J. All-cause mortality from obstructive sleep apnea in male and female patients with and without continuous positive airway pressure treatment: a registry study with 10 years of follow-up. Nat Sci Sleep 2015; 7: 43–50. [PubMed: 25914563]
40. Lisan Q, Van Sloten T, Marques Vidal P, Haba Rubio J, Heinzer R, Empana JP. Association of positive airway pressure prescription with mortality in patients with obesity and severe obstructive sleep apnea: the Sleep Heart Health Study. JAMA Otolaryngol Head Neck Surg 2019; 145: 509–15. [PubMed: 30973594]
41. Molnar MZ, Mucsi I, Novak M, et al. Association of incident obstructive sleep apnoea with outcomes in a large cohort of US veterans. Thorax 2015; 70: 888–95. [PubMed: 26038534]
42. Nakamura K, Nakamura H, Tohyama K, et al. Survival benefit of continuous positive airway pressure in Japanese patients with obstructive sleep apnea: a propensity-score matching analysis. J Clin Sleep Med 2021; 17: 211–18. [PubMed: 33006309]
43. Ou Q, Chen YC, Zhuo SQ, et al. Continuous positive airway pressure treatment reduces mortality in elderly patients with moderate to severe obstructive severe sleep apnea: a cohort study. PLoS One 2015; 10: e0127775.
44. Pépin JL, Bailly S, Rinder P, et al. Relationship between CPAP termination and all-cause mortality: a French nationwide database analysis. Chest 2022; 161: 1657–65. [PubMed: 35176275]

45. Sabil A, Launois C, Trzepizur W, et al. Association of positive airway pressure termination with mortality and non-fatal cardiovascular events in patients with obstructive sleep apnoea. Thorax 2024; 79: 1077–85. [PubMed: 39095088]
46. Silveira MG, Sampol G, Mota-Foix M, Ferrer J, Lloberes P. Cluster-derived obstructive sleep apnea phenotypes and outcomes at 5-year follow-up. J Clin Sleep Med 2022; 18: 597–607. [PubMed: 34569926]
47. Yuan X, Fang J, Wang L, et al. Adequate continuous positive airway pressure therapy reduces mortality in Chinese patients with obstructive sleep apnea. Sleep Breath 2015; 19: 911–20. [PubMed: 25487312]
48. Woehrle H, Arzt M, Ficker JH, et al. Impact of positive airway pressure (PAP)-therapy on mortality in obstructive sleep apnea (OSA): analysis of a German healthcare database. Am J Respir Crit Care Med 2023; 297: A5965.
49. Qi Y, Cai M, Zhang HM, et al. Impact of long-term continuous positive airway pressure treatment for patients with obstructive sleep apnea syndrome. Zhonghua Xin Xue Guan Bing Za Zhi 2016; 44: 144–49 (in Chinese). [PubMed: 26926508]
50. Anandam A, Patil M, Akinnusi M, Jaoude P, El-Solh AA. Cardiovascular mortality in obstructive sleep apnoea treated with continuous positive airway pressure or oral appliance: an observational study. Respirology 2013; 18: 1184–90. [PubMed: 23731062]
51. Myllylä M, Hammais A, Stepanov M, Anttalainen U, Saaresranta T, Laitinen T. Nonfatal and fatal cardiovascular disease events in CPAP compliant obstructive sleep apnea patients. Sleep Breath 2019; 23: 1209–17. [PubMed: 30848437]
52. Guo J, Sun Y, Xue LJ, et al. Effect of CPAP therapy on cardiovascular events and mortality in patients with obstructive sleep apnea: a meta-analysis. Sleep Breath 2016; 20: 965–74. [PubMed: 26873722]
53. Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. J Gen Intern Med 2011; 26: 546–50. [PubMed: 21203857]
54. Launois C, Bailly S, Sabil A, et al. Association between healthy behaviors and health care resource use with subsequent positive airway pressure therapy adherence in OSA. Chest 2024; 166: 845–56. [PubMed: 38885897]
55. Platt AB, Kuna ST, Field SH, et al. Adherence to sleep apnea therapy and use of lipid-lowering drugs: a study of the healthy-user effect. Chest 2010; 137: 102–08. [PubMed: 19820075]
56. Sterling KL, Cole KV, Chen J, et al. Analysis of a potential healthy user effect in positive airway pressure adherent patients with obstructive sleep apnea. Am J Respir Crit Care Med 2022; 205: A5072.
57. Turner BE, Steinberg JR, Weeks BT, Rodriguez F, Cullen MR. Race/ethnicity reporting and representation in US clinical trials: a cohort study. Lancet Reg Health Am 2022; 11: 100252.
58. Bonevski B, Randell M, Paul C, et al. Reaching the hard-to-reach: a systematic review of strategies for improving health and medical research with socially disadvantaged groups. BMC Med Res Methodol 2014; 14: 42. [PubMed: 24669751]
59. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S, INCOSACT Initiative (International Collaboration of Sleep Apnea Cardiovascular Trialists). Sleep apnea and cardiovascular disease: lessons from recent trials and need for team science. Circulation 2017; 136: 1840–50. [PubMed: 29109195]
60. Sánchez-de-la-Torre M, Gracia-Lavedan E, Benitez ID, et al. Adherence to CPAP treatment and the risk of recurrent cardiovascular events: a meta-analysis. JAMA 2023; 330: 1255–65. [PubMed: 37787793]
61. Malhotra A, Mesarwi O, Pepin JL, Owens RL. Endotypes and phenotypes in obstructive sleep apnea. Curr Opin Pulm Med 2020; 26: 609–14. [PubMed: 32890019]
62. Pinilla L, Esmaeili N, Labarca G, et al. Hypoxic burden to guide CPAP treatment allocation in patients with obstructive sleep apnoea: a post hoc study of the ISAACC trial. Eur Respir J 2023; 62: 2300828.

63. Azarbarzin A, Zinchuk A, Wellman A, et al. Cardiovascular benefit of continuous positive airway pressure in adults with coronary artery disease and obstructive sleep apnea without excessive sleepiness. Am J Respir Crit Care Med 2022; 206: 767–74. [PubMed: 35579605]

64. Solelhac G, Sánchez-de-la-Torre M, Blanchard M, et al. Pulse wave amplitude drops index: a biomarker of cardiovascular risk in obstructive sleep apnea. Am J Respir Crit Care Med 2023; 207: 1620–32. [PubMed: 37017487]

65. Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. BMJ 2016; 352: i1981. [PubMed: 27121591]

66. Nowak MM, Niemczyk M, Florczyk M, Kurzyna M, Pączek L. Effect of statins on all-cause mortality in adults: a systematic review and meta-analysis of propensity score-matched studies. J Clin Med 2022; 11: 5643. [PubMed: 36233511]

Research in context

Evidence before this study

Existing data regarding the effect of positive airway pressure (PAP) therapy for the treatment of obstructive sleep apnoea (OSA) on all-cause and cardiovascular mortality are inconsistent—especially the findings of randomised controlled trials (RCTs), which have largely reported neutral findings, and non-randomised controlled studies (NRCSs), which generally support a beneficial effect of PAP therapy. We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials, from database inception to Aug 22, 2023 (updated on Sept 9, 2024), with no geographical or language restrictions (appendix pp 25–26). To identify additional eligible studies, we also manually searched literature reviews and the reference lists of eligible studies and reviewed conference abstracts from major sleep and respiratory conferences held in 2022 and 2023. This search identified a gap in the literature regarding an up-to-date systematic review and meta-analysis that included both RCTs and NRCSs and fully evaluated the bias of included studies.

Added value of this study

This systematic review and meta-analysis is, to our knowledge, the largest and most comprehensive on this topic to date, including data from more than 1.1 million individuals and incorporating a comprehensive assessment of bias. Analysis of the aggregated data showed a significant overall benefit of PAP therapy versus no PAP therapy for OSA on all-cause mortality; a positive effect of PAP therapy on cardiovascular mortality was also seen on the basis of data from studies that reported this endpoint. Furthermore, available data showed a clinically relevant dose–response effect for the effect of PAP on all-cause mortality.

Implications of all the available evidence

The aggregated evidence suggests that the use of PAP therapy in a diverse clinical population of individuals with OSA has a beneficial effect on all-cause and cardiovascular mortality. Future studies should identify causal pathways for the association between treatment of OSA with PAP therapy and reduced all-cause and cardiovascular mortality, variables that might contribute to or influence the observed benefits of PAP therapy, and methods to achieve health equity in this setting. This evidence further supports the current clinical practice and policy of treating OSA.

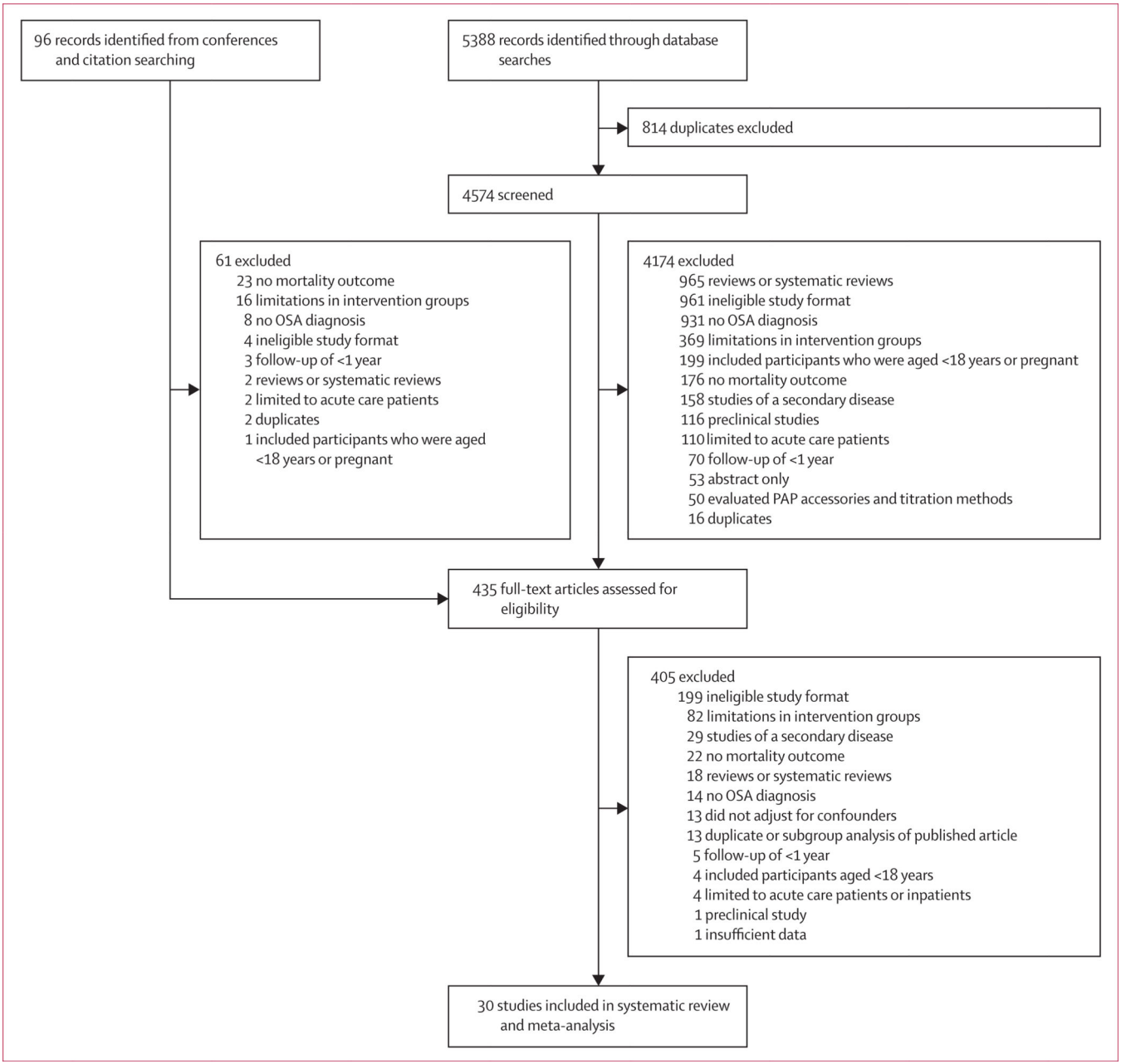

Figure 1: Study selection

OSA=obstructive sleep apnoea. PAP=positive airway pressure.

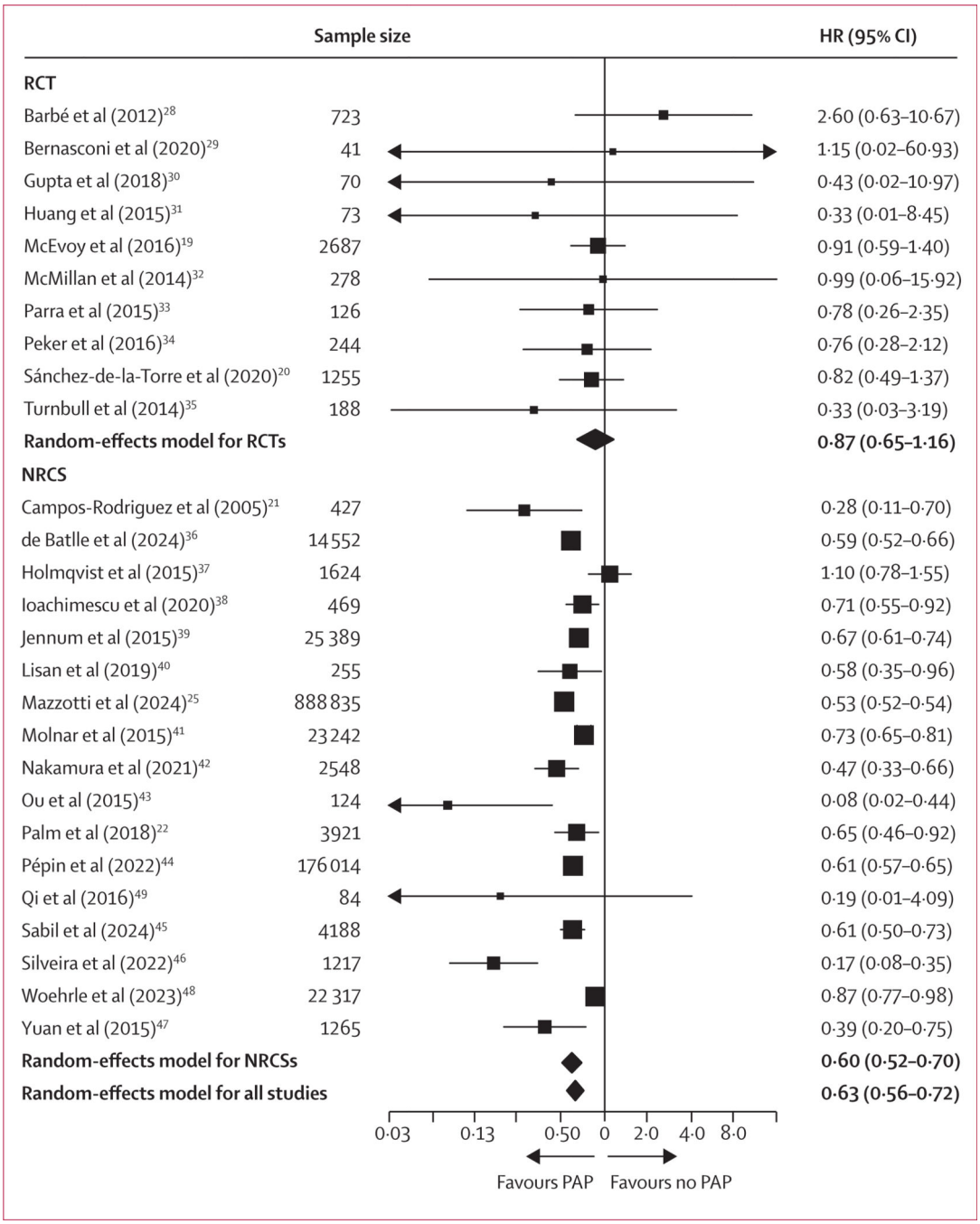

Figure 2: Forest plot showing the risk of all-cause death in the PAP vs no PAP therapy groups

Black squares indicate the point estimate and horizontal bars indicate 95% CI. Black diamonds indicate the effect estimate in study groups and overall. HR=hazard ratio. NRCS=non-randomised controlled study. PAP=positive airway pressure. RCT=randomised controlled trial.

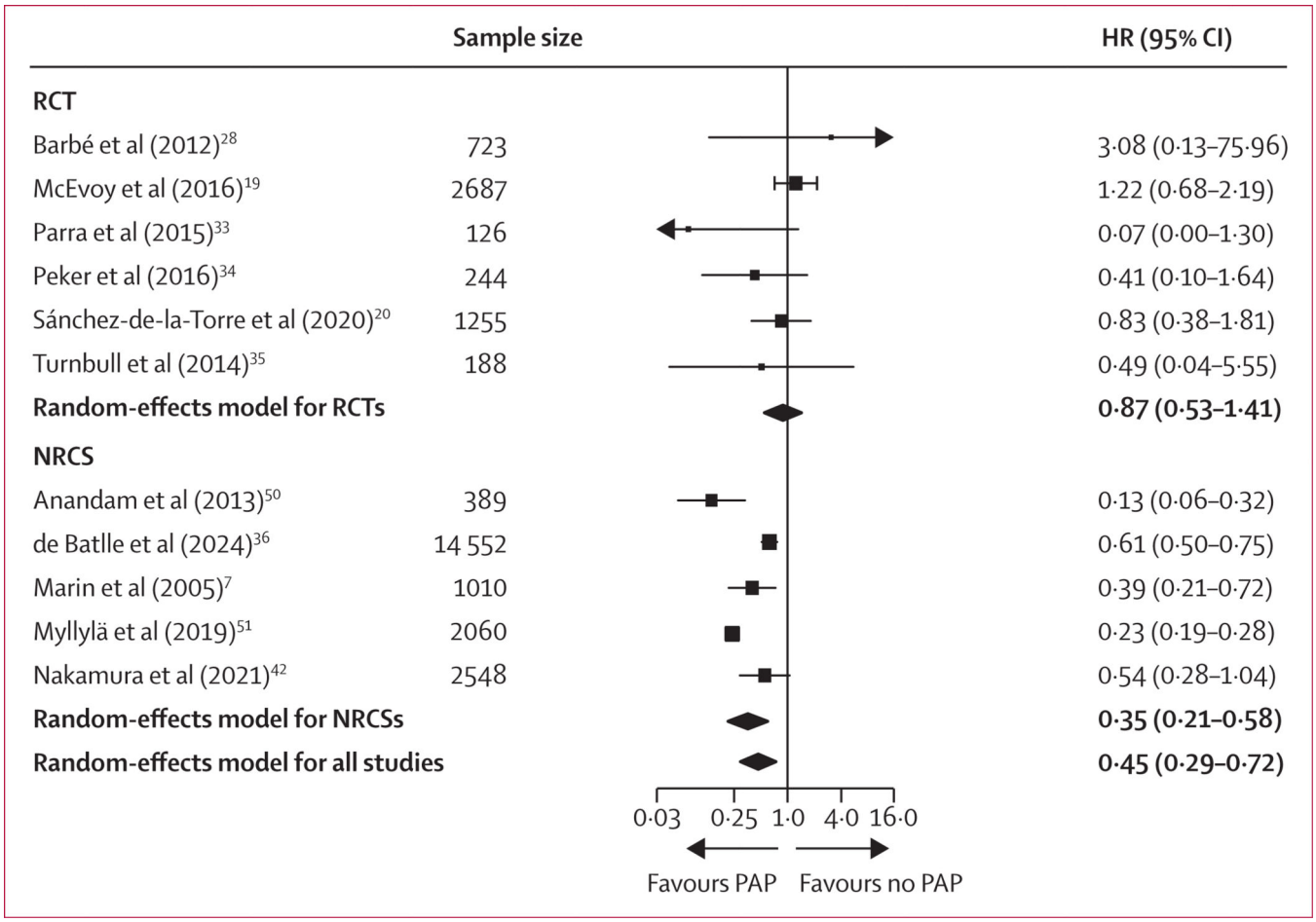

Figure 3: Forest plot showing the risk of cardiovascular death in the PAP vs no PAP therapy groups

Black squares indicate the point estimate and horizontal bars indicate 95% CI. Black diamonds indicate the effect estimate in study groups and overall. HR=hazard ratio. NRCS=non-randomised controlled study. PAP=positive airway pressure. RCT=randomised controlled trial.

Table 1:

Baseline characteristics of participants included in the all-cause mortality analysis

	Number of studies	Number of patients	Value	p value (RCT *vs* NRCS)
Age, years				
RCT	9	5497	61.7 (2.3)	..
NRCS	14	1138989	59.6 (1.8)	0.48 *
Sex				
RCT	9	5497 (4474 male, 1023 female)	81.4% male, 18.6% female (2.9)	..
NRCS	15	1164 378 (862 338 male, 302 040 female)	74.1% male, 25.9% female (2.1)	0.041 *
Race				
RCT	2	2965 (1792 White, 1173 non-White)	60.4% White, 39.6% non-White (25.0)	..
NRCS	2	912 077 (752 920 White, 159 157 non-White)	82.6% White, 17.5% non-White (25.0)	0.53 *
BMI, kg/m ^{2}				
RCT	9	5497	29.1 (0.9)	..
NRCS	7	12 728	30.5 (1.0)	0.31 *
Baseline apnoea–hypopnoea index, events per h				
RCT	7	5093	32.5 (2.6)	..
NRCS	9	14029	34.8 (2.3)	0.50 *
Follow-up, years				
RCT	10	5685	3.0 (0.5)	..
NRCS	17	1166471	5.8 (0.7)	0.0033 †
PAP adherence, h/night				
RCT	8	2717	3.6 (0.5)	..
NRCS	4	18500	6.0 (0.2)	0.0013 †

Values are n or mean (SE). NRCS=non-randomised controlled study.

PAP=positive airway pressure. RCT=randomised controlled trial.

* Calculated from a random-effects model.

† Calculated from a two-sample *t*-test.

Table 2:

Baseline characteristics of participants included in the cardiovascular mortality analysis

	Number of studies	Number of patients	Value	p value (RCT *vs* NRCS)
Age, years				
RCT	5	5035	60.8 (2.8)	..
NRCS	5	20559	55.2 (2.8)	0.15 *
Sex				
RCT	5	5035 (4097 male, 938 female)	81.4% male, 18.6% female (4.8)	..
NRCS	5	20 559 (15 960 male, 4599 female)	77.6% male, 22.4% female (4.7)	0.58 *
Race				
RCT	1	2687 (677 White, 2010 non-White)	25.2% White, 74.8% non-White (0.8)	..
NRCS	1	389 (276 White, 113 non-White)	71.0% White, 29.0% non-White (2.3)	..
BMI, kg/m ^{2}				
RCT	5	5035	29.5 (1.2)	..
NRCS	4	6007	31.4 (1.4)	0.31 *
Baseline apnoea–hypopnoea index, events per h				
RCT	4	4909	33.2 (3.8)	..
NRCS	4	6007	31.4 (3.8)	0.75 *
Follow-up, years				
RCT	6	5223	3.8 (0.4)	..
NRCS	5	20559	6.9 (1.0)	0.031 †
PAP adherence, h/night				
RCT	5	2511	3.8 (0.6)	..
NRCS	3	1579	6.2 (0.2)	0.011 †

Values are n or mean (SE). NRCS=non-randomised controlled study.

PAP=positive airway pressure. RCT=randomised controlled trial.

* Calculated from a random-effects model.

† Calculated from a two-sample *t*-test.

Table 3:

Risk of all-cause and cardiovascular mortality in the PAP and no-PAP groups based on average PAP device use

	Hazard ratio (95% CI); PAP *vs* no PAP			p value (RCT *vs* NRCS)
	PAP use 2 h/night	**PAP use 4 h/night**	**PAP use 6 h/nigh**	
All-cause mortality				
NRCS	0.57 (0.34–0.95)	0.50 (0.33–0.76)	0.44 (0.30–0.65)	..
RCT	0.95 (0.60–1.50)	0.84 (0.55–1.28)	0.74 (0.46–1.19)	0.19
Cardiovascular mortality				
NRCS	0.25 (0.06–1.09)	0.24 (0.10–0.60)	0.24 (0.14–0.40)	..
RCT	0.79 (0.31–2.01)	0.78 (0.44–1.35)	0.76 (0.36–1.63)	0.96

p value indicates the linear effect of PAP use on the log-transformed hazard ratio.

NRCS=non-randomised controlled study. PAP=positive airway pressure.

RCT=randomised controlled trial.