



# BMJ Open Sudden death in individuals with obstructive sleep apnoea: protocol for a systematic review and meta-analysis

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## ABSTRACT

**Introduction** Obstructive sleep apnoea (OSA) is a form of sleep-disordered breathing, characterised by blockage of the airway, snoring, gasping for air during sleep, daytime sleepiness and fatigue. OSA is associated with increased risk of cardiovascular and cerebrovascular morbidity and mortality, and sudden cardiac death (SCD). The magnitude of this risk varies in the literature and therefore we aim to systematically assess this risk. This study protocol proposes a meta-analysis and systematic review aimed to estimate the magnitude of the association between OSA, ‘sudden death’ and cardiovascular death.

**Methods** We will conduct a systematic review and meta-analysis of studies published from the inception of each database, which report the risk of ‘sudden death’ or cardiovascular death (including SCD) in individuals diagnosed with OSA versus persons without OSA. The primary outcome of interest in this study will be the relative risk of ‘sudden death’ in patients diagnosed with OSA in comparison to those without an OSA diagnosis. We will search the following electronic research databases: PubMed (MEDLINE), Cochrane, OVID (Healthstar), OVID (Medline), Scopus and Joana Briggs Institute EBP Database. This protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol guidelines. The checklist for this document is included in the supplemental material. Two reviewers will screen articles for inclusion criteria, extracting appropriate data and evaluating the quality of the included studies. The methodological quality of studies will be appraised using an appropriate tool. Funnel plots and the Egger’s test will be employed to evaluate potential publication bias. We will fit random-effects model with inverse-variance methods for the pooling effect estimates. We will conduct a meta-regression analysis, using numerous variables of interest including age, gender, race, body mass index, hypertension and diabetes, to explore sources of study heterogeneity.

**PROSPERO registration number** CRD42020164941.

**Ethics and dissemination** No ethics clearance was required for this protocol, for no primary data are being collected on research subjects. Only secondary analysis of pre-existing data in scientific databases will be evaluated. The findings of this meta-analysis will be published in a peer-reviewed journal and presented at scientific conferences. These results may assist professionals in the prevention and management of OSA and SCD.

## Strengths and limitations of this study

- To our knowledge, this will be the first comprehensive meta-analysis and systematic review to consolidate current research on the association of ‘sudden death’ and cardiovascular deaths among individuals with obstructive sleep apnoea.
- This study may inform future research on the management of obstructive sleep apnoea in order to prevent mortality.
- By adhering to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol Guidelines, we are ensuring transparency and reproducibility of this study.
- The potential heterogeneity in the definition of ‘sudden death’ may be a limitation.
- To address this limitation, a meta-regression model will be conducted to explore the potential sources of heterogeneity in the definition of the outcome of interest.

## INTRODUCTION

Obstructive sleep apnoea (OSA) is a chronic sleep-related disorder, in which there is obstruction of the upper airway structures during sleep, resulting in the reduction or complete blockage of airflow.<sup>1–4</sup> The clinical guidelines and diagnostic criteria of OSA is met if a patient reaches five or more apnoea-hypopnoea events per hour.<sup>5</sup> Patients with OSA are at a higher risk of developing several cardiovascular-related comorbidities, including congestive heart failure, arrhythmias and coronary artery disease (CAD).<sup>6</sup> In addition, OSA-related symptoms are associated with a decreased quality of life.<sup>7</sup> Body mass index (BMI), male gender and advancing age are all considered independent risk factors for OSA.<sup>8</sup> The prevalence of OSA in adults ranges from 3% to 7%.<sup>9</sup> A recent literature review conducted by Benjafeld *et al* estimated the global prevalence of OSA of 1 billion individuals.<sup>10</sup> In the USA, approximately 25 million adults are

diagnosed with OSA and the incidence is continuing to grow.<sup>11</sup>

OSA-related comorbidities can be an unrecognisable risk factor for 'sudden death'. 'Sudden death', as defined by WHO, is any 'non-violent, unexplained death, occurring less than 24 hours from the onset of symptoms'.<sup>12</sup> An observational cohort study found that the presence of OSA increases the risk of all-cause mortality significantly (adjusted HR 1.97; 95% CI 1.12 to 3.48).<sup>13</sup> In fact, OSA is considered a predicting factor for 'sudden cardiac death' and all-cause mortality.<sup>13–15</sup> The severity of the OSA syndrome increases the risk of this adverse outcome as well. Individuals with an apnoea-hypopnoea index (AHI) of >36 events per hour have a higher risk of death from any cause in comparison to other AHI severity scores (HR 3.30; 95% CI 1.74 to 6.26).<sup>13</sup> There is a lack of comprehensive studies focused on systematically assessing and reviewing the association between 'sudden death' and OSA.

Existing evidence on the association between OSA and the risk of 'sudden death' is limited and inconclusive. In this protocol, we propose to conduct a systematic review and meta-analysis of the association of 'sudden death' and cardiovascular deaths with OSA.

## Objectives

The objective of this study will be to assess the association of 'sudden death' and cardiovascular deaths with OSA.

### Primary objectives

- i. To calculate the pooled risk ratio of mortality associated with OSA.

### Secondary objectives

- i. To explore a dose-response relationship between sleep apnoea severity and the risk of mortality.
- ii. To determine other predictors of mortality associated with OSA such as cardiovascular diseases, stroke and obesity.

### Review questions

What is the association of OSA with 'sudden death' and cardiovascular death?

## METHODS

The present protocol has been registered with PROSPERO (CRD42020164941).

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols 2015 statement and guidelines inform and guide the development of this protocol.<sup>16</sup>

### Patient and public involvement

Patients and the general public were not involved in the development of this protocol.

## Eligibility criteria

### Inclusion criteria

We will include published studies that:

- ▶ Report rates of 'sudden death' in both patients with OSA and without OSA, including information on the incidence of the outcome.
- ▶ Published in any language. English versions of articles written in other languages will be selected.

### Exclusion criteria

We will exclude published studies that:

- ▶ Are not conducted in human subjects.
- ▶ Did not report incidence of 'sudden death' in patients with OSA.
- ▶ Are meta-analyses, literature reviews, commentaries, case reports or meeting abstracts.

### Domain

Studies that are related to 'sudden death' and OSA.

### Population

We will include research studies that report data related to 'sudden death' from participants with OSA in comparison to participants without OSA, regardless of gender and sex, or geographical location.

### Outcomes

The primary outcome will be the risk ratio of 'sudden death' in patients with OSA in comparison to populations without OSA.

### Search strategy

The following databases will be searched for articles of interest: PubMed (MEDLINE), Cochrane, OVID (Healthstar), OVID (Medline), Scopus and Joana Briggs Institute EBP Database. A snowballing method will be used to search the citation list of included papers, in order to identify further studies. Therefore, reference lists of potentially included articles will be assessed for possible eligible studies. The search will be based on predefined search terms as defined by the Medical Subject Headings (MeSH), with combinations of 'sleep' AND 'obstructive' AND 'apnoea' AND 'sudden' AND 'death' OR 'sleep' AND 'obstructive' AND 'apnoea' AND 'sudden' AND 'cardiac' AND 'death' OR 'sleep' AND 'obstructive' AND 'apnoea' AND 'death' OR 'apnoea' AND 'death' AND 'sleep'. Our search strategy includes the usage of Boolean operators, proximity operators, truncations and MeSH.

### Title and abstract screening

A comprehensive list of search results will be inputted into the Endnote software, which will quantify and exclude duplicate articles. ESH and AES review members will screen the studies independently. Titles and abstracts will be screened in the first stage. Excluded studies will be documented with a reason for their exclusion.

### Full-text screening and data extraction

Following the first stage of screening, full-text articles will be manually screened by two reviewers, while independently extracting appropriate and eligible data. We will extract the following information:

- ▶ Full title;
- ▶ Year of publication;
- ▶ Type of research study;
- ▶ Average participant follow-up;
- ▶ Number of participants with OSA;
- ▶ Number of participants without OSA;
- ▶ Median age of participants with OSA;
- ▶ Median age of participants without OSA;
- ▶ Effect measures of the association between OSA and mortality (OR, relative risk, HR and their 95% CI) if provided in the articles;
- ▶ AHI at OSA diagnosis;
- ▶ Oxygen desaturation index at OSA diagnosis;
- ▶ Obstructive sleep apnoea syndrome therapy;
- ▶ BMI of participants with OSA;
- ▶ BMI of participant without OSA;
- ▶ Proportion of the study sample that was male;
- ▶ Proportion of the study sample that smoked/used tobacco;
- ▶ Proportion of the study sample with hypertension;
- ▶ Proportion of the study sample with diabetes.

Eligible studies will report numerical and empirical findings on the association between OSA and ‘sudden death’. A third researcher (PS) will be consulted in the event of potential disagreements or discrepancies. If there is data missing from an article, we will attempt to reach out to the corresponding authors of the studies. In the case that there is no resolution for the missing data, the reviewers will decide if the study should be included or excluded for the final review and extraction.

### Assessment of methodological quality of the papers

In order to assess the methodological quality of the papers, we will be using the Newcastle-Ottawa Quality Assessment Scale. The scale is specifically applicable for case-control, cross-sectional and cohort studies.<sup>17</sup> Two authors will be responsible for independently evaluating the methodological quality of the potential included studies. The score received for a study is a comprehensive measurement of the selection, exposure and comparability categories. The maximum score is a 9. Score between ‘7’ and ‘9’ are considered ‘good quality’, whereas scores between a ‘4’ and ‘6’ are defined as ‘fair quality’, and scores between a ‘1’ and ‘3’ are deemed as ‘poor-quality’. In the event of a discrepancy or disagreement on a score assigned to a particular study, discussion among authors will be employed in order to reach a resolution. Regardless of the risk of bias or quality scores, studies will be included, but a sensitivity analysis will be conducted in order to evaluate the influence of their potential inclusion.

### Data synthesis and analysis

The primary outcome of interest for this study is the overall risk of ‘sudden death’ in persons with OSA versus without OSA. Pooled risk ratios and their 95% CIs will be reported. The random-effects model will be conducted using R software, V.3.4.3 (R, College Station, Texas, USA). We will use the metagen function of the meta-package in R Statistical Software for analysis.<sup>18</sup> We will use the random-effects model with inverse variance methods for the pooling of the log transformed effect estimates and the SEs.<sup>19</sup> SEs will be calculated via the following equations:  $\log(\text{upper } 95\% \text{ CI}) - (\text{lower } 95\% \text{ CI}) / 3.92$ . To evaluate between-study heterogeneity, the  $I^2$  statistic will be used. Between-study heterogeneity is defined as low (25%), moderate (50%) and high (75%) (significance level  $p < 0.05$ ).<sup>20</sup> We apply the random-effect model, regardless of the between-study heterogeneity. Subgroup analysis will be conducted using study designs (randomised controlled studies and observational comparative studies) and study quality scores when analysing included studies. In the event that the case definition of ‘sudden death’ differs greatly between studies, we will conduct additional subgroup analyses for ‘sudden cardiac death’ and stroke in order in order to mitigate any potential bias or heterogeneity.

### Additional analyses

We will perform sensitivity analysis by the use of subgroup meta-analyses to look at geographical differences in the mortality risk and conduct a meta-regression analysis, using study gender proportions, age, age range, mean age  $\pm$  SEM, BMI, the proportion of the study population who smoke, the proportion of the study population with hypertension, the proportion of the study population with diabetes, the proportion of the study population with OSA and the rate of ‘sudden death’ in the study population.<sup>21</sup> We will report relative risk for the association between OSA and mortality. The Egger’s test and funnel plots will be used to assess publication bias.

### Presentation of results and reporting

The PRISMA guidelines will be used and the checklist will accompany the publication of this systematic review. Quantitative data found while conducting this study will be reported and presented in tables, geographical maps and forest plots. We will present the risk ratios and their 95% CIs of mortality associated with OSA.

### Potential amendments

The protocol for this review was completed in 2020 and this study is expected to be finalised by 2021. Any amendments made to this protocol when conducting the study will be outlined and reported in the final manuscript.

**Contributors** AES, EH and PS conceived this study. EH and AES drafted the protocol. PS, VMC, AES and EH critically reviewed the protocol and provided comments. All authors approved the final protocol.

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