Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods. Methodological details regarding marginal structural models

The prescription of continuous positive airway pressure (CPAP) in asymptomatic patients with obstructive sleep apnea (OSA) and established cardiovascular diseases has not demonstrated a reduction in cardiovascular risk across various clinical trials. This result is unsurprising, given the observed low adherence among this particular patient population. However, despite these findings, it is still crucial to evaluate whether maintaining good compliance with CPAP can effectively mitigate cardiovascular risk in this group. Conducting such an analysis, though, presents significant challenges. The fluctuating nature of adherence among patients prevents them from being categorized strictly into distinct compliance groups. Moreover, extended follow-up periods can introduce changes in individuals that may confound the relationship between adherence and cardiovascular risk. To address these complexities and control for potential confounding factors, marginal structural models[1] offer valuable tools. We adjust MSM to make estimates that could compare cardiovascular risk in a hypothetical scenario in which if all patients presented full CPAP adherence versus they were non-compliers to CPAP. The specifications of the MSM employed in our study are described as follows. Initially, a directed acyclic graph was employed to illustrate the conceptual model representing the causal mechanism of time-varying CPAP adherence and time-varying confounding factors (eFigure 1). To estimate the marginal structural models, stabilized inverse probability weights were utilized, considering the binary exposure of good adherence versus poor adherence to CPAP, which varied over time. The weights were calculated based on the time-invariant and time-varying confounding factors specified in the directed acyclic graph. Sex, age, apnea-hypopnea index, antihypertensive drugs and trial were considerate as baseline factors and Epworth sleepiness scale and BMI as time-varying confounder. Changes in BMI would be informative of potential changes in apnea-hypopnea index (AHI)[2] that could affect adherence to the treatment. Moreover, previous studies suggest that BMI changes could affect adherence to therapies[3]. Finally, a potential relationship between CPAP use and BMI changes has been reported[4]. While the direct association between OSA severity and BMI is well-established, the influence that BMI at longer previous periods (e.g., k-2, k-3, etc.) may have on OSA severity at the time of evaluation remains less understood. Consequently, we contend that the impact of BMI at a specific moment will primarily manifest in the immediately following adherence period.

On one hand, stabilized weights included a denominator incorporate probability of selection for good adherences using both time-invariant and time-varying factors. On the other hand, numerator incorporates probability for selection for good adherence using only time-invariant factors. Furthermore, censoring weighting was implemented to address the potential impact of exposure on dropout. The exposure selection weights, and censoring weights were combined to account for both aspects in our analysis. Truncation percentile (0.01; 0.99)

was applied on weights. Subsequently, a marginal structural Cox model was estimated, employing robust standard error estimation to appropriately handle correlated observations. Additionally, a sensitivity analysis was performed, involving the censoring information at the first change of adherence period. This involved identifying and considering the first transition from good adherence to non-adherence and vice versa. With this information, MSM was fitted with the same methodology previously described.

eTable 1. Excluded articles and reason

Author	Year	Reason for exclusion
Robinson[5]	2006	Another outcome (hypertension)
Lozano[6]	2010	Another outcome (hypertension)
Barbe[7]	2010	Another outcome (hypertension)
Duran-Cantolla[8]	2010	Another outcome (hypertension)
Drager[9]	2011	Another outcome (hypertension)
Martinez-Garcia[10]	2013	Another outcome (hypertension)
Kushida[11]	2012	Another outcome (Non-Cardiovascular)
Bradley[12]	2005	Central apnea population
Cowei[13]	2015	Central apnea population
Glantz[14]	2017	Another outcome (Non-Cardiovascular)
Pedrosa[15]	2013	Another outcome (hypertension)
Lloberes[16]	2014	Another outcome (hypertension)
Chirinos[17]	2014	Another outcome (hypertension)
Gotlieb[18]	2014	Another outcome (Non-Cardiovascular)
Caples[18]	2019	Another outcome (Non-Cardiovascular)
Craig[19]	2009	Another outcome (Non-Cardiovascular)
Barbé[20]	2012	Wrong population (non cardiovascular)
Craig[21]	2012	Wrong population (including mild OSA)
McMillan[22]	2014	Wrong population (including mild OSA)
Huang[23]	2015	Another outcome (hypertension)
Parra[24]	2015	Short follow up

eTable 2. Additional trial characteristics

	SAVE Study	ISAACC Study	RICCADSA Study
Inclusion criteria	1. Males and females, any race, and aged between 45 and 75 years. 2. Established coronary or cerebrovascular disease. 3. Moderate-severe OSA (equivalent to apnea-hypopnea index >30/h) as determined by a ≥4% oxygen dip rate >12/h on overnight testing. 5. Written informed consent signed.	1. Men and women over 18 years old. 2. Patients admitted for acute coronary syndrome. 3. Patients with and Epworth sleepiness scale score ≤10. 4. Written informed consent signed.	1. Patients with CAD who have newly undergone percutaneous coronary intervention or coronary artery bypass graft treatment in the previous 6 months. 2. Written informed study consent. 3. OSA (apnea-hypopnea index ≥15/h) or non-OSA (apnea-hypopnea index <5/h) diagnosis on the unattended sleep recording at home.
Exclusion criteria	1. Any condition that makes the potential participant unsuitable for the study. 2. Any coronary or carotid revascularization procedure in the next 6 months. 3. Severe respiratory disease. 4. NYHA categories III-IV of heart failure. 5. Other member enrolled in SAVE trial. 6. Prior use of CPAP treatment for OSA. 7. Increased risk of a sleep-related accident and/or excessive daytime sleepiness (Epworth sleepiness scale score >15). 8. Severe nocturnal desaturation (>10% overnight recording time with arterial oxygen saturation of <80%). 9. Cheyne-Stokes respiration.	1. Prior use of CPAP treatment for OSA. 2. Inability to complete questionnaires. 3. Presence of any sleep disorders. 4. Cheyne-Stokes respiration. 5. Patients with limiting chronic diseases. 6. A medical history that may interfere with the study objectives. 7. Any medical factor, social or geographical, that may jeopardize patient compliance. 8. Any process, cardiovascular or otherwise, that limits life expectancy to less than one year. 9. Patients in cardiogenic shock who have poor expectations for short-term outcomes.	1. Patients with already treated OSA. 2. Cheyne-Stokes breathing. 3. Patients with borderline OSA (apnea-hypopnea index <15 and ≥5/h) upon the unattended sleep recording at home.
Follow-up visits	At 1, 3, 6, and 12 months, and annually thereafter.	At 1, 3, 6, 12, 18, 24, 30, and 36 months, and annually thereafter.	At 3, 6, and 12 months, and annually thereafter.

eTable 3. One-stage IPD meta-analysis for the individual components of the primary endpoint

	Hazard ratio (95% CI)	p value
Cardiovascular death	0.95 (0.62-1.47)	0.83
Myocardial infarction	1.08 (0.8-1.46)	0.61
Stroke	0.97 (0.71-1.33)	0.85
Hospitalization for heart failure*	0.91 (0.59-1.4)	0.66
Hospitalization for unstable angina*	0.96 (0.76-1.22)	0.76
Hospitalization for transient ischemic attack*	1.79 (0.86-3.73)	0.12

Mixed-effects Cox proportional hazards model adjusted by trial as random effects. CI; confidence interval. *Data available for SAVE and ISAACC trials.

eTable 4. Baseline characteristics according to CPAP compliance groups in sensitivity analysis population

	Poor adherence (N=961)	Good adherence (N=1057)
Age, years	60.6 (8.95)	61.6 (8.08)
Sex		
Male	777 (80.9%)	878 (83.1%)
Female	184 (19.1%)	179 (16.9%)
BMI, kg/m^2	28.4 [25.9;31.0]	28.3 [25.9;31.4]
Lifestyle factors		
Smoking status		
Never	329 (34.2%)	426 (40.3%)
Former	337 (35.1%)	411 (38.9%)
Current	295 (30.7%)	220 (20.8%)
Current alcohol consumption	238 (27.1%)	259 (25.5%)
Obstructive sleep apnea measures		
Apnea-hypopnea index	26.0 [18.0;39.0]	27.0 [17.2;42.0]
Oxygen desaturation index	22.9 [15.0;34.4]	25.0 [17.0;38.0]
Mean SaO_2	92.6 (6.62)	93.1 (3.36)
Minimum SaO_2	79.7 (6.82)	78.0 (6.71)
% of time with SaO_2<90%	6.52 [1.60;16.7]	8.23 [3.10;22.3]
Epworth sleepiness scale score	6.00 [4.00;8.00]	7.00 [4.00;9.00]
Medical history		
Hypertension	659 (68.6%)	777 (73.5%)
Any transient ischemic attack	247 (25.7%)	357 (33.8%)
Diabetes mellitus	281 (29.2%)	308 (29.1%)
Medication		
Antihypertensive drugs	645 (67.1%)	796 (75.3%)
Antiplatelet and antithrombotic drugs	544 (56.6%)	723 (68.4%)
Lipid-lowering drug	483 (50.3%)	608 (57.5%)

Antidiabetics oral medication	197 (20.5%)	230 (21.8%)
Insulin	54 (5.62%)	70 (6.62%)

Data are n (%), mean (standard deviation) or median [q1; q3]. q1: first quartile; q3: third quartile; CPAP: continuous positive airway pressure; BMI: body mass index;

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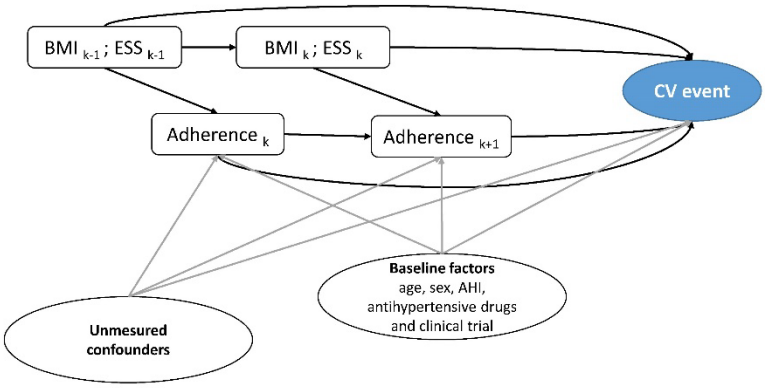
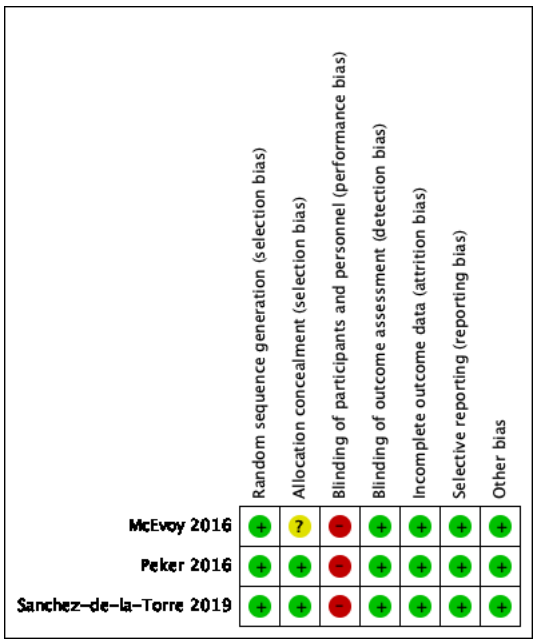
eFigure 1. Direct acyclic graph of the inverse probability of treatment weighted model to assess the effect of CPAP adherence on the risk of recurrent cardiovascular event

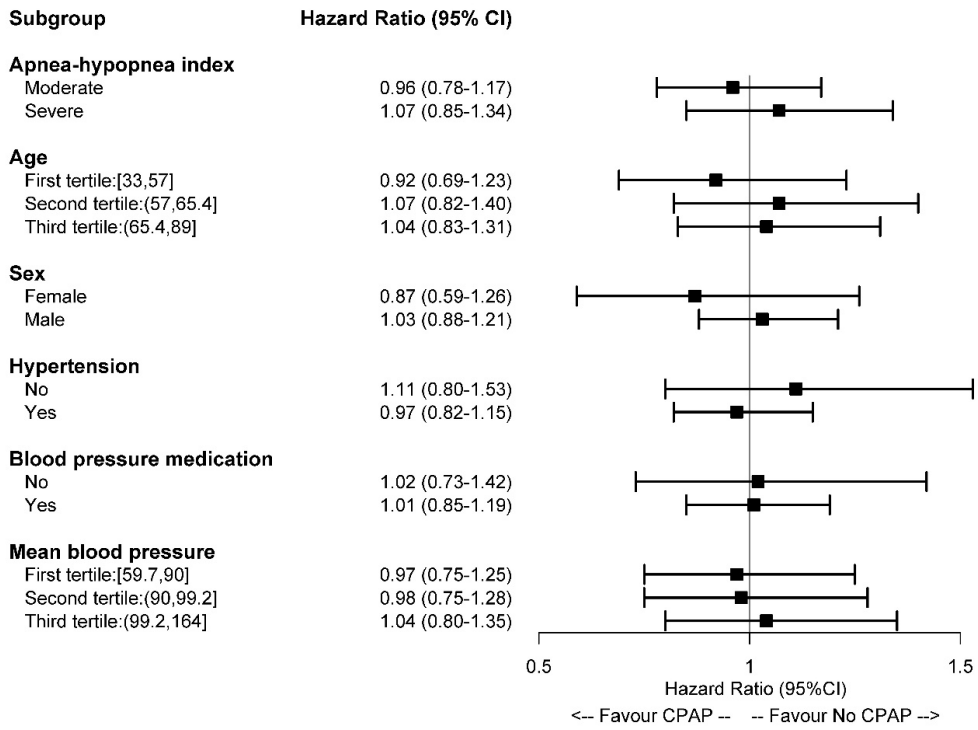


Directed acyclic graph (DAG) is used to show longitudinal confounding variables. We assumed that BMI is a potential time-varying confounding factor due to their directly relationship with cardiovascular risk and inversely related with future compliance (due to apnea-hypopnea index reduction). BMI, Epworth sleepiness scale score (ESS) and CPAP adherence are time-varying, and BMI_k, Epworth sleepiness scale score (ESS_k) and CPAP $adherence_k$ indicates measurements at visit k. The inverse probability of treatment weighting model is additionally adjusted for age, sex, apnea-hypopnea index, Epworth, antihypertensive drugs and trial as baseline factors. Abbreviations: ESS: Epworth sleepiness scale score)

eFigure 2. Risk of bias assessment: assessments regarding each risk of bias item for each randomized clinical trial included
Green (+) = low risk of bias, yellow (?) = unclear risk of bias, red (-) = high risk of bias.



eFigure 3. One-stage IPD meta-analysis of the CPAP effect for MACCEs according to the subgroup patients



Mixed-effects Cox proportional hazards model adjusted by trial as random effects. CI: confidence interval.

eAppendix. Methodological details regarding literature search strategy

1. PubMed (MEDLINE)

Last search: 23 June 2023
The following strategy will be used to search MEDLINE (PubMed):
1. "Sleep Apnea, Obstructive"[Mesh]
2. "Sleep Apnea Syndromes"[Mesh]
3. (Obstruct* OR sleep) AND (apnea* OR apnoea*)
4. Obstruct* AND (hypopnea* OR hypopnoea* OR hypoapnea* OR hypoapnoea*)
5. Upper airway resistant* AND sleep apnea*
6. Sleep AND (disorder* AND breathing)
7. OSA
8. OSAS
9. OSAHS
10. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11. "Respiration, Artificial"[Mesh]
12. "Ventilators, Mechanical"[Mesh]
13. NIPPV OR NPPV OR NIV OR NIAV OR CPAP OR (positive AND pressure)
14. #11 OR #12 OR #13
15. “Mortality"[Mesh]
16. “Acute Coronary Syndrome"[Mesh]
17. “Stroke"[Mesh]
16. “Cardiovascular system"[Mesh]
17. “Heart Failure"[Mesh] or “Heart failure, systolic"[Mesh] or “Heart failure, diastolic"[Mesh]
18. “Sleep” or “Sleep Stages” [Mesh]
19. #15 OR #16 OR #17 OR #18 OR
20. Randomized controlled trial [Publication Type]
21. #10 AND #14 AND #20
22. #21 OR #15 OR #16 OR #17 OR #18OR#19 OR #20

The MEDLINE strategy was adapted to the syntax and subject headings of the other databases.

2. EMBASE

Host: Embase.com
Date of Search: 23 June 2023
#1. (obstructive sleep apnea) (continuous positive airway pressure) (placebo)(cardiovascular)"
#2. obstructive sleep apnea
#3. sleep apnea
Filter: Classification/Clinical trial

3. COCHRANE DATABASE OF SYSTEMATIC REVIEWS

Host: Wiley
Date of search: 23 June 2023
#1 ippv or nppv or niv or niav or cpap or (positive and pressure)
#2 MeSH descriptor: explode all trees
#3 MeSH descriptor: [Respiration, Artificial] explode all trees
#4 #1 or #2 or #3
#5 MeSH descriptor: [Sleep Apnea, Obstructive] explode all trees
#6 MeSH descriptor: [Sleep disorder breathing] explode all trees
#7 MeSH descriptor: [Sleep Apnea Syndromes] explode all trees
#8 (obstruct* or sleep) and (apnea* or apnoea*)
#9 obstruct* and (hypopnea* or hypopnoea* or hypoapnea* or hypoapnoea*)
#10 Mesh descriptor: [cardiovascular]: explode all trees
#11 Mesh descriptor: [myocardial infartion]: explode all trees
#12 osahs
#13 osa
#14 osas
#15 Sleep apnea

#16 Sleep disorder breathing
#17 #5 or #6 or #7 or #8 or #9 or #12 or #13 or #14
#18 #10 or #11 or #15 or #16 #19 #4 and #15 #20 #17 or 18

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