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Relationship between CPAP termination and all-cause mortality: a French nationwide database analysis

Running title: CPAP termination and all-cause mortality

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APMC foundation Direction de la recherche Clinique du CHU de Grenoble and inter-regional research university hospital group. AVB, FL and AJ are employees of ResMed. PR, PSB and PH are employees of SEMEIA. SB and DA have no conflicts of interest to disclose.

ABBREVIATIONS

ALASKA	nAtionwide cLAimS data laKe for sleep Apnoea
CI	confidence interval
CNIL	Commission Nationale Informatique et Liberté
CPAP	continuous positive airway pressure
HR	hazard ratio
ISAACC	Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome - effect of intervention with CPAP
OSA	obstructive sleep apnea
RICCADSA	Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA
SAVE	Sleep Apnea Cardiovascular Endpoints
SNDS	Système national des données de santé

ABSTRACT

BACKGROUND Randomized controlled trials have failed to demonstrate an effect of continuous positive airway pressure (CPAP) therapy on mortality. However, these studies have a number of important limitations, including low CPAP adherence, patient selection and a small number of mortality events.

RESEARCH QUESTION What are the effects of CPAP therapy termination in the first year on all-cause mortality in obstructive sleep apnea (OSA) patients from the nationwide cLAIMS data lake for sleep Apnoea (ALASKA) study?

STUDY DESIGN AND METHODS Data from the French national health insurance reimbursement system database (SNDS) for all new CPAP users aged ≥ 18 years were analyzed. The SNDS contains comprehensive, individualized and anonymized data on health spending reimbursements for $>99\%$ of all individuals living in France. OSA diagnosis was based on specific disease codes, while CPAP prescription was identified using specific treatment modality codes. CPAP therapy termination was defined as the cessation of CPAP reimbursements triggered by the respiratory physician or sleep specialist in charge of follow-up. Patients who terminated therapy in the first year were propensity score matched with those who continued to use CPAP. The primary outcome was all-cause mortality. Three-year survival was visualized using Kaplan-Meier curves. Contributors to mortality were also determined.

RESULTS Data from two matched groups each including 88,007 patients were included (mean age 60 years, 64% male). Continuation of CPAP therapy was associated with a significantly lower risk of all-cause death compared with CPAP therapy termination (hazard ratio 0.61, 95% confidence interval 0.57–0.65; Log-rank $p < 0.01$). Incident heart failure was

also less common in patients who continued versus terminated CPAP therapy (hazard ratio 0.77, 95% confidence interval 0.71–0.82; $p < 0.01$).

INTERPRETATION These real-world data from a comprehensive, unbiased database highlight the potential for ongoing usage of CPAP treatment to reduce all-cause mortality in patients with OSA.

Key words: adherence; continuous positive airway pressure; mortality; obstructive sleep apnea

TAKE-HOME POINT

Study Question: What are the effects of CPAP therapy termination in the first year on all-cause mortality in OSA patients from the ALASKA study?

Results: In matched patient groups, continuation of CPAP therapy was associated with a significantly lower risk of all-cause death compared with CPAP therapy termination. In addition, incidence heart failure was significantly less common in patients who continued versus terminated CPAP therapy in the first year.

Interpretation: These data highlight the potential for ongoing usage of CPAP to reduce all-cause mortality in patients with OSA.

Obstructive sleep apnea (OSA) is characterized by repeated upper airway collapse during sleep. These episodes are associated with several important consequences, including sympathetic activation, marked negative intrathoracic pressure swings, intermittent oxygen desaturation, hypercapnia and arousal from sleep. In turn, these effects are thought to contribute to common comorbidities in patients with OSA, including hypertension, cardio- and cerebrovascular disease, and metabolic abnormalities.¹⁻⁴ These comorbidities could be responsible for the increased all-cause mortality risk that has been reported in patients with OSA.⁵⁻¹⁰

Despite the reported association between OSA and mortality, randomized clinical trials evaluating the effects of treating OSA on cardiovascular events and all-cause death have not demonstrated any beneficial effect of continuous positive airway pressure (CPAP) therapy, the gold-standard treatment for moderate-to-severe OSA.¹¹⁻¹³ However, the ability of CPAP to influence hard mortality endpoints may have been limited by several factors, including low adherence to CPAP and patient selection. In addition, the total number of mortality events was low in all randomized trials, limiting statistical power to detect between-group differences and perhaps not representative of what happens in the real world. Thus, although randomized controlled trials provide a high level of evidence, real-world data might be able to provide a more accurate and generalizable picture of the effects of routine clinical usage of CPAP on mortality.

The nationwide cLAimS data laKe for Sleep Apnoea (ALASKA): real life data for understanding and increasing OSA quality of care study uses data from the French national health insurance reimbursement system database. This analysis investigated all-cause mortality in new users of CPAP who terminated therapy during the first year or continued with long-term CPAP therapy.

METHODS

DATA SOURCE. This analysis included data from the French national health insurance reimbursement system database (“Système national des données de santé”; SNDS), which contains comprehensive, individualized and anonymized data on health spending reimbursements for >99% of all individuals living in France. The ALASKA project was approved by the ‘Commission Nationale Informatique et Liberté’ (CNIL), the French information technology, and personal data protection authority. Specific approval was obtained from the CNIL to perform this study (DR-2019-78, n°919194).

STUDY POPULATION. Eligible patients were adults aged ≥ 18 years who had not previously used CPAP and had initiation of CPAP therapy from January 2015 to December 2016. OSA diagnosis was based on specific disease codes, while CPAP prescription was identified using specific treatment modality codes.¹⁴

Patients who terminated CPAP during the first year of therapy were matched with those who continued CPAP therapy for one year using propensity score matching to eliminate the influence of biases and confounding factors affecting both therapy termination and mortality rates in the therapy termination and therapy continuation groups. Propensity score matching was based on the following factors: patient demographics (age and sex); insurance coverage; socioeconomic status; and comorbidities (stroke, heart failure, peripheral arterial occlusive disease, hypertension, diabetes mellitus, other cardiovascular diseases, chronic obstructive pulmonary disease, bariatric surgery, neurotic disorders, use of psychotropic medication, and kidney diseases). To account for possible selection bias, a sensitivity analysis was performed in the untruncated cohort with CPAP initiation being the

starting date in a survival Cox model with CPAP continuation as a time-dependent covariate. Variables for adjustments were the same variables used for the propensity score analysis.

STUDY PARAMETERS AND FOLLOW-UP. One year after CPAP initiation, the propensity score was applied to select a matched population of CPAP users and non-users; patients were then followed for an additional 3 years (Figure S1).

CPAP therapy termination was defined as the cessation of CPAP reimbursements triggered by the respiratory physician or sleep specialist in charge of follow-up. French national recommendations for reimbursement are CPAP device usage of >4 h/night. Reimbursement rates progressively decrease when there is very low adherence to CPAP, although delivery and reimbursement of therapy can continue when CPAP usage is 2–4 h/night, with a requirement for additional patient education and coaching. There is a mandatory follow-up visit at 4 months after CPAP initiation, then every year thereafter to determine treatment reimbursement renewal.

For this analysis, it was assumed that CPAP termination was linked with non-adherence. Individuals with a valid and documented reason for stopping CPAP therapy (i.e. sleep apnea cure after bariatric surgery, otorhinolaryngology surgery, switch to oral appliances, death) were censored in the Kaplan-Meier analysis. In the SNDS database, mortality is defined by the registered date of death but the cause of death is not available.

STATISTICAL ANALYSIS. Data are expressed as median (interquartile range) for quantitative data and as numbers (percentages) for qualitative data. Comparisons between groups (CPAP termination vs. CPAP continuation) were performed using Student t-test for quantitative data and Chi-square test for qualitative data. Mortality and the cumulative

incidence rate for heart failure were compared using Kaplan-Meier curves and between-group comparisons were performed by using the Log-rank test. These analyses were also performed separately for males and females.

The primary objective was assessed using a propensity score analysis. First, a propensity score model was performed to compute the factors significantly associated with the probability of CPAP termination during the first year. A non-parsimonious multivariable regression model was created including all major factors (list of variables and results in Table S1). A 1:1 greedy matching was performed with a caliper of 0.1%. Standardized differences were used to ensure the quality of the propensity score matching. The standardized difference was reduced for all variables after matching (Figure S2). A semi-parametric Cox model was finally used to assess the impact of CPAP termination or continuation on outcomes (mortality, incident heart failure, incident coronary artery disease, new hospitalization for diabetes, incident arrhythmias and incident hypertension); cancer was not evaluated due to the comparatively short follow-up time for this analysis. To account for mortality as a competing event for all outcomes, sensitivity analyses were performed considering only alive patients. Hazard proportionality assumption was not checked and hazard ratio (HR) values must be interpreted as an average HR rather than instantaneous HR.¹⁵

Analyses were performed using Python 3.6.7 software with the libraries Numpy 1.18.1 and Pandas 0.24.2 for data management and analysis, Statsmodel 0.12.1 for logistic regression and Lifelines 0.14.1 for Kaplan-Meier curves and Cox models. A p-value threshold of 0.05 was considered statistically significant.

RESULTS

STUDY POPULATION. The ALASKA cohort includes 480,000 patients, of whom 365,301 had at least one year of follow-up and did not have a valid reason for CPAP therapy termination (4882 patients had a valid reason for CPAP termination during the first year; see Table S2 for details). Of the 365,301, 76% (n=277,242) continued and 24% (n=88,059) terminated CPAP therapy. After propensity score matching, the study population for this analysis included 88,007 patients in each group (total of 176,014 patients) (Figure 1). As expected, propensity score matching generated two patient groups that were well matched for baseline characteristics (Table 1).

ALL-CAUSE MORTALITY. Over a 3-year observation period, death occurred in 3,204/88,007 (3.6%) patients in the CPAP therapy termination group compared with 2,053/88,007 (2.3%) patients in the therapy continuation group (Table S3). Continuation of CPAP therapy was associated with a significantly lower risk of all-cause death compared with CPAP therapy termination (HR 0.61, 95% confidence interval [CI] 0.57–0.65; Log-rank $p < 0.01$) (Figure 2). The results were similar in males and females (HR 0.63 [95% CI 0.57–0.68] and HR 0.54 [95% CI 0.47–0.62]; both $p < 0.01$) (Figure S3). The sensitivity analysis also showed a significant reduction in all-cause mortality associated with CPAP continuation: HR: 0.73 (95% CI 0.70–0.76); $p < 0.01$ (10,795 events in 336,415 patients or an event rate of 3.2%).

FACTORS CONTRIBUTING TO DEATH. The cumulative incidence of heart failure (based on disease codes entered in the SNDS database) was significantly lower in patients who continued versus terminated CPAP therapy (HR 0.77, 95% CI 0.71–0.82; Log-rank $p < 0.01$) (Table S3, Figure 3). During follow-up, incident hypertension and heart failure occurred significantly less frequently in OSA patients who continued versus terminated CPAP therapy (Table S3, Figure 4). In addition, there was a trend towards a lower risk of new

hospitalizations for diabetes in the therapy continuation versus therapy termination group ($p=0.06$) (Table S3, Figure 4). Sensitivity analysis that excluded patients censored for death during the analysis period yielded similar results to the primary analysis (Figure S4).

DISCUSSION

The results of this analysis of a comprehensive, unbiased national dataset showed a significant association between continuation of CPAP during the first year of therapy and lower all-cause mortality. One potential mechanism underlying this association may be the lower rate of incident HF seen in the group who continued CPAP compared with those who terminated therapy. In our main analysis, only patients who survive long-enough to discontinue the use of CPAP were included. As such, patients who were either deceased, had <1 year of follow-up or who discontinued CPAP during the first year were used for propensity score matching but not included in the main all-cause mortality analysis. To avoid potential selection bias due to arbitrarily splitting the dataset into two groups that were not created at baseline, we performed a sensitivity analysis using CPAP termination as a time-dependent covariate and evaluating its association with overall survival. The results of this sensitivity analysis confirmed and strengthened the study findings by showing that there was a 27% reduction in all-cause mortality in patients who continued CPAP.

Our findings contrast with those of randomized clinical trials evaluating the effects of CPAP on mortality. The Sleep Apnea Cardiovascular Endpoints (SAVE), Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome - effect of intervention with CPAP (ISAACC), and Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA (RICCADSA) studies investigated the effects of CPAP on a composite endpoint that included cardiovascular death and non-fatal cardiovascular events.¹¹⁻¹³ All found no

significant difference between the CPAP and usual care groups with respect to the primary endpoint, or for cardiovascular death alone as a secondary endpoint.¹¹⁻¹³ However, there are several factors that may have limited the ability of these studies to detect any statistically significant effect of CPAP on mortality.

Firstly, adherence to treatment was low (3.3 ± 2.3 h/night in SAVE and 2.78 ± 2.73 night in ISAACC),^{11,13} and these levels of adherence do not appear to reflect what is seen with CPAP usage in broader clinical settings.^{16,17} Device usage of ≥ 4 h/night may be needed for the benefits of therapy to be realized.^{12,18} For example, in the RICCADSA study, a preplanned analysis in patient subgroups using CPAP for ≥ 4 versus < 4 h/night showed that those using CPAP for ≥ 4 h/night had a significantly lower rate of composite endpoint events, including mortality (adjusted hazard ratio 0.29, 95% CI 0.10–0.86; $p=0.026$).¹² Furthermore, in the SAVE study, patients with OSA who were adherent to CPAP therapy had a lower risk of stroke and the composite endpoint of cerebral events than those in the usual care group.¹¹ Secondly, the trials included highly selected patient populations, namely non-sleepy OSA patients with existing cardiovascular disease. In particular, the non-inclusion of patients with excessive daytime sleepiness from randomized clinical trials for ethical reasons might exclude a group likely to adhere and respond well to CPAP therapy.¹⁹ Recently, a comparison has been done between consecutive sleep clinic patients ($n= 3,965$) and participants in the prominent recent RCTs examining the effect of CPAP on adverse cardiovascular outcomes in OSA.²⁰ Less than 20% of real-world OSA patients assembled the eligibility criteria of RCTs and routine clinic OSA patients were younger, sleepier and more likely to be female.²⁰ Finally, the total number of mortality events in each study was very small (25 in the CPAP group and 20 in the usual care group in SAVE, and 12 in the CPAP group and 14 in the usual care group in ISAACC), limiting statistical power for this endpoint.

In contrast, the current analysis includes all OSA patients in France with an indication for CPAP therapy, making it applicable to general populations, and the large number of deaths provides adequate power for mortality analyses. Furthermore, differentiating between patients who continued using CPAP and those who did not provides a clearer picture of the benefits of CPAP usage. Thus, although randomized controlled trials provide the highest level of evidence, real-world data might provide a better indication of overall effectiveness in patient populations likely to be encountered in routine clinical practice. Others have also recently suggested that design features and enrolled populations in randomized controlled trials of CPAP therapy in patients with OSA limit the ability of these trials to identify the benefits of treatment.²¹ Contrary to classical observational studies with exposed and unexposed patients, the “discontinuation design” provides a more homogeneous initial study population on which the applied propensity score matching further limits unmeasured bias. Specifically, it has recently been suggested that observational studies using propensity scores can overcome the ethical limitations around inclusion of sleep apnea patients with excessive daytime sleepiness into randomized controlled trials.²² The US Food and Drug Administration has also indicated that studies using propensity score methods are appropriate to support approval of medical devices, such as CPAP.²³

Two other recent real-world studies have also reported a significant association between CPAP usage and lower all-cause mortality.^{24,25} Similar to our approach, a retrospective analysis of patients from a sleep clinic in Japan used propensity score matching to create two study populations of OSA patients; in this case, those who used CPAP and those who did not. After a median follow-up of 6–7 years, the all-cause mortality rate was significantly lower in those who did versus did not use CPAP (4.2% vs. 7.4%; HR 0.56, 95% CI 0.41–

0.78).²⁵ This approximate doubling of all-cause mortality risk in OSA patients not using CPAP was similar to that in our study for patients who stopped versus continued CPAP therapy. The comparison group in a population-based longitudinal study from Spain was patients without OSA, who were found to be at significantly higher risk of all-cause death than OSA patients prescribed CPAP after adjustment for comorbidities and previous healthcare resource use (HR 0.44 [95% CI 0.36–0.54] in men and 0.44 [0.28–0.68 in women]).²⁴

In an earlier study, Woehrle et al. analyzed a large German healthcare database and found that patients diagnosed with sleep apnea and treated with CPAP had a significantly lower all-cause mortality rate after three and four years of follow-up compared with controls who had sleep apnea but were not treated with CPAP.²⁶ Our findings are consistent with those of the German study, which also used propensity score matching to generate the two study groups. However, our sample size is substantially larger and the source of participants more comprehensive than previous similar studies.

A large retrospective cohort study of Medicare beneficiaries with newly-diagnosed heart failure found that those who were screened for and diagnosed with sleep-disordered breathing (SDB) and treated with CPAP were significantly less likely to die over 2 years of follow-up than screened and diagnosed patients who were not treated with CPAP (HR 0.49, 95% CI 0.29–0.84).²⁷ These data highlight an important link between SDB and heart failure that is reflected in our study finding that patients who continued CPAP therapy during the first year were significantly less likely to develop incident heart failure than those who terminated therapy. This result is consistent with a recent study showing a significant association between hypoxic burden and the rate of incident heart failure in patients with OSA.²⁸

A link between CPAP usage and lower mortality was also identified in a prospective cohort study from the United Kingdom.²⁹ Patients with OSA syndrome who were treated with CPAP for >5 years were significantly more likely to be alive at the end of the study (mean follow-up 14.8±3.7 years), with a relative risk for survival of 5.63 (95% CI 4.83–6.58; p<0.001). Similarly, patients who did not adhere to CPAP therapy in the first year of therapy were at higher risk of death over the subsequent median 2.4-year follow-up period (adjusted HR 1.74, 95% CI 1.32–2.28) in a Swedish national registry-based cohort study.³⁰ Health system data from Catalan, Spain also showed a reduction in population level mortality with CPAP treatment, but this effect was only seen in males.³¹ This contrasts with our study, where reductions in mortality were consistently seen in both men and women.

While we do not currently have precise data on the specific cause of death in our study (the database includes date of death but not the cause), based on the information available it appeared that incident hypertension and heart failure were potentially important contributors to death in the group of patients who terminated CPAP therapy. In the two other recent real-world studies, the association between non-CPAP usage and mortality appeared to be largely driven by malignancy-related deaths.^{24,25} However, these studies had a longer duration of follow-up (median 5.5 to 6.5 years)^{24,25} compared with only 3 years for our analysis. Longer follow-up durations have also been employed in studies evaluating the link between OSA and cancer.³²⁻³⁴

The significant negative impact of terminating CPAP therapy in the first year highlights the importance of strategies to improve adherence to, and continuation with, CPAP. A personalized medicine approach utilizing telemedicine-based support programs has already been shown to improve PAP usage and reduce the number of patients terminating therapy in real-world settings.^{35,36} Therefore, implementation of these strategies and the associated

improvement in CPAP continuation rates have the potential to positively impact on death rates. However, additional prospective studies are needed to determine the effects of different telemonitoring programs and patient engagement tools on hard clinical endpoints, including mortality.

The database used is an important strength of this study. The French SNDS is currently one of the best anonymized claims databases in the world due to its size (600 TB) and its unbiased recruitment (including >99% of the total French population). It is not specific to any insurer, healthcare provider, or CPAP device brand. In addition, we performed careful and extended propensity score matching to ensure comparability between the CPAP termination and CPAP continuation groups, and there was a large number of mortality events for analysis (n=5,257).

Several limitations also need to be considered when interpreting the study findings. As has been highlighted previously,^{14,36,37} there are several weaknesses in databases that are designed for administrative purposes rather than clinical research, including a lack of data for some potentially important parameters. In the context of this study, that means that there are no apnea-hypopnea index data, so OSA severity is unknown. However, the fact that all patients fulfilled the criteria for initiation of CPAP provides some indication that OSA was at least moderate in severity. There are also some limitations of propensity score matching in this context because it is a post-hoc process based on available information only, meaning that we do not have data to allow propensity matching on important covariates that might modify the relationship between OSA exposure and outcomes, such as OSA severity, sleepiness, health behaviors, adherence data and body mass index. Several studies have addressed the link between sleepiness phenotypes, OSA severity (i.e. hypoxic burden) and incident cardiovascular events.^{19,38} Contrary to general population cohorts, in routine

real world practice, symptom subtypes were not associated with major adverse cardiovascular events after adjustment for confounders.³⁸ As our data did not include measurements of sleepiness and hypoxic burden we did not account for these confounders in our propensity matching. Therefore, potentially relevant covariates such as nutrition, physical activity and sleep duration (all of which are potentially linked with mortality) were not included. In addition, due to French privacy requirements, the SNDS does not contain data on smoking habits, alcohol intake or body mass index. Furthermore, we do not have any data about the actual hours of CPAP usage because the database defines CPAP usage as a binary parameter (yes or no). In the future it may be possible to link SNDS records with CPAP telemonitoring data, and individual anthropometric and lifestyle profiles, which would allow investigation of the dose-response relationship between CPAP adherence and mortality.

INTERPRETATION

This study showed that continued use of CPAP during the first year after therapy initiation is associated with a significant reduction in mortality in a large national cohort of patients with OSA compared with CPAP therapy termination. This finding adds to a growing body of evidence for the beneficial effects of CPAP usage on survival. Additional research is needed to clarify the impact of CPAP on specific causes of death, and to determine the relationship between hours of CPAP usage and mortality benefit.

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Responsibility for data: JLP assumes responsibility for the accuracy and completeness of the analyses and for the fidelity of this report to the trial protocol.

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Figure Legends

Figure 1. Flow chart of patient inclusion

Figure 2. Kaplan-Meier curves for all-cause mortality. CPAP, continuous positive airway pressure.

Figure 3. Cumulative incidence of heart failure. CPAP, continuous positive airway pressure.

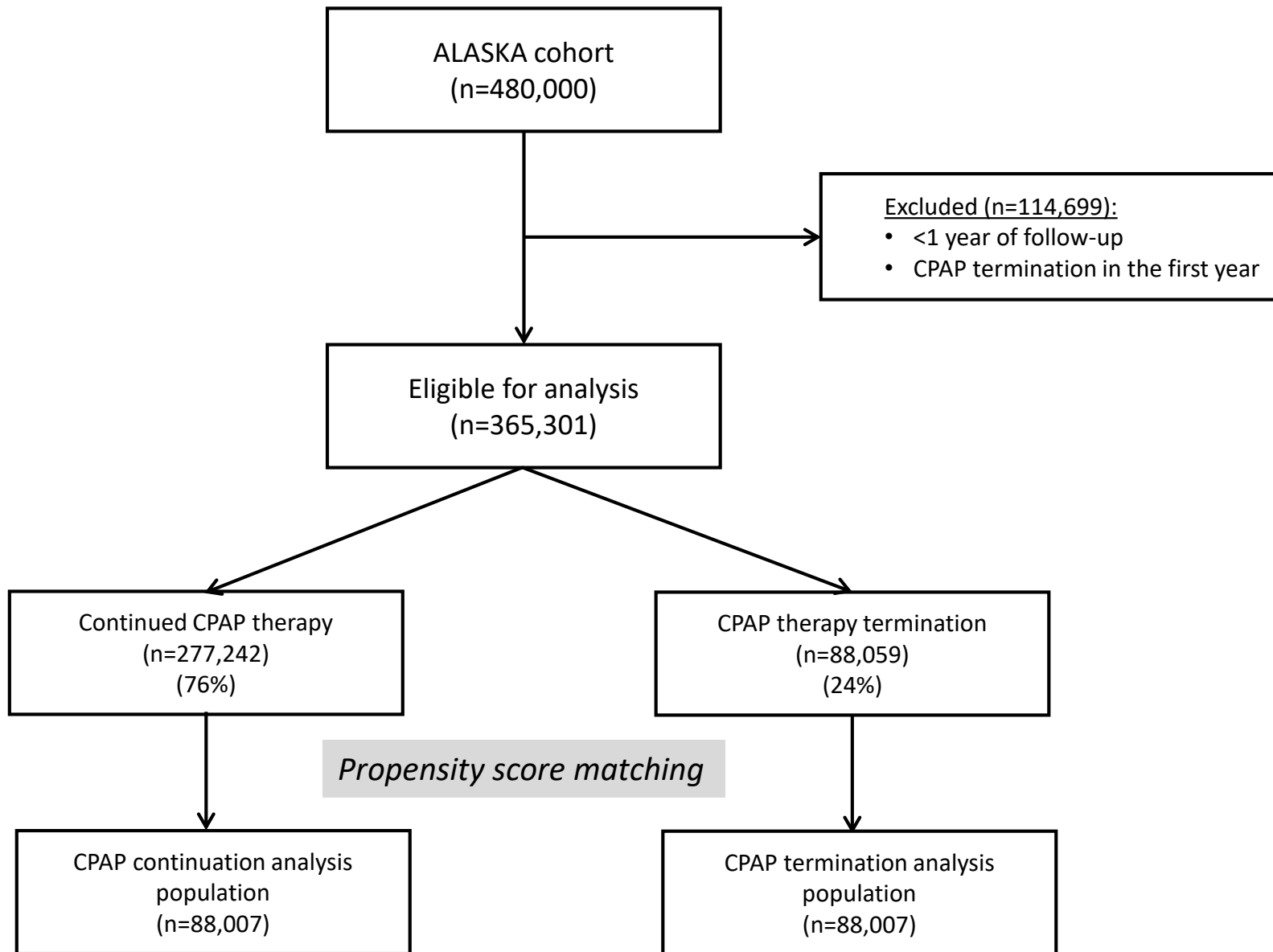
Figure 4. Risk of all-cause mortality and factors potentially contributing to death. CI, confidence interval; CPAP, continuous positive airway pressure; HR, hazard ratio. HR <1 indicates a lower risk with CPAP continuation.

Tables

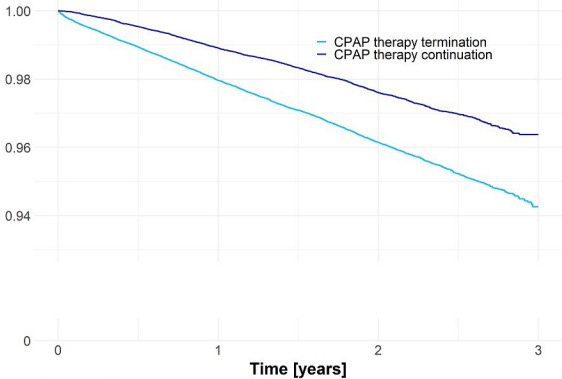
Table 1. Baseline characteristics of the matched study population

	CPAP therapy	
	Continuation (n=88,007)	Termination (n=88,007)
Age, years	60.0 [70.0–50.0]	59.0 [69.0–49.0]
Female, n (%)	32,227 (36.6)	31,666 (36.0)
Comorbidities, n (%)		
Chronic psychiatric disorders	4,621 (5.2)	4,606 (5.2)
Stroke	2,735 (3.1)	2,684 (3.1)
Heart failure	2,306 (2.6)	2,046 (2.3)
Coronary heart disease	8,023 (9.1)	8,037 (9.1)
Hypertension	42,568 (48.4)	43,231 (49.1)
Diabetes mellitus	18,610 (21.1)	18,304 (20.8)
Chronic obstructive pulmonary disease	7,156 (8.1)	7,387 (8.4)

Values are median [interquartile range], or number of patients (%).



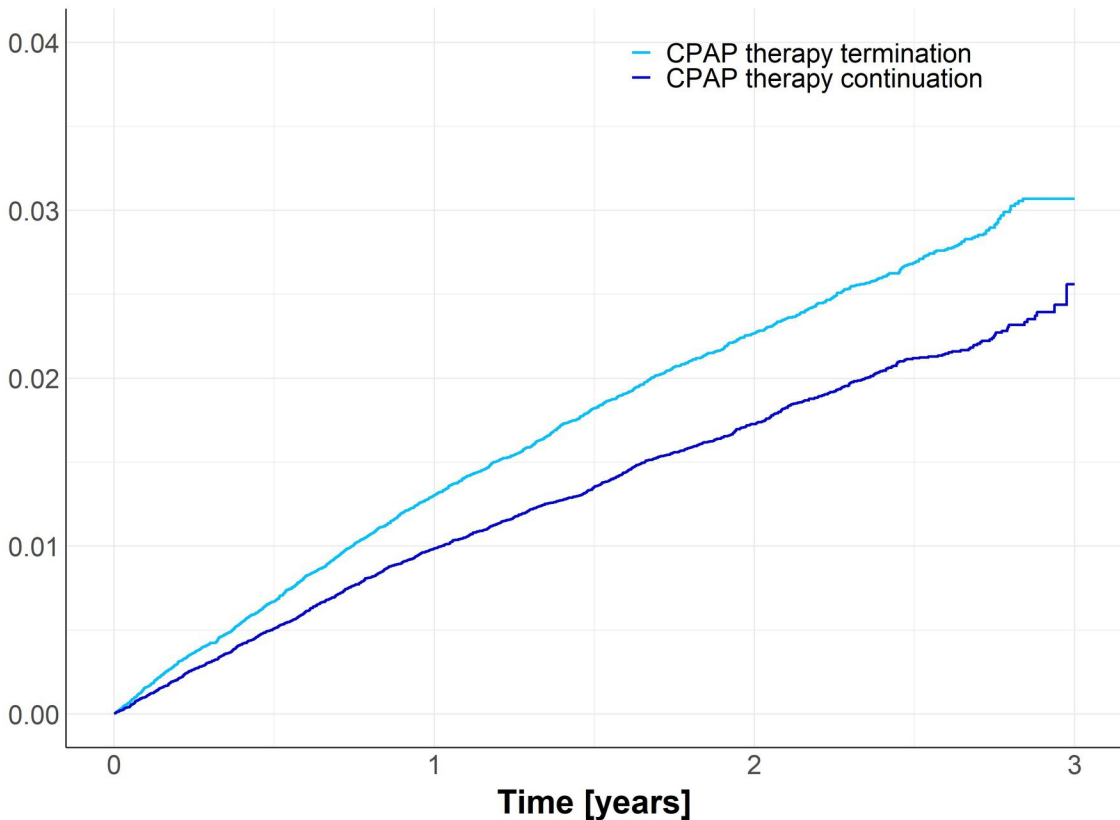
Survival probability



Number at risk

CPAP therapy termination	88,007	78,025	38,844	0
CPAP therapy continuation	88,007	83,514	41,232	0
All patients	176,014	161,539	80,076	0

Incident heart failure [%]



Number at risk

CPAP therapy termination	87,405	76,710	37,921	0
CPAP therapy continuation	87,405	82,298	40,403	0
All patients	174,810	159,008	78,324	0

