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ORIGINAL RESEARCH

# Sleep Apnea, the Risk of Developing Heart Failure, and Potential Benefits of Continuous Positive Airway Pressure (CPAP) Therapy

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***Background*—**Whether there is an association between sleep apnea (SA) and the risk of developing heart failure (HF) is unclear. Furthermore, it has never been established whether continuous positive airway pressure (CPAP) therapy can prevent development of HF. We aimed to investigate SA patients' risk of developing HF and the association of CPAP therapy.

***Methods and Results*—**Using nationwide databases, the entire Danish population was followed from 2000 until 2012. patients with SA receiving and not receiving CPAP therapy were identified and compared with the background population. The primary end point was first-time hospital contact for HF and adjusted incidence rate ratios of HF were calculated using Poisson regression models. Among 4.9 million individuals included, 40 485 developed SA during the study period (median age: 53.4 years, 78.5% men) of whom 45.2% received CPAP therapy. Crude rates of HF were increased in all patients with SA relative to the background population. In the adjusted model, the incidence rate ratios of HF were increased in the untreated SA patients of all ages, compared with the background population. Comparing the CPAP-treated patients with SA with the untreated patients with SA showed significantly lower incidence rate ratios of HF among older patients.

***Conclusions*—**In this nationwide cohort study, SA not treated with CPAP was associated with an increased risk of HF in patients of all ages. Use of CPAP therapy was associated with a lower risk of incident HF in patients >60 years of age, suggesting a protective effect of CPAP therapy in the elderly. **(*J Am Heart Assoc*. 2018;7:e008684. DOI: 10.1161/JAHA.118.008684.)**

**Key Words:** cohort study • continuous positive airway pressure therapy • database • heart failure • sleep apnea



Sleep apnea (SA) is associated with increased risk of cardiovascular events, worsening of heart failure (HF), metabolic disturbances, and overall a reduced quality of life.[1–4] One study even found an increased risk of incident HF among men with obstructive sleep apnea (OSA).[5] Continuous positive airway pressure (CPAP) therapy is a documented treatment for SA because of symptom relief, but it may also reduce endothelial damage and improve blood pressure, glucose tolerance, and cardiac function in patients with HF.[6–10] However, a direct beneficial effect of CPAP therapy on cardiovascular outcomes has never been established in a controlled setting.[11,12] However, adaptive servoventilation has recently been shown to in fact increase mortality in a randomized setting of patients with HF with reduced ejection fraction and central SA,[13] causing some concern about the use of noninvasive ventilation in these patients. Although the latter study investigated central SA patients with established chronic HF with reduced ejection fraction, it calls for further studies because the interplay between SA, cardiac disease, and pressure therapies is not fully understood.[14] It may be speculated that in patients with OSA, CPAP therapy could prevent development of HF because of its positive effect on blood pressure and metabolic function.[8–10] We therefore aimed to investigate the relationship between SA, incident HF, and the association of CPAP therapy in an unselected real-life population.

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/7/13/e008684/DC1/embed/inline-supplementary-material-1.pdf

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## Clinical Perspective

### What Is New?

- Among patients with sleep apnea, there is an increased risk of the development of heart failure across all ages.
- Among patients with sleep apnea, aged ≥60 years, the use of continuous positive airway pressure (versus no treatment) decreases the risk of the development of new-onset heart failure.

### What Are the Clinical Implications?

- Clinicians should acknowledge growing evidence of the adverse cardiovascular effects of sleep apnea, and in particular, its association with heart failure.
- Early diagnosis and treatment of sleep apnea may potentially reduce associated morbidity and mortality, in addition to increasing the quality of life.

## Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The raw data are available through Denmark's Statistics on request.

## Databases

All Danish inhabitants are provided with a unique personal identification number at birth or immigration that enables cross-linkage of information from nationwide databases.

The Danish National Patient Registry holds information on hospital contacts, including diagnoses and procedural codes. Contacts are coded per the *International Classification of Diseases* (*ICD*)—the 8th revision before 1994 (*ICD-8*) and the 10th revision thereafter (*ICD-10*).

The National Prescription Registry holds information on date and amount of all redeemed prescriptions coded per the Anatomical Therapeutic Chemical classification system.

All used Anatomical Therapeutic Chemical and *ICD* codes are shown in Table S1. The Danish Civil Registration system provides data on date of birth, sex, immigration/emigration history, and vital status.

## Study Population and Baseline Characteristics

All individuals (the entire Danish population) were included on January 1, 2000 and followed until December 31, 2012. Individuals immigrating within the study period were included at date of immigration. Exclusion criteria included age <18 or >100 years, and a prior diagnosis of SA or HF (Figure 1). The following characteristics were defined binarily as present or not present at the date of inclusion: myocardial infarction (MI), ischemic stroke, atrial fibrillation, peripheral arterial disease, chronic kidney disease, liver disease, chronic obstructive pulmonary disease, and cancer (excluding non-melanoma skin cancer). These diagnoses have been previously validated with high positive predictive values.[15] Medication was defined as a prescription that was filled up to 180 days before date of inclusion of the following medicines: statins, β-blockers, loop diuretics, antihypertensive drugs, antiplatelet agents, and NSAIDs.

In order to include patients being treated for hypertension and diabetes mellitus outside of hospitals (eg, in general practice), we defined hypertension as a combination treatment with at least 2 antihypertensive drugs and diabetes mellitus as treatment with a glucose-lowering drug, as has been done previously.[16]

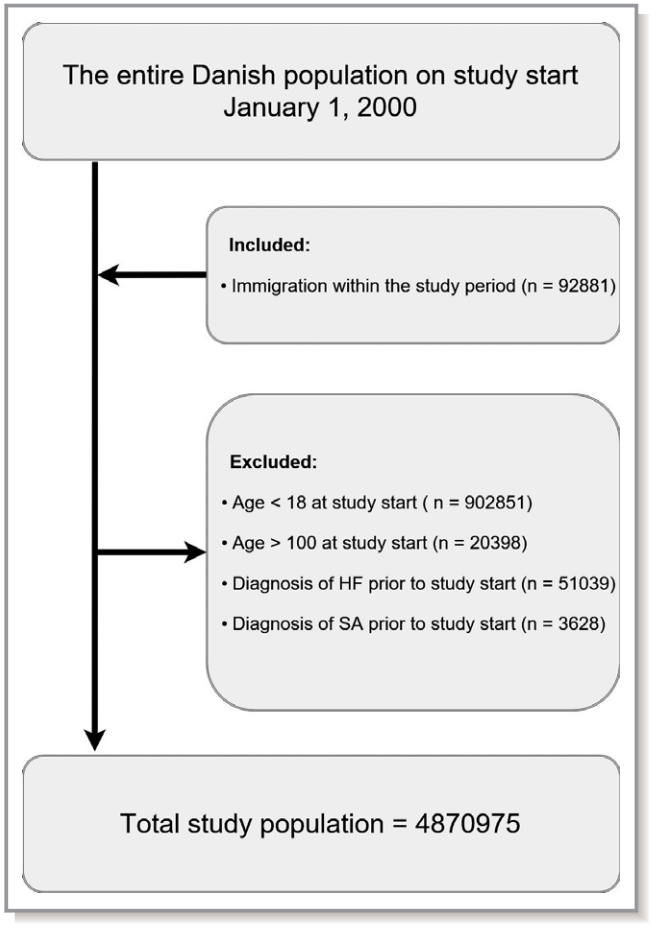


**Figure 1.** Study population, inclusions and exclusions. HF indicates heart failure; SA, sleep apnea.

## Definitions of SA and CPAP Therapy

We identified all patients in the study population registered with a diagnosis of SA. The SA diagnosis in the Danish

National Patient Registry has previously been validated with a positive predictive value of 82%.[1]

At the date of SA diagnosis, patients changed status from the background population to patients with SA. Procedural codes involving CPAP therapy were used to identify patients with SA who received CPAP therapy. To ensure adherence to therapy, 2 successive procedural codes were required: the first code representing distribution of CPAP equipment and second code indicating redistribution and probable continuous use after a tryout period. Thus, the second procedural date defined initiation of CPAP therapy.

## Outcome

HF was defined as a first-time primary or secondary diagnosis registered at hospitalization or at an outpatient visit. The following diagnoses were included: hypertensive HF, cardiomyopathy, cardiac insufficiency, left-sided HF, lung edema, and unspecified HF (Table S1). Two separate studies have validated the HF diagnosis in the Danish National Patient Registry and found positive predictive values of 84% (77.9% for first-time HF) and 81%, respectively.[17,18]

## Statistical Analysis

Both SA diagnosis and CPAP therapy were treated as time-dependent values, meaning that the subjects contributed time at-risk in the background population until the date of SA diagnosis. Individuals were followed until study end, emigration, death, or event of interest, whichever came first. A statistical interaction between age and the use of CPAP therapy was found ($P<0.0001$); thus, the patients were stratified into 2 age groups: 18 to 60 and >60 years of age. This age stratification was applied to all analyses.

Multivariable Poisson regression models were fitted to estimate incidence rate ratios (IRRs) of incident HF between 3 groups; (1) the background population (reference), (2) untreated patients with SA, and (3) patients with CPAP-treated SA. We calculated crude rates as events per 1000 person-years at risk with respect to age and follow-up time. Furthermore, we estimated IRRs using 2 different models: Model 1: Adjusted for age, sex, calendar year, and comorbidities present at the date of inclusion (including MI, ischemic stroke, hypertension, atrial fibrillation, peripheral arterial disease, chronic obstructive pulmonary disease, cancer, diabetes mellitus, and the use of NSAIDs), and Model 2: Fully adjusted model with all covariates mentioned in Model 1 incorporated as time-dependent variables (eg, if subjects developed hypertension 5 years into the study period, they contributed 5 years at-risk time to the model without hypertension and the rest of the study period the subjects were considered to have hypertension).

The latter model was also used to estimate the association of CPAP therapy. For this analysis, the reference group was SA patients not receiving CPAP therapy; thus, we compared the use of CPAP therapy versus no CPAP therapy among patients with SA only.

Interactions between use of CPAP therapy and predefined clinically relevant comorbidities were systematically checked and were found to be statistically significant for MI and hypertension; thus, we performed subgroup analyses of these groups (Table 1). We found no effect-modification for sex.

Model assumptions, including proportional hazards, independent observations, goodness-of-fit $\chi^2$ test, and homogeneity of variance, were found to be valid.

## Sensitivity Analyses

Two sensitivity analyses were performed. First, we altered the primary outcome definition to include both a HF diagnosis and a filled prescription of any dose of loop-diuretics between 45 days before to 45 days after the HF diagnosis, as has

**Table 1.** Results From Subgroup Analyses

| Subgroup | Age (y) | SA Patients Not Receiving CPAP Therapy | | SA Patients Receiving CPAP Therapy | |
|---|---|---|---|---|---|
| | | Total No. of Events | IRR (95% CI) | Total No. of Events | IRR (95% CI) |
| Patients with MI excluded | 18–60 | 184 | 1.41 (1.22–1.64) | 78 | 1.28 (1.01–1.61) |
| | >60 | 450 | 1.49 (1.35–1.64) | 190 | 1.27 (1.10–1.48) |
| Only patients with MI included | 18–60 | 42 | 0.58 (0.42–0.81) | 25 | 0.87 (0.58–1.29) |
| | >60 | 170 | 1.13 (0.97–1.32) | 75 | 0.89 (0.70–1.12) |
| Patients with HT excluded | 18–60 | 115 | 1.67 (1.38–2.02) | 51 | 2.06 (1.57–2.72) |
| | >60 | 207 | 1.53 (1.33–1.75) | 79 | 1.24 (0.99–1.56) |
| Only patients with HT included | 18–60 | 111 | 0.88 (0.73–1.08) | 52 | 0.75 (0.56–1.00) |
| | >60 | 413 | 1.29 (1.17–1.43) | 186 | 1.04 (0.90–1.21) |

All analyses were performed using the fully adjusted time-dependent Model 2 with background population as reference. CI indicates confidence intervals; CPAP, continuous positive airway pressure; HT, hypertension; IRR, incidence rate ratio; MI, myocardial infarction; SA, sleep apnea.

been done previously.[16,18] Loop-diuretics are considered first-line symptomatic treatment; thus, this restricted HF outcome was to only include potential symptomatic patients with HF.

In the second analysis, we excluded all patients with a filled prescription of any dose of loop-diuretics up to 180 days before the date of inclusion, thereby excluding patients possibly in treatment for unregistered HF.

Both analyses were performed using the adjusted time-dependent Model 2 (Table 2).

## Ethical Considerations

Statistics Denmark provided access to the databases mentioned earlier, and permission to use data from the registries was granted by the Danish Data Protection Agency (Ref. j.no. 2007-58-0015/local j.nr. GEH-2014-015, I-suite no. 02733). In Denmark, registry-based studies do not require ethical approval.

## Results

We identified 4.9 million Danish adults who were followed up to 13 years (Figure 1). During the study period, 40 485 patients (0.8%) received a first-time diagnosis of SA (86% unspecified SA, 13% obstructive SA, and <1% other forms of SA). SA patients were followed for a median time of 3.8 years (interquartile range [IQR] 1.8–6.4 years) and CPAP therapy was initiated in 45.2% with a median time to CPAP therapy initiation of 99 days (IQR 35–405 days). Patients with SA receiving CPAP therapy were older (median age of 55.7 years [IQR 47.3–63.2]) compared with the background population (43.1 years, [IQR 30.2–57.9]) as well as with the patients with SA not receiving CPAP therapy (52.4 years, [IQR 43.2–60.8]). Patients with SA receiving CPAP therapy had a higher burden of comorbidities and concomitant pharmacological therapy compared with both of the other groups (Table 3).

## Risk of Incident HF and Association of CPAP Therapy

Crude rates per 1000 person-years at risk were calculated for the background population and SA patients stratified by CPAP therapy (Figure 2 and Table 4). In the background population and in patients with SA not receiving CPAP therapy, IRRs (from the adjusted time-dependent Model 2) were increased in both age groups, but only significantly and most pronounced among the patients >60 years of age. We did not find a statistically significant difference in IRRs between the CPAP-treated patients with SA and the background population (Table 4).

In patients who had SA and who were >60 years of age, CPAP therapy was associated with a significantly lower IRR of HF compared with patients with SA of the same age who did not receive CPAP therapy. We found the same nonsignificant tendency in patients with SA between 18 and 60 years of age (Table 4).

## Subgroup and Sensitivity Analyses

The subgroup analyses were performed to evaluate effect-modification from MI and hypertension on the risk of developing HF. The results from the subgroup analyses were comparable to the main analysis (Table 1). Likewise, both sensitivity analyses (restriction of HF diagnosis and exclusion of potentially nonregistered HF patients) were comparable to the main results or nonsignificant because there were few events (Table 2).

## Discussion

This study has 2 main findings. First, SA not treated with CPAP was associated with an increased risk of HF in patients of all ages, but only significantly in patients >60 years of age. Second, use of CPAP therapy was associated with a lower risk



**Table 2.** Results From Sensitivity Analyses

| Sensitivity Analyses | Age (y) | Background Population | | SA Patients Not Receiving CPAP Therapy | | SA Patients Receiving CPAP Therapy | |
|---|---|---|---|---|---|---|---|
| | | Total No. of Events | IRR | Total No. of Events | IRR (95% CI) | Total No. of Events | IRR (95% CI) |
| (1) | 18–60 | 2520 | Ref | 21 | 0.81 (0.51–1.29) | 15 | 1.43 (0.84–2.43) |
| | >60 | 38 889 | Ref | 157 | 1.94 (1.65–2.28) | 64 | 1.59 (1.22–2.06) |
| (2) | 18–60 | 21 160 | Ref | 213 | 1.17 (1.01–1.34) | 95 | 1.06 (0.86–1.31) |
| | >60 | 130 922 | Ref | 532 | 1.37 (1.25–1.49) | 222 | 1.02 (0.89–1.17) |

(1) Outcome redefined as heart failed diagnosis+filled loop-prescription. (2) Patients with a filled loop-prescription before study start were excluded. All analyses were performed using the fully adjusted time-dependent Model 2 with background population as reference. CI indicates confidence intervals; CPAP, continuous positive airway pressure; IRR, incidence rate ratio; SA, sleep apnea.

**Table 3.** Characteristics of the Study Population

| | Total Population | SA Patients Not Receiving CPAP Therapy | SA Patients Receiving CPAP Therapy |
|---|---|---|---|
| Total, n | 4 870 975 | 22 168 | 18 317 |
| Men, n (%) | 2 430 969 (49.9) | 17 114 (77.2) | 14 654 (80.0) |
| Age (y), median (IQR) | 43.1 (30.2–57.9) | 52.4 (43.2–60.8) | 55.7 (47.3–63.2) |
| Comorbidities, n (%) | | | |
| Myocardial infarction | 68 802 (1.4) | 792 (3.6) | 760 (4.2) |
| Ischemic stroke | 85 745 (1.8) | 1051 (4.7) | 944 (5.2) |
| Hypertension | 328 510 (6.7) | 5690 (25.7) | 6565 (35.8) |
| Atrial fibrillation | 36 143 (0.7) | 803 (3.6) | 874 (4.8) |
| Peripheral arterial disease | 33 651 (0.7) | 341 (1.5) | 303 (1.7) |
| Chronic kidney disease | 21 749 (0.4) | 469 (2.1) | 450 (2.5) |
| Liver disease | 34 530 (0.7) | 405 (1.8) | 349 (1.9) |
| COPD | 58 943 (1.2) | 1042 (4.7) | 911 (5.0) |
| Cancer* | 108 911 (2.2) | 960 (4.3) | 929 (5.1) |
| Diabetes mellitus | 320 466 (6.6) | 3733 (16.8) | 3518 (19.2) |
| Medication n (%) | | | |
| Statins | 60 458 (1.2) | 782 (3.5) | 796 (4.3) |
| Loop diuretics | 104 934 (2.2) | 564 (2.5) | 500 (2.7) |
| RAS inhibitors | 165 962 (3.4) | 1554 (7.0) | 1491 (8.1) |
| β-Blockers | 159 371 (3.3) | 1098 (5.0) | 1113 (6.1) |
| Oral anticoagulants | 17 253 (0.4) | 127 (0.6) | 128 (0.7) |
| Aspirins | 171 847 (3.5) | 877 (4.0) | 811 (4.4) |
| NSAIDs | 428 388 (8.8) | 3730 (16.8) | 3499 (19.1) |
| Calcium antagonists | 158 328 (3.3) | 1213 (5.5) | 1167 (6.4) |
| Thiazides | 168 014 (3.4) | 1035 (4.7) | 2227 (12.2) |

Baseline characteristics at the date of inclusion for the total population, at the time of SA diagnosis (only the untreated patients), and at the time of initiation of CPAP therapy. COPD indicates chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; IQR, interquartile range; RAS, renin-angiotensin system; SA, sleep apnea.
*All cancers, excluding nonmelanoma skin cancers.

of incident HF in patients >60 years of age compared with patients with SA not receiving CPAP therapy.

## Risk of HF

There are different theories concerning the role of SA in the development of HF: First, obstructive SA generates a negative intrathoracic pressure, increasing both cardiac preload and afterload. Second, consecutive intermittent hypoxic periods increase oxidative stress and inflammation markers, which in turn can damage the endothelial walls. Third, disrupted sleep increases sympathetic nervous activity, leading to an increase in blood pressure and heart rate, which demands cardiac activity at a time when the heart should be regenerating.[2,19,20] In addition, several studies have shown that SA is associated with hypertension, coronary artery disease, arrhythmias, obesity, diabetes mellitus, and metabolic disturbances, all known to increase the risk of HF.[2,3,21,22] Hence, we applied many of these comorbidities in our regression models, including continuous assessment of their presence. Use of NSAIDs has been associated with increased risk of HF and was therefore included in the model as well.[23,24] Although lower estimates were found (Model 2 compared with Model 1, Table 4), the IRRs were still significantly increased; thus, SA seems to be an independent risk factor for developing HF. Nevertheless, the pathophysiology of HF and the causal pathway and interplay between SA and HF are heterogeneous and possibly other mechanisms associated with SA could be involved.

The relationship between SA and HF has been investigated in several studies. In a prospective study, nearly 4500 patients with OSA were followed and no significant association between the severity of OSA and HF was found.[5] However, the study was relatively small and the authors did

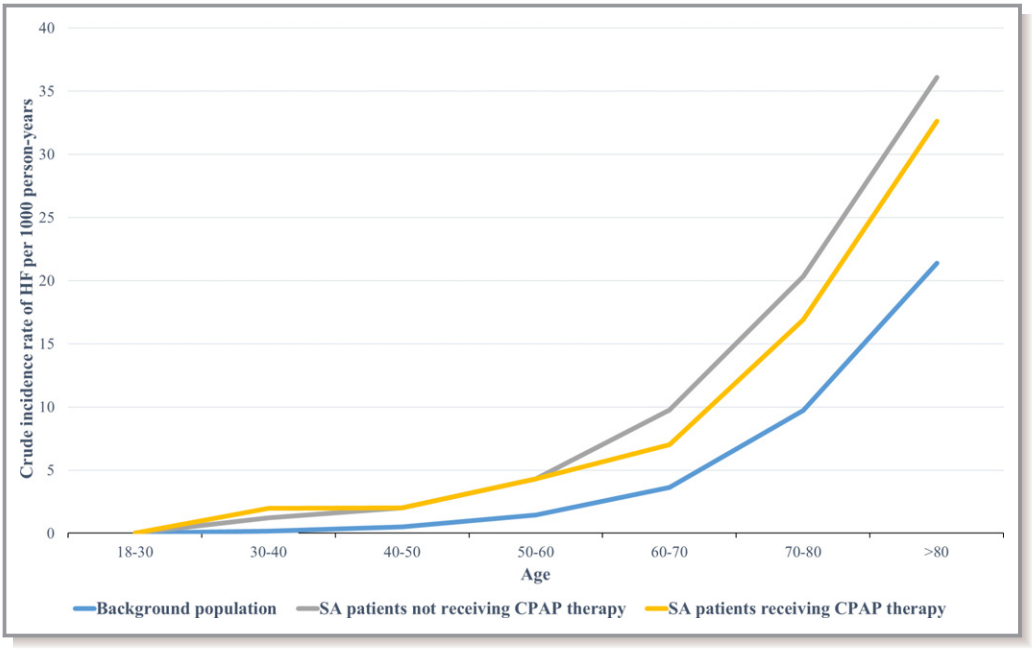


**Figure 2.** Crude incidence rates of HF stratified by 10-year age intervals and in 3 groups: background population, SA patients not receiving CPAP therapy, and SA patients receiving CPAP therapy. CPAP indicates continuous positive airway pressure; HF, heart failure; SA, sleep apnea.

not report any age-specific relation. Conversely, a matched study showed an increased risk of fatal and nonfatal cardiovascular complications in patients with severe OSA compared with healthy matched controls (matched on age and body mass index).[25] A cross-sectional study of elderly patients showed the same association between severe SA and cardiovascular disease (defined by 1 of the following: MI, angina, coronary revascularization procedure, HF or stroke), though the cross-sectional design could not tell whether the patients developed SA or HF first.[26] Our study, with up to 13 years of follow-up on >40 000 patients with SA and consecutive adjustment for other cardiovascular risk factors, is in line with the studies showing an association between SA and HF.

## Effect of CPAP Therapy

Because it provides symptom relief, CPAP therapy is first-line therapy for SA, but could theoretically also reduce the negative cardiovascular impacts of SA as it has been found to improve glucose tolerance, reduce endothelial damage, lower blood pressure, and improve cardiac function.[6–10] Consequently, one could hypothesize that CPAP therapy protects patients from developing cardiovascular disease such as HF.

The effect of CPAP therapy on cardiovascular disease has been investigated to some extent, but with conflicting results. SAVE (Results from the Survival and Ventricular Enlargement) trial found no significant difference in cardiovascular events between a "usual-care group" and a "CPAP therapy+usual-care group."[11] In line with this, a randomized controlled study of 725 patients with OSA was unable to show a significant effect of CPAP therapy on the development of HF.[12] Opposed to these neutral findings, the previously mentioned matched study by Marin et al found a potential beneficial effect of CPAP therapy on cardiovascular complications in patients with severe OSA.[25] Likewise, our study showed in, to our knowledge, the largest cohort of SA patients to date that CPAP therapy was associated with a lower risk of developing HF in patients >60 years of age. A potential difference in adherence to medical treatment in general could be an explanation for the observed difference between patients with SA who did and did not receive CPAP therapy, assuming that a patient who accepts CPAP therapy might also be more adherent to pharmacotherapy, for example. In our cohort, the CPAP-treated patients with SA received more medication on the date of inclusion compared with the patients with SA not in CPAP therapy. However, these patients also had a higher comorbidity burden (included in the model), which could explain the increase in medication (Table 3). However, these differences cannot be statistically confirmed because of the time-dependent study design and absence of independent observations, though the observed differences seem substantial. Adherence to medical treatment in patients with SA has been investigated in a cohort of 2158 patients with severe OSA; in this study the authors found high medication adherence among all patients and, remarkably, no difference in medication adherence between patients adherent and nonadherent to CPAP therapy.[27] This supports our findings of

**Table 4.** IRRs of HF in Patients With SA Receiving and Not Receiving CPAP Therapy

| | Background Population | | SA Patients Not Receiving CPAP Therapy | | SA Patients Receiving CPAP Therapy | | Association* of CPAP Therapy |
|---|---|---|---|---|---|---|---|
| | Crude Rate Per 1000 Person-Y (Total No. of Events) | IRR | Crude Rate Per 1000 Person-Y (Total No. of Events) | IRR (95% CI) | Crude Rate Per 1000 Person-Y (Total No. of Events) | IRR (95% CI) | IRR (95% CI) |
| Model 1 | | | | | | | |
| 18–60 y age | 0.60 (22 430) | Reference | 2.94 (226) | 1.61 (1.41–1.83) | 3.27 (103) | 1.68 (1.38–2.04) | 1.05 (0.83–1.32) |
| >60 y of age | 9.08 (154 611) | Reference | 13.43 (620) | 1.81 (1.67–1.96) | 10.30 (265) | 1.50 (1.33–1.69) | 0.83 (0.73–0.96) |
| Model 2 | | | | | | | |
| 18–60 y of age | 0.60 (22 430) | Reference | 2.94 (226) | 1.13 (0.99–1.30) | 3.27 (103) | 0.97 (0.79–1.19) | 0.86 (0.67–1.10) |
| >60 y of age | 9.08 (154 611) | Reference | 13.43 (620) | 1.38 (1.27–1.50) | 10.30 (265) | 1.13 (0.99–1.28) | 0.81 (0.70–0.95) |

Model 1: adjusted for age, sex, calendar year, and comorbidities present at inclusion (including myocardial infarction, ischemic stroke, hypertension, atrial fibrillation, peripheral arterial disease, chronic obstructive pulmonary disease, cancer, and diabetes mellitus), and the use of NSAIDs at the time of inclusion. Model 2: fully adjusted model with all covariates mentioned in Model 1 incorporated as time-dependent variables. CI indicates confidence intervals; CPAP, continuous positive airway pressure; HF, heart failure; IRR, incidence rate ratios; SA, sleep apnea. *Estimated by comparing the patients with SA receiving CPAP therapy to the patients with SA who did not.

CPAP therapy possibly playing an active role in reducing the risk of developing HF in SA patients. Concerningly, recently published data from the SERVE-HF (Servoventilation in Patients with Heart Failure) trial showed that adaptive servoventilation increased overall mortality risk in 1325 patients with chronic HF with reduced ejection fraction with predominantly central SA.[13] As a result, adaptive servoventilation is not recommended in patients with HF and predominantly central SA.[28] However, the safety concern that arose from this study should not be applied to patients with SA without HF receiving CPAP therapy, since adaptive servoventilation and CPAP therapy are completely different modes of applying positive airway pressure,[29,30] and the increased mortality was only demonstrated in patients already diagnosed with HF with reduced ejection fraction.[13] Interestingly, the US preventive service task force recently recommended not to screen for OSA because of insufficient evidence on benefits and harms of a screening program and, especially, because of the lack of evidence concerning the potential beneficial effect of CPAP therapy on hard outcomes.[31] Our study adds important data to the discussion concerning the cardiovascular risk of SA as well as the potential favorable effect of CPAP therapy. Although our study was observational by design and only hypothesis-generating, focus on interplay between HF and SA, including type of SA therapy, in future studies is important.

## Strengths and Limitations

Inclusion of a large, unselected, and nationwide cohort of patients with SA independent of age, sex, socioeconomic status, access to health services, and ethnicity are the major strength of this study. Main limitations are the observational study design, the use of administrative databases for all diagnoses, and the inability to eliminate the possibility of unmeasured confounders.

We did not have information on body mass index or smoking status, which could both be relevant confounders and overrepresented in the patients with SA. However, we had information on the mediators between smoking/overweight and HF (eg, arterial disease, diabetes mellitus, chronic obstructive pulmonary disease, and MI). A propensity-matched analysis could have strengthened our results, but it was not possible because of our time-dependent study design.

We lacked information on the severity of SA, and 86% of the diagnoses were unspecified. Likewise, 57% of the HF diagnoses were nonspecific, which limited us from making any assumptions as to the direct causal pathway between SA and HF. Positive predictive values of SA and HF diagnoses in the Danish National Patient Registry are high; however, sensitivities are lower, which could have led to an underestimation of our results because of type 2 errors.[1,18]

No significant association was found between use of CPAP therapy and HF among patients who have SA and are aged between 18 and 60 years. This could simply be explained by lack of power because of fewer events among the younger patients. However, another explanation could be that clinical HF has a multifactorial pathway, with factors such as hypertension and hyperlipidemia being less present among the younger patients. Some studies show a potential beneficial effect of CPAP therapy on hypertension and lipid profile, which could explain why the association between CPAP therapy and reduced risk of HF is less pronounced among the younger patients.[8,9] Finally, the pathophysiology of development of SA may differ between younger and older individuals

(eg, body mass index might be an important factor in older compared with younger patients); consequently, any effect of CPAP therapy may also differ according to age. We found effect modification of MI and hypertension and for comparing with the main results, we constructed subgroups for subgroup analyses of patients *with* previous MI, *with* previous hypertension, and *without* 1 or the other (Table 1). The results were all similar to the main analyses. However, subgroup (previous MI, patients with SA not receiving CPAP therapy, and 18–60 years of age) had a decreased IRR of HF. Possible explanations could be small number of events (power), healthy survivor bias because of early MI not resulting in HF in contrast to the high risk of MI causing immediate HF in the elderly,[32] or simply a random finding.

We had no information on the reasons for initiating CPAP therapy, nor did we know the reasons for discontinuing CPAP therapy, which is why we required 2 consecutive procedural codes for CPAP therapy to ensure adherence. Also, we lacked information on the daily compliance with CPAP therapy, as we know that use <4 hours per night only has marginal effects.

## Conclusions

In this nationwide cohort study of patients with SA, SA not treated with CPAP was associated with an increased risk of HF in patients of all ages, but only significantly and most markedly in patients >60 years of age. Use of CPAP therapy was associated with a lower risk of incident HF in patients >60 years of age, which suggests a protective effect of CPAP therapy in this group.

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## Disclosures

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# Supplemental Material

**Table S1. ICD and ATC codes.**

| | Details | ICD-8, ICD-10, and ATC codes used |
|---|---|---|
| **Study population** | | |
| Sleep Apnea | Defined from diagnosis codes, excluding specific code for central sleep apnea | ICD-10: G473 (G4731 excluded) |
| CPAP therapy | Defined from procedural codes | ICD-10: BGFC32, ZZ3911-ZZ3916 |
| **Outcome** | | |
| Heart failure | Defined from diagnosis codes including heart failure, cardiomyopathies, hypertensive heart failure, and lung edema. | ICD-10: I110, I42, I50, J819<br>ICD-8: 425, 4270-1 |
| **Comorbidity** | | |
| Ischemic stroke | Defined from diagnosis codes including ischemic stroke and transient ischemic attack | ICD-10: I63, I64, G458, G459<br>ICD-8: 433-8 |
| Myocardial infarction | Defined from diagnosis codes | ICD-10: I21-22<br>ICD-8: 410 |
| Liver disease | Defined from diagnosis codes of liver cancer, chronic liver disease, liver surgery, cirrhosis, and hepatitis | ICD-10: B15-B19, C22, D684C, I982B, K70-K77, DQ618A, Z944 |
| Diabetes mellitus | Defined from treatment with glucose lowering drugs | ATC: A10 |
| Hypertension | Defined from combination treatment with a least two classes | ATC: C02A, C02B, C02C, C02DA, C02DB, C02DD, C02DG, C02L, |

| | | |
|---|---|---|
| | of antihypertensive drugs (Adrenergic α-antagonist, non-loop-diuretics, vasodilators, beta-blockers, calcium channel blockers, and renin-angiotensin system inhibitors) | C03A, C03B, C03D, C03E, C03X, C07A, C07B, C07C, C07D, C07F, C08, C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52 |
| Chronic renal failure | Defined from diagnosis codes of chronic glomerulonephritis, chronic tubulointestinal nephropathy, chronic kidney disease, and diabetic and hypertensive nephropathy. | ICD-10: E102, E112, E132, E142, I120, M200, M313, M319, M321B, N02-N08, N11-N12, N14, N18-N19, N26, N158-N160, N162-N164, N168, Q612-Q613, Q615, Q619<br>ICD-8: 403, 404, 580-4, 590, 223, 25002, 40039, 59009, 59320, 75310-1, 75319 |
| Atrial fibrillation | Defined from diagnosis codes | ICD-10: I48 |
| Cancer | Defined from all cancer diagnosis codes, excluding non-melanoma skin cancer | ICD-10: C00-C43, C45-C97<br>ICD-8: 109-140 |
| Peripheral arterial disease | Defined from diagnosis codes | ICD-10: I709<br>ICD-8: 440 |
| Chronic obstructive pulmonary disease | Defined from diagnosis codes | ICD-10: J42-J44<br>ICD-8: 491, 492 |
| **Concomitant treatment** | | |
| Oral anticoagulants | Warfarin and non-vitamin K antagonist oral anticoagulants | ATC: BO1AA03, B01AE07 |
| Aspirin | Acetylsalicylic acid | ATC: BO1AC06 |

| | | |
|---|---|---|
| Non-steroidal anti-inflammatory drugs | | ATC: M01A |
| Statins | | ATC: C10A |
| Beta-blockers | | ATC: C07 |
| Renin angiotensin system inhibitors | Including: angiotensin-converting-enzyme inhibitors, angiotensin-II receptor blockers | ATC: C09 |
| Loop-diuretics | | ATC: C03C |
| Oral glucose-lowering drugs | | ATC: A10 |

CPAP=Continuous positive airway pressure

ATC: Anatomical Therapeutic Chemical system
ICD-8: 8th revision of the International Classification of Diseases system
ICD-10: 10th revision of the International Classification of Diseases system

Diagnoses (primary or secondary), surgical procedures, and pharmacotherapy used for defining the study population, comorbidity, concomitant treatment, and outcomes.