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The influence of atmospheric temperature on long-term CPAP-usage in patients with obstructive sleep apnea

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Abbreviation List

Apnea-Hypopnea-Index
Body Mass Index
Continuous Positive Airway Pressure
French Social Security
Global Telecommunication System

Minimal Clinical Important Difference
Quality of Life
Sleep Apnea Syndrome
surface synoptic observations
World Meteorological Organization

ABSTRACT

Background:

Although seasonal variations in CPAP-usage are often attributed to changes in temperature, no real- world study has evaluated the influence of temperature on long-term CPAP-usage.

Methods:

The TempCPAP study is a retrospective real-life cohort study. Adult patients newly treated and undergoing at least 1 month of CPAP were included. Daily 12-PM temperature data from the nearest weather station was assigned to each patient and CPAP-usage was collected using telemonitoring data. The primary objective of the study was to investigate the relationship between temperature and CPAP-usage.

Results:

8151 patients (37.2 % women) with a median age of 61 (IQ25-75: 51–71) years, initial AHI of 36 (29–49.6) events/h, treated for a median duration of 1.6 years (0.7–3.0), and with a CPAP-usage of 5.4 (3.0–6.9) h/day were included. The relationship between CPAP-usage and temperature was non-linear. The best model found two breakpoints at 18 °C and 29 °C. CPAP-usage dropped drastically when the temperature exceeded 29 °C, as each 1 °C increase was associated with a 3.6-min reduction in CPAP-usage. Compared to temperatures of less than 5 °C, temperatures above 30 °C resulted in a mean reduction in CPAP-usage of 30.3 (confidence interval (CI) 95 %): 29.3–31.4) minutes/day, achieving the minimal clinically important difference of 30 min in 46.6 % of patients.

Conclusion:

In patients undergoing long-term CPAP therapy, temperatures over 29 °C at 12-PM were associated with reduced CPAP-usage.

Trial registration:

TempCPAP is registered with health data hub (n°20475117).

1.Introduction

The prevalence of sleep apnea syndrome (SAS) among adults over 35 years old varies between 5.9 % and 79.2%, depending on the clinical symptoms observed and the criteria used for scoring apnea/hypopnea events [1,2]. Although significant advancements have been made in-developing alternative therapies, continuous positive airway pressure (CPAP) continues to be the primary treatment for SAS [3–5]. Adherence to CPA therapy is linked to enhanced quality of life (QoL [6, 7] and decreased occurrence or recurrence of major adverse cardiovascular events [8,9]. Various factors affect CPAP-usage, including psychological, socioeconomic, and demographic factors [10], in addition to mask-related side effects [4,11].

Over the past few years, global warming has taken hold, with temperatures steadily rising. The effect of season on CPAP-usage has become a subject of investigation [12–15]. Rates of CPAP-usage are at their lowest during the summer, and are at their highest during the winter [13–15]. Heatwaves are also associated with drops in CPAP-usage [12]. Although seasonal variations in CPAP adherence are often attributed to changes in temperature, to date, no real-world study has actually evaluated the association between temperature and long-term CPAP-usage [12–15].

This study aimed to fill this gap in the literature by investigating the association of temperature with CPAP-usage in patients on long-term treatment.

2.Methods

2.1.Study design and study population

This study (health data hub (n°20475117)) was a real-life cohort study conducted from October 1, 2018 to September 21, 2023 in adults (≥ 18 years old) undergoing at least 1 month of CPAP for SAS. SAS was defined according to the French Social Security (FSS) system criteria: 1) Apnea Hypopnea Index (AHI) $\geq 30/h$ (or AHI $\geq 15/h$ and more than 10/ h respiratory-effort-related arousals or cardiovascular comorbidities), and 2) associated with at least three of the following symptoms: sleepiness, snoring, headaches, asthenia, nocturia, choking or suffocation during sleep.

The Adene group, a non-profit home care provider, delivered care to the patients in the Occitanie and Auvergne-Rhone-Alpes regions of France. Patients included in this study were new patients beginning CPAP treatment between October 1, 2018 and September 21, 2023.

2.2.Collected data

Clinical data were collected at the start of CPAP (age, sex, BMI and AHI measured by polygraphy or polysomnography). CPAP data were collected daily for the duration of the study (CPAP-usage/day, AHIfLOW, pressure and leaks). For example, for a patient treated with CPAP for three years, we collected daily data on temperature, CPAP use, CPAP pressures and CPAP leaks throughout the follow-up period, representing 1095 data points for each variable.

Device-reported leak variables, as defined by each manufacturer, were included in the analysis as previously described (see Supplementary Table S1) (Rotty et al., 2021).

Temperatures at 12 p.m. were collected using the open-source database of observations from the International Surface Observation Messages (SYNOP) on the World Meteorological Organization's (WMO) Global Telecommunication System (GTS). We assigned the nearest weather station to each patient, based on their zip code (see supplementary Method S1). The choice of collecting temperature measured at 12 p.m. was conditioned by the assumption that we would find an effect of daytime temperature on CPAP-usage, and our desire to extend this research in the future. We consider that daytime temperature is particularly relevant for developing warning systems, to provide targeted information on the risk of a night of non-compliance on hot days. Indeed, patients at risk could then be individually warned and take the necessary measures to cool their sleep environment.

Length of the night data were collected using an open-source French database. The city of Montpellier was chosen to determine the length of the night because it is the prefecture of Hérault (in Occitanie), which was the department with the most patients in our database. Montpellier lies roughly in the middle of the Adene Group's geographical area.

2.3. Definition of seasons, CPAP-usage and CPAP-non-adherence

We defined winter as December to February, spring as March to May, summer as June to August and autumn as September to November according to the standards of the French Meteorological agency. CPAP-usage was defined as the mean amount of time CPAP was used each day. CPAP-non-adherence was defined as CPAP adherence <4 h/day. We used the threshold of 4 h to define non-adherence because: i) the American Academy of Sleep Medicine proposed a minimal clinically important difference at this value [4]; ii) in France, it is a threshold conditioning a level of reimbursement.

2.4. Statistical analyses

Continuous data were expressed as medians with their associated quartile ranges due to non-Gaussian distributions. Qualitative parameters were expressed as numbers and percentages. Effects of seasons, months and days on CPAP-usage were evaluated using Kruskal-Wallis tests. To represent the temperature and CPAP-usage curves from 2019 to 2023, 15-day smoothed moving averages were used. Spearman's correlation coefficient was used to measure the correlation between temperature and CPAP-usage per day. Univariate weighted linear and segmental linear regression analyses were used to study associations between CPAP-usage versus temperature per day. Weighted linear regression analyses were used to study associations between CPAP-usage versus temperature and clinical and device data. An interaction effect was used to evaluate the association of temperature evolution on clinical and device data. Regressions are exhaustively detailed in the supplementary Methods S2. All statistical analyses were performed with R (V.4.3.1).

3. Results

3.1. Patients characteristics

The flow chart of the study is depicted in Supplementary Fig. S1.

Population baseline characteristics are summarized in Table 1. Briefly, a total of 8151 patients (37.2 % women) were included in the analysis. The median age was 61 (IQ25-75: 51–71) years, the body mass index (BMI) was 30.1 (26.6–34.4) kg/m², and the initial AHI was 36 (29–49.6) events/h. During the study, 2.6 % of patients died and 29.5 % stopped CPAP therapy. The duration of CPAP treatment was 1.6 (0.7–3.0) years. Overall, 69.1 % of patients were initially treated with a nasal mask, 21.6 % with an oronasal mask and 9.3 % with a nasal pillow mask.

Table 1
Population characteristics.

	Whole population (N = 8151)
Demographics	
Age at start of care (years)	61.00 (51.00; 71.00)
Age at start of care (years), n (%)	
[18,40]	751 (9.23)
[40,50]	1190 (14.62)
[50,60]	1981 (24.34)
[60,70]	2161 (26.55)
[70,80]	1577 (19.37)
>80	480 (5.90)
Gender (women), n (%)	3031 (37.19)
BMI (kg/m ²)	30.09 (26.59; 34.37)
BMI (kg/m ²), n (%)	
<25 kg/m ²	1066 (15.36)
25–30 kg/m ²	2335 (33.65)
≥30 kg/m ²	3538 (50.99)
Diagnostic AHI (events/h)	36.00 (29.00; 49.60)
Diagnostic AHI (events/h) (more than 30), n (%)	4915 (74.20)
Device	
Duration of CPAP (years)	1.59 (0.69; 3.03)
Mean AHI _{flow} during the first-month (events/h)	2.82 (1.24; 5.72)
Mean CPAP-usage during the first-month (h)	5.36 (3.03; 6.85)
CPAP non-adherence during the first month, n (%)	2710 (33.25)
Mean pressure in the first month (cmH ₂ O)	7.48 (6.26; 8.87)
Mean pressure in the first month (cmH ₂ O), n (%)	
[4,6[1426 (20.06)
[6,8[2884 (40.57)
[8,10[1959 (27.56)
[10,12[753 (10.59)
≥12	86 (1.21)
Pressure 90/95 in the first month (cmH ₂ O)	9.41 (7.93; 10.87)
Pressure 90/95 in the first month (cmH ₂ O), n (%)	
[4,6[349 (4.99)
[6,8[1472 (21.06)
[8,10[2547 (36.45)
[10,12[2068 (29.59)
≥12	552 (7.90)
Final fixed pressure, n (%)	2296 (28.62)
Final comfort mode, n (%)	1498 (18.67)
Heated breathing tube, n (%)	1157 (14.19)
Mask	
Initial mask type, n (%)	
Nasal mask	5628 (69.05)
Nasal pillow mask	761 (9.34)
Oronasal mask	1762 (21.62)
Unintentional leaks in the first month (l/min)	5.00 (1.77; 10.76)
Unintentional large leaks in the first month (%)	0.22 (0.00; 1.67)
Global leaks in the first month (l/min)	33.33 (28.46; 39.97)
Global large leaks in the first month (%)	2.29 (0.48; 7.04)

AHI: Apnea-Hypopnea Index; AHI_{flow}: AHI reported by device; BMI: Body Mass Index; CPAP: Continuous Positive Airway Pressure; N = number of patients; Non-adherence: CPAP-usage under 4 h per day. Leaks were obtained using built-in CPAP software. Data are reported as medians and quartiles or numbers and percentages of total as appropriate. Note: The duration of CPAP treatment corresponds to the follow-up of patients from the start of CPAP until CPAP termination or, if CPAP was not discontinued, September 23, 2023. CPAP duration ranges from 1 month to 4.5 years.

During the last year of treatment, the median CPAP-usage was 5.8 (4.0–7.2) h/day (24.8 % of non-adherent patients); the median AHI-flow was 2.0 (1.0–4.1) events/h; the median pressure was 7.9 (6.5–9.4) cmH₂O; the median number of unintentional leaks was 4.2 (1.3–9.2) l/min and the median global leaks was 34.6 (28.9–41.1) l/min.

3.2. Relationship between CPAP-usage and temperature

Fig.1 illustrates the evolution of temperature at 12 p.m., CPAP-usage and length of night across the entire population from January 1, 2019 to September 21, 2023. The reduction in CPAP-usage does not appear to be due to the length of the night. There is a time lag between the shortening of the night and the decrease in CPAP-usage. On the other hand, there is a mirror effect between temperature at 12 p.m. and CPAP-usage. When there is a peak in temperature, a simultaneous downward peak in CPAP-usage also occurs. The daily relationship between mean CPAP-usage and temperature is depicted in Fig. 2. The association between CPAP-usage and temperature was confirmed by a strong negative Spearman's correlation coefficient ($r = -0.58$, $p < 0.001$). Linear regression analysis showed a significant association between mean daily CPAP-usage and temperature (slope coefficient at -0.02 , $p < 0.001$, adjust R²: 0.35). A temperature delta of 25 °C is required to achieve the minimal clinically important difference (MCID) of 30 min for CPAP-usage.

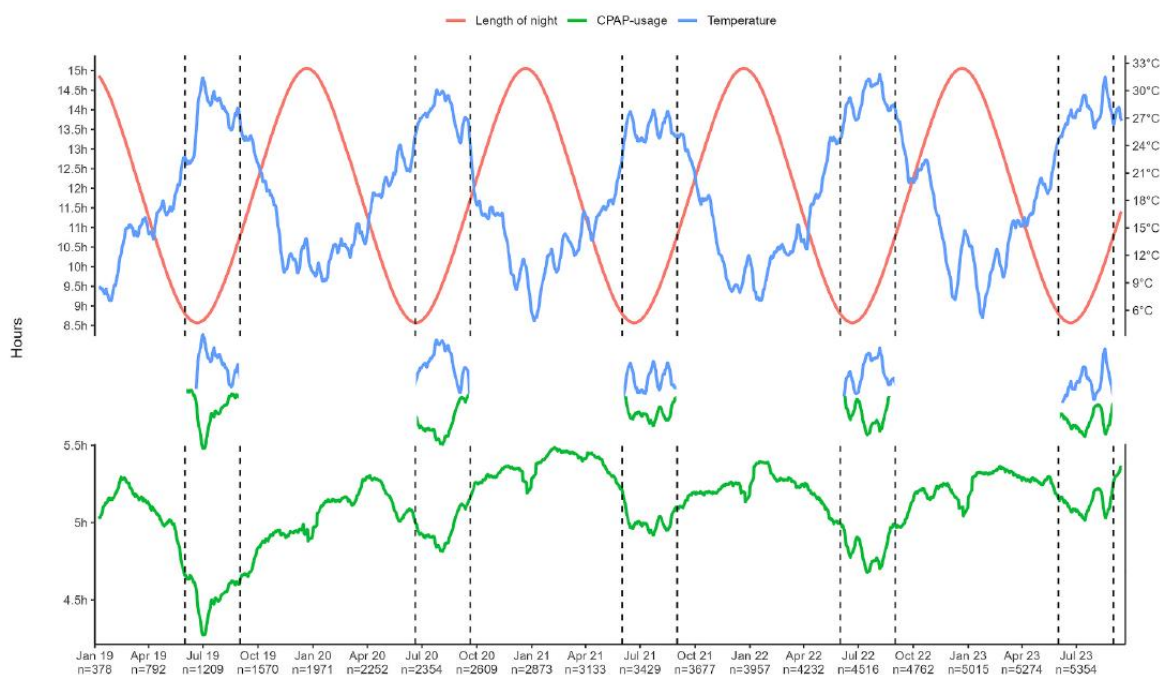


Fig. 1. Temperature at 12 p.m. and CPAP-usage per day.
 Technical note: Temperature and CPAP-usage curves are 15-day smoothed moving averages.
 Note: dotted lines correspond to zoom limits.

As the relationship between CPAP-usage and temperature is not linear, a segmental linear regression analysis was performed (see supplementary Method S2 for details). The best model (adjust R2: 0.41) had two breakpoints in temperature, at 18 °C (CI95 %: [16.5; 19.5]) and 29 °C (CI95 %: [27.6; 30.5]). The first slope of the model, when temperature was less than 18 °C, was - 0.004 [- 0.01; - 0.001] (p =0.017), the second slope, between 18 °C and 29 °C, was - 0.03 [- 0.03; - 0.02] (p <0.001) and the third slope, when temperature was more than 29 °C, was - 0.06 [- 0.08; - 0.04] (p <0.001). When the temperature at 12 p. m. exceeds 29 °C, each 1 °C increase reduces CPAP-usage by 3.6 min, consequently CPAP-usage drops drastically. For length of night, each additional hour increases CPAP-usage by 2.4 min. So, to achieve an increase of 3.6 min in CPAP-usage, 1.5 additional hours of night would be required (see Supplementary Fig. S2).

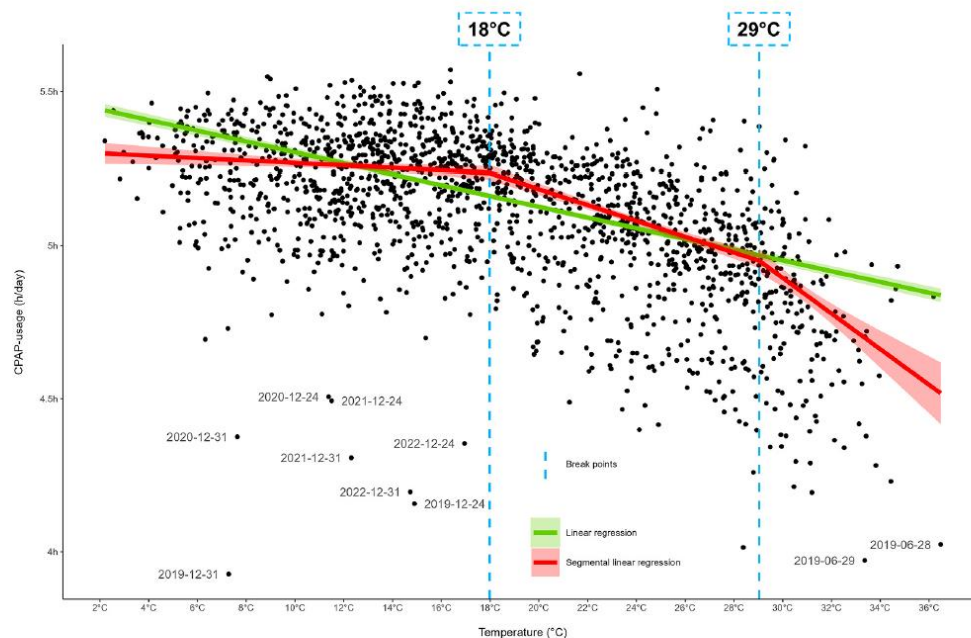


Fig. 2. CPAP-usage according to temperature at 12 pm.
Note: one point corresponds to one day.

For the whole population, the association between temperature and CPAP-usage is shown in Fig. 3. The highest mean CPAP-usage was 5.33 h, when the temperature was below 5 °C, and the lowest was 4.83 h, when the temperature was above 30 °C (Fig. 3). The mean difference of CPAP-usage between temperatures less than 5 °C and temperatures more than 30 °C was +30.3 min (see Supplementary Fig. S3, panel A, square at top right). Supplementary Fig. S3 is based on the MCID of 30 min, and shows the percentage of patients with a mean difference of CPAP-usage ≥ 30 or ≤ 30 min at different temperatures. When comparing the mean difference of CPAP-usage between ≥ 30 °C and < 5 °C, 46.6 % of the patients increased their CPAP-usage by at least 30 min (Supplementary Fig. S3, panel B, green part of the square at top right) and 21.5 % decreased their CPAP-usage by at least 30 min (Supplementary Fig. S3, panel B, red part of the square at top right).

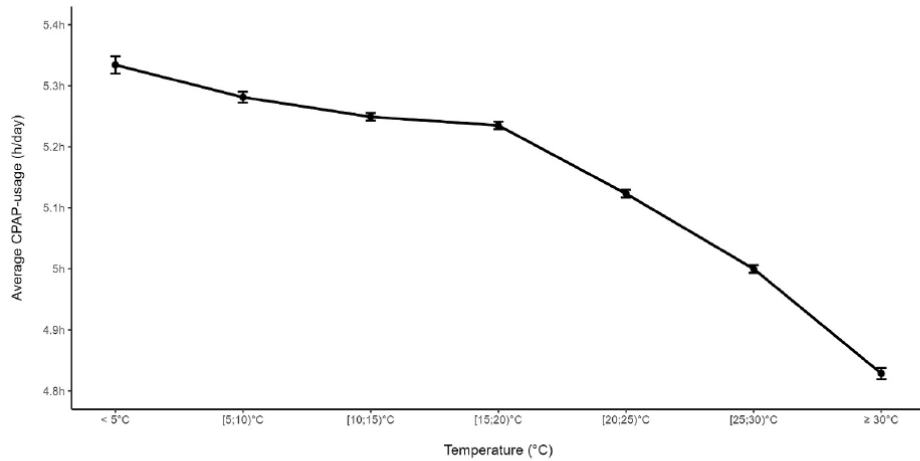


Fig. 3. Association of temperature with minimal clinically important difference in CPAP-usage.

Note for interpretation of the data: for the whole population, mean CPAP-usage when temperature was lower than 5 °C was 5.33 h.

Fig. 4 illustrates the association of temperature and CPAP-usage stratified by age (Fig. 4, panel A), gender (Fig. 4, panel B), BMI (Fig. 4, panel C) and AHI diagnostic (Fig. 4, panel D). Temperature was associated with CPAP-usage when stratified by age or AHI diagnostic. As the temperature rose, the gap in CPAP-usage between younger (18–40 years old) and older patients (>80 years old) decreased. The mean difference in CPAP-usage was - 75.3 min when the temperature was 0 °C, compared to - 9.0 min when the temperature was 35 °C. The interaction effect between temperature and age group (>80 years compared to 18–40 years as a reference) in linear regression was significant ($p < 0.001$). Similarly, as temperature increased, the difference in CPAP-usage between those with an AHI diagnostic between 15 and 30 events/h and those with an AHI diagnostic ≥ 30 events/h decreased. The mean difference in CPAP-usage was - 28.3 min when the temperature was 0 °C, compared to - 21.5 min when the temperature was 35 °C. The interaction effect between temperature and AHI diagnostic group (≥ 30 events/h compared to 15–30 events/h as a reference) in linear regression was significant ($p = 0.032$).

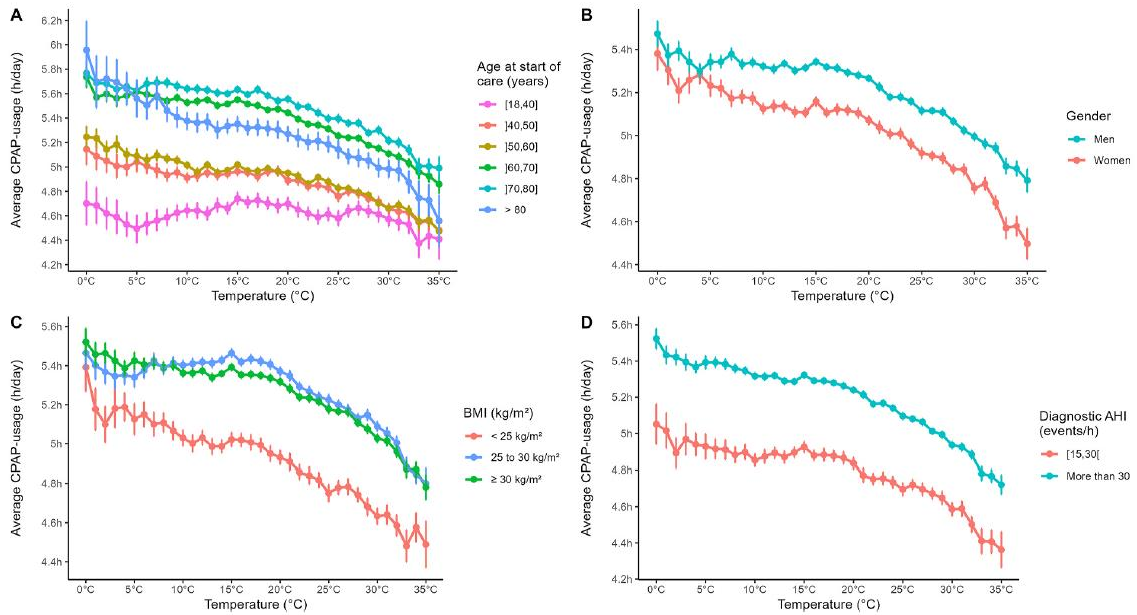


Fig. 4. CPAP-usage according to temperature and demographics data.
 Note: Data are stratified by age (panel A), gender (panel B), body mass index (panel C) and AHI diagnostic (panel D).

Fig. 5 depicts the association of temperature and CPAP-usage stratified by duration of CPAP (Fig. 5, panel A), prior year adherence (Fig. 5, panel B), heated breathing tube (Fig. 5, panel C) and current mask type (Fig. 5, panel D). Temperature was associated with CPAP-usage when stratified by heated breathing tube (yes or no). As the temperature rose, the gap in CPAP-usage between patients without heated breathing tubes and those with heated breathing tubes decreased. The mean difference in CPAP-usage was - 18.9 min when the temperature was 0 °C compared to +8.4 min when the temperature was 35 °C. At 29 °C the mean difference in CPAP-usage was no longer statistically significant, while the interaction effect between temperature and heated breathing tubes (without heated breathing tubes used as the reference) in linear regression was significant ($p < 0.001$).

3.3. The effects of seasons, heatwaves, end-of-year festivities, and months on CPAP-usage

The effects of seasons, heatwaves and end-of-year festivities on CPAP-usage are depicted in Fig. 1. In the summer, CPAP-usage falls before rising at the end of summer (see Fig. 1). Summer is the season with the lowest CPAP-usage (see Supplementary Fig. S4). Mean CPAP-usage was 4.9 (± 3.3) hours in the summer, 5.2 (± 3.3) hours in spring and autumn and 5.3 (± 3.4) hours in winter, $p < 0.001$. There was a mean difference of 18.6 (CI95 %: 18.2–19.1) minutes between winter and summer, and the drop in CPAP-usage achieved the MCID of 30 min in 39.2 % of patients. There was a mean difference of 17.7 (CI95 %: 17.3–18.1) minutes between spring and summer and the drop in CPAP-usage achieved the MCID of 30 min in 37.0 % of patients.

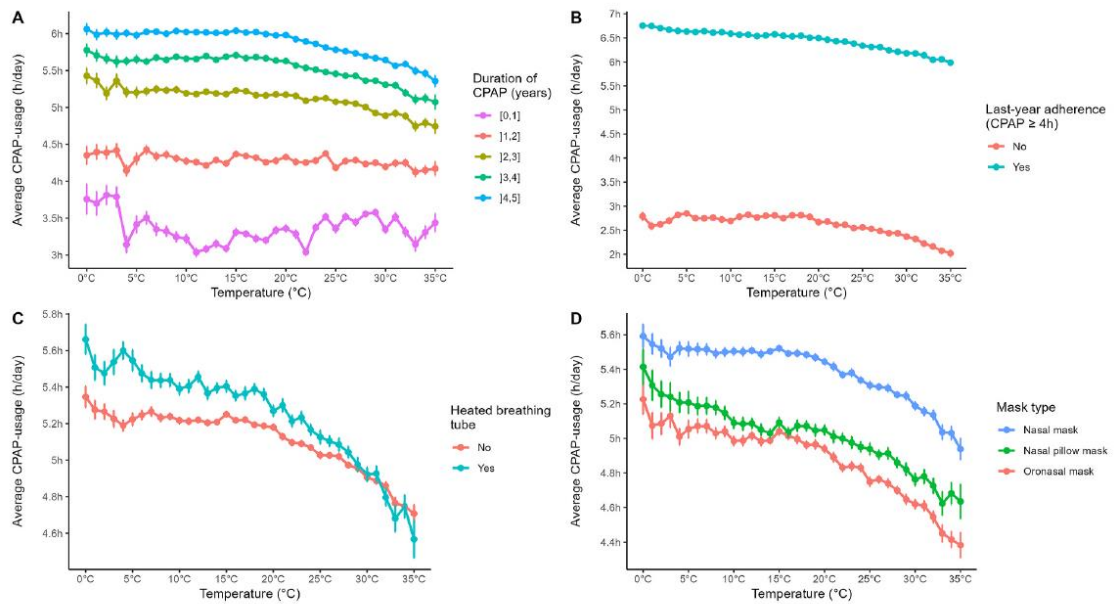


Fig. 5. CPAP-usage according to temperature and device and mask data.
 Note: Data are stratified by duration of CPAP (panel A), last-year adherence (panel B), heated breathing tube (panel C) and current mask type (panel D).

During heatwaves, we observed a mirror-like relationship between CPAP-usage and temperature. A heatwave occurred in France between June 25–30 2019, reaching 46 °C (June 28, 2019) in Hérault, Occitanie (Adène Group’s geographical area). This peak in temperature is clearly visible in Figs. 1 and 2.

End-of-year festivities (December 24 and 31) demonstrate a low level of CPAP-usage (Fig. 2).

The effects of months on mean CPAP-usage was depicted in Supplementary Fig. S5. The three summer months (June, July and August) are the months with the lowest CPAP-usage, with a minimum in July (4.9 (\pm 3.3)). CPAP-usage remains stable from January to March, and then decreases until July, before increasing again until the end of the year. We also note a drop in CPAP-usage in December. This drop is due to the end-of-year festivities, as can be seen every year in Fig. 1.

4. Discussion

To our knowledge, this study is the first to report the association between temperature and CPAP-usage in a large cohort of patients treated with long-term CPAP. The main results suggest that: 1) the relationship between CPAP-usage and temperature is not linear. The best model found two breakpoints at 18 °C and 29 °C; 2) CPAP-usage drops drastically when the temperature at 12 p.m. exceeds 29 °C, with each 1 °C increase in temperature corresponding to a 3.6 min reduction in CPAP-usage.

4.1. Relationship between temperature and CPAP-usage

Prigent et al. previously observed an inverse relationship between temperature and CPAP-usage in June, with a correlation coefficient of - 0.57 [15]. Our study not only confirms the association between temperature and CPAP-usage, but also provides new insights about the non-linear relationship between CPAP-usage and temperature. The segmental linear regression analysis found two breakpoints in temperature, at 18 °C and 29 °C. Given global warming, temperatures above 29° will occur more frequently. We observed that for temperatures >29 °C, each 1 °C increase corresponded with a 3.6 min reduction in CPAP-usage. Therefore, a 10° increase would correspond to a 36 min reduction in CPAP-usage, which is clinically significant considering that the MCID for CPAP-usage is 30 min [3]. Prigent et al. studied the relationship between temperature and CPAP-usage during the month of June and observed a negative association, with a slope of - 0.07 h for each additional degree [15]. In our study, we show that above 29 °C at 12 p.m., CPAP-usage drops drastically with a slope of - 0.06 h for each additional degree. In addition, when CPAP-usage was stratified by age, heated breathing tube (yes or no), or AHI diagnostic, the gap in CPAP-usage between groups decreased as temperature increased. It is important to note that the impact of length of day is weaker than that of temperature, given that a 3.6-min decrease in CPAP-usage is associated with both a one-degree increase above 29° and a 1.5-h decrease in length of day.

Our data suggest that patients who experience a more pronounced negative impact of temperature on CPAP-usage are older, obese individuals with an AHI greater than 30 events per hour. By exploiting the temperature data collected at 12 p.m., from a preventive point of view, informational interventions could be implemented targeting these populations. Furthermore, our results indicate that the benefit of a heated circuit on CPAP-usage diminishes progressively with increasing temperature, eventually becoming null on hot days, which is in line with expectations.

Several hypotheses can be proposed to explain the observed association between atmospheric temperature and CPAP usage: i) In older patients, the reduction in CPAP-usage during hot days may be linked to decreased sleep efficiency, as heat-related insomnia has been previously documented [16]; ii) In some patients, excessive perspiration due to elevated temperature can compromise the mask cushion seal, leading to increased air leaks [15], which in turn may reduce CPAP-usage [11].

4.2. Seasons and months association on CPAP-usage

Over the past few years, the association between season and CPAP-usage has become a subject of investigation [12–15]. Previous studies identified that summer is the season when CPAP-usage is lowest, while winter is the season with the highest CPAP-usage [13–15]. These previous studies were carried out in the northern hemisphere, and used the same definitions of seasons as the present study, which allows us to make comparisons. A study based on 141 Japanese patients, from 2015 to 2016, showed that summer was the season with the lowest CPAP-usage (5.48h/day), while winter had the highest CPAP-usage (5.93h/day)

[13]. Spring and autumn were equivalent seasons for CPAP-usage, with 5.73 h/day and 5.78 h/day respectively. Similarly, a study conducted on 954 Greek patients, based on data from 2022 to 2023, showed that summer was the season with the lowest CPAP-usage (5.58 h/day), and winter had the highest CPAP-usage (6.15 h/day) [14]. Our study confirms the same trends in CPAP-usage across the different seasons, and included a larger number of patients, more recently and over a longer period of time.

Only one other study calculated the mean differences in CPAP-usage between summer and winter months. The study, which was conducted in France over the months of January, June, and December 2021, and included over 25,000 subjects, showed that June had lower CPAP-usage than January and December [15]. Indeed, the mean difference in CPAP-usage between January and June was 22.2 min, with around 14 % of patients experiencing a decrease of at least 30 min. In our study the difference in CPAP-usage between January and June was 19.6 min, with 42.7 % of patients experiencing a decrease of at least 30 min. The greatest mean difference in CPAP-usage was observed between February and July, with a difference of 25.6 min and around 44 % of patients experiencing a decrease of at least 30 min.

4.3. Limits and strengths of the study

This study has both strengths and limitations related to its design. The main limitation is that some potential confounders associated with CPAP-usage and temperature, such as comorbidities and the presence of air conditioning at night, were not assessed. We also acknowledge that we were unable to collect data related to patients' holidays or travel.

On the other hand, we consider that our study has good external validity for northern hemisphere countries, given that our data showing a relationship between CPAP-usage and seasons are consistent with previously published findings. Our analyses included a larger number of patients than previous studies, and data related to the duration of CPAP treatment (ranging from one month of follow-up to four and a half years) and daily temperatures from the weather station closest to each patient's home, which are not available in previous studies.

Our choice to include patients with less than 6 months of follow-up may have diluted the observed association between temperature and CPAP-usage. Indeed, our results suggest that there was no association between temperature and CPAP usage for patients who had less than one year of follow-up, whereas there appeared to be an association between temperature and CPAP usage for patients who used CPAP for more than three years.

5. Conclusion

In patients undergoing long-term CPAP therapy, we report that temperature is associated with CPAP-usage. CPAP-usage drops drastically when the temperature exceeds 29 °C. If future studies confirm our results, it could be beneficial to develop preventive measures that would alert the patient about the risk of lower CPAP-usage when the temperature monitored during the day is high.

CRedit authorship contribution statement

Celia Vidal: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Data curation.

Jean-Pierre Mallet: Writing – original draft, Formal analysis.

Sarah Skinner: Writing – original draft.

Raphael Gilson: Formal analysis, Data curation.

Olivier Gaubert: Formal analysis, Data curation.

Arnaud Prigent: Writing – review & editing.

Frédéric Gagnadoux: Writing – review & editing.

Arnaud Bourdin: Writing – review & editing.

Nicolas Molinari: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Dany Jaffuel:** Writing – original draft, Formal analysis, Conceptualization.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Ethics approval and consent to participate

TempCPAP is registered with Health Data Hub (n°20475117). The protocol complied with the Declaration of Helsinki. All participants had given their written informed consent.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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