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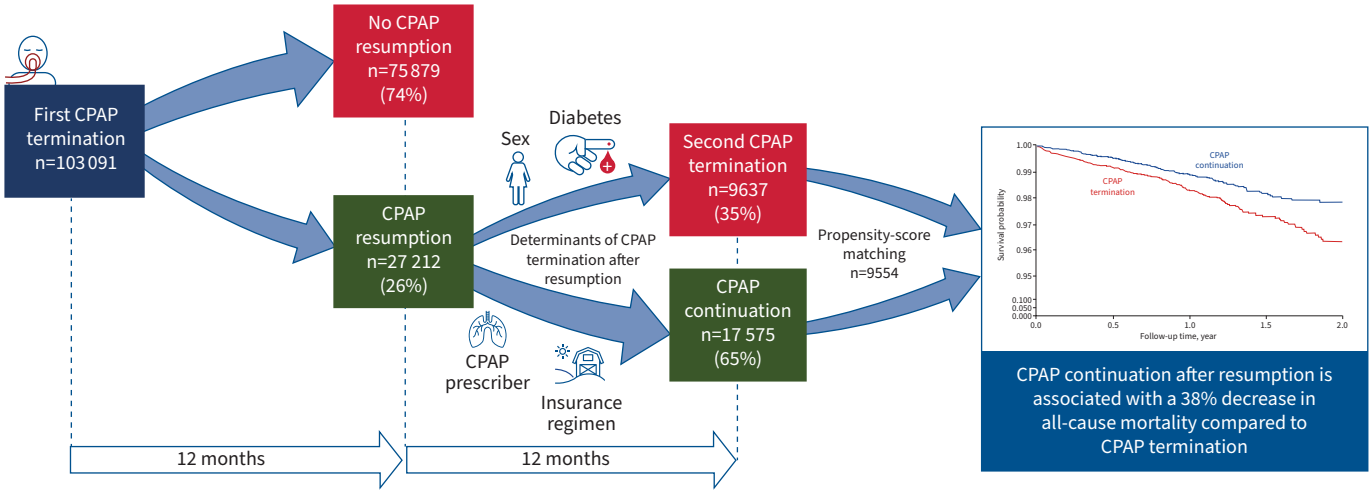

GRAPHICAL ABSTRACT After initial therapy termination, resumption and continuation of continuous positive airway pressure (CPAP) therapy was associated with lower all-cause mortality risk than therapy resumption followed by a second termination. This highlights the value of offering a second CPAP trial.

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CPAP resumption after a first termination and impact on all-cause mortality in France

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Abstract

Background Continuation of continuous positive airway pressure (CPAP) therapy after initial prescription has been shown to reduce all-cause mortality *versus* therapy termination. However, there is a lack of data on the rates and impact of resuming CPAP in patients with obstructive sleep apnoea (OSA). This analysis determined the prevalence of CPAP resumption in the year after termination, characterised determinants of CPAP resumption, and examined the impact of CPAP resumption on all-cause mortality.

Methods French national health insurance reimbursement system data for adults aged ⩾18 years were used. CPAP prescription was identified by specific treatment codes. Patients who resumed CPAP after first therapy termination and continued to use CPAP for 1 year were matched with those who resumed CPAP then terminated therapy for a second time.

Results Out of 103 091 individuals with a first CPAP termination, 26% resumed CPAP over the next 12 months, and 65% of these were still using CPAP 1 year later. Significant predictors of CPAP continuation after resumption included male sex, hypertension and CPAP prescription by a pulmonologist. In the matched population, the risk of all-cause death was 38% lower in individuals who continued using CPAP after therapy resumption *versus* those who had a second therapy discontinuation (hazard ratio 0.62, 95% CI 0.48–0.79; p=0.0001).

Conclusion These data suggest that individuals with OSA who fail initial therapy with CPAP should be offered a second trial with the device to ensure that effective therapy is not withheld from those who might benefit.

Introduction

Obstructive sleep apnoea (OSA) is the most common form of sleep disordered breathing, affecting nearly one billion individuals aged 30–69 years worldwide [1]. OSA is characterised by recurrent complete or partial pharyngeal collapse during sleep, resulting in intermittent hypoxia, intrathoracic pressure swings and arousal from sleep [2, 3]. Symptoms occurring as a direct consequence of OSA include snoring, nonrestorative sleep and excessive daytime sleepiness [2]. In addition, OSA is a risk factor for a variety of cardiovascular and metabolic comorbidities, including hypertension, atrial fibrillation and diabetes mellitus [2–8].

First-line, gold-standard therapy for moderate-to-severe OSA is continuous positive airway pressure (CPAP), which splints the upper airway open during sleep [9]. However, although CPAP is an efficacious therapy for OSA, its real-world effectiveness is challenged by patients' adherence to therapy, especially

over the long term [10, 11]. CPAP termination rates in the first 3 years after therapy initiation have been reported to be as high as 50% [12]. In addition, patients who terminate CPAP therapy have a significantly higher all-cause mortality rate than those who continue to use CPAP [13].

Millions of individuals with OSA have terminated CPAP after first therapy initiation [12, 13], and there are a variety of potential causes underlying CPAP termination or therapy failure (including symptom burden, technical aspects, intimate relationships and presence of comorbidities). However, these factors can evolve over time, and terminating CPAP therapy on one occasion does not necessarily preclude benefit from subsequent rounds of therapy. Nevertheless, this situation requires re-evaluation of treatment decisions and resumption of CPAP therapy, something that is not encouraged by many reimbursement conditions and treatment guidelines, and has not been widely studied. As a result, there is a near absence of data on persistence with, and outcomes after, a new CPAP trial after a first CPAP therapy termination. Data from one single-centre study showed that over half of all patients restarting CPAP remained on therapy at 1-year follow-up [14].

Resumption of CPAP after previous therapy failure might represent an under-used option in millions of individuals with untreated OSA. However, it is important to understand how often this occurs, and the associated success rates and outcomes of CPAP resumption. Based on existing data [13], re-initiation of CPAP might be expected to have a potentially favourable impact on hard clinical outcomes.

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 (Système National des Données de Santé (SNDS)). This analysis determined the prevalence of CPAP resumption in the year after a first episode of CPAP termination, characterised determinants of CPAP resumption after therapy termination, and examined the impact of CPAP resumption on all-cause mortality.

Methods

Data source

The SNDS database contains comprehensive, individualised and anonymised data on health spending reimbursements for almost all individuals living in France. Approval for the ALASKA project was obtained from the French information technology and personal data protection authority (Commission Nationale Informatique et Liberté (CNIL)). In addition, CNIL provided specific approval for this study (DR-2019-78, number 919194).

Study population

Adults (age ⩾18 years) who had not previously used CPAP and had CPAP therapy initiated from January 2015 to December 2016 were eligible for inclusion. In France, the apnoea–hypopnoea index cut-off for approval of CPAP is >15 events·h^{-1} with symptoms and/or comorbidities. Specific disease codes were used to identify an OSA diagnosis, and specific treatment modality codes were used to identify prescription of CPAP. In this analysis (figure 1), individuals who resumed CPAP after the first therapy termination and continued to use CPAP for 1 year were compared with those who resumed CPAP after the first therapy termination and then terminated therapy for a second time.

Study parameters and follow-up

The main objective of this analysis was to assess the prevalence of CPAP resumption in the first year after a first episode of CPAP termination. Secondary objectives were to identify determinants of CPAP resumption after initial CPAP therapy termination, and to evaluate the impact of resuming CPAP on all-cause mortality.

CPAP therapy resumption and therapy termination were defined as the resumption or cessation of CPAP reimbursements, respectively, as triggered by the physician in charge of patient follow-up. In France, follow-up visits are mandatory at 4 and 12 months after CPAP initiation and then every year thereafter. At these visits, the prescribing physician must fill in a specific form to renew or stop CPAP therapy. Continued reimbursement for a CPAP device is recommended when device usage is >4 h·night^{-1} (but reimbursement can continue when usage is 2–4 h·night^{-1} if there is additional patient education/coaching). Patients who started CPAP but were not using CPAP at the 4-month review were included in the CPAP termination group at 1 year. Participants who continued to be prescribed CPAP at the 4-month visit but had stopped at the 12-month visit were considered as 1-year CPAP terminations, while those who remained on CPAP at the 12-month visit were categorised as having continued CPAP therapy. After initial cessation of CPAP, the equipment was returned to the relevant home care provider, and new equipment

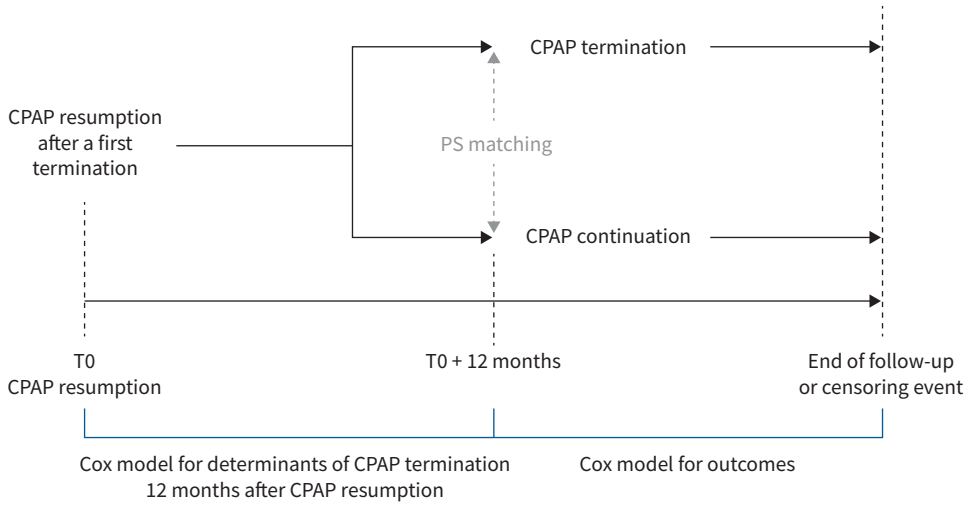

FIGURE 1 Study design. CPAP: continuous positive airway pressure; PS: propensity score.

was delivered for the second CPAP set-up. Special additional training sessions are not required for reimbursement of CPAP therapy after resumption.

For the purposes of this study, it was assumed that cessation of CPAP reimbursement (therapy termination) was due to nonadherence. Where there was a noted valid reason for stopping CPAP therapy (including switch to alternative form of therapy (mandibular advancement device or upper airway surgery) and sleep apnoea cure after bariatric surgery, all determined based on International Classification of Diseases 10 codes), individuals were excluded from the analysis (see supplementary methods for full details). In terms of mortality, the SNDS database registers a date of death, but does not detail the cause of death.

France runs a statutory health insurance (SHI) system that provides universal coverage for all residents. The system is financed through employee and employer contributions, and increasingly by earmarked taxes on a broad range of revenues. The main schemes that provide SHI are one general scheme and one specific to the agricultural sector (for farmers and farm employees); both have the same coverage and benefit policies.

Statistical analysis

Quantitative data are presented as median (interquartile range) and qualitative data are presented as number (percentage). Between-group comparisons were performed using the nonparametric Mann–Whitney test for quantitative data and the Chi-squared test for qualitative data.

After group definition, at 12 months after CPAP resumption, propensity scores were assessed using a nonparsimonious logistic regression model. The propensity score matching included age, sex, type of insurance coverage, medical specialties of the prescribers, other factors that provide an indication of the overall health status of an individual (arrhythmias, hypertension, cardiac failure, COPD, stroke and diabetes) and the use of medications to treat hypertension and diabetes. To account for any changes in healthcare trajectories since the first CPAP termination, propensity score matching was also performed for the following factors: hospitalisation for cardiovascular disease (heart failure, stroke, coronary heart disease and arrhythmias) and new medication prescriptions (antihypertensives and antidiabetics). A calliper of 0.001 was used to match groups who persisted *versus* terminated CPAP therapy using an optimal matching approach and the standardised mean difference was used to assess the balance between groups before and after matching (supplementary figure S1).

Determinants of CPAP therapy termination in the 12 months after resumption of CPAP were assessed using a multivariate logistic regression model. Variable selection for inclusion in a multivariable Cox model was driven by clinical expertise and literature knowledge [15].

To assess the impact of continuing with CPAP after therapy resumption on outcomes, Kaplan–Meier curves were used to compare groups based on age, sex and comorbidities with comparison between groups using the log-rank test. Finally, a survival Cox model was used to assess the hazard ratio (HR) and 95%

confidence interval values for the effects of CPAP continuation *versus* CPAP termination on all-cause death in propensity score matched individuals. Because these groups were already balanced, no adjustment was performed.

Python version 3.6.6 software with the libraries Numpy version 1.18.5 and Pandas version 1.1.4 was used for data management and analysis; Statsmodel version 0.12.1 was used for logistic regression; and Lifelines version 0.25.6 was used for survival Cox models. A p-value of <0.05 was considered statistically significant.

Results

Study population

Just over one-quarter of the 103 091 individuals who terminated CPAP therapy for the first time resumed CPAP over the next 12 months and were included in this analysis (n=27 212, 26%) (figure 2). The study population was characteristic of individuals with sleep apnoea who have an indication for CPAP, being middle-aged, predominantly male and with multiple comorbidities (table 1). Baseline characteristics for the propensity score matched populations (n=9554 in each group) are provided in supplementary table S1.

CPAP resumption

Of patients who resumed CPAP usage in the first year after initial therapy termination, 65% (n=17 575) continued to use CPAP therapy in the subsequent 12 months and 35% (n=9637) had a second therapy termination (figure 2). The time from first CPAP termination to resumption was significantly shorter in individuals who continued using CPAP after therapy resumption compared with those who terminated therapy for a second time (table 1).

Predictors of CPAP continuation after resumption of therapy

Using a multivariable logistic regression model, females and those with diabetes were significantly more likely to terminate CPAP after therapy resumption (OR for therapy termination 1.08, 95% CI 1.02–1.14 for females *versus* males, and 1.22, 1.08–1.37 for diabetes *versus* no diabetes; both p<0.005) (figure 3, supplementary table S2). In contrast, individuals with prescription of CPAP by a pulmonologist *versus* general practitioner (GP) (OR 0.88, 95% CI 0.83–0.93; p<0.005), and having agricultural *versus* general

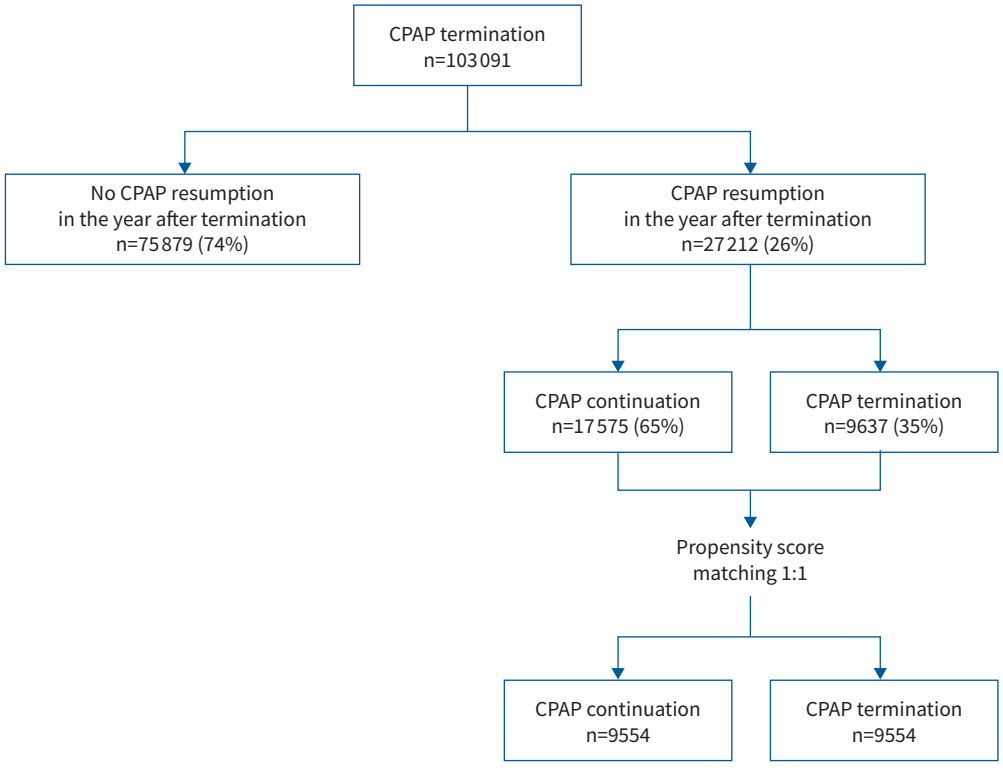

FIGURE 2 Flow chart of patient inclusion. CPAP: continuous positive airway pressure.

TABLE 1 Baseline clinical and demographic characteristics of the study population

	All patients	CPAP resumption in the first year after initial termination (n=27 212)		
		CPAP continuation	Second CPAP termination	p-value
Patients	27 212	17 575	9637	
Age years	59 (49–68)	60 (50–69)	57 (47–67)	<0.005
Female	8902 (32.7)	5678 (32.3)	3224 (33.5)	0.0551
Comorbidities				
Chronic psychiatric conditions	1550 (5.7)	939 (5.3)	611 (6.3)	<0.005
Stroke	864 (3.2)	550 (3.1)	314 (3.3)	0.5632
Heart failure	652 (2.4)	404 (2.3)	248 (2.6)	0.1589
Coronary heart disease	2489 (9.2)	1656 (9.4)	833 (8.6)	0.033
Hypertension	13 897 (51.1)	9.254 (52.7)	4632 (48.1)	<0.005
Diabetes	6054 (22.3)	3861 (22.0)	2193 (22.8)	0.1354
COPD	2389 (8.8)	1601 (9.1)	788 (8.2)	0.0094
Time from CPAP resumption to end of follow-up/censor days	784 (496–907)	786 (510–914)	727 (482–879)	<0.005
CPAP therapy duration after restart days	420 (182–693)	539 (427–789)	133 (35–196)	<0.005
Time since first CPAP termination to resumption days	189 (165–238)	183 (161–231)	196 (168–245)	<0.005

Data are presented as n, median (interquartile range) or n (%), unless otherwise stated. CPAP: continuous positive airway pressure.

insurance (OR 0.79, 95% CI 0.70–0.89; p<0.005) were less likely to terminate CPAP therapy after resuming device usage (figure 3, supplementary table S2).

All-cause mortality

In the propensity score matched population (supplementary table S3), there was a 38% reduction in the risk of all-cause death in individuals who continued using CPAP after therapy resumption compared with those who had a second therapy discontinuation (HR 0.62, 95% CI 0.48–0.79; p=0.0001) (figure 4). The number of patients with CPAP required to restart CPAP to avoid one death was calculated to be 169.

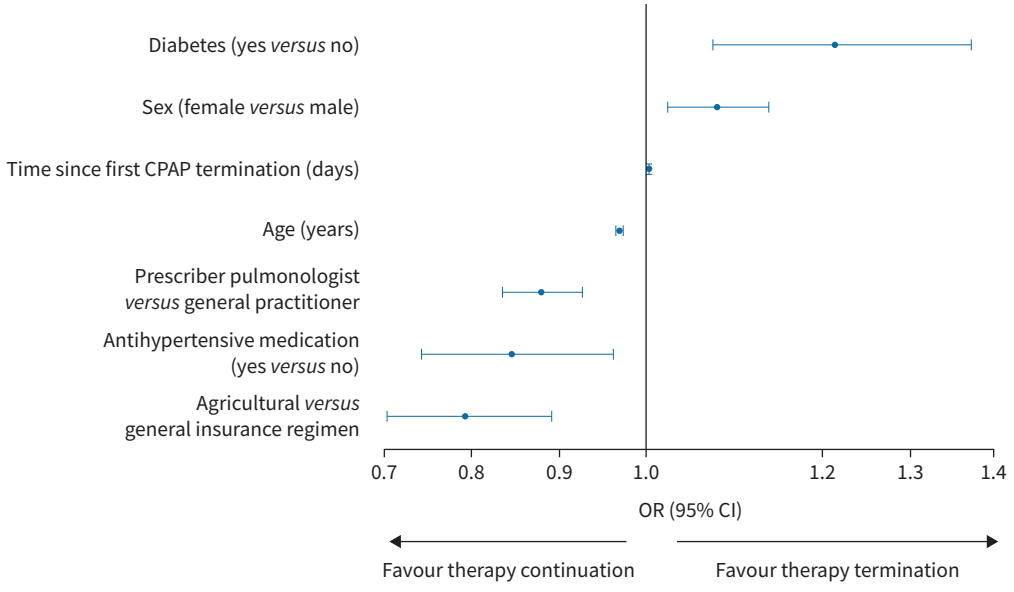

FIGURE 3 Predictors of a second continuous positive airway pressure therapy (CPAP) termination after resumption of therapy (multivariate logistic regression model).

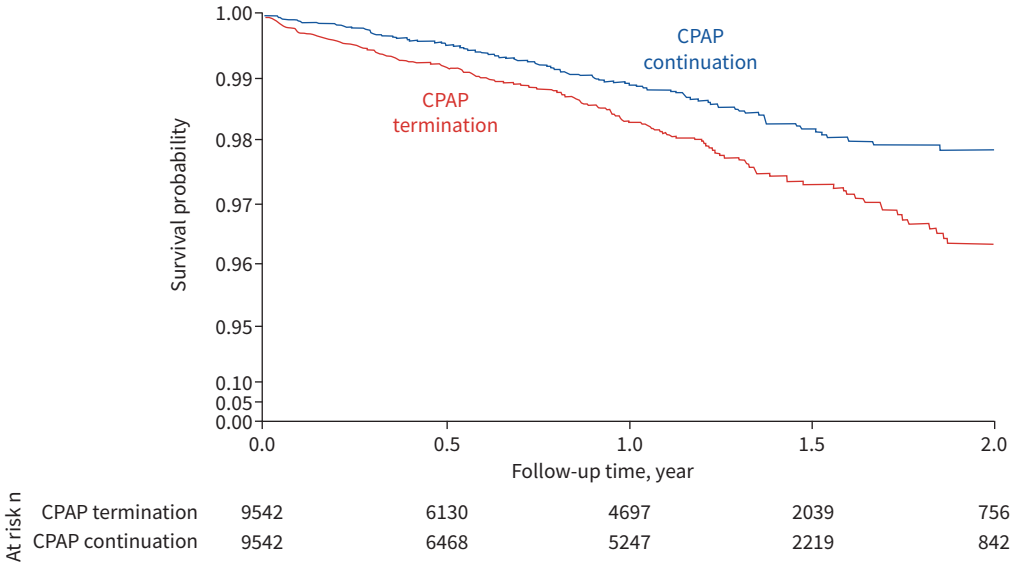

FIGURE 4 Kaplan–Meier curves showing the impact of continuous positive airway pressure (CPAP) continuation after resumption of therapy on all-cause mortality (matched population).

Discussion

This analysis of data from a comprehensive, unbiased national dataset that represented a typical population with OSA found that one-quarter of all individuals who stop using CPAP after first therapy initiation re-start CPAP within the next year, and almost two-thirds of these remain on CPAP another year later. In addition, to the best of our knowledge, this study shows for the first time that individuals who resume and remain on CPAP have a significantly lower risk of death than those with a second therapy termination. This survival benefit with continuation of CPAP is similar to that reported in all patients who initiated CPAP therapy for the first time [13]. The current findings are clinically relevant because although reimbursement criteria for CPAP often require ongoing and specific levels of device usage over defined periods of time (such as in France, and Centers for Medicare and Medicaid Services criteria in the United States), the current data suggest that resumption and continuation of therapy has clinical value in terms of reducing all-cause mortality.

To our knowledge, only one previous analysis has investigated resumption of CPAP therapy [14]. The results of this single-centre study conducted in Finland (n=224) showed that 52% of subjects referred for re-initiation of CPAP were still using the device 1 year later [14], a lower rate than the 65% observed in the current study. One consistent finding in both studies was that continuation of CPAP therapy after resumption was significantly more common in men than in women.

Also using an SNDS dataset, we have previously shown that nearly one-quarter of the 365 000 participants stopped therapy in the first year after CPAP initiation, and nearly half stopped using CPAP during the first 3 years [12]. Of these, only 6449 individuals had what was defined as a valid, or nonadherence-related, reason for stopping CPAP (*i.e.* redirection to oral appliance use, bariatric surgery or upper airway surgery) [12], leaving a significant proportion of patients who could potentially benefit from CPAP who have terminated therapy. Alternatives to CPAP therapy are supported by guidelines or expert opinions [16–18], but poorly utilised in real life. Therefore, restarting CPAP occurred in 26% of individuals who had previous CPAP therapy termination. Although the 1-year rate of continuation of resumed CPAP therapy was acceptable at 65%, the 35% rate of a second therapy termination is higher than that after first usage of CPAP (27.7%) [12]. This highlights the importance of taking measures to ensure good adherence and ongoing device usage after both first and subsequent CPAP initiations, such as telemonitoring and patient engagement tools [19–22].

The current data analysis focuses on individuals with OSA who restart CPAP after a first termination for reasons of non-adherence. Apart from restarting CPAP, there are other potential therapeutic strategies that may have been used to improve adherence and the efficacy of positive airway pressure therapy. For example, bilevel positive airway pressure has been used as an effective second-line therapy for obese patients with OSA failing regular CPAP [23, 24]. Also, studies have demonstrated that treatment-emergent

or persistent central sleep apnoea that occurs during CPAP reduces adherence to therapy, but that this is improved early after switching from CPAP to adaptive servoventilation [25, 26].

Predictors of CPAP continuation after resumption of therapy in this study were similar to those found to be relevant after a first CPAP initiation (*i.e.* older age and male sex) [12], and the impact of comorbidities such as hypertension and diabetes on persistence with CPAP therapy was also similar [12]. The presence of comorbidities could mean that individuals are more symptomatic and/or more aware of their overall risk of adverse outcomes, motivating them to adhere to therapy. However, the reasons underlying the associations seen in our study remain to be determined. A novel finding of the current analysis was that the type of insurance also had a significant impact on CPAP termination after therapy resumption. Specifically, those with farmer-specific health insurance were less likely to terminate a second trial of CPAP therapy than those with other types of insurance. This rural population has a more delayed and limited access to care and those restarting CPAP are probably highly motivated. Insurance-related findings could also potentially be related to socioeconomic factors because these have been shown to be associated with adherence to CPAP therapy, being lower in those with lower median household income and among ethnic minorities [27–29]. In the United States, differences in adherence to positive airway pressure therapy persisted even after the Affordable Care Act was passed [28].

Another factor significantly related to continuation of CPAP after therapy resumption in the current analysis was device prescription by a pulmonologist *versus* a GP, and continuation of CPAP also tended to be better when CPAP was prescribed by a cardiologist *versus* a GP. Again, these findings are clinically relevant because the high and increasing demand for OSA care has exceeded the capacity of specialist sleep services [30, 31]. There are several factors that might impact on the management of OSA in primary care, including limited access to specialist support and lack of clarity around roles for different healthcare providers [32]. In addition, it is possible that GPs have less time per appointment to spend with patients than specialists. Lack of knowledge or training could be another contributing factor, as suggested in previous publications [32, 33]. Our findings of differences in the therapy termination rate when CPAP is initiated by GPs *versus* specialists could indicate that primary care based management may not be sufficient to optimise device usage and outcomes during CPAP therapy, increasing the risk of therapy termination and failure. As a result, assessment, referral and management of OSA in many countries is now shared between sleep specialists, respiratory physicians, cardiologists and GPs [31]. Thus, although primary care models of OSA care and service delivery will differ between countries (and maybe even within the same country), successful initiation and efficacy of CPAP therapy is likely to require strong support and established networks with existing specialist sleep services [30, 34].

A key strength of this study is that it presents by far the largest dataset investigating patterns and outcomes of CPAP resumption after initial therapy termination in people with OSA. However, we only report data for the first year after resumption of CPAP and therefore longer-term follow-up of these patients is needed. In addition, individuals included in the current analysis resumed CPAP within 1 year of the first termination and it would be interesting to determine rates and outcomes of CPAP resumption when longer periods of time have elapsed since therapy termination.

Other limitations of this type of analysis have been described in detail previously [13]. To summarise, these include the use of a database designed for administrative rather than research purposes, a lack of specific data on OSA severity (although a prescription for CPAP would indicate disease of at least moderate severity), lack of information about potential confounding variables (*e.g.* alcohol intake, body mass index, physical activity level and other health behaviours) and no specific details of the level of CPAP usage (*e.g.* hours per night, days per week). There is also no information about what prompted individuals to resume CPAP therapy, and this could have influenced outcomes. For example, some people may have resumed CPAP in response to deteriorating health or an acute medical event. In terms of the effect of resuming CPAP on mortality, the contribution of “healthy adherer bias”, where individuals who adhere to therapy (in this case CPAP) are more likely to engage in other healthy behaviours, cannot be ruled out. However, all participants in this study had previously terminated a first prescription of CPAP therapy. In order to construct more efficient predictive models to identify individuals at risk of abandoning then resuming CPAP therapy, it could be helpful to undertake more systematic investigation with questionnaires that measure a person’s understanding of OSA and its treatment, and their attitudes to OSA and CPAP (*e.g.* Apnea Beliefs Scale) [35]. Finally, the mortality analysis was carried out in the propensity score matched population and included adjustment for prior medication usage.

We acknowledge that the lack of objective CPAP adherence data is a factor that limits the interpretation of our study findings and means that we are not able to demonstrate a clear dose–response relationship

between CPAP adherence and mortality. However, the finding that CPAP therapy termination (which is accurately documented by cessation of reimbursements) was associated with higher mortality rates compared with CPAP continuation is clinically relevant information, even in the absence of specific device usage/adherence information. Further studies are needed that link claims data for an individual patient with objectively measured CPAP usage data. Objective adherence data from telemonitoring are not available from this dataset. To show that CPAP termination was largely due to nonadherence, we retrospectively analysed adherence for the last 69 CPAP terminations (over 1 year) at our centre in Grenoble and found that mean CPAP adherence was low (2±2.52 $h \cdot night^{-1}$) and associated with CPAP termination.

In conclusion, the results of this analysis clearly demonstrate that individuals with OSA who fail initial therapy with CPAP should be offered a second CPAP trial. Resumption of CPAP by 169 individuals would avoid one death. Current adherence criteria and reimbursement coverage requirements could result in the withholding of therapy for many individuals who might become adherent during a second chance to use CPAP [36], and obtain survival benefit from doing so. Discontinuation and resumption of CPAP therapy is probably a common trajectory of CPAP usage in clinical practice. Therefore, our findings have potential implications for both the individual in terms of improved survival, and for society/health systems in terms of healthcare resource use and costs. There is therefore a need for improved follow-up processes for individuals who terminate CPAP therapy after first initiation. In addition, the importance of a second CPAP trial would be a relevant and important inclusion in revisions of major guidelines referring to the use of CPAP in people with OSA.

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Data sharing: Data supporting the results of this study are available from the corresponding author upon reasonable request.

Ethics statement: Approval for the ALASKA project was obtained from the French information technology and personal data protection authority, “Commission Nationale Informatique et Liberté” (CNIL). In addition, CNIL provided specific approval for this study (DR-2019-78, number 919194).

Author contributions: Representatives of the study sponsor were involved in the design of the study. Study procedures and analyses were undertaken by independent third parties, SEMEIA (P. Rinder, P. Sinal-Boucher and P. Hornus) and INSERM HP2 laboratory (S. Bailly) and artificial intelligence chair “trajectories medicine” (director and principal investigator, J-L. Pépin). The first draft of the manuscript was prepared by J-L. Pépin, who had unrestricted access to the data, with the assistance of an independent medical writer funded by ResMed. The manuscript was reviewed and edited by all the authors. All authors made the decision to submit the manuscript for publication and assume responsibility for the accuracy and completeness of the analyses and for the fidelity of this report to the trial protocol. J-L. Pépin has personally reviewed the data, understands the statistical methods employed for all analyses, and confirms an understanding of these analyses, that the methods are clearly described and that they are a fair way to report the results.

Conflict of interest: J-L. Pépin has received lecture fees or conference travel grants from ResMed, Philips, AstraZeneca, Jazz Pharmaceuticals, Agiradom and Bioprojet, and has received unrestricted research funding from ResMed, Philips, GlaxoSmithKline, Bioprojet, Fondation de la Recherche Medicale (Foundation for Medical Research), Direction de la Recherche Clinique du CHU de Grenoble (Research Branch Clinic CHU de Grenoble), and fond de dotation “Agir pour les Maladies Chroniques” (endowment fund “Acting for Chronic Diseases”). A. Malhotra is funded by the NIH, reports income from Eli Lilly, Zoll, Jazz and Livanova related to medical education, and ResMed provided a philanthropic donation to UC San Diego. P.A. Cistulli has an appointment to an endowed academic chair at the University of Sydney that was established from ResMed funding, has received research support from ResMed, SomnoMed and Zephyr Sleep Technologies, and is a consultant to ResMed, SomnoMed, Signifier Medical Technologies and Bayer. R. Tamisier has received consulting fees from ResMed, Inspire, Navigant and Jazz Pharmaceuticals, lecture fees from Agiradom, Elivie, ResMed and Philips, conference travel grants from Agiradom, and unrestricted research grants from ResMed, Vitalaire, Philips, APMC foundation Direction de la recherche Clinique du CHU de Grenoble and inter-regional research university hospital group. A.V. Benjafield, F. Lavergne and A. Josseran are employees of ResMed. P. Rinder, P. Sinel-Boucher and P. Hornus are employees of SEMEIA. S. Bailly has no conflicts of interest to disclose.

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