Dose–response relationship between obstructive sleep apnoea severity and C-reactive protein levels: data from the European Sleep Apnoea Database

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Shareable abstract (@ERSpublications)
Obstructive sleep apnoea is characterised by elevated systemic inflammation. Analysis performed in >18 000 patients across Europe established a causal relationship between OSA severity measures and CRP blood levels independent of confounders. https://bit.ly/44TK60A

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Abstract

Introduction Obstructive sleep apnoea (OSA) characterised by intermittent hypoxia promotes systemic inflammation. This study evaluated the association between OSA severity and circulating C-reactive protein (CRP) levels as marker of systemic inflammation in a pan-European patient cohort.

Methods This cross-sectional analysis of the multicentre European Sleep Apnoea Database (ESADA) cohort used inverse probability weighted regression adjustment for multiple covariates within a linear mixed-effects model (LMEM) to test the independent association between OSA severity and CRP levels. Covariates included anthropometrics and comorbidities. Study centre and year of analysis accounted for methodological variability in CRP analysis.

Results 18 445 subjects (71% male, median age 53 years (interquartile range 44–62), median apnoea–hypopnoea index (AHI) 22.1 events per h (9–44.9)) were included. CRP (median 3.0 $mg{\cdot}L^{-1}$ (1.2–5.1)) increased in a dose–response fashion across OSA severity categories (2.0 (1.0–4.0) for AHI <5 events per h; 2.5 (1.0–5.0) for AHI 5–<15 events per h); 2.9 (1.2–5.0) for AHI 15–<30 events per h; and 3.7 $mg{\cdot}L^{-1}$ (1.8–6.4) for AHI ⩾30 events per h; $p<0.001$, respectively). In the final LMEM model, AHI remained an independent predictor of CRP concentration ($p<0.001$). Other significant predictors of CRP were age and female sex. Obesity (body mass index ⩾35 $kg{\cdot}m^{-2}$) had, among other comorbidities, the strongest independent effect on CRP levels with 2.7 $mg{\cdot}L^{-1}$ (95% CI 2.45–2.90).

Conclusions Our results showed a consistent and robust dose–response relationship between OSA severity and systemic inflammation independent of usual confounders. The combination of OSA and obesity

amplified the association. Future studies should address whether elevated CRP could serve as a prognostic marker for subsequent cardiovascular events in OSA.

Introduction

Obstructive sleep apnoea (OSA) is a clinical syndrome characterised by repeated complete or partial obstruction of the upper airway during sleep. OSA alters quality of life and leads to an increase in cardiometabolic morbidity and overall mortality [1–4].

There is vast evidence that intermittent hypoxia, the hallmark feature of OSA, leads to systemic low-grade inflammation which is likely a key mediator of cardiometabolic diseases [5–7]. C-reactive protein (CRP) is recognised as the prototypic circulating marker of inflammation [8]. The CRP concentration, unlike other markers of inflammation, is not influenced by circadian factors. High-sensitivity CRP (hsCRP) has been identified as a superior biomarker if only a single blood test should be singled out to characterise inflammation. Importantly, elevated CRP is a strong predictor of future cardiovascular (CV) events [8].

However, conflicting data have been reported for the link between OSA and CRP. While some studies demonstrated higher levels in OSA patients compared with non-OSA patients [9–11] others found only a weak correlation after controlling for the presence of obesity [12–14]. In two meta-analyses, serum CRP/hs-CRP levels were higher in OSA patients compared with control subjects [15, 16]. Several additional factors such as age, sex, obesity or comorbidities can influence baseline CRP serum levels [17]. Therefore, it remains uncertain whether OSA *per se* is associated with increased CRP levels. Indeed, a recent American Heart Association statement on OSA did not identify a role for cardiovascular risk stratification by means of CRP levels in patients with OSA [18].

Thus, the aim of this analysis was to evaluate the role of CRP as a marker of systemic inflammatory burden in OSA in our large cohort controlling for numerous confounding factors by using a reference inverse of probability treatment weighting (IPTW) analysis. We hypothesised that OSA increased CRP independent of confounders. The European Sleep Apnoea Database (ESADA) cohort is suitable to address potential limitations due to rigorous classification of comorbidities and risk factors, and the adjustment for potential genetic and lifestyle factors. In addition, the cohort size provided statistical power to apply an advanced statistical model of causal inference methods on observational data.

Methods

Subjects

This was a cross-sectional analysis of the multicentre ESADA cohort. Data were collected as previously described [19]. Briefly, patients with suspected OSA, aged 18–80 years, were recruited from March 2007 to December 2022. Patients needed to provide oral and/or written informed consent to be included in the database. The ESADA database has been reviewed by the local independent ethics review boards at each participating European sleep centre.

Anthropometrics, medical history and concomitant medication were captured at baseline and subjects underwent sleep apnoea testing *via* respiratory polygraphy or a polysomnography technique according to local practice. Respiratory events and sleep were classified according to the American Academy of Sleep Medicine criteria with 4% desaturation criteria for hypopnoeas [20]. The apnoea–hypopnoea index (AHI) was used to classify patients into four severity groups for OSA: no OSA (AHI<5), mild OSA (5⩽AHI<15), moderate OSA (15⩽AHI<30) and severe OSA (AHI⩾30) [2]. In sensitivity analysis, OSA severity was also classified for measures of nocturnal hypoxia, including oxygen desaturation index (ODI) tertiles and tertiles of time below 90% oxygen saturation.

CRP

CRP was obtained by a venous blood sample taken in conjunction with the clinical evaluation at the sleep centre and the analysis in plasma or serum was performed according to local routine designed to provide either a low-sensitivity (ls) or predominantly high-sensitivity (hs) value. All patients who had a measurement of CRP at baseline were included. CRP values equal to exactly 0 $mg \cdot L^{-1}$ were considered missing (technical failure). Patients with a high inflammatory state as indicated by an elevated CRP >20 $mg \cdot L^{-1}$ [21], those taking corticosteroids (ATC H02) or patients with any form of known cancer were excluded from the analysis.

Data analysis

Data were expressed as number and percentage for qualitative variables and median and interquartile range (IQR) for quantitative variables. Comparisons between groups were performed using the Pearson's

chi-squared test for categorical variables. Due to the non-normal and asymmetric distribution of several quantitative variables (as assessed by visual inspection and Shapiro–Wilk tests), nonparametric Kruskal–Wallis tests were used to compare groups for continuous variables. Given the large sample size, these tests provide robust inference while avoiding assumptions about data distribution and variance homogeneity. Due to the low rate of missing values (<2% for each variable), single imputation using the median or mode was applied. Given the limited extent of missingness and the descriptive role of the imputed variables, we considered this approach sufficient to preserve the structure of the dataset without introducing model complexity such as multiple imputation [22]. A comparison of distributions before and after imputation is provided in supplementary table S1.

To assess the "average treatment effect" of OSA on CRP values, we used an inverse probability of treatment weighting (IPTW) regression adjusted (RA) approach for multiple exposure. For this, a directed acyclic graph (DAG) was drawn to represent the relations between the variables (figure 1) [23]. The relations between variables in the DAG were selected based on expert knowledge. Both pure risk factors and confounders had to be included to compute the weights. Instrumental variables, which are variables only related to the exposure and not related to the outcome, were not included as they will increase the variance without reducing the bias [24]. A correctly specified DAG can then provide a rational choice of confounding variables to adjust for in the computation of weights, and therefore increases the credibility of the conditional exchangeability [25].

More details of the statistical model are provided in the supplementary material. To summarise, first an ordinal regression was performed to assess individual weights by computing, for each individual, their own probability of belonging to their OSA group. The ordinal model accounts for the fact that the transition from no OSA to mild OSA may not be equivalent, in clinical impact or distribution, to the transition from moderate to severe OSA. This framework allows us to preserve the ordinal nature of the exposure while avoiding arbitrary assumptions about equal spacing between categories. The standardised mean difference was used to assess balance for covariates before and after weighting (supplementary figure S1). To account for variability in CRP measurements across European sleep centres and over time (*e.g.* differences in methodology or high- *versus* low-sensitivity assays, timing of blood sampling), random effects were included for both European "sleep centre" and "year" of CRP measurement. These random effects capture unobserved heterogeneity related to site-specific practices and temporal trends, and account for the

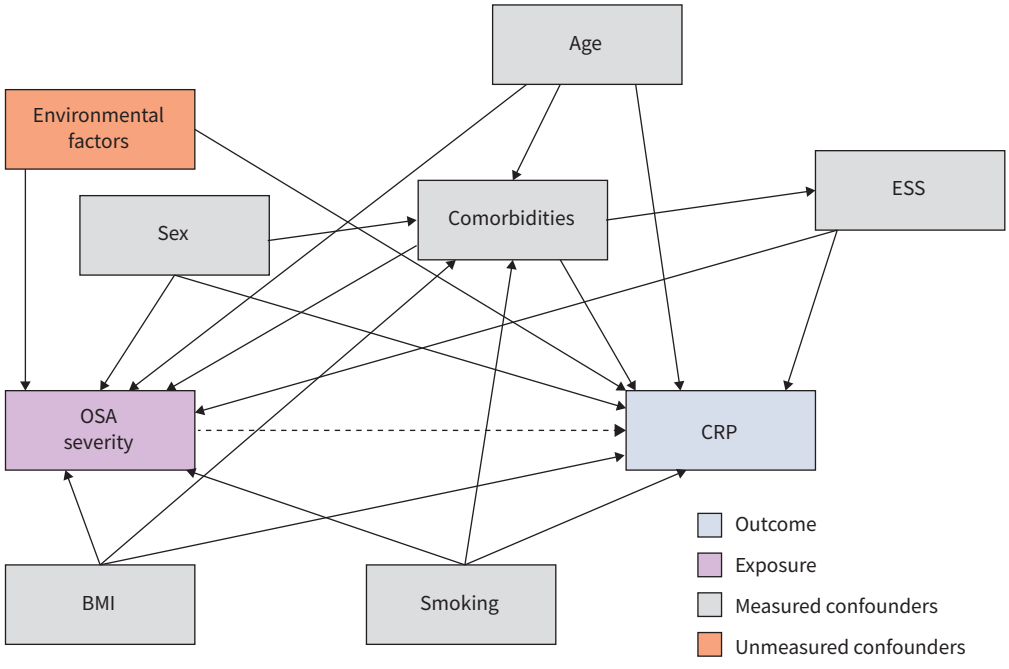

FIGURE 1 Directed acyclic graph for the causal relation between obstructive sleep apnoea (OSA) severity and C-reactive protein (CRP) levels. Dotted arrow represents the causal relation under investigation. Solid arrows represent the known relations. ESS: Epworth sleepiness scale; BMI: body mass index.

clustering of patients within centres and calendar years. This approach improves the generalisability of the results beyond the observed units by assuming that the included European sleep centres and years represent samples from larger populations. [26]. Ordinal logistic regression coefficient and weight distribution are presented in supplementary tables S2 and S3. Second, to assess the impact of OSA on CRP, a weighted mixed linear model was performed, adjusted on all the covariates used in the ordinal logistic regression (IPTW-RA). In this model, the interaction between sex and AHI severity group has been tested, but was not significant, and therefore was not included. Demographic and anthropometric data, Epworth sleepiness scale (ESS), cardiometabolic comorbidities and COPD, were included in the analysis as potential confounders.

To avoid model-based standard errors we used bootstrap confidence interval as recommended [27]. The stabilised weights and the estimates of the model were computed for each of the 1000 bootstrap samples. The SD of the estimate across those samples was considered the SE of the estimate in the original one.

Finally, the residuals of the model were investigated to verify the assumptions of linear models. Also, the significance of the random effects was assessed by removing the random-effect term and computing a likelihood ratio test between the real model and the model without random effects.

Using the same method, sensitivity analyses were performed for men and women, as well as for ODI or time <90% as markers of OSA severity instead of the AHI.

Statistical analyses were performed using R software (v.4.2.0, R Foundation for Statistical Computing, Vienna, Austria) and a p-value threshold of 0.05 was considered significant.

Results

Population

A total of 18 445 patients with a median age of 53 years (IQR 44–62), 71% male sex and median body mass index (BMI) of 30.5 $kg \cdot m^{-2}$ (26–35) from 29 European sleep centres with a median of 271 (59–769) patients enrolled per centre were included in this analysis (figure 2 and table 1). Cardiovascular comorbidities were prevalent with 42% for pre-existing systemic hypertension, 15% for diabetes mellitus, 8% for ischaemic heart disease and 6.5% for COPD. With increasing OSA severity, defined by AHI severity, subjects were older, more obese, more likely to be male and showed a higher burden of

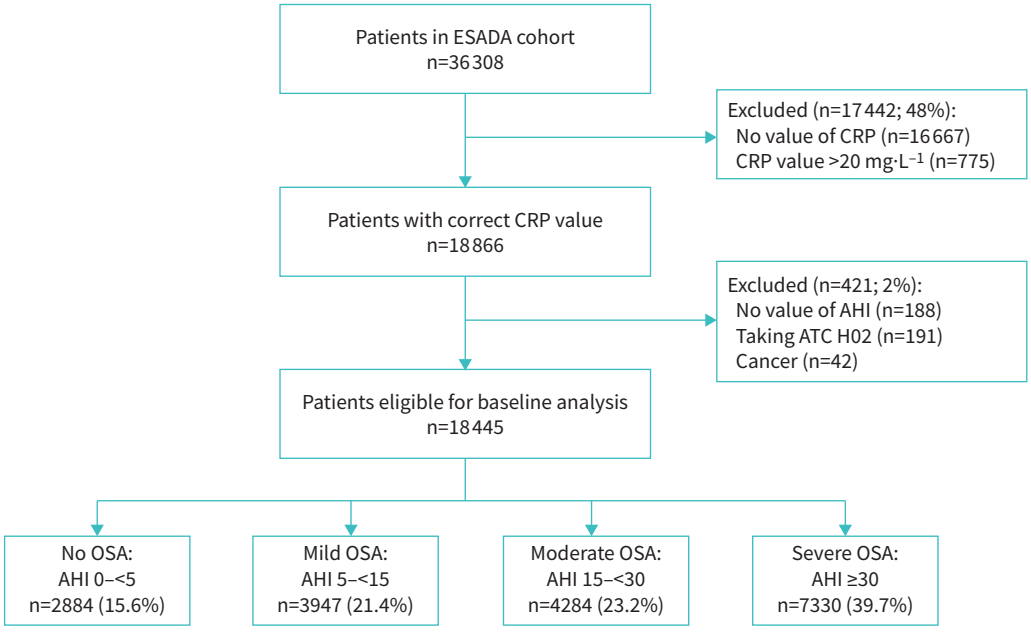

FIGURE 2 Flowchart depicting the selection of patients from the European Sleep Apnoea Database (ESADA) and categorisation of the population based on the severity of obstructive sleep apnoea (OSA), according to the apnoea–hypopnoea index (AHI) metric. CRP: C-reactive protein; ATC: anatomical therapeutic chemical (in this case, systemic corticosteroids).

TABLE 1 Clinical data: x-axis: AHI severity classes and statistics before weighting

Characteristic	All population n=18 445	No OSA n=2884	Mild OSA n=3947	Moderate OSA n=4284	Severe OSA n=7330	p-value[#]
C-reactive protein, mg·L^{-1}	3.00 (1.20–5.10)	2.0 (1.0–4.0)	2.5 (1.0–5.0)	2.9 (1.2–5.0)	3.8 (1.8–6.4)	<0.001
Age, years	53 (44–62)	46 (36–55)	52 (43–61)	55 (46–63)	55 (46–63)	<0.001
ESS score	9 (6.0–13.0)	9.0 (5.0–13.0)	9.0 (5.0–13.0)	9.0 (5.0–13.0)	10.0 (6.0–14.0)	<0.001
BMI, kg·m^{-2}	30.5 (27.0–34.9)	27.2 (24.5–30.7)	29.0 (26.0–32.5)	30.1 (27.1–34.0)	33.1 (29.5–37.4)	<0.001
BMI categories						<0.001
<25 kg·m^{-2}	2360 (13)	859 (30)	686 (17)	491 (11)	334 (4.6)	
25–<30 kg·m^{-2}	6067 (33)	1175 (41)	1573 (40)	1594 (37)	1715 (23)	
30–<35 kg·m^{-2}	5367 (29)	560 (19)	1116 (28)	1306 (30)	2511 (34)	
⩾35 kg·m^{-2}	4524 (25)	290 (10)	572 (14)	893 (21)	2770 (38)	
Current smoking	4618 (25)	721 (25)	954 (24)	991 (23)	1952 (27)	<0.001
Sex, male	13 036 (71)	1583 (55)	2574 (65)	3041 (71)	5838 (80)	<0.001
Diabetes mellitus	2665 (15)	191 (6.6)	423 (11)	606 (14)	1445 (20)	<0.001
Left ventricular hypertrophy	183 (1.0)	13 (0.5)	31 (0.8)	39 (0.9)	100 (1.4)	<0.001
Systemic hypertension	7678 (42)	617 (21)	1429 (36)	1823 (43)	3809 (52)	<0.001
Ischaemic heart disease	1525 (8.4)	103 (3.6)	308 (7.8)	359 (8.4)	755 (10)	<0.001
TIA or stroke	417 (2.3)	42 (1.5)	95 (2.4)	107 (2.5)	173 (2.4)	0.017
Status post-myocardial infarction	393 (2.2)	31 (1.1)	82 (2.1)	99 (2.3)	181 (2.5)	<0.001
Cardiac failure	720 (4.0)	57 (2.0)	109 (2.8)	160 (3.7)	394 (5.4)	<0.001
Other CV comorbidities	2173 (16)	316 (11)	699 (18)	525 (12)	633 (8.6)	<0.001
COPD	1183 (6.5)	123 (4.3)	211 (5.3)	259 (6.0)	590 (8.0)	<0.001
Neurological disease	1089 (6.0)	193 (6.7)	254 (6.4)	270 (6.3)	372 (5.1)	0.001
Psychiatric disease	1993 (11)	405 (14)	451 (11)	447 (10)	690 (9.4)	<0.001
Inflammatory disease	669 (3.7)	122 (4.2)	165 (4.2)	150 (3.5)	232 (3.2)	0.011

Data are presented as median (IQR) or n (%). OSA: obstructive sleep apnoea; ESS: Epworth sleepiness scale; BMI: body mass index; TIA: transient ischaemic attack; CV: cardiovascular. "Other CV comorbidities" denote information derived from free text not captured by the categories above. [#]: a Kruskal–Wallis test was performed for quantitative variables and a Pearson's chi-squared test was performed for qualitative variables.

comorbidities. Anthropometrics and comorbidities were comparable without clinically significant differences in ESADA subjects with and without (n=16 667) available CRP data (supplementary table S4).

CRP

The median value of CRP in the whole cohort was 3.0 mg·L^{-1} (1.2–5.1) and values increased in parallel with an increase in OSA severity defined by AHI. The median (IQR) for CRP values were 2 mg·L^{-1} (1.0–4.0) for no-OSA group, 2.5 mg·L^{-1} (1.0–5.0) for mild OSA, 2.9 mg·L^{-1} (1.2–5.0) for moderate OSA and 3.7 mg·L^{-1} (1.8–6.4) for severe OSA (p<0.0001) (figure 3). In all AHI categories, males had significantly lower values compared with females across categories.

In multivariable analysis controlling for obesity, anthropometrics and comorbidities, patients with moderate OSA and patients with severe OSA had a median CRP value augmented compared with no OSA patients (estimate of 0.28 (0.07–0.49); p=0.002; and 0.58 (0.37–0.80); p<0.001, respectively) (table 2). Males had significantly lower values than females with a mean CRP difference of 0.77 (−0.87– −0.61) (p<0.001). Regarding comorbidities, having diabetes mellitus (p<0.001), a high BMI (p<0.001), left ventricular hypertrophy (p<0.001), cardiac failure (p<0.001), COPD (p<0.001), neurological disease (p=0.017) and/or inflammatory disease (p<0.001) was significantly associated with increased CRP values. However, there was no significant association between the ESS score, systemic hypertension, transient ischaemic attack (TIA) or stroke, ischaemic heart disease and psychiatric disease and serum CRP concentration (table 2 and figure 4).

Sensitivity analyses for CRP

The association between OSA severity and CRP levels, separated for male and female patients, is presented in table 3. In males, the presence of both, moderate or severe OSA, significantly increased the CRP levels compared with no OSA (estimate of 0.33 (0.11–0.55); p=0.003; and 0.71 (0.50–0.92); p<0.001, respectively). However, in females there was a significant difference only when comparing those with severe OSA with those with no OSA (estimate of 0.49 (0.19–0.79); p=0.001). Overall, the value of those estimates was higher for males than females. In the analysis of CRP in relation to menopausal status,

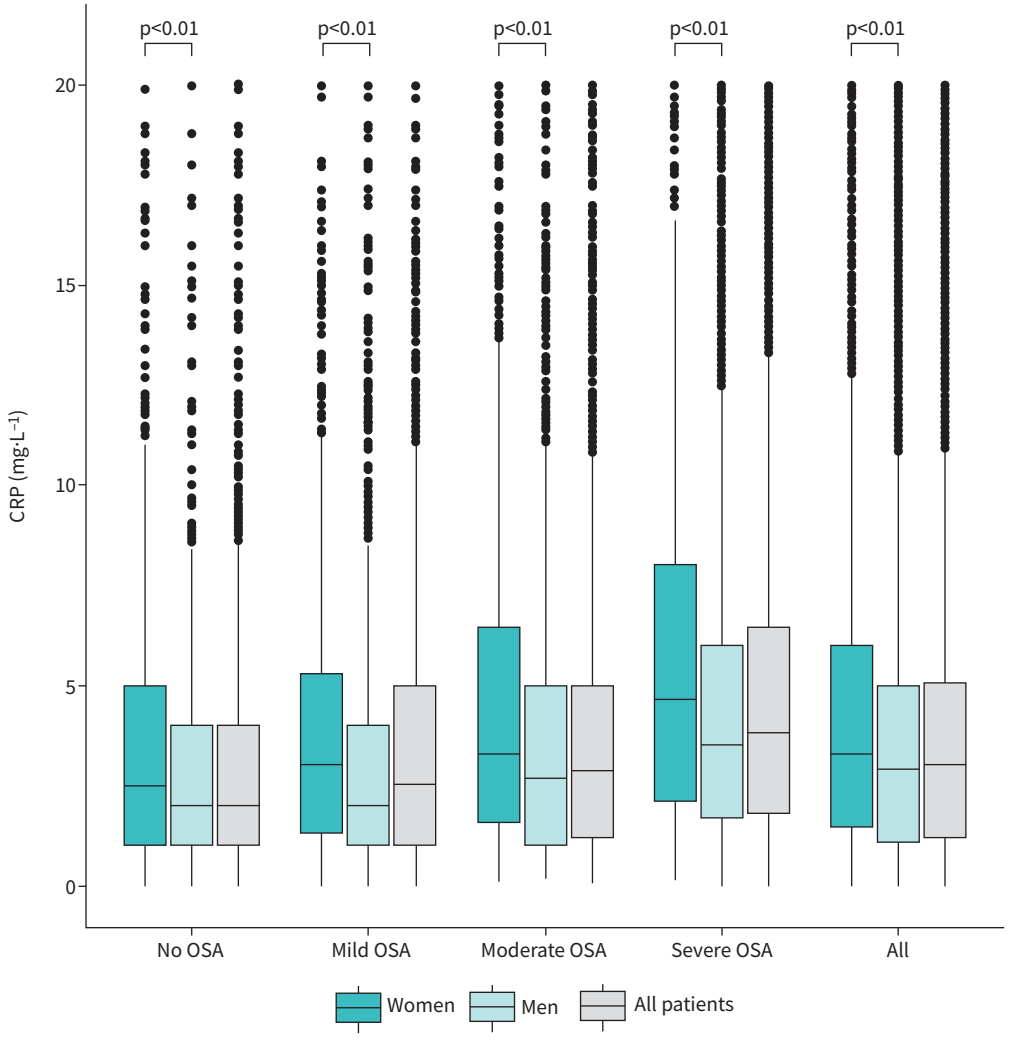

FIGURE 3 Boxplot of C-reactive protein (CRP) values according to sex and severity of obstructive sleep apnoea (OSA). Box-and-whisker plots represent CRP levels (mg·L^{-1}) across apnoea–hypopnoea index (AHI)-based OSA severity categories (no OSA, mild, moderate, severe) and for the overall population ("All"). Boxes indicate the interquartile range (IQR), with the horizontal line representing the median. Whiskers extend to the most extreme data points within 1.5×IQR from the lower and upper quartiles. Values beyond this range are displayed as individual points (outliers). Comparisons across OSA severity categories were assessed using Kruskal–Wallis tests; brackets indicate statistically significant differences (p<0.01). CRP values are plotted on a linear scale to preserve interpretability across the full range of observations.

we could not identify any significant difference in CRP values (3.20 mg·L^{-1} (1.22–6.70) for women under 45 years (n=1176) compared with 3.30 mg·L^{-1} (1.50–6.00) in women older than 55 years (n=2873); p=0.80.

A diagnosis of insomnia was reported in 4.2% of the population (n=762), and CRP values tended to be slightly lower in patients who reported insomnia (2.90 mg·L^{-1} (1.00–5.00)) compared with patients without reported insomnia of 3.00 mg·L^{-1} (1.20–5.00) (n=17 358, 96%); p=0.10.

The association between hypoxic markers of OSA and CRP levels showed consistently a significant dose–response relationship. The second and third tertiles of the ODI4 were associated with elevated CRP levels by 0.68 mg·L^{-1} (0.55–0.81) for ODI 5.8–<40 events per h and 1.8 mg·L^{-1} (1.7–2.0) for ODI ⩾40 events per h; both p<0.001, n=18 031, respectively (supplementary figures S2 and S3 and supplementary table S5). Comparably, the second and third tertile of T90 were associated with marked increased levels of

TABLE 2 Summary of the results of univariable and multivariable weighted linear regression

Characteristic	Univariate analysis			Multivariable analysis		
	β	95% CI	p-value	β	95% CI	p-value
OSA severity			<0.001			<0.001
No OSA	Ref.	Ref.		Ref.	Ref.	
Mild OSA	0.22	0.04–0.39	0.015	0.10	−0.10–0.31	0.23
Moderate OSA	0.55	0.37–0.73	<0.001	0.28	0.07–0.49	0.002
Severe OSA	1.2	1.1–1.4	<0.001	0.60	0.39–0.80	<0.001
Age	0.01	0.00–0.01	0.005	−0.01	−0.01–0.00	<0.001
ESS score	0.03	0.02–0.04	<0.001	0.00	−0.01–0.01	0.84
BMI			<0.001			<0.001
<25 kg·m^{-2}	Ref.	Ref.		Ref.	Ref.	
25–<30 kg·m^{-2}	0.51	0.35–0.68	<0.001	0.53	0.34–0.72	<0.001
30–<35 kg·m^{-2}	1.3	1.2–1.5	<0.001	1.2	0.97–1.36	<0.001
⩾35 kg·m^{-2}	3.1	2.9–3.2	<0.001	2.7	2.45–2.90	<0.001
Smoking	0.30	0.18–0.42	<0.001	0.30	0.16–0.44	<0.001
Sex male	0.77	−0.89– −0.66	<0.001	−0.75	−0.89– −0.61	<0.001
Diabetes mellitus	1.2	1.1–1.4	<0.001	0.55	0.35–0.76	<0.001
Left ventricular hypertrophy	2.0	1.5–2.5	<0.001	1.3	0.61–1.97	<0.001
Systemic hypertension	0.69	0.58–0.79	<0.001	0.09	−0.03–0.21	0.11
Ischaemic heart disease	0.50	0.31–0.69	<0.001	−0.02	−0.25–0.21	0.84
TIA or stroke	0.35	0.00–0.70	0.049	0.14	−0.22–0.49	0.43
Status post-myocardial infarction	0.32	−0.04–0.68	0.082	NA	NA	NA
Cardiac failure	1.0	0.74–1.3	<0.001	0.48	0.11–0.84	<0.001
Other CV comorbidities	0.10	−0.27–0.06	0.21	NA	NA	NA
COPD	1.2	0.98–1.4	<0.001	0.82	0.53–1.11	<0.001
Neurological disease	0.32	0.09–0.55	0.006	0.26	0.03–0.50	0.017
Psychiatric disease	0.33	0.16–0.50	<0.001	0.05	−0.13–0.23	0.53
Inflammatory disease	0.63	0.36–0.91	<0.001	0.59	0.26–0.92	<0.001

CI: confidence interval; OSA: obstructive sleep apnoea; NA: not applicable to variables that were not significant in unvariable analyses and not considered for multivariable analysis; ESS: Epworth sleepiness scale; BMI: body mass index; TIA: transient ischaemic attack; CV: cardiovascular. Ref.: reference category. "Other CV comorbidities" are derived from free text and not captured by the categories above.

CRP by 0.57 mg·L^{-1} (0.41–0.73) for T90 0.8–<51.40 min and 1.9 mg·L^{-1} (1.8; 2.1) for T90⩾51.4 min; both p<0.001, n=12 691, respectively (supplementary figures S4 and S5 and supplementary table S6). The results show that the highest tertiles of these two measures of hypoxic burden had a numerically stronger influence on CRP levels than the highest AHI category (1.8 and 1.9 mg·L^{-1} *versus* 0.58 mg·L^{-1}).

Discussion

Our data derived from the large ESADA cohort demonstrate a robust dose–response relationship between several OSA severity measures and CRP levels, independent of obesity and other frequent cardiometabolic and pulmonary comorbidities. Furthermore, OSA tended to associate with elevated CRP concentration more extensively in men than in women. This unique and large study supports the recognition of OSA as a proinflammatory disease, in particular when OSA is associated with profound hypoxic burden.

A meta-analysis, including 50 studies in adults, showed significantly elevated CRP levels in OSA patients compared with controls [16]. Interestingly, another meta-analysis including 96 studies in adults, concluded different relationships depending on the type of CRP assessment. hsCRP was significantly higher according to OSA severity compared with controls, whereas ls-CRP was not [28]. Our results, exceeding the number of patients analysed in previous meta-analyses, are consistent with the reported findings of the first meta-analysis. The collection and analysis of many confounders allowed the use of the IPTW-RA method to estimate a causal effect on observational data. Even though IPTW-RA is a well-established method to estimate the causal effect of a binary exposure, it is a novel approach to apply an extension of this method for an ordinal exposure [29]. A doubly robust estimator such as IPTW-RA is a well-known causal inference method for observational data, allowing us to account for measured confounders and reducing any mis-specification in the model [30]. Indeed, the robust dose–response relationship between OSA severity measures (event frequency and hypoxic load) and CRP levels established in our dataset further strengthens the causality between OSA and systemic inflammation.

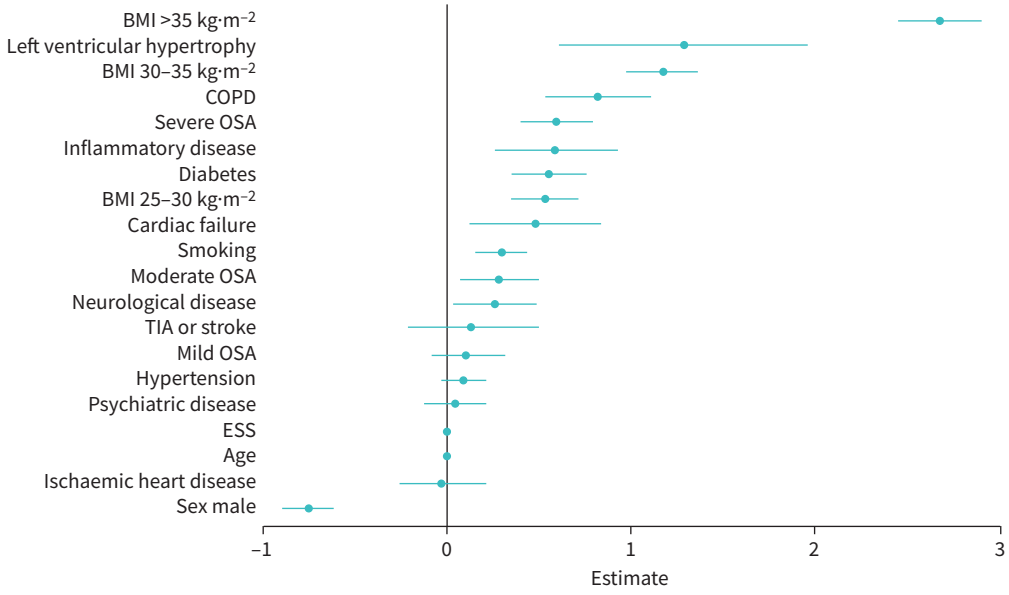

FIGURE 4 Plot of the coefficient estimates of the weighted linear regression explaining C-reactive protein values. BMI: body mass index; TIA: transient ischaemic attack; ESS: Epworth sleepiness scale; OSA: obstructive sleep apnoea. Mild OSA is defined as AHI 5–<15 events per h; moderate OSA as AHI 15–<30 events per h; severe OSA as AHI ⩾30 events per h.

The present study also showed that females had significantly higher CRP levels compared with males, in agreement with other studies [31, 32]. The mean difference in the ESADA population was 0.77 $mg \cdot L^{-1}$, whereas sex differences of 1.5 $mg \cdot L^{-1}$ [32] and 1.13 $mg \cdot L^{-1}$ [31] have been reported elsewhere. In the latter study, the mean difference changed to 0.52 $mg \cdot L^{-1}$ after excluding females using oestrogens and individuals with CRP>10 $mg \cdot L^{-1}$. Thus, the value found in our study has a consistent order of magnitude. Concerning sex differences in inflammation due to OSA, Gaines *et al*. [33] found that males with OSA had a greater proinflammatory profile. This finding is supported by our results demonstrating an independent effect size of severe OSA on median CRP levels, which was 0.71 $mg \cdot L^{-1}$ in males and 0.49 $mg \cdot L^{-1}$ in women; this difference is apparently not influenced by menopausal status. The more pronounced proinflammatory effect of OSA in males may be a result of a higher degree of hypoxia, a longer history of OSA exposure and/or a higher frequency of respiratory events often reported in male compared with female OSA patients. However, more epidemiological and mechanistic studies are needed to better understand these findings.

The sensitivity analysis suggests that hypoxic burden, reflected as intermittent hypoxia in the ODI4 or as sustained hypoxia in the T90 measure, has a very strong influence on CRP levels. This finding is in line

TABLE 3 Subgroup analysis, summary of the weighted linear regression for males and females

	Males; n=13 036		Females; n=5409	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
OSA severity		<0.001		<0.001
No OSA	Ref.		Ref.	
Mild OSA	0.21 (−0.01–0.43)	0.057	−0.18 (−0.47–0.10)	0.21
Moderate OSA	0.33 (0.11–0.55)	0.003	0.24 (−0.06–0.54)	0.12
Severe OSA	0.71 (0.50–0.92)	<0.001	0.49 (0.19–0.79)	0.001

CI: confidence interval; OSA: obstructive sleep apnoea; Ref.: reference category. The model was adjusted on the entire set of covariables but only the coefficients of the variable of interest (*i.e.* OSA severity) are displayed on the table.

with the large body of evidence linking intermittent hypoxia to inflammatory processes [3–5, 12]. The consistency and robustness of this finding further strengthen the overall study results suggesting that OSA and its associated hypoxic burden has a significant and independent contribution to low-degree inflammation.

In our study, morbid obesity was the strongest predictor of CRP levels supporting the importance of elevated BMI as a risk factor for low-grade inflammation and overall CV risk in the OSA population [34]. In this context, the therapy of comorbid obesity is critical to reduce inflammation, in particular in younger individuals. Indeed, two recent randomised trials demonstrated that both lifestyle interventions [35] and pharmacological therapy [36] targeting obesity in OSA cause a significant reduction in inflammatory markers such as CRP.

Strengths and limitations of this study

This study has several strengths. First, it is by far the largest study analysing the link between CRP as a biomarker of systemic inflammation and OSA, with a total of 18 445 patients analysed. Second, the studied population is representative of the European population, and not only of one country or region, which increases the generalisability of the results. In addition, the ESADA cohort has an extended reporting of comorbidities based on detailed data from the patient's medical record, which is important for the confounder assessment in this study [19]. Third, appropriate and advanced causal inference methods to estimate the causal effect of OSA on CRP levels have been applied in this study for the first time. Fourth, multiple sensitivity analyses all show highly conclusive results linking different measures of OSA severity, in particular hypoxia during sleep, to increased inflammation, both in male and female patients. Altogether, our study contributes robust data and significant novelty to the question of whether untreated OSA causes systemic low-grade inflammation.

However, several study limitations need to be recognised. Considerable variability in CRP measurements might have been introduced due to methodological differences between the different centres as well as over the study period over almost one and a half decade. Indeed, there is no annotation in the database on the specific use of the analysis kit and the accreditation of the analysis method in the different hospital clinical laboratories. There is also variability in the measurement of the AHI value in the ESADA [20], as patients were diagnosed with either home sleep apnoea testing (polygraphy or polysomnography) and the manual analysis was performed by multiple scorers over time. The type of sleep test used could not be included in the model because it would have violated the positivity assumption, as some centres only use one type of sleep test procedure. We have overcome this study limitation by the use of "centre" and "year" as random effects in our analysis, implying that scoring and assessment methods were stable over at least 1 year. The robustness of our statistical models despite a rather highly variable CRP analysis methodology may argue for an even stronger true association between OSA and CRP. Another aspect is the fact that a majority of patients in our study are White, a fact that could limit the generalisability of the results to other ethnic groups, as significant race differences exist in the population distribution of CRP [32, 37]. The exact menopausal status in women included in our study has not been captured in the database. However, we applied the separation of age groups <45 years and >55 years as an established method to study the systematic effect of menopausal status. Evidence suggests that OSA severity is significantly more associated with oxidative stress in elderly females when compared with elderly males [38]. However, our sensitivity analysis suggests no significant difference in CRP levels in pre- and post-menopausal women with OSA. Finally, this is an observational study and not a randomised controlled trial (RCT). CRP data were available in 54% of the patients and clinical data were comparable with the remaining individuals without CRP data, suggesting a significant bias to be unlikely. Some unmeasured or even unknown confounders could still influence the results and hence violate the conditional exchangeability assumption for the use of IPTW-RA. However, RCTs have the limitation of inclusion and exclusion of certain patient groups reducing the generalisability of the findings. The use of appropriate causal inference statistical methods appears then to be a favourable solution for such a significant pre-selection problem, even if some limitations remain.

Study implications and future research questions

Our data implicates the need for further future studies on this topic. An interventional study to address the impact of continuous positive airway pressure (CPAP) therapy on CRP concentration during at least 6 months would shed further light on associations and causality. CPAP is known to substantially reduce intermittent hypoxia and sympathetic activation in OSA. Indeed, a recent meta-analysis including randomised trials suggest that CPAP treatment causes beneficial effects on systemic inflammation and CRP levels, but the overall level of evidence was still considered to be limited [39]. There is also evidence suggesting that the ODI may be a better predictor than AHI to assess OSA severity [7, 40]. It would be

also interesting to test the impact of OSA severity metrics such as hypoxic burden [41] or arousal burden [42] on CRP as a marker of low-degree systemic inflammation. Finally, the important question of whether CRP can serve as a potential risk marker for future CV events in OSA, alone or combined with the above-mentioned markers of OSA severity, needs to be addressed in prospective outcome studies within the ESADA and other large-scale cohorts.

Conclusion

Our study showed a dose–response relationship between OSA severity and CRP levels as a biomarker of systemic inflammation in a large prospective cohort using causal inference statistical methods, suggesting a strong relationship between OSA and low-grade inflammation as a potential risk factor for cardiovascular disease. We identified a sex difference, with women having higher overall CRP levels, but men showing a more robust proinflammatory profile related to conventionally determined OSA severity. Obesity and cardiopulmonary comorbidities further increased CRP blood levels in this patient group. Further research is warranted to explore the potential relevance of measuring CRP as prognostic indicator for CV events in OSA.

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