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RESEARCH ARTICLE

C-reactive protein improves the ability to detect hypertension and insulin resistance in mild-to-moderate obstructive sleep apnea: Age effect

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Summary

C-reactive protein (CRP) appears to improve the ability to detect cardiometabolic risk in young and middle-aged adults with mild-to-moderate obstructive sleep apnea (mmOSA). The aim of this study is to assess utility of CRP in identifying the risk of hypertension and insulin resistance across a wide age range including older patients with mmOSA. Adults ($n = 216$) of a wide age range (28–90 years old, mean age 52.64 ± 12.74) with mmOSA ($5 \leq AHI < 30$) completed in-lab polysomnography or home sleep apnea testing, physical examination including blood pressure (BP) measures, structured medical history questionnaire, and blood draw for CRP and fasting glucose and insulin levels. In adults < 60 years, lnCRP but not the apnea–hypopnea index (AHI) was associated with greater odds for hypertension (odds ratio [OR] = 2.40, 95% CI = 1.20–4.84, $p = 0.01$; OR = 1.00, 95% CI = 0.92–1.08, $p = 0.92$, respectively) and with higher average systolic and diastolic BP. Also, in adults < 60 years lnCRP but not AHI, was associated with higher lnHOMA values. In contrast, in adults > 60 years neither lnCRP nor AHI were associated with greater odds for hypertension, average systolic and diastolic BP, and lnHOMA. Receiver-operating characteristics curves revealed that adding CRP to standard clinical factors (age, sex, and BMI) yielded moderately good risk models for hypertension in patients < 60 years (AUC = 0.721). In conclusion, CRP improves the ability to detect cardiometabolic risk in young and middle-aged, but not older adults with mmOSA, suggesting that inflammation may be a primary pathogenetic mechanism in younger patients with OSA.

KEYWORDS
C-reactive protein, HOMA index, hypertension, insulin resistance, sleep apnea

1 | INTRODUCTION

Mild-to-moderate obstructive sleep apnea (mmOSA) is a highly common condition in the general population, with prevalence estimates ranging from 9% to 45% depending on the diagnostic criteria and population studied (Arnardottir et al., 2016; Bixler et al., 2000; Heinzer et al., 2015; Young et al., 1997). Recent longitudinal studies have demonstrated that mmOSA is a significant risk factor for the development of cardiovascular (i.e. hypertension and heart disease) and cerebrovascular disease (i.e., stroke) in young

and middle-aged adults (Vgontzas et al., 2019; Vgontzas, He, et al., 2024).

The utility of inflammatory biomarkers, such as C-reactive protein (CRP), in identifying individuals with mmOSA who are at higher risk for cardiovascular and metabolic complications has been a topic of growing interest (Gaines, Kong, et al., 2017; Huang et al., 2023). CRP, an acute-phase reactant produced by the liver in response to inflammation, was found to be more strongly associated with hypertension and hyperglycaemia compared with the apnea–hypopnea index (AHI) in middle-aged patients with mmOSA (Gaines, Kong, et al., 2017). Also, Gaines et al. showed that incorporating CRP into standard clinical factors yielded moderately good to strong risk prediction models for these cardiometabolic outcomes in mmOSA patients (Gaines, Kong, et al., 2017). In addition, several studies have shown increased plasma levels of other inflammatory biomarkers, i.e., IL-6, TNFa levels in OSA patients (Kritikou et al., 2014; Vgontzas et al., 2000; Vgontzas et al., 2008), whereas one study found an increase in inflammatory markers in pharyngeal lavage but not in plasma (Vicente et al., 2016). Furthermore, several studies have demonstrated that the increased inflammatory markers in OSA are influenced by comorbidities such as cardiovascular disease and obesity (Testelmans et al., 2013; Vgontzas et al., 2000). These findings are consistent with the growing body of evidence suggesting that systemic inflammation plays a key role in the pathogenesis of obstructive sleep apnea (OSA)-related cardiometabolic morbidity (Gaines et al., 2018; Huang et al., 2023; Li et al., 2017; Unnikrishnan et al., 2015; Vgontzas et al., 2005).

While studies have established an association between CRP and cardiometabolic risk in young and middle-aged adults with mmOSA, it is unclear whether this relationship extends to older patients. Given the age-dependent differences in the prevalence and clinical consequences of OSA, it is plausible that the utility of CRP as a biomarker of cardiometabolic risk may vary across different age groups (Bixler et al., 2000; Edwards et al., 2014; Gaines, Kong, et al., 2017; Hoyos et al., 2017; Vgontzas et al., 2019).

Moreover, the complex interplay between ageing, inflammation, and cardiometabolic health further underscores the need to specifically examine the association between CRP, hypertension risk, and insulin resistance in older patients with mmOSA (Ferrucci & Fabbri, 2018).

Therefore, the aim of this study is to investigate whether CRP is associated with hypertension and insulin resistance risk in older patients with mmOSA and to compare the utility of CRP versus AHI in detecting these cardiometabolic risks across a wide age spectrum of these patients. We hypothesise that CRP compared with AHI is more strongly associated with hypertension and insulin resistance and that this association weakens with age.

2 | METHODS

2.1 | Participants

The study sample consisted of 216 middle-aged adults (mean age 52.64 ± 12.74) who were referred to the Sleep Research and Treatment Center, Penn State Health Hershey Medical Center for symptoms consistent with sleep apnea. Patients who met the criteria for mild to moderate obstructive sleep apnea (mmOSA) following an overnight polysomnography (PSG) study ($n = 171$) or home sleep apnea testing (HSAT) ($n = 45$) were consecutively recruited for the study. Mild OSA was defined based on AHI greater than or equal to 5 events/h but less than 15 (5 ≤AHI <15) and moderate OSA based on AHI greater than or equal to 15 events/hour but less than 30 (15≤ AHI <30) events/h. Exclusion criteria included a body mass index (BMI) of >45 (class III obesity, World Health Organization), age <18 years, current use of steroids or anti-inflammatory medications, diagnosis of insulin dependent diabetes, diagnosis of autoimmune disorder, shiftwork and current use of CPAP.

Written informed consents were obtained from all participants. All research protocols were reviewed and approved for compliance with the policy of the human subjects Institutional Review Board at Penn State University College of Medicine.

2.2 | Procedures

2.2.1 | Sleep laboratory protocol

A single-night PSG in a sound-attenuated, light- and temperature-controlled room with a comfortable, bedroom-like atmosphere was performed in 171 participants. Participants were continuously monitored using with 16-channel polygraphs, including electroencephalogram (EEG) with recommended by AASM montage (F4-M1, C4-M1, O2-M1), electrooculogram (EOG), and electromyogram (EMG) (Berry et al., 2020). Respiration was monitored via nasal cannula pressure, thermocouples, thoracic/abdominal strain gauges, and haemoglobin oxygen saturation (SpO_2) was assessed using a pulse oximeter placed on the index finger. Snoring sounds were monitored via a sensor attached to the throat. All data were recorded using Natus Embla NDx amplifiers & SleepWorks PSG Software (version 9). Visual sleep stage scoring was conducted by a registered polysomnography technologist according to standardised criteria (Berry et al., 2020). The apnea–hypopnea index (AHI; number of apneas and hypopneas summed per hour) was ascertained; an apnea was defined as a cessation of airflow with a minimum duration of 10 seconds and an associated out-of-phase strain gauge movement, while a hypopnea was characterised by a reduction of airflow by approximately 50% with an associated decrease in SpO_2 of at least 4%.

Unattended HSAT was performed in 45 participants using a type 3 portable monitor (PM) (Nox-T3, Nox Medical Inc., Reykjavik, Iceland) that can differentiate obstructive from central sleep apneas using nasal pressure, rib cage and abdominal movement signals. During the HSAT, nasal pressure as a surrogate measure of airflow, rib cage and abdominal movement by inductance plethysmography, snoring, body position, activity, and heart rate and oxygen saturation by pulse oximetry were recorded. All home sleep testing recordings were reviewed for validity and interpreted by a board-certified sleep physician.

2.2.2 | Clinical research center (CRC) follow up visit

Patients with mild-to-moderate OSA who agreed to participate in the study were scheduled for a follow up morning visit at CRC for a thorough medical assessment, including history and physical examination, blood pressure measurements, completion of sleep questionnaires and one fasting blood draw. Patients were asked to fast the night before the blood draw. The time interval between the sleep testing and the follow up visit at CRC was less than 2 weeks. Blood pressure was measured using a pneumoelectric microprocessor-controlled instrument with the appropriately sized cuffs. The accuracy of this monitor is reported to be ± 3 mmHg; in addition, internal calibration was performed before each use, and the machine was checked against a mercury sphygmomanometer at least annually. Measurement of blood pressure included three consecutive readings during a 5-min period following 10 minutes of rest in the seated position. Stage 1 hypertension was defined as systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 80 mmHg, stage 2 hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and hypertensive crisis (Stage 3) was defined as systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 120 mmHg (Whelton et al., 2018). Insulin resistance was expressed with the Homeostatic Model Assessment (HOMA) index, according to the formula (fasting plasma glucose times fasting serum insulin) divided by 405 (Matthews et al., 1985). Anthropometric parameters were obtained and the body mass index (BMI) was calculated (in kg/m^2) based on height and weight measured as part of the physical examination.

2.2.3 | Assay procedures

Fasting blood samples were collected in EDTA-containing tubes. Two tubes (3 mL EDTA and 3.5 mL serum separator) were used for analysis of fasting glucose and insulin. One 4 mL EDTA tube was centrifuged (3000 rpm for 10 minutes), aliquoted into cryotubes, and stored at −80°C until processed. CRP with high-sensitivity was measured via enzyme-linked immunosorbent assay (hsCRP) ELISA (R&D Systems, Minneapolis, MN). The intra- and inter-assay coefficients of variation for CRP were 5.5 and 6.5. The lower detection limit for hsCRP was 0.005 pg/mL.

2.3 | Statistical analysis

For comparisons of demographic, sleep, and clinical characteristics between the two age groups (< 60 years vs. ≥ 60 years old), independent sample *t*-tests were employed. Categorical variables were analysed using the Pearson Chi-Square test.

Logistic regression was performed to analyse the association of lnCRP (CRP in natural logarithm) and AHI with hypertension, and systolic/diastolic blood pressure, respectively, in the whole sample, controlling for gender, BMI and age, diabetes, method of sleep recording (PSG vs. HST), alcohol use, and smoking. Additionally, we performed sensitivity analysis, in which we excluded patients on antihypertensive medication.

The association of lnCRP and AHI with insulin resistance indices, i.e., lnHOMA index (HOMA index in natural logarithm) were examined in the whole sample using linear regression analysis controlling for gender, BMI, age, diabetes, method of sleep recording (PSG vs. HST), alcohol use, and smoking. Additionally, we performed similar sensitivity analysis, in which we excluded patients with diabetes/antidiabetic medication use.

To assess the potential effect modification of age in the association of lnCRP and AHI with hypertension, systolic/diastolic blood pressure, and insulin resistance indices, i.e., lnHOMA index, respectively, based on previously reported data we chose a clinically meaningful age cut-off point (< 60 years vs. ≥ 60 years) and repeated the above described analysis stratifying sample by these two age groups (Vgontzas et al., 2019; Vgontzas, He, et al., 2024; Vgontzas, Karagkouni, et al., 2024). Data that were not normally distributed (i.e., CRP, HOMA) were transformed by the natural logarithm before the analyses.

All analyses were performed controlling for the above-mentioned confounders.

Using the binary logistic regression models described above, we compared the probabilities of having hypertension when CRP levels were 0.5 mg/L (normal levels) and 3.0 mg/L ("high risk") in 50-year-old obese ($BMI = 30\ kg/m^2$) men with $AHI = 15$ events/h and women with $AHI = 10$ events/h as well as in 70-year-old obese ($BMI = 30\ kg/m^2$) men with $AHI = 15$ events/h and women with $AHI = 10$ events/h (a lower AHI value was used given that women tend to manifest health comorbidities at lower AHI thresholds).

In addition, we generated area under the receiver-operating characteristics (ROC) curves (AUCs) to evaluate the additive power of CRP and AHI in discriminating those with hypertension and those without. For the hypertension outcome, we evaluated the AUCs for three models: Model 1 included demographics (age, sex, BMI) as independent variables; Model 2 added AHI to Model 1; and Model 3 added CRP to Model 2. The estimated risk scores for hypertension from logistic regression models were used to construct ROC curves.

The statistical significance level selected for all analyses was $p < 0.05$. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM Corp., Armonk, NY), while ROC analyses were performed using R Statistical Software (version 4.2.2).

3 | RESULTS

3.1 | Demographic, clinical, and sleep characteristics

The participants' demographic, clinical, and sleep characteristics are presented in Table 1. Adults < 60 years had a higher BMI and lower systolic BP and AHI compared with adults ≥ 60 years. Adults

TABLE 1 Sociodemographic, sleep, inflammation, and metabolic characteristics of adults with mild-to-moderate obstructive sleep apnea.

	Whole sample ($n = 216$)	Age < 60 year ($n = 145$)	Age ≥ 60 year ($n = 67$)	p
Age (year)	52.64 (12.74)	46.28(9.34)	66.82 (6.11)	<0.01*
Male (%)	56.50	57.70	53.70	0.35
BMI (kg/m^2)	33.16 (5.67)	33.73 (5.58)	31.87 (5.69)	0.03*
AHI (events/h)	13.19 (6.64)	12.41 (6.03)	14.93 (7.60)	0.09
Systolic BP (mmHg)	125.01 (14.27)	121.78 (12.56)	131.96 (15.34)	<0.01*
Diastolic BP (mmHg)	76.45 (9.82)	76.89 (9.09)	75.51 (11.25)	0.34
Normal BP (%)	39.2	44.1	28.4	0.01*
Stage 1 hypertension (%)	42.0	43.4	38.8	0.22
Stage 2 hypertension (%)	18.9	12.4	32.8	<0.01*
Hypertensive crisis (%)	0	0	0	/
Diabetes (%)	9.8	6.7	16.7	0.04*2
Antihypertensive treatment (%)	32	28	40	0.06
LnCRP (mg/L)	1.03 (0.94)	1.09 (0.94)	0.91 (0.92)	0.18
LnHOMA (mg/dL)	0.70 (0.69)	0.72 (0.71)	0.64 (0.62)	0.44

Note: Data presented as mean (SD) or percentage; p = age <60 year vs. age ≥60 year; *p <0.05.
Abbreviations: AHI, apnea–hypoponea index; BMI, body mass index; BP, blood pressure; lnCRP, natural log C-reactive protein; lnHOMA, natural log Homeostatic Model Assessment.

< 60 years vs. adults ≥ 60 years were not different in terms of gender and diastolic BP.

3.2 | AHI versus CRP in detecting hypertension risk in adults with mmOSA

LnCRP, but not AHI, was associated with greater odds for stage 2 hypertension (odds ratio [OR] = 1.99, 95% CI = 1.22–3.25, p < 0.01 and OR = 1.02, 95% CI = 0.96–1.08, $p = 0.53$, respectively). Furthermore, lnCRP was associated with a higher average systolic ($\beta = 3.15$, p < 0.01) and diastolic BP ($\beta = 2.26$, $p = 0.02$) but not with AHI ($\beta = 0.10$, $p = 0.47$; $\beta = 0.07$, $p = 0.48$, respectively). In the sensitivity analysis, in which we excluded patients with hypertension, the results did not change.

3.3 | AHI versus CRP in detecting hypertension risk in adults with mmOSA aged < 60 years versus adults with mmOSA aged ≥ 60 years

In adults aged < 60 years, lnCRP, but not AHI, was associated with greater odds for stage 2 hypertension (odds ratio [OR] = 2.40, 95% CI = 1.20–4.84, $p = 0.01$ and OR = 1.00, 95% CI = 0.92–1.08, $p = 0.92$, respectively). In adults aged ≥ 60 years, neither lnCRP nor AHI were associated with stage 2 hypertension (OR = 1.59, 95% CI = 0.80–3.18, $p = 0.19$ and OR = 1.01, 95% CI = 0.93–1.10, $p = 0.74$, respectively). According to these models, a "typical" obese (BMI = 30 kg/m^2), middle-aged (50 years) man with AHI = 15 has a 4-fold higher relative risk of having hypertension if their CRP = 3.0 mg/L ("at risk" levels) compared with if their CRP = 0.5 mg/L (healthy levels). Similarly, an obese, middle-aged woman with AHI = 10 has a 4.4 higher relative risk of having hypertension if their CRP = 3.0 mg/L compared with if their CRP = 0.5 mg/L (Figure 1a). In contrast, in a "typical" obese (BMI = 30 kg/m^2), elderly (70 years) man with AHI = 15 as well as in an obese, elderly woman with AHI = 10, the relative risk of hypertension increases by only 1.5 or 2 times, respectively, if their level of CRP = 3.0 mg/L ("at risk" levels) compared with if their CRP = 0.5 mg/L (healthy levels) (Figure 1b).

Furthermore, in adults aged < 60 years old, lnCRP was associated with greater average systolic ($\beta = 2.79$, $p = 0.03$) and diastolic BP ($\beta = 2.26$ $p = 0.02$), while AHI was not ($\beta = 0.95$, $p = 0.59$; $\beta = -0.04$, $p = 0.75$, respectively). However, in adults ≥ 60 years, neither lnCRP nor AHI were associated with greater systolic ($\beta = 2.61$, $p = 0.20$; $\beta = -0.00$, $p = 0.99$, respectively) or diastolic BP ($\beta = 0.10$, $p = 0.49$; $\beta = -1.18$, $p = 0.30$, respectively).

3.4 | AHI versus CRP in detecting insulin resistance risk in adults with mmOSA

LnCRP, but not AHI, was associated with a greater lnHOMA index in the whole sample ($\beta = 0.11$, $p = 0.03$; $\beta = 0.01$, $p = 0.42$, respectively). In sensitivity analysis, in which we excluded patients with diabetes, the results did not change.

3.5 | AHI versus CRP in detecting insulin resistance risk in adults with mmOSA aged < 60 years versus adults with mmOSA aged ≥ 60 years

In adults aged < 60 years, lnCRP, but not AHI, was associated with a greater lnHOMA index ($\beta = 0.13$, $p = 0.05$; $\beta = 0.00$, $p = 0.47$, respectively). In adults ≥ 60 years, neither lnCRP nor AHI were

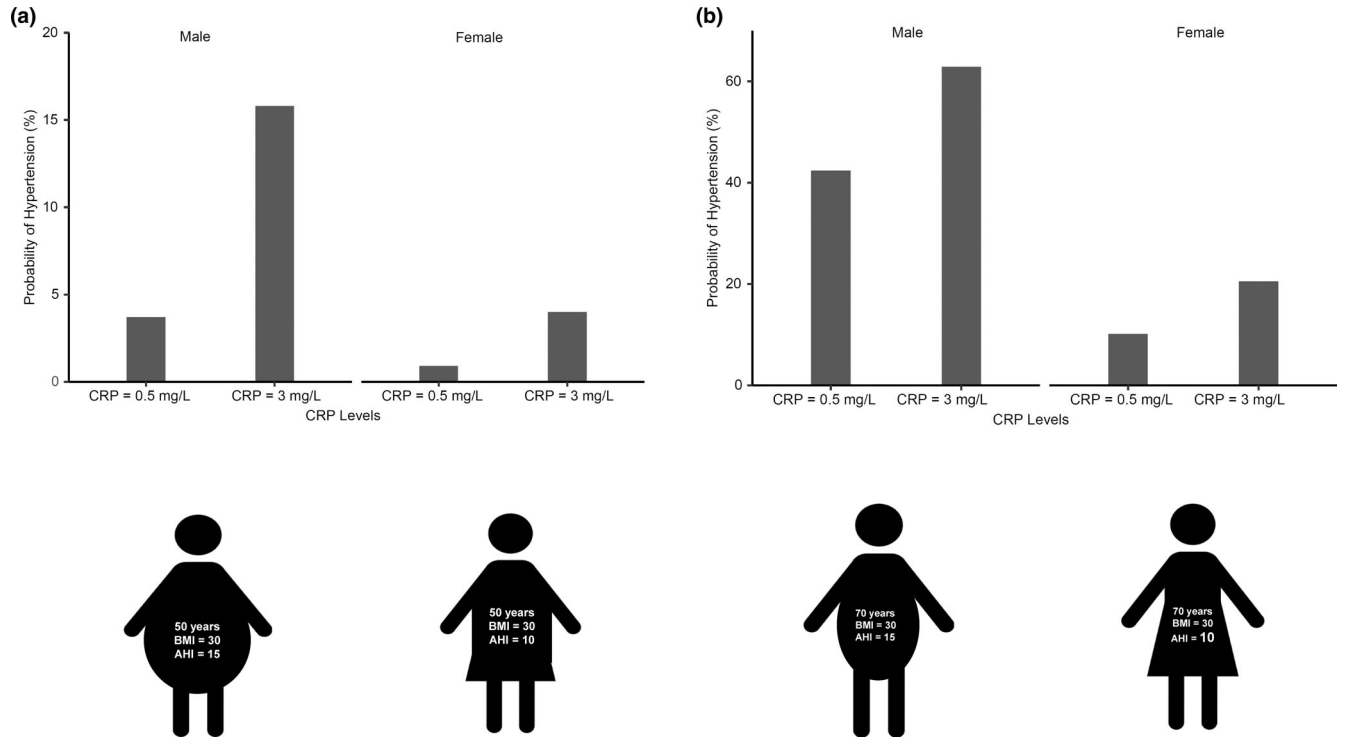

FIGURE 1 Probabilities of stage 2 hypertension in "typical" obese, middle-aged men and women (50 years old) with mild-to-moderate OSA (a) and in "typical" obese, elderly men and women (70 years old) with mild-to-moderate OSA (b) when CRP levels are in the healthy (0.5 mg/L) versus "at-risk" (3.0 mg/L) range.

associated with a greater lnHOMA index ($\beta = 0.05$, $p = 0.58$; $\beta = 0.00$, $p = 0.67$, respectively). In sensitivity analysis, in which patients with diabetes were excluded, the results did not change.

3.6 | Additive discriminative ability of AHI and CRP in detecting hypertension in adults with mmOSA aged < 60 years versus adults with mmOSA aged ≥ 60 years

We then constructed ROC curves (Figure 2) to assess the cumulative ability of demographics, AHI, and CRP to detect stage 2 hypertension. In adults < 60 years, the AUC for the model including only age, sex, and BMI (Model 1) was 0.597 (95% confidence interval [CI = 0.466–0.729]). Incorporating AHI into the model (Model 2) yielded an AUC of 0.603 (95% CI = 0.462–0.744), while adding CRP (Model 3) increased the AUC to 0.721 (95% CI =0.639–0.865), creating a moderately good model, and almost significantly superior compared with Model 1 ($p = 0.06$; Table 2; Figure 2a). In adults ≥ 60 years, the AUC for the model including demographics (Model 1) was 0.752 (95% CI = 0.639–0.865). Incorporating into the model AHI [Model 2, AUC = 0.769 (95% CI = 0.654–0.884)] and CRP [Model 3, AUC = 0.802 (95% CI = 0.697–0.907)] did not improve the discriminative accuracy compared with Model 1 (Table 2; Figure 2b).

4 | DISCUSSION

The primary findings of this study are: (a) CRP is a stronger predictor of higher blood pressure levels, stage 2 hypertension and insulin resistance in patients with mmOSA than AHI and (b) this association is stronger in young and middle-aged adults compared with older patients with mmOSA. Also, adding CRP to standard clinical measures such as age, gender and BMI results in good risk models in predicting stage 2 hypertension in young and middle-aged individuals suffering from mmOSA. These findings suggest that including a CRP measure improves the ability for clinicians to detect patients with mmOSA with cardiometabolic risk in this age spectrum. Furthermore, from a mechanistic point, it appears that inflammation may be a primary pathogenetic mechanism in mmOSA among young and middle-aged adults, but not in older ones.

The primary findings of the study suggest that CRP is a strong predictor of cardiometabolic sequelae only in young and middle aged obese and non-obese patients. A previous preliminary study showed that CRP levels were significantly associated with hypertension and hyperglycaemia compared with AHI in 60 research participants with mmOSA (Gaines, Kong, et al., 2017). However, the participants in that prior study were middle aged and predominantly non-obese, restricting the generalisability of its results. The current study included patients of a wide age range and BMI, including those with and without obesity, and recruited from a multidisciplinary sleep centre,

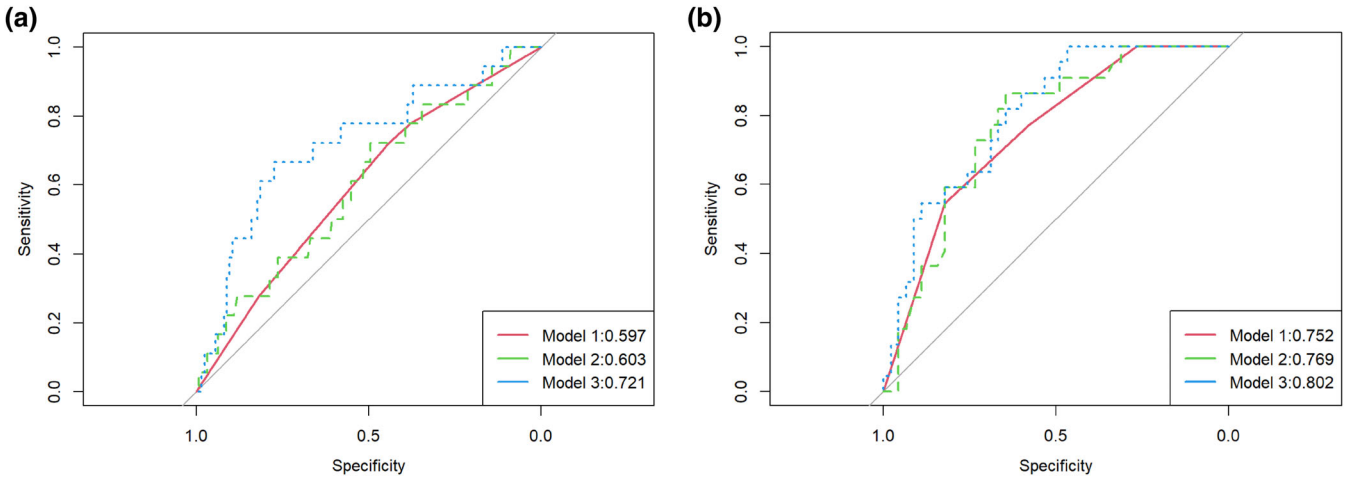

FIGURE 2 Receiver operating characteristics (ROC) curves for detecting stage 2 hypertension in adults < 60 years (a) and in adults ≥ 60 years (b). Final models (Model 3; age, sex, BMI, AHI, CRP) are represented by short dashed lines (- - - -). Long dashed lines (— — —) represent Model 2 (age, sex, BMI, AHI) as independent variables, while solid lines (———) represent Model 1 (age, sex, BMI). Hypertension defined as ≥ 140 mmHg systolic blood pressure or ≥ 90 mmHg diastolic blood pressure.

TABLE 2 Area under the ROC curves comparing AHI and CRP in identifying stage 2 hypertension in adults < 60 vs. > 60 years with mmOSA.

	AUC (95% CI)
Hypertension in adults aged < 60 years ($n = 149$)	
Age, sex, BMI	0.597 (0.466–0.729)
Age, sex, BMI, AHI	0.603 (0.462–0.744)
Age, sex, BMI, AHI, lnCRP	0.721 (0.585–0.857)
Hypertension in adults aged ≥ 60 years ($n = 67$)	
Age, sex, BMI	0.752 (0.639–0.865)
Age, sex, BMI, AHI	0.769 (0.654–0.884)
Age, sex, BMI, AHI, lnCRP	0.802 (0.697–0.907)

Note: Stage 2 hypertension defined as ≥ 140 mmHg systolic blood pressure or ≥ 90 mmHg diastolic blood pressure.
Abbreviations: AHI, apnea–hypopnea index; AUC, area under the curve; BMI, body mass index; CI, confidence interval; lnCRP, natural log C-reactive protein; mmOSA, mild to moderate obstructive sleep apnea; ROC, receiver operating characteristics.

making its results applicable to patients with mmOSA typically evaluated in sleep clinics in the USA.

In line with the findings of the current study, two earlier studies from the Penn State Child Cohort (PSCC) demonstrated that the association between inflammation, visceral adiposity, and OSA is present as early as adolescence and that inflammation may precede the development of OSA in this age group (Gaines et al., 2016; Gaines, Vgontzas, et al., 2017). Specifically, in a PSCC cross-sectional study visceral fat was significantly elevated in adolescents with moderate OSA, particularly in boys, and the levels of the inflammatory markers such as interleukin-6 (IL-6), CRP, and leptin were highest in this group (Gaines et al., 2016). Importantly, mediation analysis revealed that a significant portion of the association between visceral fat and OSA in this group of adolescents was mediated by IL-6 (42%) and CRP (82%). Building upon these findings, Gaines et al. in a longitudinal study demonstrated that increases in CRP from childhood to adolescence predicted the severity of OSA in adolescent boys (Gaines, Vgontzas, et al., 2017). These findings collectively suggest that inflammation, as indicated by elevated CRP levels, may be a primary pathogenetic factor of cardiometabolic risk in middle-aged adults, a risk that is worsened by the pathophysiological changes of OSA per se (i.e., hypoxia and sleep fragmentation).

Two recent studies by Huang et al. provide further insight into the association between inflammation and OSA risk (Huang et al., 2021; Huang et al., 2023). In their first report, Huang et al. demonstrated that CRP levels are associated with incident OSA in a multi cohort study (Huang et al., 2021). In their second report, using a genetic approach with a 49-SNP polygenic risk score for CRP as an instrumental variable, the authors reported that genetically predicted higher CRP levels were associated with a 40% increased risk of OSA associated with EDS, but not with OSA-alone or OSA without EDS (Huang et al., 2023). Furthermore, interventional studies conducted by Chirinos et al. showed that the combination of CPAP (continuous positive airway pressure) therapy and weight loss, rather than CPAP alone, led to significant improvements in CRP, insulin resistance, triglyceride levels, and central systolic pressure (Chirinos et al., 2014; Jain et al., 2017). Also, a systematic review of randomised controlled trials showed that CPAP treatment alone failed to improve inflammatory and metabolic markers in OSA patients (Jullian-Desayes et al., 2015). These findings collectively suggest that chronic inflammation may be causally related to the development of an OSA phenotype characterised by increased cardiometabolic risk and EDS, highlighting the potential role of inflammation in the pathogenesis of this clinically significant OSA subtype.

The present study's findings of a stronger association between CRP levels and increased risk of hypertension and insulin resistance in middle-aged adults with mmOSA than in older adults, provide further

evidence for the existence of age-dependent OSA phenotypes and are consistent with a recent study based on the Multi-Ethnic Study of Atherosclerosis (MESA) and two earlier studies from the Sleep Heart Health Study (SHHS) (Gaines et al., 2018; Geovanini et al., 2018; Haas et al., 2005; Newman et al., 2001). In MESA, stronger associations between AHI and higher total white blood cell count, a marker of inflammation, and glucose concentrations were observed in middle-aged than in older individuals (Geovanini et al., 2018). In two reports based on SHHS, the associations between the respiratory disturbance index and various cardiovascular disease risk factors, including blood pressure, lipid levels, and glucose metabolism were stronger in young and middle-aged adults compared with older adults and increasing AHI was significantly associated with higher odds of systolic/diastolic hypertension in those aged < 60 years but not in those aged ≥ 60 years (Newman et al., 2001; Haas et al., 2005).

It has been suggested that OSA in older adults is more strongly associated with changes in pharyngeal pressure under hypotonic conditions and differences in airway collapsibility, loop gain, upper airway muscle responsiveness, and respiratory arousal threshold, whereas OSA in young and middle-aged individuals is more closely linked to metabolic syndrome (Edwards et al., 2014; Gaines et al., 2018; Kirkness et al., 2008). The lack of association between CRP levels and cardiometabolic risk factors in older adults with mmOSA is consistent with previous studies showing that the association between OSA and hypertension, coronary heart disease, heart failure, and mortality is weaker or even non-significant in the elderly compared with young and middle-aged individuals (Bixler et al., 2000; Gottlieb et al., 2010; Kirkness et al., 2008; Lavie & Lavie, 2009; Vgontzas et al., 2019; Vgontzas, He, et al., 2024; Vgontzas, Karagkouni, et al., 2024). In contrast, the strong association between CRP levels and cardiometabolic risk in middle-aged adults with mmOSA highlights the role of inflammation as a key pathogenetic mechanism in this age group. It has been proposed that visceral obesity and insulin resistance determined by genetic, constitutional, and environmental factors are the principal culprits leading to OSA and these associations may be driven by a chronic, low-grade inflammatory state (Gaines et al., 2018; Vgontzas et al., 2005). In turn, visceral obesity and inflammation may lead to upper airway narrowing, respiratory muscle fatigue, and decreased dilator muscle contraction (Gaines et al., 2018; Vgontzas et al., 2005). Taken together, these findings support the notion that OSA in older age is a distinctly different phenotype than in the young, and that differential diagnosis, prognosis, and treatment options should be considered in this population.

The present study has clinical implications for the management of mmOSA. The findings suggest that age-specific approaches to risk stratification may be necessary to optimise patient outcomes (Gaines, Kong, et al., 2017; Vgontzas et al., 2019; Vgontzas, He, et al., 2024; Vgontzas, Karagkouni, et al., 2024). In young and middle-aged adults with mmOSA, incorporating CRP measurement in addition to standard clinical factors and AHI may improve the identification of individuals at higher risk for hypertension, insulin resistance, and other cardiometabolic complications. In contrast, the lack of association between CRP, AHI, and cardiometabolic risk factors in older adults with mmOSA suggests that different factors may be more relevant in predicting cardiometabolic risk in this population (Vgontzas et al., 2019; Vgontzas, He, et al., 2024).

Several limitations of the present study should be acknowledged. First, the cross-sectional design precludes establishing causal relationships between CRP, AHI, and cardiometabolic risk factors. Longitudinal studies are needed to further elucidate the temporal relationship between inflammation, mmOSA, and cardiometabolic morbidity. Second, the study did not assess the potential influence of other inflammatory biomarkers or cytokines on the relationship between mmOSA and cardiometabolic risk factors. Future studies should consider evaluating a broader panel of inflammatory biomarkers to gain a more comprehensive understanding of the complex interplay between inflammation and cardiometabolic risk in mmOSA. Third, while we controlled for several potential confounding factors, residual confounding cannot be ruled out entirely. Factors such as physical activity and genetic predisposition may influence both OSA and cardiometabolic metabolic health but were not fully accounted for in our analyses. Fourth, we were not able to assess blood pressure in the home setting, thus, white coat or masked hypertension could had been classified as hypertension or normal blood pressure, respectively. Fifth, while our findings suggest age-dependent associations between OSA and metabolic syndrome components, the specific age cutoff of 60 years should be interpreted with caution. The transition in these relationships is likely gradual rather than abrupt, and future studies may benefit from examining finer age categories. Finally, the subgroup analysis was post hoc analysis, so sample size calculation was not performed a priori, which affects generalisability of our findings.

5 | CONCLUSION

In conclusion, the present study demonstrates that CRP, but not AHI, is associated with a greater risk of both hypertension and insulin resistance in adults with mmOSA younger than 60 years, while neither CRP nor AHI are associated with these cardiometabolic risk factors in adults older than 60 years. These findings highlight the age-dependent differences in the relationship between, inflammation, and cardiometabolic dysfunction and mmOSA, and underscore the potential utility of CRP as a biomarker for identifying younger individuals with mmOSA at increased risk for hypertension and insulin resistance. Finally, these findings support the age dependent phenotyping of sleep apnea based on differential pathophysiological pathways, clinical impact and possible differential treatment response.

AUTHOR CONTRIBUTIONS

Slobodanka Pejovic: Data curation; methodology; writing – review and editing; writing – original draft; formal analysis; conceptualization. **Yimeng Shang:** Writing – review and editing; formal analysis; data curation. **Alexandros N. Vgontzas:** Conceptualization; investigation; funding acquisition; writing – original draft; methodology; validation; visualization; writing – review and editing; project administration; supervision. **Julio Fernandez-Mendoza:** Data curation; writing – review and editing;

methodology. **Fan He:** Data curation; writing – review and editing. **Yun Li:** Data curation; writing – review and editing. **Lan Kong:** Data curation; writing – review and editing; validation; formal analysis.

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CONFLICT OF INTEREST STATEMENT

All authors have nothing to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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