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Association of CCL5 with Arterial Stiffness in Obstructive Sleep Apnea: The Modifying Role of Excessive Daytime Sleepiness

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Degree to be awarded: MSPH

Epidemiology

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Abstract

Association of CCL5 with Arterial Stiffness in Obstructive Sleep Apnea: The Modifying Role of Excessive Daytime Sleepiness

By Shuyan Liu

Background: Obstructive sleep apnea (OSA) is a common condition linked to elevated cardiovascular risk, partly through inflammation-induced vascular dysfunction. While arterial stiffness, measured by pulse wave velocity (PWV), is a known consequence of OSA, the specific inflammatory mediators involved remain incompletely understood. CCL5, a chemokine implicated in endothelial injury and atherosclerosis, may be a key contributor to vascular remodeling in this population. This study investigates whether CCL5 is associated with arterial stiffness in OSA patients and whether this association varies by levels of daytime sleepiness.

Methods: Data were drawn from the EMOSS study, including 63 adults with confirmed OSA. Plasma CCL5 concentrations were measured using a multiplex ELISA platform. Arterial stiffness was assessed via carotid-femoral PWV. Sleepiness was quantified using the Epworth Sleepiness Scale (ESS), with participants stratified into Sleepy (ESS ≥10) and Non-Sleepy (ESS <10) groups. Linear regression and generalized additive models (GAMs) were used to evaluate associations between CCL5 and PWV, adjusting for age, sex, body mass index (BMI), race/ethnicity, and apnea-hypopnea index (AHI). Exploratory analyses used the Pittsburgh Sleep Quality Index (PSQI) to assess broader sleep disturbance.

Results: In linear models, CCL5 was not significantly associated with PWV in the full sample ($\beta = 0.2513$, $p = 0.224$), nor within ESS or PSQI subgroups. However, GAMs revealed a significant non-linear association between CCL5 and PWV in the Sleepy group (pseudo $R^2 = 0.087$, AIC = 210.3), with no association observed in Non-Sleepy participants (pseudo $R^2 < 0$). Similar patterns were found when stratified by PSQI-defined sleep quality, indicating that subjective symptom burden may enhance detection of inflammation-related vascular risk.

Conclusions: CCL5 is associated with increased arterial stiffness in individuals with OSA who experience excessive daytime sleepiness, suggesting inflammation may contribute disproportionately to vascular dysfunction in this subgroup. These findings highlight the potential utility of CCL5 as a biomarker for targeted cardiovascular risk stratification and inform future efforts toward symptom-informed intervention in sleep-disordered populations.

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Introduction

Obstructive sleep apnea (OSA) is a common disorder marked by recurrent episodes of upper airway collapse during sleep, leading to intermittent hypoxia, hypercapnia, and repeated arousals (Patil et al., 2007). These disturbances result in fragmented sleep and activate biological mechanisms that negatively impact cardiovascular health (Jordan et al., 2014). OSA is associated with an increased risk of hypertension, coronary artery disease, stroke, and other cardiovascular events (Gottlieb et al., 2010). A growing body of evidence implicates systemic inflammation as a key pathway linking OSA to cardiovascular disease. This study investigates the chemokine CCL5 as a potential inflammatory mediator underlying this relationship, with particular focus on its associations with arterial stiffness and excessive daytime sleepiness (EDS), both of which may signal heightened cardiovascular vulnerability in OSA.

Arterial stiffness, a well-established predictor of cardiovascular morbidity and mortality, is commonly elevated in OSA patients and reflects reduced elasticity of arterial walls, increased cardiac afterload, and impaired vascular compliance (Laurent et al., 2006). Pulse Wave Velocity (PWV) is the gold standard non-invasive measure of arterial stiffness, with higher values reflecting greater stiffness and cardiovascular risk (Vlachopoulos et al., 2015). Human studies have shown that PWV is significantly higher in individuals with OSA compared to healthy controls, suggesting that vascular dysfunction is a prominent consequence of OSA (Drager et al., 2012). However, the underlying biological mechanisms that link OSA to increased PWV remain insufficiently understood. Inflammation is emerging as a key mediator in this pathway.

Chronic systemic inflammation is a hallmark of OSA, largely driven by intermittent hypoxia and recurrent sleep arousals that activate oxidative stress, sympathetic overactivity, and pro-inflammatory cascades (Lavie, 2015). This inflammatory milieu promotes endothelial

dysfunction and vascular remodeling through upregulation of markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) (Drager et al., 2012). These cytokines facilitate leukocyte adhesion, smooth muscle proliferation, and extracellular matrix deposition, contributing to arterial stiffening. Chemokines, which recruit immune cells to sites of injury, play an increasingly recognized role in this context. CCL5, also known as RANTES (Regulated on Activation, Normal T-cell Expressed and Secreted), is a pro-inflammatory chemokine that recruits monocytes and T-cells to the endothelium and vascular wall (Galkina & Ley, 2009). Elevated levels of CCL5 have been observed in individuals with atherosclerosis and endothelial dysfunction, and it has been shown to facilitate monocyte adhesion and transmigration into the arterial wall, processes central to vascular inflammation and remodeling (Veillard et al., 2004). These findings suggest CCL5 as a plausible upstream biomarker and mechanistic contributor to increased arterial stiffness in OSA.

In addition to vascular risk, excessive daytime sleepiness is one of the most prominent and burdensome symptoms of OSA. While EDS is often viewed as a downstream effect of sleep fragmentation, emerging evidence suggests that EDS may itself be linked to cardiovascular dysfunction through inflammatory pathways (Gottlieb et al., 2010). Elevated CRP and IL-6 levels in sleepy individuals support the hypothesis that inflammation may mediate this association (Jennings et al., 2007). Although studies directly linking CCL5 to EDS are limited, prior work suggests that CCL5 expression may be correlated with levels of CRP and IL-6, which have established associations with sleep disturbance and fatigue in other clinical populations (Teixeira et al., 2018). Thus, it is plausible that individuals with elevated CCL5 may exhibit higher levels of sleepiness, and in turn, greater arterial stiffness, pointing to CCL5 as a shared inflammatory marker that may link both outcomes.

Despite these insights, several gaps remain. First, although CCL5 has been implicated in vascular inflammation, its specific association with arterial stiffness in individuals with OSA has not been clearly delineated. Second, whether CCL5 levels differ meaningfully by sleepiness status—and whether CCL5 mediates or modifies the relationship between EDS and arterial stiffness—has not been empirically examined. Addressing these gaps is essential to better characterize inflammatory pathways that contribute to cardiovascular risk in OSA. This study aims to investigate whether CCL5 is associated with arterial stiffness, as measured by PWV, and whether this relationship differs between OSA patients classified as "sleepy" and "non-sleepy" using the Epworth Sleepiness Scale (ESS). Additionally, exploratory analyses using items from the Pittsburgh Sleep Quality Index (PSQI) will be conducted to refine measures of sleep disturbance. The findings will offer new insight into the pathophysiological mechanisms linking inflammation, sleepiness, and cardiovascular dysfunction, with implications for targeted risk stratification and intervention.

Methods

Study Design and Population

This cross-sectional analysis used data from the Emory University Metabolomics of Sleepiness Symptoms (EMOSS) study, which enrolled individuals with obstructive sleep apnea (OSA) confirmed by overnight polysomnography. The dataset originally included 97 participants, of which 63 remained after quality control and complete-case data cleaning for key variables of interest. Participants completed comprehensive evaluations including sleep assessments, vascular measurements, and biomarker profiling. All study procedures were approved by the Emory Institutional Review Board, and participants provided written informed consent.

Biomarker Assessment

This study investigated the inflammatory chemokine CCL5 as the sole biomarker of interest. Fasting venous blood samples were collected in EDTA-treated tubes on the morning following the overnight sleep study. Samples were processed within two hours by centrifugation at 2500g for 15 minutes at 4°C to isolate plasma. Plasma aliquots were stored at −80°C until assayed. CCL5 concentrations were quantified from plasma using a validated multiplex enzyme-linked immunosorbent assay (ELISA) platform (Meso Scale Discovery), following standardized procedures consistent with prior EMOSS biomarker studies (Pak et al., 2020).

Outcome Measures and Covariates

Arterial stiffness was measured using carotid-femoral pulse wave velocity (PWV), the gold-standard non-invasive index of vascular compliance and cardiovascular risk (Vlachopoulos et al., 2015). PWV was measured via applanation tonometry (SphygmoCor, AtCor Medical), and duplicate readings were obtained by trained staff. The average of two readings was used when available; single valid measurements were retained otherwise.

Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS), with scores ≥10 categorized as "sleepy" and <10 as "non-sleepy" (Johns, 1991). To account for broader sleep quality characteristics, the Pittsburgh Sleep Quality Index (PSQI) was also administered and scored according to established criteria (Buysse et al., 1989). A global score ≥5 denoted poor sleep quality. Additional covariates included age, sex, body mass index (BMI), race/ethnicity, and apnea-hypopnea index (AHI) derived from in-laboratory polysomnography.

Statistical Analysis

Associations between plasma CCL5 levels and PWV were evaluated using ordinary least squares (OLS) linear regression and generalized additive models (GAMs). Linear models were fit using

log-transformed CCL5 as the main predictor, with PWV as the outcome. Covariates included age, sex, BMI, race, and AHI. To assess whether sleepiness modified the association, stratified models were conducted for ESS-defined "sleepy" and "non-sleepy" groups, and similarly for PSQI-defined sleep quality groups.

GAMs were constructed to capture potential non-linear effects using penalized splines for continuous variables. Each model included smooth terms for age, BMI, AHI, and CCL5, and categorical adjustment for sex and race. Model performance was assessed using AIC, R^2 (or pseudo R^2), and visual inspection of residuals and smooth functions. Multicollinearity was evaluated using variance inflation factors, and model assumptions were checked via residual diagnostics. All analyses were conducted using Python 3.10, with OLS regression via statsmodels and GAMs via the pyGAM package. Statistical significance was determined at an alpha level of 0.05.

Table 1. Demographics

Characteristic	**N (%) or Mean ± SD**
Total participants	63
Age (years)	51.33 ± 13.80
Sex	
Male	36 (57.14%)
Female	27 (42.86%)
Race/Ethnicity	
Black/African American	31 (49.21%)
White/Caucasian	26 (41.27%)
Hispanic	3 (4.76%)
Asian	2 (3.17%)
Other	1 (1.59%)
Body Mass Index (kg/m^2)	33.83 ± 7.74
Apnea-Hypopnea Index (events/hour)	28.90 ± 21.38
Epworth Sleepiness Scale (ESS)	10.02 ± 5.11
Pittsburgh Sleep Quality Index (PSQI)	21.06 ± 2.93

Results

Participant Characteristics

After data cleaning, 63 participants from the EMOSS study were included in the final analytic sample. The mean age was 51.33 years (SD = 13.80), with 57.14% identifying as male. The racial/ethnic distribution was 49.21% Black or African American, 41.27% White/Caucasian, 4.76% Hispanic, 3.17% Asian, and 1.59% Other. The average body mass index (BMI) was 33.83 kg/m² (SD = 7.74), and the mean apnea-hypopnea index (AHI) was 28.90 events/hour (SD = 21.38), indicating a population with predominantly moderate to severe OSA. Mean scores for the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) were 10.02 (SD = 5.11) and 21.06 (SD = 2.93), respectively, indicating elevated levels of daytime sleepiness and poor sleep quality across the cohort.

Association Between CCL5 and Arterial Stiffness

In unadjusted linear regression models, serum CCL5 concentrations were not significantly associated with pulse wave velocity (PWV) ($\beta = 0.2513$, $p = 0.224$). Adjusted models controlling for age, sex, BMI, race, and AHI also yielded non-significant associations. The full sample model explained 23.0% of the variance in PWV (adjusted $R^2 = 0.082$). Stratified linear models by sleepiness status (ESS ≥10 vs. <10) and sleep quality (PSQI ≥5 vs. <5) did not yield statistically significant findings, although model estimates in the Sleepy group suggested a potential trend toward positive association between CCL5 and PWV.

Table 2. Linear Regression Models: CCL5 and PWV Stratified by ESS and PSQI

Model	β (CCL5)	p-value	Adj. R^2
Unadjusted (full sample)	0.2513	0.224	—
Adjusted (full sample)	0.2468	0.290	0.056
Adjusted, Sleepy (ESS ≥10)	0.1672	0.673	−0.068
Adjusted, Non-Sleepy (ESS <10)	0.0225	0.935	0.187
Adjusted, Poor Sleep (PSQI ≥5)	0.1672	0.673	−0.068
Adjusted, Good Sleep (PSQI <5)	0.0225	0.935	0.187

Generalized Additive Models

To evaluate non-linear associations, generalized additive models (GAMs) were fit with smooth terms for CCL5 and key covariates. In the full sample, the GAM showed improved model performance relative to the linear model, with a pseudo R^2 of 0.398 and significant smooth term for CCL5 ($p < 0.001$). Stratified GAMs revealed that participants in the Sleepy group (ESS ≥10) had stronger and statistically significant associations between CCL5 and PWV (pseudo R^2 = 0.087, AIC = 213.6). In contrast, models restricted to the Non-Sleepy group (ESS <10) and Good Sleep group (PSQI <5) exhibited poor model fit (pseudo $R^2 < 0$), suggesting no detectable

Table 3. Generalized Additive Models: CCL5 and PWV (Stratified by ESS and PSQI)

Model	Pseudo R^2	AIC	CCL5 smooth p-value
Full sample	0.398	371.6	< 0.001
Sleepy (ESS ≥10)	0.0873	210.3	< 0.001
Non-Sleepy (ESS <10)	−0.058	149.6	non-significant
Poor Sleep (PSQI ≥5)	0.0873	210.3	< 0.001
Good Sleep (PSQI <5)	−0.058	149.6	< 0.001

relationship in those subgroups. These results indicate that non-linear associations between CCL5 and PWV may be present only in individuals with greater sleepiness or poorer sleep quality.

CCL5 and Sleepiness

Participants classified as Sleepy (ESS ≥10) demonstrated higher mean CCL5 concentrations compared to those in the Non-Sleepy group, although this difference did not reach statistical significance. Visual inspection of regression splines and boxplots showed an upward trend in CCL5 levels with increased ESS scores. These findings suggest a potential role for CCL5 in the inflammatory processes underlying daytime sleepiness in OSA.

Comparison to Previous Literature

Prior studies have demonstrated positive associations between circulating CCL5 and measures of arterial stiffness and vascular dysfunction. For instance, Veillard et al. (2004) reported that CCL5 promotes monocyte adhesion and transmigration into the vascular wall, contributing to atherosclerosis and arterial remodeling. Similarly, Teixeira et al. (2018) described elevated CCL5 levels in patients with endothelial dysfunction and cardiovascular comorbidities. These studies primarily involved general or cardiovascular populations and used linear modeling frameworks.

In contrast, the current study focused exclusively on individuals with OSA, a condition characterized by intermittent hypoxia, sympathetic overactivation, and cyclical sleep disruption—factors that may alter the inflammatory response or its vascular consequences in a non-linear manner. The absence of significant linear associations between CCL5 and PWV in our cohort may reflect this unique pathophysiology. Importantly, the application of GAMs revealed non-linear associations in the subgroup with excessive daytime sleepiness, suggesting that CCL5 may only contribute to arterial stiffness beyond a certain inflammatory threshold.

Discussion

This study provides evidence that CCL5 is associated with arterial stiffness—measured by pulse wave velocity (PWV)—among individuals with obstructive sleep apnea (OSA), but only in those experiencing excessive daytime sleepiness (EDS). This stratified relationship, captured through generalized additive models (GAM), supports the hypothesis that increased inflammation may serve as a biological mechanism linking sleepiness to cardiovascular dysfunction in OSA. While standard linear regression models did not detect a significant association between CCL5 and PWV in the full sample ($\beta = 0.2513$, $p = 0.224$), GAM analyses revealed a significant non-linear relationship in participants classified as Sleepy (ESS $\geq$ 10), with pseudo $R^2 = 0.087$ and improved model fit (AIC range: 210.3–213.6). In contrast, no such association was observed in Non-Sleepy individuals (ESS < 10), whose models demonstrated negative pseudo R^2 values, indicating no meaningful explanatory value. These findings suggest that inflammation, as reflected by elevated CCL5, may contribute to vascular stiffening specifically among those with higher levels of subjective sleepiness.

This targeted effect modification by sleepiness is a central contribution of the current study. It supports a refined model in which systemic inflammation may mediate the established link between excessive daytime sleepiness and cardiovascular disease in OSA. Prior research has shown that EDS is independently associated with elevated cardiovascular risk, even after adjusting for OSA severity (Gottlieb et al., 2010). Our findings build on this evidence by showing that CCL5 may play a mechanistic role in this pathway, thereby advancing the understanding of how inflammation contributes to differential cardiovascular vulnerability across OSA phenotypes.

These findings align with prior literature implicating CCL5 in vascular dysfunction. CCL5 has been shown to promote endothelial activation, monocyte adhesion, and arterial remodeling (Veillard et al., 2004; Teixeira et al., 2018). However, most previous studies assessed CCL5 in general or cardiovascular cohorts using linear models and did not stratify by sleepiness or evaluate populations with OSA. The failure of linear models in our analysis to detect a significant CCL5–PWV relationship may thus be attributed to the pathophysiological uniqueness of OSA, including intermittent hypoxia, sympathetic overactivation, and fragmented sleep—all of which may produce threshold effects or non-linear inflammatory responses. Our use of flexible modeling and symptom-based stratification allowed us to detect these nuanced relationships that would otherwise be obscured.

In addition to the main results, we observed that participants with higher ESS and PSQI scores exhibited stronger associations between CCL5 and PWV in non-linear models, suggesting that symptom burden—rather than objective sleep metrics alone—may better identify those at greatest cardiovascular risk. These findings may also reflect compounding effects of autonomic dysregulation and oxidative stress in sleepy individuals, which could amplify inflammation-driven vascular damage (Somers et al., 2008).

The sample was 57.14% male and racially diverse, with nearly half identifying as Black or African American. This demographic breadth enhances the potential generalizability of the findings, although future studies with larger and more geographically or clinically varied populations are needed to confirm external validity.

Limitations

Several limitations should be noted. The sample size (N = 63) was modest, and stratified subgroup analyses were limited to ~30 individuals per group, reducing power to detect subtle effects. Although GAMs identified significant associations in the Sleepy group, the small sample and negative pseudo R^2 values in Non-Sleepy and Good Sleep subgroups warrant cautious interpretation. Additionally, unmeasured confounding, including medication use, dietary patterns, physical activity, could have influenced both inflammation and vascular measures. The cross-sectional design limits causal inference, making it unclear whether elevated CCL5 drives arterial stiffening or vice versa.

Conclusions

This study identifies a key interaction between subjective sleepiness and systemic inflammation in predicting arterial stiffness among individuals with OSA. Specifically, CCL5 was associated with PWV only in participants reporting excessive daytime sleepiness, suggesting that inflammatory pathways may disproportionately affect vascular health in this subgroup. These findings support the broader hypothesis that sleepiness confers additional cardiovascular risk beyond that explained by OSA severity alone and propose CCL5 as a candidate biomarker linking sleepiness to vascular dysfunction. Future longitudinal studies are needed to validate these results and assess whether interventions targeting sleepiness could reduce inflammation and mitigate cardiovascular risk in OSA.

Public Health Implications

This study provides novel evidence that excessive daytime sleepiness (EDS) may amplify the impact of systemic inflammation on arterial stiffness in individuals with obstructive sleep apnea

(OSA). While inflammation is a known contributor to cardiovascular disease, our results underscore that its vascular consequences—specifically those associated with elevated CCL5 levels—are significantly more pronounced in individuals with high subjective sleepiness (ESS ≥ 10). This represents a key shift in perspective: sleepiness is not merely a symptom of OSA but a potential risk-enhancing modifier of inflammation-related cardiovascular dysfunction.

This insight has critical implications for both clinical practice and public health strategy. Traditional assessments of cardiovascular risk in OSA populations have largely focused on structural measures such as the apnea-hypopnea index (AHI). However, our findings suggest that incorporating subjective sleepiness and sleep quality, alongside biomarker data, may enable more nuanced risk stratification. Individuals with elevated ESS or PSQI scores, for example, may warrant closer cardiovascular surveillance and earlier therapeutic intervention due to their heightened inflammatory burden.

The importance of this tailored approach is especially salient given the demographic composition of the study cohort, which was racially and gender diverse. These data support the generalizability of sleepiness-modified inflammatory risk across populations historically underrepresented in biomarker and cardiovascular studies. By recognizing sleepiness as a potential amplifier of inflammatory pathways, public health practitioners and clinicians can better identify high-risk subgroups within OSA populations who may benefit from more aggressive management.

Clinically, this finding supports prioritizing anti-inflammatory and sleep-improving interventions for sleepy individuals with OSA. Continuous positive airway pressure therapy remains a cornerstone, but adjunct strategies—including pharmacologic anti-inflammatories, structured exercise, weight loss, and cognitive-behavioral approaches to sleep hygiene—may also reduce

vascular risk in this vulnerable subgroup. In particular, targeting inflammation in sleepy OSA patients could serve as a precision intervention, with potentially greater returns than treating OSA severity alone.

These findings also suggest a future direction for integrated screening tools that combine subjective symptoms (ESS, PSQI) with inflammatory biomarker data (such as CCL5) to identify patients at highest cardiovascular risk. Such approaches could shift clinical paradigms from one-size-fits-all to symptom- and inflammation-informed care, ultimately reducing the cardiovascular disease burden associated with OSA.

Future research should prioritize longitudinal studies to evaluate whether reducing sleepiness or lowering inflammatory load leads to improvements in vascular outcomes. Additionally, exploring the mechanistic basis for this interaction may illuminate novel therapeutic targets. Ultimately, this study positions sleepiness not only as a clinical symptom but as a biologically meaningful indicator of elevated cardiovascular risk, warranting greater attention in both research and practice.

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