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A preliminary study on the relationship between sleep, depression and cardiovascular dysfunction in a 4 sample population

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ABSTRACT

Background: Major Depressive Disorder (MDD) has been linked in the literature to poorer prognosis in patients with cardiovascular dysfunction, although the mechanisms of this relationship remain unclear. Underlying Sleep Disordered Breathing (SDB) serves as a potential candidate to explain this effect due to its downstream effects on inflammatory activation and decreased nitric oxide (NO) bioavailability, both of which have been shown to contribute to the pathophysiology of both MDD and cardiovascular disease (CVD).

Methods: This study utilizes overnight polysomnography and an inflammation panel to examine the links between cardiovascular dysfunction and sleep difficulties in control participants and patients diagnosed with SDB only, MDD only, and both SDB and MDD.

Results: Results demonstrate a strong positive relationship between sleep dysfunction and the nitric oxide synthesis inhibitor Symmetric Dimethyl Arginine (SDMA) in the MDD-only cohort, suggesting a link between SDMA-mediated NO dysregulation and CVD pathogenesis in individuals with MDD. Additionally, hypopneas, a form of sleep impairment characterized by partial reduction of airflow, were found to play a significant role in the relationship between SDB and cardiovascular dysfunction in MDD-only patients.

Conclusions: Results of this study demonstrate the need for widespread screening for SDB in MDD populations to detect predisposition to CVD, and also offer SDMA as a new potential target for CVD treatment in individuals with MDD.

1. Introduction

Sleep-Disordered Breathing (SDB) and Major Depressive Disorder (MDD) have each been independently associated with substantial morbidity, impairment, and disability in patients with Cardiovascular Disease (CVD). Although the relationship between SDB and CVD has been well established, it is unclear how MDD is directly associated with CVD. Many literatures are now suggesting MDD as an independent risk factor for CVD and for increased all-cause mortality in patients with Coronary Heart Disease (CHD). Studies have shown that increased positive affect is a protective factor against 10-year incident CHD [1], and severe symptoms of depression have been independently associated with poorer prognosis and increased all-cause mortality in patients with Congestive Heart Failure (CHF) [2,3]. The mechanisms responsible for this relationship remain controversial. It is uncertain whether the relationship between MDD and CVD can be attributed to a direct causal role, or whether diagnosed or subclinical SDB within the population of MDD patients is, at least in part, responsible.

Previous studies have found MDD and SDB to be highly comorbid. Deldin, Phillips and Thomas [4] demonstrated the prevalence of SDB in patients diagnosed with MDD, with these individuals reporting greater sleep abnormalities, airflow-limitation events, and oxygen desaturation during sleep than healthy controls. Depression rates among Obstructive Sleep Apnea (OSA) patients are shown to be as high as 30-40%, approximately 6 times more

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prevalent than within the general population [5,6]. Moreover, in a recent meta-analysis, 48.1% of people diagnosed with MDD were found to display some level of SDB [7]. SDB has more recently been suggested as a potential link between CVD and MDD, citing the downstream effects of sleep dysfunction that can contribute to MDD and CVD pathogenesis such as inflammatory activation and reduced nitric oxide bioavailability [8].

Intermittent hypoxia during sleep is associated with the activation of proinflammatory cytokines, which may moderate several subsequent physiological changes contributing to both CVD and MDD onset [9]. Irregular blood serum concentrations of (IL-6) have been associated with both heightened risk of heart attack and with altered brain circuitry and function contributing to depressive behavior [10–13]. Nitric oxide synthase inhibition, another symptom of SDB, may also be partially responsible for downstream irregularities contributing to CVD and MDD pathogenesis. The nitric oxide synthesis inhibitors asymmetrical dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA) have been linked to increased inflammation, endothelial damage, and acute coronary heart events [9,14–16]. ADMA and SDMA production also acts as a competing pathway for the conversion of L-arginine to nitric oxide (Fig. 1), contributing to the onset of depression through competitive inhibition that alters arginine bioavailability [17]. These previously reported contributions of inflammation and NO inhibition, both of which are downstream effects of SDB, to the pathogenesis of both CVD and MDD give reason to believe that SDB may be the underlying factor in the relationship between CVD and MDD.

Despite this, previous studies linking MDD to poorer cardiovascular prognosis have neglected to look at SDB as a causal factor. With high comorbidity between MDD and SDB and 80–90% of moderate to severe cases of Obstructive Sleep Apnea (OSA) going undiagnosed, there is reason to question whether undetected SDB among these cohorts may be contributing to cardiovascular failure [18]. Therefore, the aim of the present study is to investigate the mechanisms contributing to decreased heart function and potentially leading to increased CVD as indexed by metabolic products SDMA and ADMA as well as an inflammatory cytokine panel in four groups of individuals: MDD-only (no SDB diagnosis), SDB-only (no MDD diagnosis), SDB + MDD and healthy controls (neither SDB nor MDD diagnoses). We predict that SDB will be related to depression.

2. Methods

2.1. Participants

Fifty-eight research participants were recruited and placed into 4 subgroups: SDB-only, MDD-only, SDB + MDD, and healthy controls (HC). Thirty-two patients were recruited from individuals receiving baseline sleep assessments at the UM Sleep Disorders Clinic and that met both our inclusion and exclusion criteria. None had begun treatment for SDB prior to the study. Of these 32 participants that screened positive for SDB, 12 also screened positive for MDD based on a minimum QIDS score and were placed in the SDB + MDD group, while the remaining 20 screened negative for MDD and comprised the SDB-only group. Thirteen MDD-only participants were recruited from ongoing MDD studies being conducted at UM and screened negative for SDB. Thirteen healthy controls were recruited from the Ann Arbor area through advertisements and by contacting previous research study participants who had indicated interest in future studies. Participants were excluded based on the following criteria: history of any serious medical conditions including hepatic, renal, gastrointestinal, respiratory, or hematologic disease, significant neurological disorder, autoimmune disorders, chronic infection, rheumatoid arthritis, uncorrected hypothyroidism or hyperthyroidism, cancer (within the 5 years prior to assessment), and substance dependence.

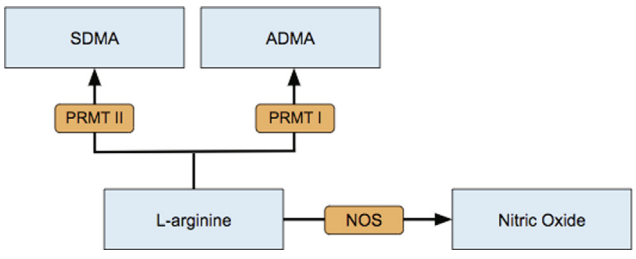


Fig. 1. Nitric Oxide Metabolic Pathway. An illustration of the competing pathways through which L-arginine is metabolized into SDMA, ADMA, and Nitric Oxide. Conversion to SDMA and ADMA occurs through post-translational methylation protein arginine methyltransferases (Type 1 PRMT for ADMA, Type 2 PRMT for SDMA). L-arginine is converted to Nitric Oxide through Nitric Oxide Synthase (NOS).

2.2. Procedure

2.2.1. Depression

Because the participants were recruited from multiple sources and ongoing studies, the researchers conducted the Structured Clinical Interview for the DSM-IV on patients in the MDD only group and all controls in order to verify their diagnostic status. Baseline depression of the research participants was also recorded using self-report measures to assess the severity of the depression at the time of the sleep assessment.

2.2.2. Sleep dysfunction

Severity of the participants' sleep disordered breathing was assessed and recorded based on overnight polysomnography. Severity of SDB was measured by the respiratory disturbance index (RDI), apnea-hypopnea index (AHI), respiratory event-related arousals (RERA), Non-REM AHI, REM AHI, obstructive apnea index (OAI), central apnea index (CAI) and hypopnea index (HypI). Sleep apnea diagnosis is usually defined as at least five events per hour. Although the hypopnea index was not utilized for screening or building subgroups, as it is weighed equally with apneas in the AHI, we utilized this measure for conducting statistical analyses due to a previous study by Cheng et al. (2012) that found hypopneas to be uniquely important in establishing the SDB-MDD relationship [19].

2.2.3. Cardiovascular dysfunction

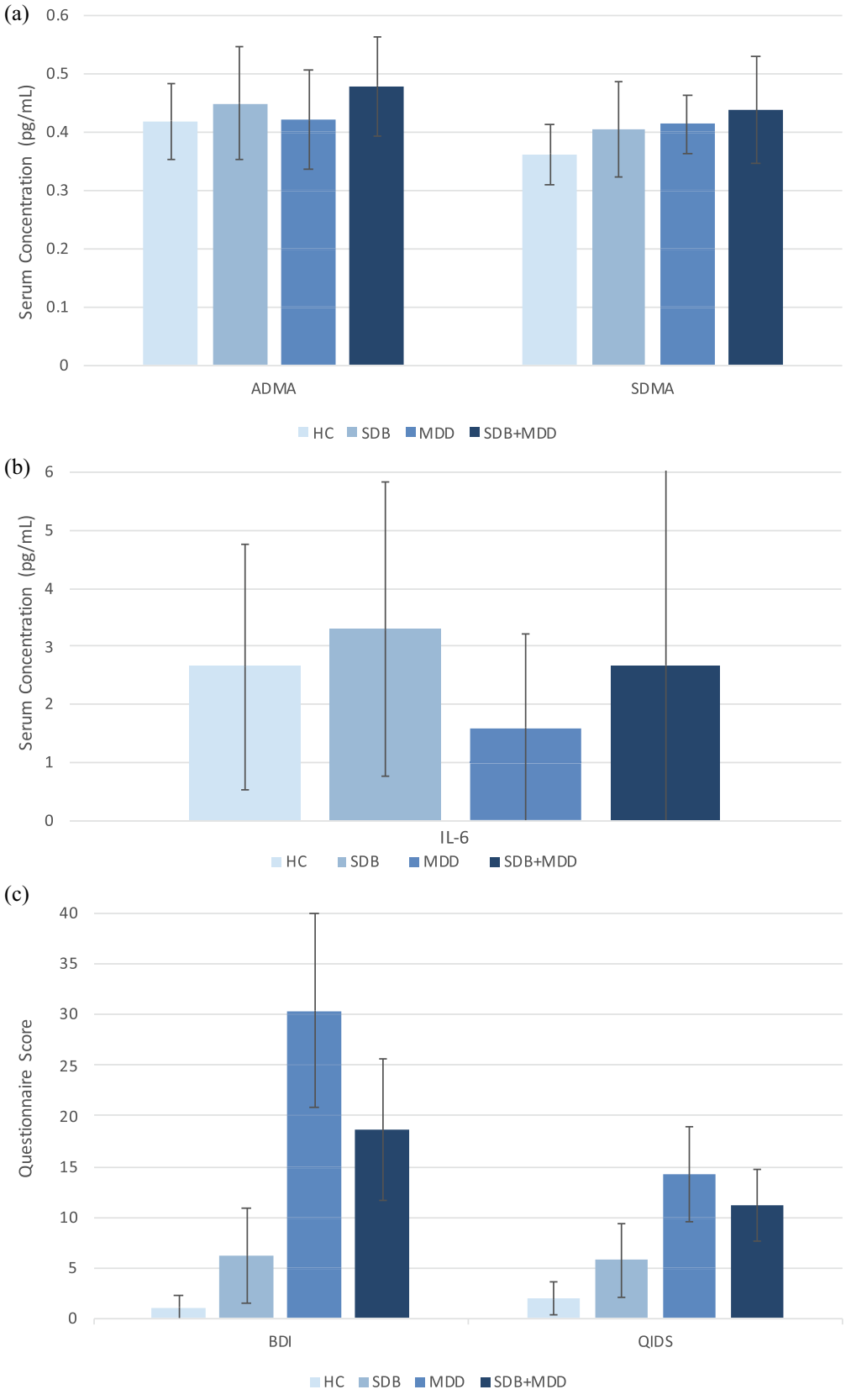
To assess cardiovascular dysfunction, the research team measured the relevant physiological indicators of cardiovascular disease: the decrease in NO availability, measured by asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA) and the degree of inflammatory activation measured by the inflammatory cytokine IL-6.[1] Blood samples were collected by the Michigan Clinical Research Unit staff between 6:00 AM and 9:00 AM following research participants' overnight sleep study. Samples were analyzed for ADMA, SDMA and cytokine levels.

2.3. Statistical analysis

Blood samples were analyzed using a 2x2 ANOVA design with presence/absence of MDD as one factor and presence/absence of SDB as one factor. Blood values, sleep measures, and depression levels were analyzed using correlational and regression analyses.

[1] The cytokine panel also consisted of the inflammatory markers IL-1β, IL-2, TNFα, and IFNγ. However, due to immeasurable results or lack of variability, these data were unable to be utilized in statistical analyses.

The research team evaluated whether patients' severity of SDB and MDD and the extent of cytokine presence and increases in ADMA and SDMA are related. All statistical analyses were performed on each of the individual healthy control (HC), SDB-only, MDD-only, and SDB + MDD cohorts. Statistical analyses were also performed across the entire study population, referred to from here on as the aggregate sample, in order to analyze continuous trends that spanned across individuals of varying diagnoses. Polysomnography data was not recovered for the HC cohort, therefore excluding the HC cohort from aggregate analyses involving SDB variables.



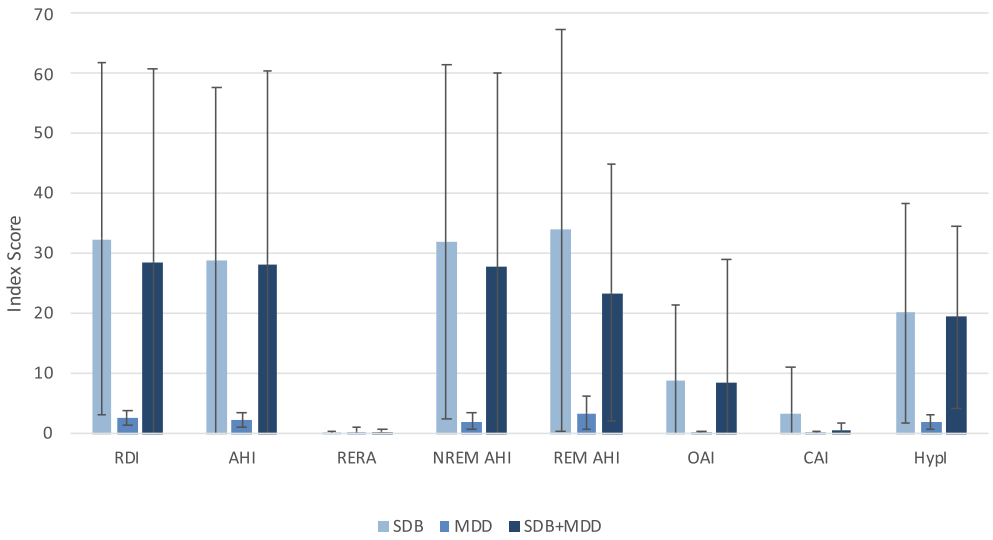


Fig. 3. Mean Sleep Indices by Subgroup. A bar graph illustrating the results of the overnight sleep study. ANOVA revealed the SDB-only and SDB + MDD cohorts to have significantly greater average RDI, AHI, NREM AHI, REM AHI, and HypI scores than those of the MDD-only group. There were no significant differences between the SDB-only and SDB + MDD polysomnography scores. Values are displayed as mean ± standard deviation.

3. Results

3.1. Analysis of variance

ANOVA results are displayed in Figs. 2a-c and 3. No significant variations in mean serum concentrations for cardiovascular dysfunction markers ADMA, SDMA or IL-6 were found between any of the groups. Depression levels in HC and SDB-only groups were found to be significantly lower than those of the MDD-only and SDB + MDD cohorts. Average RDI, AHI, NREM AHI, REM AHI, and HypI scores were significantly higher in the SDB-only and SDB + MDD groups than the MDD-only cohort.

3.2. Nitric oxide synthesis inhibitors

Correlations between measures of sleep dysfunction severity and measures of cardiovascular dysfunction are displayed in Table 1. Results from correlational analyses revealed SDMA to be correlated with several measures of SDB in the MDD-only group. These effects were not present in the other cohorts, the aggregate data set, or when analyzing all participants with MDD present together (MDD-only and MDD + SDB groups). Of the indices for Obstructive Apnea, Central Apnea, and Hypopnea, SDMA was only significantly correlated with hypopneas ($r = 0.81$, $p < 0.01$) in the MDD-only group (Fig. 4). The nitric oxide inhibitor ADMA was not found to correlate with any measures of sleep severity in either the aggregate sample or when analyzing the cohorts individually.

3.3. Hypopneas

Correlations between hypopneas and measures of cardiovascular dysfunction are displayed in Table 1. In regression analyses, the hypopnea index significantly predicted SDMA concentrations in the MDD-only group, $b = 0.81$, $t(9) = 3.91$, $p < 0.01$. In the MDD-only group, hypopneas also explained a significant proportion of variance in SDMA, $R^2 = 0.61$, $F(1,9) = 15.31$, $p < 0.01$. These effects were not seen when performing regression analyses on the other cohorts or on the aggregate sample. Obstructive apnea index and central apnea index were not found to account for significant variance in SDMA levels, either in the aggregate sample or analysis of individual cohorts.

The hypopnea index was also found to positively correlate with IL-6 concentration in the aggregate sample ($r = 0.37$, $p = 0.04$), as well as the MDD-only cohort ($r = 0.64$, $p = 0.04$) (Fig. 5). In the aggregate sample (no HC), the hypopnea index significantly predicted IL-6 blood serum concentrations, $b = 0.37$, $t(31) = 2.17$, $p = 0.04$. Hypopneas also explained a significant proportion of variance in IL-6 concentrations, $R^2 = 0.11$, $F(1,30) = 4.73$, $p = 0.04$. Hypopnea prediction of IL-6 was also seen in the MDD-only cohort, $b = 0.64$, $t(9) = 2.35$, $p = 0.04$. Hypopneas explained a significant proportion of IL-6 variance in the MDD-only cohort, $R^2 = 0.34$, $F(1,9) = 5.53$, $p = 0.04$. This effect was not seen in the other cohorts when analyzing them individually. Obstructive apnea index and central apnea index were not found to account for significant variance in IL-6 serum concentration, either in the aggregate sample or analysis of individual cohorts.

3.4. Depression and Anxiety

Correlations between sleep disorder severity and depression are displayed in Table 2A. Within the aggregate data, measures of sleep dysfunction utilized in this study had significant negative correlations with BDI, QIDS, and Anhedonic Depression (as measured by the Mood and Anxiety Symptom Questionnaire). Correlations between sleep disorder severity and anxiety are displayed in Table 2B. Measures of SDB had significant negative correlations

Fig. 2. Mean Depression, NO Inhibitor, and Inflammatory Levels by Subgroup. a) A bar graph illustrating the concentration levels of NO synthesis inhibitors in blood serum collected after an overnight sleep study. ANOVA revealed no significant variance in concentrations of ADMA or SDMA between any of the groups. Values are displayed as mean ± standard deviation. b). A bar graph illustrating the concentration levels of inflammatory biomarker IL-6 in blood serum collected after an overnight sleep study. ANOVA revealed no significant variance in concentrations of IL-6 between any of the groups. Values are displayed as mean ± standard deviation. c) A bar graph illustrating the QIDS and BDI scores of participants reported on the day of the overnight sleep study. ANOVA revealed HC and SDB-only groups to have significantly lower scores than the MDD-only and SDB + MDD cohorts. HC were found to have significantly lower scores than the SDB-only cohort when analyzing QIDS, but not BDI. The MDD-only cohort was also found to have significantly higher depression levels than the SDB + MDD cohort when analyzing BDI scores, but not QIDS. Values are displayed as mean ± standard deviation.

Table 1
Correlations between sleep-disordered breathing and cardiovascular dysfunction.

Cohort	Sleep Index	ADMA	SDMA	IL-6
Aggregate	RDI	0.22	0.09	0.31
n = 34	AHI	0.09	−0.07	0.31
	RERA	0.04	0.04	−0.22
	NREM AHI	0.22	0.08	0.31
	REM AHI	0.20	0.10	−0.19
	OAI	0.27	0.24	0.18
	CAI	−0.15	0.01	0.05
	HypI	0.20	−0.06	0.37*
SDB-only	RDI	0.19	0.30	0.11
n = 15	AHI	−0.16	−0.05	0.14
	RERA	−0.08	−0.30	−0.17
	NREM AHI	0.20	0.33	0.13
	REM AHI	0.12	0.17	−0.02
	OAI	0.42	0.63*	−0.01
	CAI	−0.22	0.07	−0.08
	HypI	0.11	0.03	0.22
MDD-only	RDI	0.25	0.72*	0.52
n = 10	AHI	0.32	0.81**	0.57
	RERA	−0.16	−0.20	−0.15
	NREM AHI	0.35	0.76*	0.54
	REM AHI	0.26	0.65*	0.64*
	OAI	−0.04	0.21	−0.20
	CAI	−0.47	0.04	−0.03
	HypI	0.40	0.81**	0.64*
SDB + MDD	RDI	0.25	0.04	0.62
n = 9	AHI	0.24	0.03	0.63
	RERA	0.51	0.76*	−0.38
	NREM AHI	0.20	−0.01	0.62
	REM AHI	0.49	0.35	0.41
	OAI	0.19	0.09	0.50
	CAI	0.07	−0.01	0.48
	HypI	0.24	−0.06	0.66

Note: Healthy control (HC) polysomnography data was not retrieved and is therefore not included in the aggregate sample results.
* $p < 0.05$, two-tailed.
** $p < 0.01$, two-tailed.

with all measures of anxiety and distress. While all measures of anxiety showed relations to SDB, the relationship of trait anxiety (as measured by the State-Trait Anxiety Inventory) with sleep dysfunction more robust than that of state anxiety and sleep dysfunction, as measured by the Rosenthal and Rubin's comparison of correlation coefficients displayed in Table 2C [20].

4. Discussion

This study examined the relationships between inflammation, nitric oxide bioavailability, sleep dysfunction, and depression in individuals diagnosed with SDB, MDD, and both SDB and MDD. Overall, findings suggest a strong relationship between SDB and SDMA in individuals diagnosed with MDD only. Using measures of sleep severity, we are able to account for a large proportion of the variance in SDMA concentrations, with heightened SDMA being a known contributor to downstream cardiovascular dysfunction. This effect was not seen when examining ADMA, another known inhibitor of nitric oxide synthesis, suggesting a specific role of the SDMA pathway in the onset of cardiovascular dysfunction in patients diagnosed with MDD.

Additionally, hypopneas were found to play a unique role in the relationship between sleep dysfunction and cardiovascular difficulties. Hypopneas are a form of sleep dysfunction that are characterized by abnormally slow and shallow breathing. In the MDD-only cohort, hypopneas were found to account for significant variance in SDMA serum concentration. Additionally, significant links between hypopneas and IL-6 serum concentrations were found both in the aggregate data and in the MDD-only cohort, with hypopneas accounting for a significant amount of the variance in IL-6. This contrasted with the lack of significant outcomes when analyzing central apneas and obstructive apneas, which are both forms of SDB that result in complete cessation of breathing. This is consistent with a previous report by Cheng et al. [19], which similarly demonstrated that hypopneas play an important role in establishing the relationship between SDB and MDD that is present even in the absence of clinically diagnosed SDB. Hypopneas emerging as a consequential form of SDB in both the concentrations of SDMA and IL-6 further suggests that this less drastic reduction of respiratory effort and airflow, as opposed to apneas resulting in full suspension of breath, may be essential to our understanding of poorer cardiovascular prognosis in MDD patients. Alternatively, it could be the case that we are seeing two potential and unique rela-

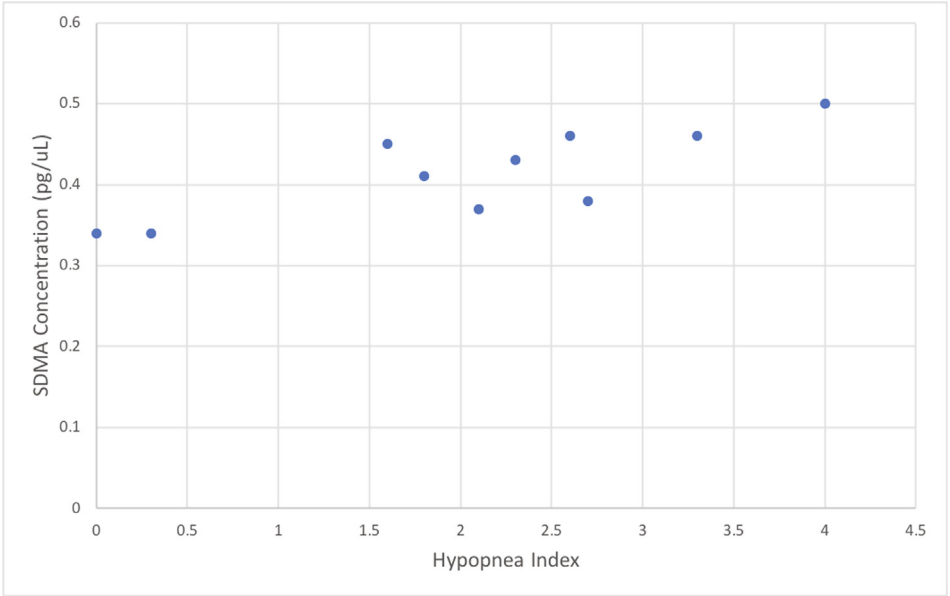


Fig. 4. Hypopneas and SDMA in MDD-only Participants. A scatterplot illustrating the relationship between hypopnea index and SDMA concentration after an overnight polysomnography for MDD-only participants (n = 10). Pearson's r = 0.81, $p < 0.01$.

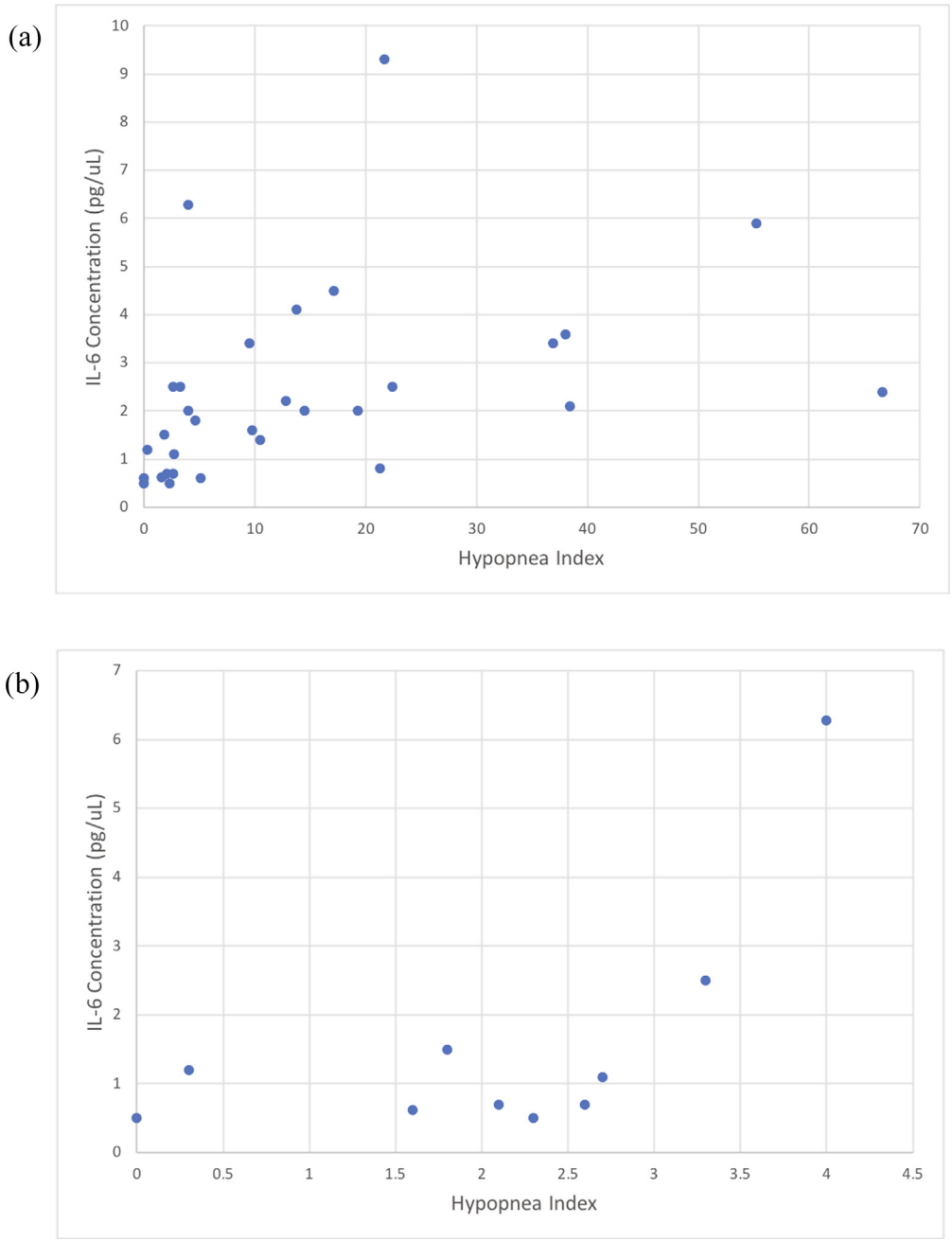


Fig. 5. Hypopneas and IL-6 in Aggregate Sample and MDD-only participants. a) A scatterplot illustrating the relationship between hypopnea index and IL-6 concentration after an overnight polysomnography across all study participants with PSG data (n = 34). Pearson's r = 0.37, $p < 0.05$. b) A scatterplot illustrating the relationship between hypopnea index and IL-6 concentration after an overnight polysomnography for MDD-only participants (n = 10). Pearson's r = 0.64, $p < 0.05$.

tionships between SDB and depression. It has been demonstrated that SDB can cause mood changes [21] that can be remediated with CPAP [22] and may account for the relationships we see in the SDB + MDD group. However, the hypopnea relationship in MDD-only raises the possibility that there is a unique causal pathway between SDB and MDD, perhaps in the other direction. That is, inflammatory processes could cause depression and SDB. This would align with the school of thought that there are multiple forms of depression.

Positive links between measures of SDB and measures of cardiovascular dysfunction in participants diagnosed with MDD support the argument that the heightened cardiovascular difficulties in individuals experiencing depression may be due to underlying sleep problems. Moreover, hypopneas, rather than apneas, played particular importance in the links with SDMA and IL-6 in the MDD-only cohort. Hypopneas, characterized by partial suspension of breath during sleep, are likely to go undiagnosed in MDD patient cohorts, pointing to this as a major potential mediating variable between MDD and SDB. These results have strong implications for current research into depression-related cardiovascular dysfunction, calling for a further focus on the specific roles of hypopneas and nitric oxide bioavailability.

5. Limitations

Limitations of our study include the small sample size, especially when performing statistical tests on individual cohorts,

Table 2
Correlations between sleep-disordered breathing and depression/anxiety.

2A

Cohort	Sleep Index	BDI (n = 30)	QIDS (n = 31)	MASQAD (n = 31)
Aggregate n = 34	RDI	−0.44*	−0.44*	−0.39*
	AHI	−0.37*	−0.35*	−0.37*
	RERA	0.02	−0.05	0.17
	NREM AHI	−0.44*	−0.45*	−0.40*
	REM AHI	−0.49*	−0.40*	−0.38*
	OAI	−0.25	−0.37*	−0.23
	CAI	−0.32	−0.38*	−0.30
	HypI	−0.43*	−0.32	−0.38*

2B

Cohort	Sleep Index	MASQGD	MASQAA	State Anxiety	Trait Anxiety
Aggregate n = 31	RDI	−0.52**	−0.39*	−0.31	−0.59***
	AHI	−0.44*	−0.33	−0.21	−0.50**
	RERA	0.05	0.10	0.02	0.33
	NREM AHI	−0.53**	−0.37*	−0.31	−0.61***
	REM AHI	−0.41*	−0.37*	−0.41*	−0.57***
	OAI	−0.39*	−0.38*	−0.19	−0.42*
	CAI	−0.35	−0.26	−0.37*	−0.40*
	HypI	−0.44*	−0.26	−0.26	−0.54**

2C

Cohort	Sleep Index	*Z*	*p*
Aggregate n = 31	RDI	−2.51	0.006**
	AHI	−2.37	0.009**
	NREM AHI	−2.62	0.004**
	REM AHI	−1.42	0.078
	OAI	−1.84	0.033*
	CAI	−0.27	0.392
	HypI	−2.34	0.010**

Note: 3 study participants did not complete surveys for MASQGC, MASQAA, State Anxiety, and Trait Anxiety, resulting in an n = 31 for these analyses, rather than the previous n = 34 for our aggregate group (SDB + MDD, SDB, and MDD cohorts combined).

which limited the power of our analyses. A post-hoc achieved power analysis using G*Power3.1 demonstrated sufficient power (power = 0.9) to evaluate moderate to large effect sizes (d = 0.5), but insufficient power (power = 0.43) to evaluate small to moderate effect sizes (d = 0.3), suggesting likelihood of Type II error for weaker relationships within our study population and the need for further study with a larger cohort [23]. Another limitation is participant exclusion based upon self-report data of prior medical conditions, leading to potential for inaccurate reports or disregard of undiagnosed medical complications. Additionally, despite rigorous exclusionary criteria that largely prevented severe comorbidities, we were unable to investigate cardiovascular comorbidities that may have had independent effects on the NO pathway. Additionally, although AASM guidelines were followed for the accurate diagnosis of OSA, the study was conducted over only a single night, limiting our ability to fully characterize the severity of participants' condition. Potential selection biases are also present, as the study population was largely comprised of well-educated Caucasian individuals and our MDD-only cohort was recruited from multiple other MDD studies, which is selective towards individuals with high depression severity. Lastly, polysomnography data for the controls was not recovered, preventing the comparison of the effects of sleep dysfunction severity in our SDB, MDD, and SDB + MDD cohorts to healthy subjects.

6. Conclusion

In conclusion, the results of the present study indicate the importance of heightened SDMA in reduction of nitric oxide bioavailability leading to poorer cardiovascular diagnosis in individuals diagnosed with MDD. Additionally, results reveal the importance of hypopneas as a potential risk marker for inflammatory cytokine upregulation and nitric oxide inhibition that contribute to CVD pathology. These findings highlight the need for better screening of symptoms of sleep dysfunction, such as hypopneas, in individuals with depression to determine their risk for cardiovascular difficulties. The demonstrated link of SDMA, rather than ADMA, with sleep difficulties in patients with MDD also presents new potential targets, such as Type 2 PRMTs or SDMA itself, for the treatment and prevention of CVD symptomatology in these individuals.

Declaration of Competing Interest

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

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