ELDERLY SLEEP AND STRESS

Sleep Disturbance, Norepinephrine, and D-Dimer Are All Related in Elderly Caregivers of People With Alzheimer Disease

Brent T. Mausbach, PhD1; Sonia Ancoli-Israel, PhD1,2; Roland von Känel, MD1,3; Thomas L. Patterson, PhD1; Kirstin Aschbacher, BA1; Paul J. Mills, PhD1; Michael G. Ziegler, MD1; Joel E. Dimsdale, MD1; Susan Calleran, MS1; Igor Grant, MD1

1Department of Psychiatry, University of California, San Diego, CA; 2San Diego Veterans Affairs Healthcare System; 3Department of General Internal Medicine, University Hospital, Bern, Switzerland; 4Department of Medicine, University of California, San Diego, CA

Study Objective: Caregiving for a relative with Alzheimer disease has been associated with sympathoadrenal medullary arousal and morbidity and mortality. In this study, we examined if sleep disturbance of elderly caregivers was associated with physiologic markers of cardiovascular risk, including plasma norepinephrine, epinephrine, and the hemostasis marker D-dimer.

Design: Cross-sectional.

Setting: Community-based sample of elderly caregivers of spouses with Alzheimer disease assessed within their homes.

Participants: A sample of 40 elderly spousal caregivers of patients with Alzheimer disease.

Measurements and Results: Participants underwent in-home full-night polysomnography and had plasma assayed for norepinephrine and epinephrine. Using multiple regression analyses and controlling for a number of cardiovascular risk factors (e.g., age, sex, blood pressure, body mass index), increased wake after sleep onset was positively associated with norepinephrine levels ($\beta = .35; t = 2.45, df = 32, p = .020$) and plasma D-dimer ($\beta = .31; t = 2.18, df = 29, p = .038$). Further, plasma norepinephrine was significantly associated with D-dimer ($\beta = .34; t = 2.11, df = 29, p = .044$). Additional analyses indicated that norepinephrine accounted for 28% of the relationship between wake after sleep onset and D-dimer. No association was observed between sleep variables and epinephrine.

Conclusions: These findings provide preliminary evidence that sleep disturbance may contribute to morbidity in caregivers through sympathoadrenal medullary arousal and downstream physiologic effects such as altering the hemostasis environment.

Keywords: Sleep, Alzheimer disease, caregiving, SAM arousal, catecholamines, coagulation, cardiovascular disease

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INTRODUCTION

THE STRESS OF CARING FOR A LOVED ONE WITH ALZHEIMER DISEASE (AD) HAS BEEN WELL DOCUMENTED IN THE LITERATURE.1-2 STRESSES ASSOCIATED WITH caregiving, such as care-recipient problem behaviors, a mismatch between demands and resources (i.e., overload), and affective disturbance may promote sympathoadrenal medullary (SAM) activation. Indeed, research suggests that caregivers have an elevated basal concentration of plasma catecholamines, as compared with noncaregivers,3 and increased depressive symptoms in caregivers appear to exaggerate the norepinephrine response to psychological stress.4

The stress of caregiving also raises the risk of premature mortality. In a study comparing caregivers of people with and without dementia, Schulz and colleagues found an elevated risk for mortality among those caregivers reporting high levels of strain.5 Indeed, other research suggests that caregivers of people with dementia report greater strain than do caregivers of people without dementia.6 This elevated mortality risk may be due in part to the effects of caregiving stress on the cardiovascular system.7,8

Although affective disturbance and caregiving stress appear to be related to SAM arousal, other factors associated with stress, such as sleep disturbance, may provide an alternate explanation for these relationships. Poor sleep is common among caregivers9 and has been associated with increased risk for heart disease.10 Wilcox and King11 examined sleep in 90 caregivers of patients with AD and found that caregivers reported more sleep complaints than did age-matched, healthy people who were not caregivers. In that study, the most common complaint was being awakened during the night, with more than half of the caregivers reporting nighttime disruptions caused by the care recipient. In another study, Happe and Berger12 found that 27% of caregivers of people with Parkinson disease experienced frequent sleep disturbances and that sleep disturbance was proportionate to the level of caregiving stress.

Sleep disturbance, and in particular obstructive sleep apnea (OSA), has been linked with a number of biologic outcomes related to cardiovascular disease.13-16 In a review of the relationship between sleep fragmentation and biologic outcomes, Shamsuzaman et al14 concluded that sleep fragmentation plays a role in the initiation and progression of cardiac and vascular disease. OSA, which results in sleep fragmentation, has also been associated with endothelial dysfunction, increased circulating C-reactive protein, interleukin-6, fibrinogen, and reduced fibrinolytic activity,16-18 as well as an increase in plasma and urinary norepinephrine.19-21 The latter findings strongly suggest that OSA confers a hypercoagulable...
ble state, possibly related to SAM during apnea. These findings are consistent with other studies showing that OSA may increase one’s risk for cardiovascular disease in general and vascular dysfunction specifically.

More recent research suggests that poor sleep in general, not only OSA, may also be associated with a hypercoagulable state. For example, longer wake time after sleep onset (WASO) and lower sleep efficiency have been associated with elevated plasma concentrations of the procoagulant marker fibrin D-dimer. D-dimer is a degradation product of fibrin, which, in turn, is the end product of an activated coagulation system. Plasma D-dimer thus indicates both fibrin formation and its subsequent lysis by the fibrinolytic system. Moreover, D-dimer is a downstream cardiovascular risk marker that is responsive to sympathetic activation. Recent publications indicate that D-dimer levels less than 500 ng per mL suggest almost no risk for deep venous thrombosis or pulmonary embolism, whereas D-dimer levels of 750 ng per mL or more place one at a significantly elevated risk for the development of recurrent venous thromboembolism.

Catecholamine surge with sympathetic activation has been implicated in hemostasis. Specifically, epinephrine has long been associated with hastened blood coagulation, and elevated plasma concentrations of catecholamines and D-dimer, all potential risk factors for a hypercoagulable state and cardiovascular disease.

In summary, studies have suggested that the stress associated with caregiving may increase the risk of cardiovascular disease. Caregivers of people with AD, for example, have been noted to have a mild increase in blood pressure and elevated plasma concentrations of catecholamines and D-dimer, all potential risk factors for a hypercoagulable state and cardiovascular disease.

In this study, we were interested in expanding our previous findings that sleep disturbance is related to hypercoagulation by exploring whether sleep disturbance was itself related to markers of SAM arousal and whether this arousal may also be associated with hypercoagulability. Such a relationship could point to one mechanism whereby caregiving stress translates into cardiovascular risk. This potential mechanistic path has some support from previous research demonstrating that poor sleep is common among caregivers and has been associated with increased risk for heart disease. Additionally, separate studies have identified that poor sleep is associated with plasma concentrations of norepinephrine and D-dimer. Therefore, we were interested in whether objective measures of poor sleep, namely WASO, over and beyond the respiratory variables associated with OSA (i.e., apnea-hypopnea index [AHI] and oxygen desaturation), might be associated with hypercoagulability. Further, we were interested in examining whether sleep-related SAM arousal, as evidenced by plasma catecholamine levels, would be associated with a marker of hypercoagulation, namely D-dimer. We hypothesized that poor sleep would be associated with greater plasma concentrations of norepinephrine and D-dimer, and that norepinephrine would be positively correlated with plasma concentrations of D-dimer. Finally, we examined the extent to which the relationship between poor sleep and D-dimer was accounted for by elevations in plasma catecholamines.

METHODS

Participants

Participants were 40 caregivers of persons with AD, who volunteered for a study on the psychobiologic consequences of stress. The majority of participants were recruited from professional referrals (e.g., physicians, social workers, etc.), the University of California San Diego Alzheimer’s Disease Research Center, and media advertisements. Most caregivers (93%) identified themselves as Caucasian. The study protocol was approved by the University of California San Diego Institutional Review Board, and all participants provided written informed consent prior to enrollment in the study. The current sample consists of a subset of caregivers from our previously published manuscript on the relationships between sleep disturbance and D-dimer levels. Specifically, this subset consists of caregivers for whom catecholamine data were also available.

Participants were required to be a spousal caregiver of someone with a documented diagnosis of AD and living at home with their care recipient at the time of enrollment. In addition, caregivers were required to be 55 years of age or older and free of serious medical conditions (e.g., cancer). Exclusion criteria included (1) taking beta-blocking medication, (2) taking steroids, (3) a blood pressure greater than 200/120 mm Hg, or (4) receiving treatment with anticoagulant medication because these factors may interfere with or alter clotting activity.

Procedures

During an initial home visit, a research nurse met with participants to review the study protocol and obtain written consent. During this visit, a semistructured interview was conducted to obtain information on risk factors potentially related to the outcomes in this study, including demographic information, medical history, and depressive symptoms. Following this assessment, the nurse had the participant sit comfortably at rest for 15 minutes, during which 3 blood pressure measurements were taken using a Critikon Dinamap 8100 adult/pediatric noninvasive blood pressure monitor. Participants then had a 22-gauge indwelling venous catheter placed in their forearm for blood drawing. Once drawn, all blood samples were placed on ice. Venous blood drawn through the 22-gauge forearm catheter was dispensed into polypropylene tubes containing 3.8% sodium citrate (9:1, v/v). D-dimer was spun within 3 hours at 1600 rpm for 10 minutes at room temperature, whereas norepinephrine was spun in a refrigerated centrifuge.

At a later date, a sleep technician met with participants in their homes to explain the details of polysomnography (PSG), attach the sleep recorder, and ensure that participants were comfortable for the overnight PSG. On average, the sleep technician met with participants 30 days (interquartile range: 19-45 days) after the initial blood draw. All participants slept at their habitual sleep times and recorded “lights out” (i.e., the time at which he or she attempted to fall sleep) in a diary. Furthermore, reported “lights out” time was verified using PSG recordings of movement followed by alpha waves, indicating eyes closed. Participants un-
plugged the PSG equipment immediately upon waking, marking “lights on” time.

**Outcome Measures**

**Biologic Outcomes**

Once the blood samples were returned to the laboratory, they were centrifuged and plasma was stored at -80°C until assayed. Catecholamines were assayed using catechol-O-methyltransferase (COMT)-based radioenzymatic assays with a preconcentration step to extract catecholamines from 1 mL of plasma and concentrated in 0.1 mL of dilute acid. This assay is 10 times as sensitive as standard assays for catecholamines. Plasma D-dimer was measured by an enzyme-linked immunosorbent assay (Asserachrom® Stago, Asnières, France).

**Independent Variables**

**Medical Data**

For this study, participants’ smoking history was dummy coded as 0 for no history or 1 for past or present smoker. Body mass index was calculated as the ratio between weight in kilograms and height in meters squared. For blood pressure, the average of 3 diastolic and systolic measurements was used to calculate mean arterial pressure.

**Depressive Symptoms**

The depression subscale of the Brief Symptom Inventory-Depression was used to assess depressive symptoms. For this scale, participants are asked to rate how much each item “had caused distress during the past 6 months, including today.” Response choices ranged from 0 (not at all) to 4 (extremely). Average responses to the 6 items were used to calculate an overall score. The Brief Symptom Inventory-Depression has demonstrated excellent psychometric properties. For example, it is comparable to the Beck Depression Inventory and the Hamilton Rating Scale for Depression in accurately detecting cases of depression in the elderly, and scores on the Brief Symptom Inventory-Depression are highly correlated with those of the Beck Depression Inventory and Hamilton Rating Scale for Depression.

**Sleep Recordings**

PSG was recorded with the Embla portable recording system (Flaga Medical Devices/Medcare, Reykjavik, Iceland), which recorded electroencephalography (C3 and C4 derivations), electro-oculography (left outer canthus, right outer canthus derivations), submental electromyography, thoracic and abdominal respiratory efforts (piezoelectric bands), airflow (nasal pressure transducer and cannula for oral air flow), electrocardiography, and oximetry.

Sleep records were scored for sleep stages using the Rechtschaffen and Kales criteria and for number of apneas and hypopneas, number of desaturations ≥ 3%, and percentage of time spent at SaO2 < 90%. Total sleep time (TST), wake after sleep onset (WASO), and sleep-onset latency (SOL) were computed along with the AHI (the number of apneas and hypopneas per hour of sleep). Sleep-onset latency (SOL) was defined as the time between lights out (as reported by the participant) and the first 60 seconds of stage 2 sleep. An apnea was defined as a greater than 90% decrease in airflow amplitude, lasting at least 10 seconds. A hypopnea was defined as a 30% to 90% decrease in amplitude, lasting at least 10 seconds associated with a desaturation of ≥ 3%.

**Data Analysis**

Preliminary examination for normality indicated that norepinephrine, D-dimer, and SOL required log transformations, whereas Brief Symptom Inventory-Depression, WASO, and AHI scores required square-root transformations.

Our primary analyses utilized multiple linear regressions to examine the relations between sleep disturbance, catecholamine levels, and D-dimer. Specifically, we used the mediational approach described by Baron and Kenny and Holmbeck to examine the extent to which the relationship between sleep disturbance and D-dimer was accounted for by catecholamines (e.g., norepinephrine). This approach requires a series of regressions that examine the relationships between (1) the independent variable (sleep disturbance) and the proposed mediator (catecholamine levels), (2) the independent variable and the dependent variable (plasma D-dimer), and (3) the mediator and the dependent variable. If each of these regressions was significant, a final regression was run that included both sleep disturbance (e.g., WASO) and catecholamine levels (e.g., norepinephrine) as “predictors” of D-dimer. For a full mediating effect to exist (i.e., catecholamines account for 100% of the relationship between sleep disturbance and D-dimer), the relationship between sleep disturbance and D-dimer is zero after catecholamines are included in the model. A partial mediating effect exists when the relationship between sleep disturbance and D-dimer is reduced when catecholamines are included in the model. Using the formula provided by Mckinnon and Dwyer, we estimated the percentage of the sleep disturbance to D-dimer path accounted for by catecholamines. In all regression models age, sex, mean arterial pressure, smoking history, body mass index, and Brief Symptom Inventory-Depression scores were entered as covariates. Because the relationship between sleep disturbance and our outcomes might be better accounted for by apnea-related events, we conducted secondary analyses using AHI and time spent at an SaO2 < 90% as covariates to determine if significant relationships between sleep disturbance and outcomes remained after controlling for these variables.

**RESULTS**

Table 1 shows demographic and health characteristics for the caregivers. The mean age of the caregivers was 73 (± 8 years), and 95% were Caucasian. We present results of our regression analyses using transformed variables in the text below. As a tool to aid the reader in interpreting the magnitude of the relationship between variables in our model, we present coefficients for the raw (untransformed) variables for each of our outcomes (ie, norepinephrine, epinephrine, and D-dimer) in Table 2.

**Associations Between Sleep Variables and Catecholamine Levels**

Results of our first overall multiple regression, which examined the relationship between WASO and plasma norepinephrine, was significant (F = 2.85, df = 7, 32, p = .020; R2 = .38). Within this model, WASO was positively associated with norepinephrine
Table 1—Characteristics of the Sample

<table>
<thead>
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<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
<th>No.</th>
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<td>35</td>
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<td>≥ 43,000</td>
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<td>BMI, kg/m²</td>
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<td>Systolic</td>
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<td>17.8</td>
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<td>Diastolic</td>
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<td>12.0</td>
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<td>Norepinephrine, pg/mL</td>
<td>518.5</td>
<td>266.8</td>
<td>198.0-1535.5</td>
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<td>Epinephrine, pg/mL</td>
<td>35.6</td>
<td>31.3</td>
<td>7.6-185.9</td>
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<td>D-dimer, ng/mL</td>
<td>834.2</td>
<td>682.1</td>
<td>239.1-3269.1</td>
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<td>WASO, min</td>
<td>84.1</td>
<td>48.4</td>
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<td>TST, min</td>
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<td>89.2</td>
<td>68.0-534</td>
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<td>SOL, min</td>
<td>18.0</td>
<td>33.4</td>
<td>0.0-192.0</td>
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<td>AHI, no./h</td>
<td>9.7</td>
<td>11.9</td>
<td>0.0-49.8</td>
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<tr>
<td>SaO₂ &lt; 90%, % of TST</td>
<td>3.2</td>
<td>12.5</td>
<td>0.0-79.4</td>
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</table>

*aSix caregivers did not provide income data. BMI refers to body mass index; WASO, wake after sleep onset; TST, total sleep time; SOL, sleep-onset latency; AHI, apnea-hypopnea index.

levels ($\beta = .34, t = 2.39, df = 32, p = .023; \Delta R^2 = .11$), indicating that caregivers with greater time spent awake during the night had elevated plasma norepinephrine concentrations. No other covariates (e.g., age, sex, etc.) reached significance (all p values > .05). As seen in Table 2, norepinephrine levels for 84 minutes awake after sleep onset were approximately 397 pg/mL, with each additional minute spent awake associated with a 2-pg/mL rise in plasma norepinephrine levels. Two additional regression analyses indicated that neither SOL (t = -0.46, df = 32, p = .652) nor TST (t = -0.49, df = 32, p = .631) was correlated with norepinephrine level.

We next examined the relations between sleep variables and epinephrine. One participant was removed from these analyses due to an outlying epinephrine value. Results of these analyses indicated that none of our sleep variables (i.e., WASO, SOL, TST, AHI) was significantly associated with plasma epinephrine levels (all p values > .15).

Secondary Analysis Controlling for Apnea-related Sleep Variables

Two additional regression analyses were conducted to determine if the relationship between WASO and norepinephrine was better accounted for by apnea-related events. In both of these analyses, neither AHI (p values > .56) nor time spent at SaO₂ < 90% (p values > .52) was associated with norepinephrine level. However, WASO remained significantly related to norepinephrine level in both models (p < .05).

Associations Between Sleep Variables and D-dimer

Given the significant relationship between norepinephrine plasma D-dimer, our next regression examined the relationship between WASO and plasma D-dimer. This analysis included 38 participants, because 2 participants had missing D-dimer data. Those with missing data did not differ on any demographic or health characteristics (all p values > .29). The overall model included our demographic and health covariates (i.e., age, blood pressure) as well as AHI, given its theoretical relationship with cardiovascular disease. The overall regression, which included all covariates, accounted for 47% of the variance in D-dimer (F = 3.40, df = 8, 29, p = .007). Within this model, WASO was significantly related to plasma D-dimer (t = 2.18, df = 29, p = .038; $\Delta R^2 = .09$).

Associations Between Catecholamines and D-dimer

Next, we examined the relationship between catecholamines and plasma D-dimer. Results of our first regression indicated that epinephrine was not significantly related to D-dimer (p > .87). Our second regression model, which included norepinephrine and covariates (i.e., age, sex, mean arterial pressure, smoking history, body mass index, depressive symptoms, and AHI), was significant (F = 3.34, df = 8, 29, p = .008) and accounted for 48% of the variance in plasma D-dimer. In this multiple regression analysis, norepinephrine was significantly associated with D-dimer ($\beta = .34, t = 2.11, df = 29, p = .044; \Delta R^2 = .08$), with higher norepinephrine levels being associated with higher D-dimer values.

Because all conditions of Baron and Kenny’s mediational analyses were met for WASO, norepinephrine, and D-dimer, a final analysis was conducted in which D-dimer was regressed onto both WASO and norepinephrine. Results indicated that neither WASO (t = 1.38, df = 28, p = .177) nor norepinephrine (t = 1.29, df = 28, p = .209) remained significant predictors of D-dimer. Using the formula provided by Mckinnon and Dwyer,40 we estimated that approximately 28% of the WASO-to-D-dimer path was accounted for by norepinephrine.

DISCUSSION

The results of this study lend support for the hypothesis that...
sleep disturbance, commonly found in caregivers, is associated with plasma concentrations of norepinephrine and D-dimer. In addition, norepinephrine, a measure of SAM arousal, correlates with elevation in D-dimer, a marker of hypercoagulability previously linked to cardiovascular risk.\textsuperscript{41} Although previous research has independently demonstrated that sleep disturbance is associated with SAM activation\textsuperscript{42-44} and D-dimer,\textsuperscript{39} and that SAM activation is related to coagulation,\textsuperscript{32-35,45} ours is the first to demonstrate a relationship among each of these factors within the same sample. Specifically, this study provides preliminary evidence that poor sleep, over and beyond the effects of OSA, such as AHI and oxygen desaturation indexes,\textsuperscript{38} might also be associated with hypercoagulability. We demonstrated that 28% of the relationship between WASO and D-dimer was accounted for by plasma norepinephrine level, which suggests that SAM arousal may play a partial role in the relationship between sleep and hypercoagulation. This may expand the hemostasis literature by suggesting that more general sleep impairment, if related to increased SAM arousal, may elicit a procoagulant milieu much like OSA does.

Although this study found that WASO was significantly associated with elevations in plasma norepinephrine, which in turn were associated with increased D-dimer, our cross-sectional design precludes us from determining the causality of our results. In addition, our sleep assessments and blood draws did not occur on subsequent days but, rather, were separated in time. Finally, although neither WASO nor norepinephrine was significantly related to D-dimer in our final regression analysis, norepinephrine still accounted for 28% of the WASO-to-D-dimer relationship, suggesting that these nonsignificant relationships may be due to our small sample size. However, despite these limitations, we believe our demonstration that sleep disturbance, norepinephrine, and D-dimer are all interrelated lays preliminary groundwork to examine the relationship between sleep disturbance and D-dimer, which in turn promotes hypercoagulation. This speculation on our part is suggested by previous literature demonstrating that sleep disturbance may cause SAM activation,\textsuperscript{42,43} with loss of sleep serving to elevate nocturnal catecholamine levels.\textsuperscript{44} In turn, norepinephrine has been shown to have procoagulant effects, such as platelet activation and increases in activity of clotting factor VIII.\textsuperscript{31,35} Therefore, we urge future researchers to utilize experimental and longitudinal designs to examine the temporal relationships between general sleep disturbance, SAM activation, and hypercoagulability using larger samples.

Although our data demonstrate relationships between WASO, norepinephrine, and D-dimer, no such relationships were observed for sleep, epinephrine, and D-dimer. It is possible that, if mild sleep disturbance potentiates release of norepinephrine, this disturbance is not enough to stimulate release of epinephrine. Indeed, other studies have demonstrated differential catecholamine release as a function of specific stressors,\textsuperscript{46} with norepinephrine more readily released under mild stress.\textsuperscript{47,48} In fact, 95% of our sample evidenced 60 to 90 minutes of sleep disturbance (i.e., WASO), which may be sufficient to produce significant increases in norepinephrine, whereas even longer periods could be necessary to produce significant increases in epinephrine. Again, others must examine this hypothesis experimentally to determine the causal mechanisms behind differential catecholamine release.

Although epinephrine has long been known to have procoagulant effects,\textsuperscript{31,33} our results suggest that norepinephrine was more strongly associated with downstream coagulation activity (i.e., D-dimer levels) in relation to poor sleep. This is consistent with previous literature demonstrating the procoagulant effects of infused norepinephrine or norepinephrine surge elicited by acute mental stress in healthy individuals.\textsuperscript{31,34} In addition, by demonstrating that norepinephrine, but not epinephrine, was linked with D-dimer, our findings expand upon those of Ikarugi and colleagues,\textsuperscript{35} who found that norepinephrine, but not epinephrine, was related to platelet activity following sympathetic activation in response to physical exercise. However, we acknowledge that, given the lack of an association between poor sleep and epinephrine levels, the increase in the latter might have been too subtle to elicit coagulation activation.

Identifying a relationship between poor sleep and SAM arousal provides potential implications for how to improve caregivers’ overall health and possibly reducing their risk for cardiovascular disease. Specifically, interventions that help caregivers normalize sleep may also reduce SAM arousal and procoagulant activity. McCurry and colleagues\textsuperscript{46} examined the efficacy of a behavioral intervention for reducing sleep disturbance in a sample of caregivers of people with dementia. This intervention included strategies for sleep hygiene, stimulus control, and sleep compression and was superior to a wait-list control condition for improving sleep. Future researchers may wish to examine whether these improvements in sleep also produce reductions in SAM arousal in general and norepinephrine specifically.

In sum, our findings provide preliminary evidence that poor sleep, over and beyond the effects of OSA, is associated with increased SAM (as evidenced by plasma norepinephrine concentrations), which in turn is associated with plasma D-dimer, a widely used clinical marker of coagulation activation. Further, our mediational analysis indicated that norepinephrine accounted for 28% of the relationship between WASO and D-dimer. These data lay the initial groundwork for examining potential mechanisms by which poor sleep in general may be linked with cardiovascular health\textsuperscript{3} and elevated mortality risk.\textsuperscript{3}

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