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Brief Research Report

Poor sleep and inflammatory gene expression among care partners of persons living with dementia: a pilot trial of a behavioral sleep intervention

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Abstract

Objective: Poor sleep is associated with increased inflammation, thereby increasing the risk of chronic diseases and mortality. However, the effects of behavioral sleep interventions on the upstream inflammatory system are unknown among family care partners (CP). The present study explored the role of a behavioral sleep intervention program on inflammatory gene expression.

Methods: This was part of a randomized controlled trial of a sleep intervention for dementia care dyads with sleep problems. Thirty dyads were randomized to sleep intervention or control groups. Sleep outcomes for CP were assessed with 1 week of actigraphy and sleep diary, and the Pittsburgh Sleep Quality Index. Other information included CP demographics, body mass index, and intensity of caregiving tasks. All outcomes were collected at baseline, post-treatment, and 3-month follow-up.

Results: Neither group showed any significant differential changes in gene expression from baseline to post-treatment or 3-month follow-up. A decrease in inflammatory gene expression was significantly associated with more nights of good sleep (i.e. nights without trouble falling or staying asleep at night). This finding remained significant after controlling for group (intervention/control), timepoint (baseline, post-treatment, and 3-month follow-up), and CP characteristics (e.g. age and ethnicity).

Conclusions: Although better sleep was associated with decreased inflammatory gene expression, this study did not demonstrate any benefits of a behavioral sleep intervention over control, most likely due to a small sample. Studies with larger sample sizes are needed to test the specific aspects of disturbed sleep that relate to inflammatory biology among CP of persons living with dementia.

Key words: immune function; behavioral sleep medicine; geriatrics; insomnia

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Statement of Significance

Sleep quality among family care partners of people living with dementia is poor and associated with increased inflammatory markers. However, the potential role of behavioral sleep interventions on upstream markers of inflammation is unknown among the family care partners. In a randomized clinical trial pilot study, no significant differences in gene expression were found in care partners who received the tailored behavioral intervention compared to those who received general sleep hygiene information only. More nights of "good sleep" (i.e. falling asleep quickly and staying asleep during the night) based on the sleep diary were correlated with reduced inflammation gene expression among family care partners. Self-reported assessments of "good sleep" quality may capture disturbed sleep related to inflammatory biology.

Sleep disturbance is common among family members who participate in the care (i.e. care partners, CP) of persons living with dementia (PLWD). CP have trouble falling and staying asleep, poor self-reported sleep quality, frequent nighttime awakenings, long duration of time awake after sleep onset, and short sleep duration, which is worse with non-CP [1, 2].

Poor sleep among CP is associated with increased inflammation (e.g. C-reactive protein [CRP], tumor necrosis factor [TNF]-α, and interleukin-6 [IL-6]) [3, 4], which increases the risk for cardiovascular and other chronic disease, and mortality. Among CP, longer wake times after sleep onset were associated with increased IL-6 [3], and lower sleep efficiency was associated with elevated IL-6 and CRP, which was significantly stronger than in spouses without a caregiving role [1].

Sleep loss is also linked to elevated expression of proinflammatory genes in circulating immune cells [5, 6]. Nonpharmacological interventions to improve sleep, such as cognitive behavioral therapy for insomnia (CBT-I) and tai chi, reduced proinflammatory gene expression among adults with insomnia, suggesting a potential role of behavioral interventions in reversing genomic markers of inflammation [7]. Despite evidence for a relationship between poor sleep and immune function, the effects of behavioral sleep interventions on the upstream inflammatory system are unknown among CP with poor sleep.

We tested whether a behavioral sleep intervention for CP decreased inflammatory gene expression at post-treatment and 3-month follow-up. We also explored whether there was an association between improvement in objective and subjective sleep and decreased inflammatory gene expression at these time points.

Methods
Study design and participants

Data for these analyses were collected in a pilot randomized controlled trial of a dyadic sleep intervention program among PLWD and their CP. PLWD were eligible for the study if they (a) had a dementia diagnosis documented in their electronic medical record, (b) were community-dwelling, (c) had ≥1 sleep problem ≥3×/week on the Neuropsychiatric Inventory Nighttime Behavior Scale [8], (d) were able to ambulate with or without an assistive device, and (e) had an eligible CP. Eligibility criteria for CP included (a) living with an eligible PLWD, (b) age ≥ 21 years, (c) regularly assisting the patient with ≥ 1 of 6 basic activities of daily living (ADLs) [9] or ≥1 of 8 Instrumental ADL (IADLs) [10] for the past 6 months, (d) Pittsburgh Sleep Quality Index (PSQI) [11] total score > 5, indicating poor sleep quality, (e) Montreal Cognitive Assessment (MoCA) [12] ≥ 23, and (g) can communicate in English. Of 168 dyads screened, 45 were enrolled and completed baseline assessment. Of these, 30 were randomized to either the intervention ("Care2Sleep") or control group. Among CP, blood was collected to test the effects of the intervention on gene expression. Due to the COVID-19 pandemic, the collection of blood samples was halted early, with 11 CP providing samples at post-treatment and 7 CP at 3-month follow-up.

Intervention

Both the Care2Sleep and control conditions involved 5, weekly 1-hour sessions, with post-treatment and 3-month follow-up. Care2Sleep is a multicomponent behavioral intervention based on key components of CBT-I, daily walking and natural light exposure, and strategies to address dementia-related problematic behaviors. The control group received education about sleep, aging, and dementia without individualized recommendations. Detailed information about each group has been reported [13, 14].

Procedures

After consent, dyads completed a baseline assessment, including wrist actigraphy (Micro Motionlogger watch, Ambulatory Monitoring, Inc.) for seven consecutive nights and questionnaires on sleep health. CP also completed sleep diaries simultaneously with actigraphy. Post-treatment assessments (identical to baseline) began after the final intervention/control session and were repeated after three months (i.e. 3-month follow-up). Our local institutional review boards approved all study activities.

Measures

CP socio-demographic information included age, gender, race, ethnicity, and intensity of caregiving tasks for ADL and IADL [9, 10]. Body mass index (BMI) was also calculated from self-reported weight and height (kg/m^2).

Sleep outcomes included nighttime sleep efficiency (i.e. percent of the time spent asleep in bed at nighttime), total sleep duration, number of nighttime awakenings, and total wake time at night as measured by actigraphy. Simultaneous sleep diary items included bedtime, get-up time, dichotomous variables (yes/no) of trouble falling asleep, staying asleep at night, whether they took a nap during the day, and total nap duration. Sleep diary data defined "good sleep" as sleep latency ≤30 minutes and wake after sleep onset ≤30 minutes at night. Total nights of "good sleep" (out of 7) were used in analyses. CP also completed the PSQI [11] to indicate their perceived sleep quality over the past week.

Blood sample collection

Blood samples were collected into PAXgene RNA tubes (Qiagen PAXgene Blood RNA Kit; Qiagen, Valencia, CA) by a trained phlebotomist. To evaluate proinflammatory gene expression, RNA was extracted from PAXgene whole blood samples (Qiagen RNeasy), tested for suitable mass (Nanodrop spectrophotometry), and subject to genome-wide transcriptional profiling by RNA sequencing using a high-efficiency mRNA-targeted enzyme system (Lexogen QuantSeq 3' FWD), as performed by the UCLA Neuroscience Genomics Core Laboratory [15]. RNA was sequenced on an Illumina NovaSeq instrument, targeting >10 million sequencing reads per sample (achieved mean = 27.7 million), with sequencing reads mapped to the GRCh38 reference human transcriptome using the STAR aligner (average mapping rate = 80%) and quantified as gene-specific reads per million mapped reads.

Transcript abundance values were normalized to gene transcripts per million mapped reads, floored at 1 transcript per million to suppress spurious variation, log2-transformed to reduce skew, and mean-centered to facilitate linear model analyses that related the average expression of 16 canonical proinflammatory gene transcripts to other study variables in the context of a linear mixed-effect model [15]. The 16 analyzed transcripts (*CXCL8*, *FOS*, *FOSB*, *FOSL2*, *IL1B*, *JUN*, *JUNB*, *JUND*, *NFKB1*, *NFKB2*, *PTGS1*, *PTGS2*, *REL*, *RELA*, *RELB*, *TNF*) were selected from a set of 19 prespecified indicator transcripts after removal of 3 that showed minimal expression level and variance in this sample (SD = 0 log2 units).

Sample size

In prior work on the gene expression outcome [7], nonpharmacological treatment altered transcriptional profiling with an effect

size of 0.98, thus a priori estimates suggested $n = 15$ per group for statistical power of >80% (alpha = 0.05) [16, 17]. Sleep disturbance reversed inflammatory gene expression with effect sizes of 2.06 and 2.59, which requires 5 per group, providing a statistical power of >80% (alpha = 0.05) [5].

Statistical analyses

Linear mixed-effects models we used to quantify the relationship between sleep measures (actigraphy parameters, sleep diary "good sleep," and PSQI) and study condition (Care2Sleep vs. control group), time point (baseline, post-treatment, and 3-month follow-up; treated as a repeated measure), while controlling for covariates including demographics (age, gender, and ethnicity) [18] and BMI [19]. Parallel linear mixed model analyses quantified the relationship between expression of the 16 inflammatory genes (each mean-centered and treated as a repeated measure to account for correlation within the subject) and study condition (Care2Sleep vs. control), time point (baseline, post-treatment, and 3-month follow-up), and where indicated, the covariates and sleep measures (addressed above). Models included a compound symmetry covariance structure to account for correlated residuals within each subject at each time point.

Results

Baseline characteristics of randomized CP ($n = 30$) are presented in Table 1. CP in the Care2Sleep group cared for PLWD with higher ADLs and IADLs than controls ($p < .05$).

Initial analyses tested for differential change over time in sleep measures (controlling for demographic factors and BMI) and found no significant Group × Time interaction for PSQI scores, actigraphy measures, or average sleep diary "good sleep" reports

(all $F_{(2, 10)} < 3.61$, $p > .06$). However, unadjusted analyses did suggest a potentially favorable effect of Care2Sleep intervention on PSQI scores ($F_{(2, 14)} = 6.39$, $p = .011$), which was driven by a significantly greater PSQI improvement for intervention participants relative to controls at the immediate post-treatment time point ($F_{(1, 14)} = 5.76$, $p = .031$) but not at the 3-month follow-up ($F_{(1, 14)} = 2.04$, $p = .175$).

In parallel analyses of the 16 proinflammatory indicator gene transcripts, results showed a significant general decline in inflammatory gene expression over time (Time main effect: $F_{(2, 569)} = 7.07$, $p < .001$) but no difference in the magnitude of that decline in the intervention group relative to controls (Group × Time interaction: $F_{(2, 569)} = 0.48$, $p = .619$, see Figure 1). Similar results emerged from analyses that controlled for age, gender, ethnicity, and BMI (Time: $F_{(2, 370)} = 4.80$, $p = .009$; Group × Time: $F_{(2, 370)} = 1.42$, $p = .243$).

Secondary analyses examined relationships between sleep measures and inflammatory gene expression while controlling for intervention conditions, time points, age, gender, ethnicity, and BMI. Results showed a significant inverse relationship between inflammatory gene expression and the average nights of "good sleep" ($F_{(1, 369)} = 5.23$, $p = .023$). Inflammatory gene expression was not associated with PSQI scores or actigraphy measures (all $F_{(1, 369)} < 2.70$, $p > .09$).

Discussion

In this pilot randomized controlled trial of the Care2Sleep multicomponent, behavioral intervention program to improve sleep among CP for PLWD, results failed to identify any consistent effect of the intervention on objective measures of sleep quality or quantity (actigraphy), or self-report measures of sleep

Table 1. Baseline participant characteristics ($N = 30$ caregivers)

	Intervention ($n = 15$)	Control ($n = 15$)
	Mean (SD)/frequency (%)	Mean (SD)/frequency (%)
Age, years	64.2 (8.8)	69.9 (12.3)
Gender, female, %	13 (86.7%)	15 (100%)
Race		
White	9 (60.0%)	7 (46.7%)
Non-White	6 (40.0%)	8 (53.3%)
Ethnicity		
Hispanic	4 (26.7%)	3 (20.0%)
Non-Hispanic	11 (73.3%)	12 (80.0%)
Body mass index	25.3 (5.5)	28.0 (6.8)
ADL help for care recipients (range 0–6)[*,†]	3.9 (2.0)	5.5 (0.8)
IADL help for care recipients (range 0–8)[*,‡]	1.3 (1.7)	3.0 (2.0)
PSQI total score (range 0–21)	7.9 (3.0)	7.6 (4.4)
Total number of nights with good sleep (range 0–7)	3.2 (1.7)	3.6 (2.4)
Sleep Efficiency by wrist actigraphy, %	79.5 (7.5)	81.0 (5.7)
Total awake time by wrist actigraphy, minutes	97.1 (38.6)	99.2 (36.8)
Total sleep duration, minutes	467.9 (53.7)	506 (88.5)
Total number of nighttime awakenings	14.2 (5.7)	14.5 (6.9)

Abbreviations: ADL, activities of daily living; IADL, instrumental ADLs; PSQI, Pittsburgh Sleep Quality Index.
[*]Higher score indicates less numbers of assistance needs on PLWD's performing ADL/IADLs.
[†]$p = .005$.
[‡]$p = .015$.
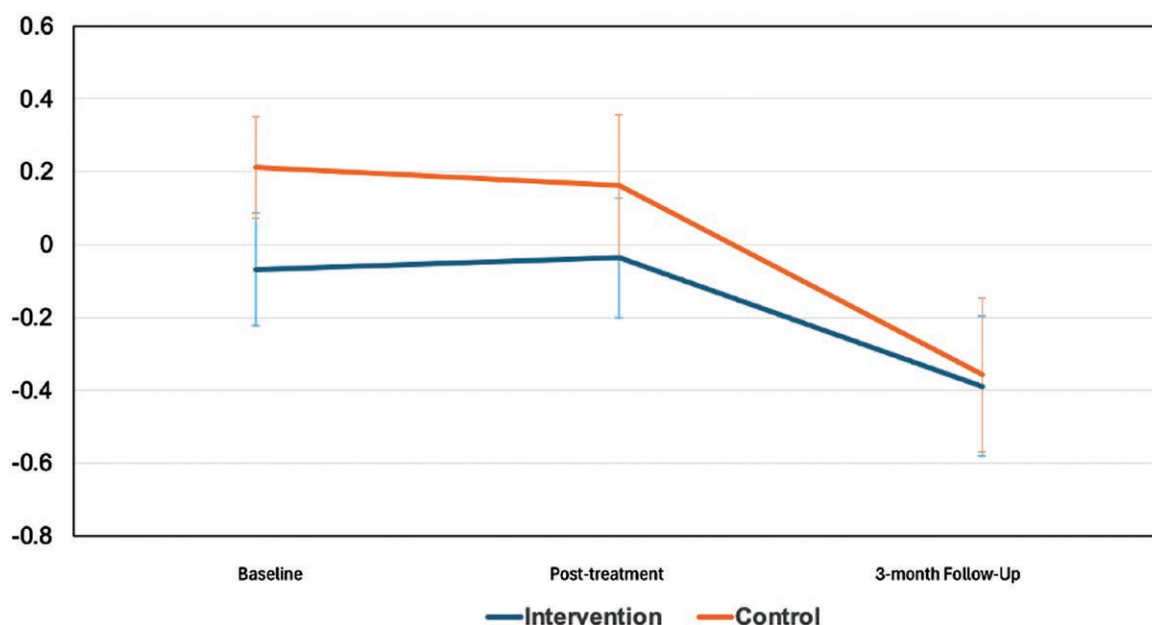
Figure 1. Inflammatory gene expression over time by group. *Note that gene expression values were mean-centered for analysis, therefore all values represent deviations from average pro-inflammatory gene expression across all participants and time points.

(diary-reported "good sleep" or PSQI survey results) or on inflammatory gene expression. However, secondary analyses identified a significant association between more diary-reported "good sleep" and lower levels of inflammatory gene expression. These results are consistent with previous research linking experimental sleep restriction to increased expression of inflammatory genes in circulating immune cells [5]. While CP with fewer nights of "good sleep" do not necessarily experience restricted sleep amount, this subjective measure of sleep quality may reflect interrupted sleep continuity leading to impaired daytime function, furthering the challenges of their caregiving role.

By contrast, actigraphy measures and sleep quality (PSQI) were not associated with inflammatory gene expression and may thus fail to capture the specific aspects of sleep disturbance that are most directly linked to inflammatory biology. This differs from prior studies [20, 21], which showed that actigraphy-measured sleep inconsistency (nightly fluctuations in sleep continuity) and lower sleep efficiency were significantly associated with cellular inflammatory markers (CRP, IL-6) in noncaregivers. Nevertheless, our conclusions remain tentative given the limited power achieved in these analyses stemming from the limited sample size. Future larger studies are needed to test whether the subjective daily assessment of "good sleep" may be a more sensitive or reliable measure of the specific aspects of disturbed sleep that relate to inflammatory biology.

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Disclosure Statement

Author Contributions

Yeonsu Song (Conceptualization [lead], Data curation [lead], Formal analysis [equal], Funding acquisition [lead], Investigation [lead], Methodology [lead], Project administration [lead], Resources [lead], Software [lead], Supervision [lead], Validation [lead], Writing—original draft [lead], Writing—review & editing [lead]), Jennifer Martin (Conceptualization [supporting], Data curation [supporting], Funding acquisition [supporting], Investigation [supporting], Methodology [supporting], Project administration [supporting], Resources [supporting], Software [supporting], Supervision [supporting], Writing—original draft [supporting], Writing—review & editing [supporting]), Susan McCurry (Conceptualization [supporting], Funding acquisition [supporting], Investigation [supporting], Methodology [supporting], Project administration [supporting], Writing—review & editing [supporting]), Monica Kelly (Writing—original draft [supporting], Writing—review & editing [supporting]), Edmond Teng (Conceptualization [supporting], Data curation [supporting], Funding acquisition [supporting], Investigation [supporting], Methodology [supporting], Resources [supporting], Supervision [supporting], Writing—original draft [supporting], Writing—review & editing [supporting]), Cathy A. Alessi (Conceptualization [supporting], Data curation [supporting], Formal analysis [supporting], Funding acquisition [supporting], Investigation [supporting], Methodology [supporting], Project administration [supporting], Resources [supporting], Writing—original draft [supporting], Writing—review & editing [supporting]), Michael

Irwin (Conceptualization [supporting], Data curation [supporting], Formal analysis [supporting], Funding acquisition [supporting], Investigation [supporting], Methodology [supporting], Project administration [supporting], Resources [supporting], Supervision [supporting], Validation [supporting], Writing—original draft [supporting], Writing—review & editing [supporting]), and Steve Cole (Conceptualization [supporting], Data curation [supporting], Formal analysis [lead], Investigation [supporting], Methodology [supporting], Project administration [supporting], Resources [supporting], Software [supporting], Supervision [supporting], Validation [supporting], Writing—original draft [supporting], Writing—review & editing [supporting])

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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