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Wearable-derived short sleep duration is associated with higher C-reactive protein in a placebo-controlled vaccine trial among young adults

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Inadequate sleep has been associated with an increased risk of mortality and various health issues. We previously conducted a placebo-controlled vaccination trial of healthy adults who were monitored by blood samples, questionnaires, and wearable devices. C-reactive protein (CRP), a systemic marker of inflammation, has been linked to numerous health outcomes, and was found to significantly increase post-vaccination in the trial. In this retrospective study, we investigated that if sleep was associated with an inflammation response triggered by perturbations from vaccine and placebo injections. Plasma hs-CRP levels were measured on the same day as the intervention, prior to the vaccine/placebo administration and two days after the intervention. Associations of sleep duration and CRP levels after vaccine/placebo administration in 188 trial participants were investigated by regression models adjusting for age, sex, body mass index (BMI), comorbidities, vaccination status (vaccination or placebo), and averaged daily steps. We found that shorter wearable-derived Total Sleep Time (TST) and Total Time in Bed (TIB), as well as subjectively assessed sleep duration from the Pittsburgh Sleep Quality Index (PSQI), were independently associated with higher incidence of CRP elevation after vaccine/placebo administration. Our study suggests that sleep deprivation could be a predictor for an increased inflammatory response and highlights a potential application of wearable-derived sleep metrics in public health.

Keywords Wearable-derived sleep duration, PSQI, C-reactive protein, Vaccine challenges, Inflammatory responses

C-reactive protein (CRP) is a systemic and sensitive marker of inflammation and infection[1]. The plasma levels of CRP increase rapidly with onset of an inflammatory stimulus and decrease quickly following the removal of the stimulus. Elevated CRP levels have been associated with inflammation, cancer, obesity, metabolic syndrome, and increased risk of cardiovascular diseases, including heart attack and stroke[1–5]. In addition, CRP was found to be elevated within the first 2 days after vaccinations[6]and returned to baseline values within 1 week[6,7]. The typical inflammatory response to vaccine has been characterized by tracking changes in inflammatory markers like CRP[8]. For example, Paine et al. found that administration of Salmonella Typhi vaccine significantly increased granulocytes and cytokines IL-6 and TNF-α with a peak after 6–8 h, and CRP with a peak after 24h[9]. Posthouwer et al. found that 48 h after influenza vaccine, alone or with the pneumococcal vaccine administration, CRP was substantially elevated[6]. It has been shown that a number of factors can affect such responses, for example cytokines can remain elevated for several weeks after vaccination in elderly[10], or have an insufficient increase in HIV-infected individuals[11], or individuals with major depressive disorder and trauma[12].

Other factors, such as sleep, may also affect the immune response to vaccinations since sleep plays an essential role in physical and physiological functions. Inadequate sleep duration has been associated with an increased risk of mortality and a variety of adverse health outcomes, such as cardiovascular disease, abdominal obesity, hypertension, and mental disorders[13–15]. Other studies have shown the importance of appropriate sleep

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duration for proper immune system function. For instance, short sleep duration has been indicated as a factor in the susceptibility to infectious illnesses such as the common cold and COVID-19[14,16–18]. Recent research found that insufficient sleep was associated with decreased immunologic response to several types of vaccines and may impair the development of immunity to vaccinations[6]. Furthermore, extreme sleep durations have been reported to lead to increased levels of inflammatory markers, particularly CRP[19–22]. A longitudinal analysis of sleep duration and biomarkers showed that longer sleep duration was associated with elevated CRP levels[21,22]. In contrast, other studies reported that subjects experiencing sleep deprivation exhibited raised CRP levels[19].

In addition to duration, sleep quality has also been reported to influence immune response. Poor sleep continuity, disturbance of sleep architecture, and poor sleep quality have been found to correlate with susceptibility to infections[9]and elevated CRP levels[17].

The digital revolution has led to a proliferation of wearable technologies that can automatically detect and track sleep in real-time[23]. Since the passive tracking of sleep metrics using wearables is more accessible and less intrusive compared to subjective sleep questionnaires and gold standard polysomnography (PSG), wearable devices are useful for monitoring sleep health in real-world settings[24–26]. Despite recent research exploring the potential and reliability of wearable-derived sleep metrics[24], the role of sleep metrics from wearables in public health remains unclear.

We recently conducted a triple-blinded, randomized clinical trial which aimed at mimicking mild inflammatory responses in real infections using vaccinations[7]. Trial participants were administered either vaccinations or placebo injections and were monitored over 4 weeks by blood samples, wearable devices, and questionnaires. Wearable devices were used to continuously monitor participant physiology (including during sleep). In terms of changes in blood biomarkers post-vaccination/placebo, we specifically found that CRP levels increased following administration of both Typhoid Vi Polysaccharide (Typhim Vi) and Pneumococcal Polysaccharide Vaccine (PPSV23) vaccines[7].

In this retrospective study, we aimed to fill the knowledge gap regarding sleep duration and inflammatory responses triggered by vaccination or placebo administrations. Specifically, we focused on objectively measured sleep duration measured by wearable devices and investigated how these sleep metrics from wearables were associated with the inflammation biomarker CRP. We focused specifically on sleep duration and efficiency as sleep has been found to be accurately detected with the Oura Generation 2 smart ring (89% accuracy in sleep vs. awake estimation)[27], which was one of the wearable devices used in the clinical trial[27–30]. While measured by the Oura ring, we did not investigate metrics such as sleep quality since they are dependent on time spent in specific sleep stages and have more variability (61% agreement with PSG in multi-state categorization)[27]and a precise assessment would require an assessment via polysomnography[31].

Methods

Summary of previously completed clinical trial

In this study, we investigated the participants who were enrolled in the Persistent Readiness Through Early Prediction (PREP) immunization study. PREP was a triple-blinded, randomized clinical trial conducted at Texas A&M University in 2022[7]. The details of the study design, participant selection, and data collection of the PREP study were published previously in Wang et al[7]. Here, we briefly summarize aspects of the trial that are relevant to the current study.

Study population

A CONSORT diagram illustrating participant assessment for eligibility, randomization, and on site visits for clinical trials data used in the current study was published previously[7]. Following a 14-day baseline period, healthy participants, aged 18–40 years, were randomly administrated either a PPSV23, Typhim Vi, or placebo vaccination (NCT05346302). Only participants who were judged to be in satisfactory health based on medical history and physical examination based on a physician's judgment were included in the trial. Participants diagnosed with chronic diseases, such as diabetes and asthma, were excluded. Data was collected at various time points over 4 weeks from blood samples, wearable devices, and questionnaires. Following a 2-week baseline period, 210 healthy participants, aged 18–40 years, were administered either a PPSV23, Typhim Vi, or placebo vaccination. Pneumococcal Polysaccharide Vaccine (PPSV23) is a vaccine designed to protect against pneumococcal disease, which is caused by *Streptococcus pneumoniae*[32]. Typhoid Vi Polysaccharide Vaccine (Typhim Vi) is designed to protect against Typhoid fever, which is a potentially life-threatening intestinal illness caused by *Salmonella Typhi*[33]. Informed consent was obtained from the participants. The study was approved by the Texas A&M University Institutional Review Board (IRB) and Human Research Protection Official, as well as registered on clinicaltrials.gov (NCT05346302), in accordance with relevant guidelines and regulations. We included clinical trial participants in the current study if they had at least 3-nights data tracked by a smart-ring wearable device (Oura ring) during the 14-day baseline period and high-sensitivity (hs)-CRP measurements available prior to interventions and after 2-days post interventions.

Assessment of sleep quality from wearable sleep metrics

To assess sleep metrics in the current study, we used data from the Oura ring (Generation 2), which continuously monitors physiological changes and sleep during the night. Derived features such as heart rate and heart rate variability (root mean square of the successive differences—RMSSD), as well as hypnogram, activity and readiness summaries for each night were provided by Oura in csv format. For each participant, we extracted daily sums of those derived features prior to vaccination and then calculated the average to obtain mean sleep duration during the 14-days baseline period. Wearable-derived Total Time in Bed (TIB) was defined as total time spent in bed throughout the night, summing the duration of Awake, Light, Rapid Eye Movement (REM), and Deep sleep stages recorded by the Oura ring. Wearable-derived Total Sleep Time (TST) was defined as total

asleep time throughout the night, summing the duration of all sleep stages (Light, REM and Deep) recorded by the Oura ring. Wearable-derived sleep efficiency (SE) was calculated as the ratio of time spent asleep to time spent in bed.

Questionnaire

The Pittsburgh Sleep Quality Index (PSQI), a self-reported questionnaire with 19 individual questions, was administered during PREP to estimate sleep quality and disturbance over the one-month time interval. The PSQI questionnaire was administered at 7 days prior to vaccination or placebo injections to record the subjective sleep matrices at baseline. Participants were asked about their sleep habits, for example bedtime, getting up time, and sleeping troubles. Scoring of those questions yields 7 "component scores", each with a scale of 0–3, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction[34]. For example, question 4 was designed to capture subjective sleep duration by asking, "*During the past month, how many hours of actual sleep did you get at night?*". The total of the 7 component scores generates a global sleep quality score ranging from 0 to 21. A high score suggests poor sleep quality. During the data collection, the daily questionnaire was collected via MyCAP, where participants were asked to self-report symptoms and any medical testing for infection that they had received[7].

Measurements of hs-CRP levels

During PREP, blood samples were drawn after fasting overnight to perform the clinical biomarker measurement. Blood samples were collected on the same day as vaccination (prior to immunization), 2 days post-vaccination, and 7 days post-vaccination. Blood samples were sent promptly to CLIA-certified Quest Diagnostics for measurement of high-sensitivity C-reactive protein (hs-CRP). Additional blood was processed and stored at −80 °C for batch-wise analysis. Participants whose results were returned as "out of range" by Quest Diagnostics were re-analyzed using the stored samples. Samples were thawed and prepared according to the standard operating procedure for the hs-CRP (part number: 05401607190) kit on the COBAS c111 (Roche Diagnostics, Indianapolis, IN).

Statistical analyses

In the current study, baseline wearable characteristics of the participants were compared by groups using Fisher's exact tests for categorical variables and Kruskal–Wallis rank sum tests for continuous variables across the sleep duration groups. To better investigate post-vaccination associations between sleep duration and incidence of hs-CRP elevation (> 0 mg/L), wearable-derived TST was categorized into three group: less than 6 h (< 6 h), up to 7 h (> = 6 h and < = 7 h) and more than 7 h (> 7 h). Wearable-derived TIB was categorized by quartile. The levels of hs-CRP elevation relative to baseline were calculated by subtracting the CRP baseline levels from the CRP levels measured on day 2 post-administration. The hs-CRP elevation event was identified by an increase in CRP levels post-administration relative to baseline levels. Multivariable logistic regression was performed, with hs-CRP elevation relative to baseline after administration as the dependent variable and the sleep duration group as the predictor variable, adjusting for age, sex, body mass index (BMI), comorbidities, vaccination status (vaccination or placebo), and averaged daily steps. Multivariable linear regression was utilized when CRP elevation levels relative to baseline were treated as a continuous dependent variable with the same predictors in the models. The pre-specified confounders were known factors that potentially affect changes in CRP levels, based on literature review, domain knowledge, and preliminary univariate analysis[35–37]. Participants were defined as having a comorbidity if they reported any medical condition according to the Charlson Comorbidity Index and any additional comorbidities. The detailed list of comorbidities was shown in Supplementary Materials in Table S1. The covariate averaged daily steps was estimated by averaging the daily steps derived from the Oura ring in the 14-days baseline prior to vaccination. Vaccination status was defined by whether the participant was administrated a vaccination (PPSV23 or Typhim Vi) or placebo in the PREP study. Additionally, we conducted a baseline model to evaluate whether hs-CRP elevation was caused by inflammation induced by vaccination/placebo injections. In the baseline model, elevated hs-CRP at baseline was defined as hs-CRP level greater than 3 mg/L[38]. All analyses were performed using Python software packages.

Results

Cohort characteristics

A total of 206 volunteers enrolled and completed the study from February to December 2022. Participants were excluded from the study if they lacked either any measurements recorded from Oura at baseline (N = 6), or hs-CRP measurements prior to vaccination and after post 2-days vaccination (N = 12). This yielded a total of 188 participants for the final analysis (Fig. 1). Participant baseline characteristics before interventions are displayed in Table S2. The median age was 23 years (interquartile [IQR], 21 to 27 years), the median body mass index was 24.9 kg/m2 (IQR, 22.3 kg/m2 to 28.3 kg/m2), and there was a male to female ratio equal to 1. The median wearable-derived TST and TIB over 14-day baseline prior to intervention were 6.60 h (IQR, 5.96, 7,13 h) (Figure S1) and 7.79 h (IQR, 7.30 to 8.56 h), respectively. The median hs-CRP levels at baseline and 2 days post-intervention were 1.1 mg/L (IQR, 0.5 to 2.4 mg/L) and 1.8 mg/L (IQR, 0.7 to 3.3 mg/L), respectively. 58% of those participants had hs-CRP increased at the 2-day post-intervention, with median change of 0.1 mg/L (IQR, −0.1 to 1.0 mg/L) (Figure S1).

Correlation between subjective and objective sleep measurements

To investigate the relationship between objective and subjective sleep measurements and further inform sleep metrics for further analysis, we compared the objective wearable-derived TST from Oura to the 7 component scores and global sleep scores from the subjective PSQI questionnaire (Table S3). Longer wearable-derived

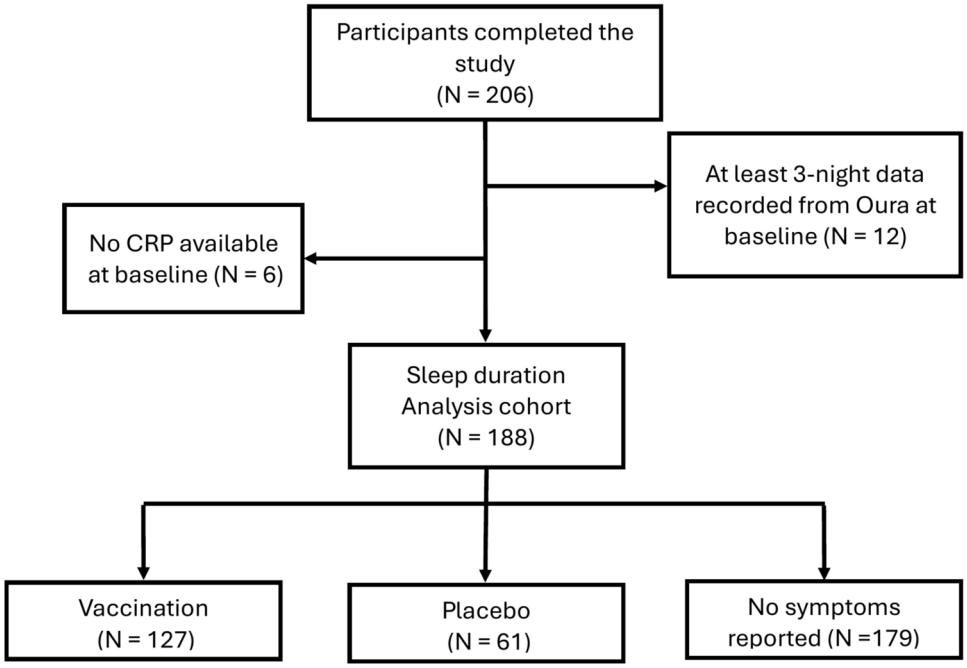

Fig. 1. Flow diagram summarizing cohort selection for sleep duration analyses.

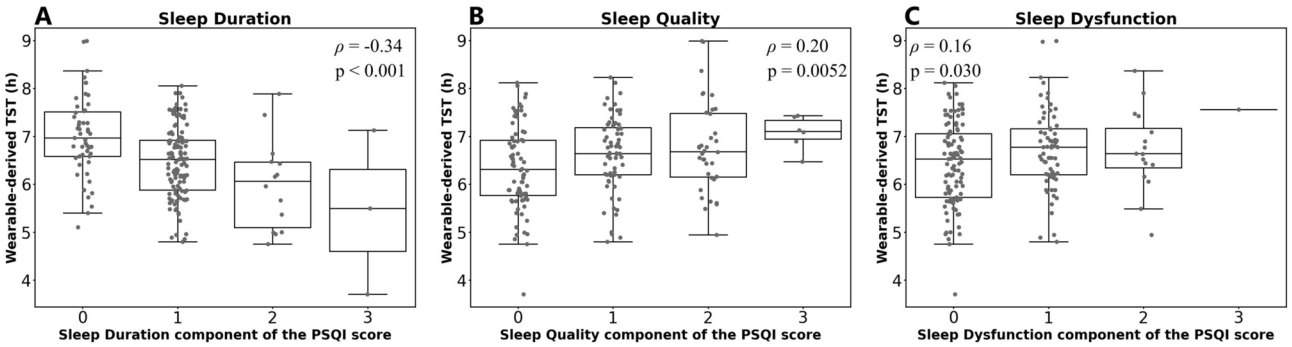

Fig. 2. The associations between objective wearable-derived sleep metrics from Oura and subjective sleep component score metrics from PSQI. Abbreviations: PSQI = Pittsburgh Sleep Quality Index.

TST was significantly correlated with lower self-reported sleep duration score (r = −0.341, p < 0.001) (Fig. 2A). Wearable-derived TST showed a significant positive correlation with sleep quality (r = 0.203; p = 0.005) and sleep dysfunction scores (r = 0.159; p = 0.030) from PQSI responses (Fig. 2B**,** Fig. 2C). However, subjective sleep latency, habitual sleep efficiency and sleep global scores exhibited non-significant positive correlations with wearable-derived sleep duration (all p > 0.05). The results were similar when comparing wearable-derived TIB and PSQI scores, except for significant correlation between TIB and PSQI sleep latency (r = 0.155; p = 0.034) and disturbance (r = 0.213; p = 0.003) component score (Table S3). However, no significant concordances were found between wearable-derived SE and PSQI scores (Table S3).

Wearable-derived TST and hs-CRP

Participant baseline characteristics and changes of hs-CRP after intervention by wearable-derived TST are displayed in Table 1. The distribution of wearable-derived TST was 26.1%, 44.7% and 29.2% for < 6, < = 7 and > 7 h, respectively (Table 1). We found that there was a higher incidence of CRP elevation (p = 0.031) after intervention (Fig. 3) and a higher proportion of males (p < 0.001) in the group with shorter TST group (< 6h) compared to other groups (Fig. 4A). In addition, longer sleepers tended to report comorbidities (p = 0.004) and psychological issues (p = 0.005) more often (Table 1, Fig. 4B**,** Fig. 4C). In a logistic regression model adjusting for potential confounders and using TST > 7 h as the reference, those who slept less than 6 h have a higher incidence of hs-CRP elevation after vaccination and placebo injections in comparison to those who slept more than 7 h (< 6 h , OR = 3.79, 95% CI: 1.45–9.91; < = 7, OR = 1.41, 95% CI: 0.66 −3.02; > 7 h, 1[reference]), suggesting that shorter sleep duration was independently associated with a higher incidence of hs-CRP elevation after intervention

	< 6 h	> = 6 and < = 7 h	> 7 h	P value
N	49	84	55	
Wearable-derived TST, hours	5.6 [5.0,5.7]	6.6 [6.3,6.8]	7.5 [7.3,7.7]	< 0.001
PSQI sleep quality score	0.0 [0.0,1.0]	1.0 [0.0,1.0]	1.0 [0.0,2.0]	0.007
PSQI sleep latency	1.0 [0.0,1.0]	1.0 [1.0,2.0]	1.0 [0.5,2.0]	0.219
PSQI sleep duration score	7.3 [6.5,8.0]	7.5 [7.0,8.3]	8.3 [8.0,9.0]	< 0.001
PSQI sleep efficiency score	1.0 [1.0,1.0]	1.0 [1.0,1.0]	1.0 [0.0,1.0]	< 0.001
PSQI sleep disturbance score	0.0 [0.0,1.0]	0.0 [0.0,1.0]	0.0 [0.0,1.0]	0.35
PSQI Sleep dysfunction score	1.0 [1.0,1.0]	1.0 [1.0,1.0]	1.0 [1.0,1.0]	0.174
PSQI sleep global score	0.0 [0.0,1.0]	1.0 [0.0,1.0]	0.0 [0.0,1.0]	0.015
CRP at baseline, mg/L	1.1 [0.3,2.3]	1.0 [0.5,2.1]	1.3 [0.6,4.2]	0.262
CRP at 2 days post intervention, mg/L	2.1 [0.7,3.4]	1.5 [0.6,2.9]	2.2 [0.7,4.0]	0.201
Changes of CRP from baseline[a], mg/L	0.6 [0.0,1.8]	0.1 [−0.1,0.7]	0.0 [−0.3,0.9]	0.044
Elevation of CRP[b], n (%)				0.031
No	13 (26.5)	38 (45.2)	28 (50.9)	
Yes	36 (73.5)	46 (54.8)	27 (49.1)	
Age, years	23.0 [22.0,25.0]	23.0 [20.8,28.0]	22.0 [20.0,26.0]	0.388
Sex, n (%)				< 0.001
F	9 (18.4)	50 (59.5)	35 (63.6)	
M	40 (81.6)	34 (40.5)	20 (36.4)	
BMI, kg/m^2	24.3 [22.6,28.0]	25.5 [22.4,28.5]	24.3 [22.0,28.1]	0.661
Mean Steps	7954.1 [6515.6,10,346.1]	7528.6 [5840.5,10,100.9]	6781.3 [5563.1,9264.0]	0.084
Mean resting heart rate, bpm	53.6 [51.0,58.1]	55.1 [50.3,60.9]	56.9 [52.0,61.4]	0.344
Mean heart rate, bpm	60.0 [57.8,66.2]	62.5 [56.4,68.7]	64.0 [59.2,69.1]	0.236
Mean RMSSD, ms	56.8 [47.6,71.0]	61.5 [43.7,82.1]	52.2 [36.4,66.0]	0.129
Any comorbidities[c], n (%)				0.004
No	45 (91.8)	71 (84.5)	37 (67.3)	
Yes	4 (8.2)	13 (15.5)	18 (32.7)	
Psychological issues[d], n (%)				0.005f
No	46 (93.9)	78 (92.9)	42 (76.4)	
Yes	3 (6.1)	6 (7.1)	13 (23.6)	
Vaccine group, n (%)				0.78
Placebo	13 (26.5)	30 (35.7)	18 (32.7)	
Typhim Vi	16 (32.7)	28 (33.3)	19 (34.5)	
PPSV23	20 (40.8)	26 (31.0)	18 (32.7)	

Table 1. Baseline characteristics of the study participants by wearable-derived TST. Definition of abbreviations: TST = Total Sleep Time; PSQI = Pittsburgh Sleep Quality Index; BMI = Body Mass Index; CRP = C-Reactive Protein; FFMI = fat free body mass index; IQR = The Interquartile Range; PPSV23 = Pneumococcal Polysaccharide vaccine, Typhim Vi = Typhoid Vi Polysaccharide vaccine; RMSSD = root mean square of the successive differences. Data presented as n (%) or median [IQR] unless otherwise noted. [a]Changes of CRP from baseline were calculated by subtracting the CRP baseline levels from the CRP levels measured on day 2 post-administration. [b]The hs-CRP elevation event was identified by an increase in CRP levels post-administration relative to baseline levels. [c]Subjects were defined as having comorbidity if they reported any medical condition according to the Charlson Comorbidity Index[55] and any additional comorbidities. [d]Psychological issues = anxiety, depression, mood disorder.

(Table 2, Fig. 5). The AUC of this logistic model to predict the hs-CRP elevation after interventions was 0.72 (Figure S2 A). Short sleep duration remained a significant predictor (p = 0.035) for increased hs-CPR levels using multivariate linear regression after adjusting for confounders (Table 2). This significant association was no longer present when sleep duration was fit as a continuous variable. For reference, in the baseline model to assess the association between wearable-derived TST and hs-CRP elevation during baseline prior to vaccination, there was no significant difference observed in the odds of hs-CRP elevation among different groups of TST (Table S4, Figure S2 B).

Wearable-derived TIB and hs-CRP

The associations between wearable-derived TIB and incidence of elevation of hs-CRP after intervention was also evaluated. Participant baseline characteristics and changes of hs-CRP after vaccination and placebo administration were compared across the wearable-derived sleep duration quartiles. The median wearable-derived TIB was 6.9, 7.5, 8.1 and 8.9 h for quartile 1, 2, 3 and 4, respectively (Table S5). We found that there were

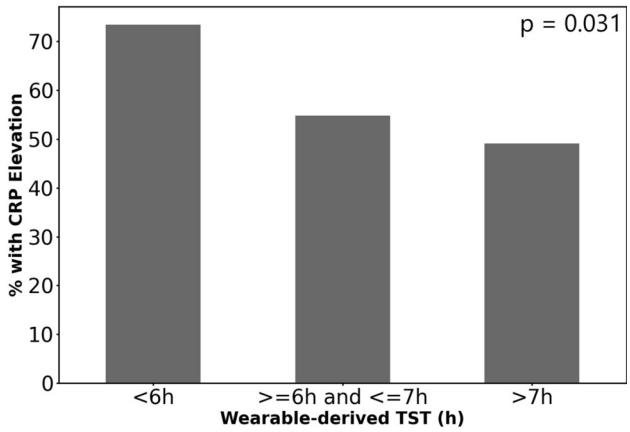

Fig. 3. Relationship between wearable-derived TST and incidence of CRP elevation after vaccination and placebo administration. The incidence of CRP elevation was 73.5% for those with less than 6 h of sleep, 54.8% for those with up to 7 h of sleep, and 49.1% for those with more than 7 h of sleep.

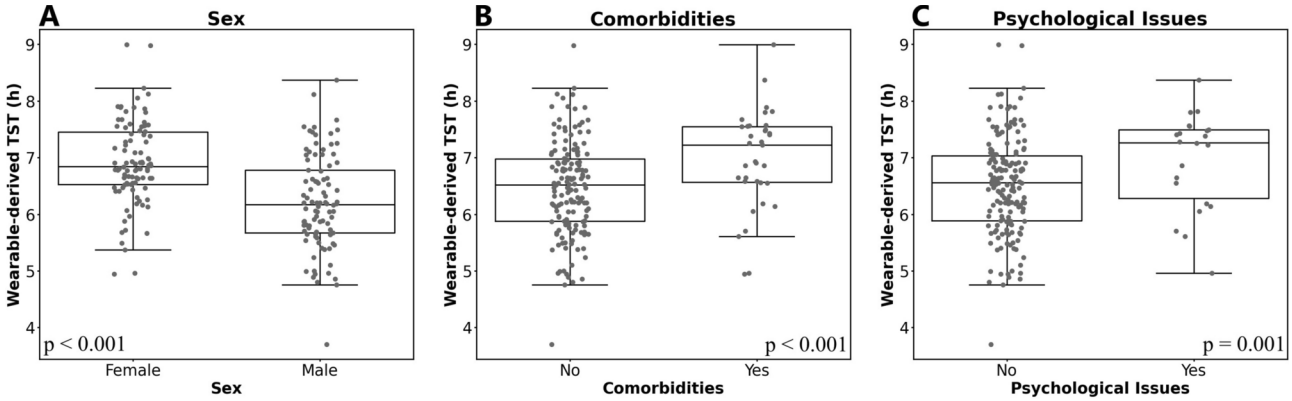

Fig. 4. Distribution of continuous wearable-derived TST by (**A**) sex, (**B**) comorbidities and (**C**) psychological issues. Abbreviations: TST = total sleep time; [a]Subjects were defined as having comorbidity if they reported any medical condition according to the Charlson Comorbidity Index[55] and any additional comorbidities. [b]Psychological issues = anxiety, depression, mood disorder.

more increases of hs-CRP from baseline after vaccination and placebo administration (p = 0.02) in an unadjusted analysis (Table S5). In a logistic regression model adjusting for potential confounders and using 3rd quartile of sleep duration as reference, those who slept least in the 1st quartile had higher incidence of hs-CRP elevation after vaccination in comparison to those who slept around 8.1 h in the 3rd quartile (1st quartile, OR = 3.30, 95% CI: 1.25–8.73; 2nd quartile, OR = 1.37, 95% CI: 0.55 −3.40; 3rd quartile, 1[reference]; 4th quartile, OR = 1.12, 95% CI: 0.46 – 2.74), suggesting that shorter wearable-derived TIB was also independently associated with higher incidence of hs-CRP elevation after vaccination/placebo administration (Table S6).

Subjective PSQI sleep duration with hs-CRP

For comparison with objective sleep duration results, we also assessed the associations between PSQI sleep duration and incidence of elevation of hs-CRP after vaccination/placebo administration. Since there were only 3 individuals who reported sleeping less than 5 h (component score = 3), we combined those who slept less than 5 h and those who slept less than 6 h (component score = 2) into one group. The distribution of wearable-derived sleep duration was 27.1%, 63.8%, and 9.1% for < 6, < = 7 and > 7h, respectively (Table S6). Similarly, there was a higher incidence of hs-CRP elevation (p = 0.024) after vaccination/placebo administration in shorter TST group (< 6h) compared to other groups (Table S7). However, no significant differences between males and females were observed across the subjective sleep duration groups. In a logistic regression model adjusting for potential confounders and using subjective sleep duration of more than 7 h as the reference, those who slept less than 6 h had higher incidence of hs-CRP elevation after vaccination /placebo administration in comparisons to those who slept more than 7 h (< = 6 h , OR = 6.78, 95% CI: 1.30- 35.4; < = 7, OR = 1.26, 95% CI: 0.62 – 2.56; > 7 h, 1[reference]). This suggests that a subjectively shorter sleep duration was independently associated with a higher incidence of hs-CRP elevation after vaccination/placebo administration (Table S8).

		Elevated hs-CRP (categorical)		Elevated hs-CRP (continuous)	
Covariate	**Comparator**	**OR [95% CI]**	**P-value**	**Estimate [95% CI]**	**P-value**
Wearable-derived TST (< 6h)	< 6 h: > 7 h	3.79 [1.45, 9.91]	0.007	3.34 [0.23, 6.45]	0.035
Wearable-derived TST (> = 6 h and < = 7h)	< = 7h and > = 6 h: > 7 h	1.41 [0.66, 3.02]	0.379	0.96 [−1.60, 3.51]	0.46
age	1 years	0.90 [0.84, 0.97]	0.004	0.073 [−0.16, 0.31]	0.54
Sex	Male: Female	0.61 [0.31, 1.22]	0.162	−1.47 [−3.70, 0.75]	0.19
BMI	1 point	1.05 [0.98,1.12]	0.179	−0.14 [−0.35, 0.072]	0.20
Comorbidities[a]	Yes: No	0.59 [0.26, 1.38]	0.228	−0.68 [−3.53, 2.17]	0.64
Vaccination status[b]	Vaccine [b]: Placebo	2.46 [1.25, 4.83]	0.009	−0.0004 [−2.26, 2.26]	1.0
steps	1000 steps	0.95 [0.85, 1.05]	0.321	−0.24 [−0.59, 0.11]	0.18

Table 2. Association of hs-CRP levels trigged by interventions with wearable-derived TST in multivariable logistic and linear regression (N = 188). Definition of abbreviations: TST = Total Sleep Time; BMI = Body Mass Index; CRP = C-Reactive Protein; CI = Confidence interval. [a]Subjects were defined as having comorbidity if they reported any medical condition according to the Charlson Comorbidity Index[55] and any additional comorbidities. [b]Vaccine = PPSV23 or Typhim Vi.

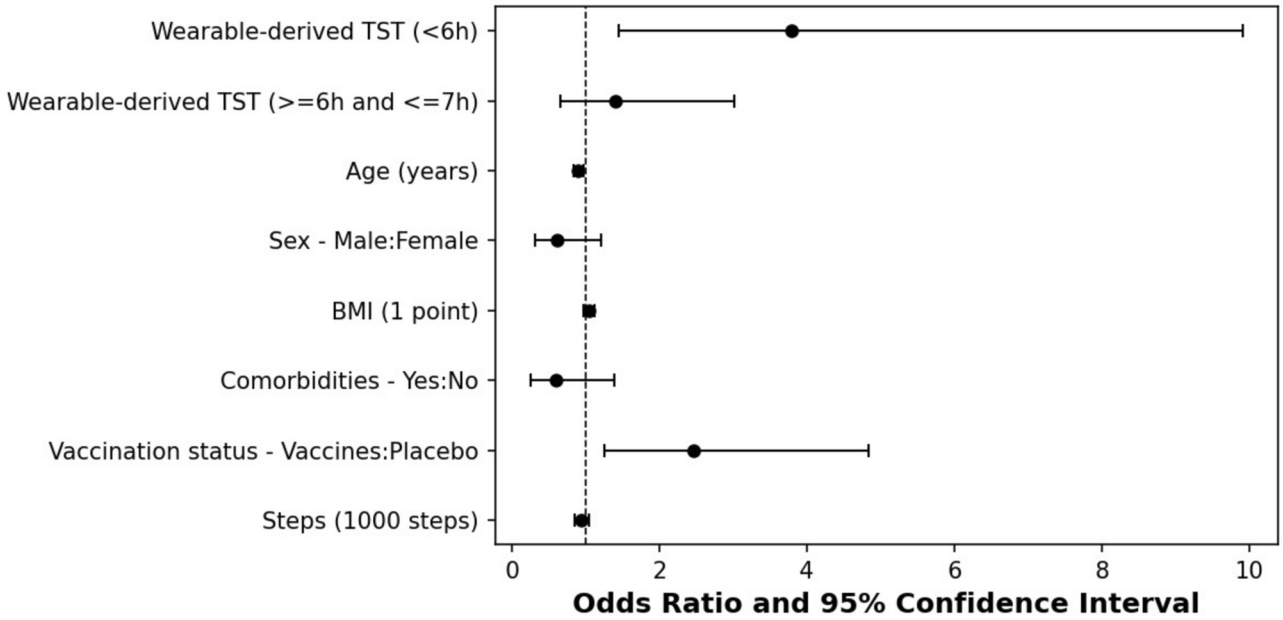

Fig. 5. Relationship between wearable-derived TST and incidence of CRP elevation after vaccination and placebo injections in a logistic model regression model adjusting for age, sex, BMI, physical activity, interventions and health status. Shorter wearable-derived TST was significantly associated with increased incidence of CRP elevation.

Sensitivity analysis

In a sensitivity analysis aimed at reducing potential effects of hs-CRP changes induced by other infections, we excluded 10 subjects who reported feeling ill and tested for infections (e.g., COVID-19, influenza, and strep throat) in the daily survey (N = 179). When we restricted the cohort by excluding those subjects, none of the analyses was substantively changed (results not shown). In a secondary sensitivity analysis, we restricted the study population administered with vaccination (N = 127). Short wearable-derived TIB was still independently associated with hs-CRP elevation (1st quartile, OR = 5.17, 95% CI: 1.48–18.05; 2nd quartile, OR = 1.66, 95% CI: 0.55–5.01; 3rd quartile, 1[reference]; 4th quartile, OR = 2.27, 95% CI: 0.77 −6.72) (Table S9). However, short

wearable-derived TST and sleep duration from PSQI were not significantly associated with a higher incidence of elevated hs-CRP, likely due to insufficient sample size (not shown).

Discussion

In this study, we demonstrated how sleep metrics from commercially available wearables could be used in public health, particularly within the context of the response to inflammation in a medium-size clinical trial cohort of 188 healthy young adults over 14-days baseline and 2-day post intervention time windows. First, we compared objectively recorded sleep metrics, including TST, SE, and TIB by Oura rings, with subjective sleep scores from PSQI. Our analysis indicated moderate correlations between wearable-derived TST and TIB with PSQI sleep duration, sleep quality and sleep dysfunction component scores. However, no significant correlations were observed between wearable-derived SE and PSQI scores. In addition, we identified both sex and health status associated with wearable-derived TST and TIB. Furthermore, our findings revealed that shorter wearable-derived TST and TIB recorded by Oura, and subjective sleep duration from PSQI at baseline, was associated with an increased incidence of hs-CRP elevation after vaccination or placebo injections, which was consistent with the correlation study that found a significant association between objective, wearable-derived sleep duration and subjective PSQI sleep duration. Importantly, this association was independent of known potential confounders, including age, sex, BMI, comorbidities, interventions (vaccination or placebo), and averaged daily steps. We also observed a significant inverse association between age and the incidence of hs-CRP elevation after intervention, which is expected given that aging was often associated with a diminished inflammatory response to vaccines due to immunosenescence[35]. To our knowledge, this is the first report of an association between wearable-derived sleep duration and experimentally induced CRP elevation in healthy young adults. Given vaccination or placebo injections could induce mild inflammation and CRP is a sensitive inflammation biomarker, our results suggest that sleep duration could represent a risk factor for inflammation triggered by such stimuli.

We first explored the correlation between objectively recorded sleep by Oura rings and subjective sleep assessments from PSQI questionnaires. We observed a significant moderate correlation between Oura-recorded TST and TIB and self-reported sleep duration sub-score from PSQI, suggesting a general agreement between the objective and subjective measurement of sleep duration, despite some discrepancies. This finding aligns with previous studies comparing objectively recorded sleep duration (using PSG, actigraphy and Fitbit) with self-reported sleep duration[26,39]. For example, Teo et al. reported a weak, but significant correlation of 0.28 between wearable-derived sleep duration (Fitbit) and self-reported sleep duration[26]. In addition, our analysis showed that wearable-derived sleep duration was significantly correlated with higher self-reported PSQI scores for sleep quality and sleep dysfunction. This indicates longer sleep duration was associated with poorer perceived sleep quality and greater sleep dysfunction. When comparing wearable-derived sleep efficiency (SE) with self-reported PSQI scores, no significant concordances were found. This finding is consistent with previous reports showing weak or no correlation between objectively-measured and PSQI-derived habitual SE[40]. One possible explanation for this discrepancy is the distinction between subjective and objective measures might be more pronounced with sleep efficiency as a metric than with sleep duration. While wearable devices like Oura ring can track the ratio of time spent asleep to time spent in bed, this does not necessarily capture the full complexity of an individual's perception of sleep experience, such as personal expectations, sensitivity, and psychological components. Our comparison between wearable-derived and PSQI-derived sleep metrics will inform investigators on the use of wearable-derived sleep measurements to refine methodologies and improve the accuracy of sleep studies in future research.

Our study protocol allowed us to investigate the relationship between wearable-derived sleep metrics with demographics, daily activities, and health status. We found that wearable-derived TST and TIB were significantly associated with sex and comorbidities, particularly physiological issues. Previous studies have reported that women tend to sleep longer than men across various study populations and age groups, attributed to a combination of physiological, biological, environmental, and social factors, which is consistent with our findings[41]. Moreover, our univariate analysis revealed that young adults with health concerns had longer recorded TST and TIB, suggesting they might exhibit altered sleep patterns. One possible explanation is that health conditions, such as stress and anxiety, could be closely linked with a variety of factors (e.g., poor sleep quality, dysregulation of the sleep–wake cycle, medication side effects), leading to increased sleep[42]. These findings underscore the importance of considering possible moderators (e.g., sex, health factors) when assessing sleep behaviors and interventions.

Although wearable-derived sleep duration has not previously been associated with vaccination-induced CRP levels, sleep duration has been associated with inflammatory biomarkers, including CRP, in various clinical studies with mixed findings[20,43–47]. In a longitudinal study, shorter sleep and decreases in sleep duration were associated with higher levels of CRP over a 5-year period, even after adjusting for demographics and occupation[47]. Both acute total and short-term partial sleep deprivation has been shown to raise basal levels of CRP in young healthy adults[43]. However, a meta-analysis of cohort studies, including 72 studies with a total sample size more than 50,000, showed that extreme long sleep duration, but not short sleep duration, was associated with higher levels of CRP and IL-6[44]. Interestingly, another large-scale study in American adults found CRP was elevated among extreme sleep sleepers (>9 h or <5 h)[20]. However, other population-based studies of healthy men and women[46], as well as young women, suggested there was no association between sleep duration and inflammatory biomarkers[45]. In our baseline model, no association was observed between sleep duration and hs-CRP elevation, using a hs-CRP cut off of 3 mg/L, before interventions. However, we found that higher BMI was associated with an increased incidence of CRP elevation, which is consistent with previous findings that BMI was a significant factor in CRP elevation, even among young adults[5].

A variety of microbial-derived factors, such as muramyl peptide and endotoxin lipopolysaccharide, and inflammatory mediators, such as cytokines interleukin (IL)–1and growth factors, were identified as sleep-

regulating factors. These factors allow the immune system to signal the brain and interact with other substances involved in sleep regulation, such as neurotransmitter[15]. In our study of interventions in a placebo-controlled vaccine trial among healthy young adults, shorter sleep duration was associated with increased incidences of hs-CRP elevation after intervention. One potential explanation is that the weakened immune system, caused by sleep deprivation, diminishes its ability to regulate inflammatory responses and increases susceptibility to stimuli, vaccinations, or placebo injections. This could lead to more exaggerated and robust inflammatory responses compared to individuals with adequate sleep, due to the reduced efficiency of the immune system in counteracting threats. Previous vaccination studies have suggested that regular sleep supports the primary immune responses to different vaccines. For instance, findings from a recent meta-analysis provide evidence demonstrate that insufficient sleep (< 5 h) around vaccination reduces the antibody responses, suggesting maintaining a healthy sleep duration could improve vaccine effectiveness[48]. Sipegel et al. reported that restricting sleep in participants resulted in a diminished antibody response to the influenza vaccine, producing approximately half the antibody levels observed in the control group at 10 days after inoculation[49]. Cellular immunology studies on sleep loss also support the changes in immune function that are relevant to host resistance. Sleep deprivation could remarkably downregulate T cell production[50] and shift the T-helper 1/T-helper 2 cytokine balance away from T-helper 1 predominance, indicated by a lower of interferon-γ/IL-4 production ratio[51]. This is consistent with previous findings that individuals with insufficient sleep were more susceptible to viruses, such as common cold virus and coronavirus[16,52]. Another potential explanation is the weakened immune system caused by sleep loss triggers the production of extra CRP to maintain and enhance antigen presentation after vaccination. The role of CRP in antigen presentation has been suggested due to its interaction with Fc-gamma receptor I, a high-affinity receptor for the Fc region of immunoglobulin, and its binding to various microorganisms[1,53]. Evidence indicates that CRP plays a protective role against bacterial infections by the activation of the classical complement pathway and facilitating opsonization for phagocytosis. For example, Szalai et al. demonstrated that expression of human CRP in CRP transgenic mice could enhance long-term antibody response to Typhimurium and decrease mortality. This effect was attributed to the increased early clearance of salmonellae from the blood and reduced dissemination of bacteria to the liver and spleen in the early stage of inoculation[54].

This study has several strengths. First, to our knowledge, this is first study to investigate associations of wearable-derived sleep duration and the incidence of CRP elevation after vaccination and placebo administration in young adults. Second, we controlled for numerous potential confounders in logistic regression to decrease the possibility of residual confounding. Third, our study protocol allowed us to study how wearable-derived sleep related to subjective sleep metrics and various factors, including demographics, health status, and lifestyle factors.

This study also has several limitations. First, since we relied on wearable-derived sleep duration based on the average over a 14-day baseline period, it is possible participants did not consistently wear the devices during the night, potentially resulting in the misclassification of sleep duration. Second, possible confounding factors remain despite adjusting for prespecified potential confounders. Third, the sample size was insufficient to further investigate the relationship in the intervention subgroup. Fourth, there was a limited number of extreme sleepers (< 5h or > 9h) in our study cohort. Finally, this study does not provide any information about underlying mechanisms between shorter sleep duration and an increased incidence of CRP after challenges.

In summary, shorter wearable-derived TST and TIB, as well as subjectively assessed sleep duration from PSQI, are associated with a higher incidence of CRP evaluation after vaccination and placebo administration in young adults, suggesting that sleep loss could be a risk factor of inflammation, particularly mild inflammation. In addition, our study highlights the potential and reliability of wearable-derived sleep metrics to provide novel insights into their applications in biomedical research and public health. Whether the CRP in response to sleep deprivation might be a protective functional response to the immune system requires further study. Further studies also are needed to investigate the potential underlying mechanisms linking shorter sleep duration with an increased incidence of CRP elevation after such challenges.

Data availability

Data that support the findings of this study are not publicly available due to the contractual obligations and data protection regulations. Requests to access these datasets should be directed to Department of defense and Philips.

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References

1. Sproston, N. R. & Ashworth, J. J. Role of C-reactive protein at sites of inflammation and infection. *Front. Immunol.* **9**, 754 (2018).
2. Allin, K. H. & Nordestgaard, B. G. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. *Crit. Rev. Clin. Lab. Sci.* **48**, 155–170 (2011).
3. Di Napoli, M. et al. Role of C-reactive protein in cerebrovascular disease: a critical review. *Expert Rev. Cardiovasc. Ther.* **9**, 1565–1584 (2011).
4. Ridker, P. M., Buring, J. E., Cook, N. R. & Rifai, N. C-Reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: An 8-year follow-up of 14 719 initially healthy american women. *Circulation* **107**, 391–397 (2003).
5. Visser, M. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* **282**, 2131 (1999).
6. Posthouwer, D., Voorbij, H. A. M., Grobbee, D. E., Numans, M. E. & Van Der Bom, J. G. Influenza and pneumococcal vaccination as a model to assess C-reactive protein response to mild inflammation. *Vaccine* **23**(3), 362–365 (2004).
7. Wang, C. et al. A randomized, triple-blinded, placebo-controlled clinical trial evaluating immune responses of Typhim Vi and PPSV23 vaccines in healthy adults: The PREP study. *Vaccine* **42**, 126292 (2024).

8. Lim, P. W., Garssen, J. & Sandalova, E. Potential use of salivary markers for longitudinal monitoring of inflammatory immune responses to vaccination. *Mediat. Inflamm.* **2016**, 6958293 (2016).
9. Paine, N. J., Ring, C., Bosch, J. A., Drayson, M. T. & Veldhuijzen Van Zanten, J. J. C. S. The time course of the inflammatory response to the Salmonella typhi vaccination. *Brain Behav. & Immun.* **30**(73), 79 (2013).
10. Trzonkowski, P., Myśliwska, J., Pawelec, G. & Myśliwski, A. From bench to bedside and back: the SENIEUR Protocol and the efficacy of influenza vaccination in the elderly. *Biogerontology* **10**, 83–94 (2009).
11. Parmigiani, A. et al. Impaired antibody response to influenza vaccine in HIV-infected and uninfected aging women is associated with immune activation and inflammation. *PLoS ONE* **8**, e79816 (2013).
12. Xiao, K. et al. Immune response to vaccination in adults with mental disorders: A systematic review. *J. Affect. Disord.* **304**, 66–77 (2022).
13. King, C., Knutson, K., Rathouz, P. J. & Sidney, S. Short sleep duration and incident coronary artery calcification. *JAMA* **300**(24), 2859 (2008).
14. Irwin, M. R. Sleep and inflammation: Partners in sickness and in health. *Nat. Rev. Immunol.* **19**, 702–715 (2019).
15. Garbarino, S., Lanteri, P., Bragazzi, N. L., Magnavita, N. & Scoditti, E. Role of sleep deprivation in immune-related disease risk and outcomes. *Commun. Biol.* **4**, 1304 (2021).
16. Prather, A. A., Janicki-Deverts, D., Hall, M. H. & Cohen, S. Behaviorally assessed sleep and susceptibility to the common cold. *Sleep* **38**, 1353–1359 (2015).
17. Mello, M. T. D. et al. Sleep and COVID-19: Considerations about immunity, pathophysiology, and treatment. *Sleep Sci.* **13**, 199–209 (2020).
18. Cohen, S., Doyle, W. J., Skoner, D. P., Rabin, B. S. & Gwaltney, J. M. Social ties and susceptibility to the common cold. *JAMA* **277**, 1940–1944 (1997).
19. Chiang, J.-K. Short duration of sleep is associated with elevated high-sensitivity C-reactive protein level in taiwanese adults: A cross-sectional study. *J. Clin. Sleep Med.* **10**, 743–749 (2014).
20. Grandner, M. A. et al. Extreme sleep durations and increased C-reactive protein: Effects of sex and ethnoracial group. *Sleep* **36**, 769–779 (2013).
21. Jackowska, M., Kumari, M. & Steptoe, A. Sleep and biomarkers in the English Longitudinal Study of Ageing: Associations with C-reactive protein, fibrinogen, dehydroepiandrosterone sulfate and hemoglobin. *Psychoneuroendocrinology* **38**, 1484–1493 (2013).
22. Lee, H.-W. et al. Association of sleep duration and quality with elevated hs-CRP among healthy Korean adults. *PLoS ONE* **15**, e0238053 (2020).
23. Li, C., Bian, Y., Zhao, Z., Liu, Y. & Guo, Y. Advances in biointegrated wearable and implantable optoelectronic devices for cardiac healthcare. *Cyborg. Bionic. Syst.* **5**, 0172 (2024).
24. De Zambotti, M., Cellini, N., Goldstone, A., Colrain, I. M. & Baker, F. C. Wearable sleep technology in clinical and research settings. *Med. & Sci. Sports & Exerc.* **51**, 1538–1557 (2019).
25. Conroy, B. et al. Real-time infection prediction with wearable physiological monitoring and AI to aid military workforce readiness during COVID-19. *Sci. Rep.* **12**, 3797 (2022).
26. Teo, J. X. et al. Digital phenotyping by consumer wearables identifies sleep-associated markers of cardiovascular disease risk and biological aging. *Commun. Biol.* **2**, 361 (2019).
27. Miller, D. J., Sargent, C. & Roach, G. D. A Validation of six wearable devices for estimating sleep, heart rate and heart rate variability in healthy adults. *Sensors* **22**, 6317 (2022).
28. De Zambotti, M., Rosas, L., Colrain, I. M. & Baker, F. C. The sleep of the ring: Comparison of the ŌURA sleep tracker against polysomnography. *Behav. Sleep Med.* **17**, 124–136 (2019).
29. Henriksen, A., Svartdal, F., Grimsgaard, S., Hartvigsen, G. & Hopstock, L. A. Polar Vantage and Oura Physical Activity and Sleep Trackers: Validation and Comparison Study. *JMIR Form Res* **6**, e27248 (2022).
30. Lomas, E. Oura accuracy further validated by new study from the university of Tokyo. *The Pulse Blog* https://ouraring.com/blog/oura-ring-accuracy-validation-study-university-of-tokyo/ (2024)
31. Roberts, D. M., Schade, M. M., Mathew, G. M., Gartenberg, D. & Buxton, O. M. Detecting sleep using heart rate and motion data from multisensor consumer-grade wearables, relative to wrist actigraphy and polysomnography. *Sleep* **43**, 7. https://doi.org/10.1093/sleep/zsaa045 (2020).
32. CDC. Pneumococcal vaccination. *pneumococcal disease* https://www.cdc.gov/pneumococcal/vaccines/index.html (2025)
33. CDC. Typhoid vaccine VIS. *vaccines & immunizations* https://www.cdc.gov/vaccines/hcp/current-vis/typhoid.html (2025)
34. Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R. & Kupfer, D. J. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Res.* **28**, 193–213 (1989).
35. Lee, K.-A., Flores, R. R., Jang, I. H., Saathoff, A. & Robbins, P. D. Immune senescence immunosenescence and aging. *Front. Aging* **3**, 900028 (2022).
36. Orysiak, J., Młynarczyk, M., Piec, R. & Jakubiak, A. Lifestyle and environmental factors may induce airway and systemic inflammation in firefighters. *Environ. Sci. Pollut. Res. Int.* **29**, 73741–73768 (2022).
37. Pope, J. E. & Choy, E. H. C-reactive protein and implications in rheumatoid arthritis and associated comorbidities. *Semin. Arthritis Rheum.* **51**, 219–229 (2021).
38. Parker, C. H. et al. Effect of influenza vaccination on resting metabolic rate and c-reactive protein concentrations in healthy young adults. *PLoS ONE* **18**, e0295540 (2023).
39. Landry, G. J., Best, J. R. & Liu-Ambrose, T. Measuring sleep quality in older adults: A comparison using subjective and objective methods. *Front. Aging Neurosci.* https://doi.org/10.3389/fnagi.2015.00166 (2015).
40. Buysse, D. J. et al. Relationships between the pittsburgh sleep quality index (PSQI), epworth sleepiness scale (ESS), and clinical/polysomnographic measures in a community sample. *J. Clin. Sleep Med.* **4**, 563–571 (2008).
41. Mallampalli, M. P. & Carter, C. L. Exploring sex and gender differences in sleep health: A society for women's health research report. *J. Women's Health* **23**, 553–562 (2014).
42. Kalmbach, D. A., Anderson, J. R. & Drake, C. L. The impact of stress on sleep: Pathogenic sleep reactivity as a vulnerability to insomnia and circadian disorders. *J. Sleep Res.* **27**, e12710 (2018).
43. Meier-Ewert, H. K. et al. Effect of sleep loss on C-Reactive protein, an inflammatory marker of cardiovascular risk. *J. Am. Coll. Cardiol.* **43**, 678–683 (2004).
44. Irwin, M. R., Olmstead, R. & Carroll, J. E. Sleep disturbance, sleep duration, and inflammation: A systematic review and meta-analysis of cohort studies and experimental sleep deprivation. *Biol. Psychiatry* **80**, 40–52 (2016).
45. Okun, M. L., Coussons-Read, M. & Hall, M. Disturbed sleep is associated with increased C-reactive protein in young women. *Brain Behav. & Immun.* **23**, 351–354 (2009).
46. Suarez, E. C. Self-reported symptoms of sleep disturbance and inflammation, coagulation, insulin resistance and psychosocial distress: Evidence for gender disparity. *Brain Behav. & Immun.* **22**, 960–968 (2008).
47. Ferrie, J. E. et al. Associations Between change in sleep duration and inflammation: findings on C-reactive protein and interleukin 6 in the whitehall II study. *Am. J. Epidemiol.* **178**, 956–961 (2013).
48. Spiegel, K. et al. A meta-analysis of the associations between insufficient sleep duration and antibody response to vaccination. *Curr. Biol.* **33**, 998-1005.e2 (2023).
49. Spiegel, K. Effect of sleep deprivation on response to immunizaton. *JAMA* **288**, 1471 (2002).

50. Irwin, M. et al. Partial night sleep deprivation reduces natural killer and celhdar immune responses in humans. *FASEB J.* **10**, 643–653 (1996).
51. Dimitrov, S., Lange, T., Tieken, S., Fehm, H. L. & Born, J. Sleep associated regulation of T helper 1/T helper 2 cytokine balance in humans. *Brain Behav. & Immun.* **18**, 341–348 (2004).
52. Xue, P. et al. Persistent short nighttime sleep duration is associated with a greater post-COVID risk in fully mRNA-vaccinated individuals. *Transl. Psychiatry* **13**, 32 (2023).
53. Du Clos, T. W. & Mold, C. C-Reactive protein: An activator of innate immunity and a modulator of adaptive immunity. *IR* **30**(3), 261–278 (2004).
54. Szalai, A. J., VanCott, J. L., McGhee, J. R., Volanakis, J. E. & Benjamin, W. H. Human C-reactive protein is protective against fatal *salmonella enterica* serovar typhimurium infection in transgenic mice. *Infect. Immun.* **68**, 5652–5656 (2000).
55. Charlson, M. E., Pompei, P., Ales, K. L. & MacKenzie, C. R. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J. Chronic Dis.* **40**, 373–383 (1987).

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Author contributions

CW, SM, DM, BC designed the study. CW wrote the main manuscript text. LR and GC collected data for the study. CW analyzed the data. RD supported the figure preparation. All authors contributed to literature review, conceptualization, and editing of the manuscript.

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Declarations

The field study reported here was performed in accordance with relevant guidelines and regulations, including receiving preapprovals for all protocols by the Texas A&M University Institutional Review Board review boards and Human Research Protection Official, informed consent from the participants and the trial registration on clinicaltrials.gov (NCT05346302).

Competing interests

Authors CW, SM, RD, AL, IS and BC are employees of Philips North America. Author DM was an employee of Philips North America. Authors LR, GC and ND are employees of Texas A&M University. All authors declare no other competing interests.

Additional information

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