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Inflammation, sleep disturbances, and depressed mood among community-dwelling older men

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Abstract

Objective—High rates of sleep disturbances occur in depression. Sleep disturbances are linked to heightened inflammation. We sought to determine if sleep disturbances explain a portion of the putative inflammation – depression association among older adults. In late life, age-related immunoregulation changes may modify the inflammation-depression relationship.

Methods—Cross-sectional associations of a panel of serum inflammatory markers with probable depression (measured with the Geriatric Depression Scale) were assessed among 2,560 community-dwelling older men. We tested whether inflammatory marker - probable depression associations were independent of chronic diseases, as well as objective and subjectively measured sleep disturbances. We also tested whether inflammation-probable depression associations were moderated by age.

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Conflicts of Interest

The authors have no competing interests to report.

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Results—Inflammatory markers were not independently associated with higher odds of probable depression. A significant age by C - reactive protein (CRP) interaction ($p=0.01$) was detected such that the strength of the CRP - probable depression association decreased with age. When stratifying by the median age of 76, elevated odds of probable depression were found for men with CRP levels above the median only among the younger group ($OR = 2.08$, 95% CI 1.18–3.69). In the final adjusted model, independent effects of chronic diseases and subjective sleep disturbances contributed to a total of 37% attenuation of the original OR (adjusted $OR = 1.68$, 95% CI 0.911–3.10, $p = .09$).

Conclusions—In late-life, associations between inflammatory markers and mood may be explained by both chronic diseases and subjectively reported sleep disturbances. Our findings indicate that the association of CRP with probable depression diminishes in strength with age.

Keywords

Aging; depression; epidemiology; inflammation; late-life; sleep

Major depressive disorder (MDD) has been conceptualized as an inflammatory illness (1), and findings from meta-analysis support associations between inflammatory markers (C-reactive protein (CRP), interleukin-1, and interleukin-6 (IL-6)) and depression (2). Whether these associations are specific to MDD pathophysiology or if they are attributable to one or many of depression's common co-travelers has yet to be conclusively determined. Although previous research has adjusted analyses for important confounding variables such as adiposity, medical conditions and medication use, prior studies have failed to consider the potentially role of sleep disturbances.

Sleep disturbances are more common among community dwelling older adults with depressive symptoms (3, 4). In adults of all ages, sleep disturbances also have been associated with increased levels of inflammatory cytokines (5, 6). The putative relationship between inflammatory markers and depressed mood may therefore be attributable to sleep disturbances. To our knowledge, the only prior observational study considering a role for sleep in the depression-inflammatory markers relationship used a case-controlled design and found that prolonged sleep initiation partially accounted for the inflammation-MDD association (7).

Research in this area has generally focused on young and middle-aged adults. Two prior studies of older adults reported associations between depressive symptoms and IL-6 levels (8, 9). Another two groups (10, 11) reported association of IL-6 and MDD, but not IL-6 and measures of depressive symptoms. Of these prior studies in older adults, three measured CRP levels: two studies found no evidence of an association of CRP and MDD independent of confounders (10, 11), whereas one study found an association of CRP and depression independent of confounders (8).

Age-related dysregulation of the inflammatory response, termed immunosenescence or “inflammaging” (12, 13), may lead to age differences in the relationship between inflammatory markers and depression. In a meta-analysis, the association between IL-6 and depression decreased in strength as the mean age of samples increased (2); no such age-

modification was observed for CRP. However, no prior studies have examined whether age moderates the association between levels of inflammatory markers and depression in late-life. In the current study, we examined whether high levels of serum inflammatory markers are associated with a higher probability of having significant depressive symptomology among community dwelling older men. We sought to determine whether associations between inflammatory markers and depressed mood are independent of sleep disturbances in late-life. We also tested whether the associations between inflammatory markers and probable depression differed by age.

Methods

Participants

The Sleep Study was conducted at six clinical centers in the United States (Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; Monongahela Valley near Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California) between December 2003 and March 2005, and included 3,135 participants from the parent Osteoporotic Fractures in Men Study (MrOS) (14, 15). To be eligible to participate in the parent study, individuals aged ≥ 65 years had to walk without assistance and be without bilateral hip replacements. For the Sleep Study, men were excluded if they regularly used positive pressure or oral appliances during sleep for treatment of sleep apnea or used overnight nocturnal oxygen therapy ($n=150$). Other reasons for non-participation were: death ($n=349$), terminated study participation ($n=39$), declined sleep study ($n=1997$), or because MrOS Sleep Study recruitment goals had already been met prior to enrollment in the sleep study ($n=324$). As part of an ancillary study, inflammatory marker assays were measured from serum collected at the Sleep Visit in 2562 men. A total of 2560 men (81.66% of the Sleep Study) with complete cytokine and depressive symptom data were included in this analysis. The institutional review boards at each clinic site approved the study, and written informed consent was obtained from all participants.

Measures

Depressive symptoms—The Geriatric Depression Scale – 15 (GDS), a validated short form (16, 17) of a screen for MDD among older persons (18) was administered to all participants. The standard cut point of ≥ 6 was used to define probable depression. This threshold yields a sensitivity of 90.9% and specificity of 64.5% compared to a DSM-IV diagnosis of MDD (17).

Inflammatory markers: Serum was collected during morning clinic visits, after an overnight fast. The following assays were completed in a single, central study laboratory. CRP was measured using the ELISA assay kit from ALPCO (CRP sensitive ELISA). This assay utilizes a sandwich Enzyme Immuno Assay, in which plate wells are coated with polyclonal antibodies to C-reactive protein. The inter-assay CVs ranged from 11.6 to 13.8%. IL-6, TNF- α , and IFN- γ were assayed using the Human ProInflammatory I 4-Plex Ultra-Sensitive Kit by MSD (catalog #K15009C-4). The sensitivity of the assay were: 0.22 pg/mL for IL-6, 0.49 pg/mL for TNF- α , and 0.40 pg/mL for IFN- γ . Inter-assay CVs range from: 2.0 to 9.9% for IL-6, 2.1 to 6.0% for TNF- α , and 1.8 to 4.5% for IFN- γ . TNF- α sRII was

measured with an ELISA from R & D Systems (Minneapolis, MN; catalog #DRT200). The normal range for TNF- α RII in serum is 1003 – 3170 pg/mL. TNF- α RII inter-assay CVs range from 3.5 to 5.1%.

Following a previous population-based study of the relationship between inflammatory markers and depressed mood (8), levels of inflammatory markers above the median were considered high.

Demographic/medical covariates: Participants completed questionnaires providing information on demographics, education, medical history, physical activity, smoking, and alcohol use. Cognitive function was measured using the Teng Modified Mini-Mental State Exam (3MS) (19). Medical history was ascertained by asking participants if they had ever received a physician diagnosis of the following medical condition: arthritis, diabetes mellitus, stroke, myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease (COPD), Parkinson's disease, and hypertension. Participants were asked to bring all current medications used within the last 30 days with them to the clinic for verification of use. Medications that were considered to potentially affect levels of inflammatory markers based on *a priori* knowledge were entered as covariates, including: antidepressants, benzodiazepines, sedatives/hypnotics, medications used for sleep, NSAIDs, and corticosteroids.

Medication use variables were combined into a composite summary score reflecting the number of relevant medications used; a medical disease summary score was computed in a similar fashion to reflect the number of chronic diseases.

Sleep covariates—Participants completed the Pittsburgh Sleep Quality Index (PSQI), a widely used, validated measure of subjective sleep disturbances and quality. Scores range from 0–21, and the standard cut-point of >5 was used to indicate poor self-reported sleep quality in these analyses. Participants also completed the Epworth Sleepiness Scale (ESS), a self-report questionnaire measuring subjective daytime sleepiness. Scores on the ESS range from 0–24, and the standard cut-point of >10 (20) was used to indicate excessive daytime sleepiness.

Participants were asked to wear actigraphs on the non-dominant wrist for a minimum of 5 consecutive 24-hour periods and were removed only for bathing or during water sports. Participants were also asked to keep a sleep log which was used to edit the data. ActionW-2 software (Ambulatory Monitoring, Inc., Ardsley, NY) was used to score actigraphy data, and details of the scoring algorithms used have been published elsewhere (21, 22). Inter-scanner reliability for scoring of this data has been previously found to be high in our group (intra-class coefficient = 0.95) (21). Actigraphy derived parameters used in this analysis were: sleep duration (<5 hours, 5–7 hours, 7–8 hours, >8 hours), sleep latency (SL; time from lights out to the beginning of sleep) dichotomized at 60 minutes, sleep efficiency dichotomized at 70% (SE; percentage of time sleeping after “lights off”), amount of time awake after sleep onset, dichotomized at greater than or equal to 90 minutes (WASO; minutes scored awake during the interval between sleep onset and final awakening), and the number of minutes asleep out of bed (daytime sleep excluding naps < 5 minutes).

Sleep studies were also completed using unattended polysomnography (Safiro, Compumedics, Inc., Melbourne, Australia) for one night in participant's own homes to minimize burden. Centrally trained and certified staff members performed home visits for setup of the sleep study units, using approaches similar to those in the Sleep Health Heart Study (23). Polysomnography data quality was excellent, with a failure rate of less than 4% and more than 70% of studies graded as being of excellent or outstanding quality.

PSG derived parameters included a measure of apneas/hypopneas (24), the apnea hypopnea index (AHI), computed as the average number of apneas and hypopneas per hour of recorded sleep. Apneas were defined as a complete or almost complete cessation of airflow for more than 10 seconds. Hypopneas were defined as a >30% reduction in amplitude of either respiratory effort or airflow for more than 10 seconds associated with a 3% oxygen desaturation (25). Parameters also included were: 10% of total sleep time (TST) where arterial oxygen saturation was below 90% (10% TST with $\text{SaO}_2 < 90\%$), and any time during sleep arterial oxygen saturation was below 80% (any TST with $\text{SaO}_2 < 80\%$).

Statistical analysis—Demographic/medical/sleep covariates were examined by participatory status (in the Sleep Study compared to the ancillary cytokine study) and by depressed status using Chi-squared and T-tests for categorical and continuous outcomes, respectively. Unadjusted associations between depressed status and inflammatory markers (above vs. below the median level) were examined using Chi-squared tests. In the main analyses, inflammatory markers were dichotomized around the median to represent high vs. low levels, and entered as predictors of depressed status in separate logistic regression models. Covariates (see above) were selected *a priori*, based on known associations with the predictors or outcome

In Model 1, adjustments were made for demographic/lifestyle characteristics listed in Table 1. Model 2 included covariates in Model 1 + adjustments for chronic diseases and medication use (summary scores). Model 3 included covariates in Model 1 + adjustments for sleep covariates which were associated with depressed status at the bivariate level with $p \leq 0.10$ and medication use. The final model (Model 4) included a cytokine predictor, demographic/lifestyle factors, and both chronic disease/medication summary scores and the selected sleep covariates.

To determine whether age moderates the association between inflammatory markers and probable depression, we included inflammatory marker x age interactions. After detecting a significant age x CRP interaction ($p = 0.01$), we computed results stratified by the median age of 76 (recalculating inflammatory marker quartiles and medians within these stratified groups).

Results

Compared to all Sleep Study participants, men in the ancillary cytokine study were more often Caucasian ($p < 0.0001$), less educated ($p = 0.04$), less often experiencing probable depression ($p = 0.02$), with higher cognitive function scores ($p = 0.001$), less daytime sleepiness ($p = 0.01$), and taking more medications on average ($p = 0.0005$). The analytic

cohort did not significantly differ from the Sleep Study participants in terms of age, measures of adiposity, physical activity, medical conditions or other sleep disturbances.

The mean age of the analytic sample was 76.4 years (SD=5.51) and probable depression was found in 5.63% of participating men. Sleep disturbances were common in the sample overall, for example 44.22% of men reported subjective sleep disturbances. Compared with men without probable depression, men with probable depression were older, less educated, more likely to use antidepressants, benzodiazepines, and NSAIDs (Table 1). Men with probable depression were also more likely to have a history of CHF, hypertension, rheumatoid arthritis, osteoarthritis, stroke, Parkinson's, and COPD. Men with probable depression had lower cognitive function and physical activity scores.

PSQI detected poor sleep quality and ESS detected excessive daytime sleepiness were found more often in men with probable depression (Table 2). Men with probable depression were also more likely to have 10% of their TST with SaO₂ < 90%, to have SE < 70%, and to have a SL ≥ 60 minutes. Additionally, men with probable depression spent a greater number of minutes in daytime sleep.

The prevalence of probable depression in men above the median level of inflammatory markers compared to below indicated differences at the bivariate level (Table 3). For example, the prevalence of probable depression in men with high levels of CRP was 7.27%, compared to 5.23% in men with CRP below the median ($p=0.03$). Similarly, 7.97% of men with sTNF-sRII above the median had probable depression, compared to 4.53% of men with low levels of this marker ($p=0.0003$). This pattern of findings was apparent in the younger, but not older age strata.

After adjustments, being above the median in these inflammatory markers was not generally associated with higher odds of probable depression (Table 4). Exceptions included marginally significant elevated odds ratios (OR) in men with sTNF-sRII levels above the median ($p=0.05$) in Model 1. After adjustments for chronic disease and sleep disturbances separately this OR failed to retain significance and was reduced by 56% and 35%, respectively. In the final model which included both chronic disease and sleep measures, the OR was reduced by a total of 70%. Of the sleep disturbance variables, this attenuation was accounted for (not shown in tables) by significantly increased odds of having probable depression for men with PSQI detected subjective sleep disturbances (Model 4: OR=3.34, 95% CI 2.22–5.03, $p<0.0001$) and ESS detected excessive daytime sleepiness (Model 4: OR=2.04, 95% CI 1.31–3.16, $p=0.002$).

A significant age by C - reactive protein (CRP) interaction ($p=0.01$) was detected such that the strength of the CRP - probable depression association decreased with age. In the younger age group (<76 years), the odds of probable depression was for individuals with CRP above the median level were 2.08 times higher than men without high CRP ($p=0.01$). After adjusting chronic diseases/medication use variables in Model 2 or sleep variables in Model 3, the elevated odds for probable depression in men with above median values of CRP remained significantly elevated (Model 2: $p=0.03$; Model 3: $p=0.04$) however the OR was attenuated by 14% and 20%, respectively. In the final model which included both chronic

disease and sleep measures, the OR was reduced by a total of 37% and failed to retain significance ($p = 0.09$). Of the sleep disturbance variables, this attenuation was accounted for (not shown in tables) by significantly increased odds of having probable depression in men with PSQI detected subjective sleep disturbances (Model 4: OR=5.91, 95% CI 2.73–12.77, $p<0.0001$) and ESS detected excessive daytime sleepiness (Model 4: OR=1.98, 95% CI 1.01–3.90, $p=0.047$).

Independent associations of the chronic disease summary score and increased odds of probable depression were detected in all models. For example, in the model including CRP among the younger age strata, for each additional chronic disease the odds of probable depression increased by 53% (OR 95% CI 1.18–1.98, $p=0.001$).

Analyses were repeated after excluding participants reporting psychoactive medication use (antidepressants, benzodiazepines, or sedatives/hypnotics) and the pattern of results was not substantively altered.

Post-hoc analysis

In a follow-up analysis we note that men in the older age-strata had higher levels of IL-6, TNF- α , TNF-SRII, and tended to have a greater number of markers above the median level (all p values < 0.0001).

Discussion

In this cohort of older men overall we found that associations of elevated inflammatory markers with probable depression were not independent of chronic diseases and sleep disturbances. We found that age moderated associations such that high levels of CRP were related to increased odds of probable depression among the younger (<76 years) but not older age strata (≥ 76 years). Finding the CRP-probable depression relationship only among the younger group may be attributable to age-related immune changes leading to a non-specific increase in the activation of the inflammatory response (12). IL-6 is a potent stimulator of CRP (26) and among the measured markers, CRP may be the most representative of systemic inflammation. If age-related changes lead to a non-specific inflammatory response, generally high levels of inflammation in the oldest men in our study could decrease the signal-to-noise ratio and effectively “dilute” any association with depression. It is also possible that the observed interaction is attributable to age-related differences in our outcome classification. Our measure of probable depression (the GDS) may, depending on age, reflect different underlying conditions with differing relationships to inflammation.

Although higher levels of inflammatory markers appeared to be related to higher odds of probable depression, these associations were attributable to independent effects of chronic diseases and sleep disturbances. Similar percent attenuations of the CRP OR (among the younger age strata) in Models 2 and 3 which entered chronic disease and sleep disturbances separately indicate that these factors explain roughly the same amount of the variance in depressed mood attributed to CRP. The sleep disturbances that attenuated the association of inflammatory markers and probable depression were poor self-reported sleep quality (PSQI)

and excessive daytime sleepiness (ESS). Although objective measures of sleep disturbances were entered into these models, only these self-reported measures were independently associated with depressed status. Since the depressed mood, PSQI, and ESS measures were self-reported, a significant association of these (subjective) measures may reflect the same underlying reporting process. Nevertheless, perceived poor sleep quality appeared to explain some of the variance in depressed mood that had been attributed to levels of inflammatory markers.

Although our cross-sectional analyses did not test temporality, levels of inflammatory markers have been shown to predict future PSQI scores (27), and a mechanism whereby inflammatory markers are associated with depressed mood via subjective sleep quality is plausible. Experimental administration of endotoxin raises levels of inflammatory cytokines and has been linked to perceived tiredness (28), although to our knowledge no prior research has demonstrated that inducing an inflammatory response disrupts measures objectively measured sleep.

We did not consistently document an association between IL-6 and probable depression, even in unadjusted analyses. Since assay techniques were not standardized across all previously reported studies of inflammatory markers and depression in older adults, methodological differences may explain some between study variation. Our measure of probable depression, the GDS, does not measure nor mandates the episode duration criterion required for a full diagnosis; generally, the GDS has lower specificity than sensitivity (i.e. see (29)). The probable depression group therefore may have included participants who were not experiencing a diagnosable depressive episode and this could have biased our results towards the null. In a meta-analysis, associations between inflammatory markers and depression were found to be more robust in clinical compared to community-based studies (2). Among studies of older adults, Bremner et al. (10) and Tiemeier et al. (11) did not find an association between IL-6 and depressive symptoms, despite identifying an association between IL-6 and diagnosed MDD.

Our study is therefore limited by relying on a screening tool for MDD without full diagnostic measures. An additional limitation was that our data were cross-sectional, and we cannot assess temporality in the associations between levels of inflammatory markers, chronic disease, sleep disturbances, and depression. Since the study sample consisted of only older men who were mostly white, these findings do not necessarily generalize to younger individuals, women, or other ethnic groups. Our analytic sample was less likely to be depressed than Sleep Study participants who were not included in the ancillary cytokine study, and this may have biased our results towards the null. Although we measured several pro-inflammatory cytokines, the inflammatory response is vastly more complex than captured with our measures, and it is possible that other markers would show a different pattern of association. Finally, stratification by median age was not specified during the study's design, and statistical power may have become an issue as the number of participants who screened positive for probable depression was reduced within strata.

Strengths of our study include the use of a wide array of relevant lifestyle and medical covariates, including the novel use of objective and subjective sleep measures to test

whether the depression-inflammation association is independent of sleep disturbances. Considerable previous research has documented a link between depression and cardiovascular risk (30). Although our study cannot comment on potential behavioral links between depression and cardiovascular disease, we have examined a pertinent biological pathway involved in cardiovascular disease. In our sample, it appears that higher levels of CRP and sTNF-RII are related to probable depression. However our adjusted analyses indicate that (as opposed to an independent association of inflammatory markers and depressed mood), individuals with chronic disease and/or sleep disturbances have both higher levels of inflammatory markers and depressed mood. These findings suggest that treating physical illness and sleep problems may be an effective strategy towards reducing the prevalence of depression and associated cardiovascular risk.

Future research is needed to examine the roles of subjective and objective sleep disturbance in the relationship between inflammatory markers and fully diagnosed MDD. Additionally, the timing and predictors of potential age-related changes to the inflammatory response have not been established. Longitudinal research is needed to further characterize the dynamic relationships between inflammatory markers, chronic diseases, and both subjective and objective sleep disturbances in relation to depression.

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Table 1

Associations between demographic/lifestyle/medical characteristics and depressed status

	Probable depression (n = 160)	No probable depression (n = 2400)	p
Age, mean (sd)	77.24 (5.63)	76.30 (5.50)	0.04
Caucasian %	91.25	91.21	0.99
BMI, mean (sd)	27.14 (4.00)	27.15 (3.75)	0.95
Waist Circumference (cm), mean (sd)	100.87 (10.62)	99.42 (10.80)	0.10
Smoking Status			
Current Smoker	3.13	1.88	0.06
Past Smoker	65.00	57.46	
Never Smoker	31.88	40.67	
Alcohol use (drinks per week)			
1	49.38	46.71	0.52
2–13	47.50	47.54	
14+	3.13	5.42	
Education			
Less than high school	10.63	5.17	0.0077
High school diploma	18.75	16.46	
College/Graduate school	70.63	78.38	
Teng 3MSE Score	90.41 (8.00)	93.00 (5.74)	<0.0001
Physical activity (PASE)	109.30 (64.30)	149.00 (70.40)	<0.0001
Current antidepressant use	24.38	6.75	<0.0001
Current benzodiazepine use	15.00	3.96	<0.0001
Current non-benzodiazepine anxiolytic/hypnotic use	1.25	2.13	0.77
Current NSAID use	28.75	20.88	0.02
Drug summary score (# of relevant medications)	1.16	0.61	<0.0001
MI	22.50	17.33	0.10
CHF	12.50	5.17	<0.0001
Hypertension	57.50	49.13	0.04
Rheumatoid arthritis	15.63	7.46	0.0001
Osteoarthritis	45.00	22.92	<0.0001

	Probable depression (n = 160)	No probable depression (n = 2400)	p
Stroke	10.00	3.38	<0.0001
Diabetes	13.75	11.58	0.41
Parkinson's	4.38	1.04	0.0002
COPD	11.88	4.79	<0.0001
Chronic disease summary score (# of relevant chronic diseases)	1.93	1.23	<0.0001

Percent (%) in each group are shown unless otherwise noted

Table 2

Associations between sleep variables and depressed status (%)

	Men		p
	Probable depression (n = 160)	No probable depression (n = 2400)	
<u>Self-reported sleep variables</u>			
PSQI >5	77.50	41.75	<.0001
ESS > 10	24.38	11.46	<.0001
<u>SDB variables</u>			
AHI 30	21.25	17.08	0.18
10% TST SaO2 < 90%	18.75	12.08	0.01
any ST SaO2 < 80%	6.25	6.83	0.78
<u>Sleep duration</u>			
< 5 hours	15.00	11.67	0.06
5–7 hours	46.25	57.04	
>7 and <=8 hours	30.63	24.08	
> 8 hours	8.13	7.13	
<u>Other actigraph measures</u>			
SE < 70%	28.75	18.04	0.0008
SL 60 minutes	19.38	9.83	0.0001
WASO 90 minutes	35.63	31.33	0.26
Daytime sleep (in minutes; mean (SD))	70.62 (58.88)	54.04 (51.92)	0.0007

Table 3

Prevalence of probable depression among participants with high¹ and low inflammatory cytokines levels (overall and within age strata)

	Men Overall		Men < 76 years old		Men ≥ 76 years old	
	% Probable depression	p	% Probable depression	p	% Probable depression	p
CRP						
Low	5.23	0.03	3.16	0.002	7.29	0.93
High ¹	7.27		7.09		7.41	
IL-6						
Low	5.36	0.07	4.27	0.16	6.82	0.47
High ¹	7.11		5.99		7.87	
TNF-α						
Low	5.86	0.41	4.42	0.25	7.28	0.92
High ¹	6.64		5.84		7.42	
sTNF-RII						
Low	4.53	0.0003	3.63	0.02	6.19	0.11
High ¹	7.97		6.62		8.50	
IFN-γ						
Low	5.94	0.51	4.42	0.25	7.43	0.91
High ¹	6.56		5.84		7.26	

¹ High level is defined as above sample median levels.

Median levels for men overall: CRP 1.517 mg/L; IL-6 1.078 pg/mL; TNF-α 5.128 pg/mL; sTNF-RII 3545.90 pg/mL; IFN-γ 1.865 pg/mL;

Median levels for younger (<76 years) men: CRP 1.515 mg/L; IL-6 0.958 pg/mL; TNF-α 4.986 pg/mL; sTNF-RII 3264.60 pg/mL; IFN-γ 1.826 pg/mL;

Median levels for older (≥ 76 years) men: CRP 1.517 mg/L; IL-6 1.842 pg/mL; TNF-α 5.278 pg/mL; sTNF-RII 3905.30 pg/mL; IFN-γ 1.927 pg/mL;

Table 4

Odds ratios for probable depression according to being above versus below median cytokine levels

	Men Overall n = 2560		Men < 76 years old n = 1267		Men 76 years old n = 1293	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
CRP						
Model 1	1.31 (0.93–1.85)	0.13	2.08 (1.18–3.69)	0.01	0.95 (0.61–1.49)	0.82
Model 2	1.29 (0.91–1.83)	0.15	1.93 (1.08–3.45)	0.03	0.98 (0.62–1.54)	0.91
Model 3	1.27 (0.88–1.82)	0.20	1.86 (1.02–3.40)	0.04	0.97 (0.60–1.57)	0.90
Model 4	1.24 (0.86–1.79)	0.26	1.68 (0.91–3.10)	0.09	0.99 (0.61–1.61)	0.97
IL-6						
Model 1	1.08 (0.77–1.53)	0.65	1.24 (0.72–2.12)	0.44	0.92 (0.58–1.44)	0.71
Model 2	1.02 (0.71–1.45)	0.92	1.09 (0.62–1.90)	0.77	0.85 (0.54–1.35)	0.50
Model 3	1.07 (0.74–1.55)	0.72	1.13 (0.63–2.02)	0.68	0.98 (0.60–1.60)	0.94
Model 4	0.98 (0.67–1.42)	0.91	1.96 (0.53–1.76)	0.91	0.91 (0.56–1.49)	0.71
TNF-α						
Model 1	0.95 (0.68–1.33)	0.76	1.12 (0.66–1.91)	0.68	0.91 (0.58–1.41)	0.66
Model 2	0.89 (0.63–1.26)	0.51	1.04 (0.60–1.81)	0.88	0.85 (0.54–1.34)	0.49
Model 3	0.94 (0.66–1.34)	0.73	1.09 (0.62–1.94)	0.75	0.91 (0.57–1.45)	0.68
Model 4	0.89 (0.62–1.27)	0.51	0.95 (0.53–1.70)	0.76	0.89 (0.55–1.43)	0.63
sTNF-RII						
Model 1	1.43 (1.00–2.06)	0.05	1.58 (0.91–2.77)	0.11	1.17 (0.74–1.84)	0.51
Model 2	1.19 (0.82–1.73)	0.36	1.32 (0.74–2.34)	0.35	0.98 (0.61–1.57)	0.93
Model 3	1.28 (0.88–1.87)	0.20	1.42 (0.78–2.60)	0.26	1.01 (0.62–1.65)	0.96
Model 4	1.13 (0.77–1.66)	0.54	1.18 (0.64–2.19)	0.60	0.93 (0.57–1.53)	0.78
IFN-γ						
Model 1	1.21 (0.87–1.69)	0.25	1.41 (0.84–2.37)	0.20	1.11 (0.72–1.72)	0.63
Model 2	1.13 (0.81–1.59)	0.47	1.47 (0.86–2.52)	0.16	0.98 (0.63–1.54)	0.94
Model 3	1.15 (0.81–1.64)	0.42	1.24 (0.71–2.17)	0.46	1.05 (0.66–1.68)	0.83
Model 4	1.12 (0.79–1.59)	0.54	1.22 (0.69–2.16)	0.50	1.02 (0.64–1.64)	0.92

Model 1: adjusted for demographic/lifestyle characteristics (from Table 1) and study site; Model 2: adjusted for covariates from Model 1 + chronic diseases and medication use; Model 3: adjusted for covariates from Model 1 + sleep variables and medication use; Model 4: adjusted for all covariates

Median levels for men overall: CRP 1.517 mg/L; IL-6 1.078 pg/mL; TNF- α 5.128 pg/mL; sTNF-RII 3545.90 pg/mL; IFN- γ 1.865 pg/mL;
 Median levels for younger (<76 years) men: CRP 1.515 mg/L; IL-6 0.958 pg/mL; TNF- α 4.986 pg/mL; sTNF-RII 3264.60 pg/mL; IFN- γ 1.826 pg/mL;
 Median levels for older ($\geq$ 76 years) men: CRP 1.517 mg/L; IL-6 1.842 pg/mL; TNF- α 5.278 pg/mL; sTNF-RII 3905.30 pg/mL; IFN- γ 1.927 pg/mL;