Brain, Behavior, & Immunity - Health 30 (2023) 100634

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Sleep quality mediates the relationship between systemic inflammation and neurocognitive performance

Rachel R. Jin [a,b], Carman Nga-Man Cheung [c], Clive H.Y. Wong [d], Chelsea C.W. Lo [c], Crystal P.I. Lee [c], Hing Wai Tsang [e], Preeti Dinesh Virwani [c], Patrick Ip [e], Kui Kai Lau [a,f,*], Tatia M.C. Lee [a,b,**]

[a] State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong, China
[b] Laboratory of Neuropsychology and Human Neuroscience, The University of Hong Kong, Hong Kong, China
[c] Department of Medicine, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China
[d] Department of Psychology, The Education University of Hong Kong, Hong Kong, China
[e] Department of Paediatrics and Adolescent Medicine, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China
[f] Division of Neurology, Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong, China

ARTICLE INFO

Keywords:
Inflammation
Sleep quality
Human cognition
Cognitive impairment

ABSTRACT

Background: Systemic inflammation is a significant mechanism underpinning adverse cognitive changes. Sleep quality is a crucial factor associated with systemic inflammation and neurocognitive health. Elevated levels of pro-inflammatory cytokines in the periphery help mark inflammation. With this background, we examined the relationship between systemic inflammation, subjective sleep quality, and neurocognitive performance in adults.
Method & Results: In 252 healthy adults, we measured the systemic inflammation reflected by serum levels of IL-6, IL-12, IL-18, TNF-α and IFN-γ, subjective sleep quality reflected by the global scores of the Pittsburgh Sleep Quality Index, and their neurocognitive performance measured by the Hong Kong Montreal Cognitive Assessment. We observed that neurocognitive performance was negatively related to IL-18 ($p = 0.046$) and positively related to sleep quality ($p = 0.006$). We did not observe significant associations between other cytokines and neurocognitive performance. Furthermore, we found that sleep quality as a mediator explained the relationship between IL-18 and neurocognitive performance depending on the levels of IL-12 (index of moderated mediation: 95% CI = [0.0047, 0.0664]). Better subjective sleep quality buffered the negative effect of IL-18 on neurocognitive performance when IL-12 was low (bootstrapping 95% CI: [- 0.0824, - 0.0018]). On the contrary, poor subjective sleep quality mediated the association between higher IL-18 and poorer neurocognitive performance when IL-12 was elevated (bootstrapping 95% CI: [0.0004, 0.0608]).
Conclusion & Implications: Our findings indicate that systemic inflammation was negatively associated with neurocognitive performance. Sleep quality regulated by IL-18/IL-12 axis activation could be a potential mechanism underpinning neurocognitive changes. Our results illustrate the intricate relationships between immune functioning, sleep quality and neurocognitive performance. These insights are essential to understand the potential mechanisms underpinning neurocognitive changes, paving the way for the development of preventive interventions for the risk of cognitive impairment.

1. Introduction

Systemic inflammation is an essential mechanism underlying cognitive decline and neurocognitive disorders (Bradburn et al., 2019; Heppner et al., 2015; Marsland et al., 2015). It manifests as a low-grade, long-term elevation of multiple inflammatory markers in blood circulation, which is distinguished from the acute inflammatory response in local tissues (Holmes, 2013). Systemic inflammation induces neuroinflammation, together with blood-brain barrier breakdown and neuropathological protein aggregation provokes neurodegenerative changes (Galea, 2021; Hoogland et al., 2015; Kempuraj et al., 2016; Perry, 2010). Elevated peripheral inflammatory markers (i.e.,

* Corresponding author. Division of Neurology, Department of Medicine, School of Clinical Medicine, The University of Hong Kong, SAR, Hong Kong, China.
** Corresponding author. Rm 656, The Jockey Club Tower, The University of Hong Kong, Pokfulam Road, Hong Kong, China.
E-mail addresses: gkklau@hku.hk (K.K. Lau), tmclee@hku.hk (T.M.C. Lee).

https://doi.org/10.1016/j.bbih.2023.100634
Received 27 April 2023; Accepted 30 April 2023
Available online 5 May 2023

interleukin [IL]-6, IL-18 and tumour necrosis factor [TNF]-α) and a higher level of neuroinflammation have been detected in people suffering from Alzheimer's disease (AD) and mild cognitive impairment (MCI) (Bradburn et al., 2019; Cheng et al., 2022; Darweesh et al., 2018; Leonardo and Fregni, 2023; Shen et al., 2019). Particularly, the T helper (Th) 1 response plays a particularly important role in maintaining systemic inflammation, which is further associated with neurocognitive deficits. In specific, IL-12 contributes to promoting pro-inflammatory responses by interacting with IL-18, stimulating Th1 development and producing pro-inflammatory cytokines (e.g., IFN- γ and TNF-α) (Daroff and Aminoff, 2014; Nakanishi, 2018). Such association is further sustained by the evidence that IL12/IL18 axis activation boosts TNF-α and IL-1β production, and triggers IFN-γ-dependent neuroinflammatory response (Kannan et al., 2011). Research found that APP/PS1 mice treated with Th1 and Th17 T effector cells exhibit memory impairments and systemic inflammation, increased amyloid burden, and exacerbated microglia-mediated neuroinflammation (Machhi et al., 2021).

Sleep is a vital process associated with both systemic inflammation and cognition. Multiple cytokines (i.e., IL1β, TNF- α, IL-18) regulate the sleep process and quality. Intracerebroventricular injection of IL-18 increases non-rapid eye movement sleep in rabbits and rats (Kubota et al., 2001). IL-18-associated inflammasome activation was observed in patients with severe obstructive sleep apnea (OSA) compared to controls (Díaz-García et al., 2022). Sleep was also found to be strongly associated with increased pre-mDCs that produce IL-12, a key inducer of Th1 responses (Dimitrov et al., 2007). Generally, based on current data, a conceptual model proposed by Besedovsky et al. (2019) elucidates that mild immune challenges will enhance or intensify NREM sleep, while more robust immune responses characterized by a significant increase in cytokine (like fever or severe infection) would cause sleep fragmentation, feelings of nonrestorative sleep, and daytime fatigue (Imeri and Opp, 2009; Irwin, 2019; Mullington et al., 2000).

Sleep quality has substantial implications for cognitive health. Declines in subjective and objective sleep quality are associated with poorer cognitive performance and increased risk of neurocognitive disorders, especially in older adults and individuals with medical conditions (Potvin et al., 2012; Xu et al., 2020; Yaffe et al., 2014). Ma et al. (2019) reported a dose-response relationship between lower habitual sleep efficiency and a higher risk of memory impairment and poor cognitive function in older people. A meta-analysis concludes that poor objective sleep quality, characterised by lower restlessness at night and lower sleep onset latency, predicts better memory and executive functioning in older adults (Qin et al., 2022). Cognitive impairment is also present in many sleep disorders (e.g., sleep restriction/deprivation, insomnia, chronic obstructive pulmonary disease; Olaithe et al., 2018), suggesting the fundamental role of sleep quality in maintaining neurocognitive health.

Despite the significant relationship between systemic inflammation, sleep quality, and neurocognitive functioning, research targeting the mechanism of the relationship between inflammation and cognition in humans has been scarce. Moreover, the interplays between these cytokines in association with sleep and neurocognitive processes are still unclear. Therefore, we conducted this study to investigate the relationship between systemic inflammation and neurocognitive performance. We further looked into how sleep quality explained this association. We first hypothesized that there would be a negative relationship between the serum level of cytokines (i.e., IL-6, IL-12, IL-18, IFN- γ and TNF-α) and neurocognitive performance. Considering the interaction of IL-12 and IL-18 in promoting Th1 response, we further speculated that systemic inflammation characterised as IL-12/IL-18 axis hyperactivation might regulate sleep quality. Finally, subjective sleep quality mediates the relationship between systemic inflammation and neurocognitive performance, which is modulated by the IL-12/IL18 axis.

2. Materials and methods

2.1. Participants

We recruited 284 healthy Cantonese-speaking Chinese adult participants aged between 39 and 65 (140 men) between July 2018 and June 2020 through community recruitment by open advertisements. We excluded those with previously diagnosed symptomatic cardiovascular or cerebrovascular disease; underlying malignancy, neurodegenerative disease and autoimmune disorders; recent gastroenteritis, febrile illness and vaccination within four weeks; and those with prior antibiotic, anti-inflammatory drugs, systemic steroid and sleep-related, antidepressants and psychotropic medication use. All participants had normal or corrected-to-normal vision and hearing. The Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster approved this study (HKU/HA HKW IRB UW 18–498). The experimental procedure followed the Helsinki Declaration. All participants gave their informed consent to participate in the study. Three participants were excluded due to outliers (exceeding mean ± 4 * standard deviation) in variables of inflammatory markers (i.e., IL-12 and IL-18). Another three participants were further excluded due to missing values in Pittsburgh Sleep Quality Index and Hong Kong Montreal Cognitive Assessment. Finally, 252 subjects were included in the analyses.

2.2. Assays and materials

2.2.1. Biomedical assays

All the blood samples were centrifuged to extract the serum part and stored in the −80 °C refrigerator. The serum concentration of IL-12 and IL-18 was determined by LEGENDplex™ 13-plex pro-inflammatory cytokine panel (BioLegend Inc., USA) according to the protocol specified by the manufacturer. The concentrations were transformed into picograms per millilitre (pg/mL).

2.2.2. Hong Kong montreal cognitive assessment (HK-MoCA)

Hong Kong Montreal Cognitive Assessment is a screening tool for detecting cognitive impairment (Yeung et al., 2014). To yield a global score, it measures different cognitive domains, including short-term memory, executive functions, attention, and focus. The overall score is 30, and a lower than 26 score suggests mild cognitive impairment and a lower than 22 score might indicate the possible onset of dementia. The Hong Kong version of MoCA has been validated by Wong et al. (2009).

2.2.3. Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh sleep quality index (PSQI) is a generic measure of the quality and disturbances of sleep over one month in clinical and research settings (Mollayeva et al., 2016). The questionnaire consists of 19 self-assessed questions covering 7 components: 1) sleep quality, 2) sleep latency, 3) sleep duration, 4) sleep efficiency, 5) sleep disorders, 6) medication used to sleep, and 7) daytime sleepiness. Each component generates a score from 0 to 3. The sum of the scores of these 7 components yields a global score from 0 to 21. It has a sensitivity of 89.6% and a specificity of 86.5% for identifying individuals with sleep disorders with a cut-off score of 5 (Buysse et al., 1989). The Chinese version of PSQI has been validated by Tsai et al. (2005).

2.2.4. Covariates

Demographic characteristics, healthy lifestyles, long-term medication intakes, and emotional states were considered covariates. In specific, demographic characteristics include age, sex and education level. Healthy lifestyles reflected by body mass index (BMI), smoking habits and drinking habits were controlled due to their impact on oxidative stress and inflammation (Batatinha et al., 2019; Niemann et al., 2017). Long-term medication intakes including anti-hypertensive agents, statins and Traditional Chinese Medication were controlled to exclude their

potential pharmacological effects on sleep and neurocognitive processes (Broncel et al., 2015; Gelber et al., 2013). We also controlled for the emotional state due to its interaction with sleep and cognition (Del Brutto et al., 2015; Zou et al., 2020). The emotional states of depression, anxiety and stress over the previous week were measured by Depression, Anxiety and Stress Scales (DASS-21) (Lovibond and Lovibond, 1995; Wang et al., 2016). Finally, the STOP-BANG score was controlled to rule out the effect of obstructive sleep apnea risk on sleep quality and inflammatory responses (Al-Mughales et al., 2022).

2.3. Data collection procedures

Upon arriving at the research centre, participants were instructed to complete a questionnaire that collected their basic demographic information, as well as past health and medication history. Anthropometric measures were taken and the body mass index (BMI) was calculated. Then, participants completed the PSQI, DASS-21 and STOP-BANG questionnaires with proper instructions. One experimenter administered the HK-MoCA with detailed instructions, and the overall scores were calculated and recorded. Finally, a registered nurse performed the whole blood drawing (5 mL per person). All participants received the blood draw in the morning at an approximately similar time.

2.4. Statistical analysis

Data analysis was conducted using the Statistical Packages for Social Sciences (SPSS) version 23.0 (IBM, 2015). We first applied log transformation for each variable to remove the skewness of distributions. We used the formula LN (1 + variable) for IL-18, IL-12, DASS-21 and PSQI to correct the positive skewness and the formula LN (31 - HK-MoCA) for HK-MoCA to correct the negative skewness. Next, we did a partial correlation analysis among IL-18, IL-12, subjective sleep quality, and neurocognitive performance while controlling for covariates. Multiple regressions were conducted to examine the association between IL-18 and HK-MoCA, as well as PSQI and HK-MoCA. Finally, the moderating effect of IL-12 on the association between IL-18 and PSQI and the conditional indirect effect of PSQI on the relationship between IL-18 and HK-MoCA was tested by the Bootstrapping technique (Shrout and Bolger, 2002) in PROCESS macro 4.0 (Hayes, 2017) with model 1 and model 7. The total bootstrapping sample was set at 10,000 to get the bias-corrected and accelerated (Bca) 95% confidence intervals (CI). The moderating effect was supported when the interaction term was significant at $p < 0.05$ (two-tailed) and the Bca 95% CI did not include zero. The conditional indirect effect was supported when the Bca 95% CI of the index of moderated mediation did not include zero. A set of covariates including age, sex, BMI, education level, smoking and drinking habits, medication intake including anti-hypertensive agents, statins and Traditional Chinese Medicine, STOP-BANG score, and total score of DASS-21 was controlled in the correlation, regression, moderation and moderated mediation analyses.

3. Results

3.1. Characteristics of the participants

The descriptive statistics of demographics, covariates, inflammatory markers, neurocognitive performance, and subjective sleep quality of the participants included in the statistical analysis are listed in Table 1 below. The average age of participants was 54.66 and 51.39% were male.

3.2. Differences in the levels of significant inflammatory markers and subjective sleep quality between individuals with good and poor neurocognitive performance

We half-split the sample (HK-MoCA score >28 or ≤ 28) and conducted an independent sample *t*-test to compare inflammatory markers and sleep quality between individuals with good and poor neurocognitive performance. Table 2 shows the average levels of IL-6, IL-12, IL-18, TNF-α, IFN-γ and PSQI scores in each group.

Table 1
Demographics, covariates, inflammatory markers, neurocognitive performance, and subjective sleep quality of the participants.

	N	M (SD) or %	Minimum	Maximum
Demographics and covariates				
Age	252	54.66 (6.35)	39	65
Sex				
Male	131	52%		
Female	121	48%		
Body Mass Index	252	23.69 (3.50)	15.2	36.7
Education level (years)				
0–3	2	0.8%		
4–6	16	6.3%		
7–9	21	8.3%		
10–12	88	34.9%		
>12	124	49.2%		
Smoking habits				
Never smoker	198	78.6%		
Former smoker	41	15.9%		
Current smoker	14	5.6%		
Drink habits (units/per week)				
0	118	46.8%		
0–14	124	49.2%		
>14	10	4.0%		
Medication intakes				
Antihypertensive agents	39	15.5%		
Statins	17	6.7%		
Traditional Chinese Medication	23	9.1%		
Depression, Anxiety and Stress Scale	252	4.23 (5.34)	0	30
STOP-BANG score	251	2.25 (1.36)	0	7
Inflammatory markers (pg/mL)				
IL-6	252	11.93 (23.00)	0	261.97
IL-12	252	4.45 (6.63)	0	49.14
IL-18	252	324.90 (202.24)	5.56	1084.26
TNF-α	252	19.97 (50.55)	0	539.87
IFN-γ	252	9.45 (17.15)	0	153.36
Neurocognitive performance				
Hong Kong Montreal Cognitive Assessment	252	28.06 (2.00)	18	30
Subjective sleep quality				
Pittsburgh Sleep Quality Index	252	5.04 (2.92)	0	16

Table 2
Differences between individuals with good and poor neurocognitive performances on levels of major inflammatory markers and subjective sleep quality.

	Good Performance (N = 131)		Poor Performance (N = 121)		*p*	*p-critical*[a]
	M	SD	M	SD		
IL-6	11.68	25.16	12.20	20.51	0.86	0.12
IL-12	4.11	4.75	4.81	8.19	0.40	0.08
IL-18	297.09	185.98	355.01	215.23	0.02 *	0.04
TNF-α	20.06	41.34	19.87	59.10	0.98	0.16
IFN-γ	8.61	11.69	10.36	21.58	0.98	0.2
PSQI	4.71	2.67	5.39	3.13	0.07	–

a. Critical p-values corrected for multiple comparisons using the Benjamini-Hochberg method with a 20% false discovery rate.
*The result is significant after corrections.

3.3. Relationships between inflammatory markers, subjective sleep quality, and neurocognitive performance

After natural log transformation, we conducted a partial correlation analysis among inflammatory markers, subjective sleep quality, and neurocognitive performance while controlling for covariates. Table 3 presents the Pearson's r between each pair of variables. IL-18 was positively associated with reversed HK-MoCA scores ($r = 0.13$, $p = 0.45$), suggesting a negative link between IL-18 and neurocognitive performance. IL-18 was not associated with PSQI ($r = 0.02$, $p = 0.72$). IL-12 was negatively correlated with PSQI ($r = -0.16$, $p = 0.02$), indicating that IL-12 was positively associated with better subjective sleep quality. IL-12 was not associated with HK-MoCA scores ($r = -0.04$, $p = 0.54$). PSQI was positively associated with reversed HK-MoCA scores ($r = 0.17$, $p = 0.01$), suggesting that subjective sleep quality and neurocognitive performance are positively associated. All inflammatory markers are significantly correlated, except for IL-12 and IL-18.

Multiple regression was applied to test the association between reversed HK-MoCA score and IL-18 while controlling for age, sex, BMI, smoking and drinking habit, medication intake including anti-hypertensive agents, statins and Traditional Chinese Medicine, STOP-BANG score, and total score of DASS-21. Higher IL-18 was associated with a higher reversed HK-MoCA score after 10,000 times of bootstrapping,$B = 0.097$, beta = 0.12, $p = 0.046$, 95% BCa = [0.002, 0192]. It suggests that higher levels of IL-18 are associated with poorer neurocognitive performance. After controlling for the same set of covariates, PSQI was positively associated with reversed HK-MoCA after 10,000 times of bootstrapping, $B = 0.22$, beta = 0.162, $p = 0.006$, 95% BCa = [0.057, 0.377]. It indicates that worse subjective sleep quality is correlated with poorer neurocognitive performance.

3.4. Moderating effect of IL-12 on the association between IL-18 and subjective sleep quality

We further conducted a moderation analysis to test the regulatory role of IL-12 on the IL-18 and PSQI relationship based on the hypothesis that systemic inflammation, characterized by IL-12/IL-18 axis hyperactivation, might affect sleep quality. The overall model was statistically significant, R-Squared = 0.30, $F(14, 237) = 1.72$, $p = 0.05$. The results showed that IL-12 significantly moderates the relationship between IL-18 and PSQI while controlling for the same set of covariates as above (R-squared change = 0.033, $F(1, 237) = 8.49$, beta = 0.15, $p = 0.004$).

The interaction is depicted in Fig. 1. The interaction was probed by testing the conditional effects of IL-18 at three levels of IL-12, one standard deviation below the mean (Low IL-12 group), at the mean (Average IL-12 group), and one standard deviation above the mean (High IL-12 group). Specifically, IL-18 is negatively associated with PSQI (beta = -0.17, $p = 0.02$, 95% CI = [-0.3122, -0.0248]) when IL-12 is at a relatively low level. When IL-12 is at its average level, no association between IL-18 and PSQI was observed (beta = -0.02, $p = 0.58$, 95% CI = [-0.1007, 0.0566]). Nevertheless, IL-18 is positively associated with PSQI (beta = 0.12, $p = 0.02$, 95% CI = [0.0179, 0.2309]) when the level of IL-12 is high. In sum, it suggests that higher IL-18 is associated with good subjective sleep quality when IL-12 is low, but would be associated with poor subjective sleep quality under the elevation of IL-12.

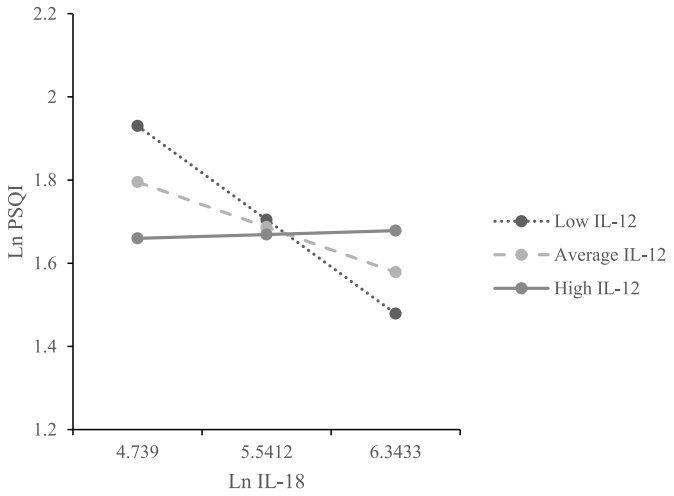

Fig. 1. IL-12 as a moderator between IL-18 and PSQI.
Notes: IL-12: interleukin 12; IL-18: interleukin 18; PSQI: Pittsburgh Sleep Quality Index.

Table 3
Partial correlations between inflammatory markers, PSQI, and reversed HK-MoCA (N = 252).

	IL-18	IL-6	TNF-α	IFN-γ	PSQI	HK-MoCA (reversed)
IL-12	.02	.53 ***	.48 ***	.41 ***	- .16 *	- .04
IL-18		.20 **	.20 **	.24 **	.02	.13 *
IL-6			.60 ***	.65 ***	- .01	.001
TNF-α				.71 ***	- .03	- .04
IFN-γ					- .06	- .07
PSQI						.17 *

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).
***. Correlation is significant at the 0.001 level (2-tailed).
Notes: IL-12: interleukin 12; IL-18: interleukin 18; TNF-α: tumor necrosis factor alpha; IFN-γ: interferon gamma; PSQI: Pittsburgh Sleep Quality Index; HK-MoCA: Hong Kong Montreal Cognitive Assessment.

3.5. Conditional indirect effects of IL-18 on neurocognitive performance through subjective sleep quality

To examine whether subjective sleep quality mediates the association between systemic inflammation and neurocognitive performance, we conducted the moderated mediation analysis to test the indirect effect of IL-18 on HK-MoCA score via PSQI. The result of the moderated mediation analysis (N = 252) confirms the mediating role of subjective sleep quality in the relation between IL-18 and neurocognitive performance, which varied depending on the level of IL-12. Specifically, the mediating role of PSQI was significant and positive (β = 0.026, bootstrapping 95% CI: [0.0004, 0.0608]) when IL-12 was high, whereas the mediating role of PSQI was negative (β = -0.036, bootstrapping 95% CI: [-0.0824, -0.0018]) when IL-12 was low when controlling for the same set of covariates as above. No indirect effect was detected when IL-12 was at its average level (β = -0.005, bootstrapping 95% CI: [-0.0269, 0.0130]). There was no direct effect of IL-18 on HK-MoCA score (β = 0.08, bootstrapping 95% CI: [-0.0096, 0.1777]). In sum, a higher level of IL-18 was associated with a higher PSQI score when IL-12 was elevated, and a higher PSQI score was associated with a lower HK-MoCA score. However, elevated IL-18 level was associated with a lower PSQI score and a higher HK-MoCA score when IL-12 was low. In other words, subjective sleep quality explains the association between IL-18 and neurocognitive performance. For individuals with lower circulating levels of IL-12, IL-18 concentration is associated with better subjective sleep quality and better neurocognitive performance. Only those with concurrently elevated levels of IL-18 and IL-12 would experience sleep disturbance which is further associated with deficits in neurocognitive performance (Fig. 2).

4. Discussion

The findings of this study revealed that neurocognitive performance was negatively related to systemic inflammation which is marked by IL-18 and positively related to sleep quality. Furthermore, sleep quality mediated the neurocognitive performance and IL-18 relationship,

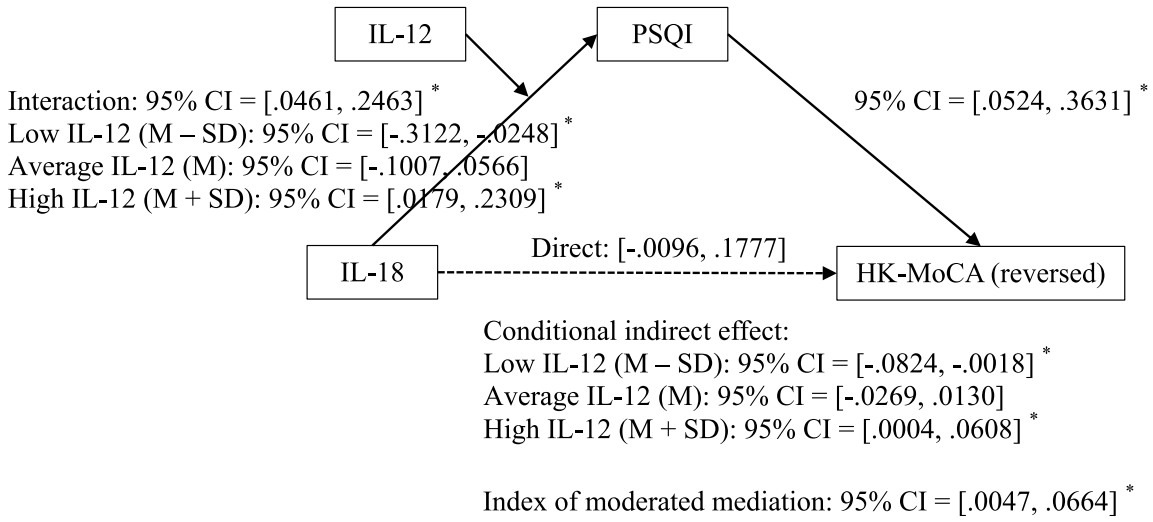

Fig. 2. Conditional indirect effect of IL-18 on neurocognitive performance through subjective sleep quality at different levels of IL-12. Notes: interleukin (IL)-18 is the independent variable, reversed Hong Kong Montreal Cognitive Assessment (HK-MoCA) is the dependent variable, Pittsburgh Sleep Quality Index (PSQI) is the mediator, and IL-12 is the moderator. Alongside each arrow is each effect's bootstrapping confidence interval (CI). Solid lines and * indicate significant relationships ($p < 0.05$) while the dashed line indicates nonsignificant relationships. M and SD are the mean and standard deviation values of IL-12.

depending on the circulating levels of IL-12. Specifically, we observed that IL-18 was inversely associated with subjective sleep quality only when IL-12 was relatively high but positively related to reported sleep quality when IL-12 was relatively low. Sleep quality is an intermediate factor bridging the link between IL-18/IL-12 axis-associated systemic inflammation and changes in neurocognitive performance.

Our findings were in line with existing evidence on the positive association between peripheral levels of IL-18 and neurocognitive deficits in older adults with MCI (Cheng et al., 2022) and patients with AD (Bossù et al., 2008; Chen et al., 2014; Swardfager et al., 2010) and further extended it in healthy individuals. IL-18 participates in regulating several immune pathways including inflammasome activation and the development of Th1, Th2 and Th17 responses (Harel et al., 2022; Sharma and Kanneganti, 2021). In CNS, it shows various effects in the modulation of long-term potentiation, regulating hypothalamic-pituitary axis activity, and interacting with neuropathological protein accumulation (Alboni et al., 2010; Curran and O'Connor, 2001; Tzeng et al., 2018). Research also discovered that IL-18 is a central marker among a network of inflammatory molecules associated with significant white matter injury related to cerebrovascular disease, which is widely reported to be associated with neurocognitive deficits (Altendahl et al., 2020; Lampe et al., 2019).

However, we did not find significant associations between neurocognitive dysfunctions and other major inflammatory markers including TNF-α, IL-6 and IFN-γ, which have been widely reported to be related to neurocognitive impairment (Monteiro et al., 2016; Shen et al., 2019). Generally, the discrepancies might be due to methodological variations in the measurement of cytokines across different studies, or the effects may have been masked by other protective factors, or the ceiling effect that most participants have normal to intact neurocognitive performance. Specifically, different markers may exert their effects via distinct signalling pathways and play different roles in regulating neurocognitive functioning (Alboni et al., 2010; Ćokić et al., 2015; Erta et al., 2012). Thus, future research may closely examine whether the relationship between systemic inflammation and neurocognitive deficits is general or specific to certain molecules or pathways.

Significantly, we testified the interaction between IL-18 and IL-12 in relation to the quality of sleep. It is consistent with previous findings of the sleep-promoting effect of IL-18 in animals (Kubota et al., 2001), and the dual effect of inflammation on sleep based on the framework proposed by Besedovsky et al. (2019). We speculate that IL-18/IL-12 axis is involved in sleep regulation by their synergistic effects in maintaining the balance of Th1/Th2 responses (Dimitrov et al., 2004; Said et al., 2019). The co-existence of IL-18 and IL-12 promotes a shift toward Th1 differentiation (Dinarello, 1999), which triggers the subsequent profiles changes in immune cells (e.g., Th1 and natural killer cells) and cytokines (e.g., IFN- γ and TNF-α), interacting with hormone, neurotransmitters and brain regions controlling sleep-wake processes. Such an explanation is further supported by the findings on the sleep regulatory effect of IFN-γ and TNF-α (Besedovsky et al., 2019). Although we did not find significant associations between IFN- γ, and TNF-α with MoCA and PSQI, we speculate that other lifestyle and physiological factors are also involved in the interaction among this network of inflammatory molecules that might buffer or mask the effects. Future research in animals and humans could further address how altered activations in different immunological axis and pathways are associated with changes in sleep quality (Besedovsky et al., 2019).

We also replicated the existing findings of the negative association between the global PSQI score and MoCA score (Fu et al., 2021; Liao et al., 2022) in older adults without dementia, and verified that the indirect effect of IL-18 on HK-MoCA via the mediator PSQI differs depending on the levels of IL-12. We found that better nocturnal sleep quality protected the body against unfavourable neurocognitive changes under mild inflammation. Nevertheless, more disturbed sleep was related to deficient neurocognitive performance when the IL-18/IL-12 axis was activated. Previous studies have identified the mediating effect of white blood cells in explaining nighttime sleep and napping on cognition (Hu et al., 2021) and the moderating effect of systemic inflammation in the longitudinal association between nighttime wakefulness and incidence of all-cause and AD dementia (Baril et al., 2021). Previous studies also identified the role of inflammation in the pathophysiology of cognitive declines in obstructive sleep apnea (OSA). Inflammation indicated by high-sensitive C-reactive protein moderates the association between OSA and executive function in adults aged older than 70 years (Thompson et al., 2022). In sum, the reciprocal association between sleep disturbance, impaired synaptic plasticity, neuroinflammation, disrupted neurogenesis, and altered neurotransmitter levels contribute to neurocognitive declines (Yaffe et al., 2014). In accordance, our research underlines that sleep as a critical process correlated with the well-functioning of innate and adaptive immunity mediates the adverse effect of systemic inflammation on human neurocognitive performance particularly depending on IL-12/IL18 axis

activation, refining our current understanding of immune dysfunctions and human cognition.

The present study has both theoretical and translational implications. First, it reveals the unfavourable effect of systemic inflammation on human neurocognitive performance and highlights sleep quality as a mediating factor in the link between systemic inflammation and changes in neurocognitive performance, modulated by IL-18/IL-12 axis activation. This study provides empirical support for future research exploring the intricate interactions between immune systems, sleep health, and neurocognitive health. Likewise, other neurobiological and psychosocial factors that underpin or moderate the relationships between inflammation and human cognition are worth exploring. These include structural (i.e., Besga et al., 2017; Boots et al., 2020), functional (i.e., Swartz et al., 2021), and network-level (Marsland et al., 2017) brain changes that mediate the immune dysfunctions and neurocognitive changes as well as the moderating factors, i.e., hair cortisol levels (van den Heuvel et al., 2022), depression (Krogh et al., 2014), and lipoproteins (van den Kommer et al., 2012). The current study also provides insights into designing pharmacological and behavioural interventions and/or preventions to buffer neurocognitive declines by controlling systemic inflammation and optimising sleep quality. It suggests that subjective sleep quality is a modifiable factor that could be improved by interventions like neurocognitive behavioural therapy for insomnia to buffer the effect of inflammation on neurocognitive performance. Meanwhile, lifestyle management approaches, for example, regular and moderate exercise (Nascimento et al., 2014; Qi et al., 2021), and nutrition management (Miquel et al., 2018) might also be beneficial in controlling systemic inflammation, managing sleep disturbances, and promoting neurocognitive functioning (Custodero et al., 2018).

Several limitations are worth noting. First, we should interpret the causal relationship between systemic inflammation, subjective sleep quality, and deficits in neurocognitive performance cautiously, considering the cross-sectional design of the current study. Future studies with longitudinal and prospective designs will help clarify the immunophysiological mechanism underpinning human neurocognitive declines. Second, we only recruited Cantonese-speaking Chinese adults, which lacked racial/ethnic diversity. Future research recruiting individuals from multiple ethnicities will help examine whether the current results could be generalised to a larger population. Third, we only measured a key group of inflammatory markers related to Th1 response, which might represent the full picture of the immune-cognition relationship. Future research may consider measuring a more extensive network of cytokines to compare the effects of different markers and the roles of different types of Th responses. Fourth, we measured only subjective sleep quality, which might differ from objective sleep quality measured by actigraphy or polysomnography (PSG). Future research may continue to investigate the effect of cytokines on objective and subjective sleep qualities in humans and scrutinize the underpinning immunological pathways using animal studies. Finally, due to time constraints, we employed the scores on the HK-MoCA as a proxy of the neurocognitive performance. Future studies would consider using comprehensive neuropsychological measures to identify whether systemic inflammation has general or specific neurocognitive effects, for example, to compare the general and domain-specific changes.

5. Conclusions

The present study demonstrates the detrimental effects of systemic inflammation on neurocognitive performance in healthy middle-aged to elderly individuals. The association between IL-18 and human neurocognitive performance is further explained by a sleep-dependent mechanism moderated by the IL-18/IL-12 axis activation. These findings inspire further explorations of the effect of systemic inflammation and neuroinflammatory response on human cognition and provide insights for developing interventions and prevention strategies aiming at promoting immune functioning and sleep health to delay or alter neurocognitive declines and impairments.

Funding

This project is supported by Hong Kong Research Grant Council General Research Fund (Ref: 17600621).

Declaration of competing interest

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

Data availability

Data will be made available on request.

References

Alboni, S., Cervia, D., Sugama, S., Conti, B., 2010. Interleukin 18 in the CNS. J. Neuroinflammation 7, 9. https://doi.org/10.1186/1742-2094-7-9.

Al-Mughales, J., Wali, S.O., Manzar, M.D., Alhejaili, F., Gozal, D., 2022. Pro-inflammatory markers in patients with obstructive sleep apnea and the effect of Continuous Positive Airway Pressure therapy. Sleep science (Sao Paulo, Brazil) 15, 20–27. https://doi.org/10.5935/1984-0063.20200117. Spec 1).

Altendahl, M., Maillard, P., Harvey, D., Cotter, D., Walters, S., Wolf, A., Singh, B., Kakarla, V., Azizkhanian, I., Sheth, S.A., Xiao, G., Fox, E., You, M., Leng, M., Elashoff, D., Kramer, J.H., Decarli, C., Elahi, F., Hinman, J.D., 2020. An IL-18-centered inflammatory network as a biomarker for cerebral white matter injury. PLoS One 15 (1), e0227835. https://doi.org/10.1371/journal.pone.0227835.

Baril, A.A., Beiser, A.S., Redline, S., McGrath, E.R., Aparicio, H.J., Gottlieb, D.J., Seshadri, S., Pase, M.P., Himali, J.J., 2021. Systemic inflammation as a moderator between sleep and incident dementia. Sleep 44 (2), zsaa164. https://doi.org/10.1093/sleep/zsaa164.

Batatinha, H.A.P., Rosa Neto, J.C., Krüger, K., 2019. Inflammatory features of obesity and smoke exposure and the immunologic effects of exercise. Exerc. Immunol. Rev. 25, 96–111.

Besedovsky, L., Lange, T., Haack, M., 2019. The sleep-immune crosstalk in health and disease. Physiol. Rev. 99, 1325–1380.

Besga, A., Chyzhyk, D., Gonzalez-Ortega, I., Echeveste, J., Graña-Lecuona, M., Graña, M., Gonzalez-Pinto, A., 2017. White matter tract integrity in Alzheimer's disease vs. late onset bipolar disorder and its correlation with systemic inflammation and oxidative stress biomarkers. Front. Aging Neurosci. 9, 179.

Boots, E.A., Castellanos, K.J., Zhan, L., Barnes, L.L., Tussing-Humphreys, L., Deoni, S., Lamar, M., 2020. Inflammation, cognition, and white matter in older adults: an examination by race. Front. Aging Neurosci. 12, 553998 https://doi.org/10.3389/fnagi.2020.553998.

Bossù, P., Ciaramella, A., Salani, F., Bizzoni, F., Varsi, E., Di Iulio, F., Giubilei, F., Gianni, W., Trequattrini, A., Moro, M.L., Bernardini, S., Caltagirone, C., Spalletta, G., 2008. Interleukin-18 produced by peripheral blood cells is increased in Alzheimer's disease and correlates with cognitive impairment. Brain Behav. Immun. 22 (4), 487–492. https://doi.org/10.1016/j.bbi.2007.10.001.

Bradburn, S., Murgatroyd, C., Ray, N., 2019. Neuroinflammation in mild cognitive impairment and Alzheimer's disease: a meta-analysis. Ageing Res. Rev. 50, 1–8.

Broncel, M., Gorzelak-Pabiś, P., Sahebkar, A., Serejko, K., Ursoniu, S., Rysz, J., Corina Serban, M., Możdżan, M., Banach, M., Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group, 2015. Sleep changes following statin therapy: a systematic review and meta-analysis of randomized placebo-controlled polysomnographic trials. Arch. Med. Sci. : AMS 11 (5), 915–926. https://doi.org/10.5114/aoms.2015.54841.

Buysse, D.J., Reynolds III, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatr. Res. 28 (2), 193–213.

Chen, J.M., Jiang, G.X., Li, Q.W., Zhou, Z.M., Cheng, Q., 2014. Increased serum levels of interleukin-18,-23 and-17 in Chinese patients with Alzheimer's disease. Dement. Geriatr. Cognit. Disord. 38 (5–6), 321–329.

Cheng, L., Dong, R., Song, C., Li, X., Zhang, L., Shi, M., Lv, C., Wang, L., Kou, J., Xie, H., Feng, W., Zhao, H., 2022. Mediation effects of IL-1beta and IL-18 on the association between vitamin D levels and mild cognitive impairment among Chinese older adults: a case-control study in taiyuan, China. Front. Aging Neurosci. 14, 836311 https://doi.org/10.3389/fnagi.2022.836311.

Čokić, V.P., Mitrović-Ajtić, O., Beleslin-Čokić, B.B., Marković, D., Buač, M., Diklić, M., Kraguljac-Kurtović, N., Damjanović, S., Milenković, P., Gotić, M., Raj, P.K., 2015. Proinflammatory cytokine IL-6 and JAK-STAT signaling pathway in myeloproliferative neoplasms. Mediat. Inflamm., 453020 https://doi.org/10.1155/2015/453020, 2015.

Curran, B., O'Connor, J.J., 2001. The pro-inflammatory cytokine interleukin-18 impairs long-term potentiation and NMDA receptor-mediated transmission in the rat hippocampus in vitro. Neuroscience 108 (1), 83–90. https://doi.org/10.1016/s0306-4522(01)00405-5.

Custodero, C., Mankowski, R.T., Lee, S.A., Chen, Z., Wu, S., Manini, T.M., Hincapie Echeverri, J., Sabba, C., Beavers, D.P., Cauley, J.A., Espeland, M.A., Fielding, R.A., Kritchevsky, S.B., Liu, C.K., McDermott, M.M., Miller, M.E., Tracy, R.P., Newman, A. B., Ambrosius, W.T., Anton, S.D., 2018. Evidence-based nutritional and pharmacological interventions targeting chronic low-grade inflammation in middle-age and older adults: a systematic review and meta-analysis. Ageing Res. Rev. 46, 42–59. https://doi.org/10.1016/j.arr.2018.05.004.

Daroff, R.B., Aminoff, M.J., 2014. Encyclopedia of the Neurological Sciences. Academic press.

Darweesh, S.K., Wolters, F.J., Ikram, M.A., de Wolf, F., Bos, D., Hofman, A., 2018. Inflammatory markers and the risk of dementia and Alzheimer's disease: a meta-analysis. Alzheimer's Dementia 14 (11), 1450–1459.

Del Brutto, O.H., Mera, R.M., Del Brutto, V.J., Maestre, G.E., Gardener, H., Zambrano, M., Wright, C.B., 2015. Influence of depression, anxiety and stress on cognitive performance in community-dwelling older adults living in rural Ecuador: results of the Atahualpa Project. Geriatr. Gerontol. Int. 15 (4), 508–514. https://doi.org/10.1111/ggi.12305.

Díaz-García, E., García-Tovar, S., Alfaro, E., Jaureguizar, A., Casitas, R., Sánchez-Sánchez, B., Zamarrón, E., Fernández-Lahera, J., López-Collazo, E., Cubillos-Zapata, C., García-Río, F., 2022. Inflammasome activation: a keystone of proinflammatory response in obstructive sleep apnea. Am. J. Respir. Crit. Care Med. 205 (11), 1337–1348. https://doi.org/10.1164/rccm.202106-1445OC.

Dimitrov, S., Lange, T., Nohroudi, K., Born, J., 2007. Number and function of circulating human antigen presenting cells regulated by sleep. Sleep 30 (4), 401–411. https://doi.org/10.1093/sleep/30.4.401.

Dimitrov, S., Lange, T., Tieken, S., Fehm, H.L., Born, J., 2004. Sleep associated regulation of T helper 1/T helper 2 cytokine balance in humans. Brain Behav. Immun. 18 (4), 341–348.

Dinarello, C.A., 1999. IL-18: a TH1-inducing, proinflammatory cytokine and new member of the IL-1 family. J. Allergy Clin. Immunol. 103 (1 Pt 1), 11–24. https://doi.org/10.1016/s0091-6749(99)70518-x.

Erta, M., Quintana, A., Hidalgo, J., 2012. Interleukin-6, a major cytokine in the central nervous system. Int. J. Biol. Sci. 8 (9), 1254–1266. https://doi.org/10.7150/ijbs.4679.

Fu, Y., Wang, Z.T., Qu, Y., Wang, X.T., Ma, Y.H., Bi, Y.L., Dong, Q., Tan, L., Yu, J.T., 2021. Sleep characteristics and cognitive function in older adults without dementia: the CABLE study. J. Alzheim. Dis. : JAD 84 (3), 1029–1038. https://doi.org/10.3233/JAD-215017.

Galea, I., 2021. The blood–brain barrier in systemic infection and inflammation. Cell. Mol. Immunol. 18 (11), 2489–2501.

Gelber, R.P., Ross, G.W., Petrovitch, H., Masaki, K.H., Launer, L.J., White, L.R., 2013. Antihypertensive medication use and risk of cognitive impairment: the Honolulu-Asia Aging Study. Neurology 81 (10), 888–895. https://doi.org/10.1212/WNL.0b013e3182a351d4.

Harel, M., Fauteux-Daniel, S., Girard-Guyonvarc'h, C., Gabay, C., 2022. Balance between interleukin-18 and interleukin-18 binding protein in auto-inflammatory diseases. Cytokine 150, 155781.

Hayes, A.F., 2017. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach. Guilford publications.

Heppner, F.L., Ransohoff, R.M., Becher, B., 2015. Immune attack: the role of inflammation in Alzheimer disease. Nat. Rev. Neurosci. 16 (6), 358–372. https://doi.org/10.1038/nrn3880.

Holmes, C., 2013. Systemic inflammation and Alzheimer's disease. Neuropathol. Appl. Neurobiol. 39 (1), 51–68.

Hoogland, I., Houbolt, C., van Westerloo, D.J., van Gool, W.A., van de Beek, D., 2015. Systemic inflammation and microglial activation: systematic review of animal experiments. J. Neuroinflammation 12 (1), 1–13.

Hu, M., Shu, X., Feng, H., Xiao, L.D., 2021. Sleep, inflammation and cognitive function in middle-aged and older adults: a population-based study. J. Affect. Disord. 284, 120–125.

IBM, Corp, 2015. IBM SPSS Statistics for Windows. IBM Corp, Armonk, NY. Version 23.0.

Imeri, L., Opp, M.R., 2009. How (and why) the immune system makes us sleep. Nat. Rev. Neurosci. 10 (3), 199–210.

Irwin, M.R., 2019. Sleep and inflammation: partners in sickness and in health. Nat. Rev. Immunol. 19 (11), 702–715.

Kannan, Y., Yu, J., Raices, R.M., Seshadri, S., Wei, M., Caligiuri, M.A., Wewers, M.D., 2011. IκBζ augments IL-12- and IL-18-mediated IFN-γ production in human NK cells. Blood 117 (10), 2855–2863. https://doi.org/10.1182/blood-2010-07-294702.

Kempuraj, D., Thangavel, R., Natteru, P.A., Selvakumar, G.P., Saeed, D., Zahoor, H., Zaheer, S., Iyer, S.S., Zaheer, A., 2016. Neuroinflammation induces neurodegeneration. J. Neurol. Neurosurg. Spine 1 (1), 1003.

Krogh, J., Benros, M.E., Jørgensen, M.B., Vesterager, L., Elfving, B., Nordentoft, M., 2014. The association between depressive symptoms, cognitive function, and inflammation in major depression. Brain Behav. Immun. 35, 70–76. https://doi.org/10.1016/j.bbi.2013.08.014.

Kubota, T., Fang, J., Brown, R.A., Krueger, J.M., 2001. Interleukin-18 promotes sleep in rabbits and rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 281 (3), R828–R838. https://doi.org/10.1152/ajpregu.2001.281.3.R828.

Lampe, L., Kharabian-Masouleh, S., Kynast, J., Arelin, K., Steele, C.J., Löffler, M., Witte, A.V., Schroeter, M.L., Villringer, A., Bazin, P.L., 2019. Lesion location matters: the relationships between white matter hyperintensities on cognition in the healthy elderly. J. Cerebr. Blood Flow Metabol. : Off. J. Int. Soc. Cerebr. Blood Flow Metabol. 39 (1), 36–43. https://doi.org/10.1177/0271678X17740501.

Leonardo, S., Fregni, F., 2023. Association of inflammation and cognition in the elderly: a systematic review and meta-analysis. Front. Aging Neurosci. 15.

Liao, H., Liao, S., Gao, Y.J., Mu, J.P., Wang, X., Chen, D.S., 2022. Correlation between sleep time, sleep quality, and emotional and cognitive function in the elderly. BioMed Res. Int. 2022, 9709536 https://doi.org/10.1155/2022/9709536.

Lovibond, P.F., Lovibond, S.H., 1995. The structure of negative emotional states: comparison of the depression anxiety stress Scales (DASS) with the beck depression and anxiety inventories. Behav. Res. Ther. 33 (3), 335–343.

Ma, X.Q., Jiang, C.Q., Xu, L., Zhang, W.S., Zhu, F., Jin, Y.L., Thomas, G.N., Lam, T.H., 2019. Sleep quality and cognitive impairment in older Chinese: guangzhou biobank cohort study. Age Ageing 49 (1), 119–124. https://doi.org/10.1093/ageing/afz120.

Machhi, J., Yeapuri, P., Lu, Y., Foster, E., Chikhale, R., Herskovitz, J., Namminga, K.L., Olson, K.E., Abdelmoaty, M.M., Gao, J., Quadros, R.M., Kiyota, T., Jingjing, L., Kevadiya, B.D., Wang, X., Liu, Y., Poluektova, L.Y., Gurumurthy, C.B., Mosley, R.L., Gendelman, H.E., 2021. CD4+ effector T cells accelerate Alzheimer's disease in mice. J. Neuroinflammation 18 (1), 272. https://doi.org/10.1186/s12974-021-02308-7.

Marsland, A.L., Gianaros, P.J., Kuan, D.C., Sheu, L.K., Krajina, K., Manuck, S.B., 2015. Brain morphology links systemic inflammation to cognitive function in midlife adults. Brain Behav. Immun. 48, 195–204. https://doi.org/10.1016/j.bbi.2015.03.015.

Marsland, A.L., Kuan, D.C.H., Sheu, L.K., Krajina, K., Kraynak, T.E., Manuck, S.B., Gianaros, P.J., 2017. Systemic inflammation and resting state connectivity of the default mode network. Brain Behav. Immun. 62, 162–170.

Miquel, S., Champ, C., Day, J., Aarts, E., Bahr, B.A., Bakker, M., Bánáti, D., Calabrese, V., Cederholm, T., Cryan, J., Dye, L., Farrimond, J.A., Korosi, A., Layé, S., Maudsley, S., Milenkovic, D., Mohajeri, M.H., Sijben, J., Solomon, A., Spencer, J., et al., 2018. Poor cognitive ageing: vulnerabilities, mechanisms and the impact of nutritional interventions. Ageing Res. Rev. 42, 40–55. https://doi.org/10.1016/j.arr.2017.12.004.

Mollayeva, T., Thurairajah, P., Burton, K., Mollayeva, S., Shapiro, C.M., Colantonio, A., 2016. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: a systematic review and meta-analysis. Sleep Med. Rev. 25, 52–73.

Monteiro, S., Ferreira, F.M., Pinto, V., Roque, S., Morais, M., de Sá-Calçada, D., Mota, C., Correia-Neves, M., Cerqueira, J.J., 2016. Absence of IFNγ promotes hippocampal plasticity and enhances cognitive performance. Transl. Psychiatry 6 (1), e707. https://doi.org/10.1038/tp.2015.194.

Mullington, J., Korth, C., Hermann, D.M., Orth, A., Galanos, C., Holsboer, F., Pollmächer, T., 2000. Dose-dependent effects of endotoxin on human sleep. Am. J. Physiol. Regul. Integr. Comp. Physiol. 278 (4), R947–R955.

Nakanishi, K., 2018. Unique action of interleukin-18 on T cells and other immune cells. Front. Immunol. 9, 763. https://doi.org/10.3389/fimmu.2018.00763.

Nascimento, C.M., Pereira, J.R., de Andrade, L.P., Garuffi, M., Talib, L.L., Forlenza, O.V., Cancela, J.M., Cominetti, M.R., Stella, F., 2014. Physical exercise in MCI elderly promotes reduction of pro-inflammatory cytokines and improvements on cognition and BDNF peripheral levels. Curr. Alzheimer Res. 11 (8), 799–805. https://doi.org/10.2174/1567205011081409101228 49.

Niemann, B., Rohrbach, S., Miller, M.R., Newby, D.E., Fuster, V., Kovacic, J.C., 2017. Oxidative stress and cardiovascular risk: obesity, diabetes, smoking, and pollution: part 3 of a 3-part series. J. Am. Coll. Cardiol. 70 (2), 230–251.

Olaithe, M., Bucks, R.S., Hillman, D.R., Eastwood, P.R., 2018. Cognitive deficits in obstructive sleep apnea: insights from a meta-review and comparison with deficits observed in COPD, insomnia, and sleep deprivation. Sleep Med. Rev. 38, 39–49. https://doi.org/10.1016/j.smrv.2017.03.005.

Perry, V.H., 2010. Contribution of systemic inflammation to chronic neurodegeneration. Acta Neuropathol. 120 (3), 277–286. https://doi.org/10.1007/s00401-010-0722-x.

Potvin, O., Lorrain, D., Forget, H., Dubé, M., Grenier, S., Préville, M., Hudon, C., 2012. Sleep quality and 1-year incident cognitive impairment in community-dwelling older adults. Sleep 35 (4), 491–499. https://doi.org/10.5665/sleep.1732.

Qi, D., Wong, N.M.L., Shao, R., Man, I.S.C., Wong, C.H.Y., Yuen, L.P., Chan, C.C.H., Lee, T.M.C., 2021. Qigong exercise enhances cognitive functions in the elderly via an interleukin-6-hippocampus pathway: a randomized active-controlled trial. Brain Behav. Immun. 95, 381–390. https://doi.org/10.1016/j.bbi.2021.04.011.

Qin, S., Leong, R.L.F., Ong, J.L., Chee, M.W.L., 2022. Associations between objectively measured sleep parameters and cognition in healthy older adults: a meta-analysis. Sleep Med. Rev. 67, 101734 https://doi.org/10.1016/j.smrv.2022.101734. Advance online publication.

Said, E.A., Al-Abri, M.A., Al-Saidi, I., Al-Balushi, M.S., Al-Busaidi, J.Z., Al-Reesi, I., Koh, C.Y., Idris, M.A., Al-Jabri, A.A., Habbal, O., 2019. Sleep deprivation alters neutrophil functions and levels of Th1-related chemokines and $CD4^+$ T cells in the blood. Sleep & breathing = Schlaf & Atmung 23 (4), 1331–1339. https://doi.org/10.1007/s11325-019-01851-1.

Sharma, B.R., Kanneganti, T.D., 2021. NLRP3 inflammasome in cancer and metabolic diseases. Nat. Immunol. 22 (5), 550–559.

Shen, X.N., Niu, L.D., Wang, Y.J., Cao, X.P., Liu, Q., Tan, L., Zhang, C., Yu, J.T., 2019. Inflammatory markers in Alzheimer's disease and mild cognitive impairment: a meta-analysis and systematic review of 170 studies. J. Neurol. Neurosurg. Psychiatry 90 (5), 590–598. https://doi.org/10.1136/jnnp-2018-319148.

Shrout, P.E., Bolger, N., 2002. Mediation in experimental and non- experimental studies: new procedures and recommendations. Psychol. Methods 7 (4), 422–445.

Swardfager, W., Lanctôt, K., Rothenburg, L., Wong, A., Cappell, J., Herrmann, N., 2010. A meta-analysis of cytokines in Alzheimer's disease. Biol. Psychiatr. 68 (10), 930–941. https://doi.org/10.1016/j.biopsych.2010.06.012.

Swartz, J.R., Carranza, A.F., Tully, L.M., Knodt, A.R., Jiang, J., Irwin, M.R., Hostinar, C. E., 2021. Associations between peripheral inflammation and resting state functional connectivity in adolescents. Brain Behav. Immun. 95, 96–105. https://doi.org/10.1016/j.bbi.2021.02.018.

Thompson, C., Legault, J., Moullec, G., Martineau-Dussault, M.È., Baltzan, M., Cross, N., Dang-Vu, T.T., Gervais, N., Einstein, G., Hanly, P., Ayas, N., Lorrain, D., Kaminska, M., Gagnon, J.F., Lim, A., Carrier, J., Gosselin, N., 2022. Association between risk of obstructive sleep apnea, inflammation and cognition after 45 years old in the Canadian Longitudinal Study on Aging. Sleep Med. 91, 21–30. https://doi.org/10.1016/j.sleep.2022.02.006.

Tsai, P.S., Wang, S.Y., Wang, M.Y., Su, C.T., Yang, T.T., Huang, C.J., Fang, S.C., 2005. Psychometric evaluation of the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI) in primary insomnia and control subjects. Qual. Life Res. 14 (8), 1943–1952.

Tzeng, T.C., Hasegawa, Y., Iguchi, R., Cheung, A., Caffrey, D.R., Thatcher, E.J., Mao, W., Germain, G., Tamburro, N.D., Okabe, S., Heneka, M.T., Latz, E., Futai, K., Golenbock, D.T., 2018. Inflammasome-derived cytokine IL18 suppresses amyloid-induced seizures in Alzheimer-prone mice. Proc. Natl. Acad. Sci. U. S. A 115 (36), 9002–9007. https://doi.org/10.1073/pnas.1801802115.

van den Heuvel, L.L., Suliman, S., Bröcker, E., Kilian, S., Stalder, T., Kirschbaum, C., Seedat, S., 2022. The association between hair cortisol levels, inflammation and cognitive functioning in females. Psychoneuroendocrinology 136, 105619.

van den Kommer, T.N., Dik, M.G., Comijs, H.C., Jonker, C., Deeg, D.J., 2012. The role of lipoproteins and inflammation in cognitive decline: do they interact? Neurobiol. Aging 33 (1), 196-e1.

Wang, K., Shi, H.S., Geng, F.L., Zou, L.Q., Tan, S.P., Wang, Y., Neumann, D.L., Shum, D. H., Chan, R.C., 2016. Cross-cultural validation of the depression anxiety stress scale-21 in China. Psychol. Assess. 28 (5) https://doi.org/10.1037/pas0000207 e88–e100.

Wong, A., Xiong, Y.Y., Kwan, P.W., Chan, A.Y., Lam, W.W., Wang, K., Chu, W.C., Nyenhuis, D.L., Nasreddine, Z., Wong, L.K., Mok, V.C., 2009. The validity, reliability and clinical utility of the Hong Kong Montreal Cognitive Assessment (HK-MoCA) in patients with cerebral small vessel disease. Dement. Geriatr. Cognit. Disord. 28 (1), 81–87. https://doi.org/10.1159/000232589.

Xu, W., Tan, C.C., Zou, J.J., Cao, X.P., Tan, L., 2020. Sleep problems and risk of all-cause cognitive decline or dementia: an updated systematic review and meta-analysis. J. Neurol. Neurosurg. Psychiatr. 91 (3), 236–244.

Yaffe, K., Falvey, C.M., Hoang, T., 2014. Connections between sleep and cognition in older adults. Lancet Neurol. 13 (10), 1017–1028.

Yeung, P.Y., Wong, L.L., Chan, C.C., Leung, J.L., Yung, C.Y., 2014. A validation study of the Hong Kong version of Montreal Cognitive Assessment (HK-MoCA) in Chinese older adults in Hong Kong. Hong Kong medical journal = Xianggang yi xue za zhi 20 (6), 504–510. https://doi.org/10.12809/hkmj144219.

Zou, P., Wang, X., Sun, L., Liu, K., Hou, G., Yang, W., Liu, C., Yang, H., Zhou, N., Zhang, G., Ling, X., Liu, J., Cao, J., Ao, L., Chen, Q., 2020. Poorer sleep quality correlated with mental health problems in college students: a longitudinal observational study among 686 males. J. Psychosom. Res. 136, 110177 https://doi.org/10.1016/j.jpsychores.2020.110177.