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Peripheral interleukin-6 levels and working memory in non-obese adults: A post-hoc analysis from the CALERIE study

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A B S T R A C T

Objectives: This analysis aimed to investigate the association among interleukin 6 (IL-6) levels, caloric intake, and working memory and to explore the potential mediators of these associations using the public dataset from the Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE) clinical trial.
Methods: The CALERIE study was designed to evaluate the effects of 2 y of prolonged caloric restriction in humans. Individuals were randomized to caloric restriction (CR; n = 145) or an ad libitum diet (AL; n = 75) for 2 y. The outcome measures used herein were spatial working memory tests (i.e., total number of errors and strategy). Generalized estimating equations were used to assess the effects of treatment, time, and potential moderators (e.g., sleep and physical activities).
Results: At baseline, there was an effect of hours of sleep, alcohol intake, and physical activities (i.e., mean total metabolic equivalent of task hours per day [MET-hours/day]) on IL-6 levels. The association between IL-6 and energy intake was moderated by MET-hours/day. The longitudinal analysis indicated that there was an effect of time, but not of treatment, on IL-6 levels, with decreasing values in both the CR and AL groups. Changes in IL-6 levels were associated with changes in working memory performance, but there were no between-group (i.e., CR vs. AL) differences.
Conclusions: We observed an association between changes in IL-6 levels and improvement in spatial working memory tests. IL-6 was associated with higher caloric consumption, poorer sleep quality, and lower levels of physical activity.

Introduction

Accumulating evidence indicates that a high diet content of sugar and fat may negatively affect cognitive function [1]. Although there are multiple explanatory variables, one leading candidate is disturbances in inflammatory mediators [2]. Substantial findings support the involvement of inflammatory cytokines in the reduction of adaptive neuroplasticity in healthy individuals, and multiple studies implicate interleukin 6 (IL-6) as the most replicated proinflammatory alteration [3,4]. Such a relationship could ultimately be related to changes in cognitive functioning [5].

In addition to obesity, chronic inflammation is associated with insulin resistance, diabetes, cancer, cardiovascular disorders, and neuropsychiatric disorders [6–8]. As visceral and subcutaneous adipose tissue increases, monocytes, CD4+, and CD8+ T cells migrate and infiltrate them and initiate the release of proinflammatory mediators, which are linked to local insulin resistance [9,10]. Consequently, the adipose tissue microenvironment is the principal source of proinflammatory IL-6 [11], a mediator of adaptive immunity and inflammatory reactions. Increased levels of inflammation are related to obesity and have been associated with impaired cognitive performance in middle-aged individuals, with IL-6 inversely related to cognitive capacity [12–14].

Exercise and caloric restriction (CR) are strategies commonly prescribed to treat obesity [15,16]. Murine models submitted to CR, exercise, or a high-fat diet successfully demonstrated that while physical activity increased the number of natural killer cells in the adipose tissue and IL-6 in serum levels, caloric restriction increased the CD4+/CD8+ cell ratio and monocyte chemoattractant protein-1 levels

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[17]. In fact, the authors proposed that exercise and CR modulate resident immune cells in adipose tissues differently in spite of an equivalent body weight reduction [17]. In a separate study, all mice submitted to CR, compared with a high-fat diet control group, exhibited lower production of proinflammatory cytokines IL-1β and tumor necrosis factor-α and a trend toward lower levels of IL-6, as well as lower production of prostaglandin E2, which is a lipid molecule with proinflammatory and T cell-suppressive properties [18,19]. Studies have demonstrated that CR positively affects the immune system functions, including both the innate and acquired immune systems; extends survival and maximal lifespan in experimental animal models; and delays the onset of age-related diseases that are related to inflammation [13,20–23].

Although several diet interventions claim to affect cognition, there are very few well-designed studies to support a significant effect in humans [24–27]. In addition, data on the relationship between cognitive improvements and immune-inflammation levels after CR in humans is scant.

The Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE) study was funded by the National Institutes of Health and designed to evaluate the biological effects of 2 y of prolonged CR in humans [28,29]. The primary aim of this study was to test the hypothesis that 2 y of sustained 25% CR in men and women ages 21 to 50 y would slow aging and protect against age-related diseases process [30]. A previous analysis in this sample has shown that CR induced a significant and persistent inhibition of inflammation without impairing key in vivo indicators of cell-mediated immunity [31]. However, data on the effects of the intervention on working memory and IL-6 as well as potential moderators have not been explored.

Given the recent findings on the effect of CR for the immune-inflammatory system in non-obese subjects and animal models and inconsistency in findings related to cognition, this study aimed to investigate the association between IL-6 levels and working memory in CR and to explore the potential mediators of these associations using the public dataset from the CALERIE clinical trial.

Methods

Study design and sample

The CALERIE study design, recruitment strategies, baseline data, intervention, and main outcomes are described elsewhere [29,30,32,33]. In summary, the study was a parallel-group, randomized clinical trial that compared 2 y of 25% CR with 2 y of ad libitum diet (AL). The randomization ratio was 2:1 in favor of CR, and randomization was stratified by site, sex, and body mass index (BMI; calculated as weight in kg divided by height in m^2), dichotomized as normal weight (22.0–24.9 kg) or overweight (25.0–27.9 kg).

A total of 220 healthy volunteers across three sites (Tufts University, Pennington Biomedical Research Center, and Washington University School of Medicine) were recruited beginning in May 2007. The study participants were men ages 21 to 50 y and women ages 21 to 47 y with an initial BMI of $\geq$22 kg/m^2 and <28 kg/ m^2, respectively.

Assessments

Working memory tests

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a validated and widely used method to assess cognitive performance. CANTAB is composed of highly sensitive, precise, and objective measures of cognitive functions, which has been correlated to neural networks and previously determined reliable neurocognitive tests [34–36]. The spatial working memory (SWM) test included in the CANTAB battery was used to evaluate construct SWM. The SWM task requires retention and manipulation of visuospatial information. This self-ordered test has notable executive function demands and provides a reliable mensuration of strategy and working memory errors. For our analysis, the outcome measures were SWM total number of errors (SWMTE), defined as the number of times a box is selected that is certain not to contain a blue token and therefore should not have been visited by the subject (i.e., between errors + within errors – double errors); and strategy (SWMS), defined as problems with six or more boxes with the number of distinct boxes used by the subject to begin a new search for a token within the same problem.

Clinical assessments

For the clinical assessment, the following instruments we used the following: 1) Pittsburgh Sleep Quality Index (PSQI), which is a self-rated questionnaire designed to evaluate sleep quality and disturbances over a 1-mo time interval and includes subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction [37]; 2) Profile of Mood States, which is an instrument to evaluate transient mood states that assesses six dimensions of mood changes (tension or anxiety, anger or hostility, vigor or activity, fatigue or inertia, depression or dejection, confusion or bewilderment) [38,39]; and 3) Perceived Stress Scale, which is a widely-used instrument to measure the intensity of psychological stress, using Likert-scale items to ask individuals to rate the frequency of experienced stress over the last month [40].

Interleukin-6 measurement

IL-6 was measured by multiplex immunoassay in accordance with the manufacturer's instructions (Human Serum Adipokine Panel B, Millipore, Billerica, MA).

Caloric restriction protocol

Participants randomized to the CR group were provided with meals for the first 27 d of the intervention and encouraged to adhere to the prescribed foods and menus. Participants were required to pick up the provided meals at the centers using site-specific schedules. Participants rotated through three different diet patterns (low fat, Mediterranean, and low glycemic load). These varied diets were provided for educational purposes related to food selection and portion size. Three-day cycle menus were used, and each participant was on each diet type for 9 d. For participants who wanted to follow a vegetarian diet, a 3-d cycle vegetarian menu was provided. All diets contained 14 g fiber/1000 kcal. Two-thirds of a cup (80 kcal, 19g fiber) of Fiber One bran cereal was also offered. The centers did not serve alcohol, and alcohol consumption was discouraged during the meal-provision phase to maintain the 25% CR level. However, alcohol was permitted after the 4-wk feeding phase for the remainder of the intervention, but no more than two drinks/d and no more than 14 drinks/wk for men and 10 for women. The CR prescription level for each participant was calculated on the basis of baseline total energy expenditure results derived from the doubly-labeled water [28].

Physical activity

Physical activity of 30 min/d of a moderate level at minimum 5 d/wk was advised, but no efforts were made to change participants' exercise habits or activity levels. The procedures for BMI and mean metabolic equivalent of task h/d (MET-hours/day) are described elsewhere [28].

Statistical analysis

Independent sample t and χ^2 tests were used for baseline characteristics. Generalized linear models were used to assess associations between IL-6 tests and associated variables (i.e., age, sex, mood, sleep, caloric intake, and exercise variables). IL-6 levels had a positively skewed distribution; therefore, we used gamma with log-link models. For the analyses in which SWM tests were the outcome, because they consisted of count data with a positively skewed distribution, we used negative binomial models. The interaction term for each moderating variable (e.g., BMI × energy intake) was added to separate models to assess moderation at baseline.

For the analyses of longitudinal data, due to the non-normal distribution of working memory tests, we used generalized estimating equation models with negative binomial and log-link specification and assumed an unstructured covariance structure. Generalized estimating equation models are more tolerant of missing data [41]; therefore, we chose not to use an intent-to-treat criterion. The independent variables were treatment and time (visit) and the treatment and time interaction. Age, sex, and education level were included as covariates. Possible moderators were analyzed (e.g., treatment × time × sleep) in separate models. Due to the nonlinearity of the models, the estimated β coefficients were transformed into rate ratio (RR) estimates.

Results

Baseline analyses

The demographic variables of the sample at baseline are shown in Table 1.

Association between energy intake and interleukin-6 levels

The results of the unadjusted analysis indicated a positive correlation between SWMTE scores and IL-6 peripheral levels ($R = 0.189$; $P = 0.006$). There was no statistically significant correlation between IL-6 at baseline and SWMS, age, BMI, energy intake, fat intake, carbohydrate intake, protein intake, alcohol intake, number of hours of sleep, sleep efficiency, PSQI total score, Profile of Mood States total score, Perceived Stress Scale total score, and total MET-h/d. The results of the adjusted analysis for age and sex are presented in Table 2.

Moderating effect of associated variables on the association between energy intake and interleukin 6 at baseline

We also tested possible moderating effects of BMI, hours of sleep, mood, stress, daily energy expenditure, and MET on associations between energy intake and IL-6. All analyses were adjusted for age and sex. Only the levels of physical activity exerted a moderating effect (RR = 0.989; 95% confidence interval [CI], 0.980–0.999; $P = 0.791$; Fig. 1).

Longitudinal analyses

Changes in interleukin-6 peripheral levels during the follow-up period

Both groups displayed a decrease in IL-6 peripheral levels in 12 and 24 mo. There was an effect of time on IL-6 considering the whole sample ($P = 0.030$). There was no effect of group ($P = 0.661$) or time × group interaction ($P = 0.733$).

Effect of possible moderators of longitudinal changes in interleukin-6 peripheral levels

We tested for possible moderator effects of sleep problems, mood disturbances, perceived stress, and physical activity in longitudinal changes of IL-6 levels in the sample, as well as the effects of CR. Overall, there was a time (mo 12 RR = 1.258; 95% CI, 1.081–1.464; $P = 0.003$; mo 24 RR = 1.240; 95% CI, 1.059–1.451; $P = 0.008$), and time × treatment effects for PSQI total score (mo 12 RR = 0.811; 95% CI, 0.666–0.987; $P = 0.036$; mo 24 RR = 0.854; 95% CI, 0.711–1.027; $P = 0.093$). There were effects of time on mood disturbances (mo 12 $\beta = 2.356$; 95% CI, 0.134–4.579; $P = 0.038$; mo 24 $\beta = 3.089$; 95% CI, 0.924–5.255; $P = 0.005$), on perceived stress (mo 12 RR = 1.099; 95% CI, 0.888–1.361; $P = 0.386$; mo 24 RR = 1.233; 95 % CI, 1.030–1.475; $P = 0.022$), and on total MET-h/d (mo 12 RR = 0.990; 95% CI, 0.977–1.003; $P = 0.119$; mo 24 RR = 0.986; 95% CI, 0.975–0.997; $P = 0.009$), but no time × treatment effect.

After adjustment for changes in BMI, a trend was observed for a significant time × treatment × MET-h/d interaction on IL-6 levels ($P = 0.070$). At mo 24, there were significant time × MET-h/d (RR = 0.904; 95% CI, 0.835; 0.979; $P = 0.024$) and time × treatment × MET-h/d interactions (RR = 1.125; 95% CI, 1.018–1.244; $P = 0.021$), indicating that changes in MET-h/d had different effects in IL-6 between the CR and AL groups (Fig. 2).

Association between working memory and IL-6 levels

With regard to a possible effect of changes in IL-6 on changes in working memory performance, we observed an effect of IL-6 over time on working memory assessed by SWMS and SWMTE. Changes in IL-6 peripheral levels were associated with SWMS changes across time ($P = 0.004$), mainly in month 24 (visit 12 × IL-6: RR = 0.987; 95% CI, 0.972–1.002; $P = 0.093$; visit 24 × IL-6: RR = 0.986; 95% CI, 0.974–0.998; $P = 0.018$). In addition, there was a trend for a group effect in the association between changes in IL-6 and SWMS ($P = 0.050$), but IL-6 did not moderate the time × intervention interaction ($P = 0.595$).

With regard to SWMTE, we observed changes in IL-6 levels that were associated with the performance in this test ($P = 0.020$); however, because there was an opposite effect of visits 12 and 24, the results for each visit did not achieve statistical significance (visit 12 × IL-6: RR = 1.005; 95% CI, 0.919–1.100; $P = 0.908$; visit 24 × IL-6: RR = 0.937; 95% CI, 0.858–1.023; $P = 0.147$). The effect of changes in

Table 1
Demographic and baseline characteristics of subjects

	Caloric restriction (n = 145)	Ad libitum diet (n = 75)	*P*-value
Female, n	100	53	0.878
Age, mean (SD), y	37.87	37.85	0.987
Hours of sleep, mean (SD)	7.89 (0.95)	7.82 (0.126)	0.671
Sleep efficiency, mean (SD)	88.97 (1.56)	91.28 (1.73)	0.360
PSS total score, mean (SD)	2.51 (0.16)	2.52 (0.23)	0.973
METs total score, mean (SD)	34.44 (0.20)	34.28 (0.23)	0.633
DEE, mean (SD)	2034.71 (26.78)	1987.85 (36.75)	0.306
SWMTE, mean (SD)	18.66 (1.42)	25.90 (2.71)	0.036
SWMS, mean (SD)	31.02 (0.50)	31.81 (0.74)	0.369

DEE, daily energy expenditure; MET, metabolic equivalent of task; PSS, perceived stress scale; SD, standard deviation; SWMS, spatial working memory strategy; SWMTE, spatial working memory total number of errors.

Table 2
Associations between interleukin 6 and variables of interest, adjusted for age and sex, at baseline

	Interleukin 6 RR	95% CI	*P*-value
Sleep hours	0.888	0.817; 0.965	0.005
POMS	0.995	0.988; 1.003	0.214
BMI	1.024	0.970; 1.081	0.390
DEE*	1.310	0.906; 1.080	0.151
MET*	1.046	1.002; 1.092	0.039
Energy intake	0.984	0.952; 1.017	0.330
Fat	0.998	0.993; 1.002	0.227
Carbohydrates	1.000	0.999; 1.001	0.942
Protein	0.997	0.992; 1.002	0.227
Alcohol	0.992	0.985; 0.999	0.038
SWMTE†	1.051	0.968; 1.140	0.236
SWMS†	1.010	0.994; 1.026	0.215

BMI, body mass index; CI, confidence interval; DEE, daily energy expenditure; MET, metabolic equivalent of task; POMS, Profile of Mood States; RR, rate ratio; SWMS, spatial working memory strategy; SWMTE, spatial working memory total number of errors.
*Adjusted for BMI.
†Adjusted for education.

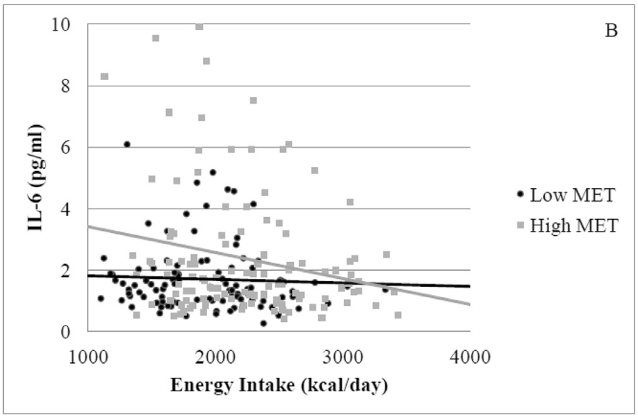

Fig. 1. Positive moderating effect of physical exercise in interleukin-6 peripheral levels varies by total metabolic equivalent of task at baseline. Individuals who practice low levels of exercise have a positive association between caloric intake and inerleukin-6 levels but a negative association was found among those who practice moderate-to-high levels of exercise.

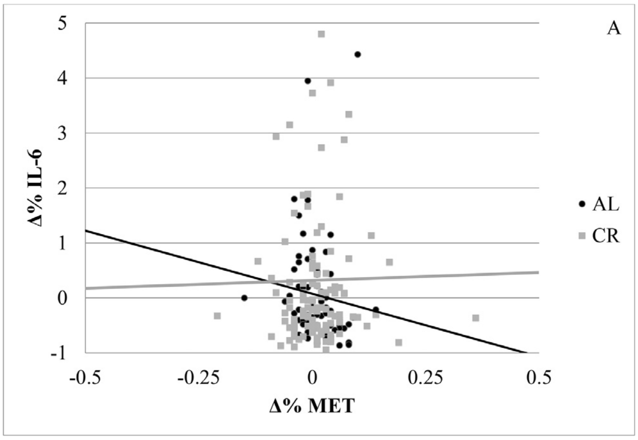

Fig. 2. Differential effect of caloric restriction and ad libitum diet in the association between interleukin-6 peripheral levels and changes in physical exercise.

IL-6 in the SWMTE scores was different between the groups ($P = 0.001$; Fig. 3), but no moderator effect of IL-6 in the time × intervention interaction ($P = 0.789$) was observed.

Discussion

In the present study, we observed an association between energy intake and levels of IL-6 moderated by energy expenditure as operationalized by METs (Fig. 1). When divided into high and low/moderate METs, we observed a negative curve of association between IL-6 levels and energy intake, where lower energy intake was linked with lower IL-6 levels. IL-6 acts on glucose uptake in the skeletal muscle, lipolysis in the muscle and adipose tissue, and hepatic gluconeogenesis. IL-6 levels are closely related with exercise intensity and duration (i.e., prolonged contraction of skeletal muscle releases greater concentrations of this cytokine in circulation) [42]. Exhaustive acute exercise can promote an increase of IL-6 up to 100 times in addition to skeletal muscle glycogen depletion [43]. Alternately, chronic exercise suppresses proinflammatory cytokines (tumor necrosis factor-α and IL-6) and increases antiinflammatory cytokines (IL-4, IL-10, and transforming growth factor-β) [44,45].

In the longitudinal analyses, both groups presented a significant reduction of IL-6 levels at 12 and 24 mo, but no effect of group or group × time interaction for the decrease in IL-6 was observed. The

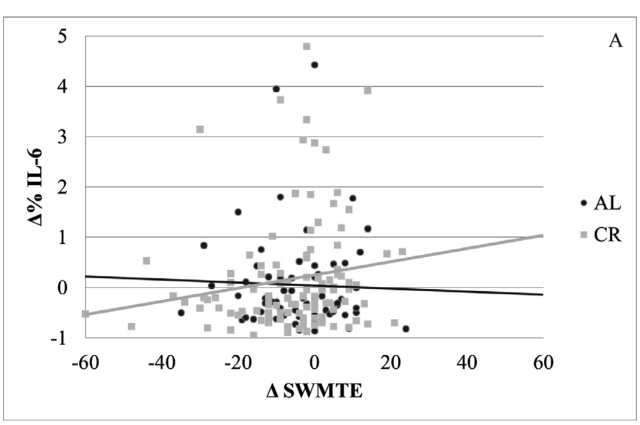

Fig. 3. Differential effect of group in the association between changes in interleukin-6 and changes in performance in spatial working memory total number of errors test in 24 mo.

lack of statistical significance in the difference between the two treatment arms may be related to the small effect size of the proposed intervention [32]. However, a significant moderation effect of sleep quality was observed when separating the sample by PSQI total scores. Individuals with a lower sleep quality in the AL group had higher levels of IL-6, with a deterioration of sleep quality over time. A similar finding was not observed in the CR group.

Longer periods of time awake may affect caloric intake and promote the synthesis of proinflammatory cytokines [46]. This relation may contribute to an increase in IL-6, which is involved in sleep-wake behaviors [47]. Sleep restriction and decreased sleep quality have been previously associated with increased caloric intake and insulin resistance with long-term consequences. Nutritional states have also been associated with changes in sleep architecture, with high-fat diet worsening the effects of sleep restriction and decreased sleep quality [46].

With regard to working memory, we observed that changes in IL-6 levels were associated with changes in SWMTE in the CR group only, with a more significant improvement in test performance, as shown by a reduction in the total number of errors associated with a higher decrease in IL-6. In addition, there was a trend for group effect in the association between changes in IL-6 and SWMS.

Higher levels of IL-6 have been consistently associated with poorer performance on tests of encoding and recall of information [48] and working memory [49–51]. A recent study evaluated the relationship between intracellular cytokine production and memory and attention in healthy older individuals [5]. The authors strongly suggested that a higher percentage of activated monocytes positive for IL-1b expression (pro IL-6 production) was associated with poorer performance on aspects of SWM, and mean IL-6 cell production was associated with poorer performance on tests for working memory as assessed by the CANTAB [5]. Other studies support that higher concentrations of IL-1b and IL-6 are associated with negative effects on hippocampal pathways-related memory in animal and human studies [52].

Although our findings are preliminary and require replication, the results contribute to the current limited knowledge of inflammatory pathway and cognition in non-obese individuals. Specifically, the results illustrate a mechanism wherein changes in IL-6 levels are related to changes in working memory in CR, using the public dataset from a robust multicenter clinical trial. In addition, we explored potential moderators of these associations such as sleep quality and exercise.

However, these findings are exploratory and should be interpreted in light of their limitations. First, the sample was composed of healthy non-obese individuals only, which limits the generalizability of our findings. Second, with regard to cognition, the observed deficits were not clinically relevant, and the lack of an intelligence quotient estimate limits the use of the working memory tests. Third, the small magnitude of the changes in working memory tests in CR and AL groups limits the power of the study. Last, the peripheral levels of IL-6 may not accurately reflect changes in cortical and subcortical levels. In addition, whether the changes in IL-6 that were detected in the study indicate inflammation is limited. Moreover, IL-6 interacts in a complex manner with other interleukins to mediate immune-inflammation, which limits the interpretation of our findings.

Conclusions

Taken together, the results of this study suggest an association between changes in IL-6 levels and improvements in working memory tests, and the improvements in the working memory tasks are associated with greater reductions in IL-6 levels. Potential moderators are sleep quality and reduced physical activity.

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