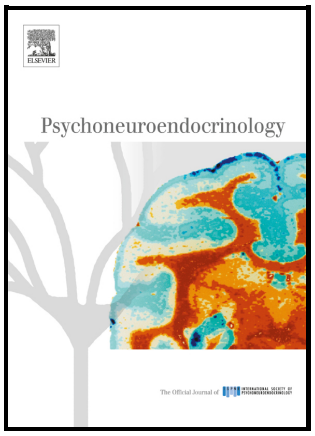

Body mass index, systemic inflammation and cognitive performance in adolescents: a cross-sectional study

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Xavier Caldú

Body mass index, systemic inflammation and cognitive performance in adolescents: a cross-sectional study

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ABSTRACT

Background:

Excessive body weight has been related to lower cognitive performance. One of the mechanisms through which excess body weight may affect cognition is inflammation.

Hypothesis:

Our hypothesis is that both body mass index (BMI) and circulating levels of inflammatory biomarkers will be negatively related to cognitive performance.

Design:

Cross-sectional study.

Setting:

Users of the public health centres of the *Consorci Sanitari de Terrassa* (Terrassa, Spain) between 2010 and 2017 aged 12 to 21 years.

Participants:

One hundred and five adolescents (46 normoweight, 18 overweight, 41 obese).

Measurements:

Levels of high sensitivity C-reactive protein, interleukin 6, tumour necrosis factor α (TNFα) and fibrinogen were determined from blood samples. Cognitive performance was evaluated and six cognitive composites were obtained: working memory, cognitive flexibility, inhibitory control, decision-making, verbal memory, and fine motor speed. A single multivariate general lineal model was used to assess the influence of the four inflammatory biomarkers, as well as participants' BMI, sex, and age on the 6 cognitive indexes.

Results.

An inverse relationship between BMI and inhibitory control (F = 5.688, p = .019; β = -.212, p = .031), verbal memory (F = 5.404, p = .022; β = -.255, p = .009) and fine motor speed (F = 9.038, p = .003; β = -.319, p = .001) was observed. Levels of TNFα and fibrinogen were inversely related to inhibitory control (F = 5.055, p = .027; β = -.226, p = .021) and verbal memory (F = 4.732, p = .032; β = -.274, p = .005), respectively.

Limitations:

The cross-sectional nature of the study, the use of cognitive tests designed for clinical purposes, and the use of BMI as a proxy for adiposity are limitations of our study that must be taken into account when interpreting results.

Conclusions.

Our data indicate that some components of executive functions, together with verbal memory, are sensitive to specific obesity-related inflammatory agents at early ages.

Keywords:

obesity, overweight, inflammation, cognition, executive functions, memory.

1. INTRODUCTION

The prevalence of obesity has doubled since 1980 and, alarmingly, child and adolescent obesity has skyrocketed during the latest decades, exceeding the increase in adult obesity in many countries (Weihrauch-Blüher and Wiegand, 2018). Obesity-related comorbidities start as early as in childhood, increasing the risk of hyperinsulinemia, insulin resistance, prediabetes, and type 2 diabetes, amongst other health complications that can lead to increased mortality and premature death (Lee and Yoon, 2018). Consequently, excess weight during childhood and adolescence has emerged as one of the most serious issues in public health (Lee and Yoon, 2018; Weihrauch-Blüher and Wiegand, 2018).

Beyond the physiological and psychological deleterious effects of obesity, excessive weight has also been related to lower cognitive performance (Tanaka et al., 2020). Performance in

executive functions and memory have been found to be lower in adults with excess weight (Farruggia and Small, 2019). At younger ages, most of the studies have focused on executive functioning (Miller and Spencer, 2014), showing a reduction in several executive domains including inhibitory control, working memory, cognitive flexibility, planning and decision-making (Liang et al., 2014; Mamrot and Hanć, 2019) (Likhitweerawong et al., 2022). Besides executive functions, attention, visuospatial performance, and motor skills also appear to be negatively related to body mass (Barros et al., 2022; Liang et al., 2014). On the other hand, studies on other cognitive functions, such as language, learning, memory, or general cognitive function have provided mixed results (Liang et al., 2014).

The mechanisms by which excess weight may influence cognition are not yet fully understood. One of these potential mechanisms is inflammation. Adipose tissue is not only a reservoir for energy, but also an immune organ (Stolarczyk, 2017). A sustained positive energy balance over time leads to excessive fat accumulation in adipocytes (Reilly and Saltiel, 2017) and these hypertrophied adipocytes, along with the adipose tissue-resident immune cells (mainly lymphocytes and macrophages), increase circulating levels of proinflammatory cytokines such as tumour necrosis factor alpha (TNFα) and interleukin-6 (IL-6), as well as other proinflammatory factors such as C-reactive protein (CRP) and fibrinogen, thus triggering a low-grade chronic inflammatory state (Spyridaki et al., 2016). This sustained inflammatory state can lead to neuroinflammation, which has been negatively related to brain structure and cognitive performance (Gómez-Apo et al., 2021, p.). In fact, the link between systemic inflammation and cognitive impairment in adults is well documented (Lin et al., 2018). Several studies have shown associations between serum concentrations of inflammatory biomarkers and worse performance in memory, spatial reasoning, processing speed, attention, and executive functions (Heringa et al., 2014; Lin et al., 2018; Marsland et al., 2006).

Our study aims at distinguishing between the effects of BMI and those related to systemic inflammation on different aspects of cognition in adolescents. For that purpose, we measured the levels of four commonly used biomarkers of inflammation and carried out an extensive evaluation of cognitive functions previously described to be negatively related to body mass. Our hypothesis is that both BMI and circulating levels of inflammatory biomarkers will be negatively related to cognitive performance. Precisely determining how body weight and inflammation are related to cognitive performance is a step forward in the obtention of a more realistic view of paediatric obesity and of its possible links with cognition.

2. METHODS

2.1. Subjects. For this cross-sectional study, adolescents aged 12 to 21 were recruited from public health centres of the *Consorci Sanitari de Terrassa* (CST) (Terrassa, Spain). Recruitment and data collection were carried out between 2010 and 2017. Inclusion criteria were: sex and age specific BMI over the 5th percentile according to the 2000 Centers for Disease Control and Prevention (CDC) growth charts (Kuczmarski et al., 2002) or a BMI higher than 18.5 kg/m^2 if they were older than 17. Potential participants were briefly interviewed to screen for a history of significant developmental, neurological, or systemic disorders (e.g., diabetes, thyroid disease, and metabolic syndrome), psychiatric illness (including eating disorders, such as bulimia or binge eating disorder), or history of substance abuse. Eligible subjects were programmed for a second session in which a medical examination and a blood draw were performed, either at the *Unitat d'Endocrinologia Pediàtrica* of the *Hospital de Terrassa* (for participants under 19 years of age) or at the *Centre d'Atenció Primària Terrassa Nord* (for older participants). This medical examination allowed to take anthropometric measures (i.e., weight and height) and to assure the absence of any exclusion criteria. In a third session, those who obtained medical approval underwent an extensive neuropsychological assessment at the *Unitat de Neuropsicologia Clínica* of the *Hospital de Terrassa* to explore executive functions, memory, and fine motor speed. The mean lapse between the medical and the

neuropsychological evaluation was 2 months. The neuropsychological evaluation was carried out in a single session, and it also helped to discard the presence of global cognitive impairment. IQ was estimated through the Vocabulary subtest of the Wechsler Adult Intelligence Scale III (WAIS-III) or the Wechsler Intelligence Scale for Children IV (WISC-IV). A scalar score lower than 7 implied the exclusion of the study.

Written informed consent was obtained from each participant (or their parents when they were under 18 years of age). The Ethics Committee for Clinical Research of the CST, and the Institutional Ethics Committee (CBUB) and the Institutional Review Board of the University of Barcelona approved the current study (IRB 00003099, assurance number: FWA00004225; http:// www.ub.edu/recerca/comissiobioetica.htm), which was conducted in accordance with the Helsinki Declaration.

2.2. Measures

Blood samples were collected for the measurement of serum concentrations of high-sensitivity CRP (hs-CRP), IL-6 and TNFα, and plasma levels of fibrinogen. Blood draws were carried out between 8:00 and 8:30 a.m. after an overnight fast. Serum and plasma samples were separated as soon as possible, coded, and stored at −80 °C at the Logistics Park of Health (CatLab) until further analysis.

Concentrations of hs-CRP and fibrinogen were determined at CatLab through nephelometry (Beckman Coulter Immage 800) and PT-derived fibrinogen assay, respectively. Fibrinogen values of 47 participants were quantified with STA-Neoplastin-Plus reactive (STA-Rack), while for the rest of the sample Recombiplastin 2G reactive (ACLTOP 700) was used. The inter-assay coefficients for STA-Rack and ACLTOP 700 were 6.52% and 3.18%, respectively, and the intra-assay coefficient of variability for ACLTOP 700 was 0.75%. We cannot provide the intra-assay coefficient of STA-Rack because these data are currently missing. Serum levels of IL-6 and TNFα were analysed at the *Centre de Recerca en Metabolisme* (*Universitat de Barcelona*). IL-6

was measured using a Quantikine HS ELISA Human IL-6 (R&D Systems, Ref. HS600C Lot P178994) and TNFα was quantified by Quantikine HS ELISA Human TNFα (R&D Systems, Ref. HSTA00E Lot P174731). The inter-assay coefficients of variability for IL-6 and TNFα were 6.7% and 6.5%, respectively. The intra-assay coefficients of variability for IL-6 and TNFα were 4.1% and 2%, respectively. The detection threshold for both IL-6 and TNFα was 0.156 pg/ml and only subjects with IL-6 and TNFα levels above this threshold were included in our sample. As noted above, participants with hs-CRP values > 10 mg/L were also excluded (Pearson et al., 2003).

Working memory (WM) was measured using the scalar score of the Letter-Number subtest (LN) of the WAIS or the WISC and the accuracy of responses in a N-back computerized task. The accuracy of responses in the N-back was calculated by subtracting incorrect responses from correct responses across three 2- back cycles.

Cognitive flexibility was determined from the perseverative errors in a computerized version of the Wisconsin Card Sorting Test (WCST) and from the Trail Making Test (TMT) part B minus A. In the TMT, the execution time (in seconds) of part A was subtracted from part B in order to remove the speed element from the test (Lezak, 1995), providing a better flexibility measure than TMT part B.

Inhibitory control was measured with the interference score of the Stroop's test and with the number of commission errors in the Conners' Continuous Performance Test-II (CPT-II). The interference score was calculated according to this formula: [incongruent sheet – (word sheet * colour sheet) / (word sheet + colour sheet)]. High interference values indicate better ability to suppress automatic responses. Commission errors in the CPT-II were used to estimate the inhibition capacity, as they have been interpreted as a failure to stop a response (Soreni et al., 2009).

Decision-making was estimated trough the global net score of a computerized version of the Iowa Gambling Task (IGT) and with the geometric mean of delay discounting rates of the Monetary Choice Questionnaire (MCQ), also known as Kirby Delay-Discounting Questionnaire. The global net score for the IGT was calculated by subtracting the total number of cards selected from decks A and B from the chosen cards chosen from decks C and D (i.e., [C+D] – [A+B]). A positive score reflects a tendency toward good decision-making, while negative scores suggest a disadvantageous performance. The geometric mean of the rates for the small, medium, and large reward magnitudes of the MCQ was used to determine the reduction in the present value of a future reward as the delay to that reward increases. Hence, higher geometric mean values involve more impulsive decisions and less ability to delay reward.

Verbal memory was measured using the long-term free recall of the California Verbal Learning Test-II (CVLT-II). The total number of free recalled words after an interval of 20 minutes was used to measure the efficiency of verbal memory.

Fine motor speed was determined through the needed time to complete the Grooved Pegboard Test (GPT). The task was repeated twice, once for the dominant and once for the non-dominant hand. If a peg falls during the attempt to get into the hole, it is considered a drop. Each drop was computed as one extra second in the total time. The total time in seconds for each hand was used to quantify the fine motor speed. Lower scores were interpreted as a faster motor speed.

BMI was transformed into BMI z-score (BMIz) using the 2000 CDC growth charts (Kuczmarski et al., 2002). Considering that this guide only allows to calculate BMIz until 20 years of age, the BMIz of our seven 21-year-old volunteers was estimated as if they were 20.

2.3. Statistical Analyses

Firstly, target raw scores of each neuropsychological test were z-scaled. Then, these new scores were clustered into six composite z-scores, which represent different cognitive

domains: WM, flexibility, inhibitory control, decision-making, verbal memory, and fine motor speed. These composites were calculated as follows: WM = ($Z_{\text{scalar score LN subtest}} + Z_{\text{accuracy of responses N-back}}$) / 2; flexibility = ($-Z_{\text{perseverative errors WCST}} + -Z_{\text{TMT (part B – part A)}}$) / 2; inhibitory control = ($Z_{\text{interference score Stroop}} + -Z_{\text{commission errors CPT-II}}$) / 2; decision-making = ($Z_{\text{global net score IGT}} + -Z_{\text{geometric mean MCQ}}$) / 2; verbal memory = ($Z_{\text{long-delay free recall CVLT-II}}$); fine motor speed = ($-Z_{\text{dominant hand GPT}} + -Z_{\text{non-dominant hand GPT}}$) / 2. Higher scores of these indices point to better cognitive performance.

Data were analysed with SPSS software v. 27 (IBM Corporation, Armonk, NY). A single multivariate general lineal model was applied with the four inflammatory biomarkers and participants' BMI, sex, and age as predictors and scores in the 6 cognitive indexes as dependent variables. For significant results, individual regression analyses were performed to determine the direction of the relationship.

A statistical power analysis was performed with the software G*Power (Faul et al., 2007). For $f^2 = 0.15$, $\alpha = 0.05$, and a power of 0.8, the estimated sample size was 103 subjects.

3. RESULTS

From the 138 volunteers who agreed to participate in the study, 4 were excluded after medical visit and 5 were ruled out for having CRP values > 10 mg/L, which are indicative of a possible acute infection (Pearson et al., 2003). Furthermore, 24 additional candidates were also discarded, as their TNFα and IL-6 values were not available. Therefore, the final sample was composed by 105 adolescents and young adults (age = 15.89 ± 2.68; 56 females), of whom 65 were already included in a previous work (Prats-Soteras et al., 2020). Table 1 shows demographic, anthropometric, and inflammatory characteristics of the sample. Although the final sample size was 105 participants, a few of them had missing data in some indices. Briefly, there were the following missing values: WM index (n=5, from which n=1 was excluded for low

reliability response (i.e., more incorrect than correct responses in the N-back test), decision-making index (n=4) and both flexibility and inhibitory control indices (n=1). Regarding the outliers (± 3 SD) treatment, four of the outliers found (two in the TMT part B and two in the GPT) were changed and replaced by the highest score to meet normality assumptions and three of the outliers found in the MCQ were not changed, since adolescents with these outlier scores showed valid results in all response-consistency indices of this test.

Table 2 shows correlation and p values for all the variables included in the study. Table 3 shows results of the multivariate general linear model. Regarding demographic variables, participants' age was related to inhibitory control ($F = 12.069$, $p < .001$) and fine motor speed ($F = 5.469$, $p = .022$) and sex was related to working memory ($F = 5.474$, $p = .022$) and fine motor speed ($F = 9.868$, $p = .002$). Age was directly related to inhibitory control ($\beta = .368$, $p < .001$) and fine motor speed ($\beta = .247$, $p = .001$). Women scored better than men in fine motor speed ($\beta = .341$, $p < .001$) and men scored better than women in working memory ($\beta = -.204$, $p = .042$).

BMIz showed a significant effect on inhibitory control ($F = 5.688$, $p = .019$), verbal memory ($F = 5.404$, $p = .022$) and fine motor speed ($F = 9.038$, $p = .003$). The relationship between BMIz and these three cognitive indexes was inverse, as shown by the individual regression analyses (inhibitory control: $\beta = -.212$, $p = .031$; verbal memory: $\beta = -.255$, $p = .009$; fine motor speed: $\beta = -.319$, $p = .001$).

Among inflammatory biomarkers, a significant relationship was found between TNFα and inhibitory control ($F = 5.055$, $p = .027$) and between fibrinogen and verbal memory ($F = 4.732$, $p = .032$). In both cases, the relationship between levels of inflammatory biomarkers and cognitive indexes was inverse (TNFα - inhibitory control: $\beta = -.226$, $p = .021$; fibrinogen – verbal memory: $\beta = -.274$, $p = .005$). Likewise, a trend was observed between TNFα and the standardized residuals of fine motor speed ($F = 3.113$, $p = .081$).

4. DISCUSSION

In the present study we aimed to assess whether BMI and the levels of circulating inflammatory biomarkers are related to cognitive performance in adolescents. For that purpose, we determined four common inflammatory biomarkers (hs-CRP, IL-6, TNFα and fibrinogen) in our sample of adolescents and analysed their relationship with six composites reflecting different cognitive domains. As we expected, our analyses confirmed the relationship between both BMI and inflammation and cognition. Specifically, BMI was negatively related to inhibitory control, verbal memory, and fine motor speed. Further, inhibitory control and verbal memory were negatively related to circulating levels of TNFα and fibrinogen, respectively.

Obesity has been associated with worse cognitive performance (O'Brien et al., 2017). Among all cognitive domains, executive functions and memory seem to be especially sensitive to the effects of unhealthy excess weight (Farruggia and Small, 2019). Interestingly, both executive functions and memory have been reported to improve after weight loss (Arjmand et al., 2022; Chávez-Manzanera et al., 2022), although results to date regarding the effects of obesity interventions and cognitive improvement have been controversial (Martin et al., 2014) and have shown, when observed, small and quite heterogenous effects (Likhitweerawong et al., 2022). Executive functions include several specific subcomponents. One of the core components of executive functions is inhibitory control, which refers to the capacity of avoiding preponderant responses in favour of more adaptive ones and is a key function for food consumption regulation. In individuals with obesity, reduced levels of inhibitory control have been described (Lavagnino et al., 2016). Further, it has been shown that lower levels of impulsivity are associated with greater weight loss in individuals following weight loss programmes (Galioto et al., 2016) and that cognitive training targeting inhibition also results in larger weight losses (Yang et al., 2019). Our results are in harmony with these previous findings. Although we did not find any relationship between BMI and the rest of composites reflecting other core executive functions, we did observe an association between BMI and

inhibitory control. These reductions in inhibitory control have been related to the inability to regulate eating behaviours, making it difficult to resist the consumption of highly caloric foods (Nederkoorn et al., 2006), thus contributing to the development or maintenance of obesity.

We also observed an association between BMI and our verbal memory composite. Although less studied than executive functions, there is evidence that memory processes are related to obesity and eating behaviours (Seitz et al., 2021). In humans, excess body weight affects memory performance (Gunstad et al., 2006) and in animals dietary-induced obesity alters memory (Fan et al., 2022). Besides, amnesic patients and experimental animals with impaired episodic memory due to lesions in the hippocampus and its vicinities are prone to excess food intake and obesity (Higgs et al., 2008; Rozin et al., 2016). Thus, our findings of memory decreases related to BMI fit well with previous data and suggest that lower memory performance associated with body mass is already evident at early ages.

Motor performance has also been reported to be reduced in obesity (Gentier et al., 2013), specially, gross motor function (Barros et al., 2022). Reductions in gross motor function are supposed to be the consequence of the greater load on the body due to the excess mass of the muscles implicated in a specific movement (Hue et al., 2007). Regarding fine motor control, results are controversial. While some studies have reported no association between excess weight and fine motor control (Marmeleira et al., 2017; Matarma et al., 2018), some others indicate that obesity is also associated with diminished fine motor performance (D'Hondt et al., 2008; Gentier et al., 2013). It has been suggested that lower fine motor performance observed in obesity may be due to the higher postural demands imposed by increased body mass (D'Hondt et al., 2008). However, in our study, as in previous ones (D'Hondt et al., 2008; Gentier et al., 2013), such reductions in fine motor control are observed in situations where postural effects are greatly diminished. Although these observations do not allow to rule out the possibility that reductions are due to postural or mechanical demands imposed by heavier

body parts involved in movements, it has been suggested that they could be reflecting perceptual-motor coordination difficulties (D'Hondt et al., 2008; Gentier et al., 2013). Our data adds up to the evidence that obesity affects fine motor control too, even when the postural and mechanical burden associated with higher body weight is controlled.

Although the study of the structural and functional correlates of obesity-related cognitive deficits is beyond the scope of the present work, it is worth mentioning that our results are also coherent with neuroanatomical and functional findings reported by previous studies. There is mounting evidence of the structural and functional brain changes associated with overweight and obesity, which involve both grey and white matter structures (Gómez-Apo et al., 2021). Although obesity has been associated with general modifications in the brain (Beyer et al., 2019; Geha et al., 2017), some structures seem to be especially sensitive. One of these structures is the medial temporal lobe, including the hippocampus, in which differences in both grey (Bobb et al., 2014) and white (Stanek et al., 2011) matter have been described. These structural changes are thought to underlay some of the cognitive features observed in obesity, such as those affecting verbal memory. In the same line, obesity has been consistently related to structural and functional changes in prefrontal regions (García-García et al., 2019; Marqués-Iturria et al., 2013) which are key structures for executive control. However, despite the amount of evidence relating excess weight with brain structure and function, whether these differences precede or are a consequence of obesity is to be determined. In this sense, two theories may potentially explain the relationship between obesity and cognition. On one hand, from the dual systems model perspective, certain risky choices, such as overeating or choosing highly caloric foods instead of healthier ones, would be explained by the incapacity of a putative brain regulatory system to consistently restrain potentially hazardous impulses (Shulman et al., 2016). Alternatively, from an immunologic model point of view, the higher levels of proinflammatory cytokines released by the greater amount of adipose tissue present in individuals with obesity would compromise their self-regulatory system, hindering their

capacity to make healthy food choices (Shields et al., 2017). Nonetheless, this immunologic model does not rule out the possibility that the low-grade inflammatory state present in obesity may both contribute to, and be caused by, the disorder. Probably, the most plausible explanation lies on a bidirectional relationship between obesity and brain structure and function (García-García et al., 2019). According to this bidirectional view, lower levels in certain cognitive functions, such as memory or inhibitory control, would impose difficulties to keep certain healthy eating behaviours. For example, low levels of inhibitory control may hinder avoiding highly caloric foods in favour of more nutritive ones and not being able to precisely remember the amount and lapse from the last intake may promote higher and more frequent food intakes. At the same time, this excessive food consumption that leads to obesity has been associated with cognitive decline (Fan et al., 2022), thus closing a vicious cycle between obesity and cognition.

The ways obesity may be related to cognitive performance are diverse. Among them, the low-grade inflammatory state induced by obesity is currently receiving great attention. It is well known that inflammation is an early consequence of obesity, and that this inflammatory state may in turn affect brain functioning (Miller and Spencer, 2014). However, the specific relationship between different inflammatory biomarkers and specific cognitive domains and whether this relationship depends on individuals' age is not fully known. For instance, a recent study carried out in a large sample of children aged 10 years did not find any relationship between any of the five obesity-related inflammatory biomarkers assessed (namely, white blood cell count, IL-6, IL-1, TNFα and PCR) and executive functions, including cognitive flexibility, cognitive inhibition and working memory (Adelantado-Renau et al., 2019). Here, we show that at least some components of executive functioning, as well as verbal memory, are sensitive to circulating inflammatory biomarkers at early ages. Participants in our study, though, although young, were slightly older than those in Adelantado-Renau's study (Adelantado-Renau et al., 2019). Given that at older ages, the affectation of executive

functions associated to increased body mass appears to be a consistent observation, it may well be that the effects of the inflammatory state elicited by obesity require a certain lapse of time to become evident. However, methodological issues (e.g., assessment tools, data analysis) cannot be ruled out as potential explanations for these discrepancies. As expected, the circulating levels of the four inflammatory biomarkers analysed in the present study were correlated with BMI. Besides, two of the biomarkers, TNFα and fibrinogen, were related to inhibitory control and verbal memory, respectively. There is evidence that obesity is associated with a persistent low-grade inflammatory state that affects brain structure (Prats-Soteras et al., 2020, p.) and function (Chen et al., 2018). However, in humans, especially in young populations, data regarding how different inflammatory biomarkers specifically affect cognition are scarce. In this regard, it is well-known that IL-6 exerts both pro- and anti-inflammatory effects, depending on its signalling pathway (McElvaney et al., 2021; Scheller et al., 2011; Wueest and Konrad, 2020), and that these opposite effects are time- and cell-type-dependent (Kern et al., 2018). Although levels of IL-6 have been consistently described to be increased in obesity, whether they are producing pro- or anti-inflammatory effects may be complex to determine. One possibility could be that, at least at young ages, the anti-inflammatory effects of IL-6 were intense enough to counteract its inflammatory effects. In contrast, TNFα exerts only inflammatory effects (Kern et al., 2018) and that could explain why it already affects cognitive performance at early ages. This explanation would also be coherent with the observed effect of fibrinogen and the lack of effect of CRP in our sample. Both fibrinogen and CRP are synthesised and released by the liver in response to TNFα and IL-6, respectively. Thus, the anti-inflammatory effects of IL-6 could reduce CRP synthesis and release so that CRP levels, although higher in excess weight subjects, would not reach sufficient levels to produce a significant effect. On the other hand, fibrinogen production, stimulated by the inflammatory effects of TNFα, would be able to reach high enough levels to produce an effect on cognition. However, the reason why only inhibitory control and verbal

memory appear to be sensitive to the levels of these two specific inflammatory agents remains elusive.

Our study presents some limitations that must be considered when interpreting results. First, the cross-sectional nature of our study does not allow to establish whether the worse performance in executive functions is a cause or a consequence of BMI and its associated increase in inflammatory biomarkers. Second, although the cognitive tests we have used to evaluate cognitive performance are widely used in non-clinical populations, they have been designed essentially for clinical purposes, so they may lack the sufficient sensitivity to bring to light subtler variations. Third, the determination of inflammatory biomarkers from only one single-point blood sample does not allow to ascertain whether they correspond to a stable, chronic, or to a transient, acute inflammatory profile. Finally, although BMI is a very common parameter to determine weight status, it does not necessarily reflect adiposity. In this sense, direct measures of central adiposity may be more closely related to the inflammatory status and thus more precisely capture the relationship with cognitive performance.

In summary, our data indicate that some cognitive functions could be especially sensitive to certain specific inflammatory agents, but further research in this field is warranted to precisely determine these specificities.

5. CONCLUSIONS

Our data suggest that BMI and inflammatory state are associated to poorer cognitive performance in adolescents. The cognitive areas that appear to be more sensitive to this inflammatory state are inhibitory control and verbal memory, which, in turn, are related to circulating levels of specific inflammatory biomarkers, namely TNFα and fibrinogen, respectively.

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7. REFERENCES

Adelantado-Renau, M., Esteban-Cornejo, I., Rodriguez-Ayllon, M., Cadenas-Sanchez, C., Gil-Cosano, J.J., Mora-Gonzalez, J., Solis-Urra, P., Verdejo-Román, J., Aguilera, C.M., Escolano-Margarit, M.V., Verdejo-Garcia, A., Catena, A., Moliner-Urdiales, D., Ortega, F.B., 2019. Inflammatory biomarkers and brain health indicators in children with overweight and obesity: The ActiveBrains project. Brain. Behav. Immun. 81, 588–597. https://doi.org/10.1016/J.BBI.2019.07.020

Arjmand, G., Abbas-Zadeh, M., Eftekhari, M.H., 2022. Effect of MIND diet intervention on cognitive performance and brain structure in healthy obese women: a randomized controlled trial. Sci. Rep. 12. https://doi.org/10.1038/S41598-021-04258-9

Barros, W.M.A., Silva, K.G. da, Silva, R.K.P., Souza, A.P. da S., Silva, A.B.J. da, Silva, M.R.M., Fernandes, M.S. de S., Souza, S.L. de, Souza, V. de O.N., 2022. Effects of Overweight/Obesity on Motor Performance in Children: A Systematic Review. Front. Endocrinol. 12. https://doi.org/10.3389/FENDO.2021.759165

Beyer, F., Masouleh, S.K., Kratzsch, J., Schroeter, M.L., Röhr, S., Riedel-Heller, S.G., Villringer, A., Veronica Witte, A., 2019. A Metabolic Obesity Profile Is Associated With Decreased Gray Matter Volume in Cognitively Healthy Older Adults. Front. Aging Neurosci. 11. https://doi.org/10.3389/FNAGI.2019.00202

Bobb, J.F., Schwartz, B.S., Davatzikos, C., Caffo, B., 2014. Cross-sectional and longitudinal association of body mass index and brain volume. Hum. Brain Mapp. 35, 75–88. https://doi.org/10.1002/HBM.22159

Chávez-Manzanera, E., Ramírez-Flores, M., Duran, M., Torres, M., Ramírez, M., Kaufer-Horwitz, M., Stephano, S., Quiroz-Casian, L., Cantú-Brito, C., Chiquete, E., 2022. Influence of Weight Loss on Cognitive Functions: A Pilot Study of a Multidisciplinary Intervention Program for Obesity Treatment. Brain Sci. 12. https://doi.org/10.3390/BRAINSCI12040509

Chen, S., Jia, Y., Woltering, S., 2018. Neural differences of inhibitory control between

adolescents with obesity and their peers. Int. J. Obes. 2005 42, 1753–1761. https://doi.org/10.1038/S41366-018-0142-X

D'Hondt, E., Deforche, B., De Bourdeaudhuij, I., Lenoir, M., 2008. Childhood obesity affects fine motor skill performance under different postural constraints. Neurosci. Lett. 440, 72–75. https://doi.org/10.1016/J.NEULET.2008.05.056

Fan, R., Hua, Y., Shen, J., Xiao, R., Ma, W., 2022. Dietary fatty acids affect learning and memory ability via regulating inflammatory factors in obese mice. J. Nutr. Biochem. 103. https://doi.org/10.1016/J.JNUTBIO.2022.108959

Farruggia, M.C., Small, D.M., 2019. Effects of adiposity and metabolic dysfunction on cognition: A review. Physiol. Behav. 208. https://doi.org/10.1016/J.PHYSBEH.2019.112578

Faul, F., Erdfelder, E., Lang, A.-G., Buchner, A., 2007. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav. Res. Methods 39, 175–191. https://doi.org/10.3758/bf03193146

Galioto, R., Bond, D., Gunstad, J., Pera, V., Rathier, L., Tremont, G., 2016. Executive functions predict weight loss in a medically supervised weight loss programme. Obes. Sci. Pract. 2, 334–340. https://doi.org/10.1002/OSP4.70

García-García, I., Michaud, A., Dadar, M., Zeighami, Y., Neseliler, S., Collins, D.L., Evans, A.C., Dagher, A., 2019. Neuroanatomical differences in obesity: meta-analytic findings and their validation in an independent dataset. Int. J. Obes. 2005 43, 943–951. https://doi.org/10.1038/S41366-018-0164-4

Geha, P., Cecchi, G., Todd Constable, R., Abdallah, C., Small, D.M., 2017. Reorganization of brain connectivity in obesity. Hum. Brain Mapp. 38, 1403–1420. https://doi.org/10.1002/HBM.23462

Gentier, I., D'Hondt, E., Shultz, S., Deforche, B., Augustijn, M., Hoorne, S., Verlaecke, K., De Bourdeaudhuij, I., Lenoir, M., 2013. Fine and gross motor skills differ between healthy-weight and obese children. Res. Dev. Disabil. 34, 4043–4051. https://doi.org/10.1016/J.RIDD.2013.08.040

Gómez-Apo, E., Mondragón-Maya, A., Ferrari-Díaz, M., Silva-Pereyra, J., 2021. Structural Brain Changes Associated with Overweight and Obesity. J. Obes. 2021. https://doi.org/10.1155/2021/6613385

Gunstad, J., Paul, R.H., Cohen, R.A., Tate, D.F., Gordon, E., 2006. Obesity is associated with memory deficits in young and middle-aged adults. Eat. Weight Disord. EWD 11. https://doi.org/10.1007/BF03327747

Heringa, S.M., van den Berg, E., Reijmer, Y.D., Nijpels, G., Stehouwer, C.D.A., Schalkwijk, C.G., Teerlink, T., Scheffer, P.G., van den Hurk, K., Kappelle, L.J., Dekker, J.M., Biessels, G.J., 2014. Markers of low-grade inflammation and endothelial dysfunction are related to reduced information processing speed and executive functioning in an older population - the Hoorn Study. Psychoneuroendocrinology 40, 108–118. https://doi.org/10.1016/j.psyneuen.2013.11.011

Higgs, S., Williamson, A.C., Rotshtein, P., Humphreys, G.W., 2008. Sensory-specific satiety is intact in amnesics who eat multiple meals. Psychol. Sci. 19, 623–628.

https://doi.org/10.1111/J.1467-9280.2008.02132.X

Hue, O., Simoneau, M., Marcotte, J., Berrigan, F., Doré, J., Marceau, P., Marceau, S., Tremblay, A., Teasdale, N., 2007. Body weight is a strong predictor of postural stability. Gait Posture 26, 32–38. https://doi.org/10.1016/J.GAITPOST.2006.07.005

Kern, L., Mittenbühler, M., Vesting, A., Ostermann, A., Wunderlich, C., Wunderlich, F., 2018. Obesity-Induced TNFα and IL-6 Signaling: The Missing Link between Obesity and Inflammation—Driven Liver and Colorectal Cancers. Cancers 11, 24. https://doi.org/10.3390/cancers11010024

Kuczmarski, R.J., Ogden, C.L., Guo, S.S., Grummer-Strawn, L.M., Flegal, K.M., Mei, Z., Wei, R., Curtin, L.R., Roche, A.F., Johnson, C.L., 2002. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat. 11. 1–190.

Lavagnino, L., Arnone, D., Cao, B., Soares, J.C., Selvaraj, S., 2016. Inhibitory control in obesity and binge eating disorder: A systematic review and meta-analysis of neurocognitive and neuroimaging studies. Neurosci. Biobehav. Rev. 68, 714–726. https://doi.org/10.1016/J.NEUBIOREV.2016.06.041

Lee, E.Y., Yoon, K.-H., 2018. Epidemic obesity in children and adolescents: risk factors and prevention. Front. Med. 12, 658–666. https://doi.org/10.1007/s11684-018-0640-1

Lezak, M.D., 1995. Neuropsychological assessment, 3rd ed. ed. Oxford University Press, New York.

Liang, J., Matheson, B.E., Kaye, W.H., Boutelle, K.N., 2014. Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. Int. J. Obes. 2005 38, 494–506. https://doi.org/10.1038/ijo.2013.142

Likhitweerawong, N., Louthrenoo, O., Boonchooduang, N., Tangwijitsakul, H., Srisurapanont, M., 2022. Bidirectional prediction between weight status and executive function in children and adolescents: A systematic review and meta-analysis of longitudinal studies. Obes. Rev. Off. J. Int. Assoc. Study Obes. 23, e13458. https://doi.org/10.1111/obr.13458

Lin, T., Liu, G.A., Perez, E., Rainer, R.D., Febo, M., Cruz-Almeida, Y., Ebner, N.C., 2018. Systemic Inflammation Mediates Age-Related Cognitive Deficits. Front. Aging Neurosci. 10, 236. https://doi.org/10.3389/fnagi.2018.00236

Mamrot, P., Hanć, T., 2019. The association of the executive functions with overweight and obesity indicators in children and adolescents: A literature review. Neurosci. Biobehav. Rev. 107, 59–68. https://doi.org/10.1016/j.neubiorev.2019.08.021

Marmeleira, J., Veiga, G., Cansado, H., Raimundo, A., 2017. Relationship between motor proficiency and body composition in 6- to 10-year-old children. J. Paediatr. Child Health 53, 348–353. https://doi.org/10.1111/JPC.13446

Marqués-Iturria, I., Pueyo, R., Garolera, M., Segura, B., Junqué, C., García-García, I., José Sender-Palacios, M., Vernet-Vernet, M., Narberhaus, A., Ariza, M., Jurado, M.Á., 2013. Frontal cortical thinning and subcortical volume reductions in early adulthood obesity. Psychiatry Res. 214, 109–15. https://doi.org/10.1016/j.pscychresns.2013.06.004

Marsland, A.L., Petersen, K.L., Sathanoori, R., Muldoon, M.F., Neumann, S.A., Ryan, C., Flory, J.D., Manuck, S.B., 2006. Interleukin-6 covaries inversely with cognitive performance among

middle-aged community volunteers. Psychosom. Med. 68, 895–903. https://doi.org/10.1097/01.psy.0000238451.22174.92

Martin, A., Saunders, D.H., Shenkin, S.D., Sproule, J., 2014. Lifestyle intervention for improving school achievement in overweight or obese children and adolescents. Cochrane Database Syst. Rev. CD009728. https://doi.org/10.1002/14651858.CD009728.pub2

Matarma, T., Lagström, H., Hurme, S., Tammelin, T.H., Kulmala, J., Barnett, L.M., Koski, P., 2018. Motor skills in association with physical activity, sedentary time, body fat, and day care attendance in 5-6-year-old children-The STEPS Study. Scand. J. Med. Sci. Sports 28, 2668–2676. https://doi.org/10.1111/SMS.13264

McElvaney, O.J., Curley, G.F., Rose-John, S., McElvaney, N.G., 2021. Interleukin-6: obstacles to targeting a complex cytokine in critical illness. Lancet Respir. Med. 9, 643–654. https://doi.org/10.1016/S2213-2600(21)00103-X

Miller, A.A., Spencer, S.J., 2014. Obesity and neuroinflammation: a pathway to cognitive impairment. Brain. Behav. Immun. 42, 10–21. https://doi.org/10.1016/J.BBI.2014.04.001

Nederkoorn, C., Braet, C., Van Eijs, Y., Tanghe, A., Jansen, A., 2006. Why obese children cannot resist food: the role of impulsivity. Eat. Behav. 7, 315–322. https://doi.org/10.1016/J.EATBEH.2005.11.005

O'Brien, P.D., Hinder, L.M., Callaghan, B.C., Feldman, E.L., 2017. Neurological consequences of obesity. Lancet Neurol. 16, 465–477. https://doi.org/10.1016/S1474-4422(17)30084-4

Pearson, T.A., Mensah, G.A., Alexander, R.W., Anderson, J.L., Cannon, R.O., Criqui, M., Fadl, Y.Y., Fortmann, S.P., Hong, Y., Myers, G.L., Rifai, N., Smith, S.C., Taubert, K., Tracy, R.P., Vinicor, F., Centers for Disease Control and Prevention, American Heart Association, 2003. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 107, 499–511. https://doi.org/10.1161/01.cir.0000052939.59093.45

Prats-Soteras, X., Jurado, M.A., Ottino-González, J., García-García, I., Segura, B., Caldú, X., Sánchez-Garre, C., Miró, N., Tor, C., Sender-Palacios, M., Garolera, M., 2020. Inflammatory agents partially explain associations between cortical thickness, surface area, and body mass in adolescents and young adulthood. Int. J. Obes. 2005 44, 1487–1496. https://doi.org/10.1038/S41366-020-0582-Y

Reilly, S.M., Saltiel, A.R., 2017. Adapting to obesity with adipose tissue inflammation. Nat. Rev. Endocrinol. 13, 633–643. https://doi.org/10.1038/nrendo.2017.90

Rozin, P., Dow, S., Moscovitch, M., Rajaram, S., 2016. What Causes Humans to Begin and End a Meal? A Role for Memory for What Has Been Eaten, as Evidenced by a Study of Multiple Meal Eating in Amnesic Patients: Httpsdoiorg1011111467-928000073 9, 392–396. https://doi.org/10.1111/1467-9280.00073

Scheller, J., Chalaris, A., Schmidt-Arras, D., Rose-John, S., 2011. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim. Biophys. Acta 1813, 878–888. https://doi.org/10.1016/j.bbamcr.2011.01.034

Seitz, B.M., Tomiyama, A.J., Blaisdell, A.P., 2021. Eating behavior as a new frontier in memory

research. Neurosci. Biobehav. Rev. 127, 795–807. https://doi.org/10.1016/J.NEUBIOREV.2021.05.024

Shields, G.S., Moons, W.G., Slavich, G.M., 2017. Inflammation, Self-Regulation, and Health: An Immunologic Model of Self-Regulatory Failure. Perspect. Psychol. Sci. J. Assoc. Psychol. Sci. 12, 588–612. https://doi.org/10.1177/1745691616689091

Shulman, E.P., Smith, A.R., Silva, K., Icenogle, G., Duell, N., Chein, J., Steinberg, L., 2016. The dual systems model: Review, reappraisal, and reaffirmation. Dev. Cogn. Neurosci. 17, 103–117. https://doi.org/10.1016/j.dcn.2015.12.010

Soreni, N., Crosbie, J., Ickowicz, A., Schachar, R., 2009. Stop signal and Conners' continuous performance tasks: test--retest reliability of two inhibition measures in ADHD children. J. Atten. Disord. 13, 137–143. https://doi.org/10.1177/1087054708326110

Spyridaki, E.C., Avgoustinaki, P.D., Margioris, A.N., 2016. Obesity, inflammation and cognition. Curr. Opin. Behav. Sci., Diet, behavior and brain function 9, 169–175. https://doi.org/10.1016/j.cobeha.2016.05.004

Stanek, K.M., Grieve, S.M., Brickman, A.M., Korgaonkar, M.S., Paul, R.H., Cohen, R.A., Gunstad, J.J., 2011. Obesity Is Associated With Reduced White Matter Integrity in Otherwise Healthy Adults*. Obesity 19, 500–504. https://doi.org/10.1038/OBY.2010.312

Stolarczyk, E., 2017. Adipose tissue inflammation in obesity: a metabolic or immune response? Curr. Opin. Pharmacol. 37, 35–40. https://doi.org/10.1016/j.coph.2017.08.006

Tanaka, H., Gourley, D.D., Dekhtyar, M., Haley, A.P., 2020. Cognition, Brain Structure, and Brain Function in Individuals with Obesity and Related Disorders. Curr. Obes. Rep. 9, 544–549. https://doi.org/10.1007/S13679-020-00412-Y

Weihrauch-Blüher, S., Wiegand, S., 2018. Risk Factors and Implications of Childhood Obesity. Curr. Obes. Rep. 7, 254–259. https://doi.org/10.1007/S13679-018-0320-0

Wueest, S., Konrad, D., 2020. The controversial role of IL-6 in adipose tissue on obesity-induced dysregulation of glucose metabolism. Am. J. Physiol.-Endocrinol. Metab. 319, E607–E613. https://doi.org/10.1152/ajpendo.00306.2020

Yang, Y., Shields, G.S., Wu, Q., Liu, Y., Chen, H., Guo, C., 2019. Cognitive training on eating behaviour and weight loss: A meta-analysis and systematic review. Obes. Rev. 20, 1628–1641. https://doi.org/10.1111/OBR.12916

TABLES

Table 1

Demographic, anthropometric, and inflammatory characteristics.

BMIz = body mass index z-score; HW = healthy weight; OW = overweight; O = obese; F = female; M = male; IQ estimation = Intelligence Quotient estimation; hs-CRP = high-sensitivity C-reactive protein; mg/dL = milligrams per decilitre; TNFα = tumour necrosis factor alpha; pg/mL = picograms per millilitre; IL-6 = Interleukin-6; g/L = grams per litre.

[a] Serum levels of fibrinogen considering all participants and both assay types (i.e., STA-Rack and ACLTOP 700).

	Mean	SD	Range
Age (years)	15.89	2.68	12–21
BMIz	1.04	1.06	-1.50–2.69
Gender (F/M)	56/49		
Weight status (HW/OW/O)	46/18/41		
Years of education	9.69	2.62	6–19
IQ estimation (scalar score)	10.95	2.19	7–17
hs-CRP (mg/dL)	2.07	2.55	0.11–9.94
TNFα (pg/mL)	0.87	0.34	0.26–1.95
IL-6 (pg/mL)	1.84	1.71	0.18–9.26
Fibrinogen[a] (g/L)	3.58	0.70	2.23–6.21
Fibrinogen STA-Rack (g/L)	3.29	0.54	2.23–4.48
Fibrinogen ACLTOP 700 (g/L)	3.81	0.73	2.56–6.21

Table 2

Pearson correlations between variables included in the study.

	Sex	Age	BMIz	hs-CRP	IL-6	TNFα	Fibrinogen	F	IC	WM	DM	VM	FMS
Sex	1	.067	-.154	.033	-0.42	-.117	.166	-.039	.167	-.204*	-.161	.038	.341**
Age	.067	1	-.108	.183	-.178	-.100	.100	.117	.368**	.022	.000	.018	.247*
BMIz	-.154	-.108	1	.422**	.460**	.338**	.398**	-.096	-.239*	-.109	-.133	-.255**	-.366**
hs-CRP	.033	.183	.422**	1	.347**	.215*	.547**	.051	.080	.014	-.233*	-260**	-.109
IL-6	-0.42	-.178	.460**	.347**	1	.225*	.202*	-.045	-.055	-.042	-.113	.008	-.178
TNFα	-.117	-.100	.338**	.215*	.225*	1	.225*	.054	-.249*	.001	-.019	-.001	.008
Fibrinogen	.166	.100	.398**	.547**	.202*	.225*	1	-.002	.010	-.059	-.184	-.274**	-.029
F	-.039	.117	-.096	.051	-.045	.054	-.002	1	.061	.323**	.019	-.054	.178
IC	.167	.368**	-.239*	.080	-.055	-.249*	.010	.061	1	.188	-.002	.170	.218*
WM	-.204*	.022	-.109	.014	-.042	.001	-.059	.323**	.188	1	-.009	.187	.079
DM	-.161	.000	-.133	-.233*	-.113	-.019	-.184	.019	-.002	-.009	1	.001	.033
VM	.038	.018	-.255**	-.260**	.008	-.001	-.274**	-.054	.170	.187	.001	1	.104
FMS	.341**	.247*	-.366**	-.109	-.178	.008	-.029	.178	.218*	.079	.104	.104	1

* < 0.05, ** < 0.01. F: flexibility; IC: inhibitory control; WM: working memory; DM: decision-making; VM: verbal memory; FMS: fine motor speed.

Table 3. F and p values (in parentheses) for the multiple general linear model

	F	IC	WM	DM	VM	FMS
Age	1.135 (.290)	12.069 (<.001)	.001 (.976)	.418 (.520)	.460 (.499)	5.469 (.022)
Sex	.105 (.746)	1.180 (.182)	5.474 (.022)	1.340 (.250)	.038 (.846)	9.868 (.002)
BMI	1.032 (.312)	5.688 (.019)	2.112 (.150)	.127 (.723)	5.404 (.022)	9.038 (.003)
hs-CRP	.302 (.584)	.593 (.443)	.849 (.359)	2.491 (.118)	.285 (.595)	.666 (.417)
IL-6	.001 (.971)	1.545 (.217)	.001 (.982)	.027 (.871)	2.629 (.109)	.038 (.845)
TNFα	.529 (.469)	5.055 (.027)	.023 (.881)	.535 (.466)	2.360 (.128)	2.908 (.092)
Fibrinogen	.002 (.968)	.107 (.745)	.021 (.886)	.033 (.857	4.732 (.032)	.202 (.654)

F: flexibility; IC: inhibitory control; WM: working memory; DM: decision-making; VM: verbal memory; FMS: fine motor speed.

Declaration of Competing Interest

none.

Highlights

- Body mass index is inversely related to inhibitory control, verbal memory, and fine motor speed.
- Circulating levels of TNF-α are inversely related to inhibitory control in adolescents.
- Circulating levels of fibrinogen are inversely related to verbal memory adolescents.