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The association between obesity and lower working memory is mediated by inflammation: Findings from a nationally representative dataset of U.S. adults

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ABSTRACT

Obesity is often accompanied by lower working memory (e.g., a lower ability to keep goal-relevant information in mind) relative to healthy weight individuals. Understanding this relative working memory impairment has important clinical implications, as working memory is thought to facilitate adherence to weight management programs. Theoretical models of obesity, self-regulation, and inflammation suggest that inflammation plays a role in obesity-related working memory impairments, but to date no study has tested this prediction. Therefore, the current study examined whether inflammation statistically mediated the relationship between obesity and working memory in a nationally representative dataset of U.S. adults from Wave IV of The National Longitudinal Study of Adolescent to Adult Health (N = 11,546, age range 25–34). Inflammation was quantified via C-reactive protein (CRP) level, and working memory was assessed using a modified digit span backward task. As expected, cross-sectional analyses showed that a body mass index (BMI) indicative of obesity—as well as greater BMI when BMI was analyzed continuously—and greater CRP were each related to lower working memory. Critically, we found that CRP levels statistically mediated the relationships between obesity/greater BMI and working memory, with CRP accounting for 44.1% of the variance explained in working memory by BMI. Moreover, these findings held both with and without controlling for relevant covariates, including demographic characteristics (e.g., age), socioeconomic status, and behavioral factors (e.g., smoking). Our results therefore point to inflammation as playing an important role in the relationship between obesity and working memory, and suggest that interventions aimed at reducing inflammation may help lessen the cognitive burden of obesity.

1. Introduction

A common finding in obesity research is that obesity is associated with lower cognitive performance, and it is perhaps most consistently associated with relative deficits in executive functions (e.g., the higher cognitive processes that enable planning, forethought, and goal-directed action) (Liang et al., 2014; Rotge et al., 2017; Vainik et al., 2013; Vainik et al., 2018; Yang et al., inpress a,b). For example, in our recent meta-analysis which included 4904 overweight/obese participants across 72 studies, we found that obesity was associated with broad deficits in executive functions relative to healthy weight individuals, including poorer cognitive flexibility, inhibition, and working memory (Yang et al., 2018).

Working memory refers to the ability to keep information in mind and mentally work with it (Diamond, 2013; see also Miyake and Friedman, 2012). Although working memory is intimately related to other higher cognitive functions, it can be distinguished from them on a latent level (Miyake and Friedman, 2012). Working memory is important for self-regulation in temporally extended situations—such as an extended weight loss management program—in that it permits keeping goals recruited from long-term memory in mind, which is important in situations full of temptations and distractions (Hofmann et al., 2011; Hofmann et al., 2012; Dohle et al., 2018). Working memory capacity can also facilitate other components of self-regulation, such as emotion regulation (Ilkowska and Engle, 2010; Schmeichel et al., 2008). In addition, by keeping goals in mind, working memory supports another executive function component—namely, inhibitory control (i.e., the ability to inhibit thoughts or prepotent responses in

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order to engage in goal-directed rather than habitual actions) (Diamond, 2013)—, which is also important for self-regulation (Dohle et al., 2018; Yang et al., inpress a,b). Relative impairments in working memory have a number of implications for obesity, as working memory has been implicated in the self-regulation of eating behavior (Hofmann et al., 2011; Hofmann et al., 2012; Dohle et al., 2018). For example, relatively lower working memory performance (e.g., measured by visuospatial span task) is associated with greater loss of control eating in overweight individuals (e.g., Goldschmidt et al., 2018), less frequent fruit and vegetable consumption (e.g., Allom and Mullan, 2014), and more energy-dense food intake (e.g., Nyaradi et al., 2014; Whitelock et al., 2018). Perhaps most notably, improving working memory capacity via training reduces emotional eating (Houben et al., 2016) and food intake (Dassen et al., 2018a,b), though it should be noted that although these studies found that working memory training decreased participants' weight relative to baseline, participants in a training condition did not show a greater decrease in weight relative to baseline than a control group (Dassen et al., 2018a,b; Houben et al., 2016). In addition, it should be noted that there is some inconsistency in the literature (e.g., Limbers and Young, 2015). In short, although there are theoretical reasons to expect that poor working memory could contribute to obesity, the empirical literature on this to date is relatively sparse and somewhat inconsistent, highlighting the need for more research in this area.

There is another possible reason to expect a potential link between working memory and obesity in addition to the theoretical one given above. In particular, obesity may also indirectly impair executive functions including working memory through its effects on inflammation and inflammatory activity (Castanon et al., 2015; Lowe et al., 2019; Lasselin et al., 2016; Miller and Spencer, 2014; Ottino-González et al., 2019; Spyridaki et al., 2016). It is often thought that obesity may confer a state of sustained, low-grade inflammation, originating from adipose tissue and changes in gut microbiota composition (Gregor and Hotamisligil, 2011; Boulangé et al., 2016). The inflammatory milieu of obesity is characterized heightened levels of proinflammatory cytokines (e.g., interleukin-6, IL-6; Park et al., 2010) and acute phase proteins (e.g., C-reactive protein, CRP; Choi et al., 2013) relative to healthy weight individuals. More important to the current manuscript, heightened inflammation can impair working memory (Beydoun et al., 2019; Marsland et al., 2015; Trevizol et al., 2019; Windham et al., 2014). As might be expected, then, in healthy younger and middle-aged adults, inflammatory biomarkers have been inversely associated with working memory (e.g., Marsland et al., 2015; Ottino-González et al., 2019). These findings have been succinctly summarized in a recent theoretical model, the immunologic model of self-regulatory failure, which proposes that immune system activity—especially inflammatory activity—impairs executive functions including working memory and other forms of self-regulation through its effects on the neural underpinnings of those processes (e.g., the prefrontal cortex) (Shields et al., 2017). In sum, obesity can upregulate basal inflammatory activity, and heightened basal inflammatory activity can in turn impair cognition.

Some studies have indeed found correlational support for the idea that obesity impairs cognitive performance through its effects on inflammation. For example, two studies have found that CRP—considered an important index of systemic inflammatory activity—was negatively related to executive function (i.e., cognitive flexibility) in overweight or obese individuals (Lasselin et al., 2016; Ottino-González et al., 2019). Even more, two longitudinal studies have found that inflammation mediated associations between components of executive function (e.g., attentional switching, verbal fluency) and obesity (Bourassa and Sbarra, 2017; Mac Giollabhui et al., 2019).

Despite the importance of the above findings, a crucial missing piece in our understanding of obesity, cognition, and putative biological mechanisms is that to date, no study has examined the role of inflammation in working memory within obesity (though see Trevizol et al., 2019, for an examination of these associations in non-obese individuals). The present study therefore examined whether inflammation statistically mediates the association between obesity and lower working memory. We tested this possibility in a nationally representative sample of U.S. adults from Wave IV of The National Longitudinal Study of Adolescent to Adult Health (Add Health). Drawing on literature showing that obesity is associated with lower working memory and that inflammation can impair working memory, we hypothesized that inflammation would statistically mediate the association between obesity and working memory. Moreover, we expected this mediational effect to hold with and without controlling for relevant covariates.

2. Methods

2.1. Participants and procedure

Restricted cross-sectional data from Wave IV of Add Health were used for this study (Harris et al., 2009). Of the 15,701 participants interviewed in Wave IV, individuals who were not pregnant, had a CRP level below 10 mg/L (e.g., individuals without acute infections, see section 2.2.2, and see Supplemental Material for analyses including all CRP levels), and had a body mass index (BMI) of normal weight (18.5–24.9), overweight (25–29.9), or obese weight (above 29.9) were selected for analysis. The final sample therefore consisted of the 11,546 participants (5699 females, M_{age} = 29.1, SD_{age} = 1.76, age range = 25–34) meeting these criteria with complete data for BMI, CRP, and working memory, though only 10,715 participants had complete data for all covariates considered (Table 1).

2.2. Measures

2.2.1. Body mass index

BMI was calculated using the standard formula weight (kilograms) divided by height (meters) squared (BMI = kg/m^2). Weight and height were measured by the interviewer using a digital scale and measuring tape, respectively. Obesity was defined as a BMI ≥ 30 kg/m^2. The decision to use obese vs. non-obese, rather than overweight/obese vs. normal-weight as the independent variable was based on current evidence indicating very small working memory impairment among overweight individuals, with level of working memory in the overweight group more comparable to normal weight than obese individuals (Yang et al., 2018).

2.2.2. Inflammation

CRP was measured as a marker of systemic inflammation. In-depth documentation of the Add Health hs-CRP assay and quality control are available online (Whitsel et al., 2013). Briefly, CRP was assessed via dried blood spots (DBS), which were collected immediately following the completion of study questionnaires, and these DBS were stored in a −70 °C freezer until assayed using a previously published sandwich ELISA method (McDade et al., 2004) at the University of Washington, Department of Laboratory Medicine. Cross-validation using paired plasma samples and dried blood spots in a sample of 87 participants indicated strong correlation and linear association between CRP concentrations from these two methods, r = 0.98 (Whitsel et al., 2013). Sensitivity of the CRP assay was 0.035 mg/L, intra-assay variation was 8.1% and inter-assay variation was 11%. Natural log transformations were applied to CRP levels to correct skewness (using the raw CRP values did not alter the results; see Supplemental Material). Finally, as mentioned above, we excluded participants with CRP levels > 10 mg/L (n = 1817), as these a CRP level > 10 mg/L indicates acute infection or other acute health condition, not basal inflammation (O'Connor et al., 2009) (including values of CRP > 10 mg/L did not alter the results; see Supplemental Material).

Table 1
Sample Descriptive Characteristics.

	Whole sample (N = 11546)	Non-obese (n = 7611)	Obese (n = 3935)	p
Age (years) (M ± SD)[a]	29.1 ± 1.76	29.05 ± 1.76	29.20 ± 1.75	< 0.01
Sex (%)[b]				< 0.01
Men	50.64%	49.38%	53.09%	
Women	49.36%	50.62%	46.91%	
Race (%)[b]				< 0.01
White	71.11%	72.41%	68.97%	
African American	21.49%	19.76%	24.95%	
American Indian	0.94%	0.91%	1.02%	
Asian	6.27%	6.92%	5.06%	
SES (M ± SD)[a]	0.77 ± 0.92	0.72 ± 0.90	0.88 ± 0.95	< 0.01
Smoke status (%)[b]				> 0.05
Smoker	37.33%	38.06%	36.77%	
Non-smoker	61.90%	61.94%	63.23%	
Drinking status (%)[b]				< 0.01
Drinker	48.74%	52.26%	42.15%	
Non-drinker	51.51%	47.74%	57.85%	
Physical activity (M ± SD)[a]	1.70 ± 2.71	1.85 ± 2.78	1.41 ± 2.55	< 0.01
Depression symptoms (M ± SD)[a]	6.04 ± 4.67	5.88 ± 4.57	6.36 ± 4.86	< 0.01
Subclinical symptoms (M ± SD)[a]	0.41 ± 0.70	0.41 ± 0.69	0.43 ± 0.72	> 0.05
Illness (M ± SD)[a]	0.43 ± 0.66	0.42 ± 0.65	0.45 ± 0.68	< 0.01
Medication (M ± SD)[a]	0.61 ± 0.96	0.60 ± 0.95	0.63 ± 0.98	> 0.05
Body mass index (M ± SD)[a]	28.52 ± 6.65	24.73 ± 2.98	35.85 ± 5.56	< 0.01
Working memory (M ± SD)[a]	4.19 ± 1.51	4.26 ± 1.51	4.06 ± 1.50	< 0.01
C-reactive protein (raw values) (M ± SD)[a]	2.51 ± 2.38	1.90 ± 1.99	3.71 ± 2.61	< 0.01

Note: numbers may not sum to total sample number due to missing data. Valid percentages are shown for ease of interpretation. CRP means/SDs exclude participants with values higher than 10 pg/mL, per our analytic strategy. M = mean; SD = standard deviation. [a]Independent samples t test; [b]χ^2 test.

2.2.3. Working memory

Working memory was measured using a modified digit span backward task. In this task, the interviewer read strings of numbers and asked the participant to repeat them in reverse (e.g., if the interviewer said "5-1-7-4-2", the correct response would be "2-4-7-1-5"). The task began with a two-number string. Respondents had two possible trials to recall the number series at each level, up to a total of seven possible levels. If the respondent answered correctly on the first trial of a given level, a second trial at that level was not administered at that level and the task moved on to the next level. When the respondents could not repeat a number series in reverse in either trial at a given level, the task ended. The highest level a participant successfully passed was used as the dependent variable (i.e., that participant's backward digit span), with higher scores indicating better working memory. Raw scores can therefore range from 0 to 7.

2.2.4. Covariates

Demographic variables, socioeconomic status (SES), and behavioral factors were considered as covariates because these variables have been previously associated with BMI, CRP, and working memory (Claassen et al., 2019; Milaniak and Jaffee, 2019).

Demographic variables consisted of age, sex and race. Approximate current age was calculated by subtracting the respondent's year of birth from the year which Wave IV data was collected; sex was self-reported; and race was identified by the interviewer.

SES was indexed using a conjunction of use of public assistance, education, and income at Wave IV (Luo and Waite, 2005; Yang et al., 2017). Use of public assistance (i.e., welfare) was categorized as (0) no use of public assistance, or (1) use of public assistance; education was categorized as (0) more than high school, or (1) high school or less; and income was categorized as (0) above the bottom quartile of the sample's income distribution, or (1) in the bottom quartile of the sample's income distribution. These indices were summed to create a composite measure of SES. SES could thus range from 0 to 3, with 3 representing the lowest level of SES.

Behavioral factors included as covariates were smoking, alcohol use, physical exercise, depressive symptoms, illnesses and medications. For the coding of smoking, participants were asked, "During the past 30 days, on how many days did you smoke cigarettes?" Those who smoked on one or more days were considered current smokers (Stanton et al., 2016). For the coding of alcohol use: participants were asked, "During the past 12 months, on how many days did you drink alcohol?", and those who said they drank once a month or more were considered drinkers (Stanton et al., 2016). Physical activity was calculated as the sum of two items ("In the past 7 days, how many times did you participate in individual sports such as running, wrestling, swimming, cross-country skiing, cycle racing, or martial arts?" and "In the past 7 days, how many times did you participate in gymnastics, weight lifting, or strength training?") that were coded as 0 = not at all, 1 = 1 time, 2 = 2 times, 3 = 3 times, 4 = 4 times, 5 = 5 times, 6 = 6 times, and 7 = 7 or more times. The sum of the two items could thus range from 0 to 14. Depressive symptoms were measured using a shortened version of the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). Ten items, with responses ranging from zero ("never or rarely") to three ("most of the time or all of the time"), measured participants' symptoms of depression in the past seven days. The summed score could thus ranges from 0 to 30, with higher scores indicating higher levels of depressive symptoms. The scale demonstrated good internal consistency in this sample (α = 0.84). Finally, illnesses and medications were assessed with checklists of recent health conditions. Drawing on prior field-based, epidemiological research (Shanahan et al., 2014) and in accordance with the Add Health documentation (Whitsel et al., 2013), we included the following covariates: (a) Subclinical symptoms: a count of the number of symptoms the participants reported, including cold or flu-like symptoms, fever, night sweats, nausea or vomiting or diarrhea, blood in stool or in urine, frequent urination, and skin rash or abscess in the past 2 weeks; (b) Infectious/inflammatory diseases: a count of both lifetime diagnoses of chronic conditions including asthma or chronic bronchitis or emphysema, hepatitis C, and gum disease, active infection, injury, acute illness, surgery, and active seasonal allergies in the past 4 weeks; (c) Medications that may affect CRP: a count of the number of relevant medications used, including NSAID/Salicylate, Cox-2 inhibitors, inhaled corticosteroids, corticotropin/glucocorticoids, anti-rheumatic/anti-psoriatic, immunosuppressive, and anti-inflammatory medications. Counts ≥3 for the illnesses and medications variables were collapsed to

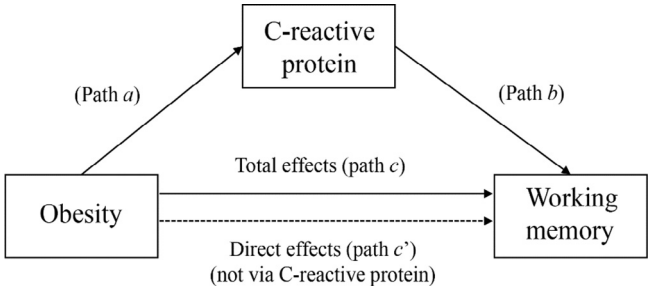

Fig. 1. Diagram illustrating the mediation model examining associations between obesity and working memory via C-reactive protein.

a value of "'3". Count of illnesses and medications variables could thus range from 0 to 3.

2.3. Analytic strategy

Analyses were performed using R version 3.6.0. First, independent samples t-tests and Pearson correlation analyses were conducted to assess the relationships between obesity/BMI, working memory, and CRP. In addition, multiple regressions were conducted to assess the relationships between obesity/BMI, working memory, and CRP while controlling for covariates. Finally, mediation of the association between obesity and working memory via CRP (Fig. 1) was tested using the `mediation` R package, version 4.4.7. The mediation model was also run using BMI as a continuous measure to ensure that dichotomizing the continuous variable of BMI did not alter the results. In the present mediation analysis, the total effect (path *c*) of obesity on working memory consists of a direct effect (path *c'*) of obesity on working memory and an indirect effect (path $a \times b$) of obesity on working memory via the mediator, which is CRP. Path *a* represents the effect of obesity on CRP, and path *b* is the effect of CRP on working memory. Quasi-Bayesian approximation with 10,000 Monte Carlo draws was used to estimate the total effect, direct effect, and mediated effect and their credible intervals. All mediation analyses adjusted for covariates (removing covariates did not alter the results; see Supplemental Material).

3. Results

3.1. Correlations between obesity, working memory and CRP

For the primary variables of interest, independent samples t-tests showed that obesity was associated with greater CRP, t (11,544) = 43.55, mean difference = 1.81, 95% CI [1.73, 1.90], $p < .001$, $d = 0.86$, and worse working memory performance, t (11,544) = 6.71, mean difference = 0.20, 95% CI [0.14, 0.26], $p < .001$, $d = -0.13$. Using BMI instead of obesity as a predictor produced functionally equivalent results; Pearson correlation analyses showed that greater BMI was associated with greater CRP, r (11,544) = 0.43, 95% CI [0.42, 45], $p < .001$, and worse working memory performance, r(11,544) = −0.06, 95% CI [−0.08, −0.04], $p < .001$. Further, in support of our primary hypotheses, greater CRP was also associated with worse working memory performance, r (11,544) = −0.06, 95% CI [−0.08, −0.04], $p < .001$.

Controlling for covariates (listed in section 2.2.4) did not alter the above pattern of results. In particular, multiple regression analyses showed that obesity remained a significant predictor of CRP, β = 0.37, 95% CI [0.35, 0.39], $p < .001$, and worse working memory, β = −0.04, 95% CI [−0.06, −0.02], $p < .001$, as did BMI (β_{CRP} = .43, 95% CI_{CRP} [0.41, 0.45], $p_{CRP} < .001$; $\beta_{working\ memory}$ = −0.03, 95% $CI_{working\ memory}$ [−0.05, −0.01], $p = .001$). Similarly, CRP remained a significant predictor of worse working memory performance, β = −0.04, 95% CI [−0.06, −0.02], $p < .001$.

Table 2
Models Testing Mediation of the Association Between Obesity/BMI and Working Memory by CRP.

	β	*p*	95% CI
Obesity			
Total effect (path *c*)	−0.0364	< 0.001	[−0.0552, −0.0180]
Direct effect (path *c'*)	−0.0254	0.010	[−0.0455, −0.0059]
Indirect effect	−0.0110	0.003	[−0.0182, −0.0038]
BMI			
Total effect (path *c*)	−0.0314	< 0.001	[−0.0502, −0.0125]
Direct effect (path *c'*)	−0.0176	0.103	[−0.0383, 0.0037]
Indirect effect	−0.0138	0.002	[−0.0227, −0.0049]

Analyses are adjusted for covariates. SE = standard error; CI = confidence interval; BMI = body mass index; CRP = C-reactive protein.

In short, our primary variables of interest related to each other in the hypothesized manner.

3.2. Examining CRP as mediator of the association between obesity and lower working memory

Table 2 summarizes the results of the mediation analyses (path *c*, path *c'*, and indirect effects in Fig. 1). In these analyses, obesity was related to lower working memory (path *c*: β = −0.04, 95% CI_c [−0.06, −0.02], $p < .001$; path *c'*: β = −0.03, 95% $CI_{c'}$ [−0.05, −0.01], $p = .010$). Critically, and as hypothesized, there was a significant indirect effect of obesity on working memory via CRP, β = −0.01, 95% CI_{ab} [−0.02, −0.00], $p = .003$, such that obese individuals showed higher CRP levels than non-obese individuals, β = 0.37, 95% CI[0.35, 0.38], $p < .001$, and more CRP was related to lower working memory, β = −0.03, CI[−0.05, −0.01], $p = .003$. Notably, this indirect effect through CRP accounted for 30.2% of the variance explained in working memory by obesity (proportion mediated = 0.30, 95% CI [0.10, 0.70], $p = .003$).

Similar findings were observed when BMI was entered into the model in place of obesity, with results showing that greater BMI was directly related to poor working memory only when the indirect path through CRP was not accounted for (path c: β = −0.03, 95% CI_c[−0.05, −0.01], $p < .001$; path c': β = −0.02, 95% $CI_{c'}$ [−0.04, 0.00], $p = .103$). Critically, as hypothesized, there was a significant indirect effect via CRP, β = −0.01, 95% CI_{ab} [−0.02, −0.01], $p = .002$, such that high BMI was associated with more CRP, β = 0.43, 95% CI [0.41, 0.45], $p < .001$, and more CRP was related to lower working memory, β = −0.03, 95% CI [−0.05, −0.01], $p = .003$. Notably, this indirect effect through CRP accounted for 44.1% of the variance explained in working memory by BMI (proportion mediated = 0.44, 95% CI [0.14, > 0.99], $p = .002$).

In short, obesity was indirectly associated with lower working memory performance via relatively higher levels of CRP. This mediating effect of CRP was present when weight was analyzed categorically (i.e., obese vs. non-obese) or continuously (i.e., BMI).

4. Discussion

Although some prior work has found links between obesity, inflammation, and lower working memory (Marsland et al., 2006; Yang et al., 2018), no study to date had examined the role that inflammation may play in obesity-related working memory deficits. We examined this potential role, and found that inflammation statistically mediated the association between obesity and working memory—accounting for between 30% and 44% of the variance explained by excessive weight in working memory—in a nationally representative young sample of U.S. adults (mean age = 29). Our results therefore could be taken to indicate that obesity-related inflammation may be one biological pathway underpinning links between excessive weight and lower

working memory. It should be noted, however, that the effect size of the association between obesity and lower working memory observed in our study was small.

Our results are consistent with previous studies that have found inflammation plays a role in weight-related deficits in other executive function components (Bourassa and Sbarra 2017; Mac Giollabhui et al., 2019). For example, in the English Longitudinal Study of Ageing (ELSA) study, Bourassa and Sbarra (2017) found that greater BMI was indirectly associated with declines in verbal fluency over 6 years via relatively higher levels of CRP. In addition, in a diverse community sample of urban adolescents, Mac Giollabhui et al. (2019) found that a higher BMI predicted worse attentional switching via higher levels of circulating IL-6. Thus, both these results and ours provide preliminary evidence in support of the idea that obesity-related inflammation may play a role in obesity-related executive function impairments (for reviews, see O'Brien et al., 2017; Miller and Spencer, 2014; Nguyen et al., 2014; Solas et al., 2017; Spyridaki et al., 2016).

Although the current study cannot elucidate the mechanisms underlying the observed association between obesity-related inflammation and obesity-related working memory impairments, we can speculate. First, inflammatory activity can activate the hypothalamic-pituitaryadrenal axis (Silverman and Sternberg, 2012), and leads to increased circulating cortisol, an important component of the stress response, which might impair working memory (Shields et al., 2015). Second, inflammatory activity modulates the kynurenine pathway both in the periphery and in the brain (Schwarcz et al., 2012), which has been linked to cognitive deficits (Stone and Darlington, 2013). Third, proinflammatory cytokines can exert direct effects on their receptors within the prefrontal cortex (Audet et al., 2011) and hippocampus (Sparkman et al., 2006), and impair working memory at least in part via those mechanisms (Sparkman et al., 2006). Finally, impairing working memory via a more circuitous route, elevated levels a variety of pro-inflammatory cytokines (e.g., IL-6) in obesity individuals can induce neuroinflammation (e.g., chronic activation of microglia, brain production of inflammatory cytokines) through various pathways (e.g., Guillemot-Legris and Muccioli, 2017). Further, neuroinflammation can disrupt neuronal processes important to cognition (e.g., synaptic plasticity, neurogenesis) (Hao et al., 2016) and affect brain structures such as the hippocampus (Marsland et al., 2008), frontal cortex (Gu et al., 2017; Shields et al., 2017; Shobin et al., 2017), presumably impairing working memory. However, it should be noted that these speculative mechanisms are derived primarily from animal works, and more research with human participants is needed to determine the mechanisms underpinning the association between obesity-related inflammation and obesity-related working memory impairments.

Our results may have important clinical implications, as they may inform interventions targeted at weight management, as working memory has been thought to facilitate adherence to weight loss programs in obesity via keeping weight loss goals—recruited from long-term memory—in mind when important (Dassen et al., 2018a,b; Dohle et al., 2018; see also Hofmann et al. 2012). Because we found that inflammation statistically accounted for a large portion of the variance explained in working memory by obesity (though note that the total variance explained in working memory by obesity was small), our results could be taken to suggest that anti-inflammatory interventions may help prevent or manage working memory deficits in obesity. By improving individuals' capacities to maintain active mental representations of (self-regulatory) goals and shield those goals from distraction, these anti-inflammatory interventions might help obese individuals to make healthy food choices, adhere to a prescribed diet, and manage their weight. Further intervention studies are required to address this possibility.

Our study has several strengths. First, using a theory-driven mediation model, it extends prior research by providing the first evidence that inflammation is one potential biological mechanism underlying the association between obesity and poor working memory. Furthermore, this statistical mediation was observed in a large, nationally representative dataset of U.S. young adults. Importantly, the significance of the statistical modeling held when weight was analyzed categorically (i.e., with obesity as a factor) or continuously (i.e., with BMI as a continuous predictor) as well as when several key potential confounding factors were adjusted.

Nevertheless, some limitations of current study should be addressed. First, the cross-sectional design of our study prohibits conclusions about causal direction of the associations between obesity, inflammation, and working memory. As hypothesized by previous reviews (e.g., Miller and Spencer, 2014), it is conceivable that greater inflammation in obesity—originating from adipose tissue and changes in gut microbiota composition—could impair working memory. However, it is also possible that working memory impairments influence the adoption of healthy lifestyles and behaviors, contributing to the development of obesity, and thereby upregulate inflammation through greater adipose tissue. Working memory or CRP was not assessed in earlier waves of Add Health data collection, precluding the examination of prospective associations between obesity, CRP, and working memory. Consequently, future studies should use longitudinal data (e.g., future data of Add Health) to examine prospective links between obesity, inflammation, and working memory. Second, we only examined inflammation as a potential biological mechanism underlying the association between obesity and poor working memory; future studies should also examine other potential (biological) mechanisms underlying the association between obesity and executive function. Third, we used BMI as a proxy for adiposity, but BMI is a relatively coarse measure of body density, and it does not consider relevant physical characteristics, such as muscle mass and anthropometric features (Bergman et al., 2011). Future research should replicate and extend this work using more direct measures of adiposity. Relatedly, we were only able to assess associations with a single measure of working memory. Future research should replicate these findings using alternative tests of working memory. Fourth, because a modified digit span backward task was used to measure working memory, the reliability and validity of this task were largely unknown and need to be further investigated. Fifth, because only working memory was assessed, it is unclear from our study if obesity-related cognitive deficits are selective to working memory or if the effects we observed are due to broader obesity-related impairments in cognition. Sixth, our study was a relatively younger sample, and we could not assess any developmental effects of obesity or inflammation on working memory (e.g., Shields et al., 2017). Seventh, the Add Health protocol did not require participants to fast or provide blood samples at the same time of day. Future studies should examine these associations using more standardized procedures. In addition, although we adjusted for several key covariates, we cannot completely rule out the possibility of other confounds that might also have influenced the results. Finally, although we found that inflammation statistically accounted for a large portion of the variance explained in working memory by obesity, the total variance explained in working memory by obesity was small. Future studies should examine whether these small but statistically significant findings have any practical or real-word significance.

In conclusion, using a sample drawn from a nationally representative study of U.S. adults, we found that obesity (as well as greater BMI) was related to increased systemic inflammation, which was itself related to lower working memory. Critically, we found that inflammation statistically mediated the association between obesity (as well as BMI) and working memory. These results therefore suggest that obesity-related inflammation might be one biological pathway underpinning the link between excessive weight and poor working memory.

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Author Contributions

Yingkai Yang, Hong Chen and Cheng Guo developed the concept for this article. Yingkai Yang analyzed the data and wrote the manuscript. Grant S. Shields revised the manuscript, verified the primary analyses, and conducted additional analyses. Qian Wu and Yanling Liu provided critical revisions to the paper, and all authors read and approved the final version.

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