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ARTICLE

Pediatrics

Visceral fat-related systemic inflammation and the adolescent brain: a mediating role of circulating glycerophosphocholines

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Abstract

Objective Life-long maintenance of brain health is important for the prevention of cognitive impairment in older age. Low-grade peripheral inflammation associated with excess visceral fat (VF) may influence brain structure and function. Here we examined (i) if this type of inflammation is associated with altered white-matter (WM) microstructure and lower cognitive functioning in adolescents, and (ii) if recently identified circulating glycerophosphocholines (GPCs) can index this type of inflammation and associated variations in WM microstructure and cognitive functioning.

Subjects We studied a community-based sample of 872 adolescents (12–18 years, 48% males) in whom we assessed VF and WM microstructure with magnetic resonance imaging, processing speed with cognitive testing, serum C-reactive protein (CRP, a common marker of peripheral inflammation) with a high-sensitivity assay, and serum levels of a panel of 64 GPCs with advanced mass spectrometry.

Results VF was associated with CRP, and CRP in turn was associated with "altered" WM microstructure and lower processing speed (all $p < 0.003$). Further, "altered" WM microstructure was associated with lower processing speed ($p < 0.0001$). Of all 64 tested GPCs, 4 were associated with both VF and CRP (at Bonferroni corrected $p < 0.0004$). One of them, PC16:0/2:0, was also associated with WM microstructure ($p < 0.0001$) and processing speed ($p = 0.0003$), and mediated the directed associations between VF and both WM microstructure ($p < 0.0001$) and processing speed ($p = 0.02$). As a mediator, PC16:0/2:0 explained 21% of shared variance between VF and WM microstructure, and 22% of shared variance between VF and processing speed. Similar associations were observed in an auxiliary study of 80 middle-aged adults.

Conclusions Our results show that VF-related peripheral inflammation is associated with "altered" WM microstructure and lower cognitive functioning already in adolescents, and a specific circulating GPC may be a new molecule indexing this VF-related peripheral inflammation and its influences on brain structure and function.

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Introduction

Life-long maintenance of brain health is important for the prevention of cognitive impairment and dementia in older age [1]. A growing body of research suggests that *low-grade* systemic inflammation may impact adversely brain health [2–14]. Excess body fat, and visceral fat (VF) in particular, may be one of the most common causes of low-grade systemic inflammation in the industrialized world[15, 16]. This is because obesity and overweight are common (affecting >30% of youth and >60% of adults in Canada and the United States [17]), and fat tissues secrete pro-inflammatory molecules that can trigger and potentiate systemic inflammation[15, 16]. But not all fat tissues are equally pro-inflammatory, and not all individuals with excess body fat develop low-grade systemic inflammation. VF compared with subcutaneous fat (SF) secretes more pro-inflammatory molecules [15, 18], and surgical removal of VF (but not that of SF) diminishes systemic inflammation [7, 19–22]. Thus, individuals with preferentially visceral (vs. subcutaneous) accumulation of body fat are at higher risk of developing low-grade systemic inflammation [7, 22–24].

Role of VF or VF-associated peripheral inflammation in brain health has not been studied extensively. Several large-scale cohorts ($n > 500$ participants) have quantified VF accurately with magnetic resonance imaging (MRI) or computed tomography, but only a few of these have also assessed structural properties of the brain with MRI. One of the first such studies investigated a community-based cohort of 733 middle-aged and older adults, and showed that higher VF is associated with lower brain volume, and that this association is independent of global adiposity (as assessed with body mass index (BMI)), but it is diminished when adjusted for C-reactive protein (CRP), suggesting it may involve peripheral inflammation [25]. More recent studies of middle-aged and older adults free of cerebrovascular disease (sample sizes between 500 and 2000 participants) demonstrated that VF was associated with higher incidence of white-matter (WM) lesions (hyperintensities and lacunar infarcts) [26–28], and that these associations remained significant after additional adjusting for BMI, and obesity-associated disorders, namely hypertension, diabetes mellitus and dyslipidemia [26–28].

Our previous research of 950 adolescents showed that higher VF is associated with: (i) "altered" WM microstructure [29], and (ii) lower cognitive functioning, particularly processing speed [30]. Here we investigate if low-grade systemic inflammation may be a mechanistic pathway that links higher VF to the observed variations in WM microstructure and lower processing speed. In this context, we investigate a recently identified panel 64 glycerophosphocholines (GPCs) [31], which may be novel markers of VF-related peripheral inflammation. Previously studied GPCs have been shown to (i) vary with adiposity [32–34], (ii) modulate signaling, migration and adhesion functions of blood immune cells and their interactions with endothelial cells, and thus integrity of endothelial barriers [35–38] and (iii) be associated with clinical outcomes related to peripheral inflammation, including cognitive impairment and dementia [34, 39–42].

Table. 1 Characteristics of participants

	Median/ number	Interquartile range
Adolescents		
Sex (males/females)	413/459	N/A
Age (years)	14.8	13.4–16.4
Height (cm)	163.0	156.5–169.7
Weight (kg)	56.4	48.6–65.6
BMI (kg/m^2)	20.9	18.8–23.5
Visceral fat (cm^3)	15.5	10.7–25.4
C-reactive protein (mg/L)	0.4	0.2–1.1
White-matter T1W-SI (normalized)	1.20	1.19–1.21
White-matter MTR (Z-score)	0.21	−0.35–0.67
Processing speed (score)	144	124–163
Adults		
Sex (males/females)	33/47	N/A
Age (years)	50.3	47.7–53.5
Height (cm)	164.3	160.0–170.4
Weight (kg)	76.2	66.4–86.3
BMI (kg/m^2)	28.0	24.0–31.9
Visceral fat (cm^3)	71.0	40.0–127.2
White-matter T1W-SI (normalized)	1.33	1.31–1.35

T1W-SI T1-weighted signal intensity, *MTR* magnetization transfer ratio

Methods

Participants

We studied a community-based sample of 905 adolescents (48% male, 12–18 years) from the Saguenay Youth Study (SYS) [43]. These were all adolescent participants with (i) blood data on CRP and 64 GPCs, (ii) MRI data on visceral adiposity and brain structure and (iii) behavioral data on processing speed. From these, we excluded 33 participants with CRP > 10 mg/L to avoid possible confounding by acute-phase inflammatory response, as suggested previously [44] (Table 1). The SYS was recruited, as a cohort of adolescent sibships, via high schools in the Saguenay/Lac Saint-Jean region of Quebec, Canada. Details of recruitment, testing

procedures, and exclusion criteria are provided elsewhere; all participants are of a single white ethnicity [43].

To explore whether associations observed in adolescents are also present in adults, we performed an auxiliary study of a small set of middle-aged adults. These were 80 parents of the adolescents in whom we determined serum levels of the GPC most significantly associated with tested outcomes in the primary (adolescent) study, and in whom we acquired quality-controlled MRI images of the brain and VF.

The research ethics committees of the Chicoutimi Hospital (Quebec, Canada) and the Hospital for Sick Children in Toronto (Ontario, Canada) approved the study protocol. All adolescent participants and their parents signed informed assent and consent, respectively, after receiving a complete description of the study.

Measurements

All participants underwent an extensive 15-h protocol [43], including the following assessments:

MRI of VF: VF was measured from T1-weighted (T1W) images of the abdomen acquired on a Gyroscan NT 1.0-T scanner (Philips Healthcare). A 10-mm thick axial slice at the level of the umbilicus was selected to quantify VF, in cm^3, using sliceOmatic software (TomoVision, Magog, QC, Canada).

MRI of the brain: WM microstructure was assessed as follows. (i) *T1W imaging* was performed with Gyroscan NT 1.0-T scanner (Philips Healthcare) using a three-dimensional radio frequency (RF)-spoiled gradient echo sequence consisting of 160 slices, 1-mm isotropic resolution, TR = 25 ms, TE = 4.2 ms, and flip angle = 30°. An in-house image-processing pipeline was used to derive T1W-signal intensity (T1W-SI) values of WM voxels [29]. Mean T1W-SI of WM voxels (cerebral lobes only) normalized by mean T1W-SI of the whole brain was the main variable studied here [29]. In addition, (ii) *magnetization transfer ratio (MTR) imaging* was performed with the same scanner in 683 of the 872 studied participants. MTR imaging consisted of MT_{ON} and MT_{OFF} acquisitions, each with 54–60 slices, 3-mm slice thickness, 1-mm in-plane resolution, TR = 41 ms, TE = 7.9 ms, and flip angle 30°. The MT_{ON} acquisition included a Gaussian RF saturation pulse of 7.68 ms duration, off-resonance frequency 1.5 kHz, and effective pulse angle 500°. Mean MTR of WM voxels (cerebral lobes only) was the main variable.

Processing speed: Automatic detection processing speed, which is a cognitive domain that we found previously to be most strongly associated with VF [30], was analyzed here; it was measured using the Ruff 2 and 7 Selective Attention Test [45].

Serum CRP: Sera from morning blood samples drawn after overnight fasting were used to measure the concentrations of CRP using a high-sensitivity assay (Beckman Coulter), with detection limits of 0.08–80 mg/L.

Targeted serum lipidomics (64 GPCs) with mass spectrometry: Separate aliquots of the same sera were used to measure circulating levels of 64 GPCs, using liquid chromatography-electrospray ionization-mass spectrometry (LC-ESI-MS) targeted for GPCs within the 450–680 m/z range [31, 46]. Circulating levels of individual GPCs were expressed in pmol-equivalents of PC13:0/0:0, which is a non-naturally occurring GPC used as an internal standard at 1.4 µM concentration [46].

Assessments of puberty development: Participants completed an eight-item self-report measure of physical development based on Tanner stages with separate forms for males and females [47, 48].

Data analysis

We tested: (i) whether VF-related systemic inflammation is associated with WM microstructure and processing speed, and (ii) if any of the 64 measured GPCs index this type of systemic inflammation and mediate the relationship between VF and brain structure/processing speed.

First, we assessed associations of VF and CRP with WM properties and processing speed. *Second,* we tested if any of the 64 measured GPCs were associated with VF and CRP. *Third*, we examined if any GPCs associated with both VF and CRP were also associated with WM microstructure and processing speed, and if they mediated the directed associations between VF and both WM microstructure and processing speed.

Prior to any of the above analyses, we examined all outcome measures for normality of distribution and, if not normally distributed, we log-transformed (VF and GPCs) or rank-transformed (CRP) them. To evaluate the above-specified associations, we used multivariable mixed-effect linear models with exchangeable covariance structure (lme4 package in R [49]). Fixed effects were used to adjust for potentially confounding effects of sex, age and height (when relevant), and random effects were used to account for family relatedness (the SYS cohort consists of adolescent sibships). To identify GPCs significantly associated with both VF and CRP, we applied Bonferroni correction for multiple comparisons ($64 \times 2 = 128$, $p < 0.0004$). To examine if GPCs—associated with both VF and CRP—mediate the directed associations between VF (as a primary exposure) and both WM microstructure and processing speed (as outcomes), we employed Sobel's test of mediation in R [50]. This test adopts the regression-based approach by Baron and Kenny [51]. It examines the relationships between (a) exposure and outcome, (b) exposure and mediator and (c) mediator and outcome. It tests for the presence of mediation by demonstrating that both (i) all

Table. 2 Associations between VF, CRP, WM microstructure (WM T1W-SI), and processing speed

	Visceral fat		C-reactive protein		White-matter T1W-SI	
	t-Value	*p*-Value	*t*-Value	*p*-Value	*t*-Value	*p*-Value
Visceral fat	–	–	–	–	–	–
C-reactive protein	12.51	<0.0001	–	–	–	–
White-matter T1W-SI	8.37	<0.0001	5.57	<0.0001	–	–
Processing speed	−4.22	<0.0001	−2.98	0.003	−3.96	<0.0001

T1W-SI white-matter T1-weighted signal intensity

(a–c) relationships are significant and (ii) the magnitude of the exposure to outcome relationship is significantly attenuated when controlled for the mediator. These relationships were assessed with linear mixed-effects regression modeling (additionally controlling for age, sex and height as fixed effects, and family relatedness as random effects).

Results

VF-related peripheral inflammation vs. WM microstructure and processing speed

In the studied 872 adolescents (Table 1), VF was positively associated with CRP ($t = 12.51$, $p < 0.0001$), and VF and CRP were each positively associated with WM T1W-SI ($t = 8.37$, $p < 0.0001$ and $t = 5.57$, $p < 0.0001$, respectively) and negatively associated with processing speed ($t = -4.22$, $p < 0.0001$ and $t = -2.98$, $p = 0.003$, respectively; Table 2). In addition, WM T1W-SI was negatively associated with processing speed ($t = -3.96$ $p < 0.0001$, Table 2). The associations of VF with CRP, WM T1W-SI and processing speed remained significant after additional adjusting for BMI (all $p < 0.0001$).

Circulating GPCs vs. VF-related peripheral inflammation

After Bonferroni correction for multiple comparisons (at $p < 0.0004$), 18 out of the 64 tested GPCs were associated with CRP, and 4 of these GPCs were also associated with VF (Fig. 1a). These four GPCs included three species negatively associated with both CRP and VF, and one species positively associated with both CRP and VF. All three negatively associated species belonged to a small cluster of correlated GPCs (cluster C1, Fig. 1b), and the one positively associated specie, i.e., PC20:0/2:0, was part of another small cluster of correlated GPCs (cluster C2, Fig. 1b). None of the four GPCs have been previously studied for association with systemic inflammation.

Our panel of 64 GPCs did include some previously studied species, namely, PC18:2/0:0 and PC18:1/0:0. Similarly to previous studies of older adults [32–34], these GPCs were associated negatively with CRP, but they were not associated with VF and their associations with CRP were substantially less strong than those we observed with our new GPCs (Fig. 1a).

Circulating GPCs indexing VF-related peripheral inflammation vs. WM microstructure and processing speed

All four GPCs identified above as associated with both VF and CRP were also associated with WM T1W-SI and three of them were also associated with processing speed (Table 3). PC16:0/2:0 showed the most significant associations with both WM T1W-SI ($t = -7.51$, $p < 0.0001$) and processing speed ($t = 3.21$, $p = 0.001$; Table 3). This GPC was also the only of the four GPCs that demonstrated a significant mediatory role in the directed associations between VF and WM T1W-SI ($p < 0.0001$) and between VF and processing speed ($p = 0.02$), as assessed with Sobel's test of mediation (Table 4 and Fig. 2). As a mediator, PC16:0/2:0 explained 21% of shared variance between VF and WM T1W-SI, and 22% of shared variance between VF and processing speed.

In additional analyses, PC16:0/2:0 remained associated with VF, CRP, WM T1W-SI and processing speed after adjusting for pubertal stage (all remaining $p < 0.0001$), indicating these associations are not confounded by puberty. Moreover, PC16:0/2:0 was associated with VF and WM T1W-SI not only in adolescents but also in middle-aged adults ($n = 80$, 41% males, 40–60 years [Table 1]; $p < 0.0001$ and $p = 0.01$, respectively). The associations were similar, with the estimated effect of PC16:0/2:0 on VF being -0.23 ± 0.06 in adults and -0.19 ± 0.02 in adolescents, and the estimated effect of PC16:0/2:0 on WM T1W-SI being -0.022 ± 0.009 in adults and -0.018 ± 0.002 in adolescents. Finally, in a subset of adolescents ($n = 683$), WM microstructure properties were also evaluated with MTR. Similar to WM T1W-SI, PC16:0/2:0 was negatively associated with WM MTR ($t = -3.54$, $p < 0.0001$).

Discussion

The results of the present study suggest that, already in adolescents, VF-related systemic inflammation may influence WM microstructure and cognitive functioning, and that a specific circulating GPC may be a new molecule

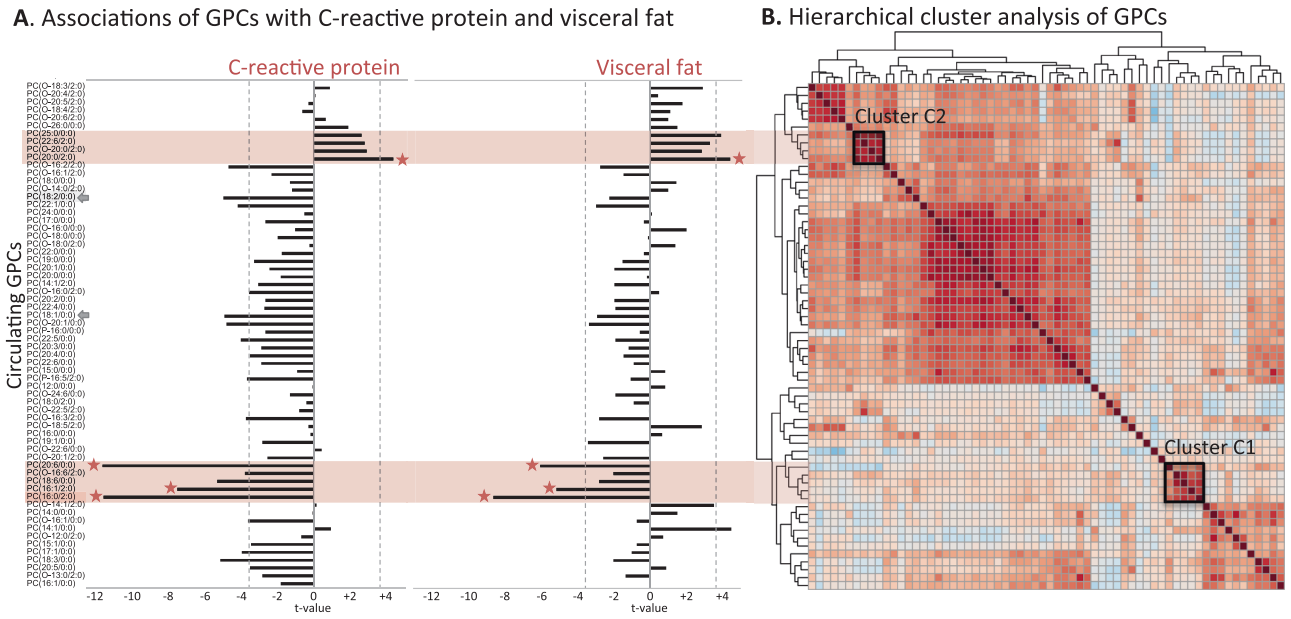

Fig. 1 Associations of circulating glycerophosphocholines (GPCs) with systemic inflammation (C-reactive protein) and visceral fat. **a** Associations of 64 GPCs with C-reactive protein and visceral fat are presented as horizontal lines proportional to *t*-values from multivariable linear mixed-effect models. Associations significant after Bonferroni correction for multiple comparisons (128 comparisons = 64 GPCs × 2 outcomes; $p < 0.0004$) are indicated by vertical dotted lines. Stars indicate four GPCs statistically significantly associated with both visceral fat and C-reactive protein. Gray arrows indicate GPCs previously shown to be associated with C-reactive protein. GPCs are ordered based on hierarchical cluster analysis (http://www.metaboanalyst.ca), with a heat map of pairwise correlations shown in panel (**b**). Clusters C1 and C2 containing GPCs associated with both C-reactive protein and visceral fat (after Bonferroni correction) are indicated by black boxes

Table. 3 GPCs associated with VF-related peripheral inflammation and their associations with WM microstructure (WM T1W-SI) and processing speed

GPCs	Visceral fat		C-reactive protein		WM T1W-SI		Processing speed	
	t-Value	*p*-Value	*t*-Value	*p*-Value	*t*-Value	*p*-Value	*t*-Value	*p*-Value
PC16:0/2:0	−8.77	<0.0001	−11.65	<0.0001	−7.51	<0.0001	3.21	0.001
PC16:1/2:0	−5.23	<0.0001	−7.54	<0.0001	−6.37	<0.0001	2.50	0.01
PC20:6/0:0	−6.15	<0.0001	−11.70	<0.0001	−7.21	<0.0001	2.23	0.03
PC20:0/2:0	4.45	<0.0001	4.39	<0.0001	1.67	0.09	−0.64	0.05

VF visceral fat, *GPCs* glycerophosphocholines, *WM T1W-SI* white-matter T1-weighted signal intensity

Table 4 GPCs associated with VF-related peripheral inflammation and their mediating effects between VF and both WM microstructure (WM T1W-SI) and processing speed

GPCs	WM T1W-SI		Processing speed	
	z-Score	*p*-Value	*z*-Score	*p*-Value
PC16:0/2:0	4.5	<0.0001	−2.3	0.02
PC16:1/2:0	3.6	0.0003	−1.7	0.09
PC20:6/0:0	4.1	<0.0001	−1.3	0.20
PC20:0/2:0	0.4	0.73	0.1	0.95

VF visceral fat, *GPCs* glycerophosphocholines, *WM T1W-SI* white-matter T1-weighted signal intensity

indexing this VF-related systemic inflammation and its influences on brain structure and function.

A growing body of research suggests that low-grade systemic inflammation may impair brain health in middle-aged and older-aged adults. The present study is one of the first ones to suggest that such low-grade inflammation may alter brain health already in adolescents. In middle-aged and older-aged adults, large-scale population-based studied showed that low-grade systemic inflammation is associated with future development of dementia [8–12], lower volumes of brain regions susceptible to neurodegeneration [52], and altered microstructure of WM [53–55]. The cellular substrates of these macro- and micro-structure alterations of the brain, and their temporal relationships prior to the development of full-blown dementia, are not known. Nonetheless, research in animal models shows that low-grade systemic inflammation (including that induced by dietary obesity) can induce low-grade inflammation in the brain, characterized by enhanced

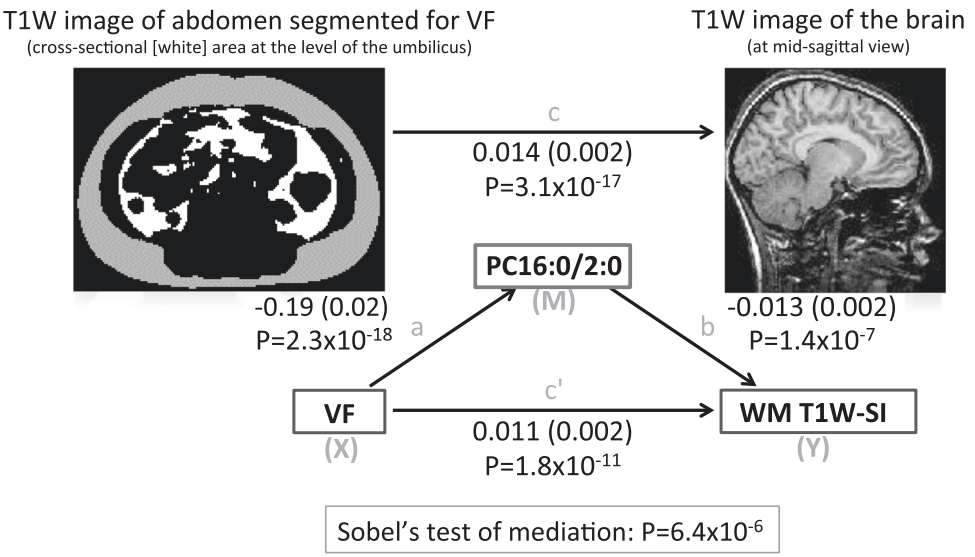

Fig. 2 Path diagram of Sobel's test of mediation testing PC16:0/2:0 as a mediator between visceral adiposity and white-matter microstructure. Path diagram shows that PC16:0/2:0 acts as a mediator (M) of the directed association between visceral fat (VF; indicated in white in a cross-sectional image of abdomen [encircled by subcutaneous fat shown in gray]) as a potential primary exposure (X) and white-matter T1-weighted signal intensity (WM T1W-SI) as an outcome (Y). Estimates (standard errors) and *p*-values are shown for each path

presence of activated microglia and astrocytes, which enhance production of cytokines and chemokines, and decrease homeostatic functions, such as the removal of cellular and myelin debris [2–7]. These changes are associated with microstructural alterations of neurons (e.g., lower density of dendrites), and accompanied by impairment in learning and memory [4–7]. Taken together, it is plausible that neuroinflammation leads to diffuse microstructural alterations of brain tissue detectable with MRI.

In the present study, we assessed WM microstructure with two MRI metrics, namely T1W-SI and MTR. MRI measures brain structure indirectly—it measures electromagnetic waves emitted by hydrogens after the application of RF pulses, localizing the signal by spatially varying magnetic gradients [56]. These signals (contrast) depend on the density of hydrogens and their magnetic properties. Magnetic properties of hydrogens in turn depend on hydrogens' mobility, with hydrogens bound to water being more "mobile" than hydrogens bound to macromolecules (e.g., phospholipids, proteins and carbohydrates in myelin or cellular membranes) [56]. For T1W imaging, the signal is dependent on T1 relaxation, which is the time for magnetic properties of hydrogens to return to equilibrium after the application of electromagnetic waves. Higher content of tissue water (mobile hydrogens) lengthens T1 relaxation time, whereas higher content of tissue macromolecules (motion-restricted hydrogens) shortens it [56]. T1 relaxation time is inversely related to T1W-SI studied here. For MTR imaging, the signal is dependent on the transfer of magnetization between mobile hydrogens bound to water and motionally restricted hydrogens bound to macromolecules [57, 58]. In the present study, VF-related systemic inflammation was associated with higher T1W-SI and MTR values, thus both indicating WM microstructural variations characterized by a higher tissue content of macromolecules (vs. water), as a function of low-grade systemic inflammation. It is not known, however, which specific macromolecules and which cellular compartments contribute to this phenomena—they may reflect some of the tissue changes described in animal models of systemic inflammation-induced neuroinflammation [4–7].

In the present study, we identified a novel blood molecule (PC16:0/2:0) that may index VF-related systemic inflammation, and correlated variations in WM microstructure and cognitive functioning. We showed that PC16:0/2:0 is associated with visceral adiposity and an established marker of systemic inflammation (CRP), as well as with WM T1W-SI and MTR, and processing speed. We also showed that PC16:0/2:0 mediates the associations between visceral adiposity and WM microstructure and cognitive functioning. The exact molecular function of PC16:0/2:0 is not currently known. This GPC was not studied in the context of inflammation previously. But the pattern of associations of this GPC is similar to that of previously studied GPCs—they were negatively associated with adiposity and peripheral inflammation [32–34], and with clinical outcomes, including cognitive impairment and dementia [34, 39–42]. As such, these molecules may index some "protective" mechanisms that may counteract the "adversity" of VF-related systemic inflammation.

The current study is limited in that it is a cross-sectional study, and thus cannot prove causal relationships between visceral adiposity, systemic inflammation, and brain structure and function. Future longitudinal studies are required to confirm our cross-sectional observations, and to assess how timing and duration of exposure to VF-associated systemic inflammation influence the observed body–brain relationships (and their potential reversal through interventions). Since we studied adolescents and their middle-aged parents

(who are genetically related), future replication research in independent cohorts is also required. Nonetheless, here we studied a large cohort of individuals, observed consistent brain-imaging results with two different imaging modalities, and saw similar associations in adolescents and adults. Further, the present study is a lipidomics study carried out with advanced mass spectrometry (e.g., LC-ESI-MS), which is a method that quantifies circulating molecules with unprecedented specificity and sensitivity [46, 59].

In summary, the results of the present study suggest that VF-related systemic inflammation is associated with altered WM microstructure and lower cognitive functioning already in adolescents, and a specific circulating GPC may be a new molecule indexing this VF-related systemic inflammation and its influences on brain health.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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