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ARTICLE

Association of life course adiposity with risk of incident dementia: a prospective cohort study of 322,336 participants

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Cohort studies report inconsistent associations between body mass index (BMI) and all-cause incident dementia. Furthermore, evidence on fat distribution and body composition measures are scarce and few studies estimated the association between early life adiposity and dementia risk. Here, we included 322,336 participants from UK biobank to investigate the longitudinal association between life course adiposity and risk of all-cause incident dementia and to explore the underlying mechanisms driven by metabolites, inflammatory cells and brain structures. Among the 322,336 individuals (mean (SD) age, 62.24 (5.41) years; 53.9% women) in the study, during a median 8.74 years of follow-up, 5083 all-cause incident dementia events occurred. The risk of dementia was 22% higher with plumper childhood body size ($p < 0.001$). A strong U-shaped association was observed between adult BMI and dementia. More fat and less fat-free mass distribution on arms were associated with a higher risk of dementia. Interestingly, similar U-shaped associations were found between BMI and four metabolites (i.e., 3-hydroxybutrate, acetone, citrate and polyunsaturated fatty acids), four inflammatory cells (i.e., neutrophil, lymphocyte, monocyte and leukocyte) and abnormalities in brain structure that were also related to dementia. The findings that adiposity is associated with metabolites, inflammatory cells and abnormalities in brain structure that were related to dementia risk might provide clues to underlying biological mechanisms. Interventions to prevent dementia should begin early in life and include not only BMI control but fat distribution and body composition.

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INTRODUCTION

Obesity, commonly defined by body mass index (BMI) ≥30 kg/m^2, is considered as a modifiable factor in preventing dementia [1, 2]. Excess weight has been reported to be detrimental to dementia, while reversed risk associations between overweight or obesity and dementia were observed in several studies, which was hypothesized to result from reverse causality that subclinical dementia causes the decrease in BMI [3, 4]. Such divergences raise the need for estimating the associations in a life-course approach covering a period preceding any preclinical neurodegenerative changes, such as in childhood.

Broadly, BMI has low sensitivity to adiposity [5]. Large inter-individual variability exists in body composition and fat distribution for those with a similar BMI [5]. Previous studies have indicated that high fat mass as well as low muscle mass are related to cognitive decline and mortality [6, 7], and that different waist-to-hip ratio (WHR) levels with similar BMI are differently linked to metabolic profiles [8] and brain volumes [9]. However, objectively measured adiposity indicators such as arm fat mass ratio (AFR) and arm fat-free mass ratio (AFFR), have not been comprehensively investigated in previous dementia-related longitudinal studies.

To date, the mechanisms underlying associations of adiposity with cognitive impairment or dementia are not fully understood. Plasma metabolomics has been used to depicture alterations in circulating metabolites that could reflect the interaction of genetic and environmental factors, which benefits for understanding the pathophysiology of dementia [10–12]. Adiposity alters the systemic metabolism [13, 14], but studies on whether adiposity-related metabolic change contributed to adiposity-dementia associations are scarce. Thus, we included all metabolites detected by untargeted high-throughput nuclear magnetic resonance (NMR) spectroscopy, which could systematically investigate the metabolic change underlying the adiposity-dementia associations. Moreover, adiposity has been characterized as an inflammatory state [15, 16], accompanied by infiltration and proliferation of cells of the innate and the adaptive immune systems [17]. There are evidence indicating that peripheral immunity associated with incidence of dementia and shaped inflammatory responses in dementia [18, 19]. Therefore, we assessed the effect of systematic inflammation markers on adiposity-dementia association, which included lymphocytes, neutrophils, monocytes, leukocytes and c reactive protein (CRP) [20–23]. In addition, adiposity is associated with brain morphometry including white matter hyperintensities

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and temporal lobe atrophy [24, 25], which are more pronounce in dementia [26]. Understanding the impact of adiposity on these biological factors may shed light on the mediators and pathways between adiposity and dementia.

This study primarily aimed to investigate the association between life course adiposity and the risk of all-cause incident dementia. Second, to explore the underlying mechanisms, the study investigated whether metabolites, inflammation and structural brain abnormalities mediated the association between adiposity and dementia.

METHODS

Data source and study population

This study is based on data from the UK Biobank (UKB) study that received approval from the National Information Governance Board for Health and Social Care and the National Health Service North West Multicenter Research Ethics Committee. All participants provided informed consent through electronic signature at baseline assessment. The UKB is a large-scale cohort with over 500,000 participants aged 37 to 73 years at baseline (2006–2010) [27]. The data cover detailed demographic, health, physical measures and clinical outcomes at baseline and ongoing longitudinal follow-up [28]. For the present study, the participants were recruited between Jan 1, 2006 and Dec 31, 2010 (Field ID 53) and were followed up until the date of earliest incident dementia diagnosis, the last time of hospital inpatient admission, or the date of the last data collected by the general practitioner, date of death or loss of follow-up, whichever came first. After exclusion of participants with dementia at baseline or without data of follow-up ($N = 80{,}569$), less than 50 years old ($N = 84{,}355$), or who were non-white ($N = 15{,}233$), 322,336 participants remained for the main analysis in this study (Supplementary Fig. 1). The present analyses were conducted under UKB application number 19542.

Life course adiposity measures

The original adiposity measures used from the UKB dataset and the calculation processes are detailed in Supplementary Table 1. Life course overall adiposity was comprised of birth weight, childhood body size and adulthood BMI. The information on birth weight was obtained by asking participants to enter their own birth weight in verbal interview. Childhood body size was measured by the participants' answers to "When you were 10 years old, compared to average would you describe yourself as thinner, plumper, or about average?". Birth weight and BMI were also treated as categorical variables as recommended by World Health Organization. Central adiposity was measured through waist circumstance (WC), WHR and waist-to-height ratio (WHtR).

The original data of the fat content of the whole body, trunk, arms and legs were estimated by bio-electrical impedance analysis [29]. The body fat distribution measures were interpreted as arm/leg/trunk fat (-free) mass ratio (AFR, LFR, TFR, AFFR, LFFR and TFFR) [30], which represented fat (-free) mass distribution in reference to the whole body. Specifically, they were calculated with the formula: Arm fat mass ratio = [Arm fat mass-left + Arm fat mass-right]/Whole body fat mass (leg and fat-free mass in the same way); Trunk fat mass ratio = Trunk fat mass/Whole body fat mass (fat-free mass in the same way). Body composition was interpreted as whole body fat mass (BFM), whole body fat-free mass (BFFM) and whole body/arm/leg/trunk fat percentage (BFP, AFP, LFP and TFP). For limbs, we took the average of right and left measures. Furthermore, to further confirm the results of the above measures, we included fat mass and fat-free mass (lean mass) index for arms, legs, trunk and whole body and Trunk/Limbs fat mass ratio (TLiFR). They were calculated with the formula: Arm fat mass index = [Arm fat mass-left + Arm fat mass-right]/[2*Height^2] (leg and fat-free mass in the same way); TLiFR = Trunk fat mass/([(Arm fat mass-left + Arm fat mass-right)/2 + (Leg fat mass-left + Leg fat mass-right)/2]/2).

Covariate

Covariates are described in the Supplementary Methods.

Dementia diagnosis

All-cause dementia was diagnosed according to the International Classification of Diseases ICD-9 codes (290, 291.2, 294.1, 331.0–331.2, 331.5, 331.0 and 290.4) and ICD-10 codes (A81.0, F00, F01, F02, F03, F05.1, F10.6, G31.0, G31.1, and G31.8), if any of the above codes presented a primary or secondary diagnosis in the health records, or presented as a potential cause of death in the death register. Additionally, dementia diagnoses were also ascertained from primary care data using Read codes (version 2 [Read v2] and version 3 [CTV3 or Read v3]). Alzheimer's disease (AD) and vascular dementia (VD) were diagnosed by ICD-9 codes (AD, 331.0; VD, 290.4) and ICD-10 codes (AD, F00, G30; VD, F01, I67.3). The incident dementia events were defined as diagnosis after recruitment.

Plasma metabolites and inflammatory markers

Data of plasma metabolites and inflammatory markers (inflammatory cells and CRP) were obtained from baseline blood tests of UKB participants taken at the initial assessment visit (https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100080). Details of data processing can be found on the UKB website (http://biobank.ndph.ox.ac.uk/showcase/showcase/docs/haematology.pdf and https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/nmrm_companion_doc.pdf). For metabolites, we included all metabolites available in absolute levels ($n = 168$) obtained with NMR, which include detailed measures of cholesterol metabolism, fatty acids, and various low-molecular weight metabolites. For inflammatory markers, we extracted data of neutrophils, monocytes, lymphocytes, and platelets [19] and level of CRP.

Brain imaging data

The imaging derived phenotypes used in this study included 68 cortical regions, 40 subcortical regions and tract-specific fractional anisotropy (FA) and mean diffusivity (MD) values of the 48 white matter tracts ($N = 23{,}714$). Brain MRI data are described in detail in the Supplementary Methods.

Statistical analysis

Basic characteristics for participants were presented as mean (standard deviation (SD)) for continuous variables and number (percentage) for categorical variables. The study design is presented in Supplementary Fig. 1. First, Cox-proportional hazard regression models were used to estimate the linear and non-linear associations for each adiposity measure with incident all-cause dementia. For the continuous variables, scaling was done by dividing the variables by their SDs such that the hazard ratios (HRs) represents the risk of per SD increment of the adiposity measures. Model 1 was adjusted for age at baseline, sex, apolipoprotein E (*ApoE*) *ε4* carrier status, education, total physical activity, BMI (for variables other than BMI, BFM and BFFM); and height (for BFM and BFFM only), and was chosen as the priority model. Model 2 was additionally adjusted for depression status, social-economic status, smoking and alcohol intake status. To explore the potential non-linear effects, restricted cubic spline (RCS) terms were introduced in the models. Bonferroni corrections were conducted to correct for multiple comparisons. Then we calculated the quantitative change in linearity below and above the change point of each type of adiposity if non-linearity was detected. Subsequently, mediation model analysis was conducted to investigate whether the association of plumper childhood body size with dementia was mediated by adulthood obesity. Second, two sensitivity analyses were conducted by excluding participants with follow-up duration <8 years and by excluding participants with non-dementia-related death. We utilized interaction terms for age, sex, and *ApoE-ε4* to estimate whether the strata effect existed ($p < 0.1$) in different subgroups. After that, three subgroup analyses were performed through stratification of sex, age (i.e., 50–65 years and >65 years), and *ApoE-ε4* carrier status (carrier and non-carrier status). We also investigated the associations of adiposity with early onset (age at dementia onset <65) and late onset (age at dementia onset ≥65) dementia, AD and VD.

Third, we performed metabolic and inflammatory mechanism analyses. First, a linear regression was used to assess the associations between adiposity and metabolites or inflammatory cells and a non-linear regression ($y = \beta x^2 + \alpha x + c$) was used to examine the non-linear relationships of BMI and these markers. Each regression was adjusted for the covariates in Model 1. For each type of metabolites or inflammatory markers, adjusted SD differences and 95% confidence intervals (CIs) associated with 1-SD higher adiposity were estimated. Second, the associations of metabolites and inflammatory markers (survived Bonferroni correction in the above analysis) with incident dementia were analyzed using Cox-proportional hazard regression adjusting for covariates in Model 1. HRs were computed for 1 SD higher metabolite or cell level. Last, we performed mediation analyses for those variables significantly and consistently related to all adiposity measures and risk of dementia, aiming

to investigate to what degree these metabolites or inflammatory cells contributed to the adiposity-dementia association.

Lastly, a linear regression model was used to investigate the association of adiposity measures and dementia with brain morphometric measures, and a non-linear regression model ($y = \beta x^2 + \alpha x + c$) was used for BMI, whole BFM and AFP, adjusting for covariates in Model 2 as well as the scanning site of the imaging. An F-statistic was obtained for these associations and Bonferroni corrections were conducted to correct for multiple comparisons.

We report in the Supplementary Methods: (1) adiposity measures, covariates and brain imaging data, and (2) mediation analyses in detail. All analyses were conducted using R version 4.0.3. The significance threshold is a two-sided $p < 0.05$ after adjustment.

RESULTS

Among the 322,336 individuals (mean (SD) age, 62.24 (5.41) years; 53.9% women) in the study, during an average 8.74 years of follow-up, 5038 all-cause incident dementia events occurred. Supplementary Table 2 shows the baseline demographic and health characteristics of participants by incident all-cause dementia status.

Life course adiposity was associated with incident dementia

In the prospective longitudinal analysis, overall life course adiposity showed a significant association with all-cause dementia (Figs. 1A and 2, Table 1 and Supplementary Figs. 2 and 3). Birth weight was negatively related to dementia risk ($p_{linear} = 0.001$, $p_{non\text{-}linear} = 0.038$) and compared with a normal birth weight, a 128% higher risk was found with the extremely low birth weight ($p = 0.002$). Compared with an average body size, the risk of dementia was 22% higher for plumper body size in childhood ($p < 0.001$) and 7% higher for thinner body size ($p = 0.054$). The association between adult BMI and dementia was U-shaped ($p_{non\text{-}linear} < 0.001$). Specifically, dose-response relationship analysis revealed that dementia risk significantly decreased when BMI was below the break points (i.e., 29.2 kg/m^2 for males and 28.5 kg/m^2 for females; HR per 1 kg/m^2 (95% CI) = 0.94 (0.92–0.96) for males and 0.95 (0.93–0.98) for females; Fig. 2 and Supplementary Table 3), but increased overall when BMI exceeded the break points. Furthermore, in relative to normal weight, 19% and 14% lower risk were found for overweight and class I obesity, respectively (terms defined in Table 1). The mediation analysis showed that adulthood obesity significantly mediated the association between plumper childhood body size and dementia (Mediation proportion = 17.40%, $p < 0.001$), as detailed in Fig. 1B.

Both RCS models and Cox-proportional regression models were applied to estimate associations between other adiposity measures and incident dementia. Central adiposity was detrimental to dementia (WC, HR (95% CI) = 1.01 (1.00–1.02), $p_{non\text{-}linear} < 0.001$; WHR, HR (95% CI) = 4.44 (2.61–7.56), $p_{non\text{-}linear} < 0.001$; and WHtR, 6.71 (4.65–9.68), $p_{non\text{-}linear} < 0.001$); Table 1 and Supplementary Fig. 2). The risk of WC, per 5 cm increase, to dementia was significantly increased when WC was above the cutoff, a result that was similarly observed for WHR (Fig. 2). Fat mass and fat-free mass distribution also had significant but complex correlations with dementia risk (Table 1, Supplementary Figs. 2 and 3 and Supplementary Table 4). Specifically, more fat mass distribution on limbs and less on trunk were related to higher incidence of dementia (TLiFR, 0.94 (0.91–0.98)). Less fat-free mass distribution on arms and more on legs were associated with higher incidence of dementia. For fat composition, the association between BFM and dementia was U-shaped (Table 1 and Supplementary Fig. 2), while no significant association was observed for BFFM. Consistently, FMI for arms, legs and trunk have U-shaped association with dementia, while associations for LMI did not pass multiple test except for LLMI (Supplementary Fig. 3). Fat percentage of whole body, legs and trunk were protective for incident dementia when the values are below the break points (Fig. 2, Supplementary Fig. 2 and Supplementary Table 3), while the association for AFP was U-shaped (Supplementary Fig. 2). Lastly, BMR had a beneficial effect on dementia risk. The break points for each measures that determine the changes in HR trend and the quantitative HRs are presented in Fig. 2 and Supplementary Table 3.

These associations were statistically significant and robust after inclusion of non-white participants (Supplementary Table 5) and applying the fully-adjusted model (Model 2, Table 1 and Supplementary Fig. 3), as well as when excluding participants with follow-up duration <8 years (Supplementary Fig. 4 and Supplementary Table 6). As expected by the interaction effects by age, sex, and *ApoE-ε4* (Supplementary Table 7), we performed three subgroup analyses. First, when stratifying participants by age (50–65 years and >65 years, Supplementary Fig. 5 and Supplementary Table 8), we found that the linear association between birth weight and risk of dementia remained significant in younger participants while disappeared in older individuals. Other associations were still statistically significant in both age groups. Second, we stratified the participants by sex (Supplementary Fig. 6 and Supplementary Table 9). The associations between birth weight, waist circumference, LFR, TFR and risk of dementia were more significant in female while the association of TFFR and risk of dementia was significant in male only. Third, there was some evidence of heterogeneity by *ApoE-ε4* carrier status (Supplementary Fig. 7 and Supplementary Table 10). The protective effects of overweight and obesity were more significant in individuals who are *ApoE-ε4* carriers while the adverse effect of underweight was only significant in people who are not. Moreover, the association between birth weight and risk of dementia was only significant in *ApoE-ε4* non-carrier group while the association of BFFM was only significant in *ApoE-ε4* carrier group. As for the associations with subtypes of dementia, there was an indication that the adiposity measures-dementia associations were attributable to late-onset dementia rather than to early onset dementia, especially for BMI, waist circumference, trunk fat-free mass ratio, whole BFM, body fat percentage and trunk fat percentage (Supplementary Fig. 8 and Supplementary Table 11). Finally, thinner or plumper childhood body size were significantly related to VD risk only. Overweight was protective for both AD and VD, while obesity was protective for AD but detrimental to VD (Supplementary Figs. 9 and 10 and Supplementary Tables 12 and 13).

Metabolites and inflammatory cells mediated the adiposity-dementia association

After correction for multiple testing, many metabolites and inflammatory cells showed significant association with adiposity measures (Supplementary Tables 14 and 15). Interestingly, four metabolites and eight inflammatory cell percentages or counts had U-shaped associations with BMI (Supplementary Tables 16 and 17). Next, we performed Cox regression analyses to investigate the associations between those metabolites and inflammatory cells with risk of dementia. Only six metabolites and five inflammatory cell counts or percentages were found to be significantly associated with risk of dementia (i.e., 3-hydroxybutyrate, acetone, acetoacetate, citrate, polyunsaturated fatty acids, glucose; the percentages of neutrophil, lymphocyte, and monocytes and the counts of neutrophil and leukocyte) (Supplementary Tables 18 and 19).

For each adiposity measures, mediation analysis was performed for the metabolites and inflammatory cells that showed significant associations with both the adiposity measure and risk of dementia with consistent directions. We found that the relation between BMI and dementia was significantly mediated by those five metabolites and five inflammatory cells (Supplementary Table 20). Glucose, neutrophil, lymphocyte percentage partly mediated the association between central adiposity and dementia. Polyunsaturated fatty acids and neutrophil percentage mediated the effect of

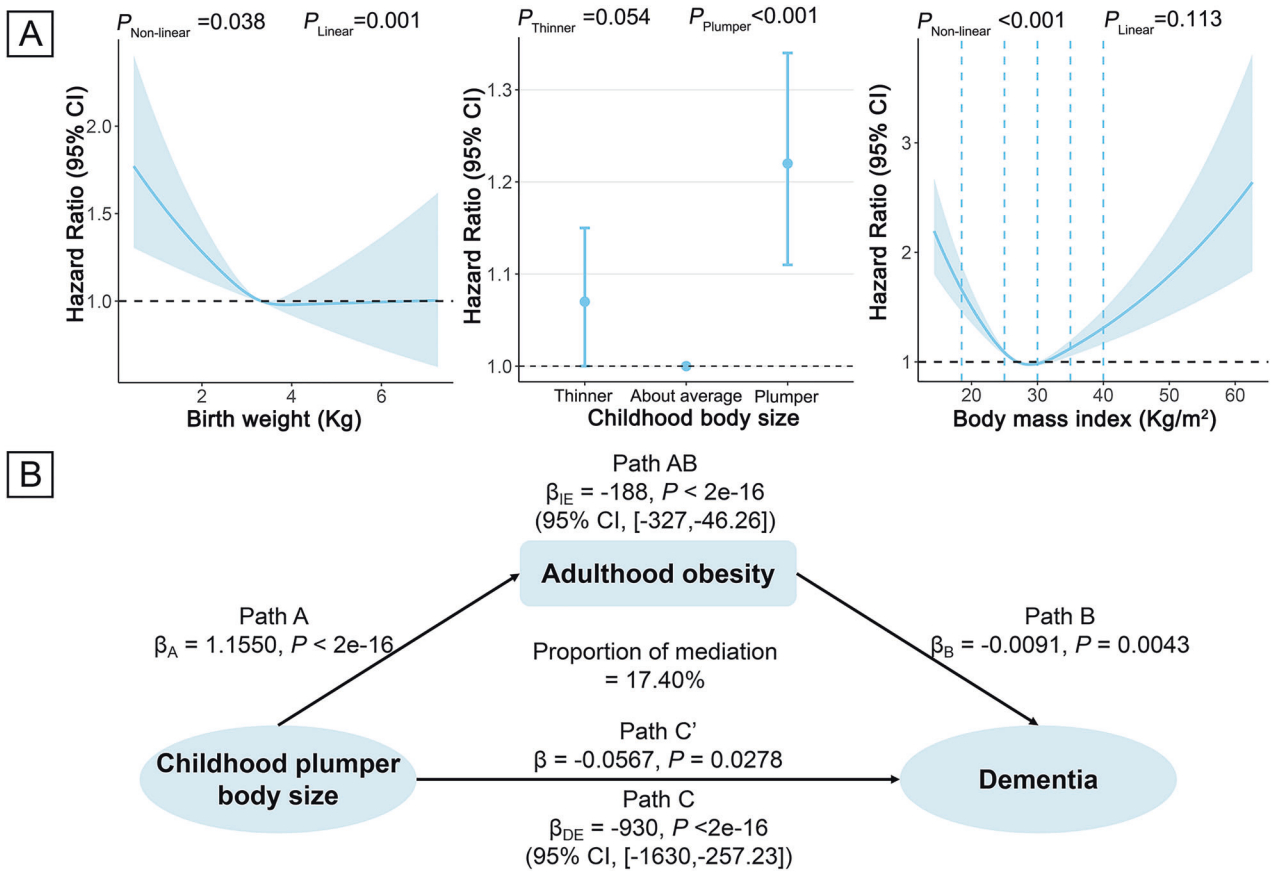

Fig. 1 Associations between life course adiposity and all-cause incident dementia. A Non-linear relationships were estimated using restricted cubic splines and linear relationships were estimated using Cox-proportional hazards regression analysis. The *p* values for non-linear and linear associations are listed in the figures for all outcomes. Estimates adjusted for age at baseline, sex, *ApoE-ε4* carrier status, education, total physical activity, BMI for variables except for BMI, body fat mass and body fat-free mass and height for body fat mass and body fat-free mass (model 1). Dashed vertical lines in the right-hand panel represent WHO BMI category thresholds of 18.5 kg/m² (underweight to normal weight), 25 kg/m² (normal weight to overweight), 30 kg/m² (overweight to class I obesity), 35 kg/m² (class I obesity to class II obesity) and 40 kg/m² (class II obesity to class III obesity). **B** Mediation analysis: the mediation implemented by adulthood obesity from childhood plumper body size to dementia was significant (Proportion of mediation = 17.40%). Path A: effect of the independent variable, childhood plumper body size, on the mediator, adulthood obesity. Path B: effect of the mediator (adulthood obesity) on the outcome (dementia). Path C indicates the direct effect of the childhood plumper body size on the outcome (dementia) controlling for the mediator (adulthood obesity). The indirect path AB shows that the adulthood obesity mediates part of the effect of childhood plumper body size on dementia ($\beta = -188$, $p < 2 \times 10^{-16}$).

fat distribution and body composition (Fig. 3 and Supplementary Table 20). The mediation effects remained after inclusion of non-white participants. Full results can be found in Supplementary Table 20.

Associations between adiposity measures and brain structure

The results revealed significantly non-linear associations between BMI and mean thickness of dementia-related cortical regions, including superior frontal cortex (left hemisphere, $p_{Dementia} < 0.001$, $p_{BMI} < 0.001$, right hemisphere, $p_{Dementia} < 0.001$, $p_{BMI} < 0.001$) and middle temporal cortex; and subcortical gray matter volume, including hippocampus (left hemisphere, $p_{Dementia} < 0.001$, $p_{BMI} < 0.001$, right hemisphere, $p_{Dementia} < 0.001$, $p_{BMI} < 0.001$) and amygdala (Fig. 4A and Supplementary Tables 21–24). Furthermore, BMI and mean cortical thickness and subcortical volume demonstrated an inverted U-shaped association, with BMI at about 30 kg/m^2 corresponding to the largest cortical thickness and subcortical gray volume (Fig. 4A), which was consistent with the result of the Cox regression for least risk of incident dementia (Fig. 1). Significantly non-linear associations were found between BMI and FA and MD values in the majority of the white matter tracts (Supplementary Table 25), including fornix, left superior longitudinal fasciculus (SLF) and cingulum cingulate gyrus (CG). Similarly, we also observed significant associations between other adiposity measures and dementia-related brain regions, with the full results in Supplementary Table 24. Briefly, 9 of 18 other adiposity measures were significantly associated with middle temporal cortical thickness in the left hemisphere, eight with superior temporal cortical thickness in the right hemisphere, seven with left amygdala, six with right amygdala and 11 with bilateral hippocampus (Fig. 4B, with all mentioned regions Bonferroni-corrected $p < 0.05$).

DISCUSSION

In this study, we aimed to investigate the associations between life course adiposity and risk of incident all-cause dementia. We found that a plumper body size in childhood was detrimental to dementia prevalence. Adulthood (50–73 years old) BMI had a U-shaped association with risk of dementia, and partly mediated the childhood body size-dementia association. Fat distribution on the abdomen, arms, legs and trunk were all significantly related to dementia risk. These findings are consistent with the hypothesis that adiposity has an impact on dementia risk, starting decades before a clinically-diagnosed event and covering a wide range of

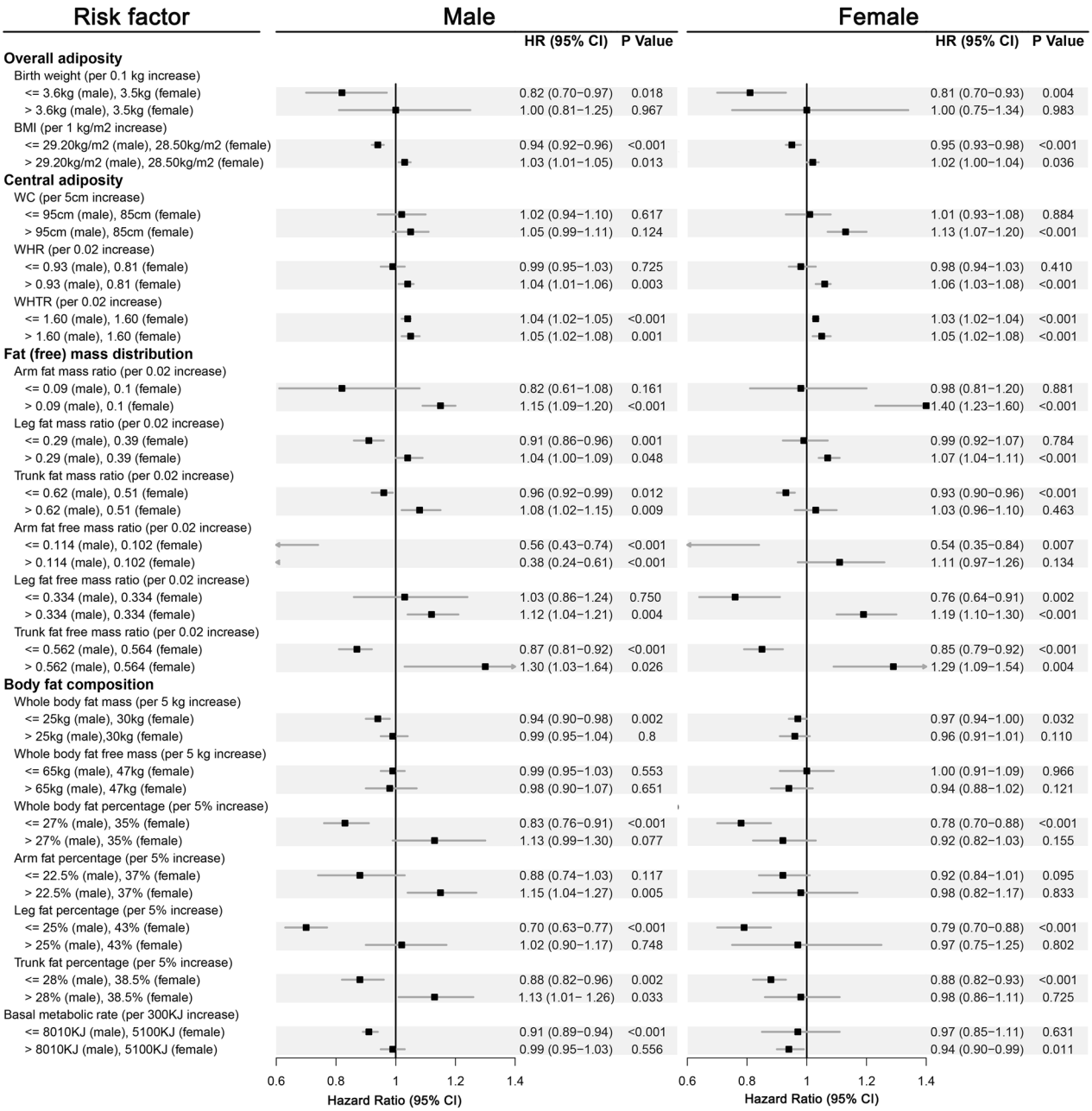

Fig. 2 Sex-specific estimated cutoffs in the adiposity-dementia association, and associations with dementia below and above cutoffs. Black squares represent hazard ratios, gray horizontal lines indicate corresponding 95% confidence intervals around hazard ratios. Hazard ratios were calculated using Cox-proportional hazards regression analysis after adjustments for age at baseline, sex, *ApoE-ε4* carrier status, education, total physical activity, BMI for variables except for BMI, body fat mass and body fat-free mass and height for body fat mass and body fat-free mass. HR hazard ratio, CI confidence interval, BMI body mass index, WC waist circumference, WHR waist-to-hip ratio, WHtR waist-to-height ratio.

adiposity measures besides the typically-focused BMI. In subsequent metabolic and inflammatory analyses we identified five metabolites and five inflammatory cells linked to both BMI in adulthood and dementia, providing clues to underlying biological mechanisms. Moreover, adiposity was negatively associated with abnormalities in brain structure that has also been observed in dementia pathophysiology [31, 32], giving a hint of the underlying brain mechanisms of adiposity on dementia risk.

This study contributes to a sparse literature comprehensively estimating the influence of life course general adiposity on dementia. One recent study examined the relationship between BMI in early adulthood and dementia using a pooled cohort spanning the life course and found that higher BMI early in the life course increased dementia risk [33]. Although we did not study the early adulthood BMI, we observed that childhood plumper body size is detrimental, resulting in an increased risk of dementia, thus extending the previous studies and further verifying the life course consecutive risk of adiposity. A Mendelian randomization (MR) study demonstrated that the associations between childhood body size and risk of cardiovascular disease and type 2 diabetes in adulthood can be attributed to individuals remaining large into later life [34].

Table 1. Hazard ratios for adiposity and all-cause incident dementia.

Adiposity measures	All-cause dementia					
	Model 1[a]			Model 2[b]		
	HR (95% CI)[c]	*P*_linear[d]	*P*_non-linear[e]	HR (95% CI)[c]	*P*_linear[d]	*P*_non-linear[e]
Overall adiposity						
Birth weight (kg)	0.69 (0.55–0.86)	0.001	0.038	0.70 (0.55–0.88)	0.003	0.081
Birth weight categories						
Extremely low (<1.0)	2.28 (1.37–3.80)	0.002		2.18 (1.26–3.77)	0.005	
Very low (1.0–1.5)	1.23 (0.83–1.82)	0.312		1.23 (0.81–1.86)	0.324	
Low (1.5–2.5)	1.09 (0.93–1.27)	0.279		1.08 (0.91–1.27)	0.368	
Normal (2.5–4.0)	1 [Reference]			1 [Reference]		
High (>4.0)	0.96 (0.84–1.10)	0.546		0.95 (0.82–1.10)	0.481	
Early life body size						
Thinner	1.07 (1.00–1.15)	0.054		1.04 (0.96–1.12)	0.323	
About average	1 [Reference]			1 [Reference]		
Plumper	1.22 (1.11–1.34)	<0.001		1.18 (1.07–1.30)	0.001	
Body mass index (kg/m^2)	0.85 (0.70–1.04)	0.113	<0.001	0.72 (0.58–0.88)	0.002	<0.001
Body mass index categories						
Underweight (<18.5)	1.46 (1.00–2.14)	0.050		1.35 (0.90–2.02)	0.151	
Normal weight (18.5–24.9)	1 [Reference]			1 [Reference]		
Overweight (25.0–29.9)	0.81 (0.75–0.87)	<0.001		0.80 (0.74–0.86)	<0.001	
Class I obesity (30.0–34.9)	0.86 (0.79–0.94)	0.001		0.81 (0.73–0.89)	<0.001	
Class II obesity (35.0–39.9)	0.99 (0.86–1.13)	0.851		0.89 (0.77–1.04)	0.147	
Class III obesity (>40.0)	1.13 (0.91–1.41)	0.271		1.02 (0.80–1.28)	0.896	
Central adiposity						
Waist circumference	2.53 (1.54–4.15)	<0.001	<0.001	2.21 (1.31–3.74)	0.003	<0.001
Waist-to-hip ratio	3.73 (2.33–5.97)	<0.001	0.061	3.24 (1.96–5.34)	<0.001	0.062
Waist-to-height ratio	14.15 (8.49–23.59)	<0.001	<0.001	10.76 (6.23–18.59)	<0.001	<0.001
Fat (-free) mass distribution						
Arm fat mass ratio	1.98 (1.62–2.42)	<0.001	0.044	1.80 (1.44–2.26)	<0.001	0.007
Leg fat mass ratio	1.61 (1.19–2.19)	0.002	<0.001	1.67 (1.21–2.31)	0.002	<0.001
Trunk fat mass ratio	0.34 (0.21–0.54)	<0.001	<0.001	0.34 (0.21–0.56)	<0.001	0.001
Arm fat-free mass ratio	0.04 (0.02–0.08)	<0.001	0.699	0.07 (0.03–0.14)	<0.001	0.869
Leg fat-free mass ratio	8.00 (3.89–16.45)	<0.001	0.001	6.90 (3.19–14.90)	<0.001	<0.001
Trunk fat-free mass ratio	0.11 (0.03–0.42)	0.001	<0.001	0.10 (0.02–0.44)	0.002	<0.001
Fat composition						
Whole body fat mass	0.82 (0.74–0.91)	<0.001	<0.001	0.76 (0.68–0.84)	<0.001	<0.001
Whole body fat-free mass	0.81 (0.58–1.13)	0.214	0.719	0.70 (0.49–0.99)	0.048	0.038
Whole body fat percentage	0.40 (0.30–0.54)	<0.001	0.022	0.37 (0.27–0.51)	<0.001	0.071
Arm fat percentage	0.92 (0.67–1.25)	0.580	0.014	0.74 (0.53–1.02)	0.071	0.028
Leg fat percentage	0.29 (0.20–0.41)	<0.001	0.162	0.28 (0.19–0.41)	<0.001	0.311
Trunk fat percentage	0.53 (0.43–0.67)	<0.001	<0.001	0.52 (0.41–0.65)	<0.001	<0.001
Basal metabolic rate	0.29 (0.20–0.42)	<0.001	<0.001	0.36 (0.24–0.53)	<0.001	<0.001

HR hazard ratio, *CI* confidence interval.
[a]Model 1: adjusted for age, sex, *ApoE* ε4 carrier status, education, physical activity, BMI (except for BMI, whole body fat mass and whole body fat-free mass), height (for whole body fat mass and whole body fat-free mass).
[b]Model 2: additionally adjusted for Townsend index, depression status, smoking status, alcohol consumption status.
[c]HR of all-cause dementia per 1 SD higher adiposity measures.
[d]*P*_linear was estimated by Cox-proportional hazard regression models.
[e]*P*_non-linear was estimated by restricted cubic spline models.

We observed similar phenomenon in incident dementia via mediation analysis, although not with as large an effect size as this MR study. Of note, in this study, compared with normal weight, both overweight and class I obesity were protective for dementia in participants over 50 years old. These protective effects are controversial in previous epidemic studies [35, 36], and were mostly explained by reverse causation [3, 37]. However, the significant U-shaped relationships in our main analysis and age stratification

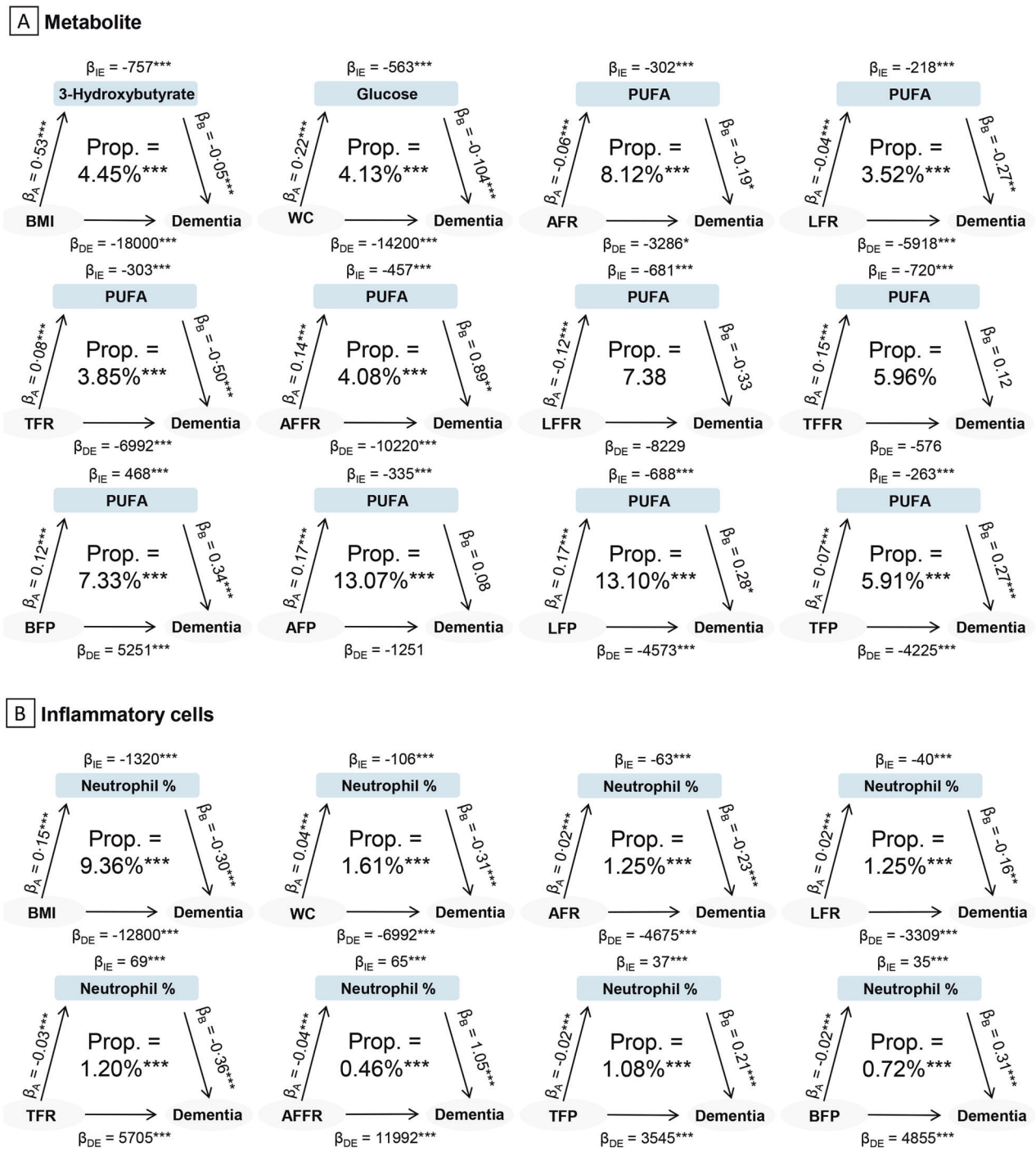

Fig. 3 The relationship between adiposity, metabolites, inflammatory cells and dementia. A The results of mediation analysis between adiposity, metabolites and dementia. Standardized coefficients are presented in the figure. β_A indicates the effect of the independent variable, adiposity measure, on the mediator, metabolite. β_B indicates the effect of the mediator (metabolite) on the outcome (dementia). β_{IE} indicates the indirect effect of adiposity on dementia. β_{DE} indicates the direct effect of adiposity on dementia. **B** The results of mediation analysis between adiposity, inflammatory cells and dementia. Standardized coefficients were presented in the figure. ***indicates a *p* value <0.001. **indicates a *p* value <0.01. *indicates a *p* value <0.05. IE indirect effect, DE direct effect, Prop proportion of mediation, PUFA polyunsaturated fatty acid, BMI body mass index, WC waist circumference, AFR arm fat mass ratio, LFR leg fat mass ratio, TFR trunk fat mass ratio, AFFR arm fat-free mass, LFFR leg fat-free mass ratio, TFFR trunk fat-free mass ratio, BFP body fat percentage, AFP arm fat percentage, LFP leg fat percentage, TFP trunk fat percentage.

analysis revealed that the cutoffs of BMI were located in the overweight category, which, to some degree, explained the apparently protective effects of overweight and clarified the substantially detrimental effects of obesity.

Furthermore, to our knowledge, this is the first and largest study to investigate the longitudinal associations between fat distribution, body composition and risk of dementia. Only a few studies have investigated central adiposity and body composition [38–42].

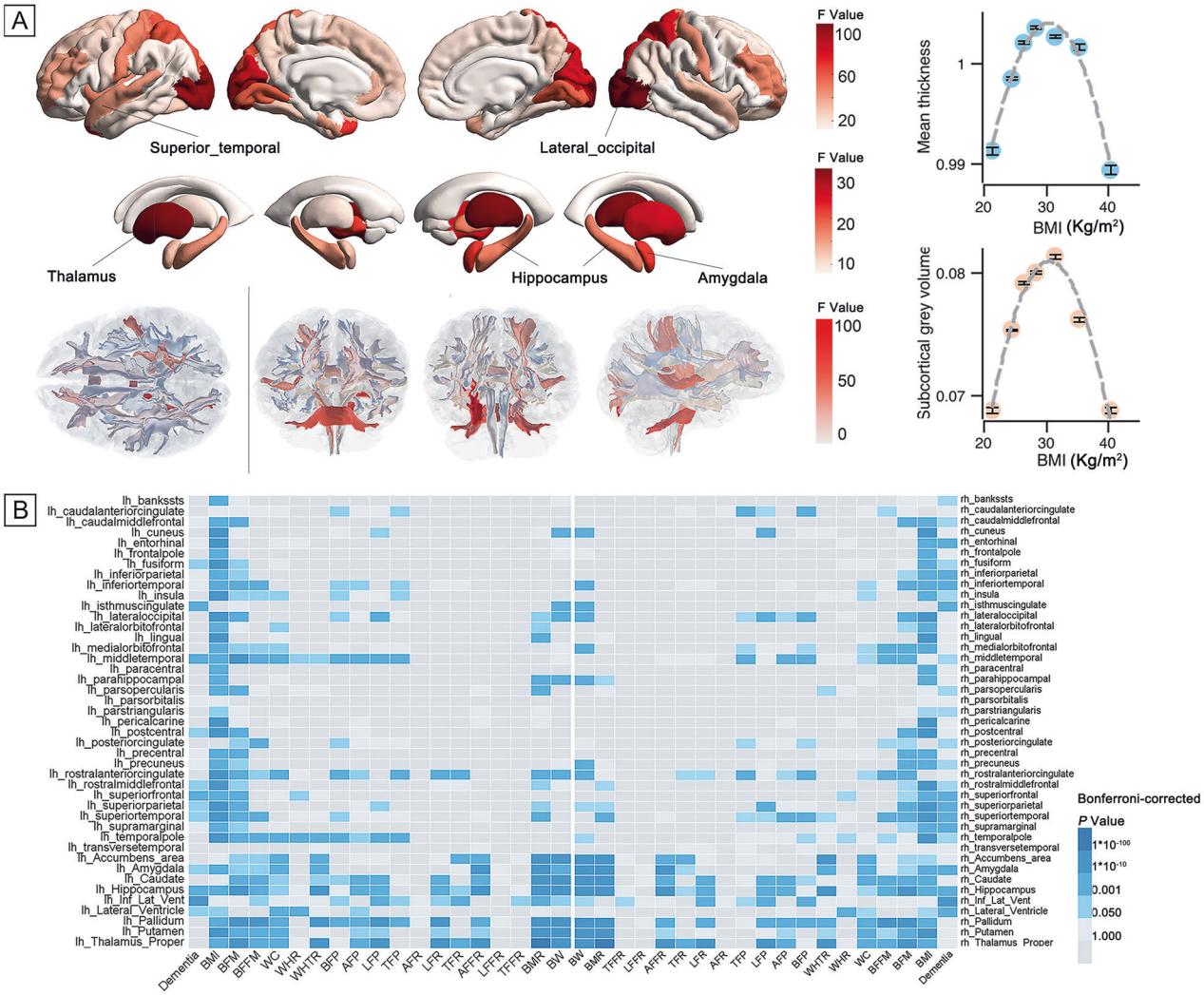

Fig. 4 Associations between adiposity and brain structure. A Left panel, cortical and subcortical regions and white matter tracts with their thickness, volume or FA and MD values significantly and nonlinearly associated with BMI (Bonferroni-corrected, $p < 0.005$); Right panel, significant non-linear associations of BMI with global mean of thickness and subcortical gray volumes. Here, we only show the regions with *F* value >20. **B** The heatmap shows the Bonferroni-corrected *p* values for the associations between dementia and adiposity measures with brain structure.

Previous body fat distribution research on central adiposity showed that WC and WHR increased dementia risk [38, 39], which aligns closely with our results. Abdominal visceral fat accumulation is related to higher levels of blood adipocytokines that are detrimental to the brain [43, 44], and also affects metabolic status as metabolically favorable adiposity was defined as decreased WHR with increasing BMI [45]. In aspects of general body composition, our study provided new insights into the observed U-shaped association between BMI and dementia that it may largely be attributed to BFM, while no significant association was observed between BFFM and dementia. Previous studies reported either negative results for both BFM and BFFM [40, 41] or reverse results [42]. However, these studies were restricted to an older population with a comparatively smaller sample size, and did not go further into the fat or lean mass composition in different regions of whole body. Our further analyses of the arms, legs and trunk were consistent with that of whole body, which also indicated a more significant non-linear relationship in FMI rather than LMI. Specifically, significant non-linear relationship between FMI of arms, legs, and trunk and risk of dementia were observed while significant non-linear association was only presented in LMI of legs. Furthermore, our study evaluated the associations between the fat distribution on major compartments of human body and incident dementia. We found that compared to trunk, more fat mass distribution on limbs were related to higher risk of dementia, and compared to arms, more fat-free mass distribution on legs were associated with higher incidence of dementia. However, studies on fat or fat-free mass distribution on limbs are scarce, future research are needed for confirmation and interpretation of our results. In our subsequent analyses, we tried to explain the possible mechanisms in aspect of metabolism, inflammation and brain structure.

As mentioned above, since the underlying mechanisms of the complicated relationship between adiposity and dementia have been infrequently investigated, we performed exploratory analyses to study whether plasma metabolite and inflammatory cells play a role. First, we identified three metabolites (i.e., 3-hydroxybutyrate, acetone, and citrate) in plasma whose higher concentration were associated with higher risk of dementia had U-shaped association with BMI and partially mediate the BMI-dementia association. In our study, ketone bodies (i.e., 3-hydroxybutyrate and acetone) were detrimental to dementia

risk, which is consistent with a previous study that reported that elevated plasma 3-hydroxybutyrate resulted in lower levels of cognitive function among boys [46]. Previous studies have argued that it may be neuroprotective through possible mechanisms of anti-oxidative stress, and maintaining energy supply [47, 48]. Second, an inverted U-shaped association was observed between polyunsaturated fatty acids and BMI and the polyunsaturated fatty acids were protective for dementia. Moreover, polyunsaturated fatty acid mediated the association between most of the fat distribution and body composition measures and risk of dementia. The polyunsaturated fatty acids could lower inflammatory molecules [49]. An animal experiment study found that dietary docosahexaenoic acid enrichment resulted in higher level of polyunsaturated fatty acid and could diminish endocannabinoid system activation which is related to increased adiposity [50]. Third, the percentages of the four inflammatory cells (i.e., neutrophil, lymphocyte, eosinophil and monocyte) had U-shaped association with BMI, with neutrophil percentage being detrimental and the other three being protective for dementia. Neutrophil percentage mediated the association between fat mass distribution measures and risk of dementia. Neutrophil-lymphocyte ratio is a reliable measure of systemic inflammation, which is positively associated with risk of cognitive dysfunction and mild cognitive impairment [51, 52]. Our observations on metabolites and inflammatory cells are consistent with the hypothesis that metabolic disturbance and inflammation mediate the U-shape association between BMI and dementia. Confirmatory research in independent samples is recommended.

Strong associations between adiposity and brain structure were revealed in this study involving several dementia-related brain regions, which included middle temporal and superior temporal gyri, hippocampus, amygdala and FA and MD values of the fornix, SLF and CG. Our finding of significant correlation between adiposity and these brain regions is in accordance with previous studies [53, 54], which demonstrated the importance of temporal cortex and hippocampus in dementia pathology. Middle and superior temporal regions are involved in cognitive functions such as episodic memory [55], speech perception [56] and motion processing [57]. Hippocampus and amygdala are crucial to cognition processing [58–60]. Previous study found that higher total fat mass was associated with better brain connectivity [61]. Consequently, adiposity may result in an increased dementia risk via structural abnormalities of these regions, while whether other brain regions mediated the adiposity-dementia association and the exact mechanisms need further investigation. Generally, adiposity could influence cognitive function via some independent biologic mechanisms such as the fat-brain axis [62]. The compounds secreted by adipose tissues such as peripheral leptin, TNF-α, IL-6 are able to cross the blood-brain barrier and affect brain function [63]. Directly administrating leptin into the hippocampus of mice improves memory processing and could shape the hypothalamus during the earliest stages [64]. Moreover, the non-linear association between BMI and cortical thickness and subcortical volumes further emphasizes the importance of maintaining a proper BMI for brain and cognitive health, instead of pursuing simply a loss or gain of fat.

The strengths of this study include the large sample size, prospective design, assessment of not only overall but also regional-specific adiposity measures, coverage of a wide range of blood-based metabolites, inflammatory cells and brain morphometric measures to investigate the underlying biological mechanisms. We also acknowledge some limitations. First, participants were restricted to the "White" population, consequently, our results maybe not generalizable to other ethnicities or populations. Second, we excluded participants younger than 50 years old; thus, the associations between adiposity measures and all-cause incident dementia maybe not applicable to people in other age groups, such as early adulthood and older populations. Third, since 15 years is the longest follow-up duration in UKB cohort, there exists the possibility of reverse causation since previous studies considered that over 30 years follow-up can mitigate reverse causation bias. Last, for systematic inflammation, we lack of cytokine data, which are also important inflammatory markers.

In conclusion, adiposity in both childhood and adulthood was significantly associated with risk of dementia, and fat distribution on specific regions were related to dementia independent of BMI. A possible mechanism for the associations is the finding that adiposity is associated with metabolites, inflammatory cells and abnormalities in brain structure that were related to dementia risk. Interventions to prevent dementia should begin early in life and include not only BMI control but fat distribution and body composition.

DATA AVAILABILITY

The data that support the findings of this study are available from 343 UK Biobank project site, subject to registration and application process. Further details can be found at https://www.ukbiobank.ac.uk.

REFERENCES

1. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396:413–46.
2. Gustafson D. Adiposity indices and dementia. Lancet Neurol. 2006;5:713–20.
3. Kivimäki M, Luukkonen R, Batty GD, Ferrie JE, Pentti J, Nyberg ST, et al. Body mass index and risk of dementia: analysis of individual-level data from 1.3 million individuals. Alzheimers Dement. 2018;14:601–9.
4. Singh-Manoux A, Dugravot A, Shipley M, Brunner EJ, Elbaz A, Sabia S, et al. Obesity trajectories and risk of dementia: 28 years of follow-up in the Whitehall II Study. Alzheimers Dement. 2018;14:178–86.
5. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. Metabolism. 2019;92:6–10.
6. Rodríguez-Fernández JM, Danies E, Martínez-Ortega J, Chen WC. Cognitive decline, body mass index, and waist circumference in community-dwelling elderly participants. J Geriatr Psychiatry Neurol. 2017;30:67–76.
7. Srikanthan P, Horwich TB, Tseng CH. Relation of muscle mass and fat mass to cardiovascular disease mortality. Am J Cardiol. 2016;117:1355–60.
8. Winkler TW, Günther F, Höllerer S, Zimmermann M, Loos RJ, Kutalik Z, et al. A joint view on genetic variants for adiposity differentiates subtypes with distinct metabolic implications. Nat Commun. 2018;9:1946.
9. Mulugeta A, Lumsden A, Hyppönen E. Unlocking the causal link of metabolically different adiposity subtypes with brain volumes and the risks of dementia and stroke: a Mendelian randomization study. Neurobiol Aging. 2021;102:161–9.
10. Xu XH, Huang Y, Wang G, Chen SD. Metabolomics: a novel approach to identify potential diagnostic biomarkers and pathogenesis in Alzheimer's disease. Neurosci Bull. 2012;28:641–8.
11. Kaddurah-Daouk R, Kristal BS, Weinshilboum RM. Metabolomics: a global biochemical approach to drug response and disease. Annu Rev Pharm Toxicol. 2008;48:653–83.
12. Trushina E, Mielke MM. Recent advances in the application of metabolomics to Alzheimer's disease. Biochim Biophys Acta. 2014;1842:1232–9.
13. Würtz P, Wang Q, Kangas AJ, Richmond RC, Skarp J, Tiainen M, et al. Metabolic signatures of adiposity in young adults: Mendelian randomization analysis and effects of weight change. PLoS Med. 2014;11:e1001765.
14. Xu K, Shi L, Zhang B, Mi B, Yang J, Sun X, et al. Distinct metabolite profiles of adiposity indices and their relationships with habitual diet in young adults. Nutr Metab Cardiovasc Dis. 2021;31:2122–30.
15. Bahceci M, Gokalp D, Bahceci S, Tuzcu A, Atmaca S, Arikan S. The correlation between adiposity and adiponectin, tumor necrosis factor alpha, interleukin-6 and high sensitivity C-reactive protein levels. Is adipocyte size associated with inflammation in adults? J Endocrinol Invest. 2007;30:210–4.
16. Windham BG, Simpson BN, Lirette S, Bridges J, Bielak L, Peyser PA, et al. Associations between inflammation and cognitive function in African Americans and European Americans. J Am Geriatr Soc. 2014;62:2303–10.
17. Bharath LP, Ip BC, Nikolajczyk BS. Adaptive immunity and metabolic health: harmony becomes dissonant in obesity and aging. Compr Physiol. 2017;7:1307–37.
18. Wu KM, Zhang YR, Huang YY, Dong Q, Tan L, Yu JT. The role of the immune system in Alzheimer's disease. Ageing Res Rev. 2021;70:101409.

19. Zhang YR, Wang JJ, Chen SF, Wang HF, Li YZ, Ou YN, et al. Peripheral immunity is associated with the risk of incident dementia. Mol Psychiatry. 2022:1–7. https://doi.org/10.1038/s41380-022-01446-5. Online ahead of print.
20. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. Nat Rev Immunol. 2013;13:159–75.
21. Shi C, Pamer EG. Monocyte recruitment during infection and inflammation. Nat Rev Immunol. 2011;11:762–74.
22. Ley K, Laudanna C, Cybulsky MI, Nourshargh S. Getting to the site of inflammation: the leukocyte adhesion cascade updated. Nat Rev Immunol. 2007;7:678–89.
23. Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. Front Immunol. 2018;9:754.
24. Windham BG, Lirette ST, Fornage M, Benjamin EJ, Parker KG, Turner ST, et al. Associations of brain structure with adiposity and changes in adiposity in a middle-aged and older biracial population. J Gerontol A Biol Sci Med Sci. 2017;72:825–31.
25. Isaac V, Sim S, Zheng H, Zagorodnov V, Tai ES, Chee M. Adverse associations between visceral adiposity, brain structure, and cognitive performance in healthy elderly. Front Aging Neurosci. 2011;3:12.
26. Gudmundsson P, Olesen PJ, Simoni M, Pantoni L, Östling S, Kern S, et al. White matter lesions and temporal lobe atrophy related to incidence of both dementia and major depression in 70-year-olds followed over 10 years. Eur J Neurol. 2015;22:781–8.
27. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature. 2018;562:203–9.
28. Palmer LJ. UK Biobank: bank on it. Lancet. 2007;369:1980–2.
29. Mally K, Trentmann J, Heller M, Dittmar M. Reliability and accuracy of segmental bioelectrical impedance analysis for assessing muscle and fat mass in older Europeans: a comparison with dual-energy X-ray absorptiometry. Eur J Appl Physiol. 2011;111:1879–87.
30. Rask-Andersen M, Karlsson T, Ek WE, Johansson Å. Genome-wide association study of body fat distribution identifies adiposity loci and sex-specific genetic effects. Nat Commun. 2019;10:339.
31. Szewczyk P, Zimny A, Trypka E, Wojtyńska R, Leszek J, Sąsiadek M. Assessment of degradation of the selected projectile, commissural and association brain fibers in patients with Alzheimer's disease on diffusion tensor MR imaging. Pol J Radio. 2010;75:7–14.
32. Kantarci K, Avula R, Senjem ML, Samikoglu AR, Zhang B, Weigand SD, et al. Dementia with Lewy bodies and Alzheimer disease: neurodegenerative patterns characterized by DTI. Neurology. 2010;74:1814–21.
33. Zeki Al Hazzouri A, Vittinghoff E, Hoang T, Golden SH, Fitzpatrick AL, Zhang A, et al. Body mass index in early adulthood and dementia in late life: findings from a pooled cohort. Alzheimers Dement. 2021;17:1798–807.
34. Richardson TG, Sanderson E, Elsworth B, Tilling K, Davey Smith G. Use of genetic variation to separate the effects of early and later life adiposity on disease risk: mendelian randomisation study. BMJ. 2020;369:m1203.
35. Pedditzi E, Peters R, Beckett N. The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. Age Ageing. 2016;45:14–21.
36. Qizilbash N, Gregson J, Johnson ME, Pearce N, Douglas I, Wing K, et al. BMI and risk of dementia in two million people over two decades: a retrospective cohort study. Lancet Diabetes Endocrinol. 2015;3:431–6.
37. Suemoto CK, Gilsanz P, Mayeda ER, Glymour MM. Body mass index and cognitive function: the potential for reverse causation. Int J Obes. 2015;39:1383–9.
38. Kerwin DR, Gaussoin SA, Chlebowski RT, Kuller LH, Vitolins M, Coker LH, et al. Interaction between body mass index and central adiposity and risk of incident cognitive impairment and dementia: results from the Women's Health Initiative Memory Study. J Am Geriatr Soc. 2011;59:107–12.
39. Ma Y, Ajnakina O, Steptoe A, Cadar D. Higher risk of dementia in English older individuals who are overweight or obese. Int J Epidemiol. 2020;49:1353–65.
40. Abellan van Kan G, Rolland Y, Gillette-Guyonnet S, Gardette V, Annweiler C, Beauchet O, et al. Gait speed, body composition, and dementia. The EPIDOS-Toulouse cohort. J Gerontol A Biol Sci Med Sci. 2012;67:425–32.
41. van Kan GA, Cesari M, Gillette-Guyonnet S, Dupuy C, Vellas B, Rolland Y. Association of a 7-year percent change in fat mass and muscle mass with subsequent cognitive dysfunction: the EPIDOS-Toulouse cohort. J Cachexia Sarcopenia Muscle. 2013;4:225–9.
42. Cui C, Mackey RH, Shaaban CE, Kuller LH, Lopez OL, Sekikawa A. Associations of body composition with incident dementia in older adults: Cardiovascular Health Study-Cognition Study. Alzheimers Dement. 2020;16:1402–11.
43. Letra L, Santana I, Seiça R. Obesity as a risk factor for Alzheimer's disease: the role of adipocytokines. Metab Brain Dis. 2014;29:563–8.
44. Park HS, Park JY, Yu R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6. Diabetes Res Clin Pr. 2005;69:29–35.
45. Yaghootkar H, Lotta LA, Tyrrell J, Smit RA, Jones SE, Donnelly L, et al. Genetic evidence for a link between favorable adiposity and lower risk of type 2 diabetes, hypertension, and heart disease. Diabetes. 2016;65:2448–60.
46. Sotelo-Orozco J, Abbeduto L, Hertz-Picciotto I, Slupsky CM. Association between plasma metabolites and psychometric scores among children with developmental disabilities: investigating sex-differences. Front Psychiatry. 2020;11:579538.
47. Yang H, Shan W, Zhu F, Wu J, Wang Q. Ketone bodies in neurological diseases: focus on neuroprotection and underlying mechanisms. Front Neurol. 2019;10:585.
48. Mujica-Parodi LR, Amgalan A, Sultan SF, Antal B, Sun X, Skiena S, et al. Diet modulates brain network stability, a biomarker for brain aging, in young adults. Proc Natl Acad Sci USA. 2020;117:6170–7.
49. Batetta B, Griinari M, Carta G, Murru E, Ligresti A, Cordeddu L, et al. Endocannabinoids may mediate the ability of (n-3) fatty acids to reduce ectopic fat and inflammatory mediators in obese Zucker rats. J Nutr. 2009;139:1495–501.
50. Kim J, Carlson ME, Kuchel GA, Newman JW, Watkins BA. Dietary DHA reduces downstream endocannabinoid and inflammatory gene expression and epididymal fat mass while improving aspects of glucose use in muscle in C57BL/6J mice. Int J Obes. 2016;40:129–37.
51. An P, Zhou X, Du Y, Zhao J, Song A, Liu H, et al. Association of neutrophil-lymphocyte ratio with mild cognitive impairment in elderly Chinese adults: a case-control study. Curr Alzheimer Res. 2019;16:1309–15.
52. Rembach A, Watt AD, Wilson WJ, Rainey-Smith S, Ellis KA, Rowe CC, et al. An increased neutrophil-lymphocyte ratio in Alzheimer's disease is a function of age and is weakly correlated with neocortical amyloid accumulation. J Neuroimmunol. 2014;273:65–71.
53. Zhang Y, Schuff N, Jahng GH, Bayne W, Mori S, Schad L, et al. Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease. Neurology. 2007;68:13–19.
54. Salat DH, Tuch DS, van der Kouwe AJ, Greve DN, Pappu V, Lee SY, et al. White matter pathology isolates the hippocampal formation in Alzheimer's disease. Neurobiol Aging. 2010;31:244–56.
55. Squire LR, Stark CE, Clark RE. The medial temporal lobe. Annu Rev Neurosci. 2004;27:279–306.
56. Hickok G, Poeppel D. The cortical organization of speech processing. Nat Rev Neurosci. 2007;8:393–402.
57. Beauchamp MS. The social mysteries of the superior temporal sulcus. Trends Cogn Sci. 2015;19:489–90.
58. Lisman J, Buzsáki G, Eichenbaum H, Nadel L, Ranganath C, Redish AD. Viewpoints: how the hippocampus contributes to memory, navigation and cognition. Nat Neurosci. 2017;20:1434–47.
59. Lazarov O, Hollands C. Hippocampal neurogenesis: learning to remember. Prog Neurobiol. 2016;138-140:1–18.
60. Catani M, Dell'acqua F, Thiebaut, de Schotten M. A revised limbic system model for memory, emotion and behaviour. Neurosci Biobehav Rev. 2013;37:1724–37.
61. Cárdenas D, Madinabeitia I, Vera J, de Teresa C, Alarcón F, Jiménez R, et al. Better brain connectivity is associated with higher total fat mass and lower visceral adipose tissue in military pilots. Sci Rep. 2020;10:610.
62. Elmquist JK, Flier JS. Neuroscience. The fat-brain axis enters a new dimension. Science. 2004;304:63–4.
63. Arnoldussen IA, Kiliaan AJ, Gustafson DR. Obesity and dementia: adipokines interact with the brain. Eur Neuropsychopharmacol. 2014;24:1982–99.
64. Harvey J, Shanley LJ, O'Malley D, Irving AJ. Leptin: a potential cognitive enhancer? Biochem Soc Trans. 2005;33:1029–32.

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AUTHOR CONTRIBUTIONS

JTY generated the hypothesis and designed the study. JTY and WC had full access to all of the data in the study. JFF and WC were responsible for the cohort data. YTD

performed the association analysis between life course adiposity and incident dementia. YZL and WC conducted the brain imaging analysis. YTD and YRZ performed the metabolite and inflammatory cell analyses. YTD, YZL, ADS, JS, and JTY wrote the first draft of the report and SYH, YNO, SDC, LY, JFF, WC, ADS, JS, WC, and JTY helped in revising the text. QD, JFF, WC, and JTY provide administrative, technical and material support. All authors read and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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