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Sustained visceral fat loss is associated with attenuated brain atrophy and improved cognitive function in late midlife

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We examined whether long-term exposure to visceral-adipose-tissue (VAT) influences brain atrophy and cognitive performance years after lifestyle intervention. In the Follow-Interventions-Trials (FIT) project, 533 adults (age=61.4 y, 86% men) from four prior 18-24-month lifestyle randomized-clinical-trials underwent abdominal/brain magnetic-resonance-imaging (MRI)s and Montreal-Cognitive-Assessment (MoCA) testing 5–16 y after interventions. Lower VAT exposure, calculated by area-under-the-curve, from baseline, post-intervention, and follow-up, independently resulted in higher MoCA scores. VAT loss during intervention predicted higher brain volumes at follow-up, independent of weight loss. Among participants with three brain and VAT MRI scans, lower long-term VAT was associated with a slower rate of brain atrophy. These patterns were not observed for deep/superficial subcutaneous-adipose-tissues. Improved glycemic control parameters, rather than lipid or inflammatory markers, were mostly related to the favorable longitudinal brain outcomes. This long-term, large-scale intervention and follow-up MRI study suggests that sustained visceral fat loss, rather than weight loss, is linked to better cognition and attenuation of brain atrophy years later, mainly via improved glycemic control. **Trial registration:** DIRECT (Clinical-trials-identifier: NCT00160108); CASCADE (Clinical-trials-identifier: NCT00784433); CENTRAL (Clinical-trials-identifier: NCT01530724); DIRECT-PLUS (Clinical-trials-identifier: NCT03020186).

Visceral adipose tissue (VAT) has emerged as a critical factor in brain aging. Large studies and systematic reviews consistently find strong associations between VAT and adverse brain outcomes[1–7]. Specifically, higher VAT levels predict greater brain atrophy, including lower hippocampal[2,8], gray matter[2,3], and white matter volumes[2], larger ventricular volume[8], and cognitive decline[1,4,6–8]. Despite robust observational evidence, there is a limited understanding of whether long-term exposure to lower visceral adiposity, independent of weight loss, can attenuate brain atrophy and protect cognitive function over time.

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The Magnetic Resonance Imaging (MRI) Follow Interventions Trials (FIT) project addresses this gap by leveraging multiple abdominal adipose depot measurements obtained via MRI in two completed randomized controlled trials (RCTs): CENTRAL[9] and DIRECT-PLUS[10–12]. In addition, we conducted cross-sectional analyses of VAT, brain atrophy, and cognitive function using follow-up data from all four RCTs (DIRECT[13], CASCADE[14,15], CENTRAL[9], and DIRECT-PLUS[10–12]). By combining repeated VAT measurements, brain MRI, and cognitive testing, we investigated how visceral adiposity influences brain atrophy and cognitive performance, and whether reductions in VAT preserved brain structure and function years after intervention.

Results

Participant retention and follow-up

Of the 881 eligible RCT participants from the DIRECT, CASCADE, CENTRAL, and DIRECT-PLUS trials, 647 participants (73.4%) were successfully identified for the FIT project (The study timeline and data acquisition are illustrated in Fig. 1. Figure 1A created with BioRender.com. The study flow diagram is provided in Fig. 1B). Of these, 599 (92.6% of 647) completed assessments, and 48 were deceased cases. Among the 599 participants with 5–16 years of follow-up data, brain MRI structural analyses were performed for 533 (89% of 599) participants (Table 1).

Participant baseline characteristics at the start of the interventions

At RCT baseline, the cohort was 86% male, with a mean age of 52.0 years, a body mass index (BMI) of 30.4, and a waist circumference (WC) of 106.4 cm. Among participants from CENTRAL and DIRECT-PLUS who had baseline adipose depot measurements ($n = 344$), the mean VAT area was 139.3 (VAT proportion = 28.7%). Participants from DIRECT-PLUS also had baseline brain MRI measures ($n = 211$): Total Brain (TB) = 74.2% of Intracranial Volume (ICV), Gray Matter (GM) = 30.6% of ICV, White Matter (WM) = 30.8% of ICV, Total Ventricles (TV) = 1.7% of ICV, and Hippocampal Occupancy Score (HOC) = 0.9. Among DIRECT-PLUS participants with available genetic data, 17% were apolipoprotein E ε4 allele (APOE ε4) carriers.

5–16-year follow-up characteristics

At follow-up (Table 1), the mean participant age was 61.4 years, with an average BMI of 30.1 kg/m^2, and WC of 102.5 cm. VAT area averaged 131 cm^2 (VAT proportion = 29.9%). Brain structure measurements included TB = 72.2% of ICV, GM = 29.6% of ICV, WM = 30.0% of ICV, TV = 2.5% of ICV, and HOC = 0.8. The mean Montreal Cognitive Assessment (MoCA) score was 23.6. Dietary assessment at follow-up showed a mean Mediterranean Diet (MED) diet adherence score of 7.0.

Cross-sectional Analysis of the Interaction Between Visceral Adipose Tissue (VAT) and Brain Volumes in Association with Cognitive Function (MoCA) at Follow-Up

We examined the associations between VAT and cognitive performance and assessed whether brain structural volumes modified these associations ($n = 527$, Fig. 2A). Linear regression models revealed significant interactions between VAT and several brain volume parameters in relation to MoCA scores. Significant interaction terms were observed between VAT and TB (VAT × TB; $\beta = -0.30$, $p = 0.032$), HOC (VAT × HOC; $\beta = -0.29$, $p = 0.048$), and WM (VAT × WM; $\beta = -0.3$, $p = 0.028$). In the model including TB, VAT showed a negative main effect ($\beta = -0.52$, $p = 0.003$), whereas TB showed a positive one ($\beta = 0.39$, $p = 0.068$). In the model including WM, VAT again demonstrated a negative effect ($\beta = -0.5$, $p = 0.004$), while WM was positively associated ($\beta = 0.42$, $p = 0.012$). Similarly, in the model including HOC, VAT showed a negative association ($\beta = -0.5$, $p = 0.004$), while HOC showed a positive association ($\beta = 0.39$, $p = 0.068$). Conversely, interactions involving deep subcutaneous adipose tissue (DSAT) and superficial subcutaneous adipose tissue (SSAT) levels were not significantly associated with MoCA scores. As illustrated in Fig. 2A, participants with mid or high brain volumes exhibited a more pronounced inverse association between VAT and MoCA scores. In contrast, among individuals with low brain volumes, MoCA scores remained relatively stable across the range of VAT values. All statistical analyses tested interactions between continuous standardized measures of VAT and brain volumes in linear regression models, with MoCA score as the outcome. These models were adjusted for age, sex, BMI, and MED diet adherence score (full model results are provided in Supplementary Data 1). In an additional categorical analysis, adjusted for age, sex, BMI, and MED score, participants with 18-25 MoCA scores had significantly higher VAT compared with those with a normal cognition score ($\beta = 0.21$, $p < 0.01$). In contrast, differences in SSAT and DSAT across MoCA categories were not statistically significant (18-25 vs. >=26 MoCA score: $\beta = 0.07$ for SSAT and $\beta = 0.11$ for DSAT). Likewise, none of the adipose tissue depots showed significant differences between individuals with dementia-range MoCA scores (<18) and those with normal cognition. In parallel models in which BMI, rather than VAT, was specified as the main adiposity exposure, BMI did not show significant interactions with brain volumes in relation to cognitive performance, either in models without VAT or in models additionally adjusted for VAT (model results shown in Supplementary Data 2). The BMI-brain interaction terms were consistently non-significant, in contrast to the significant VAT-brain interactions observed in our primary analyses. In sensitivity analyses adjusted for incretin-based anti-obesity medication use, no significant associations were observed, and the inclusion of this covariate did not change the MoCA-related findings (Supplementary Data 3).

Longitudinal analysis of cumulative abdominal adipose tissue exposure and cognitive function at follow-up

Among participants with complete longitudinal adiposity measurements across three time points (baseline, 18 months, and follow-up) from the DIRECT-PLUS and CENTRAL trials ($n = 295$), we examined the associations between cumulative abdominal adipose tissue exposure (area under the curve (AUC)) and cognitive outcomes at follow-up (Fig. 2B). A significant inverse association was found between cumulative VAT exposure and cognitive performance, as reflected by both MoCA ($\beta = -0.49$, $p = 0.032$) and MoCA-Memory Index Score (MIS) ($\beta = -0.75$, $p = 0.028$), using a fixed-effect meta-analysis for the two trials. However, using the same fixed-effect model, no significant associations were found for either deep or superficial SAT levels. These associations remained significant after adjustment for age, sex, BMI, diet adherence score, and brain anatomy structure (HOC). Full model results are provided in Supplementary Data 4. Similarly, in longitudinal models using BMI area under the curve (BMI AUC) as the adiposity exposure, no significant associations were observed between BMI AUC and cognitive scores (Supplementary Data 5).

Longitudinal analysis of visceral adipose tissue (VAT) change during the intervention and brain structural outcomes at follow-up

Among participants with available baseline and end-of-intervention VAT measurements from the CENTRAL and DIRECT-PLUS trials ($n = 297$), the mean VAT change during the 18-month intervention was −24% ±23.4%. We examined the associations between changes in abdominal adipose depots during the intervention period and brain structure and cognitive function at 5 and 10 years post-intervention using a fixed-effect meta-analysis (Fig. 3). A greater reduction in VAT area during the intervention was associated with better preservation of brain structure at follow-up, as reflected by higher TB ($\beta = -0.13$, $p = 0.05$) and higher GM ($\beta = -0.19$, $p = 0.01$). Additionally, a reduction in VAT proportion was significantly associated with a higher HOC score ($\beta = -0.10$, $p = 0.028$) at follow-up. These associations remained robust

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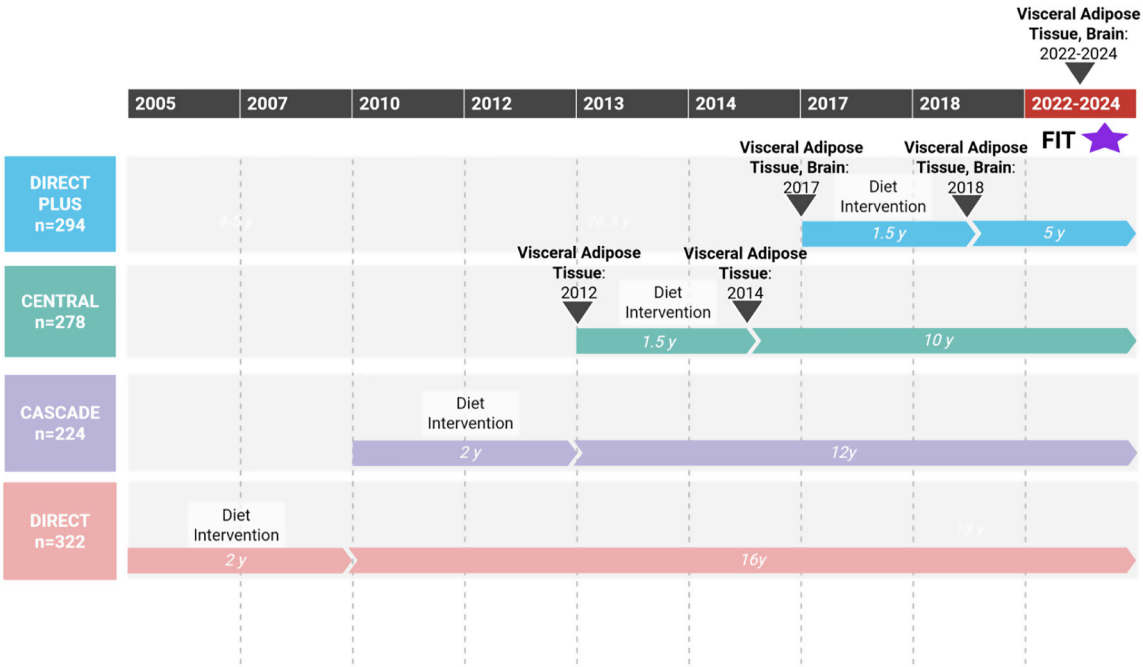
A. Timeline | Description of BRAIN-VAT MRI FIT's Study:



B. Flowchart from BRAIN-VAT MRI FIT's Study:

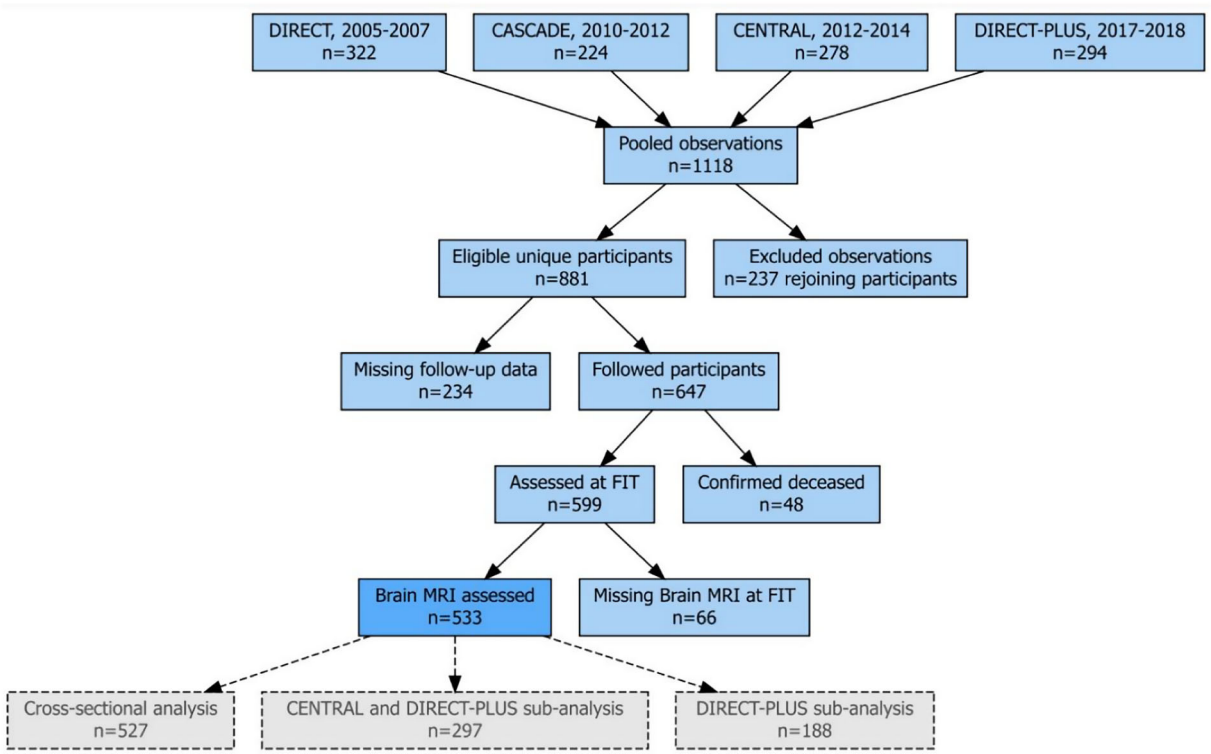


Fig. 1 | Study timeline and participant flow of the BRAIN-VAT MRI FIT study. **A** Timeline of the four randomized controlled trials contributing to the BRAIN-VAT MRI FIT study**:** DIRECT, CASCADE, CENTRAL, and DIRECT-PLUS. The timeline illustrates the duration of dietary interventions, the timing of visceral adipose tissue (VAT) assessments, and brain MRI measurements, including long-term follow-up at the FIT trial (2022–2024). Sample sizes for each dietary trial are indicated. Created in BioRender. P, D. (2026) https://BioRender.com/9n52smq. **B** Flowchart of participant inclusion and exclusion. A total of 1118 observations from the four trials were pooled, yielding 881 eligible unique participants after excluding rejoining participants. Of these, 647 participants were followed longitudinally, 599 attended the FIT, and 533 underwent brain MRI assessment. The final analytical samples used for cross-sectional and sub-analyses are shown.

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Table 1 | Baseline (Pre-Intervention) and 5–16-Year MRI-Assessed Follow-Up Characteristics of the FIT Participants from DIRECT, CASCADE, CENTRAL, and DIRECT-PLUS 18-24-Month Trials (*n* = 533)

	Follow-up		Baseline (pre-intervention)	
Characteristic (*N* = 533)	***N***		***N***	
Sex				
Male	533	461 (86%)	533	461 (86%)
Age, years	533	61.44 ± 11.34	533	52.04 ± 9.54
Whole brain, % of ICV	533	72.16 ± 2.67	211	74.24 ± 2.50
Gray matter, % of ICV	533	29.62 ± 1.38	211	30.61 ± 1.49
White matter, % of ICV	533	30.04 ± 1.84	211	30.82 ± 1.61
Total ventricles, % of ICV	533	2.46 ± 1.35	211	1.73 ± 0.82
Hippocampal occupancy score (HOC)	533	0.79 ± 0.11	211	0.86 ± 0.06
MoCA score	531	23.56 ± 3.50	-	-
VAT area, cm²	530	130.96 ± 62.55	344	139.32 ± 53.73
Deep SAT area, cm²	527	196.92 ± 82.17	341	227.12 ± 72.82
Superficial SAT area, cm²	525	114.77 ± 52.24	335	125.03 ± 56.18
VAT proportion, %	525	29.86 ± 10.23	335	28.67 ± 8.46
BMI, Kg/m²	532	30.10 ± 4.19	533	30.36 ± 3.80
Weight, Kg	532	87.97 ± 14.67	533	89.90 ± 13.38
Waist circumference, cm	532	102.48 ± 11.37	527	106.43 ± 9.39
Diastolic blood pressure, mmHg	532	77.65 ± 12.29	530	79.65 ± 10.28
Systolic blood pressure, mmHg	532	133.98 ± 17.35	530	129.16 ± 15.35
Physical activity, MET-h/week	513	41.61 ± 52.22	427	29.73 ± 31.36
Fasting glucose, mg/dL	530	107.98 ± 30.06	529	108.87 ± 30.68
Fasting insulin, µU/mL	531	15.07 ± 9.09	525	14.76 ± 8.40
HOMA-IR	529	4.01 ± 2.68	520	4.00 ± 2.56
HbA1c, %	527	6.04 ± 1.06	450	5.82 ± 0.90
Triglycerides, mg/dL	531	149.85 ± 84.24	527	153.53 ± 75.45
HDL-C, mg/dL	531	46.15 ± 11.71	527	43.73 ± 11.65
LDL-C, mg/dL	531	108.57 ± 37.62	528	117.25 ± 33.15
Total Cholesterol, mg/dL	531	184.77 ± 43.09	528	189.67 ± 36.06
Triglycerides/HDL-C	531	3.66 ± 2.89	527	3.99 ± 2.79
hsCRP, mg/L	530	3.31 ± 4.11	529	3.83 ± 5.08
APOE-ε4 allele, %	–	–	235	40 (17.02%)

*Mean ± standard deviation (SD) for continuous variables; *n* (%) for categorical variables.

after adjustment for multiple potential confounders, including age, baseline fat depot levels, BMI changes during intervention, and follow-up, MED diet adherence score at follow-up, dual trial participation, sex, diet group, and their interaction. In contrast, reductions in deep and superficial SAT during the intervention were not associated with brain structure outcomes at follow-up (model details in Supplementary Data 6). However, in additional analyses, relative change in BMI during the intervention was not significantly associated with brain structural measures at follow-up (model details in Supplementary Data 7). In contrast, this BMI change was negatively associated with MoCA score at follow-up ($\beta = -0.153$, $p = 0.014$). Sex-by-intervention interaction did not reach statistical significance in any of the models (Supplementary Data 8).

Interaction between longitudinal visceral adipose tissue (VAT) exposure and brain atrophy rate

Among participants from the DIRECT-PLUS trial with repeated brain MRI measurements over three time points: baseline, 18 months, and 5 years ($n = 188$), we evaluated the association between cumulative VAT exposure and the rate of brain structural change over time (Fig. 4). Interaction analyses using linear mixed-effects models (LMM) revealed that the association between VAT exposure and brain volume significantly differed according to the rate of brain change. In these longitudinal models, a significant main effect of time was observed across all brain volume structures: TB ($\beta = -0.02$, $p < 0.001$), GM ($\beta = -0.01$, $p < 0.001$), WM ($\beta = -0.005$, $p < 0.001$), and HOC ($\beta = -0.003$, $p < 0.001$) and TV ($\beta = 0.003$, $p < 0.001$). VAT AUC did not exhibit a significant main effect in any of the models.

For HOC, significant interaction was observed between time and VAT AUC (Time × VAT AUC; $\beta = -0.0001$, $p < 0.001$) and for GM (Time × VAT AUC; $\beta = -0.001$, $p = 0.042$). Similar interactions were observed for TB ($\beta = -0.002$, $p = 0.06$) and WM ($\beta = -0.001$, $p = 0.062$). For TV, the interaction was also significant, but in the opposite (positive) direction ($\beta = 0.0007$, $p < 0.001$), consistent with ventricular expansion in the context of brain atrophy. All models were adjusted for age, sex, BMI, and MED diet adherence score (full model details in Supplementary Data 9). As shown in the density plots (Fig. 4), distributions of VAT AUC differed across brain change rate groups (slow, moderate, fast), with higher mean VAT values consistently observed in participants exhibiting faster atrophy trajectories. When the linear mixed-effects models included BMI AUC as the main exposure together with time to predict trajectories of brain structure, the interaction between BMI AUC and time was not significant (Supplementary Data 10). Also, APOE ε4 carrier status showed no significant main effect and no significant interactions with time, VAT AUC, or their combination in models across all brain outcomes.

In addition, we conducted sensitivity analyses in which baseline glycemic, lipid, and inflammatory biomarkers were individually entered as interaction terms with time in these linear mixed-effects models. All models were adjusted for visceral adipose tissue accumulation, age, sex, and MED score, and included a random intercept for participant. After false discovery rate (FDR) correction, only fasting glucose and HbA1c remained significantly associated with longitudinal brain changes through their interaction with time (time × fasting glucose: $\beta = -8.7\times10^{-5}$, $p = 0.001$; time × HbA1c: $\beta = -9.2\times10^{-5}$, $p < 0.001$). All other baseline glycemic, lipid, and inflammatory biomarkers showed no significant interactions (Supplementary Data 11).

Discussion

This MRI-assessed VAT and Brain measures over long-term interventions and follow-up suggest that sustained reduction in VAT, independent of weight loss, significantly attenuates brain atrophy and enhances cognitive function across a span of up to 10 years. Our findings demonstrate that long-term exposure to higher visceral adiposity is associated with both accelerated brain atrophy and lower cognitive performance, while sustained VAT reduction, achieved through lifestyle interventions, predicts preserved brain structure and cognition in late midlife. Specifically, lower cumulative VAT exposure is associated with attenuation of brain atrophy, higher brain volumes, and better MoCA scores at follow-up. These associations were independent of BMI, highlighting VAT as a distinct and modifiable target for preserving brain health. Glycemic control may represent a key pathway linking visceral adiposity to brain outcomes. The findings underscore the potential for long-lasting neuroprotective effects of targeted VAT loss.

This study has several limitations. The predominantly male, overweight-to-obese sample may limit generalizability to broader populations, including women and individuals with lower baseline adiposity. Although initial fat loss occurred under randomized conditions within the original trials, the 5–16-year follow-up did not involve random assignment to post-trial behavior patterns, limiting causal inference. Nonetheless, the prospective design, extended follow-up, and clear temporal sequence between MRI analyses support the

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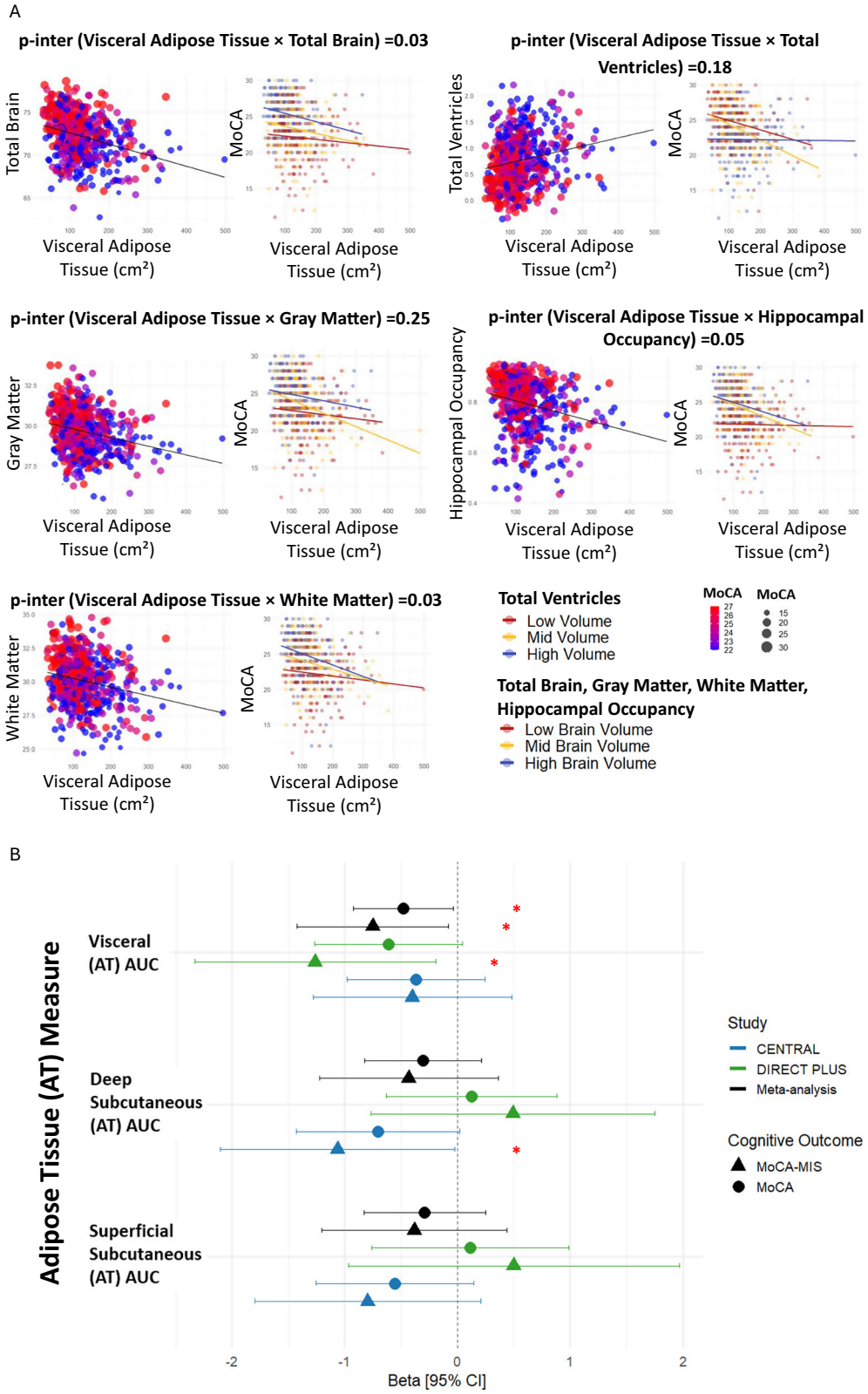

plausibility of long-term associations. Dietary and lifestyle patterns at follow-up were systematically assessed, and the MED diet adherence score was included in all multivariable models to account for post-trial behaviors. This adjustment also addresses the possibility that participants who responded well to the intervention were inherently more likely to maintain healthy dietary patterns over time, which may have independently supported brain health. Additionally, while follow-up MRI scans were analyzed for participants across all four trials, baseline and end-of-intervention abdominal adipose tissue scans were available only from CENTRAL and DIRECT-PLUS trials, and brain MRI scans were available only from the DIRECT-PLUS trial. Consequently, long-term associations between adipose depots and brain outcomes were limited to a 5- and 10-year follow-up for adipose depots and a 5-year follow-up for brain MRI. Importantly, cognitive function was not systematically

Fig. 2 | Visceral Adipose Tissue (VAT) × Brain Volume Interactions and Cumulative VAT Exposure (AUC) in Relation to Cognitive Function (MoCA). **A** Interaction Between Visceral Adipose Tissue (VAT) and Brain Volume in Association with Cognitive Function (MoCA), $n = 527$ participants. Association Between VAT and Brain Volumes: Scatter plots illustrating the associations between brain structural volumes: Total brain volume as % of intracranial volume [ICV], Gray matter volume % ICV, White matter volume % ICV, Total ventricular volume % ICV, Hippocampal occupancy score and visceral adipose tissue (VAT, cm^2). Each dot represents an individual participant. Dot color reflects cognitive function (MoCA score; Montreal Cognitive Assessment, range: 0–30), and dot size is proportional to the MoCA value. Total ventricular was log-transformed for normal distribution. VAT × Brain Volume Interaction in Association with MoCA: Scatter plots showing the association between MoCA score and VAT, stratified by tertiles of each brain volume parameter (low, mid, high volume). Separate lines are plotted for each tertile group. All models were adjusted for age, sex, body mass index (BMI), and Mediterranean (MED) diet score. p-values for the interaction term (VAT × brain volume) are shown for each brain structure. Both VAT and brain volume were modeled as continuous variables. Linear regression models were used to test the interaction between VAT and brain volume in relation to MoCA scores. Two-sided hypothesis testing was used. **B** Forest Plot: Association Between Visceral Adipose Tissue (VAT) AUC (based on 3 Time Points) and Cognitive Function at FIT ($n = 295$ participants). The forest plot presents standardized beta coefficients and 95% confidence intervals (CI) for the relationship between area-under-the-curve (AUC) measures of abdominal adiposity and cognitive outcomes assessed by the Montreal Cognitive Assessment (MoCA) and the MoCA-Memory Index Score (MoCA-MIS). Associations were evaluated using linear regression models adjusted for age, sex, BMI, MED diet score, and hippocampal occupancy. Results are shown separately for the CENTRAL trial (blue; $n = 166$ participants) and the DIRECT-PLUS trial (green; $n = 129$ participants), along with the pooled estimates from a fixed-effect meta-analysis (black). Circles represent MoCA outcomes, and triangles represent MoCA-MIS. Adipose tissue exposure measures include visceral adipose tissue (Visceral AT AUC), deep subcutaneous adipose tissue (Deep Subcutaneous AT AUC), and superficial subcutaneous adipose tissue (Superficial Subcutaneous AT AUC). AUC values were calculated based on MRI-derived fat measurements obtained at baseline, 18 months, and follow-up (5 years for DIRECT-PLUS and 10 years for CENTRAL), and were averaged per year to reflect mean annual exposure. Error bars indicate 95% CI. Asterisks denote statistically significant associations ($p < 0.05$), and exact two-sided p values for significant pooled associations were Visceral AT AUC with MoCA ($p = 0.032$; 95% CI: [−0.93, −0.04]) and with MoCA-MIS ($p = 0.028$; 95% CI: [−1.43, −0.08]). Significant trial-specific associations were Visceral AT AUC with MoCA-MIS in DIRECT-PLUS ($p = 0.020$; 95% CI: [−2.33, −0.20]) and Deep Subcutaneous AT AUC with MoCA-MIS in CENTRAL ($p = 0.044$; 95% CI: [−2.11, −0.03]). Abbreviations: CI, confidence interval; ICV, intracranial volume; AT, adipose tissue; AUC, area under the curve; MoCA, Montreal Cognitive Assessment; MoCA-MIS, MoCA Memory Index Score; BMI, body mass index; MED, Mediterranean diet.

measured at pre- or post-intervention time points, limiting the ability to assess individual-level cognitive changes over time. A further limitation is the absence of quantitative MRI measures of ectopic fat in organs such as the liver and pancreas, which are recognized as relevant to cardiometabolic and brain health. Future studies including hepatic and pancreatic fat will be needed to determine whether our findings are specific to VAT or reflect a broader ectopic fat burden. Nevertheless, within the abdominal adipose depots assessed here, VAT consistently showed stronger associations with brain atrophy and cognitive performance than superficial or deep subcutaneous fat, supporting a distinct role for visceral adiposity in the adipose-brain axis. Additional limitation of the study is the lack of Alzheimer's disease biomarker data (e.g., PET or blood-based markers), which prevents us from determining whether the accelerated atrophy rate observed in our cohort reflects underlying AD-related neurodegeneration biomarkers. This study also has important strengths. This large-scale study links dynamic, MRI-quantified VAT trajectories with long-term brain structure and cognitive outcomes over a decade. Our multi-timepoint, multi-trial design, integration of validated neuroimaging, and rigorous adjustment for dietary adherence and body weight render this work both robust and translational. These findings address a critical gap in the field, identifying visceral fat, not just obesity, as a modifiable risk factor for neurodegeneration, and present a compelling target for early intervention. In parallel analyses that substituted BMI for VAT as the primary adiposity measure, BMI showed no significant associations with brain structures, which may help explain why VAT, rather than BMI, emerges as a more specific adiposity-related risk factor in our cohort despite the expected correlation between these measures. However, changes in BMI during the dietary intervention were associated with subsequent MoCA performance at long-term follow-up, although these BMI changes were not related to brain structural outcomes. This may indicate that BMI relates to cognitive performance through additional mechanisms, such as metabolic or vascular improvements, that are not fully reflected in brain imaging measures. Our MRI-based VAT measure extends prior BMI-based literature[16] by isolating the metabolically active component of obesity most relevant to neurodegeneration, aligning with updated obesity definitions that call for adiposity measures beyond BMI[17]. While the 2024 Lancet Commission on dementia prevention identifies obesity as a modifiable midlife risk factor for dementia and does not separately characterize visceral adiposity[18], our findings suggest that visceral fat represents a particularly harmful obesity phenotype that may disproportionately drive neurodegenerative risk. Given the global rise in both obesity and dementia, these results may have direct implications for clinical practice and public health.

Our analyses revealed that the relationship between VAT and cognitive function varies as a function of brain volume, highlighting a complex interplay between adiposity and brain structure. Specifically, we found significant interactions between VAT and TB, WM, and HOC in relation to MoCA scores, suggesting that the detrimental impact of VAT on cognition is evident, particularly in individuals with greater preserved brain structure. The observation that these associations are particularly evident in individuals with relatively preserved TB, WM, and HOC further supports the notion that VAT-related cognitive impairment may precede overt neurodegeneration, emphasizing the importance of targeting visceral adiposity early in life as a modifiable risk factor for cognitive decline. Another interpretation is that the interaction between brain volume and visceral adiposity suggests that VAT is most strongly related to cognition among participants with relatively preserved brain structure, whereas in those with more pronounced atrophy, structural, vascular, and metabolic factors may already be the main determinants of cognitive performance. Thus, the VAT × brain volume interaction may reflect both the particular vulnerability of individuals with less advanced structural brain changes to metabolic insults and the damage among those with lower brain volumes, in whom cognitive impairment may already be largely determined by these factors, such that further effects of VAT are no longer detectable. The mean MoCA score in our cohort was relatively low according to the MoCA validation study[19]. Although this distribution may appear unexpected for a relatively young late-midlife sample, it is consistent with the metabolic profile of the FIT population, which was enriched with individuals with long-standing abdominal obesity, dyslipidemia, and type 2 diabetes.

These structural brain associations likely reflect underlying biological mechanisms through which chronic VAT exposure contributes to neurodegeneration. VAT is a metabolically active depot that secretes pro-inflammatory cytokines (e.g., IL-6, TNF-α, CRP)[20,21], promoting chronic low-grade systemic inflammation[22–25]. This state can induce neuroinflammation, disrupt blood-brain barrier integrity, and impair synaptic plasticity and neuronal survival. Sustained exposure to VAT-derived inflammatory mediators may also interfere with hippocampal neurogenesis and accelerate white matter degeneration, both hallmarks of age-related neurodegeneration[26–29].

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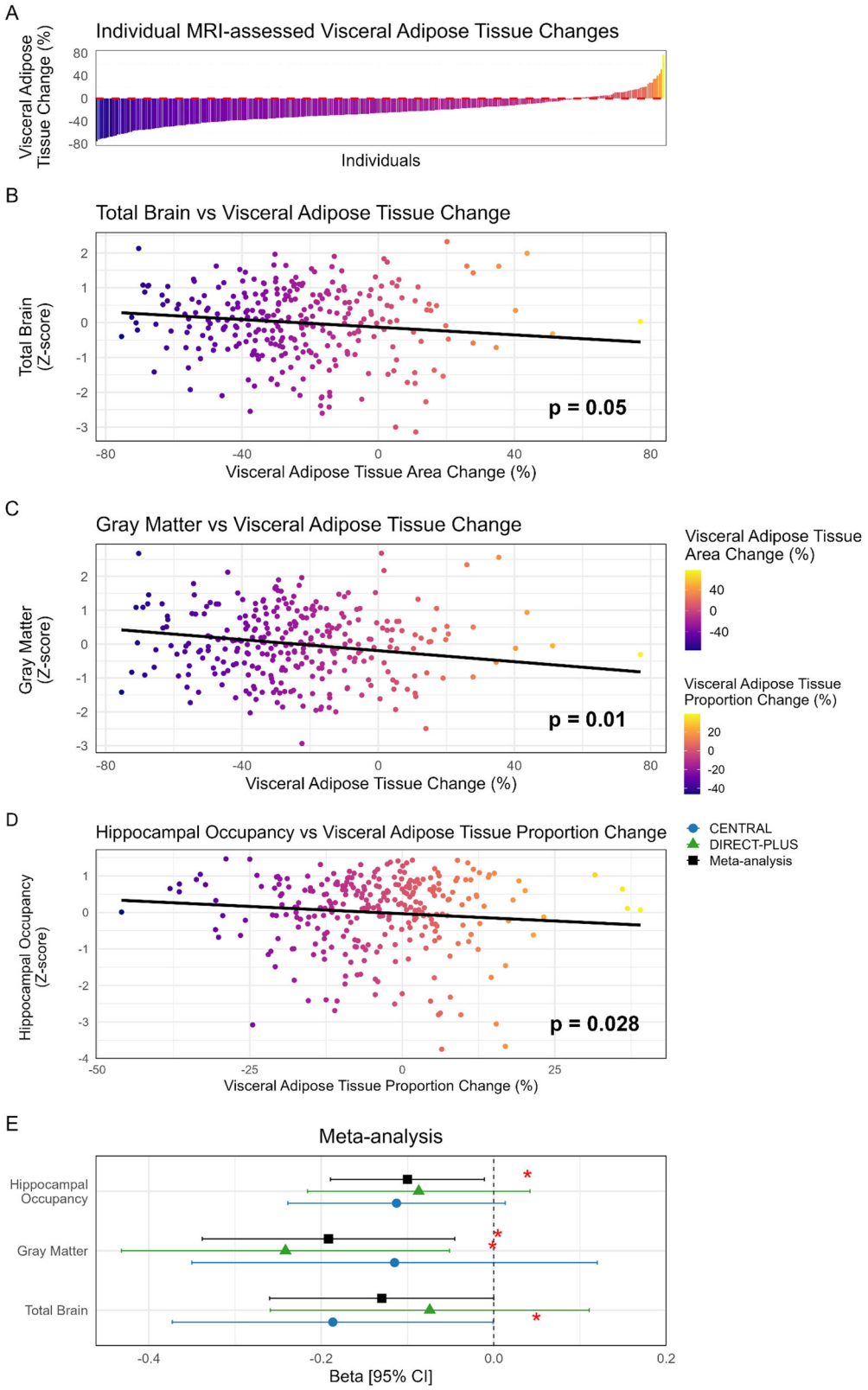

Additionally, VAT is closely linked to insulin resistance and vascular dysfunction, which contribute to impaired cerebral perfusion, microvascular damage, and reduced clearance of neurotoxic proteins such as β-amyloid. Over time, these processes may cumulatively increase vulnerability to structural brain decline[4,30,31]. To further explore the potential metabolic mechanisms linking long-term visceral adiposity exposure to brain atrophy, we conducted sensitivity analyses examining baseline glycemic, lipid, and inflammatory biomarkers as moderators of longitudinal brain change while adjusting for visceral adiposity. Among the examined biomarkers, fasting glucose and HbA1c were uniquely associated with longitudinal brain atrophy, whereas lipid-related and inflammatory markers showed no consistent associations over time. These findings are in line with our previous study, demonstrating that improvements in glycemic control were

Fig. 3 | Visceral Adipose Tissue (VAT) Change During the 18-Month Intervention and Brain Structural Outcomes at FIT Follow-Up ($n = 297$ participants). **A** Individual VAT Change During the 18-Month Intervention. Bar plot displaying the individual percent change in visceral adipose tissue (VAT) across participants, ordered from lowest to highest change. Bars are color-coded according to VAT change magnitude, as indicated by the color scale. A dashed red horizontal line at $y = 0\%$ denotes no change in VAT. **B** Association Between VAT Change and Normalized Total Brain Volume. Scatter plot illustrating the relationship between VAT percent change during the intervention and standardized total brain volume at follow-up (Z-score). Data points represent individual participants, color-coded by VAT change. Associations were evaluated using multivariable linear regression models, with standardized regression coefficients (β) and 95% confidence intervals shown. Two-sided hypothesis testing was used. The fitted regression line, derived from the fixed-effect meta-analysis model, is overlaid in black. The p value for the VAT effect is annotated on the plot. Models were adjusted for age, baseline VAT (log-transformed), BMI change during intervention, and follow-up, Mediterranean diet score at follow-up, dual trial participation, sex, diet group, and their interaction. **C** Association Between VAT Change and Normalized Cortical Gray Matter Volume. Scatter plot depicting the association between VAT change and cortical gray matter volume (Z-score) at long-term follow-up, with individual data points color-coded by VAT change. Associations were evaluated using multivariable linear regression models, with standardized regression coefficients (β) and 95% confidence intervals shown. Two-sided hypothesis testing was used. A fitted regression line from the fixed-effect meta-analysis model is overlaid in black. The p value for the VAT effect is annotated on the plot. Model adjustments are identical to those described for (**B**). **D** Association Between VAT Proportion Change and Hippocampal Occupancy Score. Scatter plot displaying the relationship between VAT proportion change during the intervention and standardized Hippocampal occupancy score at follow-up. Data points are color-coded by VAT proportion change. Associations were evaluated using multivariable linear regression models, with standardized regression coefficients (β) and 95% confidence intervals shown. Two-sided hypothesis testing was used. A fitted regression line from the fixed-effect meta-analysis model is overlaid in black. The p value for the VAT proportion effect is annotated. Model adjustments mirror those in (**B**), except for the substitution of VAT proportion predictors. **E** Forest plot of fixed-effect meta-analysis models ($n = 296$ participants). This panel displays standardized beta coefficients and 95% confidence intervals (CI) for the association between VAT change measures (x-axis) and brain outcomes (y-axis), separately for the CENTRAL and DIRECT-PLUS trials and the pooled estimate from a fixed-effect meta-analysis. Circles, triangles, and squares represent CENTRAL, DIRECT-PLUS, and pooled estimates, respectively. Asterisks indicate statistical significance ($p < 0.05$). Sample sizes were CENTRAL ($n = 167$) and DIRECT-PLUS ($n = 129$) for total brain volume and cortical gray matter analyses, and CENTRAL ($n = 167$) and DIRECT-PLUS ($n = 124$) for hippocampal occupancy analyses. Accordingly, pooled analyses included $n = 296$ for total brain volume and cortical gray matter outcomes, and $n = 291$ for hippocampal occupancy. Trial-specific estimates were derived using multivariable linear regression models adjusted for age at follow-up, baseline VAT (log-transformed), BMI change during the intervention, BMI change during follow-up, sex, Mediterranean diet group, sex × diet group interaction, Mediterranean diet score at follow-up, and dual participation in both trials. Statistical significance was assessed using two-sided hypothesis testing. Exact two-sided p values for significant pooled associations were as follows: for total brain volume, CENTRAL $p = 0.049$; 95% CI: [−0.37, -0.0006], DIRECT-PLUS $p = 0.428$; 95% CI: [−0.26, 0.11], and pooled $p = 0.050$; 95% CI: [−0.26, 0.00002]; for cortical gray matter, CENTRAL $p = 0.335$; 95% CI: [−0.35, 0.12], DIRECT-PLUS $p = 0.013$; 95% CI: [−0.43, −0.05], and pooled $p = 0.010$; 95% CI: [−0.34, −0.05]; and for hippocampal occupancy, CENTRAL $p = 0.079$; 95% CI: [−0.24, 0.01], DIRECT-PLUS $p = 0.184$; 95% CI: [−0.22, 0.04], and pooled $p = 0.028$; 95% CI: [−0.19, −0.01]. Abbreviations: CI, confidence interval; VAT, visceral adipose tissue; Z-score, standardized.

associated with attenuation of brain atrophy[32], suggesting that glycemic dysregulation may represent a key pathway linking visceral adiposity to adverse brain outcomes. Further studies are needed to elucidate the underlying biological mechanisms.

Longitudinal analyses further demonstrated that cumulative exposure to higher levels of abdominal adiposity over time is inversely associated with cognitive performance at follow-up. Specifically, cumulative VAT exposure was significantly associated with lower MoCA and MoCA-MIS scores, independent of BMI, diet adherence, and brain volume.

Repeated measures of both VAT and brain structure across three time points, allowed for the modeling of dynamic trajectories of neuroanatomical change in relation to cumulative adiposity exposure. Importantly, participants with greater cumulative VAT levels exhibited faster rates of brain atrophy across multiple regions, including GM, and HOC, while higher VAT exposure was associated with a greater rate of ventricular expansion (TV), a hallmark of brain aging. These results remained consistent after adjusting for key confounders, supporting the notion that VAT is not only a correlate of cross-sectional brain structure but also a marker of longitudinal neurodegeneration.

These results align with prior longitudinal evidence showing that visceral adiposity predicts cognitive decline across time. For example, the Health, Aging and Body Composition (ABC) study found that CT-measured VAT independently predicted global cognitive decline over several years in older adults, even after adjusting for BMI and baseline cognition[1]. Similarly, autopsy-based research demonstrated that higher levels of abdominal visceral fat were associated with increased odds of clinical dementia in late life[33]. These results reinforce the importance of addressing visceral adiposity as a chronic and modifiable risk factor for long-term neurocognitive health and are further supported by longitudinal neuroimaging studies showing that higher levels of visceral adiposity are associated with accelerated loss of gray and white matter volume over time[2]. Recent data in cognitively normal midlife adults indicate that visceral obesity is associated with greater amyloid burden and cortical thinning in Alzheimer's disease-related regions[34].

The clinical implications of this work are significant. Given the global burden of obesity[35], cognitive decline, and dementia[36], identifying modifiable risk factors for cognitive decline is a critical public health priority[37]. Building on our prior work in the DIRECT-PLUS trial, demonstrating that weight loss following an 18-month lifestyle intervention was associated with improvements in brain age[38], the current findings suggest that targeted VAT reduction, beyond general weight loss, may offer additional and more specific benefits for preserving brain structure. The lack of association between changes in deep and superficial SAT and brain outcomes further highlights the distinct and detrimental impact of VAT[39,40].

In conclusion, our findings indicate that sustained reduction of visceral adiposity is associated with preserved brain structure and improved cognitive outcomes in late midlife. These results emphasize the importance of addressing VAT as a modifiable risk factor for neurodegeneration. Public health efforts and clinical interventions focusing on VAT reduction may play a critical role in promoting healthy brain aging and reducing the risk of cognitive decline.

Methods

Study population

The DIRECT study was conducted from 2005 to 2007, enrolling 322 moderately obese adults (BMI ≥ 27 kg/m^2), or participants with type 2 diabetes (T2D) aged 40 to 65 years, or those with coronary heart disease. The 24-month retention rate was 84.6%[13]. The CASCADE trial was conducted from 2010 to 2012, enrolling 224 adults aged 40 to 75 years with T2D, and achieved a 24-month retention rate of 87%[14,15]. The CENTRAL trial, conducted from 2012 to 2014, enrolled 278 participants with abdominal obesity (WC > 102 cm in men, >88 cm in women) and/or dyslipidemia (triglycerides > 150 mg/dL, HDL-C < 40 mg/dL in men, <50 mg/dL in women), with an 18-month retention rate of 86.3%[9]. The DIRECT-PLUS trial was conducted from 2017 to 2018, enrolling 294

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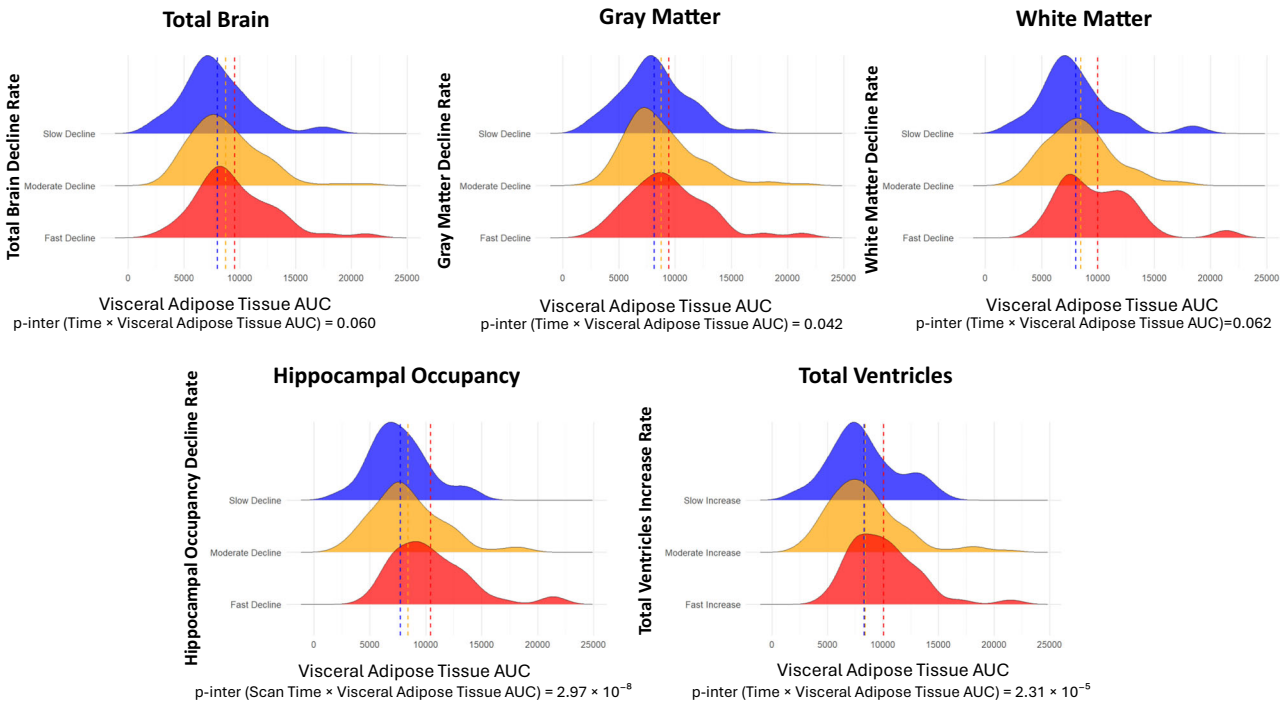

Fig. 4 | Interaction Between Visceral Adipose Tissue (VAT) AUC and Brain Atrophy Rate ($n = 188$ participants). Density plots showing the distribution of cumulative visceral adipose tissue exposure (VAT) across groups of brain volume (% of intracranial volume) change rate: low, moderate, and fast atrophy (or increase, for Total Ventricles). Brain structural measures included: Total brain volume, Gray matter volume, White matter volume, Total ventricular volume, and Hippocampal occupancy score. All brain volumes were measured at three time points: baseline, 18 months, and 5 years. VAT exposure was quantified as the area under the curve (AUC) across the same three time points as the brain volume. Each plot displays the distribution of VAT AUC within each brain change rate group. Color-coded curves represent fast (red), moderate (orange), and slow (blue) trajectories. Dashed vertical lines indicate the mean VAT AUC within each group. *p*-values represent the interaction term (Time × VAT AUC) from linear mixed-effects models in which both VAT exposure and time were modeled as continuous variables, testing whether the association between VAT and brain structure differs over time. Two-sided hypothesis testing was used. All models were adjusted for age, sex, body mass index, and Mediterranean diet score. Abbreviations: VAT, visceral adipose tissue; AUC, area under the curve.

participants with abdominal obesity over the age of 30, and achieved an 18-month retention rate of 89.8%[10–12]. Detailed exclusion criteria for each trial and sample size calculation are provided in Supplementary Methods 1. Lifestyle intervention descriptions are provided in Supplementary Methods 2. All trials were approved by the Medical Ethics Board and Helsinki Committee of Soroka University Medical Center, and all participants provided written informed consent. No financial compensation or gifts were provided. All 4 randomized controlled trials (DIRECT, CASCADE, CENTRAL, and DIRECT-PLUS) included in this work have been completed, and their primary outcomes have been published previously. Pooled data from the four RCTs comprised 1,118 observations. However, 237 participants had participated in more than one trial, yielding a final unique sample of 881 eligible participants. For the FIT follow-up study, we successfully reached 647 participants (73.4%) for follow-up assessments, including 48 deceased cases. Brain MRI structural analyses were completed for 533 participants at follow-up.

Data collection

Abdominal adipose depots were quantified using 3-Tesla MRI scanners in CENTRAL and DIRECT-PLUS RCTs and in the FIT follow-up study, using validated protocols described in the original publications[9,10]. VAT, deep SAT, and superficial SAT areas were measured at standardized anatomical levels (L4-L5, L5-S1) and quantified using semi-automated MATLAB-based software. Manual tracing of the fascia superficialis distinguished superficial from deep SAT. Observers were blinded to intervention assignment and time point. Reproducibility of VAT quantification was high (inter- and intra-rater reliability for $n = 30$: $r > 0.96$; $p < 0.001$)[9,10]. Further details on MRI acquisition parameters are provided in Supplementary Methods 2.

Brain structure volumes were assessed at three time points: baseline and 18 months during the DIRECT-PLUS trial, and at the FIT follow-up. Imaging was performed using a 3D T1-weighted turbo field echo (T1-TFE) sequence with 1.0 mm isotropic voxel resolution. Brain volumes were quantified using NeuroQuant® Software Version 4.1.2 (https://www.cortechs.ai/), an FDA-approved, fully automated software for volumetric brain analysis. Key metrics included brain structural metrics modeled as normalized region-specific volumes of the intracranial volume (%ICV), including TB volume, cortical GM, WM, TV volume, and HOC. Further details on MRI acquisition parameters and the NeuroQuant analysis pipeline are provided in Supplementary Methods 3.

Cognitive performance was assessed using MoCA with a score range: 0–30, and the MoCA-MIS with a score range: 0–15. Anthropometric indices, demographic data (including sex, as determined based on medical records), fasting blood biomarkers (further detailed in Supplementary Methods 4), and structured lifestyle questionnaires regarding diet, smoking habits, clinical data, and physical activity (PA) levels (quantified as metabolic equivalent of task (MET)-hours per week)[41] were collected at baseline, end of intervention, and follow-up (5–16 years post-RCT), with dietary patterns additionally evaluated using the validated 14-item MED Diet Adherence Screener at follow-up[42]. Missing MED score data ($n = 10$, 1.9%) were imputed using k-nearest neighbours (KNN) imputation[43].

Statistical analyses

Outcomes and data presentation. The primary outcome variables were the MoCA cognitive test score and brain structural measures, including TB, GM, WM, TV, and HOC. Abdominal adipose tissue depots, including VAT, deep SAT, and superficial SAT, were also considered as primary outcomes as well as exposures. Secondary outcome variables included demographic parameters, anthropometric, and blood biomarker measurements.

Continuous variables are presented as means with standard deviations (SD), and categorical variables as frequencies and percentages. The normality of continuous variables was assessed using histograms and the Shapiro-Wilk test. Non-normally distributed variables were log-transformed prior to modeling. For analyses involving multiple comparisons, FDR correction was applied using the Benjamini-Hochberg procedure. Statistical significance was set a priori at $p < 0.05$. *Cross-sectional Analyses* Using data from FIT follow-up study, linear regression models were used cross-sectionally to examine the associations between abdominal adipose depots and MoCA score as the outcome variable. Each adipose depot served as the primary exposure, and interaction terms between adipose depot and brain volume measures were included to assess whether associations with MoCA were modified by brain volumes. Models were adjusted for age, sex, BMI, and MED diet adherence score. We additionally performed a sensitivity analysis in which BMI replaced VAT as the primary exposure while VAT was included as an adjustment covariate. All continuous predictors were standardized (z-scores) prior to analysis. While adipose depots were modeled as continuous variables in statistical analyses, tertile stratification was applied in figures to aid visual interpretation of trends.

Longitudinal visceral adipose tissue (VAT) exposure and AUC calculation. For the CENTRAL and DIRECT-PLUS trials, cumulative adiposity exposure was calculated as AUC using the trapezoidal method[44], based on participants with complete data from all three time points (baseline, 18 months, and 5 or 10 years of follow-up, in the DIRECT-PLUS and CENTRAL trials, respectively). AUC values were normalized by follow-up duration (years) to account for differences in time intervals. Changes in anthropometric and abdominal adipose depots were calculated as relative percent changes from baseline to 18 months, and from 18 months to FIT follow-up, using the formula: $((\text{Time}_{later} - \text{Time}_{earlier})/\text{Time}_{earlier}) \times 100$.

Longitudinal pooled data analysis. In the CENTRAL and DIRECT-PLUS subset analyses, fixed-effect meta-analysis based on linear regression models assessed associations between adiposity AUCs and cognitive outcomes (MoCA total and MoCA-MIS scores assessed at the FIT follow-up, 5 and 10 years post-intervention). For participants who joined both trials, only data from their initial intervention were included in these analyses. Models included age, sex, BMI, MED score, and brain volume at follow-up as covariates. We additionally performed a sensitivity analysis in which BMI AUC replaced adiposity AUCs as the primary exposure while VAT was included as an adjustment covariate. All continuous predictors were standardized (z-scores) prior to analysis, and beta estimates with 95% confidence intervals (CI) were reported. Additional fixed-effect meta-analysis models were used to examine whether reductions in each adipose depot predicted brain structure and cognitive performance outcomes at 5 and 10-year follow-up. All brain outcomes and adipose depots predictors were standardized (Z-scores) prior to modeling. Models were adjusted for baseline fat depot, BMI changes during intervention, and follow-up, MED score assessed at follow-up, dual participation in both trials, sex, diet group, and their interactions.

Longitudinal analysis of brain atrophy and adiposity exposure (DIRECT-PLUS subset). For the DIRECT-PLUS subset analysis, longitudinal changes in brain volumes were modeled using LMMs[45], which included random intercepts for participants. Brain volume measures at baseline, end of intervention (18 months), and 5-year follow-up were modeled as the dependent variable, with time between brain assessments (in months), adipose depot AUC, and their interaction (Time × adipose depot AUC) as predictors. All continuous predictors were standardized (z-scores) prior to analysis. Covariates included age, sex, BMI, and MED score assessed at follow-up time. APOE ε4 carrier status was additionally included as a covariate, and interactions with time and VAT AUC were tested.

Changes in brain volumes were analyzed as continuous variables; however, for clarity of presentation, stratifications were applied in the figures to illustrate three categories of brain volume decline: fast, moderate, and slow. For that end, individual slopes of brain volume change were computed using subject-level linear models, with time as the independent variable. These slopes were annualized by standardizing time intervals and multiplying by 12. Participants were then stratified into three categories based on their TB slope distribution: Fast Decline (lowest quartile), Moderate Decline (middle 50%), and Slow Decline (highest quartile). Thresholds for stratification were based on the observed distribution of annualized brain volume slopes, with the lower quartile (Fast Decline- reflecting approximately-0.3 per year) and the upper quartile (Slow Decline -reflecting approximately-0.12% per year). The intermediate 50% (Moderate Decline) fell between these two values, aligning well with previously reported ranges of age-related brain atrophy in the literature (see Supplementary Table 1, and Supplementary Table 2 for the calculation of the biological rationale underlying this classification). To ensure consistency in visualization, the same quartile-based classification was applied across all brain regions. For brain regions expected to increase in volume with atrophy (TV), the categories were reversed: "Fast Increase", "Moderate Increase", and "Slow Increase". *p*-values presented in figures reflect the interaction term from the LMM (Time × VAT AUC). We additionally performed a sensitivity analysis in which BMI AUC replaced VAT AUC as the primary exposure while VAT was included as an adjustment covariate.

All statistical analyses were performed using R version 4.4.1. Key packages included metafor[46], ggplot2[47], dplyr[48], tidyr[49], lme4[50], MESS[51], ggridge[52], DiagrammerR[53], and gtsummary[54].

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The clinical data are available under restricted access due to ethical and legal restrictions related to the approved study protocol and informed consent. The data and code are available from the principal investigator (irish@bgu.ac.il) upon request, subject to approval and compliance with institutional and regulatory data-protection requirements.

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Author contributions

D.P., H.K., O.K., D.T.G.T., L.A., and N.E.K., and IShai conceptualized the FIT and performed the data collection. D.P. and H.K. performed the statistical analysis, interpreted the data, reviewed the literature, and drafted the manuscript. D.P. and A.K. performed the MRI-based brain analyses; H.K. and H.Z. performed the visceral fat analysis; T.A., A.Y., and I.H. contributed to the cognitive analyses. IShelef supervised the MRI acquisition. B.I. and U.C. analyzed the data. IShai is the principal investigator of the DIRECT-PLUS trial. All authors contributed to the interpretation of data and reviewed this work's language and intellectual content. MStumvoll, FrB, V.W., C.B., Y.C., G.B., A.R., U.Y., A.Y.M., G.T., M.B., L.Q., MSalti, F.B.H., D.D.W., M.J.S., IShelef, G.A., and IShai revised the final draft of the study and approved the final version.

Competing interests

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Additional information

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