

Sustained Visceral Fat Loss is Associated with Attenuated Brain Atrophy and Improved Cognitive Function in Late Midlife

Corresponding Author: Professor Iris Shai

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

Visceral fat has been increasingly recognized as an independent factor affecting brain health and cognition. In the Follow-Interventions-Trial (FIT) project, investigators evaluated long-term outcomes from four lifestyle randomized clinical trials to determine whether persistent reductions in visceral adipose tissue (VAT) influence brain structure and cognitive performance years after intervention. Among participants followed for 5–16 years, lower cumulative VAT exposure was associated with greater total brain, gray matter, and hippocampal volumes, higher cognitive scores, and slower rates of brain atrophy. Importantly, reductions in VAT during intervention predicted better brain outcomes independent of overall weight loss, suggesting that specifically targeting visceral fat may be a key strategy for promoting healthy brain aging. This important study demonstrates that sustained reductions in VAT resulting from lifestyle interventions are associated with slower brain atrophy over time, which in turn supports better cognitive outcomes, in this study with a maximal follow-up of 10 years. Several methodological limitations hamper enthusiasm.

The MoCA is a limited screening tool with relatively low sensitivity for detecting cognitive impairment, particularly in younger individuals such as those in this cohort (average age 61 years at follow up). In this context, the reported mean MoCA score of 23.6 is unexpectedly low, suggesting cognitive performance within the MCI to early dementia range for a relatively young sample. Please verify that this value is correct or clarify any methodological explanations for this finding. If accurate, consider analyzing the data using established MoCA cutoffs (26–30 for normal cognition, 18–25 for MCI, and below 18 for dementia) to evaluate whether visceral fat (and its changes) predicts incidence of MCI and dementia.

The interactions of brain volume with VAT on cognition suggest that once brain atrophy is substantial, additional visceral fat may no longer meaningfully affect cognition. The focus of the authors in the discussion is on the group with greater brain volumes. However, an alternative explanation is that cognitive decline may have already progressed beyond the range where VAT contributes detectably. That would once again suggest particularly low cognitive functioning in a rather young sample.

Were other regions assessed for fat quantification in the MRI analysis? Evidence suggests that fatty liver and pancreas are associated with reduced brain volumes and poorer cognitive performance. Exploring whether lifestyle-induced changes in fat levels within these regions affect cognition would be of great interest and would help clarify if the effects found are specific to VAT.

The authors appropriately adjusted for BMI in all analyses, ensuring that the assessment of VAT reflected effects independent of overall adiposity. However, the manuscript would benefit from parallel analyses using BMI to determine whether the observed relationships are truly specific to VAT (although admittedly, the lack of associations with SAT support a specific effect of VAT). The evidence linking BMI in midlife with cognitive decline and incident dementia is robust, and BMI measurement is considerably easier and more cost-effective than VAT assessment.

Adjustment for multiple comparisons was not applied in a study with a very large number of analyses.

The FIT cohort is predominantly male. It is important to address whether there is a selection bias. Also, despite the

male/female disproportionate ratio, exploring interactions between the effects of the lifestyle intervention and sex on each outcome is essential, given prior evidence suggesting stronger effects in men and the importance of tailoring personalized interventions in the future.

Reviewer #2

(Remarks to the Author)

The results of your manuscript are undeniably compelling and warrant publication in this journal. A couple of key points:

1. You don't really know in your specific cohort what is driving the increased atrophy rate as you don't have AD biomarker data (PET, blood biomarkers). This is a limitation you should note in your discussion.
2. You need to clarify if any of your cohort were on anti-obesity medications, specifically the incretin analogs (semaglutide, tirzepatide, etc.) at the time of their evaluations. I doubt it given when these medications came out but you need to state this clearly in the manuscript.
3. Your literature citations double count this citation (#2, #45):
Raji CA, Meysami S, Hashemi S, et al. Visceral and subcutaneous abdominal 785 fat predict brain volume loss at midlife in 10,001 individuals. *Aging and Disease*. 786 2024;15(4):1831.

I'd keep that reference for #2 and for #45 you need to modify that sentence to note that i) VAT has been linked to amyloid deposition as noted in this paper from the same group:

Dolatshahi M, Commean PK, Rahmani F, Liu J, Lloyd L, Nguyen C, Hantler N, Ly M, Yu G, Ippolito JE, Sirlin C, Morris JC, Benzinger TLS, Raji CA. Alzheimer Disease Pathology and Neurodegeneration in Midlife Obesity: A Pilot Study. *Aging Dis*. 2024 Aug 1;15(4):1843-1854. doi: 10.14336/AD.2023.0707. PMID: 37548931; PMCID: PMC11272197.

You also need to note foundational literature linking BMI to brain atrophy to being with while also acknowledging that this original work lacked the benefit for the more detailed evaluations you have now:

Raji CA, Ho AJ, Parikshak NN, Becker JT, Lopez OL, Kuller LH, Hua X, Leow AD, Toga AW, Thompson PM. Brain structure and obesity. *Hum Brain Mapp*. 2010 Mar;31(3):353-64. doi: 10.1002/hbm.20870. PMID: 19662657; PMCID: PMC2826530.

4. You should also cite the Lancet Commission, noting obesity as a dementia risk factor while also taking care to note that it does not separately characterize VISCERAL obesity as the main component of obesity driving the risk:
Livingston G, Huntley J, Liu KY, Costafreda SG, Selbæk G, Alladi S, Ames D, Banerjee S, Burns A, Brayne C, Fox NC, Ferri CP, Gitlin LN, Howard R, Kales HC, Kivimäki M, Larson EB, Nakasujja N, Rockwood K, Samus Q, Shirai K, Singh-Manoux A, Schneider LS, Walsh S, Yao Y, Sommerlad A, Mukadam N. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet*. 2024 Aug 10;404(10452):572-628. doi: 10.1016/S0140-6736(24)01296-0. Epub 2024 Jul 31. PMID: 39096926.

This can be separately aligned with newer Lancet guidelines noting that obesity has to be identified by more than BMI and other measures such as waist circumference, DEXA and even MRI may be considered in refining our obesity definitions:
Rubino F, Cummings DE, Eckel RH, Cohen RV, Wilding JPH, Brown WA, Stanford FC, Batterham RL, Farooqi IS, Farpour-Lambert NJ, le Roux CW, Sattar N, Baur LA, Morrison KM, Misra A, Kadowaki T, Tham KW, Sumithran P, Garvey WT, Kirwan JP, Fernández-Real JM, Corkey BE, Toplak H, Kokkinos A, Kushner RF, Branca F, Valabhji J, Blüher M, Bornstein SR, Grill HJ, Ravussin E, Gregg E, Al Busaidi NB, Alfari NF, Al Ozairi E, Carlsson LMS, Clément K, Després JP, Dixon JB, Galea G, Kaplan LM, Laferrère B, Laville M, Lim S, Luna Fuentes JR, Mooney VM, Nadglowski J Jr, Urudinachi A, Olszanecka-Glinianowicz M, Pan A, Pattou F, Schauer PR, Tschöp MH, van der Merwe MT, Vettor R, Mingrone G. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol*. 2025 Mar;13(3):221-262. doi: 10.1016/S2213-8587(24)00316-4. Epub 2025 Jan 14. Erratum in: *Lancet Diabetes Endocrinol*. 2025 Mar;13(3):e6. doi: 10.1016/S2213-8587(25)00006-3. PMID: 39824205; PMCID: PMC11870235.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

This reviewer appreciates the authors' efforts to respond fully to the concerns raised.

Reviewer #2

(Remarks to the Author)

I feel the authors did an excellent job at addressing all of my comments.

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"Sustained Visceral Fat Loss Attenuates Brain Atrophy and Enhances Cognitive Function in Late Midlife; The MRI Follow-Intervention-Trials (FIT) project"

Point-by-point response to the Reviewers' comments

Reviewer #1:

Visceral fat has been increasingly recognized as an independent factor affecting brain health and cognition. In the Follow-Interventions-Trial (FIT) project, investigators evaluated long-term outcomes from four lifestyle randomized clinical trials to determine whether persistent reductions in visceral adipose tissue (VAT) influence brain structure and cognitive performance years after intervention. Among participants followed for 5–16 years, lower cumulative VAT exposure was associated with greater total brain, gray matter, and hippocampal volumes, higher cognitive scores, and slower rates of brain atrophy. Importantly, reductions in VAT during intervention predicted better brain outcomes independent of overall weight loss, suggesting that specifically targeting visceral fat may be a key strategy for promoting healthy brain aging. This important study demonstrates that sustained reductions in VAT resulting from lifestyle interventions are associated with slower brain atrophy over time, which in turn supports better cognitive outcomes, in this study with a maximal follow-up of 10 years. Several methodological limitations hamper enthusiasm.

We greatly appreciate the recognition that our work supports targeting visceral fat as a potential strategy to promote healthy brain aging, and we hope that the revised manuscript satisfactorily addresses the remaining methodological concerns of the reviewer.

1. The MoCA is a limited screening tool with relatively low sensitivity for detecting cognitive impairment, particularly in younger individuals such as those in this cohort (average age 61 years at follow up). In this context, the reported mean

MoCA score of 23.6 is unexpectedly low, suggesting cognitive performance within the MCI to early dementia range for a relatively young sample. Please verify that this value is correct or clarify any methodological explanations for this finding. If accurate, consider analyzing the data using established MoCA cutoffs (26–30 for normal cognition, 18–25 for MCI, and below 18 for dementia) to evaluate whether visceral fat (and its changes) predicts incidence of MCI and dementia.

Response: We thank the reviewer for this important and insightful comment. We have carefully re-checked our data and confirm that the mean MoCA score of 23.6 at follow-up is correct.

Regarding the relatively low mean MoCA score observed in our FIT population, we agree that this value may appear below the normative range typically described in general population samples. According to the original MoCA validation study, a score of ≥ 26 is commonly used as the cutoff for normal cognition (Nasreddine et al., 2005, <https://doi.org/10.1111/j.1532-5415.2005.53221.x>). More recent work, however, has shown that a cutoff score of 23/30, rather than the initially recommended 26/30, reduces the false-positive rate and provides better overall diagnostic accuracy (Carson et al., 2017, <https://doi.org/10.1002/gps.4756>).

In relation to the important point raised by the reviewer regarding the relatively low mean MoCA score, the FIT cohort is not a general population sample. Participants were selected on the basis of abdominal obesity/dyslipidemia, or type 2 diabetes (CASCADE trial). Specifically, the follow-up analyses in the CENTRAL and DIRECT-PLUS intervention trials included individuals who were enrolled because of abdominal obesity and/or dyslipidemia.

Recent studies have reported that visceral adiposity is associated with lower cognitive scores, such as in a cross-sectional analysis of adults around 60 years of age (Anand et al., 2022. doi:10.1001/jamanetworkopen.2021.46324). Thus, although this may appear to be a relatively “healthy” community-dwelling population, prior abdominal obesity or diabetes is, according to the literature, consistently linked to lower cognitive performance.

In our study, we analyzed MoCA as a continuous variable to preserve statistical power and to capture the full range of cognitive performance, rather than relying solely on categorical groupings. However, as suggested by the reviewer, we conducted a complementary analysis in which MoCA scores were categorized into three clinically relevant groups (26–30, 18–25, and <18). Because MoCA data were available only at the follow-up visit, this analysis reflects cognitive status at the follow-up time point rather than the incidence of new events. In this analysis, only higher visceral adipose tissue (VAT) was significantly associated with being in the 18-25 range ($\beta = 0.21$, $p < 0.01$) compared with the normal cognition group after adjustment for age, sex, BMI, and MED score. In a manner familiar from our main analyses in which MoCA was modeled as a continuous variable, among participants with already low MoCA score (<18), further differences in VAT were no longer meaningfully associated with cognitive status. No significant associations were observed for SSAT or DSAT. Attached below the results based on these MoCA score groups:

FatType	18–25	<18
VAT	0.21**	0.11
SSAT	0.07	0.15
DSAT	0.11	0.02

These results have been added as a complementary analysis in the Results section **(Results lines 322-329):** "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 light of the reviewer's comment, we have added a dedicated paragraph in the Discussion that directly addresses the relatively low MoCA distribution **(Discussion lines 688-692):**

"The mean MoCA score in our cohort was relatively low, according to the original MoCA validation study. 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."

Taken together, the clinical characteristics of our participants ,who were recruited on the basis of abdominal obesity and dyslipidemia, and the evidence linking obesity with lower cognitive performance support the plausibility of the observed MoCA mean score in our trial. These complementary categorical findings are fully consistent with our primary continuous-scale analyses and further reinforce the visceral adipose–cognitive associations reported in the manuscript.

We hope that this clarification and the additional analyses address the reviewer's concerns and meet the reviewer's expectations.

2. The interactions of brain volume with VAT on cognition suggest that once brain atrophy is substantial, additional visceral fat may no longer meaningfully affect cognition. The focus of the authors in the discussion is on the group with greater brain volumes. However, an alternative explanation is that cognitive decline may have already progressed beyond the range where VAT contributes detectably. That would once again suggest particularly low cognitive functioning in a rather young sample.

Response: We agree with the reviewer thoughtful comment and for highlighting the implications of the brain volume × VAT interaction for interpreting cognitive performance in these relatively young participants.

We have also incorporated the reviewer's alternative interpretation of the interaction between brain volume, VAT, and cognition. Specifically, in addition to our original view that VAT appears most salient as a cognitive correlate in individuals with relatively preserved brain volume, we now note that, among participants with more pronounced

brain atrophy, cognitive decline may already have progressed to a level at which additional VAT no longer makes a detectable incremental contribution to performance.

Discussion (lines 679-688): “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.”

3. Were other regions assessed for fat quantification in the MRI analysis?

Evidence suggests that fatty liver and pancreas are associated with reduced brain volumes and poorer cognitive performance. Exploring whether lifestyle-induced changes in fat levels within these regions affect cognition would be of great interest and would help clarify if the effects found are specific to VAT.

Response: We appreciate the reviewer’s insightful comment and agree that ectopic fat in organs such as the liver and pancreas is relevant to brain health and cognition. Unfortunately, in the present study, quantitative MRI measures of hepatic and pancreatic fat were not available. However, within the adipose tissue measures available in our trial, a clear pattern emerged: visceral adipose tissue (VAT) showed the strongest and most consistent associations with brain volumes and cognition, whereas subcutaneous depots (superficial and deep SAT) did not. We clarified this point in the Discussion and explicitly acknowledge the lack of liver and pancreatic fat quantification as a limitation and a key direction for future research.

Discussion (lines 633-641): “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.”

4. The authors appropriately adjusted for BMI in all analyses, ensuring that the assessment of VAT reflected effects independent of overall adiposity. However, the manuscript would benefit from parallel analyses using BMI to determine whether the observed relationships are truly specific to VAT (although admittedly, the lack of associations with SAT supports a specific effect of VAT). The evidence linking BMI in midlife with cognitive decline and incident dementia is robust, and BMI measurement is considerably easier and more cost-effective than VAT assessment.

Response: The reviewer raises an important point, and we fully agree that BMI is an accessible and clinically relevant measure. In our primary analyses, we adjusted all VAT models for BMI to ensure that the reported associations reflect effects of visceral adiposity that are independent of overall adiposity. In response to the reviewer’s suggestion, we conducted additional parallel analyses in which BMI was entered as the primary adiposity exposure instead of VAT, both (i) without adjustment for VAT and (ii) in models that additionally included VAT.

Across these complementary analyses, BMI showed no significant interactions with brain structure in relation to cognitive outcomes, in contrast to the VAT–brain interactions observed in our cross-sectional analyses. In the longitudinal models, the interaction between BMI exposure and time of brain scan was not significant, with only a trend-level association for total ventricular volume ($p < 0.10$). These findings may further support the specific relevance of abdominal adiposity beyond overall BMI.

Approximately 43% of the FIT cohort were aged 65 years or older, an age range commonly classified as older adults by the National Institute on Aging (<https://www.nih.gov/nih-style-guide/age>, last reviewed on June 12, 2025). In this population, prior literature has described a BMI “paradox,” whereby both low and very high BMI can be associated with increased risk, while central adiposity remains

detrimental even among older adults with relatively low BMI. The absence of significant BMI-brain interactions, alongside the observed VAT-brain associations, is therefore consistent with the notion that visceral fat more directly captures the adiposity-related risk for brain health. Finally, BMI change during the 18-month intervention was significantly associated only with MoCA score at follow-up, and not with brain structural measures at FIT follow-up. This pattern may suggest that changes in BMI relate to cognitive performance through additional pathways that are not fully mediated by brain atrophy, such as vascular, metabolic, or functional mechanisms.

These new analyses have been added to the Statistics and Results section, and the extended models are summarised in the Supplementary Material.

Cross-sectional Analysis, Fig 2A, Results, lines 330–335:

“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 Figure 2A, Table 1.2). The BMI-brain interaction terms were consistently non-significant, in contrast to the significant VAT-brain interactions observed in our primary analyses.”

Statistics, lines 832-834: “We additionally performed a sensitivity analysis in which BMI replaced VAT as the primary exposure while VAT was included as an adjustment covariate. “

Longitudinal BMI AUC Analysis, Fig 2B, Results, lines 404–406:

“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 Figure 2B, Supplementary Table 2.2).

Statistics, lines 853-855: “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. “

Longitudinal change in BMI during the intervention and cognition Fig 3 (Results, lines 424–428):

“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 Figure 3, Table 3.2). In contrast, this BMI change was negatively associated with MoCA score at follow-up ($\beta = -0.153$, $p = 0.014$). “

Longitudinal LMM with BMI AUC and brain structure, Fig 4 (Results, 545-548):

“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 Figure 4, Table 4.2).“

Statistics, lines (894-896): “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.“

New Discussion Paragraph Derived From the Additional BMI Analyses (**Discussion, lines 652–660**) :

“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.“

5. Adjustment for multiple comparisons was not applied in a study with a very large number of analyses.

Response: We thank the reviewer for this important point regarding correction for multiple comparisons. Studies have demonstrated associations between visceral fat and

both brain structure and cognitive function, providing a biological and empirical rationale for focusing on VAT as the main exposure of interest.

Our hypothesis was that long-term exposure to visceral adiposity may influence the rate of brain atrophy and cognitive decline over time. We performed false-discovery rate (FDR) in analyses involving multiple comparisons, which is also added to the statistical section (lines 823-825: "For analyses involving multiple comparisons, FDR correction was applied using the Benjamini-Hochberg procedure"). However, we were concerned that applying (FDR) correction across a very small set of five brain regions would substantially increase the probability of false-negative findings. Analyses of the SAT and DSAT measures did not yield significant associations with brain structure, reinforcing the specificity of our VAT-based hypothesis.

Nevertheless, in response to the reviewer's request, we applied FDR correction across the five brain outcomes at FIT follow-up. After correction, only gray matter volume, white matter volume, and hippocampal occupancy score remained significant at $FDR < 0.10$ in relation to VAT, whereas all associations with SAT and DSAT remained clearly non-significant, as shown in Supplementary Figure 2A. This additional step is fully detailed in the extended models presented in the Supplementary Material. For example, in the longitudinal models, both hippocampal occupancy score and lateral ventricle volume remained significant after FDR correction ($FDR < 0.001$; Supplementary Figure 4, Supplementary Table 4.1).

6. The FIT cohort is predominantly male. It is important to address whether there is a selection bias. Also, despite the male/female disproportionate ratio, exploring interactions between the effects of the lifestyle intervention and sex on each outcome is essential, given prior evidence suggesting stronger effects in men and the importance of tailoring personalized interventions in the future.

Response: This comment highlights the importance of considering sex-specific responses when aiming to develop personalized lifestyle interventions.

It is true that the FIT cohort includes a higher proportion of men, a limitation shared by all of our intervention studies conducted in this unique workplace setting. This reflects

the actual demographic profile of the research site rather than a recruitment bias. At the same time, the closed and highly controlled workplace environment offers important methodological advantages, including the ability to directly monitor and standardize the provided lunch and to deliver intensive, multidisciplinary on-site dietary guidance throughout the intervention.

In response to the reviewer's request, we conducted sex-by-intervention interaction analyses in both DIRECT-PLUS and CENTRAL. These analyses did not identify significant sex-intervention interactions for any of the outcomes (Supplementary Figure 2 and Supplementary Table 3.3). We observed significant main effects of sex on Total brain volumes (women showed lower total brain volume at follow-up, $b=-0.617$, $p=0.004$), consistent with well-established sex differences in neuroanatomy reported in the literature. However, the dietary intervention effects themselves, as well as sex-by-intervention interactions, were not significant.

We have added the results of the sex-by-intervention interaction analyses to the Results section (**Results, lines 428–429**): "Sex-by-intervention interaction did not reach statistical significance in any of the models (Supplementary Figure 3, Table 3.3)"

Reviewer #2:

The results of your manuscript are undeniably compelling and warrant publication in this journal. A couple of key points:

We thank the reviewer for the positive feedback on the importance and strength of our results, and we appreciate the thoughtful comments.

1. You don't really know in your specific cohort what is driving the increased atrophy rate as you don't have AD biomarker data (PET, blood biomarkers). This is a limitation you should note in your discussion.

Response: We agree that the absence of AD biomarkers is a limitation, and in accordance with your suggestion, we have added a statement addressing this limitation in the Discussion section, **lines 641-644**): "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."

2. You need to clarify if any of your cohort were on anti-obesity medications, specifically the incretin analogs (semgalutide, tirzepatide, etc.) at the time of their evaluations. I doubt it given when these medications came out but you need to state this clearly in the manuscript.

Response: We appreciate the reviewer for this highly relevant and timely comment. In our RCT trials, data on incretin-based anti-obesity medications were not collected, as these agents were not in common clinical use during the study period. In our current follow-up dataset, however, self-reported information regarding the use of these medications is available. To address this, we conducted additional sensitivity analyses adjusting for incretin medication use. As shown in the extended models in the Supplementary Material, medication use was not significantly associated with MoCA scores and did not alter the results. A clarifying sentence has been added to the Results section (**Results, lines 335–338**). "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 Figure 2A Table 1.3)."

3. Your literature citations double count this citation (#2, #45):

Raji CA, Meysami S, Hashemi S, et al. Visceral and subcutaneous abdominal fat predict brain volume loss at midlife in 10,001 individuals. Aging and Disease. 2024;15(4):1831.

I'd keep that reference for #2 and for #45 you need to modify that sentence to note that i) VAT has been linked to amyloid deposition as noted in this paper from the same group:

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Dis. 2024 Aug 1;15(4):1843-1854. doi: 10.14336/AD.2023.0707. PMID: 37548931; PMCID: PMC11272197.

Response: We thank the reviewer for bringing our attention to the duplicated citation. We have corrected this error by keeping the original reference as citation #2 and revising citation #45 accordingly. In line with the reviewer's suggestion, we have now added the Dolatshahi et al. (2024) study, which links visceral adiposity to amyloid pathology and neurodegeneration in midlife obesity.

(Discussion lines 739-741): "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."

You also need to note foundational literature linking BMI to brain atrophy to being with while also acknowledging that this original work lacked the benefit for the more detailed evaluations you have now:

Raji CA, Ho AJ, Parikshak NN, Becker JT, Lopez OL, Kuller LH, Hua X, Leow AD, Toga AW, Thompson PM. Brain structure and obesity. Hum Brain Mapp. 2010 Mar;31(3):353-64. doi: 10.1002/hbm.20870. PMID: 19662657; PMCID: PMC2826530.

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This can be separately aligned with newer Lancet guidelines noting that obesity

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Response: We thank the reviewer for highlighting these important references, which enrich the conceptual of the manuscript. In response, we have incorporated the suggested references and revised the discussion accordingly. Below we provide the updated paragraph (**Discussion lines 660-667**):

“Our MRI-based VAT measure extends prior BMI-based literature by isolating the metabolically active component of obesity most relevant to neurodegeneration, aligning with updated obesity definitions that call for adiposity measures beyond BMI. 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, our findings suggest that visceral fat represents a particularly harmful obesity phenotype that may disproportionately drive neurodegenerative risk.”