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The quantity and quality of cardiovascular fat at midlife and future cognitive performance among women: The SWAN cardiovascular fat ancillary study

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Abstract

Introduction: Cardiovascular fat is a novel cardiovascular risk factor that may link to dementia. Fat volume and radiodensity are measurements of fat quantity and quality, respectively. Importantly, high fat radiodensity could indicate healthy or adverse metabolic processes.

Methods: The associations of cardiovascular fat [including epicardial, paracardial, and thoracic perivascular adipose tissue (PVAT)] quantity and quality assessed at mean age of 51 with

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subsequent cognitive performance measured repeatedly over 16 years of follow-up were examined using mixed models among 531 women.

Results: Higher thoracic PVAT volume was associated with a higher future episodic memory [β(SE)=0.08(0.04), p=0.033], while higher thoracic PVAT radiodensity with lower future episodic [β(SE)=−0.06(0.03), p=0.045] and working [β(SE)=−0.24 (0.08), p=0.003] memories. The latter association is prominent at higher volume of PVAT.

Discussion: Midlife thoracic PVAT may have a distinct contribution to future cognition possibly due to its distinct adipose tissue type- brown fat and anatomical proximity to the brain circulation.

Keywords

Menopause; epicardial adipose tissue; paracardial adipose tissue; mediastinal fat; thoracic perivascular adipose tissue; processing speed; working memory; episodic memory

1. BACKGROUND

Women account for about two-thirds of Alzheimer's disease cases among individuals over 65 years old in the US. (1) The deposition of brain amyloid β (Aβ) can be tracked back to midlife, (2) which overlaps with the menopause transition. As women traverse menopause, they experience an acceleration of cardiovascular disease (CVD) risk (3) including a gain in fat mass, (4) particularly abdominal visceral fat. (5) Midlife cardiovascular risk has been linked to a faster cognitive decline (6) and a higher risk of dementia in later life. (7) In addition, abdominal visceral fat has been associated with poor cognitive performance. (8) Thus, the menopause transition may be a stage of vulnerability for subsequent cognitive impairment and dementia. Characterizing risk factors that deteriorate across the menopause transition may aid in early prevention of dementia, a disease with a natural history of pathological changes spanning decades starting in midlife. (9)

Cardiovascular fat is a novel CVD risk factor (10–15) that was found to be higher after than before menopause. (16) Cardiovascular fat consists of epicardial adipose tissue (EAT; located within the pericardial sac), paracardial adipose tissue (PAT; outside the pericardial sac), and thoracic perivascular adipose tissue (PVAT; surrounding the descending thoracic aorta). Human EAT and PAT morphologically resemble white and beige adipose tissue, (17, 18) while thoracic PVAT phenotypically and functionally resembles brown adipose tissue. (19) Therefore, EAT and PAT may be dominated by white adipocytes, while thoracic PVAT may resemble brown adipose tissue. Adipose tissue volume and radiodensity from computed tomography (CT) scans are standard, noninvasive measurements of fat quantity and quality, respectively. Higher cardiovascular fat volume, usually negatively correlated with fat radiodensity, indicates higher quantity of fat tissue and is associated with higher risk of CVD. (10–12) Higher cardiovascular fat radiodensity has not been consistently associated with better health outcomes, (12–15) indicating its complex relation with fat quality. High radiodensity may reflect high metabolic activity level during either good (e.g. brown fat activation) or bad (e.g. adipose tissue inflammation) biological processes.

Few studies have assessed associations between cardiovascular fat measures and cognitive function. (20, 21) These prior studies measured fat thickness, rather than volume of fat,

which is a less reproducible metric (22) and did not assess fat radiodensity. None of the previous research evaluated the association of multiple cardiovascular fat measures at midlife with future cognitive performance. Therefore, among women transitioning through menopause, we aim to assess the independent associations of midlife cardiovascular fat volume and radiodensity with future cognitive performance. We hypothesize that lower volumes of EAT and PAT, greater volume of thoracic PVAT, and better fat quality at midlife will be associated with a higher future cognitive performance. While Black had higher prevalence of Alzheimer's disease than White, (1) midlife Black women had lower volumes of all cardiovascular fat deposits and lower education level than White women. (23) As such, we also aim to test if the above associations are modified by race. We hypothesize that the adverse associations of EAT and PAT volumes with cognitive performance is more severe among Black women.

2. METHODS

2.1 Participants

The Study of Women's Health Across the Nation (SWAN) is an ongoing multi-racial/ethnic longitudinal study of the menopause transition across 7 study sites in the U.S. (Boston, MA; Detroit, MI; Davis, CA; Los Angeles, CA; Pittsburgh, PA; Chicago, IL; or Newark, NJ). Between 1996 and 1997, 3302 women aged 42–52 years old from the 7 sites completed the baseline of SWAN (visit 0). Sixteen follow-up visits conducted at approximately annual intervals, with longer intervals during later years, were completed from the baseline visit to 2018. Cardiovascular fat measures were quantitated once at one of the following SWAN visits 4, 5, 6, or 7 (between 2000 and 2005) among 562 Black or White SWAN participants without a history of cardiovascular disease at the Pittsburgh and Chicago sites in the SWAN Cardiovascular Fat Ancillary study. Cognitive tests were initiated among active SWAN participants at visit 4 and administrated repeatedly at visit 6–10, 12, 13, and 15 (between 2000 and 2016). SWAN Cardiovascular Fat Ancillary Study participants from the Chicago site had extra measures of working memory and processing speed as a part of an ancillary study within the Chicago site at time points corresponding to SWAN baseline, visit 1, 2, 3, and 5 (between 1996 and 2003). The timeline of SWAN parent and cardiovascular fat ancillary studies was provided in the supplement file 1 (Figure S1).

Women who participated in the SWAN Cardiovascular Fat Ancillary Study and had at least one subsequent measure of cognitive performance without a history of stroke (n=2) were included in this analysis to evaluate the association between midlife cardiovascular fat and subsequent cognitive performance (Figure 1). The distribution of time differences between the cardiovascular fat assessment (the baseline of the present study) and the first subsequent cognitive test was fairly narrow [median=0.99 years (Q1=0.84, Q3=1.85)] but 4 values were greater than 4 years, and hence, we excluded those 4 women. The final data set for analysis included 531 women (2665 observations). The latest cognitive test was administered at a median of 13.4 years (Q1=5.3, Q3=14.3) after the cardiovascular fat scan, when women's mean age was 60.9 (SD=5.7) years.

Research protocols were approved by the institutional review board at each study site and all participants provided written informed consent prior to enrollment.

2.2 Study Measure

2.2.1 Cardiovascular fat volume and radiodensity—Cardiovascular fat measures were quantified at the Los Angeles Biomedical Research Institute, Harbor-UCLA Medical Center, CA using images that were previously obtained to measure coronary artery calcification and aortic calcification. Electron-beam CT with an Imatron C-150 Ultrafast scanner (GE-Imatron, South San Francisco, CA) was used to scan total heart adipose tissue (TAT) as the sum of EAT and PAT. PAT volume was measured by subtracting the EAT volume from TAT volume, as such radiodensities could only be obtained for EAT and TAT. Thoracic PVAT was quantified using an image analysis workstation equipped with Slice-O-Matic version 4.3 (Tomovision, Magog, Quebec, Canada) at the University of Pittsburgh Ultrasound Research Lab. The anatomical location of each fat depot, the scanning process and reproducibility data were described in the supplement file 1.

2.2.2 Cognitive performance—Three cognitive domains were repeatedly examined using the same test batteries across visits. All cognitive test scores represent the number of correct responses, so a higher value indicates a better performance. Processing speed was measured using the Symbol Digit Modalities Test (SDMT, range: 0–110). (24) In this test, subjects were presented with a page headed by a key that pairs the single digits 1–9 with nine symbols. After practice, participants were required to write the number corresponding to each symbol in the box below the symbol in 90 seconds without skipping. Working memory was evaluated by the Digit Span Backward Test (DBST, range: 0–12). (25) Each digit span (2 to 7 digits) was read by assessors once in order and asked participants to repeat them backward. DBST was discontinued if subjects made 2 consecutive mistakes on a specific digit length. Verbal episodic memory immediate and delayed recalls were assessed with the East Boston Memory Test (EBMT: range 0–12). (26) Women were asked to recall elements of a short story that was read to them 5 seconds ago (immediate recall) and again after around 10 minutes delay (delayed recall).

2.2.3 Study covariates—Self-reported race/ethnicity, date of birth, education level, and financial strain were collected at the SWAN screening interview. Time varying age at cognitive test completion date was used. We measured the following covariates at the same visit of cardiovascular fat CT scan: menopause status, depressive symptoms, systolic blood pressure (SBP), waist circumference, smoking status, diabetic status, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides. The heart age score was calculated from age, total cholesterol, HDL-C, SBP, smoking, and diabetes, (27) and women whose heart age was higher than chronological age were classified as at risk for CVD. The detailed information about covariate measurement was provided in the supplement file 1.

2.3 Data Analysis

The distribution of each continuous variable was examined and median, 25^{th}, and 75^{th} percentiles were reported for non-normally distributed variables. Univariate associations between baseline characteristics and cardiovascular fat measures were assessed using linear regression models. Longitudinal measures of cognitive performance using the same test over time in the same population will result in practice effect bias, improvement in test performance due to learning. (28) Similar to previous analyses from SWAN using cognitive

measures, indicator variables for the first two cognitive tests were created and adjusted for in analysis involving working memory and processing speed, and for the first four cognitive tests in analysis involving immediate and delayed recall. (29) In addition, since healthier participants may selectively remain in the cohort which could result in a retention effect bias, a new variable was created to account for the timing of drop out for each participant. This variable was set to 0 for women whose last cognitive test was assessed at visit 15, 1 for those whose last cognitive visit was visit 13, and so on to control for the retention effect.

Linear mixed effect models with random intercept were used to assess the associations of each cardiovascular fat measure with subsequent measures of working memory and processing speed over time (maximum of 8 times over 16 years of follow up). The distribution of the test scores of immediate and delayed recalls were not close to normal. Similar to a previous work from SWAN, (6) we reverse-coded the EBMT test scores so that the new outcome variables indicated the number of incorrect responses and was approximately Poisson distributed. To overcome potential overdispersion, negative binomial mixed models with random intercept were applied to assess the associations of each cardiovascular fat measure with subsequent reversely coded immediate and delayed recall. Covariates associated with both independent and dependent variables were adjusted for in the current analysis. Multiple imputation was applied on top of the mixed models, since 30 out of 531 participants had at least one missing covariate. Model 1 adjusted for practice effect, retention effect, time-varying age at cognitive test, as well as education level, study site, difficulty to pay for basics, depression status, and menopause stage from the visit when the CT scan was completed. We additionaly adjusted for race in Model 2 and included waist circumference, log transformed triglycerides, and CVD risk status, concurrent with the CT scan, in Model 3. Cardiovascular fat radiodensity and volume from the same fat depot were modelled together in Model 4. We tested interaction terms of each cardiovascular fat measure with race for cognitive performance in Model 4.

A sensitivity analysis was conducted to check the impact of missingness by fitting mixed models without multiple imputation among 501 women. To understand how different combinations of fat quantity and quality may impact cognition, we grouped women into 4 groups for each cardiovascular fat depot by using the median as the cut point to defind low vs. high (LowV/LowRD: low volume and low radiodensity, HighV/LowRD: high volume and low density, LowV/HighRD: high volume and low density, and HighV/HighRD: high volume and high density). We then fit Model 3 with multiple imputation for the newly created categorical variables for each cognitive performance. Current SAS procedure MIABALYZE is unable to summarize type III analyses, so we used median of the overall p-values from the analyses of imputed datasets as the pooling rule for categorical variable. (30) Bonferrnoni correction was applied for multiple comparison. Statistical analyses were carried out using SAS software 9.4. All P-values are two sided, and $p<0.05$ was considered to be statistically significant.

3. RESULTS

Table 1 summarizes characteristics of SWAN Cardiovascular Fat participants (N=562) and the subset of women who met the study inclusion/exclusion criteria (N=531). The

analytic sample is representative of the ancillary study population. Univariate associations between baseline characteristics and cardiovascular fat measures were listed in Table S1 of supplement file 2.

3.1. Quantity of cardiovascular fat at midlife and future cognitive performance

In the unadjusted models (Table S2 of supplement file 2), higher volumes of all cardiovascular fat depots were associated with higher immediate recall (fewer numbers of incorrect responses in the reversed scale), and higher volumes of thoracic PVAT was associated with higher delayed recall (fewer incorrect responses in the reversed scale) levels in repeated measures of cognition. Conditional on covariates in Model 1, higher volumes of EAT and PAT were associated with higher delayed recall level. However, the additional adjustment of race in Model 2 and triglycerides, CVD risk, and waist circumference in Model 3 attenuated the associations of cardiovascular fat volumes with immediate and delayed recall. In Model 3, only higher midlife thoracic PVAT volume was significantly associated with a higher future delayed recall level.

3.2. Quality of cardiovascular fat at midlife and future cognitive performance

In the unadjusted models (Table S2 of supplement file 2), higher midlife radiodensities (less negative HU) of EAT and TAT were associated with lower working memory, processing speed, immediate recall, and delayed recall levels. Higher radiodensity of thoracic PVAT was associated with lower working memory and delayed recall levels. When race was added to the covariates in Model 1, higher radiodensities of EAT and TAT were no longer associated with cognitive performance. The additional adjustment for triglycerides, waist circumference, and CVD risk did not change the results. In Model 3, only higher midlife thoracic PVAT radiodensity was associated with a lower future working memory and delayed recall levels.

3.3. Independent associations of quantity and quality measures of cardiovascular fat at midlife with future cognitive performance

There were no meaningful changes in the estimated associations when both volume and radiodensity of the same fat depot were included in the same model (Model 4 in Table S2 of supplement file 2). Figure 2 including 4 forest plots displayed changes in each cognitive test score per SD higher cardiovascular fat measures [β (95% CI)]. The associations between cardiovascular fat measures and cognitive performance did not vary by race (data not shown). The results of the sensitivity analysis were listed in Table S3 of supplement file 2. There was no obvious difference in the final results comparing Table S2 and Table S3, which indicate the missingness may be missing at random.

3.4. Associations of different combinations of cardiovascular fat quantity and quality with future cognitive performance

The least squares mean and 95% CI of each cognitive test score for women in different groups of cardiovascular fat volume and radiodensity combination were listed in Table S4 of supplement file 2. At least one pair of working memory test score among women in different groups of thoracic PVAT volume and radiodensity combination was significantly different

(overall p-value=0.030), such that women with high volume and high radiodensity thoracic PVAT had significantly lower performance in working memory compared with women with high volume and low radiodensity (Bonferroni p-value=0.024, Figure 3).

4. DISCUSSION

The current study demonstrated differential associations of volumes and radiodensities of multiple cardiovascular fat depots measured in women transitioning through menopause with future cognitive performance over 13.54 years of median follow up. Independent of multiple covariates, quantity (volume) and quality (radiodensity) of thoracic PVAT, but not of EAT, PAT or TAT, were associated in opposite directions with future cognitive performance in midlife women; such that a greater thoracic PVAT volume was significantly associated with a higher future delayed recall level (favorable), while a greater midlife thoracic PVAT radiodensity was significantly associated with lower future delayed recall and working memory levels (unfavorable). Traditional cardiovascular risk factors including diabetes, hypertension, and central obesity are more strongly associated with processing speed and executive function than with episodic memory. (6, 31) Thoracic PVAT quantity and quality, as novel cardiovascular risk factors, were linked with the early signs of Alzheimer's disease- memory loss for the first time in this research.

4.1. Midlife thoracic PVAT volume and future cognitive performance

The positive association between midlife thoracic PVAT quantity and future delayed recall emphasizes the potentially distinct contribution of midlife thoracic PVAT on cognitive performance in women. We hypothesized that it may be result from the specific adipose tissue type and anatomical location of thoracic PVAT. Compared with EAT and PAT which are dominated by white adipocytes, (17, 18) thoracic PVAT including fat surrounding aortic arch and ascending and descending thoracic aorta resembles brown fat (19, 32) and is located at a more critical anatomical location with closer proximity to the brain circulation. In contrast to white fat, brown fat improves whole-body metabolism and insulin sensitivity through energy dissipation in the form of heat. (33) Brown fat volume has been associated with a better whole-body metabolism. (34) Activated brown fat confers beneficial effects on obesity, whole-body metabolism, and cardiometabolic profiles by improving glucose and lipid metabolism. (35) In addition, since human brown fat may be a mixture of brown and beige adipocytes, (36) thoracic PVAT with higher volume may have more beige adipocytes with neuroprotective effect. (37) Mice lacking beige adipocytes were proinflammatory and had impaired memory, and the transplantation of beige adipocytes mediated anti-inflammatory effect by reducing IL-4 and restored hippocampal synaptic plasticity. (37)

4.2. Midlife thoracic PVAT radiodensity and future cognitive performance

We also identified negative associations of midlife thoracic PVAT radiodensity with future delayed recall and working memory. Thoracic PVAT can directly affect the cardiovascular system via paracrine secretion. (38) We hypothesize that it may impact cognitive function through vascular and neurodegenerative pathologies. We speculated that thoracic PVAT with high radiodensity may indicate deteriorated vascular health (39) and/or adipose tissue

inflammation, (40) thereby represents poor fat quality. (Figure 4) First, as midlife women traversing menopause, they are prone to vascular aging and inflammation due to the loss of estrogen. (41) Through paracrine secretion, vascular inflammatory cytokines may block the differentiation of preadipocytes and result in poorly differentiated adipocytes with higher radiodensity. (39) Vascular inflammation promotes plaque formation (42) in cardio-cerebrovascular systems which predispose to cognitive decline through a vascular pathway. Second, midlife women experience changes in body composition and increase in body mass index during the menopause transition. (4) High radiodensity may be a marker of adipose tissue inflammation, (40) which may be developed under obesity (43) and result in atherosclerosis. (44) Inflammed thoracic PVAT may be dysfunctional and has abnormal cytokines secretion such as increased IL-1 and IL-6 as well as reduced adiponectin. (44, 45) IL-6 may increase permeability of blood brain barrier (46) and Aβ level. (47) The reduction in adiponectin secretion may attenuate its neuroprotective effect of reducing IL-6. (48)

4.3. Comparison of future working memory level among women in different groups of thoracic PVAT volume and radiodensity combination at midlife

The adverse effect of high radiodensity seemed only to be prominent when it coexisted with high volume. We previously hypothesized that thoracic PVAT may be brown fat, the amount and activity of which reduce with aging. (49) Under obesity, brown fat can be whitened- morphologically and functionally similar to white fat, which may lead to increase in the fat volume due to the hypertrophic adipocytes.(50) Fat radiodensity may decrease at first and eventually increase because of halting preadipocyte differentiation and fibrosis. (51) In this case, women with higher dysfunctional thoracic PVAT volume may have greater amount of low-quality fat. Therefore, we speculated that the effect of volume on the association between radiodensity and working memory may be explained by a more severe inflammation among women with higher amount of low-quality thoracic PVAT.

4.4. Midlife EAT, PAT, TAT and future cognitive performance

Previous studies have reported a negative cross-sectional association of EAT thickness and cognitive performance among older participants with mean age of 72 years. (20, 21) In our study, higher midlife volumes of EAT and PAT were associated with higher future immediate and delayed recall in minimally adjusted models (Model 1). The significant associations of midlife EAT, TAT, and PAT volume with cognitive performance were attenuated after the additional adjustment for race, waist circumference, triglycerides, and/or CVD risk status in Model 3. The associations between higher radiodensities of EAT and TAT with lower cognitive performance were attenuated to non-significant levels after adjustment for race and other covariates in our study. Midlife Black women had lower volumes of all cardiovascular fat deposits than White women, (23) thereby race may partially confound these associations given the general negative correlation between fat volume and radiodensity.

4.5. The modification effect of race

The lack of racial differences in the associations of cardiovascular fat measures with cognitive performance may be explained by the complex relation among race, cardiovascular fat, and socioeconomic characteristics. First, the higher quantity of potential neuroprotective

thoracic PVAT in midlife White than Black women may counterbalance the harmful effects resulted from higher quantity of EAT and PAT. Second, per racial-obesity paradox, (23) while having heathier body composition, compared with Whites, Blacks still have worse cardiovascular health increasing their risk of dementia. The lower education level, higher rates of poverty, and greater exposure to discrimination in Blacks than Whites may amplify the adverse results of racial-obesity paradox.

4.6. Clinical implications

The clinical implications of our findings are three folds. We hypothesized that inflamed thoracic PVAT and vascular inflammation could be the two potential pathways through which PVAT quality is linked to cognitive performance level. Interestingly, inflammation in PVAT and the vasculature can be ameliorated by statins, (52, 53) which found to be associated with a lower risk of dementia in some studies. (54) Our research proposed new mechanisms for statin's neuroprotective effect and supported its potential application in dementia prevention and treatment among midlife women. The beneficial effect of thoracic PVAT on memory also support the possibility of novel treatment regarding brown fat stimulants such as $\beta 3$ adrenergic receptor agonists which can improve human's whole-body metabolism (55) and even reverse memory lost and ameliorate hippocampal Aβ deposition in mice. (56) Given the wide clinical application of CT scans as a subclinical vascular health measurement, retrospective review of midlife thoracic PVAT scans may enable us to identify women with a higher risk of developing cognitive impairment in midlife when there is better potential of cognitive restoration.

4.7. Strengths and limitations

Our current analysis has several strengths. The current study focused on midlife women who experienced changes in body composition and became more susceptible to cognitive decline over the menopause transition. The repeated assessment of cognitive performance during the subsequent 10-year follow-up until early 60s enabled us to link midlife cardiovascular fat measures with early signs of cognitive decline. The major limitation is the restriction of our current study to White and Black women, which decreased the generalizability of applying our findings to women from other racial/ethnic backgrounds and men. We also admit the residual selection bias resulted from the adjustment of retention effect, which may undermine the association by generating a sample of participants with better overall health condition. Our current analysis did not adjust for multiple comparisons since this analysis was exploratory in nature. Limited research explored physiology and pathophysiology of human thoracic PVAT, so the interpretation of our current findings mainly relied on research on animals and EAT. More studies of human thoracic PVAT are needed to exploit its therapeutic potential and find causal link between cardiovascular fat and cognitive performance.

4.8. Conclusions

To the best of our knowledge, this is the first study to identify thoracic PVAT volume and radiodensity at midlife as risk factors for future cognitive performance. Higher thoracic PVAT volume at midlife was associated with a higher future episodic memory delayed recall, while higher thoracic PVAT radiodensity at midlife was associated with lower future

working memory and episodic memory delayed recall levels over the subsequent decade. For thoracic PVAT, the negative association of high radiodensity on working memory seemed to be prominent when it coexisted with high PVAT volume. Our findings open a new possibility for future research about the contributions of thoracic PVAT in the etiology, prevention, and the intervention of dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Higher midlife PVAT volume is related to a better future episodic memory in women
- Higher midlife PVAT radiodensity is related to worse future working and episodic memories
- Negative association of high PVAT radiodensity with working memory is prominent at higher PVAT volume
- Midlife PVAT is linked to future memory loss; an early sign of Alzheimer's disease
- Midlife women's epicardial and paracardial fat are not related to future cognition

Research in Context

1. **Systemic review**: The authors reviewed the literature on PubMed using the following key words: heart fat, total heart adipose tissue, perivascular adipose tissue, pericardial adipose tissue, epicardial adipose tissue, ectopic cardiovascular fat, intra-abdominal fat, dementia, Alzheimer's disease, cognitive function, and cognitive impairment.
2. **Interpretation**: Our study newly identified midlife risk factors for future cognitive performance- quantity (volume) and quality (radiodensity) of thoracic perivascular adipose tissue (PVAT). Higher thoracic PVAT volume was associated with a higher episodic memory, while higher thoracic PVAT radiodensity with lower working and episodic memory over the next decade. Unlike traditional cardiovascular risk factors found to be related to working memory, thoracic PVAT, the novel cardiovascular risk factor, was linked to memory loss- the early sign of Alzheimer's disease.
3. **Future direction**: More studies of human thoracic PVAT are needed to fully understand its contributions to cognitive performance and exploit its therapeutic potential.

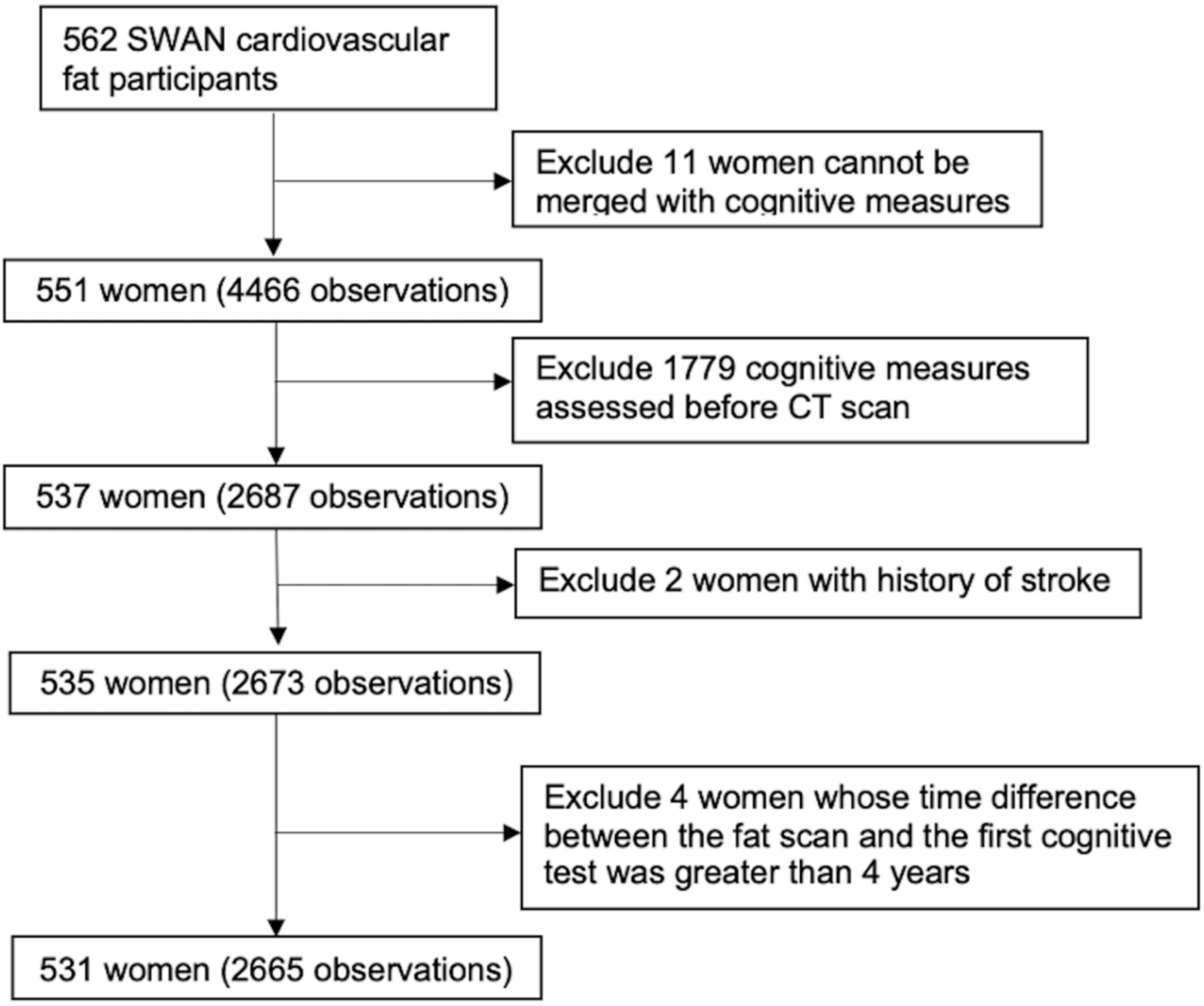

Figure 1.
Flowchart of current study sample selection

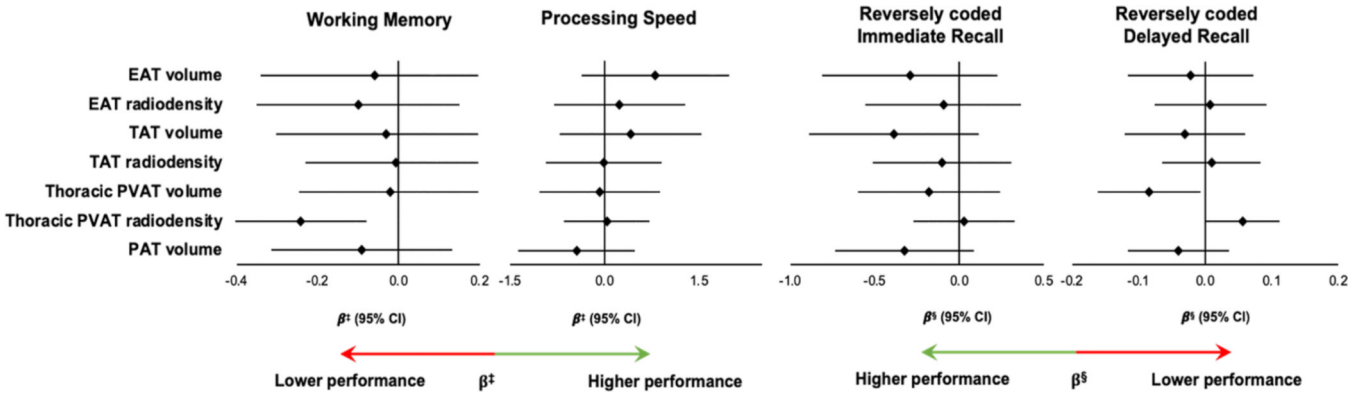

Figure 2.

Independent associations* of midlife cardiovascular fat† volume and radiodensity (modeled together) with subsequent cognitive performance.

* Mixed model with multiple imputation adjusted for practice effect, retention effect, study clinical site, education level, how hard to pay for basics, menopausal stage and depression status, age at cognitive test, race, waist circumference, log transformed triglycerides, and CVD risk. Volume and radiodensity of the same fat tissue were included in one model.

† Cardiovascular fat volumes were log transformed, and each cardiovascular fat measure was divided by its SD.

‡ β (95% CI) indicated increase in working memory test scores and processing speed test scores per one SD higher cardiovascular fat measure.

§ β (95% CI) indicated increase in reversely coded episodic memory test scores (number of incorrect responses), per one SD higher cardiovascular fat measure.

Abbreviation: EAT: epicardial adipose tissue; PAT: paracardial adipose tissue; TAT: total heart adipose tissue; PVAT : perivascular adipose tissue

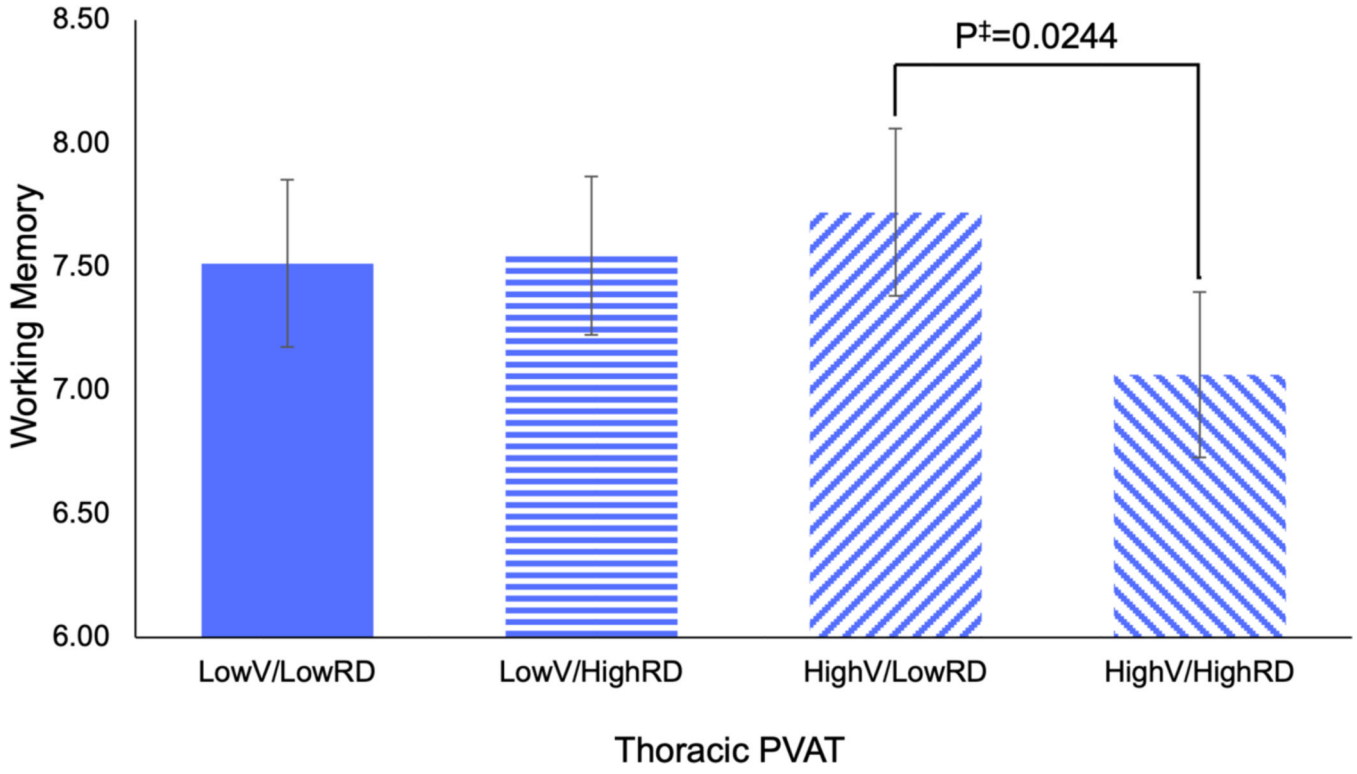

Figure 3.

The least squares mean* future working memory test score among women in different groups† of thoracic perivascular adipose tissue (PVAT) volume and radiodensity combination.

* The least squares mean (95% CI) were calculated in mixed models with multiple imputation adjusting for practice effect, retention effect, study clinical site, education level, how hard to pay for basics, menopausal stage and depression status, age at cognitive test, race, waist circumference, log transformed triglycerides, and CVD risk.

† Women in LowV/LowRD had low volume and low radiodensity, HighV/LowRD high volume and low density, LowV/HighRD high volume and low density, and HighV/HighRD high volume and high density.

‡ Bonferroni p-value for multiple comparison.

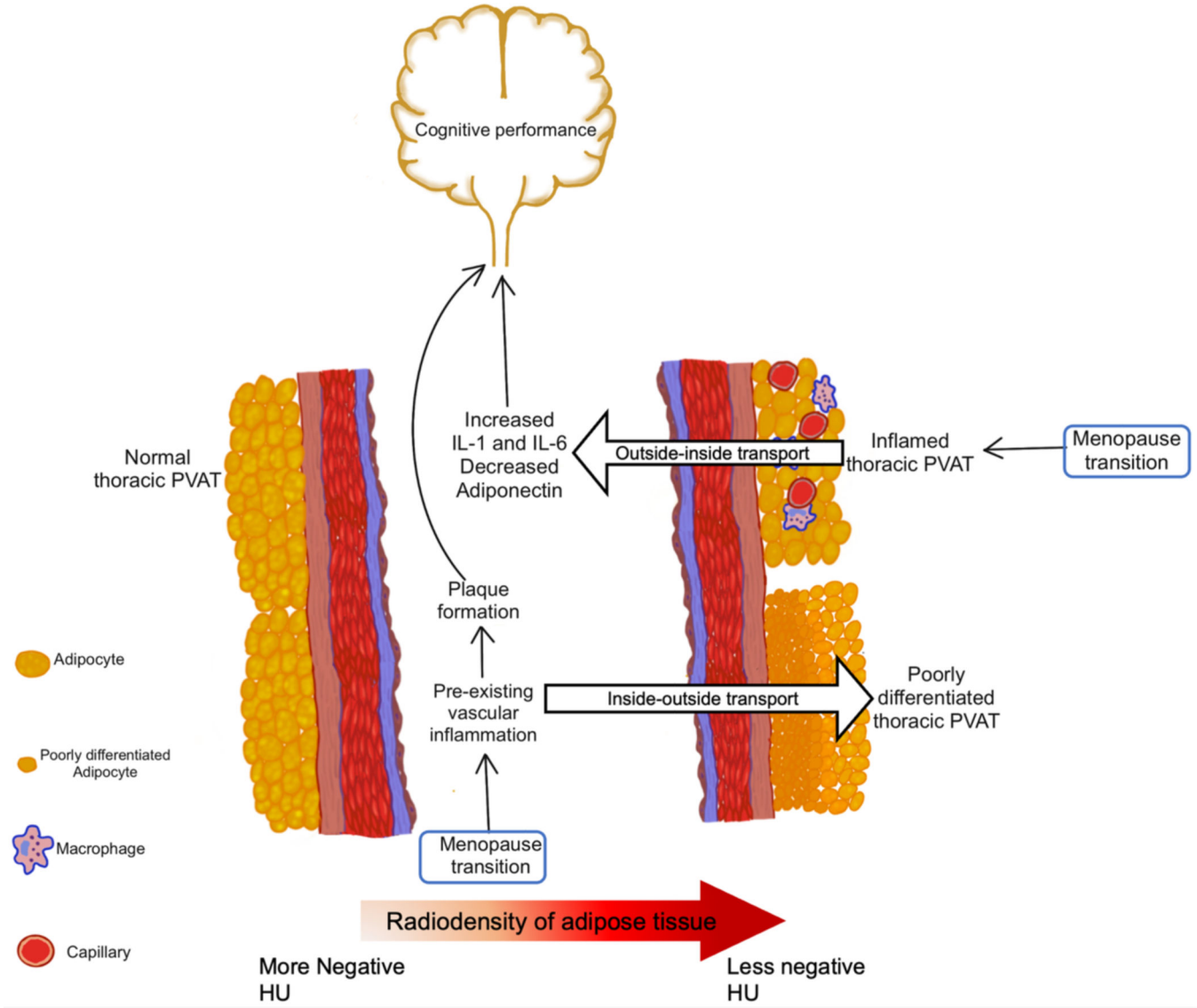

Figure 4.

Hypothetical pathological pathways between thoracic perivascular adipose tissue with high radiodensity and poor cognitive performance

NOTE. During the menopause transition, midlife women experience weight gain and deterioration in cardiovascular health, which may result in adipose tissue and vascular inflammations. Based on the bidirectional communication between perivascular adipose tissue (PVAT) and the vessel wall, the inflamed thoracic PVAT can influence endothelium- “outside-inside transport”, and pre-existing vascular inflammation can also inhibit adipocyte differentiation- “inside-outside transport”. Thus, we hypothesized that inflamed thoracic PVAT and poorly differentiated thoracic PVAT with less lipid contents may have higher radiodensity (less negative Hounsfield Unit in CT image) compared with normal thoracic PVAT, and thereby high radiodensity may indicate worse quality. Dysfunctional, inflamed thoracic PVAT may release more IL-1 and IL-6 and reduce its secretion of adiponectin. Neuroprotective adiponectin can pass blood brain barrier and reduce IL-6 which may

increase Aβ by improving amyloid precursor protein. IL-6 may also increase the permeability of blood brain barrier and impact cognitive function. In addition, vascular inflammation may promote plaque formation and atherogenesis which may impact cognitive performance.

Table 1.

Study population characteristics at the time of cardiovascular fat measurement, the baseline of the present study

Characteristics	SWAN Cardiovascular fat participants N=562	Subset of participants who meet study inclusion criteria N=531
Age, mean (SD)	50.9 (2.9)	50.9 (2.9)
Race, n (%)		
Black	208 (37.4%)	193 (36.42%)
White	348 (62.6%)	337 (63.58%)
Education level, n (%)		
<=High school	81 (15.1%)	80 (15.6%)
Some college	161 (30.0%)	150 (29.3%)
College	119 (22.2%)	112 (21.9%)
Graduate	175 (32.7%)	170 (33.2%)
Site, n (%)		
Chicago	184 (33.1%)	175 (33.0%)
Pittsburgh	216 (38.9%)	207 (39.1%)
Chicago specific	156 (28.1%)	148 (27.9%)
Menopausal status, n (%)		
Natural and surgical postmenopause	173 (31.1%)	162 (30.6%)
Late perimenopause	56 (10.1%)	53 (10.0%)
Early peri- and pre-menopause	304 (54.7%)	293 (55.9%)
Unknown due to hormone therapy use	23 (4.1%)	22 (4.2%)
Somewhat or very hard to pay for basics, n (%)	169 (31.8%)	350 (68.9%)
Current smokers, n (%)	95 (17.1%)	88 (16.6%)
At risk for CVD *, n (%)	221 (40.0%)	210 (39.6%)
Diabetes, n (%)	28 (5.0%)	26 (4.9%)
High depressive symptoms, n (%)	67(12.2%)	64 (12.2%)

Characteristics	SWAN Cardiovascular fat participants N=562	Subset of participants who meet study inclusion criteria N=531
Waist circumference, mean (SD), cm	89.0 (14.2)	88.89 (14.2)
SBP, mean (SD), mmHg	119.6 (16.6)	119.66 (16.7)
HDL-C, mean (SD), mg/dL	57.4 (14.5)	57.61 (14.5)
Triglycerides, median (Q1, Q3), mg/dL	99 (75.5, 138.0)	99 (75.0, 138.0)
EAT volume, median (Q1, Q3), cm^3	37 (27.9, 50.8)	37 (27.9, 50.7)
EAT density, mean (SD), HU	−74.8 (4.4)	−74.72 (4.4)
PAT volume, median (Q1, Q3), cm^3	9 (5.4,14.8)	9 (5.5, 14.8)
TAT volume, median (Q1, Q3), cm^3	47 (34.9, 65.4)	46 (34.7, 65.5)
TAT density, mean (SD), HU	−78.9 (3.6)	−78.89 (3.6)
Thoracic PVAT volume, median (Q1, Q3), cm^3	30 (24.1,39.1)	30 (23.9, 39.2)
Thoracic PVAT density, mean (SD), HU	−83.2 (3.5)	−83.23 (3.4)
Working memory †, mean (SD)	8 (2.5) ‡	7.78 (2.5)
Processing speed †, mean (SD)	60 (9.7) ‡	59.85 (9.7)
Immediate recall †, median (Q1, Q3)	11 (10, 12) ‡	11 (10, 12)
Delayed recall †, median (Q1, Q3)	11 (10, 12) ‡	11 (10, 12)

*Women whose heart age was higher than chronological age were classified as at risk of CVD.

†Higher scores indicate greater number of correct responses for these cognitive tests that were measured at the first available cognitive test after the cardiovascular fat scan.

‡Calculated among women with available cognitive test scores.

Abbreviation: SBP: systolic blood pressure, HDL-C: high-density lipoprotein cholesterol; EAT: epicardial adipose tissue; PAT: paracardial adipose tissue; TAT: total heart adipose tissue; PVAT : perivascular adipose tissue