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IS FAT MASS CROSS-SECTIONALLY ASSOCIATED WITH CORTICAL Aβ LOAD IN THE HUMAN BRAIN?

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Abstract: *Objectives:* The objective of this study was to examine the relationship of fat mass (FM) with brain amyloid (Aβ) load in older adults. *Methods:* Data from the Multidomain Alzheimer's Preventive Trial (MAPT) for Positron emission tomography and dual-energy X-ray absorptiometry (DXA) were used. Linear regressions controlling for appendicular muscle, age, education, clinical dementia rating scale and Apolipoprotein-E were performed to explore the relationships between FM, trunk FM and Aβ-load. *Results:* Thirty-nine participants (75.7 ± 4.2 years old) with an average BMI of 27.5 ± 4.0 kg/m2 were analyzed in this study. There were significant and positive associations of both total and trunk FM with Aβ load [0.01 (0.002-0.02) and 0.02 (0.001-0.04), respectively]; however, when adding ApoE-ε4 as a confounder, associations were no longer significant. *Conclusions:* This study has found associations between FM as measured by DXA and cerebral Aβ load, suggesting that excessive FM might be involved in AD pathology.

Key words: Obesity, fat mass, amyloid, brain.

Introduction

Large epidemiological studies have found that people who have an excessive body mass index (BMI), a proxy of fat concentration (1), in midlife increased the risk of future Alzheimer's disease (AD) (2-4). Because the worldwide prevalence of obesity is alarmingly high (5), being of epidemic proportions in some developed countries particularly the United States (6), excessive body fat could be a major contributor of the current high prevalence of AD (7) and its exponential incidence in the coming decades (8).

Animal studies have shown that high fat diet has direct negative effects on the increase of brain Aβ deposition in mice [9,10]. In humans, studies using indirect measurements of body fat, such as BMI, have shown that it is an early prognostic indicator of the progression of cognitive impairment (11, 12), linking obesity to AD. Brain cortical Aβ accumulation is a hallmark of the pathophysiology of AD and the role of excessive body fatness in this pathway is still unknown. As far as we know, no study has investigated the associations of body fat, neither indirectly (eg, BMI) nor directly (eg, dual-energy X-ray absorptiometry, DXA) measured, and amyloid load in the human brain.

The objectives of this exploratory cross-sectional study were to examine the relationship of directly and indirectly assessed fat mass with brain Aβ load in community-dwelling older adults.

Materials and Methods

We used data from the Multidomain Alzheimer's Preventive Trial (MAPT) study. The MAPT study was a large 3-year randomized controlled trial investigating the effects of a multidomain (physical activity counselling, and nutritional counselling and cognitive training) combined with omega-3, multidomain alone, omega-3 alone and placebo on cognitive decline in community-dwelling older adults. The methods and results of this study are published elsewhere (13, 14).

Participants

The 1679 participants from the MAPT study were community-dwelling men and women, aged ≥70 years old, without dementia and meeting at least one of the following criteria: slow gait speed (<0.8 meters/sec), limitation in executing ≥1 Instrumental Activity of Daily Living and spontaneous memory complaints. In our exploratory study, we included only participants that had cortical TEP scan and DXA scans, ie, 39 subjects. The study was approved by the French Ethics Committee located in Toulouse (CPP SOOM II) and the participants signed an informed consent form.

Positron emission tomography (PET) scan

The acquisition protocol for brain positron emission tomography (PET) scan has been detailed elsewhere (13). Briefly, PET acquisition debuted 50 minutes after an injection of a mean of 4 MBq/kg weight of [18F]-Florbetapir. The radiochemical purity of [18F]-Florbetapir was superior to 99.5 %. Regional standard uptake value ratios (SUVRs) were generated from semi-automated quantitative analysis with the whole cerebellum used as the reference region. The mean cortical-to-cerebellar Aβ load was predefined in six cortical regions of interest (frontal, temporal, parietal, precuneus, anterior cingulate, and posterior cingulate). A Quality Control procedure was carried out using a semi-quantification-based method. PET scans were performed throughout the 3-year period of MAPT: the mean (standard deviation, SD) was 544.0

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± 267.5 days after study baseline.

Body composition and anthropometrics

Body composition was measured using the DXA method (Hologic QDR-4500W), allowing measurement of the specific density of three continuous variables: bone mass, fat mass (FM) and fat-free mass (muscle + organs) (FFM) and this, for different body regions: upper limbs, lower limbs and trunk. The independent variables of interest were FM in total body and trunk. We calculated appendicular fat-free mass (aFFM) by summing upper and lower limbs. The measurements of body composition were performed yearly throughout the study (baseline, 1 year, 2 years and 3 years). BMI was calculated by dividing weight (in kg) with squared height (m2). Obesity was defined as BMI ≥30 kg/m2 (15).

Timing of assessments

Since Aβ load was measured at various time points throughout MAPT (544 ± 267.5 days), we decided to use the DXA measurement closest to PET scan. Average number of days between DXA and PET scan was 68 ± 84 days.

Confounders

Age (continuous), education (ordinal variable with five categories, high is better), aFFM (continuous), Clinical Dementia Rating scale (CDR) closest to PET scan and Apolipoprotein E ε4 (ApoE ε4) genotype (carriers of at least one ε4 allele versus non-carriers).

Statistical analysis

Descriptive statistics are presented as mean ± SD, median and interquartile range (IQR) or absolute numbers and percentages, as appropriate. We performed multiple linear regressions to test the association of cortical Aβ load with total FM, trunk FM, and BMI in separate models. Given the small sample size and the exploratory nature of our study, we used a progressive approach for adjusting to confounders. In the first model, we only added aFFM as a confounder. In our second model, we introduced socio-demographic variables (age and education) and CDR closest to PET scan. In the last model, we added ApoE ε4 genotype. This approach was used for each independent variable (total fat mass, trunk fat mass, and BMI cut-off lean vs. obese). Statistical significance was met when p≤0.05. All analyses were performed on Stata for Mac (version 14.1, College Station, TX).

Results

Baseline characteristics of the 39 participants are presented in table 1. The subjects were aged >75 years old and 80% of the sample were women. Mean baseline body mass index (BMI) was 27.5 ± 4 kg/m2.

The results of the linear regression analyses are presented in table 2. There was a significant and positive relationship of both total and trunk fat mass with cortical Aβ load (p=0.02 and p=0.04, respectively] when adjusting for aFFM. The results remained significant when adding age, education and CDR in the model for total fat mass (Model 2) and a trend was found for trunk fat mass (p=0.08) but were no more significant when adding Apo-ε4 to the model (Model 3, all p>0.05). For BMI (non-obesity vs. obesity), no significant relationships were found.

Table 1
Baseline characteristics of the participants

Variables	Values
Age (years), mean (SD)	75.7 (4.2)
Female, n (%)	31 (79.5)
Education, n (%)	
No primary education	3 (7.7)
Primary school certificate	8 (20.5)
Secondary education	11 (28.2)
High-school diploma	4 (10.3)
>High-school diploma	13 (33.3)
Apo-ε4 carriers, n (%)	7 (18.0)
Clinical dementia rating scale of 0.5, n (%)	30 (77)
Cortical SUVR, mean (SD)	1.2 (0.2)
BMI (kg/m2), mean (SD)	27.5 (4.0)
Obese (BMI≥30 kg/m2), n (%)	11 (28)
Appendicular muscle mass (kg), mean (SD)	19.1 (4.4)
Fat mass (kg), mean (SD)	24.1 (7.6)

Legend: SUVR= standard uptake value ratio; BMI: body mass index

Discussion

In this exploratory study, we found that fat mass was associated with cortical Aβ load in the brain of community-dwelling older adults. The results of this study propose a possible association with directly measured fat and brain amyloid, suggesting that body fat is probably involved in the pathophysiology of AD.

Our preliminary findings corroborate the results of animal studies that showed high-fat diets increased the appearance of cortical Aβ load and cognitive decline in mice (9, 10). The main body fat-related pathway that can cause this neurodegeneration is hypothesized to be fat-induced increased inflammation levels that could disrupt neural progenitors within the brain (16). Indeed, obesity is linked with neuroinflammation (17), which could disrupt cortical signaling pathways, especially in the hypothalamus region, and possibly increase cortical Aβ load. Although we did not find significant associations between obesity (as measured by BMI) and amyloid load, this may have been affected by the small sample size (only 11 participants had

Table 2
Linear regression models

	Model 1		Model 2		Model 3	
	Coefficient (95% C.I.)	p	Coefficient (95% C.I.)	p	Coefficient (95% C.I.)	p
Cortical SUVR (n=39)						
Total fat mass	0.01 (0.002-0.02)	0.02	0.01 (0.0004-0.02)	0.04	0.004 (-0.005-0.01)	0.39
Trunk fat mass	0.02 (0.001-0.04)	0.04	0.02 (-0.002-0.03)	0.08	0.005 (-0.01-0.02)	0.55
BMI cut-off (lean vs. obese)	0.13 (-0.02-0.28)	0.08	0.11 (-0.05-0.27)	0.17	0.06 (-0.09-0.20)	0.42

Model 1: adjusted for appendicular muscle mass; Model 2: adjusted for appendicular muscle mass, age and education and Clinical Dementia Rating scale; Model 3: adjusted for appendicular muscle mass, age, education, Clinical Dementia Rating scale and Apo-ε4

obesity). Another possibility that links fat mass and amyloid load is leptin dysfunction in people with elevated fat mass. It is known that leptin resistance can disrupt brain signaling and therefore increase the production and the aggregation of cortical Aβ (18). Further studies are still needed on this topic to elucidate the exact mechanisms on how fat mass is related to cortical Aβ load.

The introduction of ApoE ε4 in the regression models led to nonsignificant associations. It is known that ApoE ε4 genotype is well-associated with both increased Aβ load (19) and adiposity-related aspects. Evidence in animals shows that the ApoE ε4 allele can lead to increasing adiposity in mice by facilitating the uptake of triglyceride-rich lipoproteins to adipocytes (20). In humans, it has been shown that the presence of at least one ApoE ε4 allele can contribute to elevating low-density lipoprotein levels and coronary heart disease (21). Therefore, it is plausible to suggest that ApoE ε4 carriers would constitute an at-risk population for excessive fat mass accumulation, even though a previous study has not shown any differences on BMI across different ApoE allele combinations (22). The seven participants in our sample that were ApoE ε4 carriers (median: 32.2 kg; IQR: 21.5-36.8 kg; % of FM median: 40.6; IQR: 28.7-44.4%) had a significantly higher fat mass compared to the non-carriers (median: 22.5, IQR: 18.0-26.7 kg; % of FM median: 33.9, IQR: 28.3-37.1%). The hypothesis that APOE ε4 carriers are at increased risk for excessive fatness remains, thus, to be confirmed.

Limitations must be pointed out in this study. First and foremost, small sample size impeded us of further adjusting our model; therefore, residual confounding is not excluded. Second, PET scans were scattered all across the 3-year study follow-up; however, the average time interval between PET-scan and DXA assessments was short (approximately 70 days), which probably did not lead to substantial changes in either body composition or amyloid load during the time between measurements. Finally, this is a cross-sectional study, which prevented us of teasing out the direction of the associations.

Conclusions

To conclude, this study shows a possible link between fat mass and Aβ load in older adults. Since these are exploratory analyses, a larger observational study with a long follow-up (ideally several years) is needed to confirm and extend our findings, notably in terms of the potential role of fatness in the long-term Aβ brain accumulation. Mechanistic studies are also needed to improve the understanding of the physiological pathways linking excessive fat to AD pathology. Nonetheless, this adds relevant information regarding the presence of fat and its potential risk for the onset of AD.

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Authors' contributions: MM analysed, interpreted and wrote the manuscript. PSB was a contributor to the manuscript. YR and BV proofread the manuscript. All authors read and approved the final manuscript.

Ethical standards: The study was approved by the French Ethics Committee located in Toulouse (CPP SOOM II) and the participants signed an informed consent form.

Conflict of Interest: Drs. Maltais, de Souto Barreto, Rolland and Vellas have nothing to disclose.

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