

Obesity impacts brain metabolism and structure independently of amyloid and tau pathology in healthy elderly

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Abstract

Background: Mid-life obesity is related to increased risk for overall dementia and Alzheimer's disease (AD) dementia. In the present work, we aimed to investigate the impact of obesity on brain structure, metabolism, and cerebrospinal fluid (CSF) biomarkers of amyloid ($A\beta$ 1-42) and tau-pathology (total-tau and p-tau) in healthy elderly.

Methods: We selected healthy controls from ADNI2 with available CSF AD biomarkers and/or fluorodeoxyglucose (FDG) PET and 3T-MRI. Participants without follow-up or with significant weight loss were excluded from the analyses. Brain cortical thickness (Cth) was evaluated with Freesurfer software and FDG uptake was measured with a surface-based method using both SPM and Freesurfer softwares. We performed regression analyses between FDG uptake, CTh, CSF AD biomarkers levels and BMI and interaction analyses with age by obesity/overweight status.

Results: We included 147 individuals (mean age 73.3 years, mean BMI 27.4 Kg/m²). Higher BMI was related to less cortical thickness and higher glucose metabolism in brain areas not typically involved in AD ($FWE < 0.05$), with little overlap between them. There was no association between BMI and any of the CSF core AD biomarkers. The relationship between age and brain metabolism was modified by overweight/obesity status, but not that of age and brain structure or core CSF AD biomarkers.

Conclusions: Our data support that obesity has differential effects on brain metabolism and structure independent of an underlying AD pathophysiology in cognitively unimpaired elderly.

Background

Obesity has become a global pandemic with multiple adverse clinical consequences [1]. Accumulating evidence demonstrates that cognition is affected by an excess of body adiposity in both adults and children [2–5]. Epidemiological studies also indicate that midlife obesity increases the risk of progression to mild cognitive impairment (MCI) and overall and Alzheimer's disease (AD) dementia [6, 7]. On the contrary, higher body mass index (BMI) in late-life might be protective [8]. This obesity paradox might be associated to the confounding effect of weight loss in preclinical AD[9].

The exact mechanisms leading to cognitive impairment and neurodegeneration in persons suffering from excess of body adiposity remain to be fully elucidated [7]. Animal models suggest a significant contribution of obesity and obesity-related metabolic disturbances to AD pathophysiology [7, 10–13]. In contrast, human studies assessing the impact of obesity on amyloid and tau pathology report conflicting findings both in in vivo and in post-mortem studies. Thus, higher BMI has been related to higher, but also to lower AD burden [14–18]. On the other hand, obesity might contribute to neurodegeneration by mechanisms unrelated to AD. Obesity is a state of peripheral low grade chronic inflammation, and it is frequently associated to an abnormal peripheral sensitivity to insulin effects. In experimental models, obese-related peripheral inflammation has been linked to blood brain barrier dysfunction, neuroinflammation and neurodegeneration, while central insulin resistance has been associated to

impaired synaptic plasticity and memory [19–21]. Furthermore, obesity is a strong risk factor for hypertension, type 2 diabetes (T2D) and dyslipidemia, and it is a well-established cerebrovascular risk factor [1].

Brain atrophy and brain hypometabolism are well-recognized non-specific biomarkers of neurodegeneration. Several studies have shown an association between high BMI and brain atrophy [22]. Fewer studies have assessed the relationship between obesity and brain metabolism in cognitively healthy subjects [23–28]. In contrast to the consistent brain atrophy reported in the MRI studies, these works have reported higher brain metabolism with respect to lean controls [23–26, 28].

None of the above mentioned works, however, integrated biochemical and neuroimaging data. Multimodal studies might be useful to better understand the pathophysiological pathways involved in the deleterious impact of an excess of body adiposity on brain health and to explore whether obesity contributes to neurodegeneration by amyloid dependent or independent mechanisms.

Taking advantage of a large multicenter cohort, the Alzheimer's disease Neurodegenerative Initiative (ADNI), we aimed to investigate the relationship between BMI and brain structure, brain metabolism and core AD cerebrospinal fluid (CSF) biomarkers in cognitively unimpaired elderly. We also tested whether these changes were driven by the results obtained in younger or older individuals.

Methods

Study participants

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a \$60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. and Canada. More information can be found in the acknowledgements section (see also <http://adni-info.org/>).

For the present study, we included all cognitively healthy controls from ADNI2 with biometric and biochemical data and either (a) a 3T MRI and a FDG-PET scan with a time-lapse interval between both scans of less than one year or (b) cerebrospinal fluid (CSF) measurements of amyloid- β 1–42 ($A\beta$ 1–42), total tau (t-tau) and phosphorylated tau (p-tau).

Supplementary Fig. 1 shows the study flow-chart. We and others have previously showed that unintentional weight loss may represent a non-cognitive sign of AD [29–31] and a confounder in the relationship between obesity and brain structure [9]. Therefore, we excluded those participants with significant weight loss (i.e weight change > 5% from baseline weight) in throughout follow-up (n = 43), and those with a personal history of bariatric procedures (n = 3). Nonetheless, in supplementary Fig. 2, we present the results of main analysis in the whole cohort.

Demographic (age, sex, educational level), clinical (presence of T2D, usual medication), neuropsychological (Alzheimer Disease Assessment Scale-Cognitive [ADAS-Cog], Clinical Dementia Rating Sum of Boxes [CDR-SB] and Mini-Mental State Examination [MMSE]), anthropometric (height, weight, systolic and diastolic blood pressure) and laboratory data (fasting plasma glucose, cholesterol, and triglycerides) were downloaded from the ADNI database. BMI was calculated as weight in kilograms divided by height in meters squared.

MRI analysis

The details of MRI acquisition and pre-processing are available elsewhere (<http://adni-info.org/>). We processed the MRI images using the cortical reconstruction pipeline of Freesurfer v5.1. (<http://surfer.nmr.mgh.harvard.edu>) as previously described [32, 33]. Before realizing the statistical analyses, we checked the estimated surfaces in order to detect possible segmentation errors and performed manual editing to minimize this problem. We applied a smoothing kernel of 15 mm. In order to assess atrophy in AD vulnerable areas we extracted the mean cortical thickness values for each subject from a well validated region of interest, the Dickerson’s fingerprint (i.e. medial temporal cortex, inferior temporal gyrus, temporal pole, angular gyrus, superior frontal gyrus, superior parietal lobule, supramarginal gyrus, precuneus and inferior frontal sulcus of both hemispheres) [34].

18-Fluorodesoxyglucose PET scan analysis

The details of PET acquisition and pre-processing are available elsewhere (<http://adni-info.org/>). Briefly, PET scans were co-registered, averaged, standardized the voxel image grid with 1.5 mm cubic voxels and smoothed with a 8 mm full width at half maximum (FWHM) kernel to produce an image of a uniform resolution.

Considering PET data, each FDG-PET image was spatially-normalized to each subject’s Freesurfer anatomical MRI space using a rigid-body transformation and intensity-scaled by the pons-vermis region as previously described [35]. The resulting images were then visually-inspected in order to check for [35] errors and projected to the middle point of the cortical ribbon [36]. Before performing statistical analyses, the resulting surfaces were smoothed using a kernel of 10 mm FWHM to obtain an equivalent relative smoothing kernels for the PET and cortical thickness (CTh) maps. Surface-based smoothing introduces less bias than volume-based methods and substantially improves the reliability and the inter-subject variability [37]. In order to assess the brain metabolism in AD vulnerable areas, we extracted the mean FDG standardized uptake value ratios (SUVR) for each subject from a well validated region of interest, the Landau signature (i.e. left and right angular, temporal and posterior cingulate regions) [35].

CSF data

The details of the CSF analysis have been described in <http://adni-info.org>. Briefly, pristine aliquots were examined by the validated and highly automated Roche Elecsys® electrochemiluminescence immunoassays. This methodology minimizes inter-run variability for A β 1–42, t-tau and p-tau levels in CSF. The cutoff used for A β 1–42 was 977 pg/mL [38].

Statistical Methods

Demographic, clinical, anthropometric and cognitive variables were analyzed by R statistical software (version 3.4.4; <http://www.r-project.org>).

To assess the relationship between BMI and both the neuroimaging and core AD CSF biomarkers we performed regression analyses. For the neuroimaging evaluations, we first performed vertex-wise correlation analyses between BMI and both CTh and FDG uptake in the whole sample including age, sex and triglycerides, variables significantly correlated with BMI as covariates. The figures show only those results that survived the family-wise error (FEW) correction at $p < 0.05$ as implemented in Freesurfer. Secondly, we performed regression analyses between BMI and MRI and FDG-PET AD-signatures, mean CTh and SUVR and the core AD CSF biomarkers including age, sex and triglycerides as covariates.

To further assess a potential influence of preclinical AD, all the results were also performed in the amyloid positive and negative groups separately. Additionally, the neuroimaging results were also performed with and without including the core AD CSF biomarkers as covariates in the analyses.

Finally, we also conducted an interaction analysis to assess whether the relationships between the different biomarkers (CTh, FDG and core AD CSF biomarkers) and age were affected by the lean vs overweight/obese status.

Results

We included 147 subjects (51.7% males) in the study with a mean age of 73.3 years (range: 56.3 to 86.9) and a mean BMI of 27.4 Kg/m² (range: 20.3 to 39.1). There were no differences in these variables between the subset of patients with MRI and FDG (N = 120) and the subset of subjects with CSF data (N = 124). Table 1 summarizes the demographic, clinical, neuropsychological, anthropometrical and biochemical data for the two study subsets. There were no differences in any of the variables between the subsamples. Of the whole sample, 33% had abnormal levels of A β 1–42. BMI was weakly correlated with fasting triglycerides levels ($r = 0.19$, $p = 0.03$) and there was no correlation between BMI and education, baseline cognitive performance, systolic or diastolic blood pressure, total cholesterol or fasting glucose levels.

1. Higher body mass index is associated with increased cerebral metabolism and cortical atrophy in areas not typically involved in AD

Figure 1A and B shows the association between BMI and FDG uptake across the cortical mantle. Higher BMI was associated with higher cerebral FDG uptake in widespread brain areas including the inferior temporal lobe, insula, anterior cingulate, medial frontal regions, superior frontal, orbitofrontal regions and angular gyrus of both hemispheres (FWE < 0.05). Figure 1C and D shows the association between BMI and CTh in the same individuals. Higher BMI was associated with lower cortical thickness in multiple areas including precuneus, superior frontal and occipital regions of both hemispheres, inferior temporal zones of the left hemisphere and orbitofrontal regions of the right hemisphere (FWE < 0.05).

The areas of increased brain metabolism and less cortical thickness showed little overlap. Of note, these regions had also very little overlap with the Landau and Dickerson's signature, respectively. Moreover, BMI was not significantly associated with CTh nor with FDG in the Dickerson's and Landau's signatures ($p = 0.06$ and $p = 0.20$ respectively) (Supplementary Fig. 3).

2. Higher body mass index is not associated with CSF Alzheimer's disease biomarkers

We found no relationship between BMI and CSF A β 1–42 ($p = 0.27$), CSF p-tau ($p = 0.75$) or CSF total tau ($p = 0.92$, respectively) levels (Fig. 2). Neither did we find any association between BMI and CSF biomarkers when analyzing the amyloid positive and amyloid negative groups separately (Supplementary Fig. 4).

To further assess a potential influence of core AD biomarkers on the neuroimaging results, we first repeated the analyses including the core AD CSF biomarkers (A β 1–42 and total tau) as covariates. The results remained qualitatively the same (Supplementary Fig. 5). Moreover, we repeated the analyses in those amyloid positive and amyloid negative separately. Although the strength of association was attenuated in amyloid positive participants, higher BMI was related to higher FDG uptake in both groups. (Fig. 3).

3. The relationship between age and brain metabolism is modified by overweight/obesity status, but not that of age and brain structure or core CSF AD biomarkers

Figure 4A shows the cortical areas with a significant age by BMI interaction on brain metabolism. Significant clusters appeared in widespread areas of the frontal lobes, precuneus, temporal poles and superior parietal areas of both hemispheres. Figure 4B shows that the higher brain metabolism was found in young obese or overweight individuals ($BMI \geq 25 \text{ Kg/m}^2$) whereas no relationship with brain metabolism was found in lean subjects. The interaction analysis on brain structure, however, was not significant (Fig. 4C). For illustrative purposes, to show the relationship between age and CTh in lean vs overweight and obese individuals, we show the stratified correlation analyses between age and CTh in the extracted cluster ROI of the Fig. 1B (Fig. 4D).

The age by BMI interaction was not significant for any of the CSF AD biomarkers: $p = 0.52$ for A β 1–42, $p = 0.68$ for total tau and $p = 0.65$ for p-tau.

Discussion

In this study, we found a differential influence of obesity on brain structure and brain metabolism. Higher BMI was associated with increased brain metabolic activity (mainly driven by the younger individuals), but at the same time with less cortical thickness. The regions affected did not overlap with the typical AD vulnerable areas. Furthermore, BMI was not associated with core CSF AD biomarkers suggesting that these changes are independent of an underlying AD pathophysiology.

We first analyzed the relationship between brain metabolism and BMI. Few previous studies, two cross-sectional and three longitudinal, have assessed the relationship between brain metabolism and obesity in middle aged individuals [23, 24, 26–28]. The cross-sectional studies presented conflicting evidence. Wang et al. observed higher brain metabolism in parietal cortices in 20 middle-aged participants with morbid obesity as compared with 10 lean controls, while Volkow et al. found a negative relationship between BMI and FDG uptake in prefrontal areas [27, 28]. Of note, only 3 of the 21 participants evaluated in the latter study had BMIs in the obesity range [27]. All three longitudinal studies assessed brain metabolism in middle-aged individuals with morbid obesity before and after bariatric surgery-induced weight loss [23, 24, 26]. Marques et al. described brain hypermetabolism in 17 women with severe obesity as compared with 16 lean controls, which normalized after weight loss [23]. Brain metabolism normalization in this study was associated to cognitive improvement [23]. Tuulari et al. and Rebelos et al. did not observe differences in brain metabolism between participants suffering from morbid obesity and controls in fasting conditions, but both found higher insulin-stimulated FDG uptake [24, 26]. The low number of controls in these two studies ($n = 7$ and $n = 12$, respectively) might have limited the statistical power to detect subtle differences during fasting conditions. Nonetheless, in both studies brain metabolic abnormalities normalized after bariatric-surgery [24, 26]. Only one previous study assessed the relationship between BMI and brain FDG uptake in healthy elderly. This study, also in the ADNI cohort, included 222 participants and also showed higher brain metabolic activity in relation with higher BMI mostly in women [25]. Altogether, our results and the aforementioned studies suggest that obesity is associated to increased FDG uptake in the brain.

We also evaluated the relationship between obesity and cortical thickness in the same sample. In accordance with previous results from our group and others, we observed cortical thinning associated with increasing BMI [9, 22, 39–41].

The regions affected by atrophy and higher metabolism in our study showed little overlap with the typical vulnerable AD regions. Importantly, we did not find any association between BMI and the CTh and brain metabolism in two of the most commonly used AD signatures [34, 35]. Furthermore, we did not find any association between BMI and CSF amyloid or tau levels. The inclusion of CSF biomarkers in the analyses yielded qualitatively the same results and the stratified analyses by amyloid positivity showed a similar pattern of changes. Altogether, these results suggest that the aforementioned cortical alterations are independent of an underlying AD process.

Other cross-sectional studies in cognitively normal controls showed greater amyloid and tau burden associated with lower late life BMI [17, 18, 42]. On the contrary, the only two previous longitudinal studies showed greater amyloid deposition late in life in relation with mid-life obesity [15, 16]. Discrepancies between mid-life and late-life studies might be explained by reverse causation (i.e. AD related weight loss in preclinical AD), selection and survival biases (i.e. higher mortality and dementia risk in persons with obese might determine that only those specially protected against obesity consequences survived or/and maintained normal cognition late in life) or by the existence of additive and/or competing risk (i.e. obesity not only promote neurodegeneration throughout AD pathophysiological mechanisms and therefore only those with lower AD burden remain cognitively normal late in life) [9, 29, 30, 43]. In order to minimize the confounding effect of weight loss on the impact of obesity on the different biomarkers, we excluded those subjects with significant weight loss [9, 30]. Nonetheless, we cannot completely rule out the existence of a residual bias. In any case, our results reinforce the notion that obesity impacts on brain metabolism and structure by mechanisms not directly related with preclinical AD.

The mechanisms mediating the structural and metabolic brain abnormalities in individuals with obesity are beyond the objectives of the present work, and deserve further research [47]. Our study suggests that different mechanisms might underlie the finding of less cortical thickness and higher brain metabolism associated with a higher BMI. First, there was little overlap between the areas. Second, the relationship between age and brain metabolism, but not that of age and brain structure, was modified by excess of body weight. Younger participants drove the increased brain metabolism. Finally, the stratified analyses by amyloid positivity showed that the increased metabolism with BMI was mainly present in amyloid negative individuals while diminished CTh with BMI was present regardless of amyloid status. The finding of higher brain metabolism with increased BMI is relatively unexpected. We hypothesize that this finding might reflect obesity-induced neuroinflammation and astroglyosis. Interestingly, in the aforementioned studies with subjects who underwent bariatric surgery, higher FDG cerebral uptake correlated with markers of systemic inflammation [23, 24]. In this sense, although brain glucose metabolism is considered a marker of neuronal activity, FDG-PET signal has recently been demonstrated to be also located in astrocytes [44]. In addition, animal studies combining FDG-PET and PET with tracers for activated microglia confirmed a highly co-localized signal of increase of glucose metabolism and neuroinflammation in both wild-type aging mice and in AD transgenic mice [45, 46]. Interestingly, in wild-type mice uncoupling glucose metabolism and neuroinflammation was observed at older ages, i.e. neuroinflammation persisted but glucose metabolism returned to baseline values. This late-life uncoupling has been attributed to the progression of age-dependent neurodegeneration [46]. In this same line, a triple tracer study performed in AD transgenic mice showed age-dependent microglial activation which positively correlates with amyloid load and brain metabolism. Nonetheless, in this study brain hypermetabolism was observed specially at younger ages and declined in relation to increasing amyloid burden. Therefore, synaptic dysfunction might mask inflammation-related hypermetabolism [45]. Further studies are required to better understand the contribution of peripheral and central nervous system inflammation or other mechanisms to the brain metabolic changes which are present in obesity.

Our study has limitations. First, as it is cross-sectional, causal relationship between BMI and brain neuroimaging abnormalities cannot be assessed. Second, there is a significant bias in the ADNI cohort, which excluded participants with large vascular burden and is mainly composed by Caucasian participants. This selection bias might explain the healthier than expected phenotype of cognitively healthy ADNI participants with obesity in our cohort. Of note, we did not find the, otherwise, expected correlation between BMI and fasting plasmatic glucose and systolic or diastolic blood pressure. Third, there is evidence that both insulin resistance and variability in fasting glucose levels can affect FDG uptake among cognitively normal middle-aged individuals [47, 48]. Given that there is sparse data available in ADNI to better characterize the glucometabolic status in our subjects, the degree of increases in FDG uptake reported here needs to be confirmed among individuals with more detailed evaluation of glucose tolerance status and appropriate measures of insulin sensitivity. Nonetheless, it should be underscored that no significant correlation between fasting glucose levels and BMI was found in our cohort and that impact of insulin sensitivity on brain metabolism was not consistent among studies [23, 24, 26, 48, 49]. Fourth, other relevant variables closely related to body weight, including dietary habits and physical activity, which have been previously related to brain health, are not available in ADNI.

Conclusions

Taking advantage of multimodal data, this work supports that obesity presents a significant and divergent effect on cortical structure and brain glucose metabolism in areas not typically involved in AD and independently of core CSF AD biomarkers. Further studies are needed to explore the role of inflammation on the brain metabolic alterations found in obesity as well as AD-independent mechanisms leading to cognitive impairment and dementia in subjects with obesity.

Declarations

Ethics approval and consent to participate

The study procedures were approved by the institutional review boards of all participating centres and written informed consent was obtained from all participants or their authorised representatives (https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf).

Ethics approval was obtained from the institutional review boards of each institution involved: Oregon Health and Science University; University of Southern California; University of California—San Diego; University of Michigan; Mayo Clinic, Rochester; Baylor College of Medicine; Columbia University Medical Center; Washington University, St. Louis; University of Alabama at Birmingham; Mount Sinai School of Medicine; Rush University Medical Center; Wien Center; Johns Hopkins University; New York University; Duke University Medical Center; University of Pennsylvania; University of Kentucky; University of Pittsburgh; University of Rochester Medical Center; University of California, Irvine; University of Texas Southwestern Medical School; Emory University; University of Kansas, Medical Center; University of California, Los Angeles; Mayo Clinic, Jacksonville; Indiana University; Yale University School of Medicine;

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Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available from ADNI. All ADNI data are shared without embargo through the LONI Image and Data Archive (adni.loni.usc.edu), a secure research data repository.

Competing interests

All authors report no biomedical financial interests or potential conflicts of interest related to this work.

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Author's contributions

JP, AP, AJ and JF conceived the idea for the present study and wrote the original draft of the manuscript. JP, AP, LV and MC-I reviewed the literature using *PubMed*, meeting abstracts and presentations. JP, VM and AB conducted the neuroimaging processing and took full responsibility of the methodological part, with the collaboration of DA, RO, AC, RF and AL. AI, AC, SV, MA, AH, JV and EO contributed to the writing of the manuscript. All authors provided critical feedback, helped to develop the research, read and approved the final manuscript.

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Table

Table1. Demographic , clinical, neuropsychological, anthropometrical and biochemical data for the whole sample.

	CSF sample	MRI-PET sample	P value
n	124	120	
Males (n (%))	66 (53.2)	62 (51.7)	0.908
Age (years)	73.3 (6.2)	73.3 (6.3)	0.945
BMI Kg/m 2	27.4 (4.0)	27.2 (4.0)	0.712
SBP (mmHg)	133.5 (15.6)	133.3 (15.9)	0.918
DBP (mmHg)	73.2 (8.9)	74.2 (10.2)	0.419
FPG (mg/dL)	99.3 (17.1)	98.4 (18.3)	0.679
Total cholesterol (mg/dL)	189.7 (36.7)	191.0 (35.9)	0.789
Triglycerides (mg/dL)	134.4 (69.7)	135.3 (73.4)	0.922
Education (years)	16.7 (2.5)	16.6 (2.5)	0.852
APOE4 positive (n (%))	38 (30.6)	36 (30.0)	1.000
MMSE	29.0 (1.3)	29.1 (1.2)	0.408
ADAS-Cog 11	6.0 (3.2)	5.7 (3.1)	0.423
ADAS-Cog 13	9.4 (4.7)	9.1 (4.5)	0.570
T2D diagnosis (n (%))	23 (18.5)	19 (15.8)	0.695
CSF A β 1-42 (pg/mL)	1411.7 (693.4)	1407.6 (678.1)	0.964
CSF total tau (pg/mL)	225.9 (79.2)	222.4 (83.7)	0.748
CSF p-tau (pg/mL)	20.6 (8.1)	20.3 (8.2)	0.797

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasmatic glucose; MMSE: Mini-Mental State Examination; ADAS: Alzheimer Disease Assessment Scale-Cognitive score; T2D: type 2 diabetes; CSF: cerebrospinal fluid.

Data is expressed as mean (standard deviation) or as number (percentage).

Supplementary Figure Legends

Supplementary Figure 1. Flowchart showing the sample used in this work.

Supplementary Figure 2. Cortical vertex-wise pattern of the relationship between BMI and both FDG (A) and CTh (B) using the whole cohort without excluding those subjects with significant weight-loss in the follow-up. Only clusters that survived family wise error corrected p -value <0.05 are shown. Red-Yellow scale color is used to display positive correlations in relation with FDG uptake and Blue-Green scale is used for negative correlations in relation with CTh.

Supplementary Figure 3. Scatterplots showing the lack of correlation between BMI and Dickerson AD signature in CTh (right) and Landau AD signature in FDG (left).

Supplementary Figure 4. Scatterplots showing the lack of relationship between BMI and AD CSF biomarkers when dividing by amyloid positivity status. Top panel shows the amyloid negative subjects whereas the bottom panel shows the amyloid positive. From left to right: A β 1-42, p-tau and total tau.

Supplementary Figure 5. Cortical vertex-wise pattern of the relationship between BMI and both FDG (A) and CTh (B) adjusted by age, gender, triglycerides and CSF AD biomarkers (A β 1-42 and total tau). Only clusters that survived family wise error corrected p -value <0.05 are shown. Red-Yellow scale color is used to display positive correlations in relation with FDG uptake and Blue-Green scale is used for negative correlations in relation with CTh.

Figures

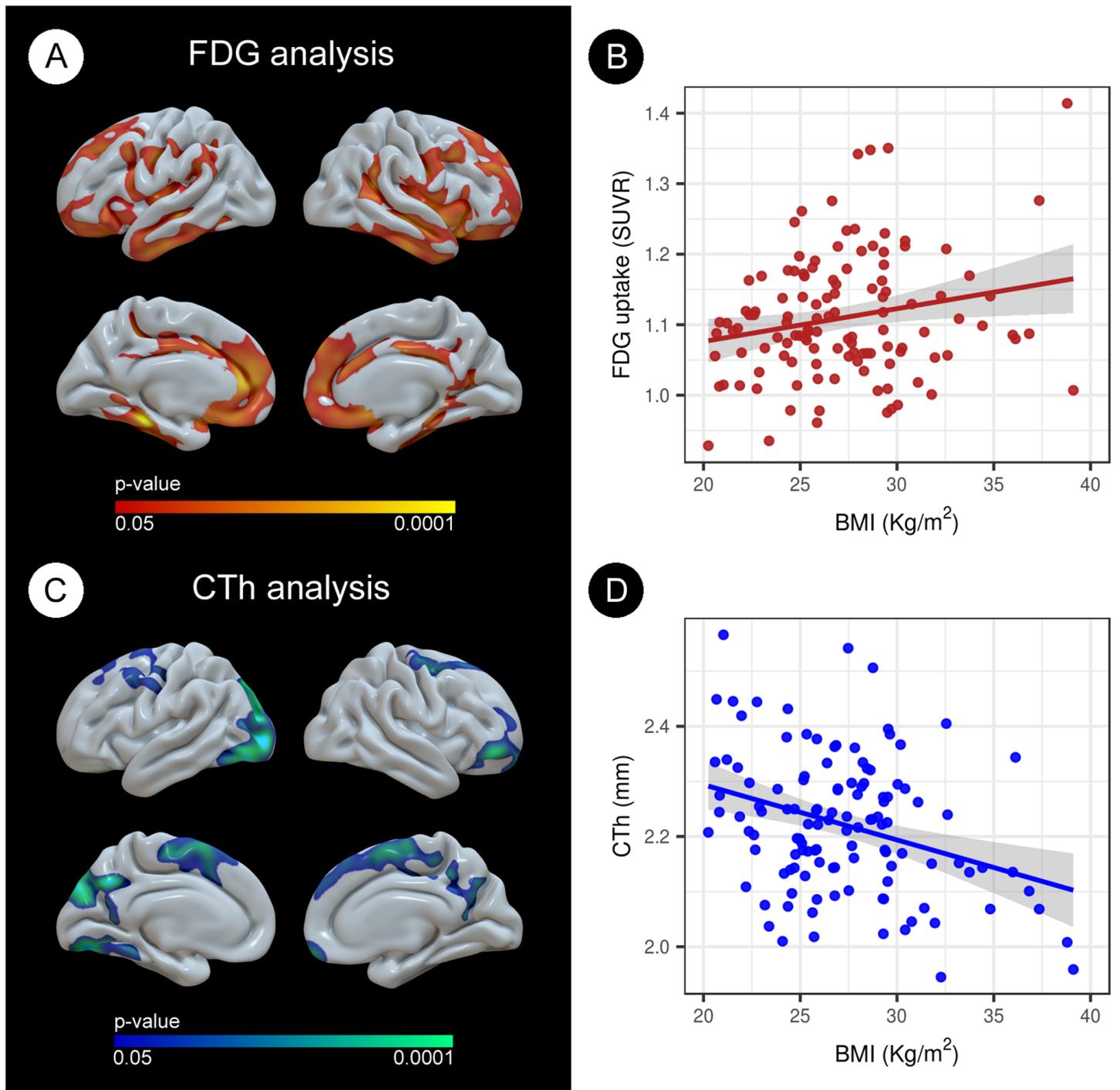


Figure 1

Cortical vertex-wise pattern of the relationship between BMI and both FDG (A) and CTh (C) adjusted by age, gender and triglycerides. Only clusters that survived family wise error corrected p-value<0.05 are shown. Red-Yellow scale color is used to display positive correlations in relation with FDG uptake and Blue-Green scale is used for negative correlations in relation with CTh. Scatterplots in B and D show the relationship between BMI and mean FDG uptake and mean CTh in the cluster ROIs in A and C.

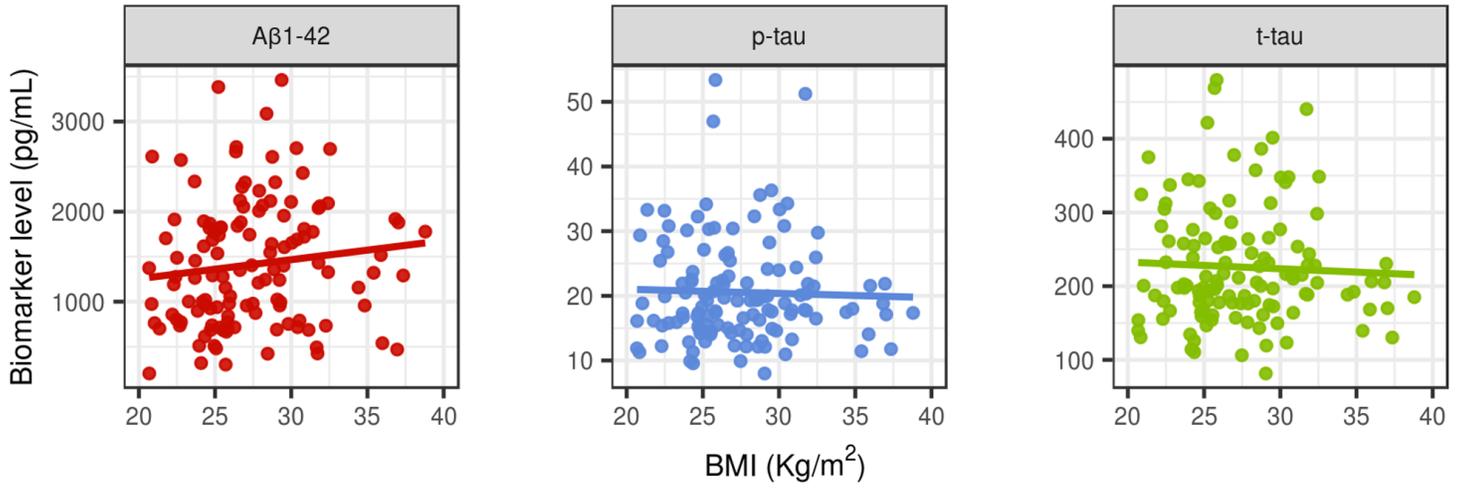


Figure 2

Scatterplots showing the lack of relationship between BMI and AD CSF biomarkers. From left to right: Aβ 1-42, p-tau and total tau.

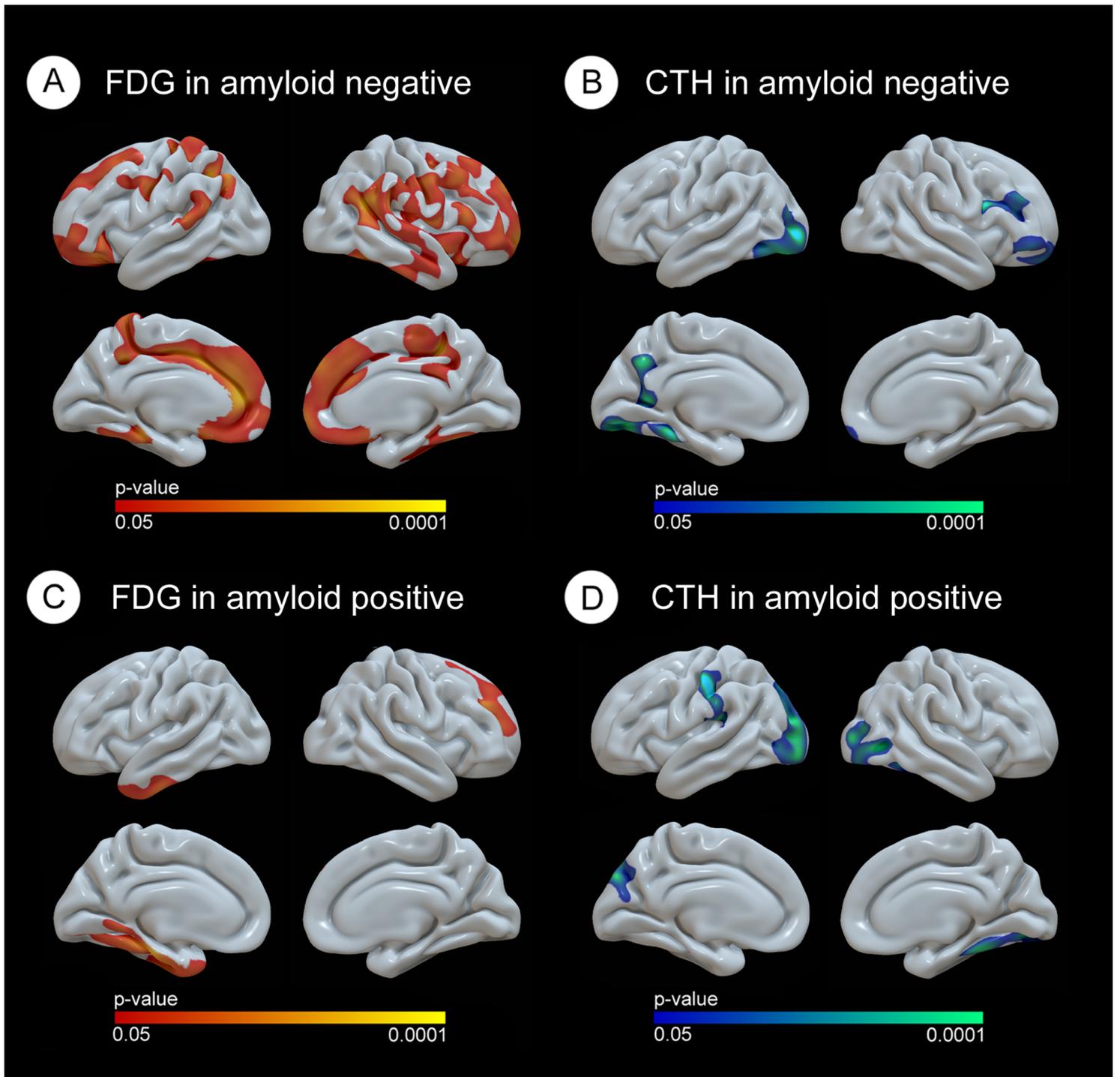


Figure 3

Cortical vertex-wise pattern of the relationship between BMI and both FDG and CTh depending on their A β 1-42 status. Only clusters that survived family wise error corrected p-value<0.05 are shown. Red-Yellow scale color is used to display positive correlations in relation with FDG uptake and Blue-Green scale is used for negative correlations in relation with CTh.

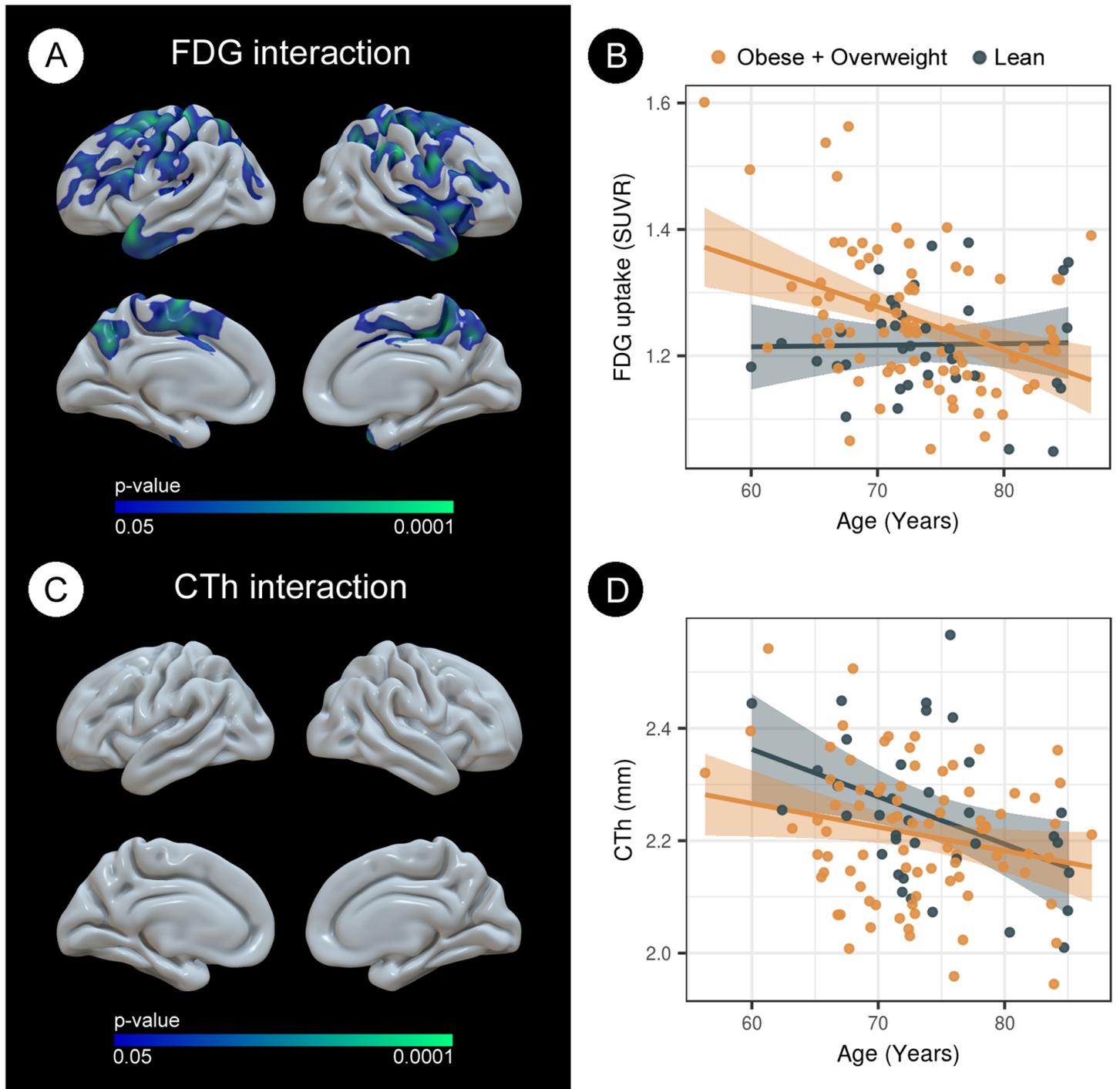


Figure 4

Interaction analysis assessing the impact of BMI and age over neuroimaging biomarkers. (A) Vertex-wise analysis. Significant clusters of the interaction with FDG uptake (FWE<0.05) are shown in blue. (B) Scatterplot showing the interaction with FDG uptake when dichotomizing BMI in two groups (lean vs overweight and obese; BMI>25 Kg/m²). (C) Vertex-wise analysis where no significance clusters in relation with CTh were found. (D) Scatterplot showing the interaction with CTh in the cluster ROI used in the Figure 1B when dichotomizing BMI in two groups (lean vs overweight and obese; BMI>25 Kg/m²).

Supplementary Files

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