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Review

Relationship between obesity and structural brain abnormality: Accumulated evidence from observational studies

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ABSTRACT

We aimed to evaluate the relationship between obesity and structural brain abnormalities assessed by magnetic resonance imaging using data from 45 observational epidemiological studies, where five articles reported prospective longitudinal results. In cross-sectional studies' analyses, the pooled weighted mean difference for total brain volume (TBV) and gray matter volume (GMV) in obese/overweight participants was -11.59 (95 % CI: -23.17 to -0.02) and -10.98 (95 % CI: -20.78 to -1.18), respectively. TBV was adversely associated with BMI and WC, GMV with BMI, and hippocampal volume with BMI, WC, and WHR. WC/WHR are associated with a risk of lacunar and white matter hyperintensity (WMH). In longitudinal studies' analyses, BMI was not statistically associated with the overall structural brain abnormalities (for continuous BMI: RR = 1.02, 95 % CI: 0.94–1.12; for categorial BMI: RR = 1.18, 95 % CI: 0.75–1.85). Small sample size of prospective longitudinal studies limited the power of its pooled estimates. A higher BMI is associated with lower brain volume while greater WC/WHR, but not BMI, is related to a risk of lacunar infarct and WMH. Future longitudinal research is needed to further elucidate the specific causal relationships and explore preventive measures.

1. Introduction

Obesity/overweight status is a frequently untreated clinical condition associated not only with a higher incidence of functional brain diseases, accelerated cognitive decline (Gunstad et al., 2007), and dementia (Whitmer et al., 2005) but also with structural brain abnormalities (or cerebral small vessel diseases), including white matter hyperintensities (WMHs) (Caunca et al., 2019), brain atrophy (Debette et al., 2010; Debette et al., 2014), cerebral microbleed (Kwon et al., 2016), and lacunar infarcts (Winter et al., 2008).

Low-grade systemic inflammation has been proposed as an essential mediator of obesity's effect on structural brain abnormalities because obesity is highly associated with inflammatory markers (A. Parimisetty et al., 2016; Pou et al., 2007).

However, the relationship between obesity/overweight status and structural brain abnormalities still remains controversial. Some studies suggest an overall inverse association between obesity parameters (body mass index [BMI]; waist-to-hip ratio [WHR]; waist circumference [WC]) and temporal lobe volume (Gustafson et al., 2004a, 2004b), total brain volume (TBV) (Gunstad et al., 2008; Ward et al., 2005), and hippocampal volume (HV) (Bruehl et al., 2009; Raji et al., 2010) in cohorts of various sociodemographic factors. Data also demonstrated a positive relationship between increasing BMI and incidence of magnetic resonance imaging (MRI)-defined brain infarcts (A. A. Gouw et al., 2008). BMI and WHR were also found to be positively associated with white matter hyperintensity volume (WMHV) (D. R. Gustafson et al., 2004a; Jagust et al., 2005). However, these results have been challenged in other studies (Albanese et al., 2015; Arnoldussen et al., 2019).

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Moreover, different fat compositions carry different metabolic risks (CS Fox et al., 2007), and there is growing evidence that abdominal obesity and visceral fat are more strongly correlated with vascular risk than global body mass (Franzosi, 2006; Romero-Corral et al., 2006). In the Framingham Offspring (Debette et al., 2010) and the Northern Manhattan (Caunca et al., 2019) studies, individuals with higher WHR or WC, two anthropometric markers of abdominal or central obesity, appeared to have lower brain volume relative to those with merely higher BMI, a marker of global obesity. No conclusive evidence is currently available on the association between obesity and structural brain abnormalities.

Considering these inconsistent findings, an up-to-date understanding of the association between obesity and structural brain abnormalities is required, which would help to refine strategies for primary prevention and inform the design of future clinical trials. We, therefore, conducted a systematic review and meta-analysis of published studies to elucidate the association between obesity and the risk of structural brain abnormalities in adults.

2. Methods

2.1. Search strategy

A detailed search on the association between overweight/obese status and the presence of structural brain abnormalities was conducted to identify all available studies. The search followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) (D. F. Stroup et al., 2000) and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (L. Shamseer et al., 2015) guidelines. We searched the electronic databases (PubMed, Web of Science, Cochrane, EMBASE) without publication year restriction, using the following search terms in all possible combinations: 'ratio, waist-hip', 'circumference, waist', 'Body Mass Index', 'obesity', 'overweight', 'white matter hyperintensities', 'brain atrophy', 'brain hemorrhage', 'lacunar stroke', 'lacunar infarct', 'total cerebral brain volume', 'white matter volume', 'brain infarction', 'brain infarct', 'cerebral microbleed', 'hippocampal volume', and 'magnetic resonance imaging'. The last search was performed on 4 April 2020. The reference lists of all retrieved articles were manually reviewed. Two independent authors (Y.H. and X. T.) analyzed each article and performed the data extraction independently. A third investigator was consulted (J.Z.) in cases of disagreement. Discrepancies were resolved by consensus.

2.2. Inclusion and exclusion criteria

Studies were considered for inclusion using the following criteria: (a) was an original article published in English; (b) clearly defined BMI, WHR, or WC and any imaging appearance of structural brain abnormalities; (c) investigated either continuous or categorial structural brain abnormalities; (d) measured the structural brain abnormalities using MRI, regardless of scanner resolution (1.5 T, 3 T, 7 T), automated assessment/visual assessment, or sequence of scan; (e) used physical diagnosis of overweight/obese status, central obesity, or continuous BMI, WHR, or WC; (f) provided quantitative measures of the association between overweight/obese status or central obesity and any type of structural brain abnormality, and their 95 % confidence intervals (CIs); (g) used cross-sectional, case-control or cohort epidemiological study design; and (h) the mean study population age was above 18 years. Exclusion criteria were as follows: (a) review studies, case reports, animal studies, or letters to the editor; (b) the publication did not clearly define clinical outcomes; (c) the articles did not provide valid data; (d) the publication provided duplicated data; and (e) the mean age of the study population was under 18 years.

2.3. Data extraction and quality assessment

According to the protocol mentioned above, we included all studies providing values (means with standard deviation or standard error) of BMI, WHR, or WC in patients with structural brain abnormalities and control subjects. The prevalence of different types of structural brain abnormalities in subjects, stratified according to overweight/obese status, was also noted.

Overweight status was defined as BMI 25–29.9 kg/m^2, obese status was defined as BMI 30.0 kg/m^2 or higher, and healthy weight was defined as BMI 18.0–24.9 kg/m^2. As a categorical variable, BMI 25 kg/m^2 or higher was defined as obese/overweight. Central obesity was defined according to the context of each article. In each study, data regarding sample size; significant clinical and demographic variables; values of BMI, WHR, and WC; and risk of different types of structural brain abnormalities were extracted independently by two investigators (M.H. and M.A.C.).

Given the characteristics of the included studies, two investigators (X.T. and Y.H.) evaluated the methodological quality of each study using the Newcastle-Ottawa scale (NOS) (A. Stang, 2010), which was developed to assess the quality of observational studies. This scoring system encompasses three major domains – selection, comparability, and exposure, and a resulting score can range between 0 and 8; a higher score represents a better methodological quality. Results of the NOS quality assessment are reported in Supplementary Table 1 and 2. The investigators discussed disagreements, aiming to reach consensus when such occurred.

2.4. Statistical analysis and risk of bias assessment

As the primary analysis, we evaluated the prevalence of different structural brain abnormalities in overweight/obese/central-obese patients. For the secondary analysis, we evaluated the obesity status of patients with different types of structural brain abnormalities.

Statistical analysis was carried out using STATA version 12.0 (Stata Corporation, College Station, TX, USA). Differences between cases and control subjects were expressed as odds ratio (OR) or risk ratio (RR) with pertinent 95 % CI for categorical variables of structural brain abnormalities. For continuous variables of structural brain abnormalities, we used a beta coefficient value (β) with pertinent 95 % CI when obesity status was defined as a continuous variable in the original article or a weighted mean difference (WMD) with pertinent 95 % CI when obesity status was defined as a dichotomous variable in the original article. If studies had both unadjusted and covariate-adjusted ORs or RRs, we extracted the latter. In cohort studies, we regarded OR as RR. We analyzed studies using beta coefficients and studies using ORs separately because the beta coefficients could be logit transformed to OR in logistic regression, but not in linear regression. Standardized increments (5 kg/m^2 of BMI, 10 cm of WC, and 0.1 of WHR) were used to analyze continuous obesity measurements and structural brain abnormalities. We converted other reported quantities or units where necessary, using a previously reported formula (Lampe et al., 2019).

Statistical heterogeneity between studies was evaluated using the I^2 metric and the variance by Tau^2. These measure the inconsistency across study results and describe the proportion of total variation in study estimates due to heterogeneity rather than sampling error. An I^2 value of 0 % indicates no heterogeneity; $<$ 25 % indicates low heterogeneity, 25%–50% indicates moderate heterogeneity, and $>$ 50 % indicates high heterogeneity (Higgins et al., 2003). P-value is another standard of heterogeneity. Random-effects models were used if $I^2 > 50$ % and P-value < 0.05, and fixed-effects models were selected if $I^2 \leq 50$ % and P-value ≥ 0.05. The results were represented graphically by funnel plots of the standardized mean difference vs. the standard error. Visual inspection of funnel plot asymmetry was performed to address a possible small-study effect. The Egger's test was performed to address publication bias over and above the subjective evaluation. A *P*-value of 0.10 was

considered statistically significant Sterne et al., 2001).

3. Results

3.1. Study selection and characteristics

After excluding duplicate results, 1,3201320 articles were retrieved. Of these, 1044 were excluded after scanning the title and/or the abstract because they were off topic, were reviews/letters/case reports, or lacked data of interest. Two hundred and twenty-four studies were excluded after evaluating the full text (Fig. 1). Fifty-two studies (Albanese et al., 2015; Anan et al., 2009; Armstrong et al., 2019; Arnoldussen et al., 2019; AY et al., 2020; Beller et al., 2019; Bobb et al., 2014; Bond et al., 2016; Bond et al., 2011; Brooks et al., 2013; Caunca et al., 2019; Cherbuin et al., 2015; Choi et al., 2009; Climie et al., 2015; Dearborn et al., 2015; Debette et al., 2010; Debette et al., 2011; Debette et al., 2014; Ding et al., 2015; Driscoll et al., 2012; Enzinger et al., 2005; Giudici et al., 2019; Gunstad et al., 2008; Hamer and Batty, 2019; Hidese et al., 2018; Higuchi et al., 2017; Ho et al., 2011; Hsu et al., 2016; Jagust et al., 2005; Hayes JP et al., 2020; Karlsson et al., 2013; Kim et al., 2012; Kim et al., 2013; Kim et al., 2017; Kuo et al., 2010; Lampe et al., 2019; Mowry et al., 2018; Naganuma et al., 2012; Okamura et al., 2018; Pasha et al., 2017; Croll PH et al., 2019; Portet et al., 2012; Taki et al., 2011; Vuorinen et al., 2011; Walhovd et al., 2014; Widya et al., 2011; Windham et al., 2017; Winter et al., 2008; Yamada et al., 2012; Yamashiro et al., 2014; Sun et al., 2020; Zade et al., 2013), including seven studies lacking compatible data for analysis and 45 studies, containing 49,439 participants, were included in the final analysis. A total of 41 studies (F. Anan et al., 2009; Arnoldussen et al., 2019; Kim AY et al., 2020; Beller et al., 2019; Bobb et al., 2014; Bond et al., 2016; Bond et al., 2011; Brooks et al., 2013; Caunca et al., 2019; Choi et al., 2009; Climie et al., 2015; Debette et al., 2010; Debette et al., 2014; Driscoll et al., 2012; Gunstad et al., 2008; Hamer and Batty, 2019; S. Hidese et al., 2018; Higuchi et al., 2017; Ho et al., 2011; Hsu et al., 2016; Jagust et al., 2005; Hayes JP et al., 2020; Karlsson et al., 2013; Kim et al., 2012; Kim et al., 2013; Kim et al., 2017; Kuo et al., 2010; Lampe et al., 2019; Mowry et al., 2018; Naganuma et al., 2012; Okamura et al., 2018; Pasha et al., 2017; Croll PH et al., 2019; Portet et al., 2012; Widya et al., 2011; Windham et al., 2017; Winter et al., 2008; Yamada et al., 2012; Yamashiro et al., 2014; Sun et al., 2020; Zade et al., 2013) provided cross-sectional data, five studies (Albanese et al., 2015; Dearborn et al., 2015; Ding et al., 2015; Croll PH et al., 2019; Vuorinen et al., 2011) provided cohort data, and one study (Croll PH et al., 2019) provided both cohort and cross-sectional data. Eleven articles in our study presented data on WHR (Caunca et al., 2019; Climie et al., 2015; Debette et al., 2010; Debette et al., 2014; Hamer and Batty, 2019; Higuchi et al., 2017;Jagust et al., 2005; Lampe et al., 2019; Pasha et al., 2017; Winter et al., 2008; Zade et al., 2013), 15 on WC (Anan et al., 2009; Arnoldussen

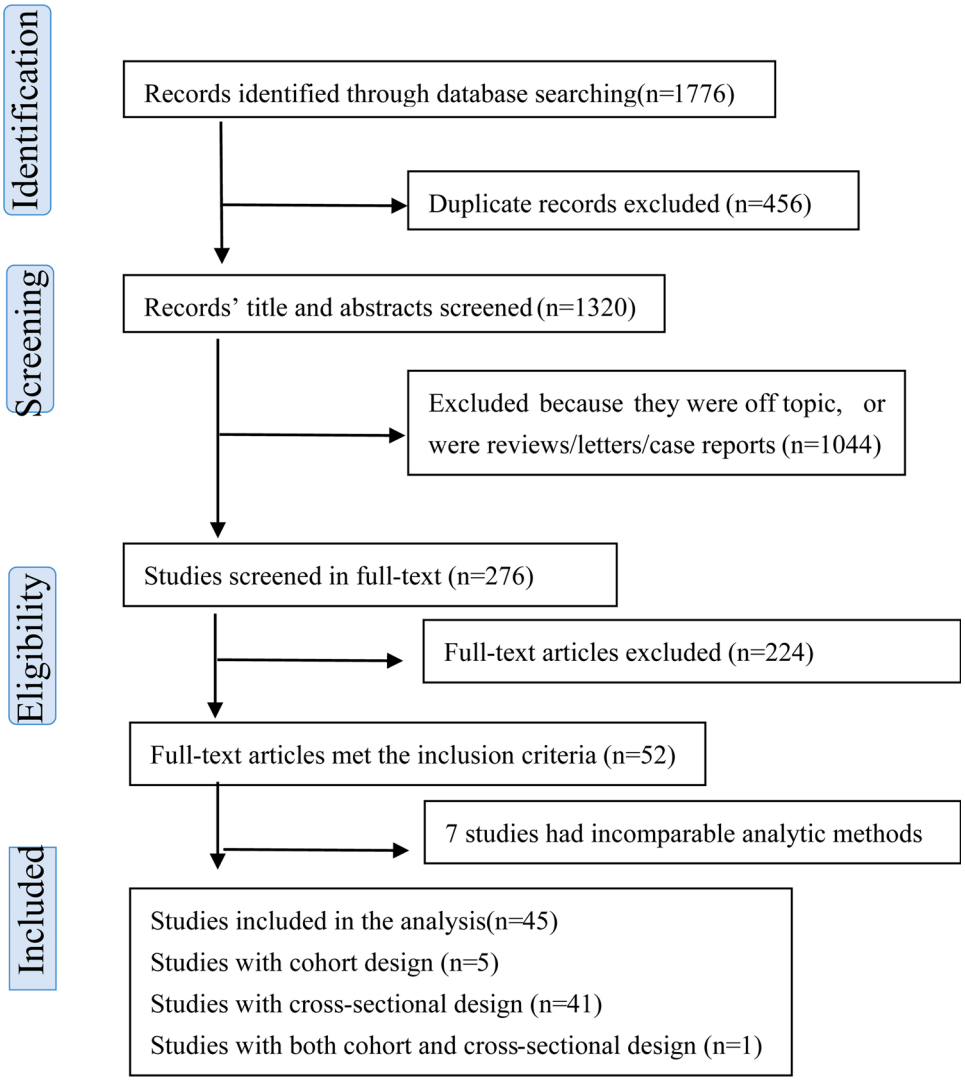

Fig. 1. Study selection process for meta-analysis.

et al., 2019; Caunca et al., 2019; Choi et al., 2009; Debette et al., 2010; Debette et al., 2014; Driscoll et al., 2012; Hsu et al., 2016; Kim et al., 2017; Kuo et al., 2010; Pasha et al., 2017; Portet et al., 2012; Windham et al., 2017; Winter et al., 2008; Yamashiro et al., 2014), and 39 articles provided BMI-related data (Albanese et al., 2015; Anan et al., 2009; Arnoldussen et al., 2019; Kim AY et al., 2020; Beller et al., 2019; Bobb et al., 2014; Bond et al., 2016; Bond et al., 2011; Brooks et al., 2013; Caunca et al., 2019; Climie et al., 2015; Dearborn et al., 2015; Debette et al., 2010; Debette et al., 2014; Ding et al., 2015; Driscoll et al., 2012; Gunstad et al., 2008;Hamer and Batty, 2019; Hidese et al., 2018; Higuchi et al., 2017; Ho et al., 2011; Hsu et al., 2016; Hayes JP et al., 2020; Karlsson et al., 2013; Kim et al., 2012; Kim et al., 2013; Kim et al., 2017; Mowry et al., 2018; Naganuma et al., 2012; Okamura et al., 2018; Croll PH et al., 2019; Vuorinen et al., 2011; Widya et al., 2011; Windham et al., 2017; Winter et al., 2008; Yamada et al., 2012; Yamashiro et al., 2014; Sun et al., 2020; Zade et al., 2013). Majority of the selected studies were carried out in high-income countries: 17 in North America, 11 in Europe, 12 in Japan/Korea, 1 in the United Kingdom, and 3 in Australia. Only one study was conducted in China, a developing country. The main characteristics of the study populations are shown in Table 1 and Supplementary Table 3. All studies received 5–8 points on the NOS during the quality assessment. Overall, the quality of the included studies was high (Supplementary Table 1–2). Data used in the current analysis are shown in Supplementary Table 4-6.

3.2. Meta-analysis results of cross-sectional studies

3.2.1. Brain volume and BMI

We analyzed the relationship between obesity, using BMI as a categorical standard, and different brain region volumes, using continuous data with mean values and standard deviation. There were eight sets of data from five studies (Kim AY et al., 2020; Bond et al., 2011; Brooks et al., 2013; Caunca et al., 2019; Gunstad et al., 2008) for TBV ($I^2 = 54.2$ %, $P = 0.03$), eight sets from five studies (Bond et al., 2011; Brooks et al., 2013; Gunstad et al., 2008; Karlsson et al., 2013; Widya et al., 2011) for gray matter volume (GMV) ($I^2 = 67.6$ %, $P = 0.003$), seven sets from four studies (Bond et al., 2011; Gunstad et al., 2008; Karlsson et al., 2013; Widya et al., 2011) for white matter volume (WMV) ($I^2 = 40.2$ %, $P = 0.12$), and seven studies (Kim AY et al., 2020; Bond et al., 2011; Hidese et al., 2018; Ho et al., 2011; Hayes JP et al., 2020;Widya et al., 2011; Sun et al., 2020) for HV ($I^2 = 82.7$ %, $P < 0.001$). The random-effects model was used for the analysis of TBV, GMV, and HV, while the fixed-effects model was used for WMV. In this part of the analysis, the unit of measure was milliliter (mL) and a minus sign meant lower volumes than the controls. All the reference group participants had healthy weight BMI (18.0–24.9 kg/m^2).

The pooled WMD for TBV in obese/overweight participants was -11.59 (95 % CI: -23.17 to -0.02), indicating a predominantly negative relationship. When assessing the data according to the BMI, the WMD for TBV in obese, overweight, and obese/overweight were -17.47 (95 % CI: -29.89 to -5.06), -1.91 (95 % CI: -15.07–11.25), and -10.82 (95 % CI: -67.66 to 46.03), respectively (Fig. 2A). In the aforementioned results, significance was only achieved when BMI was analyzed as a continuous variable, indicating the existence of an inverse association between obesity and TBV. The difference in TBV was more pronounced in obese than overweight status, as indicated by the comparatively higher BMI.

The pooled WMD for GMV was -10.98 (95 % CI: -20.78 to -1.18), indicating that BMI is related to a lower GMV. When the analysis was restricted to the obese subgroup, the WMD became -18.47 (95 % CI: -35.71 to -1.23), demonstrating a negative correlation between BMI and GMV. The WMD for GMV in the obese/overweight and overweight subgroups remained non-significant (-7.54, 95 % CI: -65.85 to 50.77 and -3.53, 95 % CI: -12.34 to 5.27, respectively) (Fig. 2B). As with the observed relationship between BMI and TBV, it is proposed that the association between BMI and GMV is notably stronger in the obesity subgroup than in the overweight subgroup.

The pooled WMD for WMV and HV showed a non-significant association with continuous BMI (-3.60, 95 % CI: -12.49 to 5.28, and 0.09, 95 % CI: -0.07 to 0.25, respectively) (Fig. 2C and 2D).

We then used the data provided by the standardized β coefficient in the linear regression model to analyze the relationship between BMI and TBV. Nine sets of data from nine studies (Arnoldussen et al., 2019; Bobb et al., 2014; Caunca et al., 2019; Debette et al., 2010; Driscoll et al., 2012; Mowry et al., 2018; Croll PH et al., 2019; Windham et al., 2017; Zade et al., 2013) were used for TBV, nine sets from eight studies (I. Arnoldussen et al., 2019; Bobb et al., 2014; Climie et al., 2015; Driscoll et al., 2012; Hamer and Batty, 2019; Hsu et al., 2016; Mowry et al., 2018; Croll PH et al., 2019) for GMV, seven sets from seven studies (Arnoldussen et al., 2019; Bobb et al., 2014; Driscoll et al., 2012; Hamer and Batty, 2019; Hsu et al., 2016; Mowry et al., 2018; Croll PH et al., 2019) for WMV, nine sets from seven studies (Arnoldussen et al., 2019; Ebba Beller et al., 2019; Bobb et al., 2014; Climie et al., 2015; Hsu et al., 2016; Croll PH et al., 2019; D. Zade et al., 2013) for HV, and eight sets from eight studies (Caunca et al., 2019; Debette et al., 2010; Hsu et al., 2016; Lampe et al., 2019; Pasha et al., 2017; Croll PH et al., 2019; Windham et al., 2017; Zade et al., 2013) for WMHV. We used the random-effects model based on the values of I^2 (TBV: $I^2 = 73.1$ %, $P < 0.001$, GMV: $I^2 = 95.5$ %, $P < 0.001$, WMV: $I^2 = 53.4$ %, $P = 0.045$, HV: $I^2 = 58.3$ %, $P = 0.014$, and WMHV: $I^2 = 93.4$ %, $P < 0.001$). BMI was negatively associated with TBV (β = -0.08, 95 % CI: -0.14 to -0.03), GMV (β = -0.57, 95 % CI: -0.80 to -0.34), and HV (β = -0.03, 95 % CI: -0.05 to -0.01), but not WMV (β = 0.00, 95 % CI: -0.12 to 0.11) or WMHV (β = 0.00, 95 % CI: -0.03 to 0.03), shown as a forest plot in Fig. 3.

3.2.2. Brain volume and WC

We meta-analyzed the association between WC and brain volumes using the standardized β coefficient in the linear regression model as an evaluation standard of the original articles. Our analysis included five sets of data from five studies (Arnoldussen et al., 2019; Caunca et al., 2019; Debette et al., 2010; Driscoll et al., 2012; Windham et al., 2017) for TBV ($I^2 = 69.7$ %, $P = 0.010$), four sets from three studies (Arnoldussen et al., 2019; Driscoll et al., 2012; Hsu et al., 2016) for GMV ($I^2 = 78.6$ %, $P = 0.003$), three sets from three studies (Arnoldussen et al., 2019; Driscoll et al., 2012; Hsu et al., 2016) for WMV ($I^2 = 72.1$ %, $P = 0.028$), four sets from two studies (Arnoldussen et al., 2019; Hsu et al., 2016) for HV ($I^2 = 0.0$ %, $P = 0.519$), and six sets from six studies (Caunca et al., 2019; Debette et al., 2010; Hsu et al., 2016; Kuo et al., 2010; Pasha et al., 2017; Windham et al., 2017) for WMHV ($I^2 = 99.3$ %, $P < 0.001$). Thus, the analysis of TBV, GMV, WMV, and WMHV was conducted using the random-effects model, while for HV, we used a fixed-effects model.

The results suggest that a higher WC is predominantly related to lower TBV (β = -0.06, 95 % CI: -0.11 to 0.00). WC was also related to a lower HV (β = -0.07, 95 % CI: -0.10 to -0.05). However, no association was found between WC and GMV, WMV, or WMHV (β = -0.10, 95 % CI: -0.21 to 0.01, β = 0.00, 95 % CI: -0.11, 0.11, and β = 0.03, 95 % CI: -0.09 to 0.14, respectively) (Supplementary Fig. 1).

3.2.3. Brain volume and WHR

In the analyses assessing the relationship between WHR and the prevalence of structural brain abnormalities, we studies three sets of data from three studies (Caunca et al., 2019; Debette et al., 2010; Zade et al., 2013) for TBV ($I^2 = 93.2$ %, $P < 0.001$), two sets from two studies (Climie et al., 2015; Hamer and Batty, 2019) for GMV ($I^2 = 96.3$ %, $P = 0.000$), three sets from three studies (Climie et al., 2015; Jagust et al., 2005; Zade et al., 2013) for HV ($I^2 = 92.4$ %, $P = 0.000$), and six sets from six studies (Caunca et al., 2019; Debette et al., 2010; Jagust et al., 2005; Lampe et al., 2019; Pasha et al., 2017; Zade et al., 2013) for WMHV ($I^2 = 81.1$ %, P = 0.000). All analyses were suitable for analysis by the random-effects model.

We found that only lower HV was associated, to some degree, with a higher WHR (β = -0.45, 95 % CI: -0.90 to 0.00). There was no

Table 1
Characteristics of studies included in the meta-analysis.

Author	Year of publication	Sample size	Country	Mean Age	Follow-up period (years)	Obesity definition	SBA definition
Albanese	2015	3864	USA	49.8	26.2(4.9)	WHO criteria (BMI < 18.5 kg/m^2 was classified as underweight, BMI of 18.5–24.9 kg/m^2 was classified as normal weight, BMI of 25–29.9 kg/m^2 was classified as overweight, and BMI ≥ 30 kg/m^2 was classified as obese)	MRI, 1.5-T Signa Twinspeed system T1/T2; Automated assessment
Anan	2009	95	Japan	58.5	/	Not declared	1.5 T units, Magnetom Vision and Symphony (Siemens Medical Systems, Erlangen, Germany) T2 Assessed by trained raters
Arnolduss	2019	503	Sweden	72.3	9	WHO criteria (BMI); Central Obesity was defined as WC $>$ 102 cm for males and $>$ 88 cm for females.	MRI, 1.5 T MRI scanner T1/T2/ fast fluid-attenuated inversion recovery (FLAIR); semiautomatic WMH segmentation method
Beller	2019	351	Germany	56.1		WHO criteria	MRI, a 3-T Magnetom Skyra FLAIR; FMRIB's Automated Segmentation Tool (FAST)
Bobb	2014	347	USA	60.1		WHO criteria	MRI, a General Electric 1.5-T Signa model T1/T2/FLAIR; Automated assessment
Bond	2011	107	Canada	22.5		WHO criteria	MRI, a Philips Achieva 3.0 Tesla scanner T2; Automated assessment
Bond	2016	79	Canada	22.8		WHO criteria	MRI, a Philips Achieva 3.0 Tesla scanner T2; Automated assessment
Brook	2013	156	Sweden	75		WHO criteria	MRI, a Philips 1.5 Tesla scanner T1; Automated assessment
Caunca	2019	1289	USA	64		BMI as WHO criteria; WC (WC $>$ 40 inches for males and WC $>$ 35 inches for females 27 inches) and WHR (WHR $>$ 0.9 for males and WHR $>$ 0.85 for females 28 inches).	MRI, a single 1.5 T Philips Intera scanner T1; Automated assessment
Choi	2009	5104	Korea	52		WC $\geq$ 90 cm for males, $\geq$ 80 cm for females	1·5 T using a MAGNETOM Espree™ (Siemens, Erlangen, Germany) or a CHORUS™ (ISOL Technology Inc., Seoul, Korea) ; T2; Assessed by radiologists
Climie	2015	560	Australia	67		Not declared	MRI, a 1.5 T General Electric Signa Excite T scanner T1/FLAIR; Processed manually
Croll	2019	3648	Australia	65.9	5.5	Not declared	MRI, a 1.5-tesla MRI scanner T1/FLAIR/DWI; Automated assessment (Visual ratings were performed for presence of lacunes or microbleeds)
Dearborn	2015	934	USA	55.9	10	Not declared	MRI, 1.5 Tesla machines T1/T2; Automated algorithm was used to segment WMH volume, with manual editing to exclude infarcts and other lesions
Debette	2010	733	USA	67		Not declared	MRI, a 1 or 1.5-tesla Siemens Magnetom T1/T2; Automated assessment
Debette	2014	1779	France	72.8		Not declared	MRI, a 1.5-Tesla Magnetom scanner T1/T2; Automated assessment
Ding	2015	486	Iceland	74.6	5.2	WHO criteria	1.5-Tscanner (SignaTwinspeed, General Electric Medical Systems); T2-weighted gradient-echo echoplanar sequence; identified by radiographers
Driscoll	2012	152	USA	69 (7.8)		BMI higher than 30 kg/m^2; Central obesity is defined as sex-specific upper quintile Normal, 18.5–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; obese, $\geq$ 30.0 kg/m^2) (National Heart, Lung, and Blood Institute, 1998)	GE Sigma 1.5 Tesla scanner (Milwaukee, WI); T1/T2; Automated assessment
Gunstad	2008	209	Australia	37.14			MRI, a 1.5 Tesla Siemens Vision Plus system T1; Automated assessment
Hamer	2019	9652	UK	55.3			

(*continued on next page*)

Table 1 (*continued*)

Author	Year of publication	Sample size	Country	Mean Age	Follow-up period (years)	Obesity definition	SBA definition
						BMI as WHO criteria; Central obesity (WHR > 0.85 for females, > 0.90 for males)	MRI, Siemens Skyra 3 T running VD13A SP4 T1/T2; Automated assessment
Hayes	2020	126	USA	74		WHO criteria	MRI, ADNI-approved 3 T MRI scanners T1; Automated assessment
Hidese	2018	601	Japan	41.2		WHO criteria	MRI, the Magnetom Symphony 1.5-tesla T1; Automated assessment
Higuchi	2017	980	Japan	59		WHO criteria	MRI, a 1.5-T scanner T2; Evaluated by specialist
Ho	2011	162	USA	74.7		Not declared	MRI, 1.5 T scanners T1/T2; Automated assessment
Hsu	2016	604	USA	57.7		Not declared	MRI, a 3.0-T Skyra Scanner and a 1.5-T Excite HD MRI scanner T1; Automated assessment
Jagust	2005	112	USA	69.7		WHO criteria	MRI, MRI (GE Signa system; General Electric, Milwaukee, Wis) T1/T2; Automated assessment
Karlsson	2013	45	Finland	46.9		WHO criteria	MRI, Philips Gyroscan Intera 1.5 T CV Nova Dual scanner T1; Automated assessment
Kim	2017	2046	Korea	50		Not declared	MRI, 1.5 T brain MRI T1/T2/FLAIR; Visual rated
Kim	2020	54	Korea	24.6		Obese: BMI $\geq$ 25 kg/m^2, and normal weight: BMI from 18.2 to 24.5 kg/m^2.	MRI, a 3 T human MRI Scanner T1; Automated assessment
Kim	2013	365	Korea	64.7		WHO obesity criteria for the Asian-Pacific Population, overweight (BMI, 23.0–24.9 kg/m^2), obese (BMI, $\geq$ 25.0 kg/m^2).	MRI, 1.5-Tesla superconducting magnet T2; Automated assessment
Kim	2012	1251	Korea	69.7		Overweight (BMI 23.0–24.9 kg/ m^2), obese (BMI $\geq$ 25.0 kg/m^2)	1.5 T superconducting magnet system (ISOL Technology Inc., Kyungki-do, Korea); T2/FLAIR; assessed by neurologists
Kuo	2010	93	Taiwan, China	72.5		Not declared	MRI, a 1.5-T MR unit T1/T2; Automated assessment
Lampe	2019	1825	Germany	59.4		Not declared	MRI, 3 Tesla on a MAGNETOM Verio scanner T1/FLAIR; Automated assessment
Mowry	2018	469	USA	42		WHO criteria	MRI, a 3 T GE Excite scanner T1/T2; Automated assessment
Naganuma	2012	237	Japan	55.9		Not declared	MRI, a field strength of 1.5 T on proton density T1/T2/FLAIR; Assessed by neurologist
Okamura	2018	798	Japan	56.2		WHO criteria	MRI, a 3.0 T MR scanner T1/T2/FLAIR; Assessed by radiologist
Pasha	2017	126	USA	49.1		Not declared	MRI, a 3 T Siemens Skyra MRI scanner T1/T2/FLAIR; Automated assessment
Portet	2012	308	France	71		WC: > 102 cm (males) and < 88 cm (females)	Not declared; T1/T2; semiautomated assessment
Sun	2020	1212	USA	75.2		WHO criteria	MRI, scanned using either 1.5 T or 3.0 T scanner T1; Automated assessment
Vuorinen	2011	112	Europe	72.8	21	Overweight: BMI of 25–30 kg/m^2; Obese: BMI of 30 kg/m^2	1.5-tesla MR unit (Magnetom Vision Format; Siemens) T2 Assessed by neurologist
Widya	2011	471	Scotland, Ireland, and the Netherlands	74.5		Not declared	MRI, a field strength of 1.5 Tesla T1; Automated assessment

(*continued on next page*)

Table 1 (*continued*)

Author	Year of publication	Sample size	Country	Mean Age	Follow-up period (years)	Obesity definition	SBA definition
Windham	2017	3398	USA	61.2		Not declared	MRI, 1.5 T brain MRI T1/T2/FLAIR; Automated assessment
Winter	2008	1137	Germany	65.8		BMI as WHO criteria; WC in males was ≤ 94.0 cm (normal weight), 94.0–101.9 cm (overweight) and ≥ 102.0 cm (obesity). In females it was ≤ 80.0 cm, 80.0–87.9 cm, and ≥ 88.0 cm, respectively; Obese females had WHR ≥ 0.85 and and obese males WHR ≥ 1.0.	MRI, not declared
Yamada	2012	384	Japan	67.5		WHO criteria	MRI, a 1.5-T MRI system T2; Automated assessment
Yamashiro	2014	506	Japan	55.3		A large WC was defined as ≥ 88 cm in females and ≥ 102 cm in males, as proposed in the NCEP-ATP III report. A specific value for large WC (≥ 90 cm in females and ≥ 85 cm in males) proposed by the Japanese Society for the Study of Obesity was also used. The BMI was calculated from height and weight measurements. In addition to a BMI of ≥ 30 kg/m^2, a BMI of ≥ 25 kg/m^2 was also used to define obesity according to the criteria for the diagnosis of 'obesity disease' in Japan	MRI, a 1.5 T MR system T1/T2; Visual rated
Zade	2013	1969	USA	61		WHO criteria	MRI, a Siemens Magnetom 1 T field strength magnetic resonance machine T2; Automated assessment

Abbreviation: BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; USA, United States of America; SBA, structural brain abnormalities; MRI, magnetic resonance imaging; WHO, World Health Organization.

relationship between WHR and other subgroups, such as TBV, GMV, or WMHV (β = -0.16, 95 % CI: -0.36 to 0.04, β = -54.11, 95 % CI: -155.46–47.25, and β = 0.09, 95 % CI: -0.04 to 0.21, respectively) (Supplementary Fig. 2).

3.2.4. Other structural brain abnormalities and BMI

We identified three categorical structural brain abnormality types, assessed as yes or no: lacunar infarct, cerebral microbleed, and WMH. Seventeen sets of data from 11 studies (Anan et al., 2009; Arnoldussen et al., 2019; Caunca et al., 2019; Debette et al., 2010; Higuchi et al., 2017; Kim et al., 2017; T. Naganuma et al., 2012; Okamura et al., 2018; Croll PH et al., 2019; Winter et al., 2008; Yamashiro et al., 2014) were included in the analysis of continuous BMI, and 17 sets from eight studies (Caunca et al., 2019; Debette et al., 2014; Kim et al., 2012; Kim et al., 2013; Okamura et al., 2018; Winter et al., 2008; Yamada et al., 2012; Yamashiro et al., 2014) were included when BMI was analyzed as a categorical variable. We used the random-effects model with continuous BMI (I^2 = 69.9 %, P < 0.001) and the fixed-effects model for categorical BMI (I^2 = 0.0 %, P = 0.850).

The pooled effect of continuous BMI on structural brain abnormalities was insignificant, with OR = 1.11 (95 % CI: 0.98–1.26). The continuous BMI analysis indicated that an increase in BMI (5 kg/m^2 per standard increment) had no effect on structural brain abnormalities (OR = 1.11, 95 % CI: 0.98–1.26), including lacunar infarct (OR = 1.12, 95 % CI: 0.97–1.29) and WMH (OR = 1.25, 95 % CI: 0.95–1.65). However, the results showed that a higher BMI was associated with lower risk of cerebral microbleed (OR = 0.73, 95 % CI: 0.53 to 0.99) (Supplementary Fig. 3).

When using BMI as a parameter of obesity, the pooled effect of overweight or obesity on structural brain abnormalities was significant (OR = 1.17, 95 % CI: 1.04–1.32), especially on lacunar infarct (OR = 1.20, 95 % CI: 1.02–1.40). Sub-group analysis showed a significant relationship between obese (BMI ≥ 30.0 kg/m^2) participants and different structural brain abnormalities, compared with that in normal weight (BMI = 18.0–24.9 kg/m^2) participants (OR = 1.30, 95 % CI: 1.05–1.60) (Fig. 4).

3.2.5. Other structural brain abnormalities and WC or WHR

We analyzed 11 groups of data from seven studies (F. Anan et al., 2009; Arnoldussen et al., 2019; Caunca et al., 2019; Debette et al., 2010; Kim et al., 2017; Winter et al., 2008; Yamashiro et al., 2014) with WC as a continuous variable and six data groups from four studies (Caunca et al., 2019; Debette et al., 2010; Higuchi et al., 2017; Winter et al., 2008) with WHR as a continuous variable. We used a random-effects model to analyze the association between structural brain abnormalities and WC, and WHR (I^2 = 79.0 %, P < 0.001 and I^2 = 93.9 %, P < 0.001, respectively). The results show that a higher WC is related to higher risk of structural brain abnormalities (OR = 1.19, 95 % CI: 1.01–1.41), but WHR was not associated with a greater risk of the different kinds of structural brain abnormalities (OR = 1.18, 95 % CI: 0.77–1.82). Moreover, the subgroup analysis also found no association between an increase in WC (10 cm per standard increment) or WHR (0.1 per standard increment) and any of the structural abnormality types (Supplementary Fig. 4).

We further analyzed central obesity as a binary outcome variable, measured by WC or WHR, for association with structural brain abnormalities, using the random-effects model (I^2 = 86.5 %, P < 0.001). The pooled effect of 12 sets of data from six studies (Caunca et al., 2019; Choi et al., 2009; S. Debette et al., 2014; Portet et al., 2012; Winter et al., 2008; Yamashiro et al., 2014) indicated that the risk of structural brain abnormalities was 1.81 times higher in subjects with central obesity than in the controls (OR = 1.81, 95 % CI: 1.34–2.44). Subgroup analysis of the different brain structural abnormality types indicated that central obesity was associated with a risk of both lacunar infarct (OR = 2.00, 95 % CI: 1.29–3.12) and WMH (OR = 1.41, 95 % CI: 1.07–1.86). The analysis also showed a higher risk of structural brain abnormalities when central obesity was measured by WC (OR = 1.73, 95 % CI: 1.31–2.29), but not by WHR (OR = 2.08, 95 % CI: 0.67–6.41) (Fig. 5).

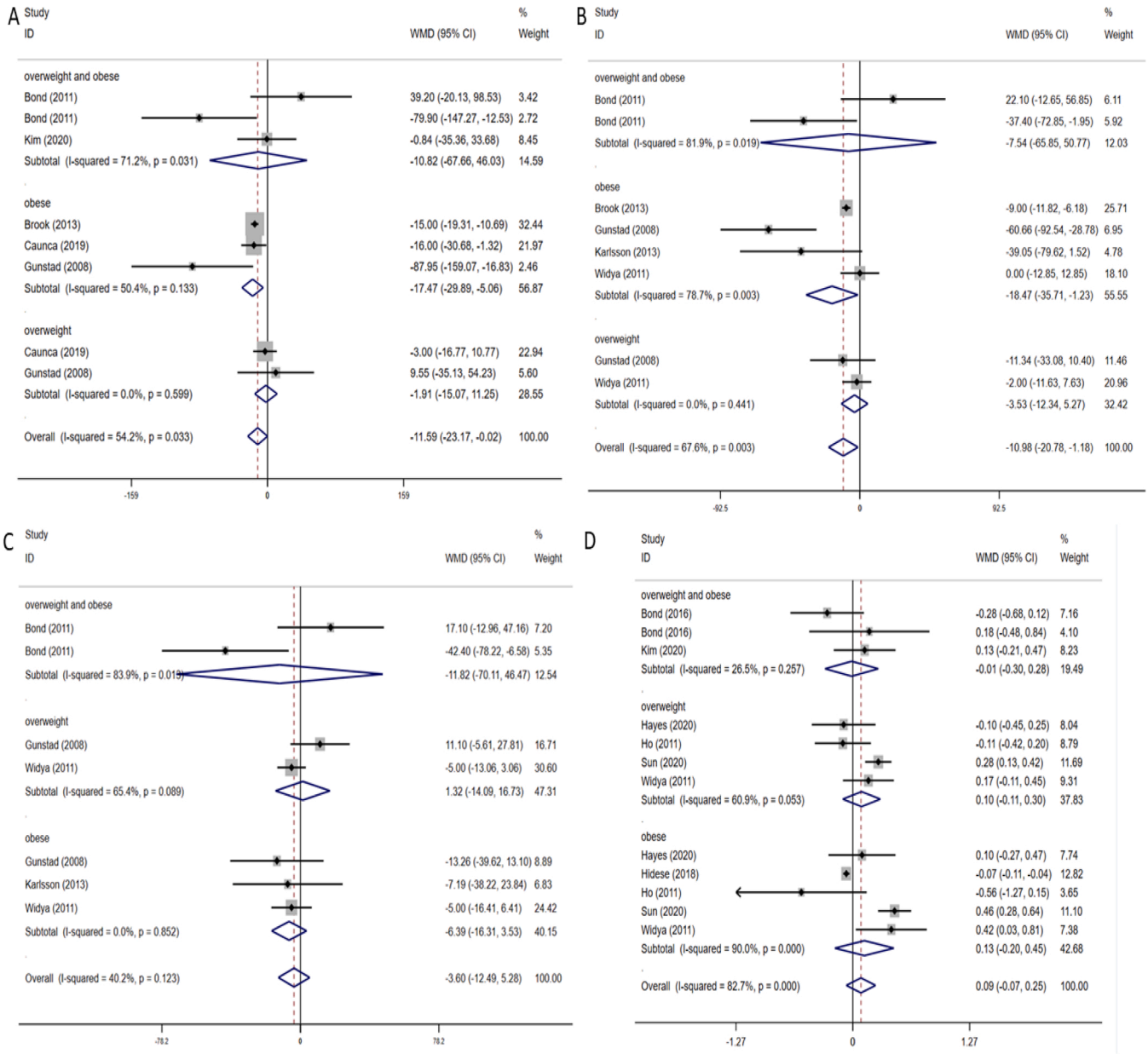

Fig. 2. Cross-sectional analysis of the association between categorical BMI and brain volume.
The association between categorical BMI and structural brain abnormalities. Total brain volume (A), gray matter volume (B), white matter volume (C), hippocampus volume (D).
Abbreviations: BMI body mass index; WMD weighted mean deviation; CI confidence interval.
Where I^2 is the variation in effect estimates attributable to heterogeneity. Overall is the pooled fixed/random effects estimate of all studies. Subtotal is the pooled fixed/random effects estimate of studies in the sub-group analysis. Weights are from fixed/random-effects analysis. %Weight is the weight assigned to each study, based on the inverse of the within- and between-study variance. The size of the gray boxes around the point estimates reflects the weight assigned to each study.

3.3. Meta-analysis results of cohort studies

Three studies provided compatible data on continuous BMI and the risk of structural brain abnormalities (Albanese et al., 2015; Dearborn et al., 2015; PH et al., 2019), and three studies provided compatible data on categorial BMI and the risk of structural brain abnormalities (Albanese et al., 2015; Ding et al., 2015; Vuorinen et al., 2011). However, there were no studies with compatible data on WC/WHR and the risk of structural brain abnormalities.

The RRs of different structural brain abnormalities from individual studies and the pooled estimates for higher BMI vs. normal BMI are shown in Supplementary Fig. 5. BMI was not significantly associated with the overall structural brain abnormalities (for continuous BMI: RR = 1.02, 95 % CI: 0.94–1.12; for categorial BMI: RR = 1.18, 95 % CI: 0.75–1.85). Notably, the analysis included only one study (Vuorinen et al., 2011) that reported a statistically significant RR for brain structural abnormality (white matter lesions) for overweight (RR = 2.53, 95 % CI: 1.70–2.98) and obese (RR = 2.94, 95 % CI: 2.44–3.03) status. The small number of included cohort studies reduced the robustness of the pooled estimate.

3.4. Systematic review of cohort studies

Eight cohort studies provided data in which the reported obesity parameters and outcome measurements were not compatible with other studies. The relevant findings were as follows: Enzinger et al. assessed

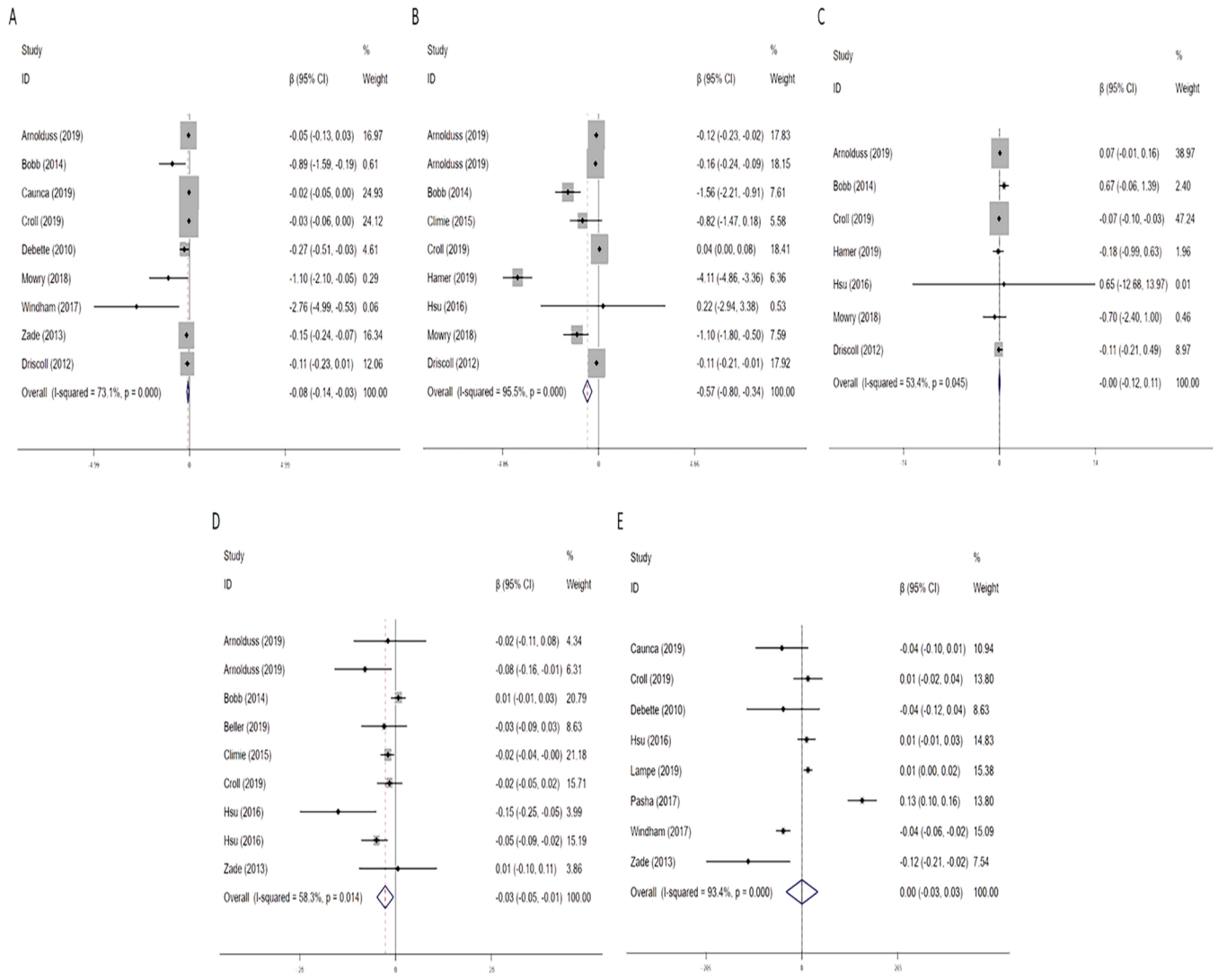

Fig. 3. Cross-sectional analysis of the association between continuous BMI and brain volume.
The association between continuous BMI and total brain volume (A), gray matter volume (B), white matter volume (C), hippocampus volume (D), white matter hyperintensity volume (E).
Abbreviations: BMI, body mass index; CI, confidence interval.
Where I^2 is the variation in effect estimates attributable to heterogeneity. Overall is the pooled random effect estimate of all studies. Subtotal is the pooled random effects estimate of studies in the subbased on the inverse of the within- and between-study variance. The size of the gray boxes around the point estimates reflects the weight assigned to each study.

the brain parenchymal fraction at baseline and subsequent annual brain volume changes over six years for 201 participants, aged 59.8 ± 5.9 years, and found that increasing BMI was significantly associated with a greater longitudinal brain volume loss (Enzinger et al., 2005). Another study of 1352 participants also reported that midlife obesity (BMI ≥ 30 kg/m^2) was associated with an increased rate of global brain atrophy and hippocampal atrophy, while continuous WHR had a null association with brain volume change (Debette et al., 2011). In a study analyzing the impact of body weight variation patterns (weight loss/stable/weight gain) on HV in 349 adults aged 70 years and older, researchers observed hippocampal atrophy among all groups of weight variation patterns after 36 months, but found no differences between the groups (Giudici et al., 2019). Moreover, a study of 420 cognitively unimpaired (Mini--Mental State Examination ≥ 26) individuals aged 60–64 years over an eight year follow-up period showed that those with a higher BMI experienced greater hippocampal atrophy (Cherbuin et al., 2015). In a longitudinal study of annual percentage change in gray matter ratio, researchers found BMI to have a significant main effect (F ratio = 2.82, p = 0.039) on the annual percentage change in gray matter ratio (Taki et al., 2011). However, another study of 295 males and 328 females, aged 55–92 years, with up to 20 years of follow-up found that in females, obesity was protective against volume loss in temporal gray matter (Armstrong et al., 2019). A longitudinal study of 203 healthy participants aged 23–87 years, claimed that a higher BMI was related to increased cortical thinning in the left brain, and this effect was independentof physical activity and did not interact with age (Walhovd et al., 2014).

As for central obesity parameters, we identified one study (Arnoldussen et al., 2019) with 503 subjects and a 9-year-follow-up period where the researchers observed that baseline obese WC (> 102 cm for males and > 88 cm for females) was associated with decreasing HV, particularly in males, and with increasing WMHV in both females and males (the cross-sectional results of this study was included in our analysis, but its longitudinal data were not compatible for analysis).

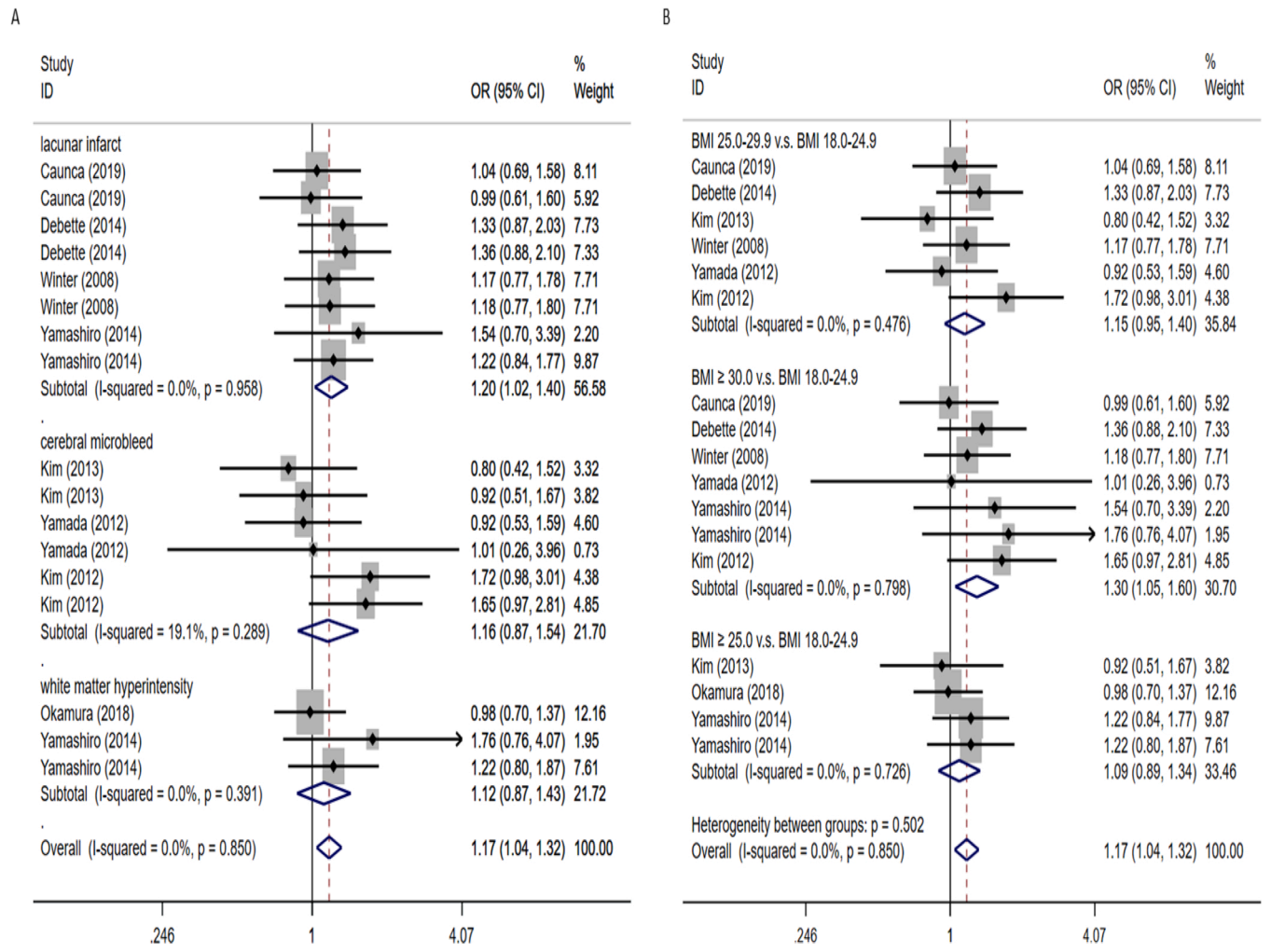

Fig. 4. Cross-sectional analysis of the association between general obesity and structural brain abnormalities.
A: The association between general obesity and different structural brain abnormalities.
B: The association between different categories of BMI and structural brain abnormalities.
The unit of BMI was kg/m^2.
Abbreviations: BMI, body mass index; OR, odd ratio; CI, confidence interval.
Where I^2 is the variation in effect estimates attributable to heterogeneity. Overall is the pooled fixed effects estimate of all studies. Subtotal is the pooled fixed effects estimate of studies in the subbased on the inverse of the within- and between-study variance. The size of the gray boxes around the point estimates reflects the weight assigned to each study.

3.5. *Sensitivity analysis*

To further adjust for potential confounders, we analyzed studies of subjects with a mean age ≥ 55 years. (F. Anan et al., 2009; Arnoldussen et al., 2019; Ebba Beller et al., 2019; Bobb et al., 2014; Brooks et al., 2013; Caunca et al., 2019; Climie et al., 2015; Dearborn et al., 2015; Debette et al., 2010; Debette et al., 2014; Ding et al., 2015; Driscoll et al., 2012; Hamer and Batty, 2019; Higuchi et al., 2017; Ho et al., 2011; Hsu et al., 2016; Jagust et al., 2005; Hayes JP et al., 2020; Kim et al., 2012; Kim et al., 2013; Kuo et al., 2010; Lampe et al., 2019; Naganuma et al., 2012; Okamura et al., 2018; Croll PH et al., 2019; Portet et al., 2012; Vuorinen et al., 2011; Widya et al., 2011; Windham et al., 2017; Winter et al., 2008; Yamada et al., 2012; Yamashiro et al., 2014; Sun et al., 2020; Zade et al., 2013) The results were consistent with the above analyses: continuous BMI was negatively associated with TBV (β = -0.08, 95 % CI: -0.13 to -0.02), GMV (β = -0.59, 95 % CI: -0.86 to -0.32), and HV (β = -0.03, 95 % CI: -0.05 to -0.01); and categorical BMI was negatively associated with TBV (WMD = -13.07, 95 % CI: -19.41 to -6.72) and GMV (WMD = -5.91, 95 % CI: -11.70 to -0.12), and was related to a higher risk of structural brain abnormalities (OR = 1.17, 95 % CI: 1.04–1.32). For studies with subjects younger than 55 years (Albanese et al., 2015; Kim AY et al., 2020; Bond et al., 2016; Bond et al., 2011; Choi et al., 2009; Gunstad et al., 2008; Hidese et al., 2018; Karlsson et al., 2013; Kim et al., 2017; Mowry et al., 2018; Pasha et al., 2017), the results were significant at the following analyses: categorical BMI were negatively associated with TBV (β = -1.10, 95 % CI: -2.13 to -0.08) and GMV (β = -0.57, 95 % CI: -0.80 to -0.34), and continuous BMI was negatively only associated with HV (WMD = -0.07, 95 % CI: -0.10 to -0.03).

We also conducted sensitivity analyses to address potential bias by cognitive status. When only analyzing studies of subjects without cognitive impairment or dementia, (Anan et al., 2009; Kim AY et al., 2020; Ebba Beller et al., 2019; Bobb et al., 2014; Brooks et al., 2013; Caunca et al., 2019; Choi et al., 2009; Climie et al., 2015; Debette et al., 2010; Gunstad et al., 2008; Hamer and Batty, 2019; Hidese et al., 2018; Higuchi et al., 2017; Hsu et al., 2016; Hayes JP et al., 2020; Karlsson et al., 2013; Kim et al., 2012; Kim et al., 2013; Kim et al., 2017; Kuo et al., 2010; Lampe et al., 2019; Mowry et al., 2018; Naganuma et al., 2012; Okamura et al., 2018; Pasha et al., 2017; Croll PH et al., 2019; Portet et al., 2012; Widya et al., 2011;Windham et al., 2017; Winter

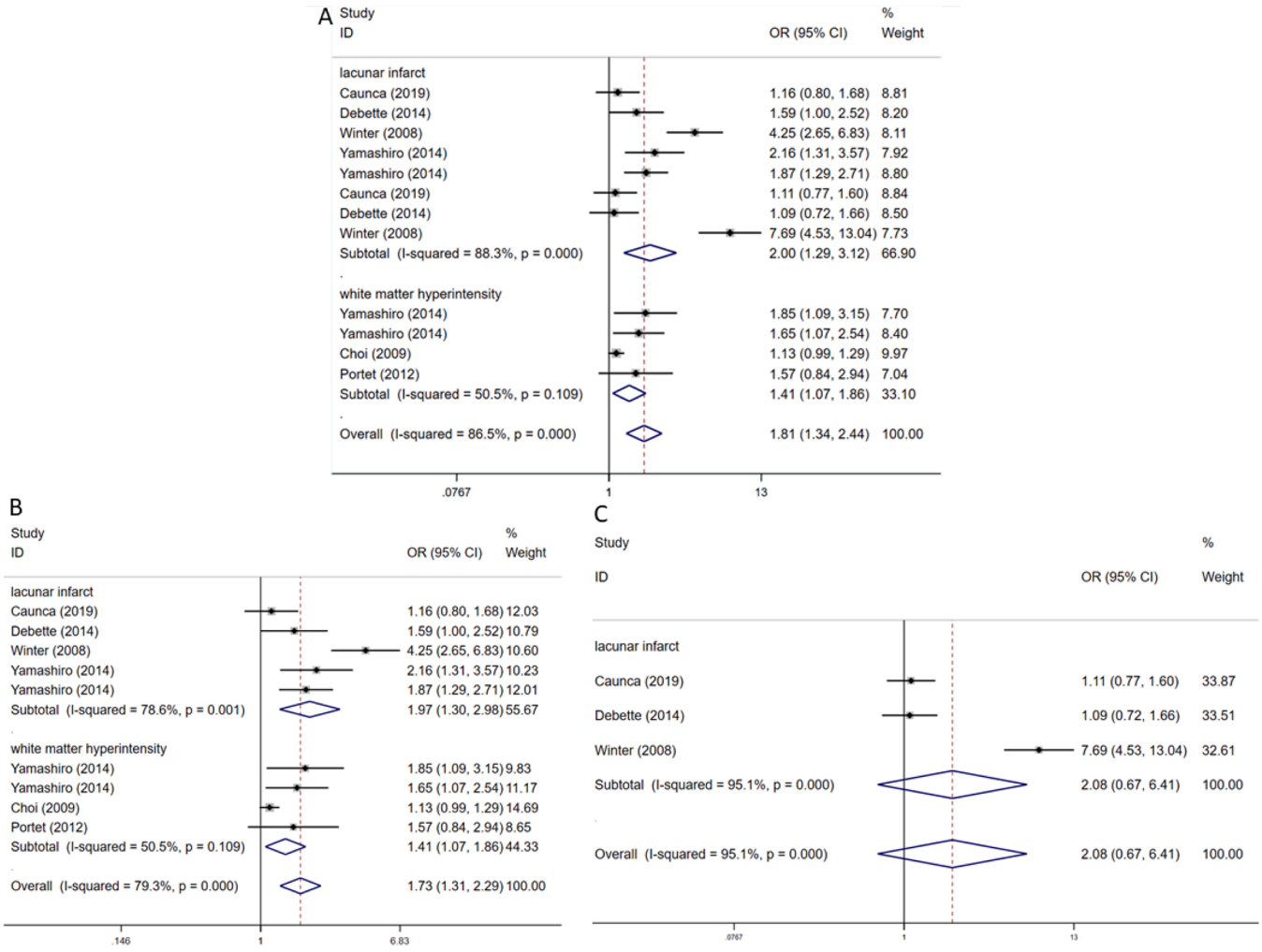

Fig. 5. Cross-sectional analysis of the association between central obesity and structural brain abnormalities.
The association between central obesity using category WC and WHR (A), category WC (B), category WHR (C) and different structural brain abnormalities.
Abbreviations: WC, waist circumference; WHR, waist-to-hip ratio; OR, odds ratio; CI, confidence interval.
Where I^2 is the variation in effect estimates attributable to heterogeneity. Overall is the pooled random effects estimate of all studies. Subtotal is the pooled random effects estimate of studies in the subbased on the inverse of the within- and between-study variance. The size of the gray boxes around the point estimates reflects the weight assigned to each study.

et al., 2008; Yamashiro et al., 2014; Sun et al., 2020; Zade et al., 2013) a greater risk of cerebral structural impairment was consistently found in obese patients compared to the overall results.

In search of another explanation for the heterogeneity in the current study, we conducted analyses according to geographic locations. The significant relationship between central obesity and structural brain abnormalities remained in the European (OR = 2.45, 95 % CI: 1.19–5.02) and Asian population (OR = 1.62, 95 % CI: 1.19–2.20), but not in the American population (OR = 1.14, 95 % CI: 0.88–1.47). Each 5 kg/m^2 increase in BMI was associated with a 1.25 times higher risk of structural brain abnormalities in Asian people (OR = 1.25, 95 % CI: 1.05–1.50). Obesity or overweight in European and Asian people was also associated with a higher risk of structural brain abnormalities (OR = 1.26, 95 % CI: 1.02–1.55 and OR = 1.17, 95 % CI: 1.00–1.37, respectively). The difference between geographic location also existed in the association between obesity/overweight and brain volume parameters. (Supplementary Table 7) Thus, geographic location can be another explanation for heterogeneity in the current analysis.

3.6. Publication bias

According to the Cochrane Handbook for Systematic Reviews of Interventions Version 6.0 (Julian P.T. Higgins et al., 2019), as a rule of thumb, tests for funnel plot asymmetry should be used only when more than ten studies are included in the meta-analysis because, when there are too few studies, the power of the tests is too low to distinguish chance from real asymmetry. In this study, the Egger's test had *P*-values > 0.05 ($P = 0.152$ and 0.536) for the relationship between continuous and categorical BMI and different types of structural brain abnormalities, indicating no significant bias among them. The funnel plot of these studies showed an asymmetrical inverted distribution, which is consistent with the Egger's test results (Supplementary Fig. 6).

4. Discussion

4.1. Principal findings

Our comprehensive meta-analysis synthesized all available compatible data from studies reporting the association of obese status with the risk of structural brain abnormalities, an analysis that has not been conducted till date. In the analyses of cohort studies, we found no statistically significant association between BMI and structural brain abnormalities. As for our analyses of cross-sectional data, we found that a higher BMI was closely related to lower TBV, while WC and WHR were

not associated with TBV. This indicates that global obesity was more closely related to TBV than central obesity.

Our results show that HV could be negatively associated with all evaluated obesity markers, which is consistent with previous studies showing a strong relationship between body fat and the hunger-satiety signals processed in the limbic system (Hargrave et al., 2016; Parimisetty et al., 2016).

Except for WHR, all parameters of obesity were adversely associated with GMV. Although the literature on WHR and GMV (and other brain irregularities) is quite extensive, epidemiologic studies are especially scarce. There were only two sets of data (Climie et al., 2015; Hamer and Batty, 2019) available for analyzing the association between WHR and GMV, leading to a lower power of the results.

In addition, our results confirm that there is no evidence supporting the relationship between obesity parameters and WMV/WMHV: a finding concordant with other studies (Caunca et al., 2019; Del Brutto et al., 2016).

As for other types of cerebral morphologic abnormalities (including lacunar infarct, WMH, and cerebral microbleed), WC/WHR showed a more robust overall relationship with the risk of these abnormalities, while BMI levels were related to a lesser extent. Specifically, central obesity was most closely related to the risk of lacunar infarct and WMH. The results of analyses related to cerebral microbleeds performed in our study were all insignificant. This also confirms the recently proposed idea that central obesity or visceral obesity has a higher predictive power than global obesity for the risk of structural brain abnormalities (S. Chang et al., 2012; Lee et al., 2013; Mooney et al., 2013).

Also, a noteworthy aspect is that in recent years, researchers have discovered a U-shaped association between age and the impact of obese status on structural brain abnormalities (Kaur et al., 2015; Kim et al., 2015a, 2015b; Qizilbash et al., 2015; Singh-Manoux et al., 2018). They found that obesity in young and early old age, but not in middle age, could increase the risk of structural and other functional brain abnormalities. To test these results, we assessed how the aging process affects the relationship between obese status and the risk of developing different structural brain abnormalities by reanalyzing the data stratified by age. Most results were similar to our overall results. Obesity measured by continuous BMI was negatively associated with total brain volume and gray matter volume among participants older than 55 years, not those younger than 55 years. Categorical obese status was associated with total brain volume and gray matter volume among all age sub-groups. However, studies focused on individuals younger than 55 years were few and the results need to be explained cautiously.

Structural brain abnormalities, including WMHs, lacunar infarct, microbleeds, and atrophy, are important causes of cognitive impairment and dementia (Wardlaw et al., 2013). These functional abnormalities can commonly coexist with structural brain abnormalities in older people. Cognitive impairment and structural brain abnormalities share risk factors such as hypertension, diabetes, and others (Dichgans and Zietemann, 2012; Vermeer et al., 2003). Thus, the cognitive status of subjects might be a potential bias. However, our sensitivity analysis in cognitively unimpaired subjects suggests that dementia or other cognitive malfunction did not substantially influence our results. Obesity status, to some extent, could be considered to have a reliable association with structural brain abnormalities.

Increasing evidence shows that central obesity plays a greater role than subcutaneous adiposity in the neurodegenerative, vascular, and metabolic processes that affect the brain's structures (Debette et al., 2010; Jagust et al., 2005; Widya et al., 2011). Intriguingly, in some analyses, we found an association with WC but not with WHR. From these results, we can infer differences between these metrics. Arguably, WC is more directly linked to the level of visceral fat than WHR. There are several problems inherent in the use of ratio indicators, such as WHR (Dobbelsteyn et al., 2001). According to the WHO STEPS protocol (World Health Organization, 2005), WC should be measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. In contrast, hip circumference is measured at the widest part of the buttocks, without any anatomical marks, leading to larger variability within and between measurements. Moreover, it might be more difficult to reach a defined accuracy for hip circumference measurement in WHR than measuring the WC because of the discrepancies in placement, tightness, type of measuring tape, and positioning of the subject. On the other hand, in the WHR calculation, massively obese individuals might end up having the same WHR value as lean individuals. These factors could limit the potential use of WHR as a central obesity parameter. This is consistent with our results: WC was associated with lower GMV and HV, while WHR was not.

4.2. Underlying mechanisms

Although it is quite clear that other complications of obesity (comorbid hypertension and diabetes) could be indirectly detrimental to the brain, the mechanism behind the association between obesity and structural changes in the brain is still not fully understood. There are several possible mechanisms by which obesity might affect the brain's structure. First, the obesity-induced chronic inflammatory state could lead to a neuroinflammatory process in the central nervous system (CNS) that might contribute to neurodegeneration. Obesity is closely associated with inflammatory factors. IL-6 and TNF-α are produced in the adipose tissue and induce hepatic production of C-reactive protein (CRP) (Pou et al., 2007). Besides, the blood-brain barrier (BBB) permeability and function are also affected in the obese state. Studies have indicated that obesity suppresses enzymatic activities and cytoskeletal proteins (e.g., neuron-specific β-tubulin, which influences cell proliferation and adult neurogenesis) in cerebral micro-vessels composing the BBB. The suppressed activity results in impaired CNS functions (Hsuchou et al., 2012a; Ouyang et al., 2014). Furthermore, it modulates the BBB permeability, allowing inflammatory factors such as CRP to enter the CNS. Once in the CNS, CRP can induce subtle glial cell activation and reactive gliosis (Hsuchou et al., 2012a; Hsuchou et al., 2012b). Second, in obese status, modulated expression of adipose tissue-derived hormones, including adiponectin, leptin, resistin, and ghrelin, could also play a role in the relationship between obesity and brain atrophy (Funahashi et al., 2003; Narita et al., 2009). Animal studies have demonstrated the downregulation of the brain-derived neurotrophic factor, a protein that was shown to promote neurogenesis and synaptic transmission, in high-fat diet-fed mice (Boitard et al., 2014; Kanoski et al., 2007). Third, the brain impacts body weight regulation and eating behavior (N. D. Volkow et al., 2017; Ziauddeen et al., 2012). Structural brain abnormalities, such as reduced GMV and HV, affect signaling pathways in the cortical and limbic tracts and alter the reward circuitry of food-related stimuli. These types of structural brain irregularities might provoke vulnerability for food addiction and obesity. In conclusion, the relationship between obesity and structural brain abnormalities might form a vicious cycle. The results of our study, however, could merely prove one aspect of this relationship because we lack the data on the impact of structural brain abnormalities on the obese status.

4.3. Strengths and limitations

The present study has several strengths. To our knowledge, this is the first meta-analysis exploring the association between obesity and structural brain abnormalities. We included 45 high quality studies with 49,439 participants, which enabled us to test the associations in different subgroups. Additionally, we performed sensitivity analyses based on geographical location and age. Thus, our meta-analysis provided good evidence for the association between obesity and structural brain abnormalities.

Several limitations of this study should be noted as well. The analyzed data were mainly from cross-sectional studies. This made it impossible to differentiate between obesity-related structural brain

abnormalities and structural brain abnormalities-induced obesity. We only found five cohort studies (Albanese et al., 2015; Dearborn et al., 2015; Ding et al., 2015; Croll PH et al., 2019; Vuorinen et al., 2011) with compatible data that were closely related to the association between BMI and structural brain abnormalities. Although we performed meta-analyses of these five studies, the sample size was too small to secure the statistical power of our study. Not many longitudinal studies on central obesity parameters like WC or WHR and structural brain abnormalities, however, have been conducted. We found more longitudinal cohort studies mainly focused on the association between functional brain abnormalities (e.g., Alzheimer's Disease, dementia, etc.) and obesity without any concerns regarding structural brain abnormalities. Second, in many studies using beta coefficient values to demonstrate the relationship between obesity markers and structural brain abnormalities, different confounders were adjusted in the original studies. Sociodemographic factors, such as age and sex, health behaviors, and vascular risk factors, among others, were adjusted among the groups for analysis. Since the original data were not available for extraction, this probably biased our estimates. Sex is an important confounder in the association between obesity and brain abnormalities and might underlie different pathways to brain changes through hormonal alterations. However, it was impossible for us to conduct a separate analysis for each sex because of the lack of data. In addition, it was not possible to transform the beta coefficient values into OR values when the data was modeled using linear regression. We, therefore, analyzed data with beta values and data with OR values separately. This may have resulted in underestimating the associations. Besides, the WC or WHR standards for central obesity varied between articles according to age, sex, and ethnic group. In the study by Hamer and Batty. (M. Hamer and G. D. Batty, 2019) for instance, researchers defined central-obesity as WHR $>$ 0.9 for males and $>$ 0.85 or females, while another study (Winter et al., 2008) defined it as WHR $>$ 1.0 for males and $>$ 0.85 for females. Although sociodemographic factors had been modified in the original articles, our results for WC and WHR as dichotomous variables should be interpreted with caution because the analyses were done without access to the original data.

4.4. Future implications

Future longitudinal studies on obesity-induced structural brain abnormalities would be of pivotal importance to enrich our findings. More research is needed to determine which specific brain regions are strongly associated with a certain type of obesity-induced brain structural abnormality and their relationship with any eventual type of cognitive decline (L. Griffanti et al., 2018). Moreover, a future study in the general population, with a broader age range, could be essential for defining a window of opportunities for preventing obesity-induced structural brain abnormalities. Particularly the relationship between obesity and structural brain changes in children has become a concern these days. Studies based on the NIH Adolescent Brain and Cognitive Development (ABCD) study (Rapuano et al., 2020; Lisa Ronan et al., 2019) demonstrated that among the recruited 2700 children between the ages of 9 and 11 years, increased BMI was associated with a significantly reduced mean cortical thickness. Two more studies found relevant evidence as well (Laurent et al., 2020; Mestre et al., 2017a, 2017b): obese children, relative to those with healthy weight, had significantly reduced hippocampal volume and cortical thickness. Additionally, more studies that evaluate the association between radiography-based measurements (for example, on CT scans) of the abdominal fat compartment with MRI markers of neurodegeneration would add accuracy to the current findings (Kanaya et al., 2009).

Most importantly, further longitudinal research focused on the impact of brain structural irregularities on fat accumulation is necessary to accurately explain this relationship. According to Mestre et al. (2017), reduced brain volume, especially HV and GMV, could lead to an increase in obesity markers through the resulting malfunctioning feeding behaviors. Studies have shown that such feeding behaviors are caused by neuronal influence on body weight regulation. Eating behavior functioning is affected through the reward circuitry of food-related stimuli, in association with subcortical gray matter, including the globus pallidus and caudate nucleus. Moreover, abnormalities of the hippocampus (Benoit et al., 2010; Davidson et al., 2007; Hargrave et al., 2016), where hunger and satiety signals are processed, could lead to altered feeding behaviors and weight regulation. However, studies assessing obesity status in patients with structural brain abnormalities are generally sparse, and concrete evidence for this relationship is currently lacking.

4.5. Conclusion

Our meta-analysis is among the most extensive studies to examine the association of several obesity measures with MRI metrics of structural brain abnormalities. We conclude that a greater BMI is associated with lower brain volume. In addition, higher WC/WHR, but not BMI, is associated with a higher risk of lacunar infarct and WMH. Future longitudinal studies, however, are needed to elucidate the causal relationships and explore the optimal approach to prevent the occurrence of these structural brain abnormalities.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2021.101445.

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