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Abdominal obesity and lower gray matter volume: a Mendelian randomization study

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ABSTRACT

We investigated the relationship of anthropometric markers of obesity with quantitative magnetic resonance imaging markers of brain aging, including measures of total brain volume (TBV), gray matter volume (GMV), hippocampal volume, white matter hyperintensity volume (WMHV), and brain infarcts, and examined causality using Mendelian randomization (MR). Analyses were performed in 1779 individuals (60.4% women, 72.8 ± 4.1 years of age) from the 3C-Dijon population-based cohort study (N = 1555 for the MR). Larger waist-to-hip-ratio (WHR) and waist circumference (WC) were associated with lower TBV ($p = 0.0001$ and $p = 0.005$), and lower GMV ($p = 0.0008$ and $p = 0.003$), independently of age, gender, body mass index (BMI), and vascular risk factors. Higher BMI, WC, and WHR were associated with larger WMHV and WC with brain infarcts, before adjusting for vascular risk factors only. We used MR to investigate the inverse relationship between WHR and GMV. One valid instrumental variable was available in women only (rs6905288), which was associated with GMV ($p = 0.015$). Age and BMI-adjusted effect estimates from the MR analysis confirmed the inverse association between GMV and WHR and are in favor of a causal association.

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1. Introduction

Over the past decades, obesity has become a major public health issue, threatening to reverse health benefits obtained by improved vascular disease prevention (Gaziano, 2010). Beside its impact on vascular events and cancer, there is mounting evidence that obesity raises the risk of cognitive decline and dementia (Gustafson, et al., 2003; Kalmijn, et al., 2000; Kivipelto, et al., 2005; Whitmer, et al., 2005).

Magnetic resonance imaging (MRI) markers of brain aging have been proposed as intermediate endpoints for clinical trials evaluating preventive treatments for dementia (Schmidt, et al., 2004). Deciphering the association of these MRI markers with obesity is important to optimize the design of preventive interventions and may further improve our understanding of the mechanisms relating overweight to dementia. Recent studies suggest an association of obesity and visceral adipose tissue with lower total or regional brain volumes (Brooks, et al., 2013; Debette, et al., 2010; Enzinger, et al., 2005; Gunstad, et al., 2008; Gustafson, et al., 2004a; Ho, et al., 2010; Jagust, et al., 2005; Pannacciulli, et al., 2006; Raji, et al., 2010; Taki, et al., 2008; Walther, et al., 2010; Ward, et al., 2005; Yokum, et al., 2012). The relationship between adiposity and vascular brain injury is more controversial, as some studies have

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observed a significant association of obesity markers with presence or burden of white matter lesions (Anan, et al., 2009; Gustafson, et al., 2004b; Jagust, et al., 2005), whereas others did not report any association (Debette, et al., 2010). An important issue with these mainly cross-sectional studies is that observed relationships may be explained, at least partly, by unmeasured confounding or reverse causation. Indeed, obesity is associated with various comorbidities (Gaziano, 2010), and while excess adiposity is often suggested as causing reduced brain volumes (Debette, et al., 2010; Gustafson, et al., 2004b; Taki, et al., 2008; Walther, et al., 2010), there is also a wealth of data proposing a reverse mechanism by which volume reductions in areas associated with reward and control could lead to abnormal eating behavior and promote obesity (Carnell, et al., 2012; Le, et al., 2009; Pannacciulli, et al., 2006; Yokum, et al., 2012). Further studies are needed to examine which components of structural brain aging are more particularly associated with obesity, and to gather evidence supporting causality.

As part of a large epidemiological study of elderly community-dwelling individuals, our aims were 2-fold: first, to investigate the association of anthropometric measures of global and abdominal adiposity with brain volumes (total brain [TBV], gray matter [GMV], hippocampal volume [HV]), and with markers of vascular brain injury (white matter hyperintensity volume [WMHV], MRI-defined brain infarcts) in the general population; and second, to examine the causality of the observed relationships by performing a Mendelian randomization study, using genes associated with adiposity as instrumental variables.

2. Methods

2.1. Study population

The 3C-Dijon study is a population-based cohort of 4931 French non-institutionalized individuals aged ≥65 years (3C-Study-Group, 2003; Godin, et al., 2008). Participants aged <80 years enrolled between June 1999 and September 2000 (n = 2,763) were invited to undergo brain MRI: 2285 subjects agreed (82.7%), but 1924 MRIs were performed because of financial limitations. After exclusion of participants without anthropometric data or quantitative measurements of brain volume, 1779 individuals were available for analyses (1074 women and 705 men; Fig. e-1). Compared to 3C-Dijon participants aged <80 years with anthropometric data who were not included in the brain MRI study, those included had less vascular risk factors and adiposity (Table e-1). For the Mendelian randomization (MR) study, analyses were restricted to 1555 participants (946 women and 609 men) with measures of brain volumes and anthropometric variables, who had successfully undergone genome-wide genotyping (Fig. e-1). The protocol was approved by the Ethics Committee of Kremlin-Bicêtre University Hospital, Paris. Participants signed an informed consent form.

2.2. Anthropometric variables

Weight and height were measured at baseline; BMI was calculated as the ratio of weight (kg) to height (m) squared. Anthropometric measures were taken at baseline using a non-elastic flexible plastic tape. Waist circumference (WC) was measured midway between the last rib and the top of the iliac crest. Hip circumference was measured at the level of the trochanter major. Waist-to-hip ratio (WHR) was calculated as the ratio of waist to hip circumferences.

2.3. Brain MRI

MRI acquisition was performed on a 1.5-Tesla Magnetom scanner (Siemens, Erlangen) (Godin, et al., 2008). Three-dimensional (3D) high-resolution T1-weighted brain volume was acquired using a 3D inversion recovery fast spoiled-gradient echo sequence and T2- and proton density (PD)–weighted brain volumes were acquired using a 2-dimensional dual spin echo sequence with 2 echo times. Images were sent to the database repository (Godin, et al., 2008), where they were analyzed with the optimized Voxel-Based Morphometry protocol (Good, et al., 2001), using Statistical Parametric Mapping 99, modified to take into account structural characteristics of the aging brain (Godin, et al., 2009; Lemaitre, et al., 2005). Gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) volumes were estimated as the integral of voxel intensities over the respective modulated tissue partition images; total intracranial volume was computed as their sum, and total brain volume (TBV) as the sum of GM volume (GMV) and WM volume. Hippocampal volume (HV, sum of left and right hippocampal regions) was computed by integrating voxel intensities of modulated GM partition images within this region of interest (Lemaitre, et al., 2005). Fully automated image processing software was developed to detect, measure, and localize WM hyperintensities and to quantify white matter hyperintensity volume (WMHV) (Maillard, et al., 2008). Brain infarcts (BI), defined as focal lesions >3 mm in diameter with the same signal characteristics as CSF, were rated on T1, T2 and PD-weighted images (Zhu, et al., 2010), and discriminated from dilated Virchow-Robin spaces using multiplanar reformatting (Zhu, et al., 2011).

2.4. Genotyping and imputations

Genotyping was performed at the French Centre National de Génotypage on Illumina Human610-Quad BeadChips (Lambert, et al., 2009); 4263 participants were successfully genotyped. After exclusion of 20 nonwhite individuals and 128 first-degree relatives, 4115 individuals with genome-wide genotypes were available, of whom 1590 had brain MRI and 1555 also had anthropometric measures (Fig. e-1). After quality control (e-Methods, section 1), 505,643 single nucleotide polymorphisms (SNPs) were available and used for imputation on the 1000 Genomes database (August 2010 release; e-Methods, section 2).

2.5. Polymorphism selection

For the MR study, performed for the association between WHR and GMV (the strongest that we observed), we searched the literature for single nucleotide polymorphisms (SNPs) associated with WHR at a genome-wide significant level ($p < 5 \times 10^{-8}$), with replication in an independent dataset. We used the most recently published and largest genome-wide association study (Heid, et al., 2010). Of 11 independent SNPs fulfilling these criteria (Table e-2), 10 were available in our dataset, of which 5 genotyped and 5 imputed (see Table e-2 for imputation quality); 1 SNP (rs4846567) was not available, and we used a proxy in complete linkage disequilibrium (rs2820446, $r^2 = 1$).

2.6. Covariates

Definitions of covariates are provided in e-Methods, section 3.

2.7. Statistical analysis

We calculated partial correlation scores between MRI markers of brain aging and anthropometric measures of adiposity, adjusting for age and gender. TBV and GMV were standardized by dividing them by total intracranial volume. WMHV was log-transformed because of a skewed distribution (Fornage, et al., 2011). TBV, GMV, HV, and WMHV were studied as continuous variables and BI

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