

Association of SBP and BMI with cognitive and structural brain phenotypes in UK Biobank

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Objective: To test for associations between SBP and BMI, with domain-specific cognitive abilities and examine which brain structural phenotypes mediate those associations.

Methods: Using cross-sectional UK Biobank data (final $N=28\,412$), we examined SBP/BMI vs. cognitive test scores of pairs-matching, matrix completion, trail making test A/B, digit symbol substitution, verbal–numerical reasoning, tower rearranging and simple reaction time. We adjusted for potential confounders of age, sex, deprivation, medication, apolipoprotein e4 genotype, smoking, population stratification and genotypic array. We tested for mediation via multiple structural brain imaging phenotypes and corrected for multiple testing with false discovery rate.

Results: We found positive associations for higher BMI with worse reaction time, reasoning, tower rearranging and matrix completion tasks by 0.024–0.067 SDs per BMI SD (all $P < 0.001$). Higher SBP was associated with worse reasoning (0.034 SDs) and matrix completion scores (–0.024 SDs; both $P < 0.001$). Both BMI and SBP were associated with multiple brain structural metrics including total grey/white matter volumes, frontal lobe volumes, white matter tract integrity and white matter hyperintensity volumes: specific metrics mediated around one-third of the associations with cognition.

Conclusion: Our findings add to the body of evidence that addressing cardiovascular risk factors may also preserve cognitive function, via specific aspects of brain structure.

Keywords: brain, cardiovascular, cognitive, epidemiology, mediation

Abbreviations: APOE, apolipoprotein e; gFA, general factor of fractional anisotropy; gMD, general factor of mean diffusivity; SNP, single nucleotide polymorphism; TMT, trail making test; WMH, white matter hyperintensities

understanding these links could have significant implications for ameliorating dementia rates [2,3].

Modifiable cardiovascular risk factors have been linked to subsequent cerebrovascular brain health, however, these studies have generally been relatively small in terms of sample size [4–7]. This means their estimates of association are less likely to be reliable (e.g. influenced by outliers) [8]. The recent SPRINT trial did not show a significant effect of SBP control on dementia rates among $N=9\,361$ randomized participants, although may have been underpowered for that outcome [9]. The largest cross-sectional single study of cardiovascular risk factors and brain health in the general population [10] showed significant associations between increased cardiovascular risk factors such as smoking history, and poorer brain structural health ($N=9\,722$). That study did not however examine concurrent cognitive abilities measured during the MRI visit, as potential mediators.

The current study aims to test for associations between higher BMI and SBP with worse cognitive abilities and assess how much of those associations are mediated by different brain structure measures. We will first estimate associations between BMI and SBP vs. cognitive test scores of trail making test (TMT) A/B; fluid intelligence (verbal–numerical reasoning [11]); simple reaction time; matrix completion and tower rearranging. Then secondly test for BMI/SBP associations with structural brain phenotypes which have been shown to underline worse cognitive abilities and faster decline in ageing: brain grey matter and white matter adjusted for head size [12,13], frontal lobe volumes [10], white matter tract integrity indexed by fractional anisotropy and mean diffusivity [14], total hippocampal volume [15] and white matter hyperintensities (WMH) volumes [16]. We will then test for mediation formally in

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INTRODUCTION

Poor cardiovascular health is a risk factor for worse cognitive and structural brain health, including dementia and stroke, potentially due to common pathologies such as atherosclerosis [1]. Better

terms of exposure (BMI/SBP), mediator (imaging) and outcome (cognitive scores) in cases of statistically significant three-way associations [17]. The principal hypothesis is that higher BMI and SBP will correlate with worse cognitive abilities and that these will be significantly mediated additively and independently by each of the imaging phenotypes. We additionally supplement the cross-sectional tests of association with causal estimates based on genetically instrumented Mendelian randomization analyses [18].

METHODOLOGY

Study design and participants

UK Biobank is a large prospective cohort study including 502 628 participants who attended one of 22 baseline assessment centres from 2006 to 2010 where they completed a series of physical, sociodemographic and medical assessments [19]. In 2014, MRI scanning of a subgroup of 100 000 participants began, and this is ongoing. As of June 2019, MRI data were available on 29 772 participants who attended one of three clinics using identical protocols (71% Cheadle, 24% Newcastle and 5% Reading). This project was completed using UK Biobank application 17689 (PI: D.M.L.).

Ethical approval

The secondary-data analysis study was conducted under generic approval from the NHS National Research Ethics Service (approval letter dated 17 June 2011, ref 11/NW/0382). Written informed consent was obtained from all participants in the study (consent for research, by UK Biobank) [20]. UK Biobank is an open access resource available to verified researchers upon application (<http://www.ukbiobank.ac.uk/>). Written informed consent was obtained from all participants in the study (consent for research, by UK Biobank).

Data availability statement

UK Biobank is an open access resource available to verified researchers upon application (<http://www.ukbiobank.ac.uk/>). Analysis syntax is available upon request.

Imaging data

We selected imaging phenotypes *a priori*, previously shown to be associated with worse cognitive ability and to decline with age: total white matter and total grey matter volumes adjusted for skull size [12]; log WMH volume [16]; overall hippocampal volume [15]; and general factor of fractional anisotropy (gFA), general factor of mean diffusivity (gMD) [14] and general factor of frontal lobe grey matter (gFrontal). The release of brain MRI data as of June 2019 is the Participant of the current study. All brain imaging data used here was processed and quality checked by UK Biobank [21,22], and we make use here of the imaging derived phenotypes. Details on the UK Biobank imaging acquisition and processing including white matter /grey matter and hippocampal segmentation, and on the white matter diffusion processing, are freely available from three sources: the UK Biobank protocol: <http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367> and documentation: <http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977> and

in protocol publications [22,23] (see open-access MRI protocol, pp.11; https://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf). Total white matter hyperintensity volumes were calculated on the basis of T1 and T2 fluid-attenuated inversion recovery, derived by UK Biobank using the Brain Intensity Abnormality Classification Algorithm [24] with the procedure detailed by Miller *et al.* [22]. White matter hyperintensity volumes were log-transformed here due to a positively skewed distribution.

We constructed general factors of white matter tract integrity using principal components analysis. These two separate factors were gFA (eigenvalue = 12.2, 55% variance explained) and gMD (eigenvalue = 12.6, 57% variance explained). Left and right hippocampal volumes were summed to create an overall value. We constructed a general factor of frontal lobe grey matter using 16 subregional volumes described in Supplementary Table 1, <http://links.lww.com/HJH/B418> (eigenvalue = 6.84, 43% variance explained). Total grey matter and white matter were corrected for skull size (by UK Biobank). Significant associations with WMH were subsequently corrected for total brain volume.

Blood pressure and BMI data

SBP was assessed using digital blood pressure (BP) monitors (HEM-7015IT; Omron Healthcare Inc., Kyoto, Japan). We used the second reading because there is evidence the first reading can overestimate BP due to white-coat syndrome [25]. Weight was measured, to the nearest 0.1 kg, using the Tanita BC-418 MA body composition analyser. Height was measured using a Seca 202 height measure. BMI was derived from weight (kg)/[height (m) × height (m)] by UK Biobank. Participants removed their shoes and heavy outer clothing before weight and height were measured. We focused on BMI in the normal to obese range and therefore, excluded 120 participants with BMI less than 18 kg/m² and 862 with BMI more than 45 kg/m². (Subsequently including these participants in the analyses made no difference to the results.) BMI/SBP data are concurrent with MRI/cognitive data.

Covariates

Participants self-reported their smoking history; current, past or never. We collated past and current smokers into 'ever' (vs. never). Participants self-reported medication use for dyslipidaemia, HRT, oral contraceptive or insulin. We excluded participants for whom these data were missing (<5%). Townsend deprivation indices were derived from postcode of residence [26]. This provides an area-based measure of socioeconomic deprivation derived from aggregated data on car ownership, household overcrowding, owner occupation and unemployment. Higher Townsend scores equate to higher levels of area-based socioeconomic deprivation. We additionally controlled for potential population stratification using UK Biobank-derived principal components 1–5, and genotypic array [27]. *Apolipoprotein e4* (APOE e4) genotype presence (vs. non e4 alleles) was derived on the basis of two single nucleotide polymorphisms (SNPs): rs7412 and rs429358, included due to previously reported associations with brain structural phenotypes [28].

Cognitive data

Five cognitive tests were administered at the MRI visit [29]. These were verbal–numerical reasoning, pairs-matching errors six-card version (memory), simple reaction time (processing speed), TMT A/B (processing speed/executive function), digit symbol substitution (number correct; executive function), matrix pattern completion (nonverbal reasoning; adapted from the common ‘matrix reasoning’) and tower rearranging (number of puzzles correct; executive function/planning; adapted from the common ‘towers of Hanoi/London’). Most of these tasks are computerized versions of well validated cognitive tests [30], whereas the tests of reasoning and reaction time are novel to UK Biobank. The MRI-specific tests have shown good reliability and validity [11,29].

Genetic data

UK Biobank genotyping was conducted by Affymetrix using a bespoke BiLEVE Axiom array for ~50 000 participants and the remaining ~450 000 on the Affymetrix UK Biobank Axiom array. All genetic data were quality controlled by UK Biobank as described by the protocol paper [27]. Further information on the genotyping process is available (<http://www.ukbiobank.ac.uk/scientists-3/genetic-data>), including detailed technical documentation (https://biobank.ctsu.ox.ac.uk/crystal/docs/genotyping_sample_workflow.pdf).

In terms of genetic instruments, we used 93 independent genome-wide significant SNPs ($P \leq 5 \times 10^{-8}$) for BMI [31] and 28 for SBP [32] (rs381815 was not genotyped). We constructed externally weighted genetic risk scores for each participant, based on effect estimates reported in each discovery genome-wide association study (GWAS).

Genetic quality controlling

We included polymorphisms in Hardy Weinberg equilibrium ($P > 0.001$), polymorphisms missingness rate less than 0.1 and minor allele frequency more than 0.01. We checked all risk allele frequencies vs. respective original GWAS frequencies, to ensure correct orientation. There were no exclusions due to strand ambiguity [33]. SNPs were conservatively pruned for linkage disequilibrium using the PLINK ‘–indep 50 5 2’ and ‘–indep-pairwise 50 5 0.5’ commands; there were no exclusions.

Statistical analysis

The cognitive outcomes were test scores of: reasoning, digit symbol substitution, pairs-matching errors matrix completion, towers rearranging, reaction time and TMT A + B. Reaction time, pairs-matching errors (+1) and TMT A + B were log-transformed due to nonnormal distributions. The imaging outcomes were: total white matter and total grey matter volumes adjusted for skull size; log WMH volume; overall hippocampal volume (left and right combined); gFA, gMD and gFrontal. Power calculations were performed using G*Power 3 [34]. PLINK v1.90 (Stata Corp., College Station, Texas, USA) was used for genetic quality controlling [35] and Stata V.14 was used for statistical analyses. We removed participants who reported a neurological condition as described previously [11]; the inclusion of which could drive type-1 errors due to skewed results. We report betas in the form of per-SD increases in dependent variables per one-SD increase in the independent variable.

Models

We used two models: partially and fully adjusted. The partially adjusted model included as covariates: age, sex, genotypic array, MRI assessment centre and five genetic principal components. The fully-adjusted model also included: Townsend score, ever-smoking, self-reported medication and *APOE* e4 allele presence vs. absence.

Mediation

We tested for evidence of mediation in cases of three-way exposure/mediator (MRI)/outcome (cognition) associations. This was tested formally using the PROCESS macro with SPSS v. 25 (IBM, Armonk, New York, USA) [17].

Instrumental variable Mendelian randomization analyses

We tested for associations between BMI and SBP allele scores with each outcome based on conventional Mendelian randomization-type instrumental variable analyses using individual-level data: two-stage least squares analysis for continuous traits (using Stata command ‘ivregress’ [36]). In instances of significant associations we supplemented this with more conservative summary-statistic based Mendelian randomization-Egger [37] method, which is more robust to the inclusion of pleiotropic SNPs which can bias causal estimates and increase the rate of false positives (i.e. type 1 errors). We aligned effect alleles and UK Biobank/discovery GWAS allele frequencies were checked for consistency. For Mendelian randomization-Egger analyses specifically we matched covariates with the discovery GWAS summary statistics: for BMI we controlled for age and sex, and SBP univariately; this made no difference to the results in any case (vs. fully adjusted SNP-outcome effect sizes).

RESULTS

Descriptives

MRI data were available on 29 680 participants. We excluded participants with non-white British ancestry, self-report vs. genetic sex mismatch, putative sex chromosomal aneuploidy, excess heterozygosity and missingness rate more than 0.1. We accounted for relatedness between participants by removing one random participant in cases where two individuals were 1st cousins or closer. This left $n = 29 200$ participants. We removed participants with a self-reported neurological condition at MRI; leaving a final study population of $N = 28 412$ participants.

The mean post-exclusions age at baseline was 63.7 years (SD = 7.49), and 12 386 (48%) participants were male. The mean BMI was 26.58 (SD = 4.29; range 18–45), and the mean SBP was 136.52 (SD = 18.69; range 75–237). A power calculation showed that, based on a one-group β slope of 0.05 where each predictor had an SD = 1, 95% power to detect an effect would be achieved with 4320 participants, suggesting the study was well powered. There were significant associations between measured and genetic risk score-estimated SBP [(standardized) $\beta = 0.08$, $P < 0.001$, $r^2 = 0.01$], and BMI ($\beta = 0.11$, $P < 0.001$, $r^2 = 0.02$). Versus an arbitrary dependent variable of log reaction time, unadjusted first-stage regression F values did not suggest weak

TABLE 1. SBP, BMI and cognitive abilities: observational estimates

	Partially adjusted	95% CIs		P	Fully adjusted	95% CIs		P
	Standardized β	Lower	Upper		Standardized β	Lower	Upper	
Log reaction time								
BMI	0.024	0.013	0.036	<0.001	0.025	0.013	0.038	<0.001
SBP	-0.007	-0.021	0.006	0.287	-0.012	-0.026	0.003	0.127
Reasoning								
BMI	-0.058	-0.070	-0.046	<0.001	-0.053	-0.066	-0.040	<0.001
SBP	-0.035	-0.050	-0.021	<0.001	-0.034	-0.049	-0.018	<0.001
Matrix completion								
BMI	-0.052	-0.067	-0.036	<0.001	-0.048	-0.064	-0.032	<0.001
SBP	-0.025	-0.044	-0.007	0.007	-0.024	-0.043	-0.004	0.020
Digit symbol								
BMI	-0.067	-0.082	-0.053	<0.001	-0.065	-0.080	-0.050	<0.001
SBP	-0.013	-0.030	0.005	0.149	0.001	-0.018	0.019	0.952
Tower rearranging								
BMI	0.011	-0.005	0.026	0.185	0.007	-0.010	0.024	0.423
SBP	-0.017	-0.036	0.002	0.079	-0.017	-0.037	0.004	0.107
Pairs matching (errors)								
BMI	-0.030	-0.042	-0.018	<0.001	-0.032	-0.045	-0.019	<0.001
SBP	-0.009	-0.023	0.006	0.241	-0.008	-0.024	0.007	0.297

The *partially-adjusted model*: age, sex, genotypic array, assessment centre and five genetic principal components. *Fully-adjusted model*: additionally corrected for self-reported medication, ever-smoking, Townsend deprivation index and APOE e4 allele presence. Betas reflect increases per SD of the dependent variable, per increase in the independent variable. Negative scores for better for reaction time; positive are better for the rest. CI, confidence interval.

instrumentation (SBP $F=311.59$, $P<0.001$; BMI $F=149.65$, $P<0.001$).

Cognitive function

There were statistically significant associations between BMI (measured at MRI visit) with poorer log reaction time, reasoning, matrix completion and digit symbol substitution scores (Table 1). Higher BMI associated with better pairs-matching performance. In terms of SBP, there were associations between higher observed values with poorer reasoning and Matrix completion. These associations were significant in fully-adjusted models and survived correction

for multiple testing with false discovery rate (FDR) [38], although effect sizes were small: varying from 0.02 to 0.06 SDs difference in cognitive scores, per SD of SBP (18.69 mmHg) and BMI (4.29 unit). A negative β is reflective of better performance on reaction time (faster responses) and pairs-matching (fewer errors), whereas for other tests negative betas are worse.

Brain imaging

As shown in Table 2, there were significant associations between measured BMI and smaller total grey matter volume, and larger WMH volume. Higher BMI was associated

TABLE 2. SBP, BMI and brain structural phenotypes: observational estimates

	Partially adjusted	95% CIs		P	Fully adjusted	95% CIs		P
	Standardized β	Lower	Upper		Standardized β	Lower	Upper	
Grey matter volume								
BMI	-0.091	-0.102	-0.079	<0.001	-0.091	-0.104	-0.079	<0.001
SBP	-0.020	-0.034	-0.007	0.003	-0.022	-0.037	-0.008	0.003
White matter volume								
BMI	0.013	-0.002	0.028	0.084	0.008	-0.008	0.023	0.334
SBP	0.021	0.005	0.038	0.013	0.021	0.002	0.039	0.027
Total hippocampal volume								
BMI	-0.006	-0.020	0.009	0.437	-0.007	-0.023	0.008	0.368
SBP	-0.011	-0.027	0.006	0.207	-0.005	-0.023	0.013	0.604
gFA: fractional anisotropy								
BMI	-0.009	-0.025	0.006	0.249	-0.006	-0.022	0.011	0.514
SBP	-0.065	-0.083	-0.047	<0.001	-0.061	-0.081	-0.041	<0.001
gMD: mean diffusivity								
BMI	-0.022	-0.038	-0.007	0.004	-0.020	-0.036	-0.003	0.018
SBP	0.092	0.074	0.110	<0.001	0.091	0.072	0.110	<0.001
White matter hyperintensity volume								
BMI	0.119	0.106	0.133	<0.001	0.115	0.101	0.130	<0.001
SBP	0.129	0.113	0.144	<0.001	0.125	0.108	0.142	<0.001
gFrontal								
BMI	0.008	-0.004	0.021	0.199	0.009	-0.005	0.023	0.205
SBP	-0.027	-0.041	-0.011	0.001	-0.025	-0.041	-0.008	0.003

The *partially-adjusted model*: age, sex, genotypic array, assessment centre and five genetic principal components. *Fully-adjusted model*: additionally corrected for self-reported medication, ever-smoking, Townsend deprivation index and APOE e4 allele presence. Betas reflect increases per SD of the dependent variable, per increase in the independent variable. White and grey matter adjusted for head size. CI, confidence interval; gFA, general factor of fractional anisotropy; gFrontal, general factor of frontal lobe volumes; gMD, general factor of mean diffusivity.

with better (i.e. lower) gMD. SBP was associated with poorer total white matter volume, gFA; gMD, gFrontal and WMH volume. The effect sizes were again small, around 0.1 SDs difference in brain phenotype values, per SD of BMI/SBP. In sensitivity analyses, the WMH associations were unaffected when adjusted for total brain volume. Significant associations all survived correction for multiple testing on the basis of FDR. (A positive β is worse for WMH volume and gMD, whereas for other values negative betas are worse.)

Mediation

We tested whether imaging measures significantly mediated the associations between BMI and SBP and cognitive scores, using cases of three-way exposure/mediator/outcome associations. Supplementary Table 3, <http://links.lww.com/HJH/B418> shows most of the imaging and cognitive phenotypes were inter-correlated at nominal P less than 0.05 based on unadjusted univariate Pearson correlations. We used the PROCESS macro Model 4 in SPSS, hypothesising multiple mediators which can be orthogonal.

The results of the mediation analyses are shown in Supplementary Table 4, <http://links.lww.com/HJH/B418>. For BMI, there was evidence that the association between BMI and digit symbol scores were significantly mediated by grey matter, gMD and WMH volume overall [overall indirect estimate = -0.007 , 95% confidence interval (CI) = -0.012 to -0.001], where the association attenuated from $\beta = -0.044$ (95% CI = -0.069 to -0.011 , $P = 0.001$) to $\beta = -0.037$ (95% CI = -0.062 to -0.011 , $P = 0.005$), around 19% mediated, mostly via WMH.

For SBP the association with reasoning scores was mediated by grey matter, gFA, gMD, gFrontal and

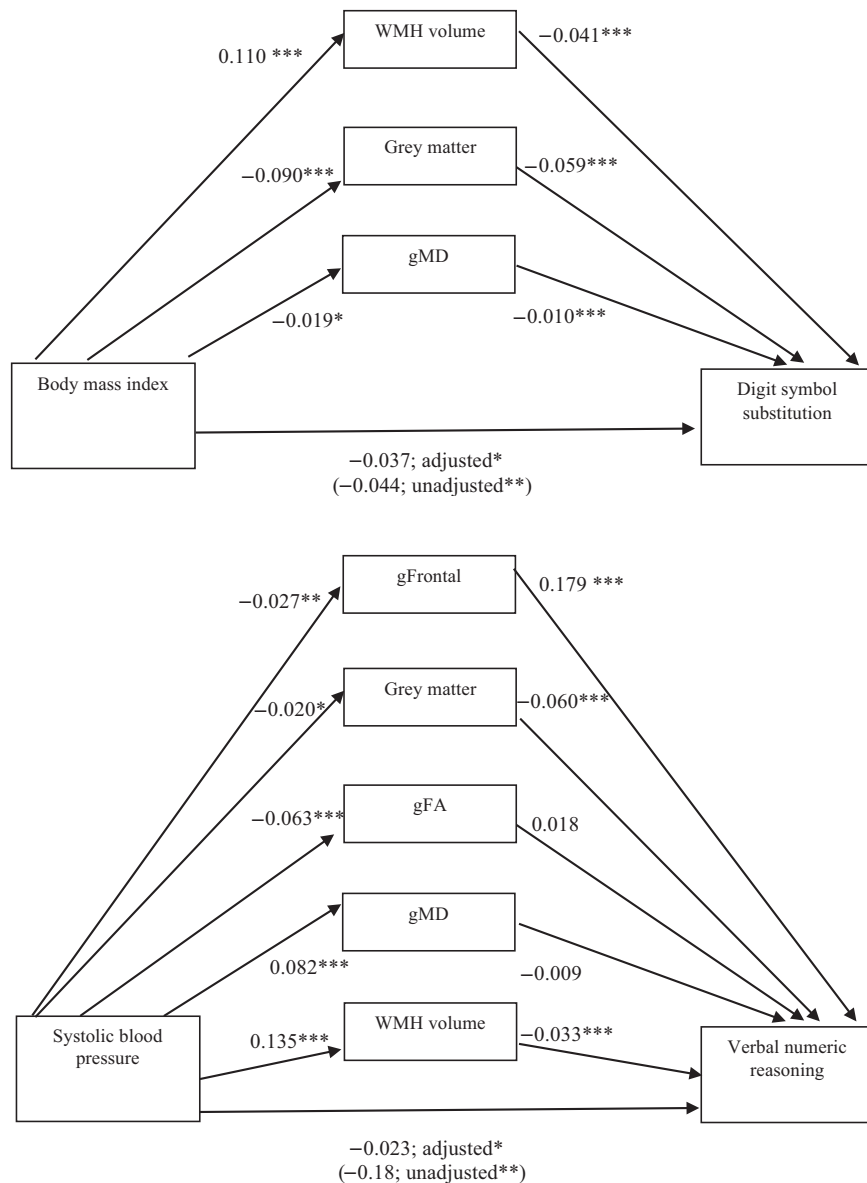


FIGURE 1 Three-way associations between SBP, BMI and cognitive abilities via brain structure phenotypes. Standardized β coefficients. gFA, general factor of fractional anisotropy; gFrontal, general factor of frontal lobe volumes; gMD, general factor of mean diffusivity; WMH, white matter hyperintensities. * $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$.

WMH (overall indirect estimate = -0.010 , 95% CI = -0.015 to -0.006), where the association attenuated from $\beta = -0.028$ (95% CI = -0.049 to -0.007 , $P = 0.009$) to $\beta = -0.18$ (95% CI = -0.044 to -0.002 , $P = 0.035$), around 36% mediation mostly via gFrontal. These are shown in Fig. 1 (note that some mediator/outcome associations were now NS in the context of multivariate list-wise regressions).

Genetically instrumented analyses

There were no statistically significant associations between genetically-instrumented BMI or SBP vs. cognitive scores (Supplementary Table 5, <http://links.lww.com/HJH/B418>). In terms of brain structure, there were associations between BMI and lower grey matter volume ($\beta = -0.200$; 95% CI = -0.320 to -0.081 ; $P = 0.001$) and between SBP and worse gFA ($\beta = -0.362$, 95% CI = -0.651 to -0.073 ; $P = 0.014$) (Supplementary Table 6, <http://links.lww.com/HJH/B418>). Using the more conservative Mendelian randomization-Egger estimates, these attenuated for BMI vs. grey matter ($\beta = -0.164$, 95% CI = -0.358 – 0.031 , $P = 0.099$) and SBP vs. gFA ($\beta = -0.005$, 95% CI = -0.033 – 0.023 , $P = 0.703$).

Sensitivity analysis

We additionally generated multivariate observational estimates of association between BMI and SBP in the same model. These results correspond to the associations reported in the earlier observational (nongenetic) analyses in terms of β/P value and are shown in Supplementary Table 7, <http://links.lww.com/HJH/B418>.

DISCUSSION

Overview

There is a lack of data in terms of single-protocol imaging studies with relatively large sample sizes and detailed information on potential confounders. UK Biobank, with more than 20 000 participants from the general population, is a large step forward. This study linked differences in common office-based assessments, easily measured at home – BMI and SBP – to cognitive and structural brain phenotypes. We found associations between BMI and SBP with poorer average values on cognitive tests related to memory, information processing speed, reasoning and executive function. These abilities are important for good quality of life for example driving and/or taking medications [39]. In terms of brain structure, BMI was associated with lower total grey matter and higher average WMH volume, which is potentially indicative of poorer cerebrovascular health [16]. SBP was associated with smaller grey matter, white matter and frontal lobe volumes, poorer white matter tract integrity and higher WMH volumes. Mediation analysis suggested one-fifth and one-third of the respective links between BMI and digit symbol tests, and SBP with verbal–numerical reasoning, were mediated by the aforementioned structural phenotypes, particularly a general factor reflecting frontal lobe volumes.

Implications

Previous studies have shown that cardiovascular risk factors are associated with poorer cognitive test scores [40], but this study is relatively rare in showing structural imaging

phenotypes which mediate a significant fraction of the association in a relatively large sample of middle-aged-to-older adults with detailed confounder data. The results are in-line with literature supporting significant frontal lobe and cerebrovascular underpinnings to executive function and information processing speed [41,42]. Our findings were robustly corrected for lifestyle, demographic and genetic factors: age, sex, smoking history, dementia risk genotype *APOE* $\epsilon 4$ [28], relevant medications and deprivation. These results support the idea that cognitive decline and brain ageing can to some extent be ameliorated by preservation of physical health. There were instances where BMI was associated with ‘better’ memory and white matter integrity mean diffusivity (vs. its generally negative associations with other brain phenotypes); highlighting the complexity of the possible relationship between cross-sectional adiposity vs. brain health.

Limitations

The study did not explore an exhaustive list of structural imaging phenotypes, of which UK Biobank has now derived several hundred. Other studies have identified structural phenotypes which underlie substantial amounts of general cognitive function [12], whereas we focused on *a priori* known substrates of cognitive abilities. There is evidence that vascular risk factors have different effects on specific brain structural phenotypes for example SBP appears to have more influence on periventricular vs. deep WMH whereas we examined total values [43]. The specific location of WMH may relate to different outcomes [43,44]. Providing further evidence of the involvement of SBP in increased WMH is a strength of this study, however, the exact pathways contributing this are still unclear [16]. It is possible that people with MRI-related contraindications, for example pacemakers are underrepresented here.

As most UK Biobank participants are of white European ancestry (90%) and we focused on those participants for purposes of homogeneity, this study does not evaluate whether increased BMI/SBP are associated with equivalent differences across ethnicities. This study was cross-sectional, which prohibits establishment of a temporal relationship. Mendelian randomization-based causal estimates supported a causal effect of BMI on grey matter (adjusted for skull size) where observational associations did not and supported a causal effect of SBP on gFA; the former suggests some reverse causality (i.e. that cross-sectional correlations underestimate an effect). The grey matter association could reflect collider bias [45] in that it is relative to skull size, and therefore, a measure of current brain size relative to lifetime maximal (i.e. decline) [46]. Note that both associations were null when using more conservative Egger estimates. This could reflect SNP pleiotropy whereby the BMI/SBP SNPs are associated with the outcomes due to processes other than BMI/SBP specifically (pleiotropy), insufficient statistical power or nonlinear associations [37].

Note that the mediation statistics were based on observational associations; we cannot state for certain that the stated proportions of mediation necessarily reflect the extent of a causal, mechanistic relationship: merely that

certain amounts variance in cross-sectional correlations between BMI/SBP can be explained by certain brain imaging metrics.

In conclusion, we showed that two commonly-assessed cardiovascular risk factors were associated with worse cognitive abilities like reasoning, information processing and executive function and that a substantial amount of those associations were cross-sectionally mediated by relatively specific brain imaging metrics. This encourages the promotion of healthy BMI and BP in the general population with regards to the preservation of cognitive health in ageing.

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Conflicts of interest

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