




# High Body Mass Index as a Causal Risk Factor for Vascular-Related Dementia: A Mendelian Randomization Study

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## Abstract

**Context:** Obesity is associated with a high risk of vascular-related dementia with metabolic risk factors as potential mediators, but questions of causality remain unanswered.

**Objective:** We aimed to determine whether high body mass index (BMI) is a causal risk factor for vascular-related dementia, and whether any effect is mediated by hypertension, hyperlipidemia, hyperglycemia, and low-grade inflammation.

**Methods:** Prospective cohort studies of the general populations from the Copenhagen area and from across the United Kingdom and consortia data were included in the study. Interventions included one-sample mendelian randomization (MR), two-sample MR, and MR in mediation analyses. Both individual-level and summary-level data was used. Main outcome measures included risk of vascular-related dementia, Alzheimer's disease, and ischemic heart disease.

**Results:** In a meta-analysis of 2 one-sample MR studies, the odds ratio (OR) for 1-SD higher BMI in predicting vascular-related dementia was 1.63 (95% CI, 1.13–2.35). In a two-sample MR study, the OR for vascular-related dementia per 1-SD higher BMI was 1.54 (1.10–2.16) using the inverse-variance weighted, 1.87 (1.22–2.85) using the weighted median, and 1.98 (1.21–3.22) using the weighted mode methods. Results from MR analyses including extended numbers of genetic variants were directionally consistent. Finally, systolic blood pressure mediated 18% (95% CI, 10%–61%) and diastolic blood pressure mediated 25% (13%–75%) of the genetic effect of BMI on vascular-related dementia.

**Conclusion:** Observationally (U-shaped) and genetically (linearly), high BMI is associated with a higher risk of vascular-related dementia, an association partly mediated through high blood pressure. This suggests that high BMI and high blood pressure are important modifiable risk factors for dementia prevention.

**Key Words:** genetics, dementia, obesity, hypertension

**Abbreviations:** BMI, body mass index; CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; CHARGE, The Cohorts for Heart and Aging Research in Genomic Epidemiology; CRP, C-reactive protein; GLGC, Global Lipids Genomics Consortium; GWAS, genome-wide association studies; ICBP, International Consortium for Blood Pressure; ICD, International Classification of Diseases; IHD, ischemic heart disease; LDL, low-density lipoprotein; MAGIC, Meta-Analysis of Glucose and Insulin-Related Traits Consortium; MR, mendelian randomization; MR PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier; OR, odds ratio; QC, quality control; RCT, randomized controlled trial.

Obesity is a growing public health concern increasing the risk of a number of diseases, including diabetes, atherosclerotic cardiovascular disease, certain types of cancer, and premature death (1–3). However, the relationship between obesity and dementia has been debated for decades with conflicting results from a range of case-control and prospective studies (4). An important finding was, however, that midlife obesity but not late-life obesity was associated with risk of dementia (5).

Recently, a large-scale meta-analysis of prospective cohorts showed that obesity was associated with a higher risk of vascular dementia (6). Alterations in risk factors induced by obesity (7), such as hypertension, hyperlipidemia, hyperglycemia, and low-grade inflammation could all be on a potential causal pathway from obesity to vascular-related dementia (8). If causality is suggested, these risk factors constitute an unexploited potential for dementia prevention (9).

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Recent meta-analyses and systematic reviews of antihypertensive, cholesterol-lowering, and antidiabetic medications have documented lower risk of dementia in treated individuals (10-12). Trials of anti-inflammatory drugs have showed no effect and have raised concerns of side effects (13). To establish a robust scientific foundation, causal aspects of these observations should be addressed. Randomized controlled trials (RCTs) are the gold standard for evaluating new treatment and prevention strategies, establishing, or rejecting causality. Nonetheless, RCTs are expensive and present challenges for the study of diseases of old age with a long prodromal phase—dementia being the classic example. Mendelian randomization (MR) may mitigate some of these challenges and is based on the random assortment of alleles during reproduction (14), resulting in distribution of genetic variants that are largely independent of behavioral and environmental factors that confound observational studies of risk factors and disease (14). Using genetic variants associated with a risk factor of interest can thus help disentangle potential causality of a relationship between a risk factor and a disease (14). Key assumptions for MR studies are 1) genetic variants are associated with the risk factor of interest, 2) there are no unmeasured confounders of the associations between genetic variants and the outcome, 3) and the genetic variants affect the outcome only through their effect on the risk factor of interest (14, 15). In MR genetic variants that reliably explain variation in the exposure at a population level are used. The gene-environment equivalence assumption is that variation in the exposure due to genetics will have the same effect on the outcome as a similar change in the exposure due to environmental factors (16).

To investigate whether body mass index (BMI) may be a causal risk factor for vascular-related dementia, we employed an MR study design. We first tested the relationship between BMI and vascular-related dementia using 3 independent studies with individual-level data. Second, we validated our findings using 6 studies with summary-level data. Third, we assessed whether the potential causal relationship between BMI and vascular-related dementia was mediated by changes in blood pressure, concentrations of low-density lipoprotein (LDL) cholesterol, plasma triglycerides, glucose, and high-sensitivity C-reactive protein (CRP). This was tested first with the variants originally genotyped because of their strong association with the risk factors of interest (17-33) (referred to as “well-established genetic variants”), and secondly with an extended number of variants from more recent genome-wide association studies (GWAS) available only in the UK Biobank (24, 31, 34-36) (referred to as “extended number of genetic variants”).

## Materials and Methods

### Study Populations

#### Copenhagen General Population Study and Copenhagen City Heart Study

The Copenhagen General Population Study (CGPS) was initiated in 2003 with ongoing enrollment. Individuals were selected based on the national Danish Civil Registration System to reflect the adult Danish population aged 20 to 100 years or older (Supplementary Table S1 provides an overview of all cohorts included in the study) (37). Data were obtained from a questionnaire, a physical examination, and a blood sample. Blood samples were drawn at the first visit of

the study. The Copenhagen City Heart Study (CCHS) was initiated in 1976 to 1978, with follow-up examinations in 1981 to 1983, 1991 to 1994, and 2001 to 2003. Participants were recruited and examined as in the CGPS. We included 126 655 individuals with available measured weight and height from the CGPS and CCHS. Participants were White and of Danish descent. The study protocol was approved before study start by the steering committees of the CGPS and the CCHS.

#### UK Biobank

The UK Biobank is a population-based health research resource consisting of approximately 500 000 people, aged between 38 years and 73 years, who were recruited between the years 2006 and 2010 from across the United Kingdom (38). The biobank is particularly focused on identifying determinants of human diseases in middle-aged and older individuals, and participants provided a range of information via questionnaires and interviews; anthropometric measures, blood pressure readings and samples of blood were also taken. A full description of the study design, participants, and quality control (QC) methods have been described in detail previously (39). We included 377 755 nonrelated White, British individuals with genetic data from the UK Biobank both for 1-sample individual-level MR analysis and 2-sample MR analysis on well-established variants and 1-sample MR using an extended number of genetic variants. Further, we included 402 743 nonrelated European individuals for the 2-sample MR analysis on an extended number of genetic variants. Access to information from participants was approved by the Patient Information Advisory Group from England and Wales. All participants provided electronic written informed consent for the study. This research has been conducted using the UK Biobank resource under application number 81499 to Lavinia Paternoster and application number 66214 to Ruth Frikke-Schmidt.

#### Genetic Investigation of ANthropometric Traits

The Genetic Investigation of ANthropometric Traits (GIANT) consortium is an international collaboration that seeks to identify genetic loci that modulate human body size and shape, including height and measures of obesity. The study included 339 224 individuals of mainly European descent from 125 studies, 82 with GWAS results. For more information, see Speliotes et al (40). There was no sample overlap with the UK Biobank.

#### International Consortium of Blood Pressure

The International Consortium of Blood Pressure (ICBP) GWAS is a consortium that investigates blood pressure genetics (35). The ICBP GWAS included 77 studies comprising data from 299 024 individuals of European descent. For more information, see Evangelou and colleagues (35). In the UK Biobank + ICBP-GWAS included in this study, there was a sample overlap with UK Biobank of 458 577 individuals.

#### Meta-Analysis of Glucose and Insulin-Related Traits Consortium

The Meta-Analysis of Glucose and Insulin-Related Traits Consortium (MAGIC) is a collaborative effort to combine data from multiple GWAS to identify loci that affect glycemic and metabolic traits (24). The MAGIC GWAS included

32 studies and 58 074 individuals of European descent. For more information, see Scott et al (24). There was no sample overlap with the UK Biobank.

### Global Lipids Genetics Consortium

The Global Lipids Genetics Consortium (GLGC) is a worldwide collaboration dedicated to investigating the genetics of lipid traits (31). The GLGC GWAS included 37 studies and 173 082 individuals of European descent. For more information, see Willer and colleagues (31). There was no sample overlap with the UK Biobank.

### Cohorts for Heart and Aging Research in Genomic Epidemiology

The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) was formed to facilitate GWAS among multiple large population-based cohort studies. The CHARGE consortium included 49 studies and 148 164 individuals of European descent (36). For more information, see Said et al (36). The UK Biobank-CHARGE meta-analysis results included in this study had a sample overlap with the UK Biobank of 427 367 individuals.

### Covariates and Laboratory Analyses Used in Individual-Level Data

BMI was calculated as measured weight (kg) divided by measured height in meters squared ( $m^2$ ) in all cohorts. Blood pressure measurements by sphygmomanometer were performed in both arms by a trained technician, with the participant resting in a supine position in CCHS and CGPS. In the UK Biobank, 2 automated measurements of blood pressure were taken a few moments apart, and a manual sphygmomanometer was used if the standard automated device could not be employed. In individuals taking antihypertensive medication, 10 mm Hg were added to the systolic and 5 mm Hg to the diastolic blood pressure measurement to correct for the effect of the medication (41). Information on current smoking, level of education, alcohol consumption, and physical activity was self-reported in all cohorts. Missing values for covariates were 0% to 1.9% in the CCHS and CGPS, and 0% to 19.2% in the UK Biobank.

In the CCHS and CGPS, nonfasting plasma total cholesterol, high-sensitivity CRP, and glucose were measured using standard hospital assays at the time of study entry. LDL cholesterol was calculated using the Friedewald equation when plasma triglycerides were 4.0 mmol/L or less and otherwise measured directly. Nonfasting plasma triglycerides were measured using standard hospital assays with enzymatic methods at the time of study entry. In the UK Biobank, total plasma cholesterol, LDL cholesterol, glucose, and triglycerides were measured by standard enzymatic methods, and high-sensitivity CRP by immunoturbidimetric methods. Blood samples were taken at random irrespective of time since and content of the last meal. Missing values for laboratory analyses were 0.9% to 3.5% in the CCHS and CGPS, and 4.7% to 12.8% in the UK Biobank. In individuals using lipid-lowering therapy, plasma triglycerides were multiplied by 1.12 ( $=1/(1 - 0.11)$ ) and plasma LDL cholesterol was multiplied by 1.23 ( $=1/(1 - 0.19)$ ) corresponding to average reductions of 11% and 19% respectively using common statin treatment regimens (42).

An ABI PRISM 7900HT Sequence Detection System (Applied Biosystems Inc) and TaqMan-based assays were used to genotype the selected variants in the CCHS and CGPS, followed by QC including sequencing and calculation of the Hardy-Weinberg equilibrium. We extracted relevant information for the same genetic variants from the UK Biobank from the genotype data release (July 2017).

Missing values were not imputed, and samples with missing values for covariates were not in general excluded from analyses. In multifactorially adjusted models of observational data, only samples with no missing values were included.

### Instrument Selection for Well-Established Genetic Variants

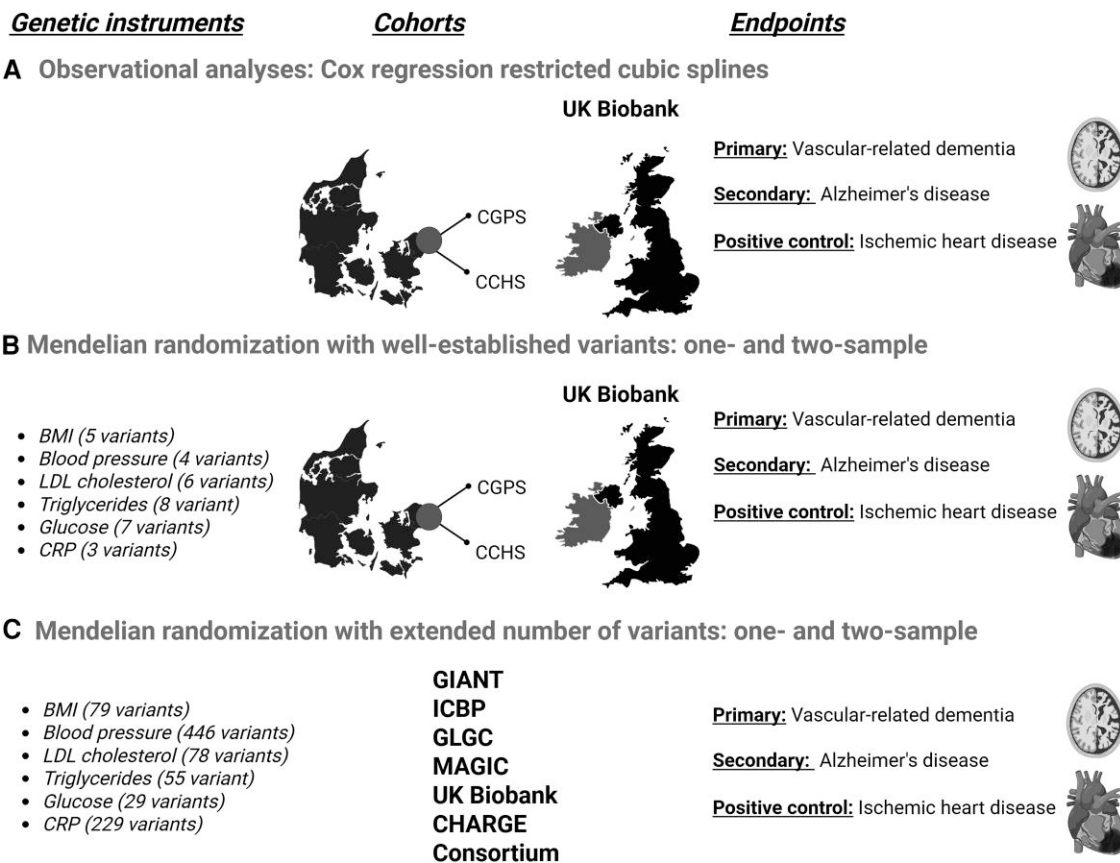
For our primary analyses we chose well-established genetic variants from targeted studies or GWAS. These genetic variants represent independent loci, show strong associations between the genotype and the relevant trait (43), and map to genes with a well-known biological function both for BMI and intermediate risk factors (Supplementary Table S2) (37). In total, 5, 4, 6, 8, 7, and 3 genetic variants were used for BMI, blood pressure, LDL cholesterol, triglycerides, glucose, and CRP, respectively, and were combined into scores used in the 1-sample and used as individual instruments in the 2-sample MR analysis. The reasoning behind including a limited number of genetic variants for each trait was to compare this approach where the biological function of each variant is well known to an approach where an extended number of variants are included, but not all their functions are well known. Importantly, none of the variants were discovered in the CGPS, CCHS, or UK Biobank, thus justifying the use of internal weights for the present analyses and minimizing the risk of “winner’s curse.” Variants included had a linkage disequilibrium threshold of  $r^2$  less than 0.05. Detailed arguments for selection of candidate variants are given in the Supplementary Methods (37), page 5.

### Instrument Selection for an Extended Number of Genetic Variants

When choosing data to include in 2-sample MR analyses, efforts were made to maximize total sample size, minimize sample overlap with the UK Biobank, and include individuals of mainly European descent. However, it was not always possible to avoid sample overlap due to the limited availability of consortia data excluding the UK Biobank. Variants included were associated with the exposure at a genome-wide significance of  $P$  less than  $5 \times 10^{-8}$  and  $r^2$  less than 0.001. We included information on genetic variant-outcome associations for the 79 variants found to be associated with BMI, 446 variants associated with systolic and diastolic blood pressure, 29 variants associated with glucose, 78 variants associated with LDL cholesterol, 55 variants associated with triglycerides, and 229 variants associated with CRP. These were combined into scores used in the 1-sample and used as individual instruments in 2-sample MR analysis. A detailed description of selected instruments is given in the Supplementary Methods (37), page 6, and Supplementary Table S3 (37).

### Endpoints

Diagnoses of diseases were according to the International Classification of Diseases (ICD). Versions 8 and 10 were



**Figure 1.** Genetic instruments, cohorts, and end points included in the study. A, Observational analyses were performed in the Copenhagen City Heart Study (CCHS), the Copenhagen General Population Study (CGPS), and the UK Biobank. B, Mendelian randomization (MR) with well-established variants was performed in the CCHS, CGPS, and the UK Biobank. C, MR with extended number of variants was performed in the GIANT consortium, ICBP, GLGC, MAGIC, CHARGE consortium, and the UK Biobank. BMI, body mass index; CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; CHARGE, The Cohorts for Heart and Aging Research in Genomic Epidemiology; CRP, C-reactive protein; GIANT, Genetic Investigation of ANthropometric Traits; GLGC, Global lipids Genetics Consortium; ICBP, International Consortium of Blood pressure; LDL, low-density lipoprotein; MAGIC, Meta-Analyses of Glucose and Insulin-Related Traits Consortium. Created with [Biorender.com](https://biorender.com).

used in the CCHS and CGPS (version 9 was never implemented in Denmark), while versions 9 and 10 were used in the UK Biobank. Alzheimer's disease was defined as ICD-8 290, ICD-9 331.0, ICD-10 F00, and G30; vascular dementia as ICD-9 290.4 and ICD-10 F01; and unspecified dementia as ICD-8 290.09, 290.18 and 290.19, ICD-9 294.2, and ICD-10 F03. Vascular-related dementia included vascular dementia and unspecified dementia. Unspecified dementia is included in the "vascular-related dementia" category because this form of dementia generally shares the same cardiovascular risk factors as vascular dementia (Supplementary Tables S4 and S5) (37). Further, since the "vascular dementia" diagnosis was not introduced in Denmark until 1994 (44), all previous cases of "vascular dementia" would have been categorized as "unspecified dementia." For these reasons the two diagnoses can be categorized as one. In Denmark, cerebrospinal fluid biomarkers and imaging studies are performed on most of the patients in the clinical setting, and Alzheimer's disease vs vascular-related dementia diagnoses are based on a compilation of these findings with clinical symptoms (45).

As high BMI previously has been shown to be a causal risk factor for ischemic heart disease (IHD) (46), we included IHD as a positive control in the present study. IHD was defined as ICD-8 410 to 414, ICD-9 410 to 414, and ICD-10: I20 to I25, including myocardial infarction (ICD-8: 410, ICD-9 410, and

ICD-10: I21-I22). In the UK Biobank IHD also included self-reported disease, which has well-known high confidence after validation (47, 48). To further support the validity of the diagnoses, *APOE* genotype frequencies are reported (Supplementary Table S6) (37). The  $\epsilon 4$  allele of the *APOE* gene is a longstanding strong benchmark for dementia risk (9, 49-51).

### Statistical Analyses in Individual-Level Data

Data were analyzed using Stata SE 17.0 and R version 4.1.0. Stepwise analytic strategies are detailed in Fig. 1. All estimates refer to the risk of outcomes per 1-SD increase in the exposure/mediator. Since plasma triglyceride and CRP concentrations are not normally distributed, their values were log-transformed before inclusion in further analyses.

Linkage disequilibrium between selected genetic variants were checked through the web-based tool LDlink (<https://ldlink.nci.nih.gov>) and variants in linkage defined as  $r^2$  of 0.05 or greater were excluded. For the 1-sample MR analysis, we generated a weighted allele score for each trait based on these variants by multiplying the adjusted  $\beta$ -coefficient for each variant by the number of relevant alleles of that variant for each individual and adding them up across all variants. Weighted allele scores using the same approach were generated for each participant in the UK Biobank in analyses

including well-established genetic variants. The same approach was used in analyses using an extended number of genetic variants in the UK Biobank.

To investigate the observational association between BMI and vascular-related dementia (see Fig. 1), we first performed Cox regression restricted cubic splines with 3 knots placed to give the best model fit in the CCHS + CGPS and in the UK Biobank. A multivariable model was fitted, adjusted for age, sex, cohort (only for CCHS + CGPS), smoking status, level of education, physical activity, and alcohol consumption. The observational associations between mediators and vascular-related dementia were analyzed using the same methods. Subsequently, we conducted linear regression analyses to investigate the associations between the BMI-weighted allele score and BMI measurement in the CCHS + CGPS and in the UK Biobank. The score was used as a continuous variable in main analyses and divided into quartiles in sensitivity analyses. The association between weighted allele scores for mediators and measured level of mediators was analyzed using the same methods.

We used 2-stage predictor substitution estimators with second-stage logistic regression from the “OneSampleMR” package (<https://cran.r-project.org/web/packages/OneSampleMR/OneSampleMR.pdf>) to fit a first-stage model of the exposure on the instruments, obtain predicted values of exposures, and then fit a second-stage model of the outcome regressed on the predicted values of the exposure. This estimates the change in risk of outcome (in odds ratios [ORs]) per unit change in genetically predicted BMI. Results were then combined in a meta-analysis for each outcome using fixed-effect models for the analyses including well-established genetic variants. The association between weighted allele scores for mediators and vascular-related dementia was analyzed using the same methods. *F*-statistics were calculated using the *ivreg* package in R.

### Statistical Analyses in Summary-Level Data

We applied 2-sample MR analyses to assess 1) the causal role of BMI on vascular-related dementia, Alzheimer’s disease, and IHD (see Fig. 1), and 2) the causal role of systolic blood pressure, diastolic blood pressure, plasma glucose, LDL cholesterol, triglycerides, and CRP on vascular-related dementia. All estimates refer to the risk of outcomes per 1-SD increase in the exposure/mediator. We included summary-level data on the genetic variant-exposure associations from the GIANT, ICBP, MAGIC, GLGC, UKB, and the CHARGE Consortium. These published GWAS summary statistics were available through the TwoSampleMR R package (2-sample MR ID: ieu-a-2, ieu-b-38, ieu-b-39, ieu-b-114, ieu-a-300, ieu-a-302, and ebi-a-GCST90029070). We included summary-level data on the genetic variant-outcome associations from the UK Biobank. Analyses were conducted in UK Biobank participants of European descent. We estimated the association of selected genetic variants with each endpoint using the BOLT-LMM (linear mixed model) software (52). Analyses were adjusted for age, sex, and a variable denoting which genotyping chip was used in the UK Biobank. Linear mixed models account for population stratification and cryptic relatedness (52). QC filtering of the UK Biobank data was conducted by R. Mitchell, G. Hemani, T. Dudding, L. Corbin, S. Harrison, and L. Paternoster as described in the published protocol (53). For the analyses including well-established genetic variants, the inverse-variance

weighted method, the MR Egger method, the weighted median method, and the weighted mode method were used. For the analyses including an extended number of genetic variants, the inverse-variance weighted method, the MR Egger method, the weighted median method, the weighted mode method, and the Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR PRESSO) method were used. For analyses including sample overlap between the UK Biobank and the exposure consortium, calculation of bias and type 1 error rate was calculated using <https://sb452.shinyapps.io/overlap/>. For further description of sensitivity analysis, see Supplementary Results (37). *F*-statistics were calculated as the  $\beta$ -coefficient for the genetic instrument squared divided by the standard error squared ( $\beta^2/SE^2$ ).

### Mediation analyses using mendelian randomization

Mediation analyses were conducted on estimates from individual-level data, since these estimates were without adjustment for other exposures/mediators, in contrast to the available summary-level data. Further, mediation analyses were conducted on the selected well-established variants to avoid noise from pleiotropy. To investigate the mediation effect of risk factors for the association between BMI and vascular-related dementia, we used the product of coefficients method in a 2-step MR framework using 2-stage least squares regression (54). This includes univariable MR (standard MR using one exposure variable) and multivariable MR, which is a technique used to estimate the causal effect of multiple exposure variables on a health outcome (55). In step 1, the effect of BMI on the mediator ( $\beta_{xm}$ ) was obtained through a univariable MR, and in step 2, the effect of each mediator on the outcome ( $\beta_{my}$ ) was carried out using multivariable MR, where both the weighted allele scores for the mediator and the exposure were included in the first- and second-stage regression. In each step, analyses were performed separately in the CCHS + CGPS and UK Biobank and then meta-analyzed using fixed-effect models. A risk factor was ascertained as a potential mediator if the pooled effect of the factor was associated with risk of vascular-related dementia. The indirect effect was then estimated by multiplying the estimates  $\beta_{xm}$  and  $\beta_{my}$ . The percentage excess risk of vascular-related dementia caused by high BMI that may be attributed to alterations of the mediators (proportion mediated) was estimated by dividing the indirect effect by the total effect ( $\beta_{xm} \times \beta_{my} / \beta_{xy}$ ). See Supplementary Table S7B (37) for exact values of  $\beta_{xm}$ ,  $\beta_{my}$ , and  $\beta_{xy}$ . The 95% CIs of the proportions mediated were obtained through bootstrapping: Bootstrap was carried out in the CCHS + CGPS and in the UK Biobank 5000 times each and then meta-analyzed. We performed mediation analysis for systolic and diastolic blood pressure as these were significantly associated with vascular-related dementia both in 1-sample and 2-sample analyses.

### Ethics Approval

The CGPS and CCHS were approved by institutional review boards and Danish ethical committees (KF-100.2039/91, KF-01-144/01, HKF-01-144/01) and were conducted according to the Declaration of Helsinki. Written informed consent was obtained from all individuals. The UK Biobank received ethical approval from the research ethics committee (REC reference for UK Biobank is 11/NW/0382) (82).

**Table 1. Baseline characteristics of individuals by cohort**

	CCHS + CGPS	UK Biobank
No. of individuals, %	126 655	377 755
Women, %	55	54
Age, y	57 (47-66)	59 (51-64)
Current smoking, %	21	10
High alcohol consumption, %	17	21
Triglycerides, mmol/L	1.4 (1.0-2.1)	1.5 (1.1-2.2)
Triglycerides, mg/dL	124 (89-177)	124 (89-177)
Lipid-lowering therapy, %	11	18
LDL cholesterol, mmol/L	3.3 (2.7-3.9)	3.6 (3.1-4.2)
LDL cholesterol, mg/dL	217 (189-244)	217 (189-244)
Glucose, mmol/L	5.2 (4.7-5.8)	4.9 (4.6-5.3)
Glucose mg/dL	94 (85-104)	88 (83-95)
Systolic blood pressure, mm Hg	140 (125-156)	137 (126-151)
Diastolic blood pressure, mm Hg	84 (77-92)	82 (76-89)
Body mass index	26 (23-28)	27 (24-30)
Physical inactivity, %	50	48
Low education	12	18
CRP, mg/dL	1.4 (1.0-2.3)	1.3 (0.7-2.8)

Sex and age were determined by central personal register number in the CCHS + CGPS and by date of birth and genetic sex in the UK Biobank. Smoking was current smoking and self-reported in all cohorts. Body mass index was calculated as measured weight (kg) divided by measured height in meters squared ( $m^2$ ) in all cohorts. High alcohol consumption was more than 14 divided by 21 units per week for women/men (1 unit = 12 g alcohol, equivalent to 1 glass of wine, 1 shot of spirit, or 1 beer (33 cL)) in the CCHS + CGPS and daily or almost daily intake of alcohol in the UK Biobank. Lipid-lowering therapy was primarily statins (yes/no) and was self-reported in all cohorts. Blood pressure measurements by sphygmomanometer were performed in both arms by a trained technician, with the participant resting in a supine position in CCHS + CGPS. In the UK Biobank, 2 automated measurements of blood pressure were taken a few moments apart, and a manual sphygmomanometer was used if the standard automated device could not be employed. Physical inactivity was 4 hours per week or less of light physical activity in leisure time in the CCHS + CGPS and 3 days per week or less with more than 10 minutes of moderate-intensity physical activity in the UK Biobank. Low education was 8 years or less in the CCHS + CGPS and 7 years or less in the UK Biobank.

Abbreviations: CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; CRP, C-reactive protein; LDL, low-density lipoprotein.

## Results

Baseline characteristics of study participants in the Copenhagen studies and the UK Biobank are shown in [Table 1](#). In 126 655 individuals from the CCHS and CGPS, 2260 developed vascular-related dementia (including 413 vascular dementia and 1847 with unspecified dementia), 2111 developed Alzheimer's disease, and 14 188 developed IHD. In 377 755 individuals from the UK Biobank, 3317 developed vascular-related dementia (including 1145 vascular dementia and 2172 with unspecified dementia), 2215 developed Alzheimer's disease, and 45 539 developed IHD. For the distribution of *APOE* genotypes, see Supplementary Table S6 ([37](#)).

### Observational Association Between Body Mass Index and Risk of Vascular-Related Dementia

In the CCHS and CGPS, the observational association between BMI and risk of vascular-related dementia was U-shaped with the nadir at a BMI of 27 on a continuous scale using restricted cubic splines after adjusting for age, sex, cohort, smoking status, education, physical activity, and alcohol

consumption ([Fig. 2A](#)). Higher BMI was associated with higher risk of IHD ([Fig. 2E](#)) while lower BMI was associated with higher risk of Alzheimer's disease ([Fig. 2C](#)). Results were largely similar in the UK Biobank ([Fig. 2B, 2D, and 2F](#)).

### Association Between Genetic Instruments and Body Mass Index

The weighted allele score for BMI generated from well-established genetic variants was confirmed to be positively associated with measured BMI (Supplementary Fig. S1) ([37](#)). The well-established genetic variants as well as an extended number of genetic variants for BMI were all associated with BMI at  $P < 5 \times 10^{-8}$  in the original GWAS ([17, 34](#)) (To see the variants see Supplementary Tables S2 and S8) ([37](#)). *F*-statistics were 520 in the CCHS + CGPS and 1997 in UK Biobank for the genetic score using well-established genetic variants. In 2-sample MR analysis (using summary-level data and well-established variants), the mean *F*-statistic was 275. *F*-statistics in analyses (using individual-level data and extended number of variants) was 4346 in the UK Biobank. In 2-sample MR analysis using an extended number of variants, the mean *F*-statistic was 66 (see Supplementary Table S8) ([37](#)).

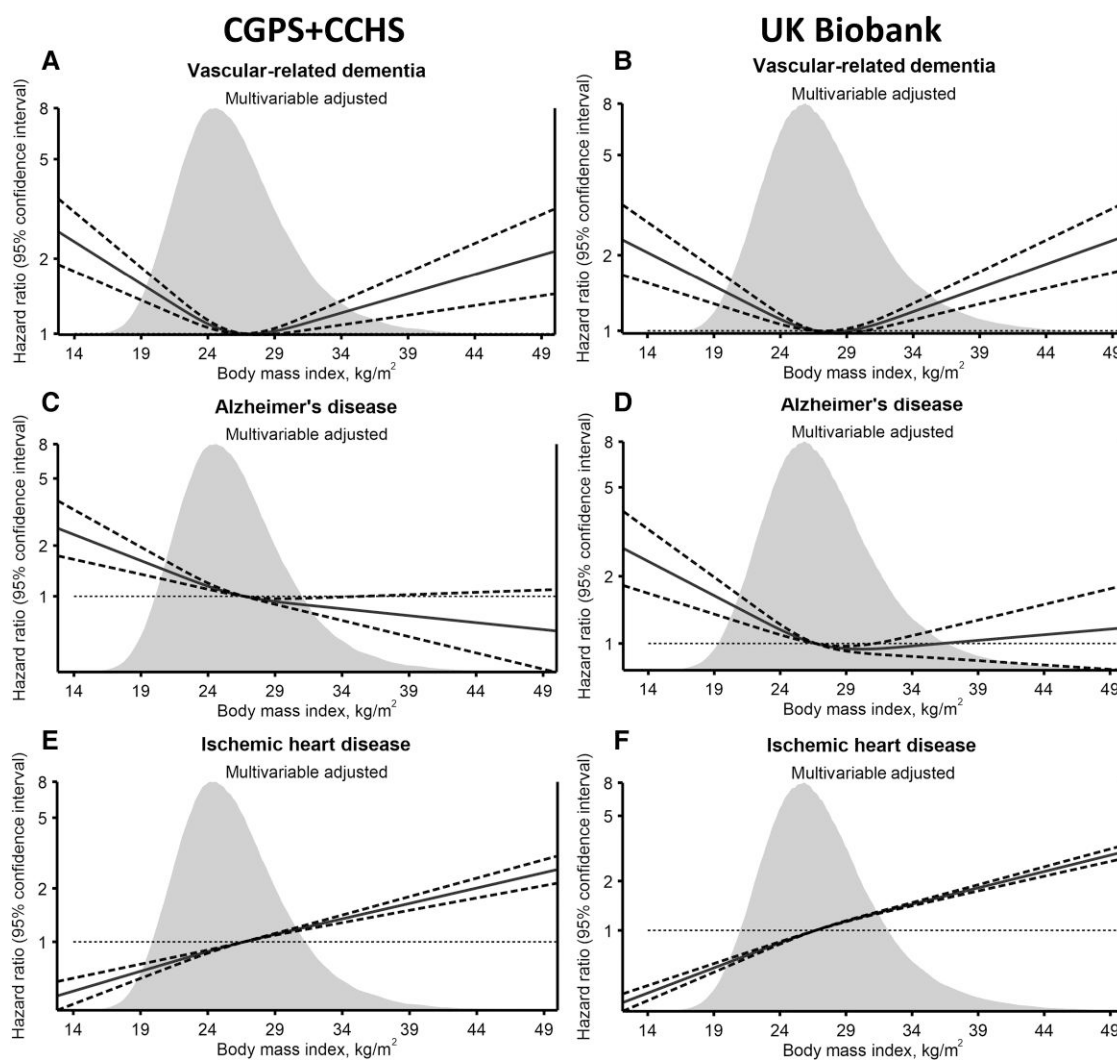
### Association Between Genetic Instruments for Body Mass Index and Vascular-Related Dementia

#### One-sample mendelian randomization

The OR for risk of vascular-related dementia per 1-SD higher BMI in analyses using well-established genetic variants was 1.63 (95% CI, 1.13, 2.35) in a meta-analysis of CCHS + CGPS and the UK Biobank ([Fig. 3A](#)). Corresponding estimates were 1.04 (0.92-1.16) for Alzheimer's disease and 1.24 (1.10-1.39) for IHD. In 1-sample MR using the UK Biobank and including an extended number of variants, the OR (95% CI) for risk of vascular-related dementia was 1.27 (0.93-1.74) per 1-SD higher BMI (Supplementary Fig. S9) ([37](#)).

#### Two-sample mendelian randomization

In 2-sample MR analysis using well-established genetic variants and summary-level data, the ORs (95% CI) per 1-SD higher BMI for vascular-related dementia were 1.54 (95% CI, 1.10-2.16) using the inverse-variance weighted, 1.87 (1.22-2.85) using weighted median, and 1.98 (1.21-3.22) using weighted mode methods ([Fig. 3B](#)). Corresponding estimates for the inverse-variance weighted method were 1.08 (0.72-1.64) for Alzheimer's disease and 1.23 (1.08-1.40) for IHD (see [Fig. 3B](#)). For additional sensitivity analyses, see [Fig. 3](#) and Supplementary Tables S9 and S10 ([37](#)). In 2-sample MR analysis using an extended number of variants and summary-level data, the ORs (95% CI) per 1-SD higher BMI for vascular-related dementia were 1.07 (0.88-1.30) using the inverse-variance weighted, 1.39 (1.02-1.89) using weighted median, and 1.47 (1.00-2.15) using weighted mode methods (see Supplementary Fig. S2) ([37](#)). Since no outliers of the genetic instruments were found, MR PRESSO was not performed. Corresponding estimates for the inverse-variance weighted method were 1.18 (0.93-1.50) for Alzheimer's disease and 1.34 (1.21-1.48) for IHD (see Supplementary Fig. S2) ([37](#)). For sensitivity analyses, see Figs. S2 and S3 to S6 ([37](#)).



**Figure 2.** Observational associations between body mass index and vascular-related dementia (panel A, B), Alzheimer's disease (panel C, D), and ischemic heart disease (panel E, F). Based on the the Copenhagen General Population Study (CGPS), Copenhagen City Heart Study (CCHS), and the UK Biobank. Hazard ratios and 95% CIs were obtained from Cox proportional hazards regression with restricted cubic splines. Analyses were adjusted for age, sex, cohort (in CGPS and CCHS), smoking status, education, physical activity, and alcohol consumption. Age adjustment was through age as time scale. Panel A, C, E includes data from CGPS and CCHS, and panel B, D, F includes data from UK Biobank.

### Observational Association Between Potential Intermediate Risk Factors and Risk of Vascular-Related Dementia

When investigating the associations between measured levels of the intermediate risk factors and risk of vascular-related dementia in the CCHS + CGPS (Supplementary Fig. S7) (37) and the UK Biobank (Supplementary Fig. S8) (37), we found U-shaped associations for diastolic blood pressure and LDL cholesterol and more linear associations for triglycerides, glucose, and CRP. Systolic blood pressure was associated linearly with risk of vascular-related dementia in CCHS + CGPS (higher systolic blood pressure and lower risk) and the association was more U-shaped in the UK Biobank.

### Association Between Genetic Instruments for Intermediate Risk Factors and Measured Levels of Intermediate Risk Factors

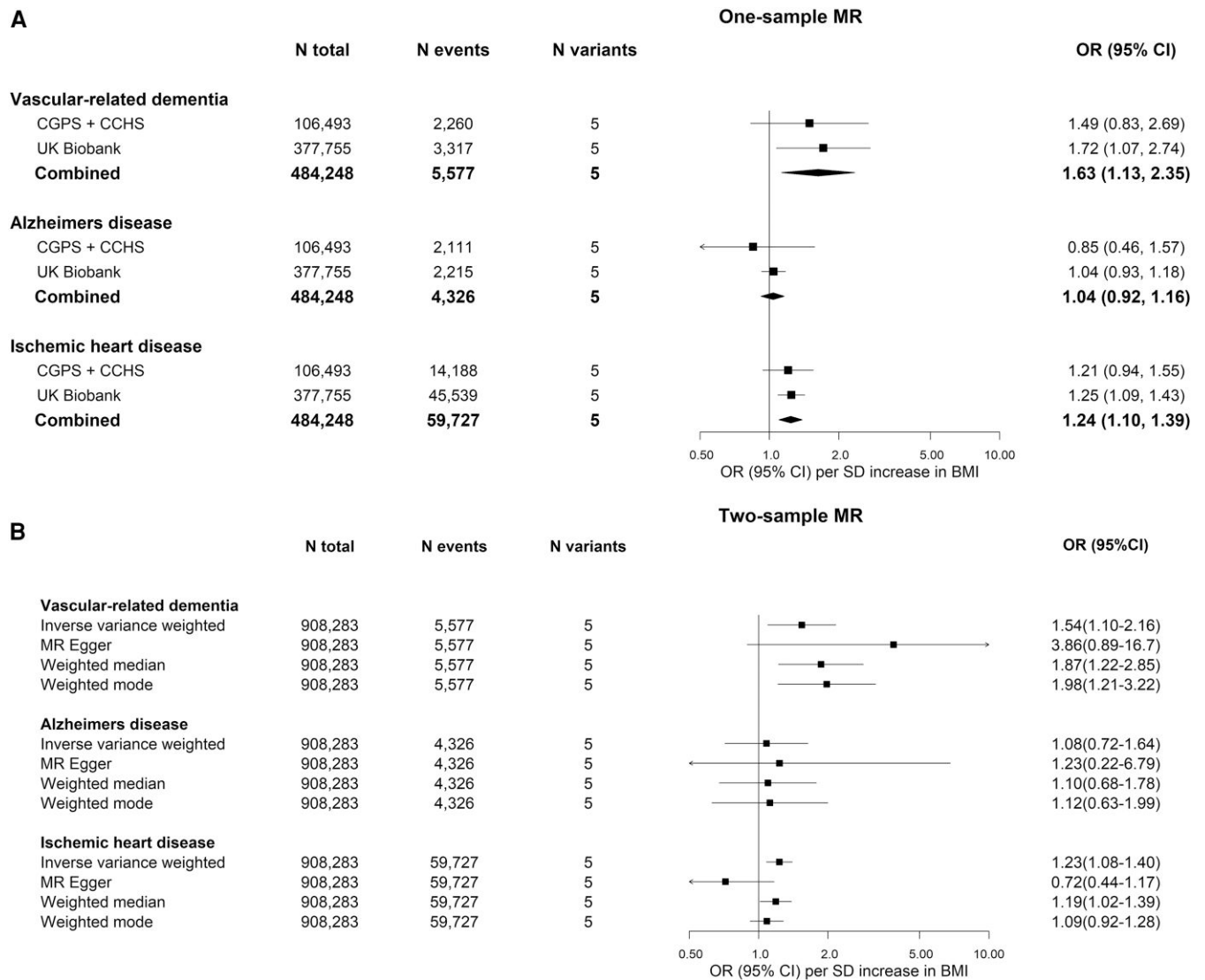
In 1-sample MR using well-established variants, *F*-statistics for instruments in the CCHS + CGPS/UK Biobank were 89/650 for systolic blood pressure, 89/513 for diastolic blood

pressure, 1011/3299 for LDL cholesterol, 3104/10 928 for triglycerides, 423/1921 for glucose, and 1035/6117 for CRP, respectively. In 2-sample MR using well-established variants *F*-statistics for instruments in the UK Biobank were 420 for systolic blood pressure, 381 for diastolic blood pressure, 232 for glucose, 1211 for LDL cholesterol, 454 for triglycerides, and 46 for CRP. In 1-sample and 2-sample MR using an extended number of variants, *F*-statistics for instruments are given in the legends to Supplementary Figs. S9 to S11 (37).

### Association Between Genetic Instruments for Intermediate Risk Factors and Risk of Vascular-Related Dementia

#### One-sample mendelian randomization

In 1-sample MR using well-established variants, the OR for risk of vascular-related dementia per 1-SD higher systolic blood pressure was 2.56 (95% CI, 1.17-5.58) in a meta-analysis of the CCHS + CGPS and UK Biobank (Fig. 4). Corresponding estimates were 3.32 (1.41-7.85) for diastolic blood pressure, 0.94 (0.73-1.23) for LDL cholesterol, 1.10



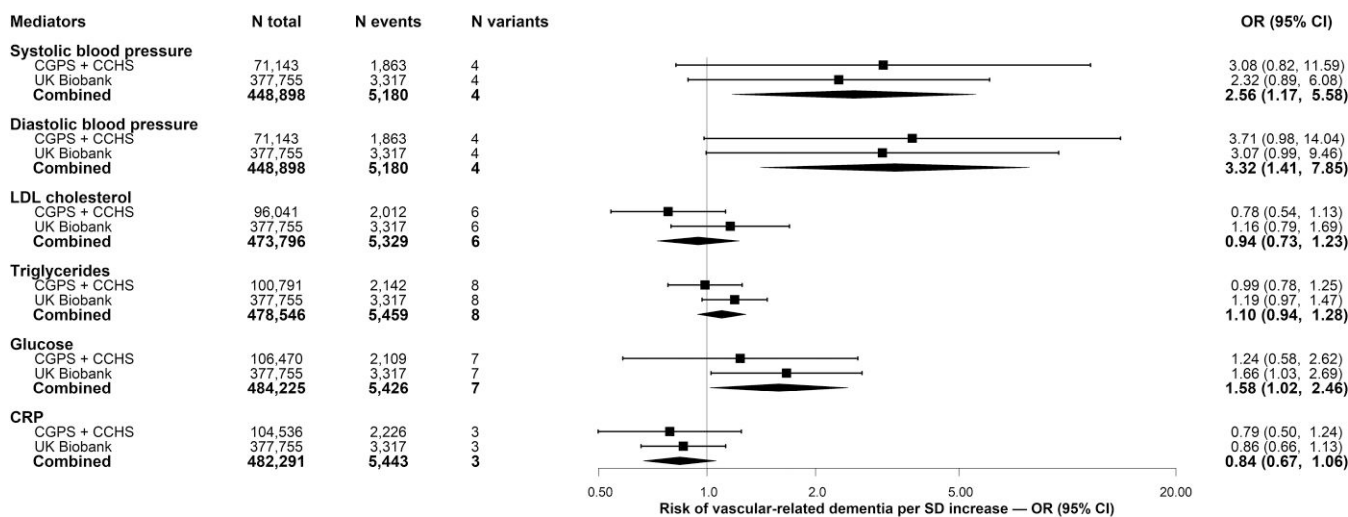
**Figure 3.** One- and two sample mendelian randomization (MR) analyses of the association between body mass index (BMI) and risk of vascular-related dementia, Alzheimer's disease, and ischemic heart disease. A, Change in the risk of vascular-related dementia, Alzheimer's disease, and ischemic heart disease is per 1-SD higher BMI. Based on the Copenhagen City Heart Study (CCHS), the Copenhagen General Population Study (CGPS), and the UK Biobank. The MR estimates were derived using the "OneSampleMR" package in all individuals with available genotypes and BMI measurement.  $F$ -statistics = 520 and 1997 in CCHS + CGPS and UK Biobank, respectively. Heterogeneity tests for meta-analyses:  $Q = 0.0$ -1.01 and  $I^2 = 0.08\%$ . One SD = 4.75 in the UK Biobank. One SD = 4.29 in CCHS + CGPS. B, Change in the risk of vascular-related dementia, Alzheimer's disease, and ischemic heart disease is per SD higher BMI. Based on the CCHS, the CGPS, UK Biobank, and the Genetic Investigation of Anthropometric Traits (GIANT) consortium. The odds ratios (ORs) per SD higher BMI were estimated using the "TwoSampleMR" R package. The estimates were derived by the inverse variance weighted method, the MR Egger method, the weighted median method, and the weighted mode method. Mean  $F$ -statistic = 275. 1 SD = 4.77.

(0.94-1.28) for triglycerides, 1.58 (1.02-2.46) for glucose, and 0.84 (0.67-1.06) for CRP. In 1-sample MR using an extended number of variants, the OR (95% CI) for risk of vascular-related dementia per 1-SD higher systolic blood pressure was 1.52 (1.26-1.85) in the UK Biobank (Supplementary Fig. S9) (37). Corresponding estimates were 1.84 (1.39-2.44) for diastolic blood pressure, 1.58 (1.34-1.86) for LDL cholesterol, 1.23 (1.05-1.44) for triglycerides, 0.95 (0.63-1.42) for glucose, and 0.23 (0.11-0.50) for CRP.

### Two-sample mendelian randomization

In 2-sample MR using well-established variants, the OR (95% CI) for risk of vascular-related dementia per

1-SD higher systolic blood pressure in analyses using well-established variants was 1.04 (95% CI, 1.01-1.08) using the inverse-variance weighted method (Fig. 5). Corresponding estimates were 1.54 (1.10-2.16) for diastolic blood pressure, 1.11 (0.84-1.46) for LDL cholesterol, 1.25 (1.03-1.51) for plasma triglycerides, 1.59 (1.01-2.51) for plasma glucose, and 0.91 (0.81-1.03) for plasma CRP, respectively. In 2-sample MR using an extended number of variants, the OR (95% CI) for risk of vascular-related dementia per 1-SD higher systolic blood pressure was 1.10 (1.06-1.15) using the inverse-variance weighted method (Supplementary Fig. S10) (37). Corresponding estimates were 1.11 (1.04-1.19) for diastolic blood pressure, 1.34 (1.12-1.61) for LDL cholesterol, 1.23 (0.96-1.57) for plasma



**Figure 4.** One-sample mendelian randomization (MR) analyses of the association between mediators and risk of vascular-related dementia. Change in the risk of vascular-related dementia is per 1 SD higher systolic and diastolic blood pressure, low-density lipoprotein (LDL) cholesterol, logarithm of plasma triglycerides, plasma glucose, and logarithm of plasma C-reactive protein (CRP). Based on the Copenhagen City Heart Study (CCHS), the Copenhagen General Population Study (CGPS), and the UK Biobank. The MR estimates were derived using the “OneSampleMR” package in all individuals with available genotypes and body mass index measurement.  $F$ -statistics = 89-10 928. Heterogeneity tests for meta-analyses:  $I^2 = 0.07-0.99$  and  $P = 0\%$ . OR, odds ratio; 1 SD for systolic blood pressure = 23.6 mm Hg in CCHS + CGPS and 18.7 mm Hg in UK Biobank, 1 SD for diastolic blood pressure = 12.6 mm Hg in CCHS + CGPS and 10.1 mm Hg in UK Biobank, 1 SD for LDL cholesterol is 0.96 mmol/L CCHS + CGPS and 0.84 mmol/L in UK Biobank, 1 SD ln(triglycerides) is 0.55 in CCHS + CGPS and 0.75 in UK Biobank, 1 SD for plasma glucose is 1.34 mmol/L in CCHS + CGPS and 1.22 mmol/L in UK Biobank, 1 SD for ln(CRP) is 0.90 in CCHS + CGPS and 1.52 in UK Biobank.

triglycerides, 1.27 (0.89-1.83) for plasma glucose, and 0.37 (0.29-0.48) for plasma CRP, respectively (Supplementary Figs. S10 and S11) (37). For sensitivity analyses, see Supplementary Results and Supplementary Figs. S10 to S19 (37).

### Proportion of Risk of Vascular-Related Dementia Mediated by Each Intermediate Risk Factor

In mediation analyses of well-established variants, systolic blood pressure accounted for 18% (95% CI, 10%-61%) and diastolic blood pressure for 25% (13%-75%) of the association between BMI and vascular-related dementia (Supplementary Table S7A) (37). Because the blood pressure GWAS used for 2-sample MR of blood pressure on vascular-related dementia was adjusted for BMI, it was not possible to use these data in mediation analyses. Further, mediation analyses were conducted on the selected well-established variants to avoid noise from pleiotropy.

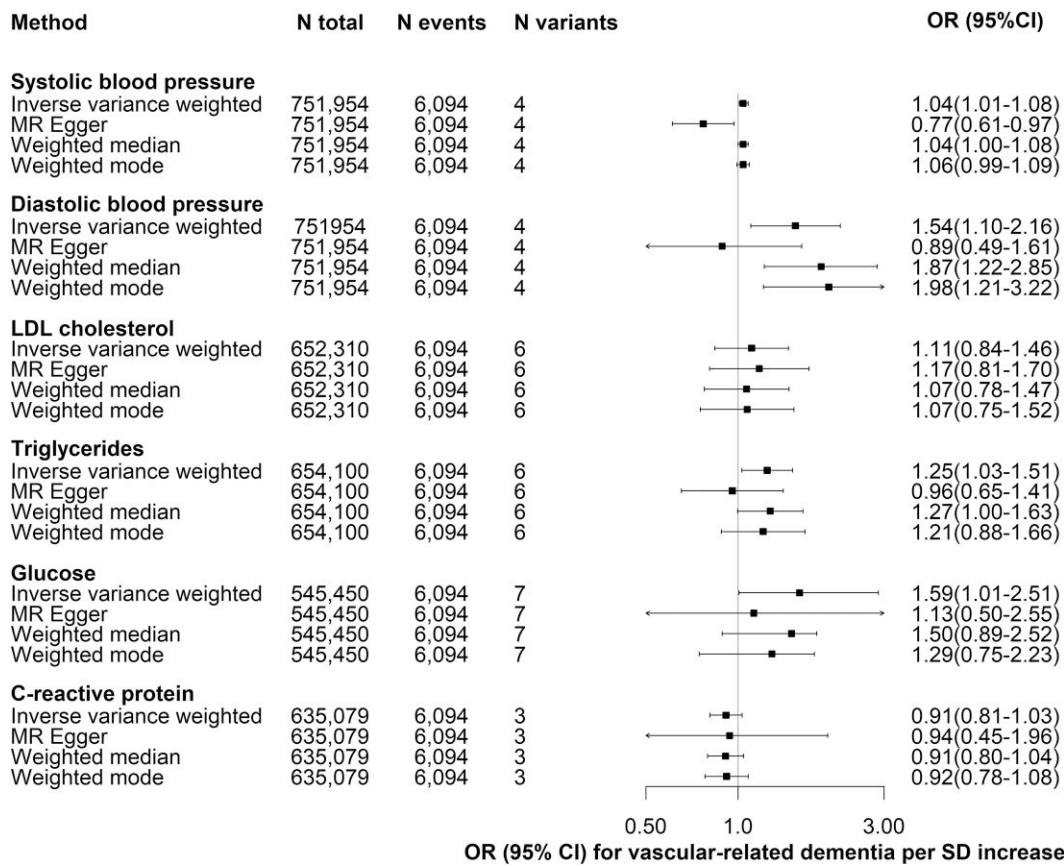
### Sensitivity Analyses

We tested the first MR assumption (whether the genetic variants used as instruments are associated with the exposure of interest) for well-established variants (Supplementary Figs. S1, S20, and S21) (37). To test for violations of the third MR assumption (the genetic variants affect the outcome only through their effect on the risk factor of interest), we tested for pleiotropy and heterogeneity in 2-sample MR analyses. In 2-sample MR using well-established variants, there was no sign of heterogeneity or pleiotropy (Supplementary Tables S9 and S10) (37). In 2-sample MR using an extended number of variants, the only analyses that showed evidence of pleiotropy was the analysis of BMI on risk of IHD ( $P = .002$ ) and the analysis of CRP on risk of vascular-related dementia ( $P = 2 \times 10^{-10}$ ). Some of the analyses showed signs of heterogeneity

(systolic and diastolic blood pressure on risk of vascular-related dementia, LDL cholesterol on risk of vascular-related dementia, triglycerides and risk of vascular-related dementia, and CRP on risk of vascular-related dementia) when using an extended number of variants (see Supplementary Figs. S3-S6 and S12-S19 and Supplementary Results) (37). Associations between measured BMI, BMI-weighted allele score and measured levels of intermediate risk factors were tested in Supplementary Figs. S22 to S25 (37). The effect of sample overlap was tested and found to be negligible (supplementary results (37)). We also tested the frequencies of the BMI-associated genetic variants in the CCHS + CGPS and UK Biobank and observed, as expected, that the frequencies of the BMI-increasing alleles are slightly higher in patients with vascular-related dementia compared to those without (Supplementary Table S11) (37). When testing the association between BMI-increasing allele score divided into quartiles and risk of vascular-related dementia, the association was seen to be approximately linear (Supplementary Figs. S26 and S27) (37). Finally, we tested the BMI of participants in the CCHS, CGPS, and UK Biobank at different times of assessment in these studies (Supplementary Table S12) (37). For the CCHS and CGPS, BMI increased at each subsequent visit after the baseline visit. In the UK Biobank no changes in BMI at different visits were observed for this subgroup.

### Discussion

In this study we applied an MR approach to investigate evidence for a causal relationship between BMI and vascular-related dementia. Observationally, we found the association between BMI and vascular-related dementia to be U-shaped, and genetically we found the association to be linear. We observed similar results using a set of well-established genetic variants and an extended number of genetic variants. Our



**Figure 5.** Two-sample mendelian randomization analyses of the association between mediators and risk of vascular-related dementia. Change in the risk of vascular-related dementia is per SD higher systolic and diastolic blood pressure, low-density lipoprotein (LDL) cholesterol, triglycerides, plasma glucose, and C-reactive protein (CRP). Based on the Copenhagen City Heart Study (CCHS), the Copenhagen General Population Study (CGPS), the UK Biobank, ICBP, MAGIC, GLGC, and CHARGE consortium. The odds ratios (OR) per 1 SD higher of the mediator were estimated using the “TwoSampleMR” R package. The estimates were derived by the inverse variance weighted method, the MR Egger method, the weighted median method, and the weighted mode method. Mean *F*-statistics for instruments were 420 for systolic blood pressure, 381 for diastolic blood pressure, 1211 for LDL cholesterol, 454 for triglycerides, 232 for glucose, and 46 for CRP. Rs268 and rs138326449 were not available in GLGC and no proxy variants were found. Therefore, only 6 instruments were available for triglycerides. Rs12509595 was used as a proxy for rs1458038, rs61235915 was used as a proxy for rs2383206, and rs2908282 was used as a proxy for 4607517. CHARGE, The Cohorts for Heart and Aging Research in Genomic Epidemiology; GLGC, Global Lipids Genomics Consortium; ICBP, International Consortium for Blood Pressure; MAGIC, Meta-Analysis of Glucose and Insulin-Related Traits Consortium.

results support that higher BMI increases the risk of vascular-related dementia. Further, by applying a genetic mediation method, we showed that this causal association is partly mediated via high systolic and diastolic blood pressure.

The biological mechanisms underlying the present findings are most likely caused by the effect of high blood pressure on the brain, where higher BMI is a direct cause of higher blood pressure (56-59). Vascular dementia is a disease characterized by strokes and microinfarcts (60), and accumulating strokes will eventually lead to brain atrophy (61). High blood pressure is a well-known causal risk factor for stroke (62), and midlife hypertension in contrast to late-life hypertension has been robustly associated with an increased risk of all-cause dementia (4, 8). Further, antihypertensive medication has been shown to reduce the risk of developing all-cause dementia as well as Alzheimer’s disease. Most observational studies have found that physical activity in early life is associated with a decreased risk of developing dementia (4). In a study by Rasmussen et al (63), physical activity was associated with a lower risk of developing vascular-related dementia. Further, in a large, double-blinded RCT, an intervention including diet, exercise, cognitive training, and vascular risk factor

monitoring reported an improvement in cognition in the intervention group compared to the control group (64).

Obesity is a growing health problem affecting more than 600 million individuals globally (65). Although weight loss could seem an obvious solution, maintaining optimal weight is a challenge (66). Thus, identifying and treating mediating risk factors on the causal pathway from obesity to diseases is paramount. Dementia is a devastating neurodegenerative disease currently affecting 50 million individuals worldwide with a steep increase in prevalence (67). Treatment and prevention options for dementia are scarce, underscoring the need to identify causal modifiable risk factors (67), as demonstrated here for risk of vascular-related dementia by high BMI mediated via high blood pressure.

Previous observational studies report conflicting results on the associations between high BMI and risk of vascular-related dementia. In the largest study so far including 1214 cases and 148 919 controls, Lee et al (6) found that BMI above 30 was associated with a higher risk of vascular dementia. They also reported that BMI below 18.5 was associated with a higher risk, as also observed by us. However, this latter association is likely to be a result of reverse causation, since

the prodromal phases of dementia are accompanied by loss of appetite and weight loss (68, 69). However, we cannot exclude that this association is mediated via other nonconventional risk factors. Whether the association between high BMI and high risk of vascular-related dementia is causal has not been investigated previously. We also found that high BMI was associated with several changes including higher blood pressure, LDL cholesterol, triglycerides, glucose, and CRP, as previously shown (43). Further, although high BMI has been shown to be associated with a low risk of Alzheimer's disease in observational studies, the majority of MR studies have not suggested causality (2, 69-74). The observational associations are most likely due to reverse causation, as discussed earlier (68). In a large meta-analysis (75), a reduced risk of Alzheimer's disease was seen in participants taking antihypertensive drugs compared to controls, and in another study (76) the use of antihypertensive medication was associated with a lower risk of developing Alzheimer's disease in those with high baseline systolic and diastolic blood pressure. In a recent study (77), however, there was no significant difference in the rate of probable dementia for adults with a blood pressure target of less than 120 mm Hg compared to less than 140 mm Hg. The genetically proxied associations indicate a potential causal role of the risk factors in general, supporting that traditional treatment with antihypertensive or weight-reducing medication is likely to offer a preventive effect on dementia. Whether BMI is a treatable risk factor for dementia will be further elucidated by current ongoing trials of the effect of semaglutide on risk of dementia (78); however, the most recent trial (Evoke phase 3 trials) has not been able to show a statistically significant reduction in risk of Alzheimer's disease (79). The presently observed positive linear relationship between BMI and risk of IHD is well established and serves as a positive control for our study (43).

Strengths of our study include well-characterized, population-based cohorts with prospective collection of endpoints, avoiding well-known biases observed in case-control designs. The validity of the dementia diagnoses is supported by the distribution of the *APOE*  $\epsilon 4$  allele in the different cohorts. Another strength is the application of recently developed methods for mediation analyses using MR. Genetic mediation methods use genetic variants as instrumental variables for the mediators. Traditional (non-instrumental variable) mediation methods use measured levels of mediators in the analyses and are reliant on the untestable assumption that the exposure, mediator, and outcome are not confounded. In contrast, the MR-based approach is less affected by confounders between the exposure or mediator and outcome as well as measurement error, thus making the generated results more robust (54). Using both a 1-sample and a 2-sample MR study design and including both a small number of carefully selected variants with known biological function as well as an extended number of variants while minimizing sample overlap further strengthens the results. Finally, to test the robustness of the main results, several sensitivity analyses were performed with similar results obtained.

Limitations of our study include studying only Europeans, which might limit the generalizability of our findings. However, variant allele frequencies for the well-established variants are similar in individuals of American and South Asian ancestry (<https://www.ensembl.org>). We cannot determine which set of genetic instruments is more valid. While the well-established variants have better-characterized

biological functions, the extended set offers greater statistical power, as reflected in the higher *F*-statistics. Another limitation is the heterogeneity of the dementia diagnoses, including vascular dementia. Further, the possibility of mixed cases of dementia or copathologies cannot be excluded, and information about vascular dementia subtypes was not available. For some of the intermediate risk factors, results differed slightly between the CCHS + CGPS and the UK Biobank. This could be due to differences in follow-up time between the 2 cohorts and thus relatively more cases in the CCHS + CGPS or differences in treatment of risk factors between the 2 populations. However, most results are directionally consistent in the CCHS + CGPS and the UK Biobank. Because we have only one BMI measurement available with sufficient statistical power for endpoints, we can only conclude on the observational association between the BMI at study entry and the subsequent risk of vascular-related dementia. Since the BMI measurement does not discriminate between fat mass and lean body mass, it is not straightforward to conclude whether both lean body mass as well as fat would increase the risk of developing vascular-related dementia. However, based on the present study, the effect of BMI seems to be working through increased blood pressure. Given that mainly increased fat mass will increase blood pressure (80) it is, however, likely that an increase in fat mass rather than lean body mass will increase the risk of dementia. Another limitation is that the ICBP GWAS used in the 2-sample MR analyses has been adjusted for BMI. However, since these data were not included in mediation analyses, this is not likely to have biased the overall results. The GWAS used in the 2-sample MR were not the most recent available, as we prioritized studies with minimal overlap with the UK Biobank. However, we do not expect that the main conclusions of our study would differ substantially if more recent GWAS were used. Although several sensitivity analyses were performed to test the validity of the MR assumptions, the possibility of horizontal pleiotropy and population stratification can never be completely excluded. When comparing the inverse variance weighted method, the weighted median method, and the weighted mode method used in the 2-sample MR, results are consistent across methods, suggesting that the results are less likely to be substantially biased by pleiotropy. The only exception is CRP, in which the seemingly "protective" effect of CRP on risk of vascular-related dementia is likely to be due to pleiotropy and not a true causal association. CRP is best instrumented using CRP cis-variants as conducted in the initial analyses using few, selected variants in both a 1-sample MR and 2-sample MR analysis. Further, BMI has been shown to be an effect modifier of the effect of CRP cis-variants on levels of CRP. As another example, HMGCR has been suggested to have pleiotropic effects other than the well-known effect on LDL cholesterol (81). It should also be noted that the estimate for the proportion mediated summing all mediators together will likely be an overestimate of the combined proportion mediated (54). Unfortunately, because weak instrument bias increases with number of exposures, it is not possible to test these associations using multivariable MR. Because of the limited availability of GWAS excluding the UK Biobank, there was a sample overlap between the exposure and outcome data used for 2-sample MR of blood pressure and CRP. However, based on the calculated potential bias and type 1 error rate, this overlap will have had a negligible effect on the overall results.

In conclusion, we find that high BMI is likely to be on the causal pathway to vascular-related dementia, and that a

substantial fraction of this risk is mediated through high blood pressure. This is important, as the treatment and prevention of elevated BMI and high blood pressure represent an unexploited opportunity for dementia prevention in the clinic.

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## Author Contributions

All authors contributed to the study conception, design, and to data collection. Material preparation and data analysis were performed by L.T.N. and J.L. The first draft of the manuscript was written by L.T.N. with subsequent editing by all authors. All authors read and approved the final manuscript.

## Disclosures

The authors have no relevant financial or nonfinancial interests to disclose.

## Data Availability

According to Danish law on data sharing, data cannot be made publicly available for the Copenhagen cohorts; however, through reasonable requests to the corresponding author additional analyses can be conducted in these cohorts. UK Biobank data can be accessed through application. Consortia data can be accessed via <https://gwas.mrcieu.ac.uk/>. The present research was conducted using the UK Biobank resource under application number 81499 to Lavinia Paternoster and application number 66214 to R.F.-S. L.T.N. and J.L. are collaborators on application number 66214 and thus have access to the UK Biobank data under this approved application. Additionally, L.T.N. is collaborator on application number 81499 and thus has access to the UK Biobank data under this approved application. The UK Biobank uses data provided by patients collected by the National Health Service as part of their care and support.

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