ORIGINAL ARTICLE

Independent Associations of Education, Intelligence, and Cognition With Hypertension and the Mediating Effects of Cardiometabolic Risk Factors: A Mendelian Randomization Study

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BACKGROUND: Education, intelligence, and cognition are associated with hypertension, but which one plays the most prominent role in the pathogenesis of hypertension and which modifiable risk factors mediate the causal effects remains unknown.

METHODS: Using summary statistics of genome-wide association studies of predominantly European ancestry, we conducted 2-sample multivariable Mendelian randomization to estimate the independent effects of education, intelligence, or cognition on hypertension (FinnGen study, 70 651 cases/223 663 controls; UK Biobank, 77 723 cases/330 366 controls) and blood pressure (International Consortium of Blood Pressure, 757 601 participants), and used 2-step Mendelian randomization to evaluate 25 potential mediators of the association and calculate the mediated proportions.

RESULTS: Meta-analysis of inverse variance weighted Mendelian randomization results from FinnGen and UK Biobank showed that genetically predicted 1-SD (4.2 years) higher education was associated with 44% (95% CI: 0.40–0.79) decreased hypertension risk and 1.682 mm Hg lower systolic and 0.898 mm Hg lower diastolic blood pressure, independently of intelligence and cognition. While the causal effects of intelligence and cognition on hypertension were not independent of education; 6 out of 25 cardiometabolic risk factors were identified as mediators of the association between education and hypertension, ranked by mediated proportions, including body mass index (mediated proportion: 30.1%), waist-to-hip ratio (22.8%), body fat percentage (14.1%), major depression (7.0%), high-density lipoprotein cholesterol (4.7%), and triglycerides (3.4%). These results were robust to sensitivity analyses.

CONCLUSIONS: Our findings illustrated the causal, independent impact of education on hypertension and blood pressure and outlined cardiometabolic mediators as priority targets for prevention of hypertension attributable to low education. (*Hypertension*. 2023;80:192–203. DOI: 10.1161/HYPERTENSIONAHA.122.20286.) ● **Supplemental Material**

Key Words: cardiometabolic risk factors ■ cognition ■ education ■ hypertension ■ intelligence ■ mediation analyses ■ Mendelian randomization

Hypertension is one of the leading risk factors for cardiovascular morbidity and mortality.[1] Education, intelligence, and cognition are robust predictors of socioeconomic achievement and have broad implications for lifestyle behaviors and health resource advantages over a person's lifespan.[2,3] Recent studies have

NOVELTY AND RELEVANCE

What Is New?

This is the first study to elucidate the causal, independent effect of education, intelligence, and cognition on hypertension and blood pressure, and to identify the mediating effects of modifiable cardiometabolic risk factors on the causal relationship.

What Is Relevant?

This Mendelian randomization study illustrates the causal effect of education on hypertension independently of intelligence and cognition, with 6 cardiometabolic risk factors as causal mediators in the pathway.

Clinical/Pathophysiological Implications?

This study provides novel evidence to the pathogenesis of hypertension and related clinical practice that increasing the duration of education, rather than improving intelligence or cognition, should be considered as an effective approach to reduce the risk of hypertension.

Several cardiovascular risk factors, including adiposity traits, depression, and lipids, should be recommended as priority targets for the prevention of hypertension attributable to low education.

Nonstandard Abbreviations and Acronyms

BF%	body fat percentage
BMI	body mass index
GWAS	genome-wide association study
HDL-C	high-density lipoprotein cholesterol
IVW	inverse variance weighted
MR	Mendelian randomization
MVMR	multivariable Mendelian randomization
SNP	single-nucleotide polymorphism
UVMR	univariable Mendelian randomization
WHR	waist-to-hip ratio

tentatively identified genetic correlations between education and intelligence as assessed by various cognitive tests, suggesting that education, intelligence, and cognition may be phenotypically and genetically related.[4] Two univariable Mendelian randomization (UVMR) studies have demonstrated that higher educational attainment and intelligence were causally associated with a decreased risk of hypertension or lower systolic blood pressure.[5,6] On the contrary, growing epidemiological evidence has advocated the potential benefits of managing modifiable cardiometabolic risk factors, mainly through lifestyle behaviors and metabolic traits, for the prevention and control of hypertension.[1,7] Thus far, it remains unclear whether education, intelligence, or cognition has an independent causal effect on hypertension and whether and to what extent potentially modifiable risk factors mediate this association. Knowledge of this topic can help deepen the understanding of the etiology of hypertension and inform prevention and intervention strategies to curb the hypertension epidemic.

Mendelian randomization (MR) is a causal inference method that exploits genetic variants as a proxy for exposure, which is akin to conducting a natural randomized control trial and can avoid some of the confounding bias and reverse causality of observational studies.[8] Multivariable Mendelian randomization (MVMR) is an expanded approach that allows for investigating the independent effects of correlated exposures on an outcome by incorporating genetic variants of each exposure into the same model.[9] In addition, a 2-step MVMR study can be applied to explore the pathways through which an exposure affects an outcome and improve causal inference in mediating effects since traditional, noninstrumental variable methods for mediation analyses would experience bias due to confounding between an exposure, mediator and outcome, and measurement error.[10]

In this study, we investigated the independent causal associations of education, intelligence, or cognition with hypertension and blood pressure using 2-sample MR, with a particular interest in evaluating the mediating effects of modifiable cardiometabolic risk factors in the pathogenesis of hypertension to facilitate clinical practice.

METHODS

The authors declare that all supporting data are available within the article and its Supplemental Material.

Study Design

This study included 2 stages of analyses (for study design see Figure 1A). In stage 1, we assessed the causal associations of education, intelligence, or cognition with hypertension and blood pressure using UVMR and MVMR, which utilized single-nucleotide polymorphisms (SNPs) as instrumental variables to proxy for each exposure. The UVMR results suggested that education and intelligence were causally associated with hypertension and blood pressure, while cognition was only causally associated with hypertension. The MVMR results further indicated that only education had an independent causal effect on hypertension and systolic and diastolic blood pressure with
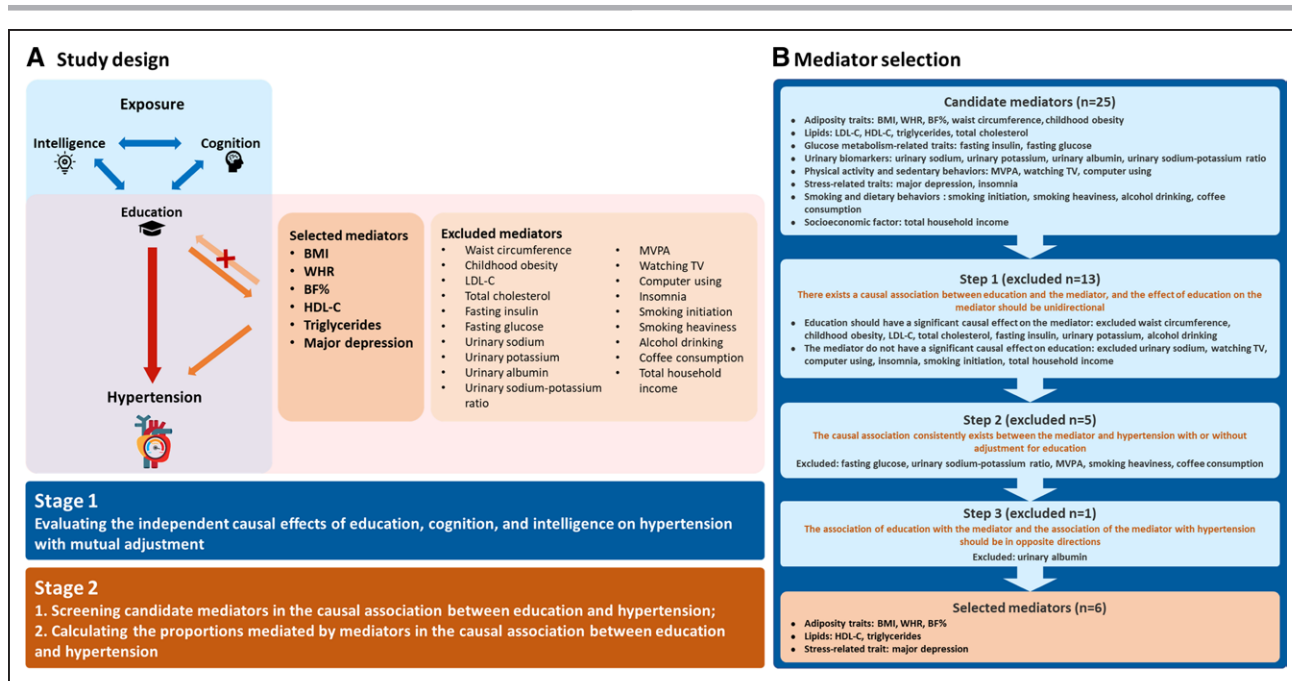
Figure 1. Overview of the study design.
A, Study design. **B**, Mediator selection process in phase 2. This study consisted of 2 stages of analyses. In stage 1, we assessed the causal associations of education, intelligence, and cognition with hypertension (main outcome) and blood pressure (secondary outcome) using univariable Mendelian randomization (UVMR) and multivariable Mendelian randomization (MVMR) to evaluate the overall and independent causal effects of each exposure on outcomes, respectively. For hypertension, the UVMR results suggested that all 3 exposures were causally associated with hypertension, while the MVMR results further indicated that only education had an independent causal effect on hypertension with mutual adjustment for intelligence and cognition. In stage 2, we first screened candidate mediators for the association between education and hypertension by stringent criteria, and then calculated their mediating effects using 2-step MR. BF% indicates body fat percentage; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MVPA, moderate to vigorous physical activity; TV, television; and WHR, waist-to-hip ratio.

mutual adjustment for intelligence, cognition, or both. Next, in stage 2, we screened candidate mediators in the association between education and hypertension and calculated their mediating effects using 2-step MR. This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization guideline.[11]

Data Sources of Exposures, Mediators, and Outcomes

In this MR study, data sources of exposures, mediators, and outcomes were derived based on summary-level data from genome-wide association studies (GWASs) conducted primarily in individuals of European ancestry (Table 1).

Exposures

Genetic instruments for education were selected from a GWAS of years of schooling in 1 131 881 individuals of European ancestry conducted by the Social Science Genetic Association Consortium, with summary data made available for 766 345 of these participants after the exclusion of participants from 23andMe because data can only be reported for up to 10 000 SNPs.[12] Genetic instruments for intelligence were selected from a GWAS meta-analysis of neurocognitive tests (primarily gauging fluid domains of cognitive functioning)-assessed intelligence in 269 867 European individuals with no evidence of heterogeneity between cohorts in the genetic associations.[4] Genetic instruments for cognition were selected from a GWAS

meta-analysis of a broadband index (g) or verbal-numerical reasoning scores in 257 841 individuals from the Cognitive Genomics Consortium and UK Biobank with low and no statistically significant values of meta-analytic tests of heterogeneity across the studied populations.[12,13] After linkage disequilibrium analyses evaluated using linkage disequilibrium link ($r^2 < 0.001$; distance threshold, 10 000 kb), 393/1271, 165/242, and 132/225 independent genome-wide significant ($P < 5 \times 10^{-8}$) SNPs were selected as the primary genetic instruments for education, intelligence, and cognition, respectively.

Mediators

Based on literature reviews, we selected 25 candidate mediators of modifiable cardiometabolic risk factors (for an overview of the process of identifying the candidate mediators see Figure S1),[14–41] which may lie on the pathways from education to hypertension or cardiovascular disease and with available genetic instruments derived from GWASs, including adiposity traits (body mass index [BMI],[14] waist-to-hip ratio [WHR],[15] body fat percentage [BF%],[16] waist circumference,[17] childhood obesity[18]), lipids (low-density lipoprotein cholesterol,[19] high-density lipoprotein cholesterol [HDL-C],[19] triglycerides,[19] total cholesterol[20]), glucose metabolism-related traits (fasting insulin[21] and fasting glucose[22]), urinary biomarkers (urinary sodium,[23] urinary potassium,[23] urinary albumin,[24] urinary sodium-potassium ratio[25]), physical activity and sedentary behaviors (moderate to vigorous physical activity,[26] watching TV,[27] computer using[27]), stress-related

Table 1. Summary of the GWAS Data Used in the MR Analyses

Phenotype	Unit	No of participants	Ancestry	Consortium/ cohort	Author	Year of publication	PubMed ID
Exposure							
Education	SD (4.2 y)	1 131 881	European	SSGAC	Lee et al	2018	30038396
Intelligence	SD	269 867	European	Meta	Savage et al	2018	29942086
Cognition	SD (0.99 points)	257 841	European	COGENT	Lee et al	2018	30038396
Outcome							
Hypertension	Event	294 314	European	FinnGen	Kurki et al	2022	NA
Hypertension	Event	408 089	European	UK Biobank	Sudlow et al	2015	25826379
SBP	mmHg	757 601	European	ICBP	Evangelou et al	2018	30224653
DBP	mmHg	757 601	European	ICBP	Evangelou et al	2018	30224653
25 candidate mediators							
Selected mediator*							
BMI	SD (4.7 kg/m²)	681 275	European	GIANT	Yengo et al	2018	30124842
WHR	SD (0.09)	212 244	European	GIANT	Shungin et al	2015	25673412
BF%	SD (6.6%)	65 831	European	Meta	Lu et al	2016	26833246
HDL-C	SD (15.5 mg/dL)	187 167	Mixed†	GLGC	Willer et al	2013	24097068
Triglycerides	SD (90.7 mg/dL)	177 861	Mixed†	GLGC	Willer et al	2013	24097068
Major depression	Event	500 199	European	PGC	Howard et al	2019	30718901
Excluded mediator							
Waist circumference	SD (12.5 cm)	231 353	European	GIANT	Shungin et al	2015	25673412
Childhood obesity	Event	13 848	European	EGG	Bradfield et al	2012	22484627
LDL-C	SD (38.7 mg/dL)	173 082	Mixed†	GLGC	Willer et al	2013	24097068
Total cholesterol	SD (41.8 mg/dL)	187 365	Mixed†	GLGC	Willer et al	2013	24097068
Fasting insulin	SD (0.79 pmol/L)	108 557	European	MAGIC	Scott et al	2012	22885924
Fasting glucose	SD (0.73 mmol/L)	58 074	European	MAGIC	Scott et al	2012	22885924
Urinary sodium	SD	326 831	European	UK Biobank	Hemani et al	2017	29846171
Urinary potassium	SD	326 816	European	UK Biobank	Hemani et al	2017	29846171
Urinary albumin	SD (0.755 log[mg/g])	382 500	European	UK Biobank	Haas et al	2018	30220432
Urinary sodium-potassium ratio	SD	326 938	European	UK Biobank	Zanetti et al	2020	32008434
MVPA	SD (2084 MET-min/wk)	377 234	European	UK Biobank	Klimentidis et al	2018	29899525
Watching TV	SD (1.5 h)	408 815	European	UK Biobank	Van de Vegte et al	2020	32317632
Computer using	SD (1.2 h)	408 815	European	UK Biobank	Van de Vegte et al	2020	32317632
Insomnia	Event	1331 010	European	UK Biobank	Jansen et al	2019	30804565
Smoking initiation	Event	607 291	European	GSCAN	Liu et al	2019	30643251
Smoking heaviness	SD (8 cigarettes/d)	337 334	European	GSCAN	Liu et al	2019	30643251
Alcohol drinking	SD (9 drinks/wk)	335 394	European	GSCAN	Liu et al	2019	30643251
Coffee consumption	SD (1% change)	375 833	European	UK Biobank	Zhong et al	2019	31046077
Total household income	SD	397 751	European	UK Biobank	Hemani et al	2018	29846171

BF% indicates body fat percentage; BMI, body mass index; COGENT, Cognitive Genomics Consortium; DBP, diastolic blood pressure; EGG, Early Growth Genetics Consortium; GIANT, Genetic Investigation of Anthropometric Traits; GLGC, Global Lipids Genetics Consortium; GSCAN, GWAS & Sequencing Consortium of Alcohol and Nicotine use; GWAS, genome-wide association study; HDL-C, high-density lipoprotein cholesterol; ICBP, International Consortium of Blood Pressure; LDL-C, low-density lipoprotein cholesterol; MAGIC, Meta-Analyses of Glucose and Insulin-related traits Consortium; MET, metabolic equivalent; MR, Mendelian randomization; MVMR, multivariable Mendelian randomization; MVPA, moderate to vigorous physical activity; NA, not available; PGC, Psychiatric Genomic Consortium; SBP, systolic blood pressure; SSGAC, Social Science Genetic Association Consortium; TV, television; and WHR, waist-to-hip ratio.

*Six out of 25 candidate mediators met all criteria of mediator selection and were included in the mediation MR analyses.

†Thirty-seven of 45 studies for summary statistics consisted primarily of individuals of European ancestry.

traits (major depression[28] and insomnia[29]), smoking and dietary behaviors (smoking initiation,[30] smoking heaviness,[31] alcohol drinking,[32] coffee consumption[33]), and socioeconomic factor (total household income).[41] The detailed information of the epidemiological evidence for the relationship between the 25 candidate mediators and hypertension or blood pressure is shown in Table S1.

We then screened for mediators of the association between education and hypertension according to the following criteria: (1) There exists a causal association between education

and the mediator, and the effect of education on the mediator should be unidirectional, because the validity of the mediation analyses may be affected if bidirectionality exists between them.[42] (2) The causal association consistently exists between the mediator and hypertension with or without adjustment for education; (3) Based on current scientific evidence, practically, the association between education and the mediator and the association between the mediator and hypertension should be in opposite directions. The detailed mediator selection process is shown in Figure 1B.

Finally, 6 cardiometabolic risk factors met all criteria and were included in the mediation analyses to evaluate their mediating effects on the causal association between education and hypertension. In 2-sample MVMR analyses, we selected genetic instruments of the combination of SNPs, which were genome-wide significant in either the GWAS of education or the GWAS of mediator after clumping summary statistics from GWASs for linkage disequilibrium threshold $r^2 < 0.001$ and distance $> 10\,000$ kb.

Outcomes

To ensure the credibility of the results, we extracted the genetic associations of instrumental variables with hypertension from 2 European consortiums: the FinnGen Study (for discovery) and UK Biobank (for replication).

The FinnGen Study, a Finnish, nationwide GWAS meta-analysis linked with longitudinal phenotype and digital health record data produced by national health registries,[43] has little overlap with the exposure or mediator GWASs to guarantee the lowest type 1 error rate. The FinnGen Study included 70 651 individuals with hypertension, defined as the presence of essential (primary) hypertension using the International Classification of Diseases diagnosis codes of version 8-10, and 223 663 individuals without essential hypertension, with 2149 individuals of any other hypertensive diseases excluded.

The UK Biobank is a prospective cohort of over 500 000 participants aged between 40 and 69 years at recruitment from the UK general population between 2006 and 2010.[44] Summary-level GWAS data on self-reported physician-diagnosed essential (primary) hypertension was obtained using the PheCode 401.1: Essential hypertension. There were 77 723 cases of hypertension and 330 366 controls in the UK Biobank, with 872 individuals of any other hypertensive diseases excluded. The large sample size of UK Biobank can validate the results investigated in FinnGen and maximize statistical power.

As secondary outcomes, we extracted the genetic associations of instrumental variables with BMI-adjusted systolic blood pressure and diastolic blood pressure in a sample of up to 757 601 individuals drawn from the International Consortium of Blood Pressure and UK Biobank, which further adjusted for antihypertensive medication use by adding 15 and 10 mm Hg to systolic blood pressure and diastolic blood pressure, respectively.[45]

All GWASs have received ethical approval from the relevant institutional review boards, participant informed consent, and stringent quality control. Ethics approval was not imperative for this study since it was obtained from summary-level data.

Statistical Analysis

UVMR and MVMR Analyses

We performed 2-sample UVMR to estimate the total effect of education, intelligence, or cognition on hypertension and blood pressure, respectively. We conducted MVMR to estimate the direct effect of education, intelligence, or cognition on hypertension and blood pressure with mutual adjustment to determine which exposure was causally associated with hypertension and blood pressure, independent of the other 2 exposures. All MR analyses fulfilled 3 critical assumptions: (1) Genetic variants must be vigorously associated with the exposure in UVMR analyses and must be vigorously associated with at least one of the multiple exposures in MVMR analyses; (2) Genetic variants must not be associated with confounders of the associations between instruments of each exposure and hypertension or blood pressure; (3) The effects of genetic variants on hypertension or blood pressure must go through each exposure.[46] Proxy SNPs in high linkage disequilibrium ($r^2 > 0.8$) were searched for genetic instruments that cannot be matched in summary data of the outcomes (https://ldlink.nci.nih.gov/). We used the inverse variance weighted (IVW) as the main UVMR and MVMR method, which combines the Wald ratio estimates of each SNP into 1 causal estimate for each exposure using the random-effects meta-analysis approach.[8] We pooled the IVW results for hypertension from FinnGen and UK Biobank using meta-analysis.

Mediation MR Analyses

We conducted mediator screening utilizing GWAS data from FinnGen as the primary source for hypertension, because FinnGen had no or very limited sample overlap with the mediator GWASs. We further replicated mediator screening process in UK Biobank and obtained similar results. A 2-step MR was performed to assess whether an intermediate risk factor has a mediating effect between education and hypertension.[47] The first step was to estimate the causal effect of genetically determined education on the mediator ($\beta 1$) using UVMR, and the second step was to estimate the causal effect of the mediator on hypertension using GWASs from FinnGen and UK Biobank, separately, with adjustment for education ($\beta 2$) using MVMR. Then, the proportion of the total effect of education on hypertension that was mediated by each mediator was estimated by dividing the indirect effect, which was calculated by multiplying the results from the 2 steps ($\beta 1 \times \beta 2_{\text{pooled}}$) by the total effect. We applied the Delta method to derive SEs using effect estimates obtained from 2-sample MR analyses.[48]

MR Sensitivity Analyses

We conducted weighted median, MR Egger, and MR pleiotropy residual sum and outlier methods to validate the robustness of the IVW results in the UVMR analyses, and applied MVMR Egger method to validate the robustness of the IVW results in MVMR analyses. The weighted median method can provide consistent estimates under the assumption that $> 50\%$ of the information contributing to the analysis comes from valid instrumental variables.[49] The MR-Egger method can assess whether genetic variants have directional pleiotropic effects on the outcome that differ on average from zero and provide a consistent estimate of the causal effect, under the InSIDE (Instrument Strength Independent of Direct Effect) assumption.[50] The MR pleiotropy residual sum and outlier method detects outlying SNPs that are potentially horizontally pleiotropic and evaluates whether exclusion of outlying SNPs influences the causal estimates under the assumption that the largest group of candidate instruments with similar estimates is the group

of valid instrumental variables.[51] We used the intercept of the MR Egger to test for pleiotropy, which may indicate potential violations of the instrumental variable assumptions underlying 2-sample MR. We also applied the Q′ heterogeneity statistic to assess the heterogeneity between instruments. We used conditional F-statistics to test for instrument validity, with an F<10 representing low instrument validity.

We considered IVW estimates as causal associations only if they had the same direction and statistical significance as at least one sensitivity analyses and did not show evidence of pleiotropy (P>0.05). Effect sizes were presented as odds ratio (OR), β coefficient, or proportion, with corresponding 95% CI. All MR analyses were conducted using R packages "TwoSampleMR," "MRPRESSO," "MendelianRandomization," "MVMR," and "metafor" in R software (version 4.0.2; the R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Total and Direct Effects of Education, Intelligence, or Cognition on Hypertension and Blood Pressure

There were strong bidirectional causal associations between education, intelligence, and cognition (Table S2). In UVMR analyses, the IVW results for hypertension from FinnGen and UK Biobank were highly consistent (Table S3), and meta-analysis of the 2 IVW results showed that genetically predicted each 1-SD longer years of schooling (OR: 0.56; [95% CI: 0.40–0.79]), higher intelligence (OR: 0.78; [95% CI: 0.72–0.84]), and better cognitive performance (OR: 0.79; [95% CI: 0.73–0.85]) were associated with a lower risk of hypertension (Figure 2A). Genetically predicted each 1-SD longer years of schooling and higher intelligence, but not cognition, were associated with lower systolic blood pressure (education: β: −2.056 mm Hg; [95% CI: −2.681 to −1.431]; intelligence: −1.092 mm Hg; [95% CI: −1.861 to −0.324]) and diastolic blood pressure (education: −0.939 mm Hg; [95% CI:−1.333 to −0.544]; intelligence: −0.528 mm Hg; [95% CI: −1.002 to −0.054]; Figure 2B). All MR results were robust to several sensitivity analyses (Table S3). Genetic instrumental variables of all exposures showed persistent heterogeneity and no pleiotropy with those of hypertension and blood pressure (Tables S4 and S5).

In MVMR analyses, the causal association between education and hypertension remained after adjusting for intelligence (IVW OR: 0.54; [95% CI: 0.37–0.79]), cognition (OR: 0.54; [95% CI: 0.41–0.72]), or both of them (OR: 0.56; [95% CI: 0.40–0.79]), while the causal associations of intelligence and cognition with hypertension were no longer statistically significant with adjustment for education (Figure 2A). Similarly, only education had an independent causal effect on systolic blood pressure (β: −1.682 mm Hg; [95% CI: −2.971 to −0.393]) and diastolic blood pressure (OR: −0.898 mmHg; [95%

CI: −1.698 to −0.098]) with adjustment for intelligence (Figure 2B). All directions and most of the statistical significance of IVW results in MVMR were consistent with those of MVMR Egger sensitivity analyses results, suggesting a low risk of bias due to horizontal pleiotropy (Table S6).

Effect of Education on Each Mediator

Of 25 candidate mediators, 6 cardiometabolic risk factors met the screening criteria and were included in mediation MR analyses (Figure 1B). In UVMR analyses, each 1-SD longer years of schooling was associated with lower BMI (IVW β: −0.305 SD; [95% CI: −0.358 to −0.251]), lower WHR (−0.290 SD; [95% CI: −0.341 to −0.240]), lower BF% (−0.261 SD; [95% CI: −0.324 to −0.198]), higher HDL-C (0.249 SD; [95% CI: 0.190–0.308]), lower triglycerides (−0.165 SD; [95% CI: −0.221 to −0.108]), and a decreased risk of major depression (OR: 0.79; [95% CI: 0.74–0.85]), with at least 2 or 3 sensitivity analyses confirmed these IVW estimates (Table 2). Genetic instrumental variables of education showed persistent heterogeneity and no pleiotropy with those of mediators (Tables S7 and S8). In bidirectional MR analyses, there was little evidence that mediators decreased or increased education significantly, with the exception of an inverse association between BMI and education, which was largely driven by horizontal pleiotropy ($P_{Egger\ intercept}$<0.001; Table S9).

Effect of Each Mediator on Hypertension With Adjustment for Education

In pooled MVMR results, each 1-SD unit higher BMI (IVW OR: 1.81; [95% CI: 1.69–1.95]); WHR (OR: 1.61; [95% CI: 1.42–1.82]); BF% (OR: 1.38; [95% CI: 1.25–1.54]); triglycerides (OR: 1.13; [95% CI: 1.08–1.19]); and major depression (OR: 1.19; [95% CI: 1.10–1.30]) were associated with an increased risk of hypertension after adjusting for education (Table 3). By contrast, each 1-SD unit higher HDL-C (OR: 0.89; [95% CI: 0.85–0.94]) was associated with a decreased risk of hypertension after adjustment for education. The instrument validity test presented sufficient instrument strength of SNPs for all variables in MVMR models, with F-statistic ranging from 25.74 through 149.72 (Table S10).

Mediating Effects of Mediators in the Association Between Education and Hypertension

Ranked by mediated proportions of 6 selected mediators including cardiometabolic risk factors of adiposity traits, stress-related trait, and lipids, the largest causal mediator from education to hypertension was BMI (30.1%; [95%
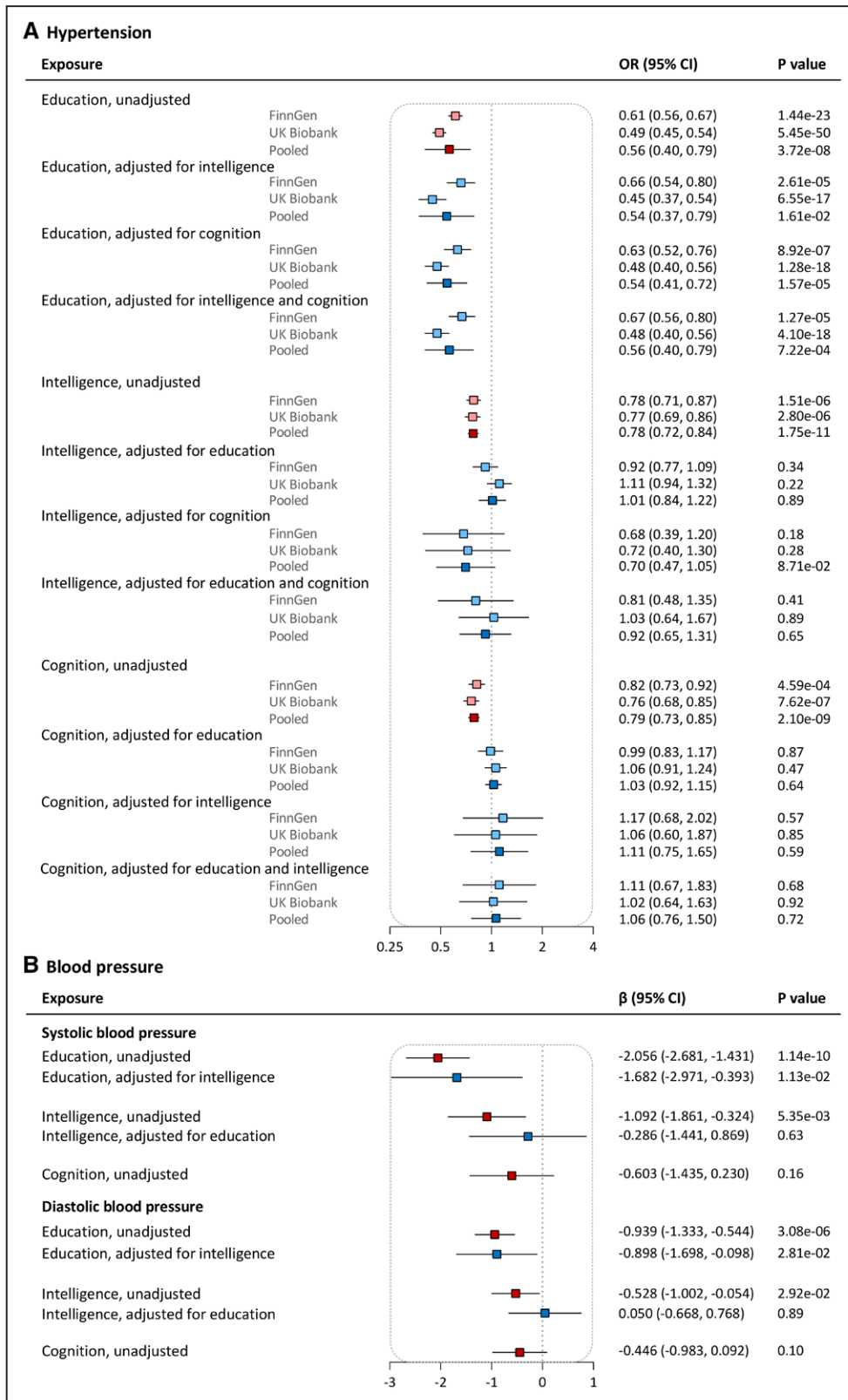
Figure 2. UVMR and MVMR estimates of the causal associations of education, intelligence, and cognition with hypertension and blood pressure.
A, Hypertension. **B**, Blood pressure. Plots (bars) represent OR (95% CI) or β (95% CI). As for hypertension, red plots represent the univariable Mendelian randomization (UVMR) results, and blue plots represent the multivariable Mendelian randomization (MVMR) results, with light ones representing the results from FinnGen/UK Biobank and dark ones representing the pooled results. As for blood pressure, red plots Hypersent the UVMR results and blue plots represent the MVMR results. OR indicates odds ratio.

Table 2. UVMR Assessing the Causal Association Between Education and Each Mediator

Mediator	Method	No of SNPs	β (95% CI)	OR (95% CI)	*P* value
BMI	IVW	295	−0.305 (−0.358 to −0.251)	…	1.66e-28
	Weighted Median	295	−0.270 (−0.308 to −0.232)	…	4.97e-44
	MR Egger	295	−0.362 (−0.569 to −0.155)	…	6.93e-04
	MR PRESSO	50*	−0.298 (−0.335 to −0.262)	…	1.14e-40
WHR	IVW	303	−0.290 (−0.341 to −0.240)	…	1.20e-29
	Weighted Median	303	−0.243 (−0.312 to −0.174)	…	4.81e-12
	MR Egger	303	−0.260 (−0.452 to −0.068)	…	8.31e-03
	MR PRESSO	1*	−0.286 (−0.335 to −0.237)	…	3.69e-25
BF%	IVW	305	−0.261 (−0.324 to −0.198)	…	3.79e-16
	Weighted Median	305	−0.283 (−0.372 to −0.193)	…	7.17e-10
	MR Egger	305	−0.481 (−0.722 to −0.240)	…	1.10e-04
	MR PRESSO	2*	−0.252 (−0.313 to −0.191)	…	1.39e-14
HDL-C	IVW	288	0.249 (0.190–0.308)	…	1.89e-16
	Weighted Median	288	0.218 (0.138–0.297)	…	9.46e-08
	MR Egger	288	0.237 (0.012–0.463)	…	4.03e-02
	MR PRESSO	0*	0.248 (0.189–0.308)	…	9.08e-15
Triglycerides	IVW	288	−0.165 (−0.221 to −0.108)	…	1.35e-08
	Weighted Median	288	−0.145 (−0.220 to −0.071)	…	1.21e-04
	MR Egger	288	−0.127 (−0.343 to 0.089)	…	0.25
	MR PRESSO	2*	−0.164 (−0.213 to −0.114)	…	3.89e-10
Major depression	IVW	370	−0.238 (−0.307 to −0.168)	0.79 (0.74–0.85)	1.94e-11
	Weighted Median	370	−0.212 (−0.284 to −0.141)	0.81 (0.75–0.87)	5.68e-09
	MR Egger	370	−0.269 (−0.520 to −0.017)	0.76 (0.59–0.98)	3.72e-02
	MR PRESSO	13*	−0.195 (−0.256 to −0.134)	0.82 (0.77–0.88)	1.35e-09

BF% indicates body fat percentage; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; IVW, inverse variance weighted; MR, Mendelian randomization; OR, odds ratio; PRESSO, pleiotropy residual sum and outlier; SNP, single-nucleotide polymorphism; UVMR, univariable Mendelian randomization; and WHR, waist-to-hip ratio.

*No of outliers.

CI: 23.7%–36.5%]), followed by WHR (22.8%; [95% CI: 15.7%–29.9%]), BF% (14.1%; [95% CI: 8.4%–19.7%]), major depression (7.0%; [95% CI: 3.1%–11.0%]), HDL-C (4.7%; [95% CI: 2.4%–7.0%]), and triglycerides (3.4%; [95% CI: 1.7%–5.2%]; Figure 3).

DISCUSSION

This MR study provided novel evidence for the causal impact of education on hypertension and blood pressure, with each additional 4.2 years of schooling decreasing an approximately 44% risk of hypertension and 1.682 mm Hg systolic blood pressure and 0.898 mm Hg diastolic blood pressure, independent of the effect of intelligence and cognition. In contrast, the causal impacts of intelligence and cognition on hypertension did not persist after adjustment for education, suggesting that their effects were largely influenced by education. We further examined the potential mediators in the pathway from education to hypertension and identified 6 out of 25 modifiable cardiometabolic risk factors as causal mediators, ranked by mediated proportion in the association between education and hypertension, including BMI (30.1%), WHR

(22.8%), BF% (14.1%), major depression (7.0%), HDL-C (4.7%), and triglycerides (3.4%). Our findings shed light on the causal protective influence of education, standing out of intelligence and cognition, on hypertension and blood pressure and the considerable mediating effect of several common cardiometabolic risk factors, primarily adiposity, in the pathogenesis from education to hypertension.

Education, intelligence, and cognition are interrelated and inseparable, with strong genetic evidence from the present study and a previous GWAS supporting the bidirectional associations between educational attainment, intelligence, and cognitive function.[4] Growing evidence from observational and MR studies has recommended that higher educational attainment was a protective factor for cardiovascular disease.[52,53] Current MR studies also suggest causal relationships of education and intelligence with hypertension.[5,6] Our results extended previous studies by adding evidence for a total causal effect of cognitive function on hypertension, and for the first time, we identified higher education as an independent protective contributor to hypertension and blood pressure independently of the influence of intelligence and cognition, but not vice versa. Compared with intelligence and cognitive

Table 3. MVMR Assessing the Causal Association Between Each Mediator and Hypertension With Adjustment for Education

Mediator	GWAS data source	β (95% CI)	OR (95% CI)	*P* value
BMI	FinnGen	0.557 (0.482−0.632)	1.75 (1.62−1.88)	1.75e-47
	UK Biobank	0.630 (0.560−0.700)	1.88 (1.75−2.01)	8.30e-70
	Pooled	0.595 (0.523−0.667)	1.81 (1.69−1.95)	8.15e-60
WHR	FinnGen	0.527 (0.343−0.711)	1.69 (1.41−2.04)	2.02e-08
	UK Biobank	0.431 (0.266−0.596)	1.54 (1.30−1.81)	2.98e-07
	Pooled	0.474 (0.351−0.597)	1.61 (1.42−1.82)	3.97e-14
BF%	FinnGen	0.377 (0.219−0.535)	1.46 (1.25−1.71)	2.84e-06
	UK Biobank	0.286 (0.148−0.424)	1.33 (1.16−1.53)	4.94e-05
	Pooled	0.325 (0.221−0.429)	1.38 (1.25−1.54)	8.39e-10
HDL-C	FinnGen	−0.101 (−0.169 to −0.033)	0.90 (0.84−0.97)	3.71e-03
	UK Biobank	−0.127 (−0.194 to −0.060)	0.88 (0.82−0.94)	2.07e-04
	Pooled	−0.114 (−0.162 to −0.066)	0.89 (0.85−0.94)	3.02e-06
Triglycerides	FinnGen	0.122 (0.052−0.192)	1.13 (1.05−1.21)	6.07e-04
	UK Biobank	0.127 (0.061−0.193)	1.14 (1.06−1.21)	1.50e-04
	Pooled	0.125 (0.077−0.173)	1.13 (1.08−1.19)	3.34e-07
Major depression	FinnGen	0.201 (0.075−0.327)	1.22 (1.08−1.39)	1.78e-03
	UK Biobank	0.159 (0.044−0.274)	1.17 (1.04−1.32)	6.82e-03
	Pooled	0.178 (0.093−0.263)	1.19 (1.10−1.30)	3.94e-05

BF% indicates body fat percentage; BMI, body mass index; GWAS, genome-wide association study; HDL-C, high-density lipoprotein cholesterol; MVMR, multivariable Mendelian randomization; OR, odds ratio; and WHR, waist-to-hip ratio.

function chiefly determined by heritability,[54] educational attainment is a more modifiable and impressionable factor that has a lasting impact on shaping economic status, accessing social resources, and forming healthy lifestyles over a person's life span.[55] Although formal educational attainment is typically completed in early adulthood, from a perspective of lifelong learning, educational attainment is a proxy indicator of opportunities for knowledge acquisition, cognitive training, and health promotion in later life.[55] Therefore, our findings provide important insights into prioritizing education policies and diminishing educational inequalities as effective precautions against hypertension and related disease burden.

Another noteworthy finding of this study is the identification and quantification of the mediating roles of cardiometabolic factors in the association between education and hypertension. In this study, we selected 25 candidate mediators comprehensively covering socioeconomic, lifestyle, and metabolic factors, and after a stringent screening of causal mediators, 6 causal mediators stood out. Interestingly, the 6 mediators included 3 adiposity traits (ie, BMI, WHR, and BF%), which individually had a mediating effect of >14.1%, with BMI itself mediating approximately 30.1% of the risk of hypertension attributable to lower education. These results are consistent with previous epidemiological and MR evidence that obesity, described primarily by BMI, has been intensively associated with hypertension,[5,56] suggesting that interventions targeting obesity may yield preferred hypotensive effects in low-education scenarios. Inferior to adiposity traits, major

depression, HDL-C, and triglycerides each mediated 7.0% to 3.4% of the causal effect of education on hypertension risk in this study. Increased levels of anti-fibrinolytic factors (eg, plasminogen activator inhibitor-1) and inflammatory markers due to depression and endothelial dysfunction and arterial stiffness due to low HDL-C and high triglycerides may partly interpret their mediating effects in the pathway to hypertension.[57,58] Notably, obesity, depression, and dyslipidemia are common conditions with major public health implications that tend to occur as comorbidities and share biological mechanisms, including genetics, immuno-inflammatory activation, neuroendocrine regulation, and energy metabolism.[59,60] Thus, the proportion mediated by each mediator in our analyses may exist overlap since the 6 mediators are interrelated.

Surprisingly, several candidate mediators supported by compelling observational studies did not play mediating roles in the pathway from education to hypertension in this study. Our UVMR findings of no causal associations of genetically determined education with waist circumference and alcohol drinking suggest that the significant associations found in observational studies[61,62] may be partially influenced by residual confounding or reverse causation bias. Moreover, several lifestyles, stress-related, and socioeconomic factors, such as watching TV, computer using, smoking initiation, insomnia, and total household income, were excluded from our mediation analyses due to their outstanding bidirectional causal associations with education, part of which are in line with the reverse causal associations reported by 1 mediation MR analysis
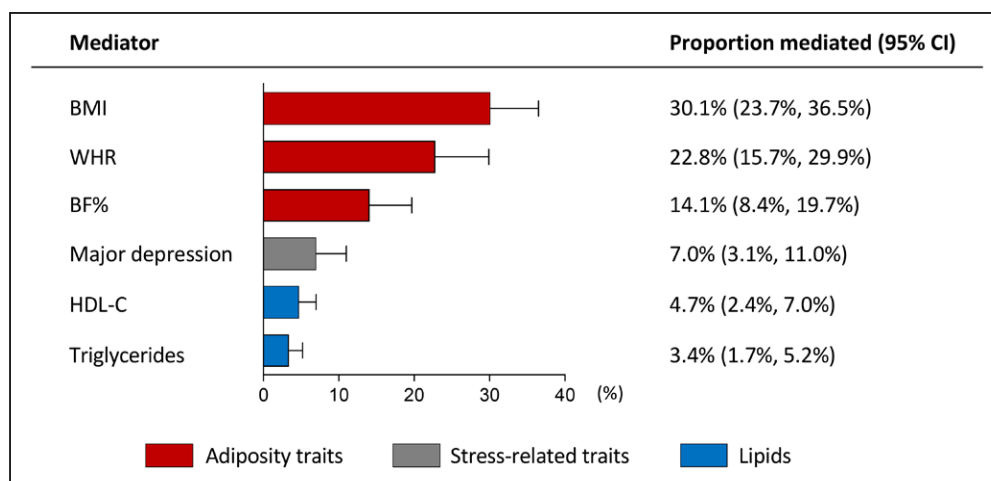
Figure 3. Mendelian randomization (MR) estimates of proportions mediated by mediators in the causal association between education and hypertension.

Histograms (bars) represent the mediated proportions (95% CIs). Red plots represent the proportions mediated by adiposity traits, grey plot represents the proportion mediated by a mediator of stress-related traits, and blue plots represent the proportions mediated by lipids. BF% indicates body fat percentage; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; and WHR, waist-to-hip ratio.

between education and type 2 diabetes.[42] In our UVMR analyses, fasting glucose, moderate to vigorous physical activity, smoking heaviness, and coffee consumption manifested no causal effect on hypertension, which are highly consistent with 1 UVMR study investigating the causal lifestyle behaviors and cardiometabolic factors for hypertension.[5] It is worth noting that the interaction between sodium and potassium is a key component of blood pressure regulation,[23] and the sodium-potassium ratio has been suggested as a stronger predictor of blood pressure than either sodium or potassium excretion alone.[25] However, we did not find a causal association between urinary sodium-potassium ratio and hypertension, which may be due to insufficient power because of the relatively low variance of urinary sodium-potassium ratio explained by genetic instruments.[63]

To the best of our knowledge, this is the first MR study to elucidate the causal effects of education on hypertension and blood pressure independently of intelligence and cognition, and to identify causal mediators in the pathway between education and hypertension. This work has several strengths. First, we used 2 GWAS sources for hypertension, including the FinnGen Study with little overlap with exposure or mediator GWASs to guarantee the lowest type 1 error rate, and the UK Biobank with a large sample size to facilitate replication and validation of the results investigated in FinnGen and maximize statistical power. Second, the robustness of the IVW estimates in this study was supported by multiple MR sensitivity analyses, each accommodated different assumptions about genetic pleiotropy.[50] Third, we set rigorous criteria for mediator screening to reduce the reverse causation of mediators on education and guarantee the credibility and rationality of the model we construct for explaining the mediating effect. This study also has some limitations. First, although

we focused on the most prevalent and important cardiometabolic risk factors as potential mediators to advance clinical practice, the mediating effect between education and hypertension cannot be fully explained in this study. For example, several potential mediators, such as poverty areas, health literacy, and access to health care, are not heritable and GWASs are not available.[64] Second, the constant existence of heterogeneity of SNPs may cause potential bias and affect the robustness of our MR results. Third, the majority of GWASs utilized in the analyses were conducted in European populations from high-income countries. Hence, the generalization of our findings to other ethnic groups or low- and middle-income countries should be further investigated. Forth, the overlap percentages of the GWASs between education and blood pressure, BMI, and major depression due to UK Biobank were approximately 31%, 32%, and 28%, respectively, which might lead to biased MR estimates toward observational association estimates.[65]

In conclusion, this MR study elaborated on the causal protective impact of education on the risk of hypertension and high blood pressure independently of intelligence and cognition and outlined 6 causal mediators of the effect of education on hypertension, including adiposity indicators, major depression, and lipids. This study adds causal evidence to the etiology of hypertension and informs prevention and intervention targets to curb the hypertension epidemic and its related disease burden.

PERSPECTIVES

Our findings imply that when policy authorities taking antihypertensive strategies into account, education should receive more attention or be a more critical intervention target than intelligence and cognition. Importantly, for

individuals with limited educational attainment, management of obesity, depression, and dyslipidemia may be the priority to reduce the public health burden from hypertension due to low education.

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