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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Table S1. Epidemiological evidence for the relationship between the 25 candidate mediators and hypertension or blood pressure

| Candidate mediator    | Epidemiological evidence                                                                                                                                 |
|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Adiposity trait**   |                                                                                                                                                            |
| BMI                   | After adjustment for baseline blood pressure, the HRs of developing isolated diastolic, systolic-diastolic, and isolated systolic hypertension for each 1-SD increase in BMI during follow-up were 1.28 (95% CI: 1.06, 1.55), 1.92 (1.72, 2.15), and 1.15 (1.04, 1.28), respectively, from the Framingham Heart Study. \(^{14}\) |
| WHR                   | The multivariate HRs of hypertension for per unit increase in WHR were 1.43 (95% CI: 1.23, 1.66), 1.24 (1.14, 1.34), 1.16 (1.03, 1.30) in 18-39, 40-59, 60-90 age-groups among men, respectively, and 1.37 (1.12, 1.68), 1.24 (1.14, 1.36), 1.10 (1.06, 1.33) in 18-39, 40-59, 60-90 age-groups among women, respectively, from a cohort study of 6,959 non-hypertensive participants aged over 18 years old in southern China. \(^{15}\) |
| BF%                   | Compared with the first quartile of BF%, the adjusted OR of hypertension in the highest BF% quartile was 3.30 (95% CI: 2.85, 3.83) in men and 2.66 (2.36, 2.99) in women, from the Henan Rural Cohort Study in five rural areas in China. \(^{16}\) |
| Waist circumference    | Compared with men with a waist circumference <94 cm, the OR of hypertension for men with a waist circumference ≥102 cm was 3.04 (95% CI: 1.13, 8.15) using casual blood pressure measure, 3.97 (1.52, 10.36) using 24 h blood pressure mean, and 5.19 (2.11, 12.8) using day-time blood pressure mean. Regardless of the blood pressure measurement (casual, 24 h or day-time), women with a waist circumference more than 88 cm had twice the risk of developing hypertension compared with women with a waist circumference <80 cm, from the Obesity Research Center of Chieti University in Italy. \(^{17}\) |
| Childhood obesity      | As compared with persons who had a normal BMI as children and were nonobese as adults, the relative risk of hypertension for subjects with consistently high adiposity status from childhood to adulthood was 2.7 (95% CI: 2.2, 3.3), from a meta-analysis of four prospective cohort studies. \(^{18}\) |
| **Lipid**             |                                                                                                                                                            |
| LDL-C                 | ORs of developing hypertension during the 7-year follow-up for a SD change in LDL-C, HDL-C, and                                                                 |
| HDL-C                 |                                                                                                                                                            |
| Triglycerides | Triglycerides in 311 middle-aged men were 1.30 (95%CI: 1.01, 1.67), 0.67 (0.50, 0.89), and 1.76 (1.35, 2.29), respectively, from the Kuopio Ischaemic Heart Disease Risk Factor Study.19 |
|---------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Total cholesterol | In Cox proportional hazards models adjusted for lifestyle and clinical risk factors, men in the highest quintile of total cholesterol had increased risks of developing hypertension of 23% compared with participants in the lowest quintile, from the Physicians’ Health Study.20 |
| Glucose metabolism-related trait | Fasting insulin | The pooled adjusted RR of hypertension was 1.54 (95% CI: 1.34, 1.76) for fasting insulin concentrations in a meta-analysis of eleven studies involving 10,230 hypertension cases.21 |
| | Fasting glucose | Compared with participants with normal baseline fasting glucose, those with impaired fasting glucose and diabetes had adjusted RR of hypertension of 1.16 (95% CI: 0.96, 1.40) and 1.41 (1.17, 1.71), respectively (P: 0.0015). The adjusted RR of incident hypertension was 1.08 (1.04, 1.13) for each mmol/L higher glucose (P <0.0001), from the Multi-Ethnic Study of Atherosclerosis.22 |
| Urinary biomarker | Urinary sodium | The interaction between sodium and potassium is a key component of blood pressure regulation.23 Urinary albumin excretion is a marker of cardiovascular risk and renal damage in hypertension.24 The sodium-potassium ratio has been suggested as a stronger predictor of blood pressure than either sodium or potassium excretion alone.25 |
| | Urinary potassium | | |
| | Urinary albumin | | |
| | Urinary sodium-potassium ratio | | |
| Physical activity or sedentary behavior | MVPA | Aerobic exercise was associated with a significant reduction in mean systolic blood pressure of 3.84 mmHg (95% CI: 2.72, 4.97) and diastolic blood pressure of 2.58 mmHg (1.81, 3.35) in a meta-analysis of 54 randomized controlled trials with 2,419 participants.26 |
| | Watching TV | A linear association was found between television viewing and hypertension ($P_{\text{non-linearity}}$: 0.679). For each 1-h/d increase in television viewing, the risk increased by 6% for hypertension, from a meta-analysis of one cohort and 13 cross-sectional studies.27 |
| | Computer using | A linear association was found between total sedentary behavior and hypertension ($P_{\text{non-linearity}}$: 0.225). For each 1-h/d increase in total sedentary behavior, the risk |
| **Stress-related trait** |  
|------------------------|  
| Major depression       | In a meta-analysis of two observational studies with 622 participants, mental stress was associated with an increased risk of hypertension (OR: 2.40; 95% CI: 1.65, 3.49; P <0.001).  
| Insomnia               | In a meta-analysis of fourteen prospective cohort studies involving 395,641 participants, the pooled RR of insomnia on hypertension was 1.21 (95%CI: 1.10, 1.33) and was statistically significant in the European population (RR: 1.08; 95%CI: 1.02, 1.14).  

| **Smoking or dietary behavior** |  
|------------------------|  
| Smoking initiation     | Among 13,529 men from the Physicians’ Health Study, former and current smoking were significantly associated with an 8% (RR: 1.08; 95% CI: 1.01, 1.15) and 15% (1.15; 1.03, 1.27) increase in the risk of incident hypertension, respectively, compared with never smoking over a median follow-up of 14.5 years.  
| Smoking heaviness       | In a prospective cohort study of 28,236 women from the Women's Health Study, multiple-adjusted hazard ratios of developing hypertension among former smokers and current smokers of 1-14 and ≥15 cigarettes/day were 1.03 (95% CI: 0.98, 1.08), 1.02 (0.92, 1.13), and 1.11 (1.03, 1.21), respectively, compared with never smokers.  
| Alcohol drinking        | If participants who drank six or more drinks per day reduced their intake by about 50%, the mean differences in systolic blood pressure and diastolic blood pressure were -5.50 mmHg (95%CI: -6.70, -4.30) and -3.97 mmHg (-4.70, -3.25), respectively, from a meta-analysis of 36 trials with 2,865 participants.  
| Coffee consumption      | A dose-response meta-analysis of 7 cohorts, including 205,349 individuals and 44,120 cases of hypertension, found a 1% decreased risk of hypertension for each additional cup of coffee per day.  

| **Socioeconomic factor** |  
|-------------------------|  
| Total household income  | The proportion of uncontrolled hypertension progressively increased with decreasing level of patient individual wealth, respectively, 72.8%, 79.3%, and 81.8% (P for trend, <0.01). Stratified analysis showed that in low-income countries, the odds of uncontrolled hypertension increased 1.37-fold (95% CI: 0.99, 1.90) and 1.88-fold (1.10, 3.21) in patients with middle and low |
individual wealth as compared with high individual wealth, from a cross-sectional survey in urban clinics of 12 countries in Sub-Saharan Africa.41

Abbreviations: BF%, body fat percentage; BMI, body mass index; CI, confidence interval; HDL-C, high density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low density lipoprotein cholesterol; MVPA, moderate to vigorous physical activity; OR, odds ratio; RR, relative risk; SD, standard deviation; TV, television; WHR, waist-to-hip ratio.
Table S2. UVMR estimating the bidirectional associations between education, intelligence, and cognition

| Exposure   | Outcome | Method          | No. of SNPs | β (95% CI)          | P value  |
|------------|---------|-----------------|-------------|---------------------|----------|
|            | Intelligence | IVW             | 330         | 0.791 (0.742, 0.840) | 6.65e-223 |
|            |          | Weighted Median | 330         | 0.734 (0.682, 0.787) | 6.71e-166 |
|            |          | MR Egger        | 330         | 0.928 (0.753, 1.103) | 4.62e-22  |
|            |          | MR PRESSO       | 9*          | 0.770 (0.725, 0.815) | 1.58e-106 |
| Education  | Cognition | IVW             | 375         | 0.785 (0.738, 0.832) | 2.97e-233 |
|            |          | Weighted Median | 375         | 0.743 (0.693, 0.792) | 1.74e-189 |
|            |          | MR Egger        | 375         | 0.934 (0.767, 1.101) | 2.00e-24  |
|            |          | MR PRESSO       | 8*          | 0.775 (0.731, 0.820) | 1.13e-116 |
|            | Intelligence | IVW             | 144         | 0.436 (0.399, 0.472) | 1.33e-119 |
|            |          | Weighted Median | 144         | 0.339 (0.306, 0.371) | 3.28e-92  |
|            |          | MR Egger        | 144         | 0.510 (0.341, 0.679) | 2.47e-08  |
|            |          | MR PRESSO       | 13*         | 0.396 (0.368, 0.424) | 1.67e-56  |
|            | Cognition | IVW             | 144         | 0.956 (0.930, 0.982) | 0.00e+00  |
|            |          | Weighted Median | 144         | 0.956 (0.909, 1.003) | 0.00e+00  |
|            |          | MR Egger        | 144         | 0.972 (0.856, 1.091) | 3.06e-34  |
|            |          | MR PRESSO       | 0*          | 0.956 (0.938, 0.974) | 3.48e-136 |
|            | Education | IVW             | 125         | 0.417 (0.378, 0.456) | 3.75e-97  |
|            |          | Weighted Median | 125         | 0.314 (0.281, 0.348) | 1.03e-75  |
|            |          | MR Egger        | 125         | 0.564 (0.394, 0.733) | 1.62e-09  |
|            |          | MR PRESSO       | 10*         | 0.387 (0.356, 0.418) | 3.98e-47  |
|            | Cognition | IVW             | 105         | 0.912 (0.883, 0.940) | 0.00e+00  |
|            |          | Weighted Median | 105         | 0.903 (0.850, 0.956) | 2.64e-245 |
|            |          | MR Egger        | 105         | 0.944 (0.825, 1.062) | 6.84e-29  |
|            |          | MR PRESSO       | 0*          | 0.912 (0.890, 0.933) | 3.02e-96  |
*NO. of outliers.
Abbreviations: CI, confidence interval; IVW, inverse variance weighted; MR, Mendelian randomization; PRESSO, pleiotropy residual sum and outlier; SNP, single nucleotide polymorphism; UVMR, univariable Mendelian randomization.
Table S3. UVMR estimating the associations of education, intelligence, or cognition with hypertension and blood pressure

| Exposure                      | Outcome                        | Method     | No. of SNPs | \( \beta \) (95% CI)          | OR (95% CI)          | P value     |
|-------------------------------|--------------------------------|------------|-------------|-------------------------------|----------------------|-------------|
| Education                     | Hypertension (FinnGen)         | IVW        | 372         | -0.493 (-0.588, -0.398)       | 0.61 (0.56, 0.67)    | 1.44e-23    |
|                               |                                | Weighted Median | 372     | -0.474 (-0.582, -0.366)       | 0.62 (0.56, 0.69)    | 7.77e-18    |
|                               |                                | MR Egger   | 372         | -0.389 (-0.742, -0.037)       | 0.68 (0.48, 0.96)    | 3.10e-02    |
|                               |                                | MR PRESSO  | 2*          | -0.481 (-0.576, -0.387)       | 0.62 (0.56, 0.68)    | 4.59e-21    |
|                               | Hypertension (UK Biobank)      | IVW        | 378         | -0.712 (-0.805, -0.618)       | 0.49 (0.45, 0.54)    | 5.45e-50    |
|                               |                                | Weighted Median | 378     | -0.680 (-0.784, -0.576)       | 0.51 (0.46, 0.56)    | 3.20e-39    |
|                               |                                | MR Egger   | 378         | -0.749 (-1.085, -0.413)       | 0.47 (0.34, 0.66)    | 1.63e-05    |
|                               |                                | MR PRESSO  | 11*         | -0.717 (-0.799, -0.635)       | 0.49 (0.45, 0.53)    | 1.72e-48    |
|                               | SBP                            | IVW        | 367         | -2.056 (-2.681, -1.431)       | /                    | 1.14e-10    |
|                               |                                | Weighted Median | 367     | -2.111 (-2.632, -1.590)       | /                    | 1.96e-15    |
|                               |                                | MR Egger   | 367         | -2.107 (-4.395, 0.182)        | /                    | 7.23e-02    |
|                               |                                | MR PRESSO  | 28*         | -2.281 (-2.774, -1.788)       | /                    | 1.05e-17    |
|                               | DBP                            | IVW        | 368         | -0.939 (-1.333, -0.544)       | /                    | 3.08e-06    |
|                               |                                | Weighted Median | 368     | -0.929 (-1.237, -0.622)       | /                    | 2.99e-09    |
|                               |                                | MR Egger   | 368         | -0.979 (-2.415, 0.458)        | /                    | 0.18        |
|                               |                                | MR PRESSO  | 37*         | -0.862 (-1.148, -0.575)       | /                    | 9.32e-09    |
|                               | Hypertension (FinnGen)         | IVW        | 143         | -0.243 (-0.342, -0.144)       | 0.78 (0.71, 0.87)    | 1.51e-06    |
|                               |                                | Weighted Median | 143     | -0.198 (-0.310, -0.086)       | 0.82 (0.73, 0.92)    | 5.33e-04    |
|                               |                                | MR Egger   | 143         | -0.231 (-0.725, 0.263)        | 0.79 (0.48, 1.30)    | 0.36        |
|                               |                                | MR PRESSO  | 44*         | -0.254 (-0.349, -0.158)       | 0.78 (0.71, 0.85)    | 6.63e-07    |
|                               | Hypertension (UK Biobank)      | IVW        | 145         | -0.258 (-0.365, -0.150)       | 0.77 (0.69, 0.86)    | 2.80e-06    |
|                               |                                | Weighted Median | 145     | -0.249 (-0.350, -0.148)       | 0.78 (0.71, 0.86)    | 1.04e-06    |
|                               |                                | MR Egger   | 145         | -0.331 (-0.825, 0.163)        | 0.72 (0.44, 1.18)    | 0.19        |
|                               |                                | MR PRESSO  | 11*         | -0.278 (-0.368, -0.188)       | 0.76 (0.69, 0.83)    | 1.18e-08    |
|                               | SBP                            | IVW        | 143         | -1.092 (-1.861, -0.324)       | /                    | 5.35e-03    |
| Cognition | Weighted Median | 143 | -0.622 (-1.174, -0.069) | / | 2.71e-02 |
|-----------|----------------|-----|-------------------------|---|----------|
| MR Egger  | 143            | -0.410 (-4.043, 3.222) | / | 0.83     |
| MR PRESSO | 22*            | -1.073 (-1.595, -0.550) | / | 1.01e-04 |
| MR Egger  | 143            | 0.335 (-1.902, 2.572)  | / | 0.77     |
| MR PRESSO | 27*            | -0.535 (-0.849, -0.222) | / | 1.10e-03 |

| DBP       | Weighted Median | 143 | -0.528 (-1.002, -0.054) | / | 2.95e-02 |
|-----------|----------------|-----|-------------------------|---|----------|
| MR Egger  | 143            | -0.364 (-0.686, -0.042) | / | 2.74e-02 |
| MR PRESSO | 22*            | -1.073 (-1.595, -0.550) | / | 1.01e-04 |
| MR Egger  | 143            | 0.335 (-1.902, 2.572)  | / | 0.77     |
| MR PRESSO | 27*            | -0.535 (-0.849, -0.222) | / | 1.10e-03 |

| Hypertension (FinnGen) | Weighted Median | 126 | -0.194 (-0.306, -0.082) | 0.82 (0.73, 0.92) | 6.62e-04 |
|------------------------|----------------|-----|-------------------------|-------------------|----------|
| MR Egger               | 126            | 0.050 (-0.474, 0.575)  | 1.05 (1.62, 1.78) | 0.85     |
| MR PRESSO              | 6*             | -0.219 (-0.318, -0.120) | 0.80 (0.73, 0.89) | 3.22e-05 |

| Hypertension (UK Biobank) | Weighted Median | 126 | -0.244 (-0.344, -0.145) | 0.78 (0.71, 0.87) | 1.44e-06 |
|---------------------------|----------------|-----|-------------------------|-------------------|----------|
| MR Egger                  | 126            | -0.016 (-0.487, 0.454)  | 0.98 (0.61, 1.58) | 0.95     |
| MR PRESSO                 | 9*             | -0.306 (-0.400, -0.213) | 0.74 (0.67, 0.81) | 2.85e-09 |

| SBP | Weighted Median | 121 | -0.603 (-1.435, 0.230) | / | 0.16     |
|-----|----------------|-----|------------------------|---|----------|
| MR Egger | 121            | -0.181 (-0.757, 0.395) | / | 0.54     |
| MR PRESSO | 17*            | -0.442 (-1.006, 0.121) | / | 0.13     |

| DBP | Weighted Median | 121 | -0.357 (-0.694, -0.019) | / | 3.84e-02 |
|-----|----------------|-----|-------------------------|---|----------|
| MR Egger | 121            | 1.480 (-0.870, 3.831)  | / | 0.22     |
| MR PRESSO | 22*            | -0.573 (-0.910, -0.235) | / | 1.33e-03 |

*NO. of outliers.<br>Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; IVW, inverse variance weighted; MR, Mendelian randomization; OR, odds ratio; PRESSO, pleiotropy residual sum and outlier; SBP, systolic blood pressure; SNP, single nucleotide polymorphism; UVMR, univariable Mendelian randomization.
### Table S4. MR heterogeneity test of the associations of education, intelligence, or cognition with hypertension and blood pressure

| Exposure       | Outcome                              | Method     | Q statistic | Q df | Q p-value   |
|----------------|--------------------------------------|------------|-------------|------|-------------|
| **Education**  | Hypertension (FinnGen)               | IVW        | 784.14      | 371  | 9.88e-32    |
|                | MR Egger                             | MR Egger   | 783.38      | 370  | 8.28e-32    |
|                | Hypertension (UK Biobank)            | IVW        | 924.57      | 377  | 6.82e-48    |
|                | MR Egger                             | MR Egger   | 924.45      | 376  | 4.50e-48    |
|                | SBP                                  | IVW        | 1739.73     | 366  | 3.04e-177   |
|                | MR Egger                             | MR Egger   | 1739.72     | 365  | 1.40e-177   |
|                | DBP                                  | IVW        | 2108.32     | 367  | 9.90e-242   |
|                | MR Egger                             | MR Egger   | 2108.30     | 366  | 4.15e-242   |
| **Intelligence**| Hypertension (FinnGen)               | IVW        | 347.23      | 142  | 3.27e-19    |
|                | MR Egger                             | MR Egger   | 347.22      | 141  | 2.07e-19    |
|                | Hypertension (UK Biobank)            | IVW        | 501.46      | 144  | 4.64e-41    |
|                | MR Egger                             | MR Egger   | 501.15      | 143  | 2.76e-41    |
|                | SBP                                  | IVW        | 1112.65     | 142  | 3.51e-150   |
|                | MR Egger                             | MR Egger   | 1111.53     | 141  | 2.03e-150   |
|                | DBP                                  | IVW        | 1283.64     | 142  | 5.66e-183   |
|                | MR Egger                             | MR Egger   | 1278.21     | 141  | 2.10e-182   |
| **Cognition**  | Hypertension (FinnGen)               | IVW        | 399.02      | 143  | 4.84e-26    |
|                | MR Egger                             | MR Egger   | 394.97      | 142  | 1.07e-25    |
|                | Hypertension (UK Biobank)            | IVW        | 423.78      | 125  | 3.80e-34    |
|                | MR Egger                             | MR Egger   | 419.64      | 124  | 8.93e-34    |
|                | SBP                                  | IVW        | 1023.69     | 120  | 2.87e-143   |
|                | MR Egger                             | MR Egger   | 1003.64     | 119  | 6.96e-140   |
|                | DBP                                  | IVW        | 1293.14     | 120  | 8.38e-196   |
|                | MR Egger                             | MR Egger   | 1264.26     | 119  | 1.27e-190   |

Abbreviations: DBP, diastolic blood pressure; df, degree of freedom; IVW, inverse variance weighted; MR, Mendelian randomization; SBP, systolic blood pressure.
Table S5. MR directional pleiotropy test (MR Egger) of the associations of education, intelligence, or cognition with hypertension and blood pressure

| Exposure | Outcome (FinnGen) | MR Egger intercept | SE     | P value |
|----------|------------------|--------------------|--------|---------|
| Education | Hypertension     | -0.0013            | 0.0022 | 0.55    |
|          | SBP              | 0.00048            | 0.0021 | 0.82    |
|          | DBP              | 0.00065            | 0.0144 | 0.96    |
|          | Hypertension     | 0.00052            | 0.0091 | 0.95    |
|          | (UK Biobank)     |                    |        |         |
|          | SBP              | 0.00025            | 0.0050 | 0.96    |
|          | DBP              | 0.0015             | 0.0050 | 0.77    |
|          | Hypertension     | -0.014             | 0.0370 | 0.71    |
|          | (UK Biobank)     |                    |        |         |
|          | SBP              | -0.018             | 0.0231 | 0.44    |
|          | DBP              | -0.018             | 0.0231 | 0.44    |
| Intelligence | Hypertension     | -0.0062            | 0.0051 | 0.23    |
|          | (FinnGen)        |                    |        |         |
|          | Hypertension     | -0.0057            | 0.0051 | 0.27    |
|          | (UK Biobank)     |                    |        |         |
|          | SBP              | -0.061             | 0.0400 | 0.13    |
|          | DBP              | -0.042             | 0.0263 | 0.10    |

Abbreviations: DBP, diastolic blood pressure; MR, Mendelian randomization; SBP, systolic blood pressure; SE, standard error.
Table S6. MVMR estimating the associations of education, intelligence, and cognition with hypertension

| Method | Exposure | β     | SE    | P     | MVMR Instrument validity test | MVMR Heterogeneity test | MVMR directional pleiotropy test |
|--------|----------|-------|-------|-------|-------------------------------|-------------------------|---------------------------------|
|        |          | F-statistic | Q statistic | P value | Q statistic | P value | Egger intercept | SE | P value |
| Hypertension (FinnGen) |          |                          |                   |         |                   |           |                  |     |         |
| Models with mutual adjustment for education, intelligence, and cognition |          |                          |                   |         |                   |           |                  |     |         |
| MV-IVW | Education | -0.403 | 0.0923 | 1.27e-05 | 28.82 | 721.72 | 1.11e-34 | 735.64 | 3.07e-36 | -0.00038 | 0.0018 | 0.83 |
|        | Intelligence | -0.215 | 0.2639 | 0.41 | | | | | | |
|        | Cognition | 0.106 | 0.2552 | 0.68 | | | | | | |
| MVMR Egger | Education | -0.388 | 0.1157 | 7.92e-04 | 28.82 | 721.72 | 1.11e-34 | 735.64 | 3.07e-36 | -0.00038 | 0.0018 | 0.83 |
|        | Intelligence | -0.207 | 0.2676 | 0.44 | | | | | | |
|        | Cognition | 0.110 | 0.2562 | 0.67 | | | | | | |
| Models with mutual adjustment for education and intelligence |          |                          |                   |         |                   |           |                  |     |         |
| MV-IVW | Education | -0.417 | 0.0993 | 2.61e-05 | 36.92 | 646.10 | 1.80e-32 | 653.68 | 3.04e-33 | -0.0036 | 0.0020 | 8.11e-02 |
|        | Intelligence | -0.084 | 0.0890 | 0.34 | | | | | | |
| MVMR Egger | Education | -0.256 | 0.1355 | 5.94e-02 | 36.92 | 646.10 | 1.80e-32 | 653.68 | 3.04e-33 | -0.0036 | 0.0020 | 8.11e-02 |
|        | Intelligence | 0.015 | 0.1054 | 0.89 | | | | | | |
| Models with mutual adjustment for education and cognition |          |                          |                   |         |                   |           |                  |     |         |
| MV-IVW | Education | -0.463 | 0.0941 | 8.92e-07 | 36.55 | 736.96 | 1.60e-38 | 746.42 | 1.49e-39 | 0.00041 | 0.0018 | 0.82 |
|        | Cognition | -0.013 | 0.0880 | 0.87 | | | | | | |
| MVMR Egger | Education | -0.480 | 0.1227 | 9.09e-05 | 36.55 | 736.96 | 1.60e-38 | 746.42 | 1.49e-39 | 0.00041 | 0.0018 | 0.82 |
|        | Cognition | -0.025 | 0.1030 | 0.81 | | | | | | |
| Models with mutual adjustment for intelligence and cognition |          |                          |                   |         |                   |           |                  |     |         |
| MV-IVW | Intelligence | -0.380 | 0.2855 | 0.18 | 11.22 | 368.78 | 6.45e-17 | 378.57 | 6.35e-18 | -0.0068 | 0.0041 | 9.43e-02 |
|        | Cognition | 0.157 | 0.2790 | 0.57 | | | | | | |
| MVMR Egger | Intelligence | -0.194 | 0.3050 | 0.53 | 11.22 | 368.78 | 6.45e-17 | 378.57 | 6.35e-18 | -0.0068 | 0.0041 | 9.43e-02 |
|        | Cognition | 0.321 | 0.2944 | 0.28 | | | | | | |
## Models with mutual adjustment for education, intelligence, and cognition

|               | Education | Intelligence | Cognition |
|---------------|-----------|--------------|-----------|
| **MV-IVW**    | -0.743    | 0.0857       | 4.10e-18  |
| MVMR Egger    | -0.772    | 0.1077       | 7.73e-13  |
| **MV-IVW**    | 0.032     | 0.2450       | 0.89      |
| MVMR Egger    | 0.016     | 0.2481       | 0.95      |
| **MV-IVW**    | 0.024     | 0.2369       | 0.92      |
| MVMR Egger    | 0.015     | 0.2379       | 0.95      |
| **MV-IVW**    | 60.12     | 808.14       | 1.23e-43  |
| MVMR Egger    |           |              |           |
| **MV-IVW**    | 840.21    | 1.07e-47     | 0.00073   |
| MVMR Egger    | 839.24    | 8.96e-48     | 0.0017    |
| **MV-IVW**    | 0.1085    | 0.2450       | 0.89      |
| MVMR Egger    | 0.016     | 0.2481       | 0.95      |
| **MV-IVW**    | 0.024     | 0.2369       | 0.92      |
| MVMR Egger    | 0.015     | 0.2379       | 0.95      |

## Models with mutual adjustment for education and intelligence

|               | Education | Intelligence |
|---------------|-----------|--------------|
| **MV-IVW**    | -0.805    | 0.0964       |
| MVMR Egger    | -0.797    | 0.1338       |
| **MV-IVW**    | 0.107     | 0.0862       |
| MVMR Egger    | 0.112     | 0.1029       |
| **MV-IVW**    | 78.69     | 768.72       |
| MVMR Egger    |           |              |
| **MV-IVW**    | 805.86    | 1.80e-51     |
| MVMR Egger    | 805.40    | 1.24e-51     |
| **MV-IVW**    | 1.68      | 1.12e-02     |
| MVMR Egger    |           |              |
| **MV-IVW**    | 560.95    | 1.77e-41     |
| MVMR Egger    | 560.32    | 1.23e-41     |
| **MV-IVW**    | 0.36      | 0.704        |
| MVMR Egger    |           |              |
| **MV-IVW**    | 12.61     | 1645.25      |
| MVMR Egger    |           |              |
| **MV-IVW**    | 166.12    | 8.80e-194    |
| MVMR Egger    | 161.95    | 1.17e-186    |

## Models with mutual adjustment for education and cognition

|               | Education | Cognition |
|---------------|-----------|-----------|
| **MV-IVW**    | -0.744    | 0.0844    |
| MVMR Egger    | -0.735    | 0.1099    |
| **MV-IVW**    | 0.059     | 0.0776    |
| MVMR Egger    | 0.112     | 0.1029    |
| **MV-IVW**    | 94.11     | 773.19    |
| MVMR Egger    |           |           |
| **MV-IVW**    | 804.13    | 1.58e-44  |
| MVMR Egger    | 803.71    | 1.12e-44  |
| **MV-IVW**    | 14.46     | 549.78    |
| MVMR Egger    |           |           |
| **MV-IVW**    | 560.95    | 1.77e-41  |
| MVMR Egger    | 560.32    | 1.23e-41  |

## Systolic blood pressure

|               | Education | Intelligence |
|---------------|-----------|--------------|
| **MV-IVW**    | -1.682    | 0.6575       |
| MVMR Egger    | -0.623    | 0.9100       |
| **MV-IVW**    | -0.286    | 0.5893       |
| MVMR Egger    | 0.361     | 0.7045       |
| **MV-IVW**    | 12.61     | 1645.25      |
| MVMR Egger    |           |              |
| **MV-IVW**    | 166.12    | 8.80e-194    |
| MVMR Egger    | 161.95    | 1.17e-186    |

## Diastolic blood pressure

|               | Education | Intelligence |
|---------------|-----------|--------------|
| **MV-IVW**    | -0.275    | 0.3166       |
| MVMR Egger    | 0.097     | 0.3053       |
| **MV-IVW**    | 0.056     | 0.2901       |
| MVMR Egger    | 0.097     | 0.3053       |
| **MV-IVW**    | 14.46     | 549.78      |
| MVMR Egger    |           |             |
| **MV-IVW**    | 560.32    | 1.23e-41    |
| MVMR Egger    |           |             |
| **MV-IVW**    | 0.36      | 0.7045      |
| MVMR Egger    |           |             |
| **MV-IVW**    | 12.61     | 1645.25     |
| MVMR Egger    |           |             |
| **MV-IVW**    | 166.12    | 8.80e-194   |
| MVMR Egger    | 161.95    | 1.17e-186   |

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### Models with mutual adjustment for education and intelligence

| Method  | Education | Intelligence | $R^2$ | $P$-value | Education | Intelligence | $R^2$ | $P$-value |
|---------|-----------|--------------|-------|-----------|-----------|--------------|-------|-----------|
| MV-IVW  | -0.898    | 0.050        | 6.28  | 1935.87   | 2.87e-02  | 0.3662       | 0.89  | 1.55e-46  |
| MV-IVW  | -0.363    | 0.378        | 6.28  | 1935.87   | 2.87e-02  | 0.3662       | 0.89  | 1.55e-46  |
| MV-IVW  | 0.5664    | 0.4381       | 6.28  | 1935.87   | 2.87e-02  | 0.3662       | 0.89  | 1.55e-46  |

**Abbreviations:** MV-IVW, multivariable inverse variance weighted; MVMR, multivariable Mendelian randomization; SE, standard error.
### Table S7. MR heterogeneity test of the association of education with each mediator

| Exposure     | Mediator     | Method   | Q statistic | Q df | Q p-value |
|--------------|--------------|----------|-------------|------|-----------|
| Education    | BMI          | IVW      | 2610.77     | 294  | 0         |
|              |              | MR Egger | 2607.93     | 293  | 0         |
|              | WHR          | IVW      | 400.36      | 302  | 1.25e-04  |
|              |              | MR Egger | 400.22      | 301  | 1.10e-04  |
|              | BF%          | IVW      | 350.98      | 304  | 3.38e-02  |
|              |              | MR Egger | 347.04      | 303  | 4.41e-02  |
|              | HDL-C        | IVW      | 398.21      | 287  | 1.48e-05  |
|              |              | MR Egger | 398.07      | 286  | 1.27e-05  |
|              | Triglycerides| IVW      | 378.87      | 287  | 2.20e-04  |
|              |              | MR Egger | 378.83      | 286  | 1.90e-04  |
|              | Major depression | IVW  | 1072.23    | 369  | 8.96e-70  |
|              |              | MR Egger | 1072.05    | 368  | 5.57e-70  |

Abbreviations: BF%, body fat percentage; BMI, body mass index; df, degree of freedom; HDL-C, high density lipoprotein cholesterol; IVW, inverse variance weighted; MR, Mendelian randomization; WHR, waist-to-hip ratio.
| Exposure  | Mediator      | Egger intercept | SE   | P value |
|-----------|---------------|-----------------|------|---------|
| Education | BMI           | 0.00073         | 0.0013 | 0.57    |
|           | WHR           | -0.00038        | 0.0012 | 0.75    |
|           | BF%           | 0.0028          | 0.0015 | 6.43e-02 |
|           | HDL-C         | 0.00045         | 0.0014 | 0.75    |
|           | Triglycerides | 0.00023         | 0.0014 | 0.86    |
|           | Major depression | 0.00040     | 0.0016 | 0.80    |

Abbreviations: BF%, body fat percentage; BMI, body mass index; HDL-C, high density lipoprotein cholesterol; MR, Mendelian randomization; SE, standard error; WHR, waist-to-hip ratio.
| Mediator      | Method      | MR results | Heterogeneity test | Directional pleiotropy test |
|--------------|-------------|------------|--------------------|-----------------------------|
|              |             | β         | SE     | P value | Q statistic | Q p-value | Egger intercept | P value |
| BMI          | IVW         | -0.139    | 0.0136 | 2.19e-24 | 3163.27      | 0         | -0.0020          | 7.00e-04          |
|              | Weighted Median | -0.093    | 0.0115 | 6.16e-16 | NA           | NA        |                  |         |
|              | MR Egger    | -0.026    | 0.0356 | 0.47    | 3089.58      | 0         |                  |         |
| WHR          | IVW         | -0.006    | 0.0234 | 0.79    | 73.77        | 3.20e-06  | -0.0070          | 7.81e-03          |
|              | Weighted Median | 0.019     | 0.0239 | 0.43    | NA           | NA        |                  |         |
|              | MR Egger    | 0.263     | 0.0957 | 1.15e-02 | 55.90        | 5.81e-04  |                  |         |
| BF%          | IVW         | -0.089    | 0.0588 | 0.13    | 111.92       | 5.97e-20  | -0.0150          | 0.13    |
|              | Weighted Median | -0.071    | 0.0315 | 2.43e-02 | NA           | NA        |                  |         |
|              | MR Egger    | 0.317     | 0.2483 | 0.24    | 82.88        | 1.28e-14  |                  |         |
| HDL-C        | IVW         | 0.023     | 0.0113 | 4.97e-02 | 469.16       | 7.30e-55  | 0.0015           | 0.11    |
|              | Weighted Median | 0.009     | 0.0084 | 0.31    | NA           | NA        |                  |         |
|              | MR Egger    | -0.006    | 0.0210 | 0.78    | 455.14       | 9.99e-53  |                  |         |
| Triglycerides| IVW         | -0.001    | 0.0109 | 0.93    | 219.02       | 4.62e-22  | -0.0012          | 0.16    |
|              | Weighted Median | 0.012     | 0.0092 | 0.20    | NA           | NA        |                  |         |
|              | MR Egger    | 0.018     | 0.0171 | 0.30    | 210.95       | 4.98e-21  |                  |         |
| Major depression | IVW     | -0.079    | 0.0349 | 2.32e-02 | 654.88       | 1.28e-108 | -0.0027          | 0.64    |
|              | Weighted Median | -0.048    | 0.0198 | 1.43e-02 | NA           | NA        |                  |         |
|              | MR Egger    | 0.008     | 0.1886 | 0.97    | 651.68       | 1.48e-108 |                  |         |

Abbreviations: BF%, body fat percentage; BMI, body mass index; HDL-C, high density lipoprotein cholesterol; IVW, inverse variance weighted; MR, Mendelian randomization; NA, not available; SE, standard error; WHR, waist-to-hip ratio.
Table S10. MVMR estimating the association of each mediator with hypertension with adjustment for education

| Mediator       | Method | Variable    | β     | SE   | P       | F-statistic | Q statistic | P value | MVMR Heterogeneity test | Q statistic | P value | MVMR directional pleiotropy test | P value |
|----------------|--------|-------------|-------|------|---------|-------------|-------------|---------|--------------------------|-------------|---------|---------------------------------|---------|
| **Hypertension (FinnGen)** |        |             |       |      |         |             |             |         |                          |             |         |                                 |         |
| BMI            | MV-IV  | Education   | -0.317| 0.0745 | 2.11e-05 | 149.72      | 1108.56     | 4.25e-54 | 1135.92  | 2.17e-57 | -0.0038 | 0.0012 | 0.75                            |         |
|                | W      | BMI         | 0.557 | 0.0385 | 1.75e-47 |             |             |         | 1135.29  | 1.67e-57 |                      |         |
|                | MVMR   | Education   | -0.322| 0.0780 | 3.71e-05 |             |             |         |            |             |         |                                 |         |
|                | Egger  | BMI         | 0.578 | 0.0748 | 1.15e-14 |             |             |         |            |             |         |                                 |         |
| WHR            | MV-IV  | Education   | -0.356| 0.0641 | 2.62e-08 | 48.88       | 535.65      | 8.50e-25 | 594.46   | 4.86e-32 | -0.0032 | 0.0012 | 6.85e-03                        |         |
|                | W      | WHR         | 0.527 | 0.0939 | 2.02e-08 |             |             |         | 594.44   | 3.09e-32 |                      |         |
|                | MVMR   | Education   | -0.420| 0.0674 | 4.69e-10 |             |             |         |            |             |         |                                 |         |
|                | Egger  | WHR         | 0.750 | 0.1239 | 1.44e-09 |             |             |         |            |             |         |                                 |         |
| BF%            | MV-IV  | Education   | -0.406| 0.0614 | 3.51e-11 | 45.18       | 396.78      | 6.34e-14 | 599.61   | 1.63e-32 | -0.00053 | 0.0012 | 0.65                            |         |
|                | W      | BF%         | 0.377 | 0.0805 | 2.84e-06 |             |             |         | 598.05   | 1.65e-32 |                      |         |
|                | MVMR   | Education   | -0.411| 0.0623 | 4.30e-11 |             |             |         |            |             |         |                                 |         |
|                | Egger  | BF%         | 0.412 | 0.1116 | 2.20e-04 |             |             |         |            |             |         |                                 |         |
| HDL-C          | MV-IV  | Education   | -0.455| 0.0733 | 5.25e-10 | 25.74       | 723.65      | 5.61e-50 | 735.63   | 1.72e-51 | -0.0031 | 0.0011 | 5.04e-03                        |         |
|                | W      | HDL-C       | -0.101| 0.0349 | 3.71e-03 |             |             |         | 735.61   | 9.89e-52 |                      |         |
|                | MVMR   | Education   | -0.397| 0.0753 | 1.34e-07 |             |             |         |            |             |         |                                 |         |
|                | Egger  | HDL-C       | -0.0361| 0.0415 | 0.38      |             |             |         |            |             |         |                                 |         |
| Triglycerides  | MV-IV  | Education   | -0.454| 0.0648 | 2.48e-12 | 32.8        | 584.74      | 2.28e-32 | 595.68   | 1.28e-33 | 0.00098 | 0.00095 | 0.30                            |         |
|                | W      | Triglycerides| 0.122 | 0.0357 | 6.07e-04 |             |             |         | 589.01   | 6.18e-33 |                      |         |
|                | MVMR   | Education   | -0.437| 0.0668 | 6.04e-11 |             |             |         |            |             |         |                                 |         |
|                | Egger  | Triglycerides| 0.104 | 0.0400 | 9.45e-03 |             |             |         |            |             |         |                                 |         |
| Major depression | MV-IV  | Education   | -0.420| 0.0556 | 4.65e-14 | 44.37       | 645.92      | 2.46e-29 | 662.87   | 3.15e-31 | 0.00016 | 0.0010 | 0.88                            |         |
|                | W      | Major depression| 0.201 | 0.0643 | 1.78e-03 |             |             |         | 657.98   | 8.31e-31 |                      |         |
|                | MVMR   | Education   | -0.418| 0.0570 | 2.42e-13 |             |             |         |            |             |         |                                 |         |
|                | Egger  | Major depression| 0.192 | 0.0857 | 2.49e-02 |             |             |         |            |             |         |                                 |         |

**Hypertension (UK Biobank)**

| Mediator | Method | Variable | β     | SE   | P       | F-statistic | Q statistic | P value | MVMR Heterogeneity test | Q statistic | P value | MVMR directional pleiotropy test | P value |
|----------|--------|----------|-------|------|---------|-------------|-------------|---------|--------------------------|-------------|---------|---------------------------------|---------|
| BMI      | MV-IV  | Education| -0.573| 0.0693 | 1.36e-16 | 265.14      | 1159.69     | 1.53e-57 | 1219.02  | 5.01e-65 | 0.0018 | 0.0011 | 0.11                            |         |
|          | W      |          |       |      |         |             |             |         |                          |             |         |                                 |         |
|                | W                  | BMI   | 0.630 | 0.0357 | 8.30e-70 |
|----------------|--------------------|-------|-------|--------|----------|
| MVMR Egger     | Education          | -0.541| 0.0722| 7.14e-14|
|                | BMI                | 0.533 | 0.0694| 1.59e-14|
| WHR            | Education          | -0.599| 0.0571| 8.03e-26|
| MVMR Egger     | WHR                | 0.431 | 0.0841| 2.98e-07|
|                | Education          | -0.631| 0.0607| 2.90e-25|
|                | WHR                | 0.540 | 0.1123| 1.53e-06|
| BF%            | MV-IV W            | -0.659| 0.0555| 7.05e-35|
|                | BF%                | 0.286 | 0.0705| 4.94e-05|
|                | Education          | -0.659| 0.0543| 5.69e-34|
|                | BF%                | 0.287 | 0.0988| 3.71e-03|
| HDL-C          | MV-IV W            | -0.703| 0.0695| 4.49e-24|
|                | HDL-C              | -0.127| 0.0343| 2.07e-04|
|                | Education          | -0.645| 0.0711| 1.13e-19|
|                | HDL-C              | -0.059| 0.0406| 0.14    |
| Triglycerides  | MV-IV W            | -0.680| 0.0597| 5.12e-30|
|                | Triglycerides      | 0.127 | 0.0335| 1.50e-04|
|                | Education          | -0.645| 0.0614| 7.75e-26|
|                | Triglycerides      | 0.090 | 0.0374| 1.63e-02|
| Major depression| MV-IV W            | -0.664| 0.0510| 8.92e-39|
|                | Major depression   | 0.159 | 0.0586| 6.82e-03|
|                | Education          | -0.667| 0.0522| 1.82e-37|
|                | Major depression   | 0.176 | 0.0786| 2.54e-02|

100.31 545.14 2.30e-24 1199.69 1.07e-62

601.15 3.86e-31 -0.0016 0.0011 0.14

579.11 2.40e-28 -7.60e-06 0.0010 0.99

575.71 4.18e-28

846.78 6.51e-66 -0.0031 0.0010 2.84e-03

842.62 1.53e-65

647.97 8.56e-39 0.0019 0.00088 2.91e-02

645.80 1.03e-38

721.05 1.78e-36 -0.00031 0.00093 0.74

720.85 1.22e-36

Abbreviations: BF%, body fat percentage; BMI, body mass index; HDL-C, high density lipoprotein cholesterol; MV-IVW, multivariable inverse variance weighted; MVMR, multivariable Mendelian randomization; SE, standard error; WHR, waist-to-hip ratio.
Figure S1. Overview of the process of identifying the mediators

We searched PubMed for papers published in English using keywords: “cardiometabolic risk factor”, “risk factor”, or “association”, combined with “hypertension”, “primary hypertension”, “blood pressure”, or “cardiometabolic disease”. A total of 44 common cardiometabolic risk factors were collected and listed in the first box of this figure by categories.

Abbreviations: BF%, body fat percentage; BMI, body mass index; CO, carbon monoxide; GWAS, genome-wide association study; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; MVPA, moderate to vigorous physical activity; NOx, nitrogen oxide; O3, ozone; PM2.5, particulate matter ≤2.5 microns; SO2, sulfur dioxide; TV, television; WHR, waist-to-hip ratio.