Causal association of body mass index with hypertension using a Mendelian randomization design

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Abstract
Observational studies have shown that obesity is a major risk factor for hypertension, but unmeasured confounding factors may exist. We used Mendelian randomization (MR) to assess the causal effect of obesity on hypertension.

The MR analysis was performed in a well-defined community cohort study of 8832 middle-aged (40–69 years) adults in Korea enrolled from 2001 to 2013. We used baseline hypertension and newly diagnosed hypertension during the 10-year follow-up period as the outcome variable. Genetic risk score associated with body mass index (BMI GRS) was used as the instrumental variable (IV) to measure the causal relationship between obesity and hypertension. The IV estimate of causal odds ratio (OR) was derived using the Wald ratio estimator and then exponentiation to express the result as an OR.

In the multivariable model adjusting for age, sex, study area, education, smoking, and current alcohol consumption, each 1 kg/m\(^2\) increase in BMI was associated with a 19% (OR: 1.19, 95% confidence interval [CI]: 1.17–1.21) increase in hypertension risk. We selected 6 single-nucleotide polymorphisms (\(P < 1.0 \times 10^{-5}\)) associated with BMI by genome-wide screening using linear regression and created 8 types of GRS. We demonstrated that each standard-deviation increase in BMI GRS was associated with a 5% to 6% (OR: 1.05–1.06) increased risk of hypertension (all \(P < .05\)). Using BMI GRS as the IV, we found a causal relationship between BMI and hypertension (OR: 1.13–1.26, all \(P < .05\) except weighted GRS \([n = 6]\)).

Using Mendelian randomization, we found that obesity is causally associated with hypertension. This information will have important public health implications, supporting evidence that obesity-reduction programs will reduce the incidence of hypertension.

Abbreviations: BMI = body mass index, BP = blood pressure, GRS = genetic risk score, CI = confidence interval, DBP = diastolic blood pressure, GRS = genetic risk score, IV = instrumental variable, KoGES = Korean Genome and Epidemiology Study, MR = Mendelian randomization, OR = odds ratio, RCTs = randomized clinical trials, SBP = systolic blood pressure, WGRS = weighted genetic risk score.

Keywords: hypertension, Mendelian randomization, obesity

1. Introduction
Hypertension is a major risk factor for ischemic heart disease, stroke, and chronic kidney disease. The global burden of these diseases increased substantially between 1990 and 2010.\textsuperscript{[1]} In 2014, approximately 22% of adults aged ≥18 years had been diagnosed with hypertension worldwide.\textsuperscript{[2]}

Obesity is a major risk factor for hypertension.\textsuperscript{[3–5]} In the Framingham study, weight loss of 6.8 kg or more over 4 years led to a 21% to 29% reduction in hypertension risk.\textsuperscript{[6]} Chandra et al showed that a higher body mass index (BMI) and visceral adiposity were significantly associated with incident hypertension in African–American participants.\textsuperscript{[7]} Lee et al observed that obesity is associated with an increased risk of hypertension in the Korean population, regardless of the presence of elements of metabolic syndrome.\textsuperscript{[8]} However, conventional observational analyses cannot avoid unmeasured confounding and reverse causation, which make it difficult to infer causality from the observed association.\textsuperscript{[9,10]}

Randomized clinical trials (RCTs) have demonstrated the effect of weight loss on blood pressure (BP).\textsuperscript{[11]} However, some RCTs have yielded mixed results. Tyson et al. found that the weight-gain group (>3%) and the weight-stable (within 3%) group both had increased systolic BP (SBP) and that these 2 groups were not significantly different in SBP.\textsuperscript{[12]} Moreover, SBP
was unchanged for the weight-loss group who lost 3% or more of their weight. Furthermore, most of the RCTs were short-term studies with small numbers of participants; therefore, the results may not be applicable to the general population and cannot address the long-term health effects of obesity. In addition, intervention could also affect other pathways. For example, weight-loss surgery (eg, Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding, or vertical sleeve gastrectomy) influences glucose metabolism more than it influences the obesity-hypertension pathway.\(^{[13]}\)

Mendelian randomization (MR) analysis using genetic variants as the instrumental variable (IV) has been increasingly used to assess causality. Genetic variants are present from conception, allocated randomly according to Mendel second law and are inherited independent of potential confounding factors.\(^{[9,10]}\) Thus, the IV (genetic variants associated with obesity) is independent of confounders in its effects on the phenotype (obesity)–outcome (hypertension) relationship.

Recently, a small number of MR studies have reported that BMI has a causal relationship with hypertension.\(^{[14-16]}\) However, these studies were conducted in Western populations. The World Health Organization reported that the prevalence of overweight (BMI \(\geq 25 \text{ kg/m}^2\)) and obesity (BMI \(\geq 30 \text{ kg/m}^2\)) is highest in the Americas (61% overweight or obese in both sexes, and 27% obese), especially in the United States (68% overweight or obese among both sexes, and 32% obese). In contrast, Koreans have a low prevalence of obesity (31% overweight or obese among both sexes and 46% obese). However, the prevalence of hypertension is similar between the United States and Korea (9.4% vs 8.4%, respectively).\(^{[2,17]}\) Because of the different prevalences of obesity but similar prevalences of hypertension between the United States and Korea, a study of the causal relationship between obesity and hypertension in Korea is needed.

A composite genetic risk score (GRS) could reduce the statistical error associated with multiple testing compared to individual single-nucleotide polymorphisms (SNPs). Thus, we analyzed the association between IV for obesity using BMI-associated GRS (BMI GRS) and risk of hypertension to explore the causal association between obesity and hypertension.

2. Methods

2.1. Study population

We used data from the Ansung-Ansan cohort within the Korean Genome and Epidemiology Study (KoGES), which was initiated in 2001 as a population-based cohort study recruiting Korean adults aged 40 to 69 years. Briefly, a total of 5020 participants (2323 men and 2697 women) in Ansung and 3188 participants (2239 men and 2779 women) in Ansan were included in the baseline examinations from June 2001 to January 2003. Follow-up surveys were conducted biennially, and study participants were followed-up to 5 times until 2012. Information about their general characteristics, lifestyle, and current medications was obtained through questionnaires. Physical examinations, including BP, anthropometric measurements, and blood sampling, were conducted by trained researchers from 2001 to 2012. During this 10-year period, a follow-up rate of 62.1% was achieved.

The criteria for exclusion were no data of genotype (n = 1196), missing BP measurements, or history of hypertension diagnosis (n = 10). After this exclusion, the present report focuses on 8832 participants for whom information about the genotype and outcome variables of hypertension were available.

An informed consent form was signed by each participant, and the study protocol was approved by the institutional review board of the Seoul National University Hospital (IRB No: 1312-033-539).

2.2. Genotype

A total of 10,004 participants were genotyped using the Affymetrix Genome-Wide Human SNP Array 5.0 (Santa Clara, CA) containing 500,568 SNPs. Genotype clustering was determined using Bayesian robust linear modeling of the Mahalanobis distance. Before statistical analysis, 17,926 markers with a genotype call rate <95%, 92,050 markers with low minor allele frequency (<0.01), and 38,364 markers with Hardy–Weinberg equilibrium \((P < 10^{-8})\) were removed, leaving 352,228 SNPs for 8842 individuals. An additional \(1.8 \times 10^8\) SNPs were found by imputation using the JPT/CHB component of HapMap as the reference. After filtering, a total of 1,590,162 genotyped and imputed SNPs were available for analyses. The genotyping methods of the KoGES have been described previously in detail.\(^{[18]}\)

2.3. BMI and lifestyle measurement

Alcohol consumption was calculated as the amount consumed per week and divided into 2 groups. Based on the guidelines for recommended alcohol consumption to lower health risks from the Korea Health Promotion Foundation, we defined low consumption of alcohol as 40 g or less for males and 20 g or less for females at one time, less than twice a week.\(^{[19]}\) They were also split into 2 groups by smoking status: <20 pack-years smoking and >20 pack-years. BMI was calculated as weight in kilograms divided by height in meters squared \((\text{kg/m}^2)\) at the baseline survey.

2.4. Hypertension assessment

The BP was measured using mercury sphygmomanometers (Baumanometer; WA Baum, Copiague, NY) according to a standardized protocol.\(^{[20]}\) All measurements in the present study were taken after at least a 5-min rest. We used an average of 3 measurements. At baseline, hypertensive participants were defined as having SBP \(\geq 140 \text{ mm Hg}\) or diastolic BP (DBP) \(\geq 90 \text{ mm Hg},\) using antihypertensive medication, or having a history of hypertension diagnosed by a doctor. After these participants were excluded, newly diagnosed cases of hypertension were defined as SBP \(\geq 140\) or DBP \(\geq 90 \text{ mm Hg}\) and taking antihypertensive drugs during the 10-year follow-up. We considered both baseline hypertension and newly diagnosed hypertension during the 10-year follow-up period.

2.5. Selection of genetic loci and GRS construction

We selected individual 32 SNPs associated with BMI using linear regression (Supplemental Table S1, http://links.lww.com/MD/C348). Because we wanted to include more SNPs, we used a liberal \(P\)-value (<1.0 \times 10^{-3}) instead of a restrictive \(P\)-value after Bonferroni correction, 5.0 \times 10^{-8}. Among these SNPs, 2 SNPs had been reported previously.\(^{[18]}\) Some SNPs were found to be in high linkage disequilibrium \((D') \geq 0.9\). Therefore, we selected 1 representative SNP from the closely linked SNPs based on the estimated size of the main genetic analysis results or significance in previous studies. Finally, 3 BMI GRSS were constructed. The
first BMI GRS was composed of 2 significant SNPs (rs17178527 and rs9939609) found in a previous study.[13] The second was composed of 4 SNPs (rs17178527, rs9939609, rs7668087, and rs11000212) selected with a cut-off \( P \)-value < \( 5 \times 10^{-6} \). The third composed of 6 SNPs (rs17178527, rs9939609, rs7668087, rs11000212, rs17130257, and rs10936246) selected with a cut-off \( P \)-value < \( 5 \times 10^{-5} \). The GRS was produced by 2 methods: a simple-count method (CGRS) and a weighted method (WGRS).[21,22] Six types (3 \times 2) of BMI GRS (CGRS \([n = 2]\), WGRS \([n = 2]\), CGRS \([n = 4]\), WGRS \([n = 4]\), CGRS \([n = 6]\), and WGRS \([n = 6]\)) were used in the analysis. We assumed an additive genetic model for each SNP, applying a linear weighting of 0, 1, or 2 to genotypes containing 0, 1, or 2 risk alleles, respectively. The simple-count model assumes that each SNP in the panel contributes equally to the risk of hypertension and was calculated by summing the values (0, 1, and 2) for each of the SNPs. The weighted GRS was calculated by multiplying each \( \beta \) coefficient obtained from linear regression by the number of corresponding risk alleles (0, 1, and 2). All \( \beta \) coefficients were positive because we reordered the sequence of genotypes of the SNPs when the weights were less than zero.

### 2.6. Statistical analysis

Multivariate logistic regression models were used to assess the association between BMI and hypertension. Model 1 was not adjusted for other variables; Model 2 was adjusted for age (years) and sex (male or female); Model 3 was further adjusted for region (Ansung or Ansan), education (\( \leq 9 \) or \( > 9 \) years of school), tobacco smoking, and current alcohol consumption. The association between BMI GRS and hypertension was evaluated in a bivariate logistic regression model. In MR analysis, we used the 6 types of BMI GRS as the IV estimators to measure the strength of the causal relationship between BMI and hypertension. The IV estimate of causal odds ratio (OR) was derived using the Wald-type estimator \( \beta_{GRS\text{-BMI}} \) estimated the effect of the GRS on BMI using linear regression.

\[
OR_{IV} = \exp \left( \frac{\ln(OR_{GRS\text{-hypertension}})}{\beta_{GRS\text{-BMI}}} \right)
\]

We also tested the difference between the IV estimators and the conventional regression-based estimators for the effect of BMI using a classical \( t \)-test. Figure 1 shows the directed acyclic graphs between exposure (BMI) and outcome (hypertension) with the genetic instrument.

In the sensitivity analysis, we conducted MR analysis using only baseline data for a cross-sectional approach. Statistical significance was set to a 2-sided \( P \)-value of < .05. All statistical analyses were performed using SAS software version 9.3 (SAS Institute Inc, Cary, NC), Plink (version 1.08, http://pngu.mgh.harvard.edu/~purcell/plink), and R version 3.1.0 (Comprehensive R Archive Network: http://cran.r-project.org).

### 3. Results

Among 8832 participants, 4179 (47.3%) were men. The average age was 52 (SD 8.92) years, and the average BMI was 24.6 (SD 3.12) kg/m². At baseline, hypertension was diagnosed in 2971 (33.6%) participants, and the remaining 5861 (66.4%) participants were not hypertensive. During the 10-year follow-up, hypertension was newly detected in 1409 participants (first follow-up: 436; second follow-up: 274; third follow-up: 232; fourth follow-up: 322; and fifth follow-up: 143) (Supplemental Fig. S1, http://links.lww.com/MD/348). Therefore, the number (proportion) of hypertension at baseline and new cases during follow-up was 4380 (49.6%) and no hypertension during follow-up was 4452 (50.4%). As shown in Table 1, there were statistically significant differences in age, area, education, alcohol consumption, and BMI measured between hypertension at baseline/follow-up and no hypertension during follow-up. Table 2 shows the demographic features of the participants according to BMI GRS quartiles using baseline and longitudinal data. The BMI GRS (in quartiles) was significantly associated with BMI (\( P \) for trend < .0001). No other population characteristics (sex, area, smoking, current alcohol drinking) were significantly associated with BMI GRS.

### Table 1

General characteristics of the study population using baseline and longitudinal data (n = 8832).

| Variable | No HTN during follow-up | HTN at baseline/follow-up | P |
|----------|-------------------------|---------------------------|---|
| Total number | 4452 (50.4) | 4380 (49.6) | < .0001 |
| Age (y) | 50.2 (8.4) | 56.1 (8.6) | < .0001 |
| Sex | | | |
| Male | 2061 (46.3) | 2118 (48.4) | .052 |
| Female | 2391 (53.7) | 2262 (51.6) | |
| Area | | | |
| Ansung | 1625 (36.5) | 2576 (58.8) | < .0001 |
| Ansan | 2827 (63.5) | 1804 (41.2) | |
| Education (years of school) | | | |
| \( \leq 9 \) | 2077 (46.9) | 2821 (65.1) | < .0001 |
| \( > 9 \) | 2350 (53.1) | 1512 (34.9) | |
| Missing | 72 | | |
| Alcohol | | | |
| Male: <40, female: <20 | 3169 (71.2) | 3011 (68.7) | .013 |
| Male: \( \geq 40 \), female: \( \geq 20 \) | 1283 (28.8) | 1369 (31.3) | |
| Smoking | | | |
| No | 2627 (59.6) | 2510 (58.3) | .211 |
| Yes | 1781 (40.4) | 1797 (41.7) | |
| Missing | 117 | | |
| BMI, kg/m² | | | |
| \( \leq 25 \) | 2961 (66.3) | 2082 (47.6) | < .0001 |
| \( \geq 25 \) | 1500 (33.7) | 2205 (52.4) | |
| Missing | 4 | | |

\( x^2 \)-test and Student \( t \)-test were used for categorical and continuous variables, respectively. BMI = body mass index, HTN = hypertension.
The association of BMI GRS and BMI with hypertension using baseline and longitudinal data.

| Characteristic | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | P for trend |
|----------------|------------|------------|------------|------------|-------------|
| BMI GRS        | 1.05 (0.18)| 1.43 (0.02)| 1.64 (0.11)| 2.01 (0.24)| <.0001      |
| BMI, kg/m²     | 24.09 (2.98)| 24.51 (3.06)| 24.76 (3.17)| 25.07 (3.38)| <.0001      |
| Ages, y        | 52.54 (8.97)| 52.20 (0.04)| 52.09 (8.86)| 52.20 (8.86)| .230        |
| Male, n (%)    | 892 (42.2) | 903 (45.6) | 874 (47.3) | 1071 (47.0) | .688        |
| Live in Ansung, n (%) | 953 (51.2) | 1032 (53.5) | 814 (51.7) | 1211 (52.6) | .237        |
| Education (>9) | 804 (43.6) | 857 (44.7) | 865 (42.6) | 1019 (45.2) | .510        |
| Smoking, n (%) | 776 (42.2) | 788 (41.5) | 638 (40.9) | 902 (40.2) | .178        |
| Current drinking, n (%) | 556 (29.8) | 571 (29.6) | 484 (30.7) | 681 (29.9) | .820        |

Data are presented as the mean (SD) or proportions. Fitting linear models for continuous variables and the Cochran-Armitage trend Chi-squared test for categorical variables were applied to analyze the trends across BMI GRS quartiles.

| Characteristic | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | P for trend |
|----------------|------------|------------|------------|------------|-------------|
| BMI, kg/m²     | 24.09 (2.98)| 24.51 (3.06)| 24.76 (3.17)| 25.07 (3.38)| <.0001      |
| Male, n (%)    | 892 (42.2) | 903 (45.6) | 874 (47.3) | 1071 (47.0) | .688        |
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Data are presented as the mean (SD) or proportions. Fitting linear models for continuous variables and the Cochran-Armitage trend Chi-squared test for categorical variables were applied to analyze the trends across BMI GRS quartiles.

Model 1 was not adjusted for other variables; Model 2, adjusted for age (years), sex (male and female); Model 3, further adjusted for area (Ansung and Ansan), education (>9 and >9 years of school), smoking and current alcohol consumption; Model 4, further adjusted for BMI.

BMI = body mass index, BMI GRS = count genetic risk score, SD = standard deviation, WGRS = weighted genetic risk score.
Figure 2. Instrumental variable-estimated association of body mass index and hypertension (baseline and newly diagnosed hypertension) using baseline and longitudinal data. CGRS = count genetic risk score, CI = confidence interval, OR = odds ratio, WGRS = weighted genetic risk score.

An important difference between conventional RCTs and MR studies using genetic polymorphisms is that MR studies evaluated the association between lifetime exposure to selected alleles in the general population with an outcome, whereas conventional RCTs provide insights for shorter periods among more selected individuals.[29]

Previously, a small number of MR studies have provided evidence supporting a causal link between BMI and hypertension. Fall et al demonstrated a significant association between the adiposity-associated variant rs9939609 at the FTO locus and SBP (+0.89 mm Hg/[kg/m²]).[14] In this study, rs9939609 at the FTO locus was included in the genetic risk score. Fall et al also constructed a GRS using 32 SNPs and reported a causal effect of adiposity on hypertension.

The strength of the present study is the well-defined community setting and a relatively large sample. To our knowledge, this is the first report showing the effect of common genetic variations related to BMI as the IV in measuring association with hypertension in an East Asian population.

With regard to the limitations of the present study, first, we built the BMI GRS based only on common variants, so we were unable to assess the potential contribution of rare variants. Second, this study did not include any subjects aged ≥70 years or <40 years, so these results may not be generalizable to populations of different ages. Similarly, the results may not be generalizable populations of different ethnicities because we used a cohort composed only of Koreans. Third, this study examined the causal effect of obesity on BP, but we could not test the impact of acute changes. Finally, because we used just a single study, we have limited MR-Egger regression to select candidate SNPs. MR-Egger regression was a 2-sample MR study in which multiple SNPs are included in MR studies.

Our main MR analysis considered both prevalent and incident hypertension cases. Additional sensitivity analyses (CGRS [n = 2] and WGRS [n = 2]) using only prevalent cases at baseline also showed a causal effect of adiposity on hypertension.

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5. Conclusion
We found that genetic predisposition for a higher BMI was associated with higher risk of hypertension in the Korean population. This MR analysis provided evidence of a causal relationship between BMI and hypertension. Our results suggest that controlling obesity may be beneficial for the prevention of hypertension.

Author contributions
Conceptualization: Yun-Chul Hong.
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