# Causal relationship between overweight and coronary heart disease: Two-sample Mendelian Randomization using MR-BASE Platform

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# Causal relationship between overweight and coronary heart disease: Two-sample Mendelian Randomization using MR-BASE Platform

A Master Thesis

Submitted to the Department of Public Health

and the Graduate School of Yonsei University

in partial fulfillment of the requirements for the degree of

Master of Public Health

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December 2021

This certifies that the master's thesis of

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The Graduate School

Yonsei University

December 2021

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# GLOSSARY OF TERMS

GWAS: Genome-Wide Association Study

SNP: Single Nucleotide Polymorphism

MR: Mendelian Randomization

IVW: Inverse Variance Weighted

RAPS: Robust Adjusted Profile Score

UVMR: Univariable Mendelian Randomization

MVMR: Multivariable Mendelian Randomization

IV: Instrumental Variables

OD: Odds Ratio

INSIDE: Instrument Strength Independent of Direct Effect

NOME: NO Measurement Error

BMI: Body Mass Index

CHD: Coronary Heart Disease

SBP: Systolic Blood Pressure

FBG: Fasting Blood Glucose

LDL: Low-Density Lipoprotein

TG: Triglycerides

TC: Total Cholesterol

T2D: Type 2 diabetes

GLUT-4: Glucose transporter type 4

# ABSTRACT

**Causal relationship between overweight and coronary heart disease: Two-sample Mendelian Randomization using MR-BASE Platform**

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(Directed by Professor Sun Ha Jee, MPH, Ph.D.)

**Background:**

Although lifestyle and environmental factors increase the risk of being overweight, genetic predisposition accounts for 40% to 85%. This study evaluated the causal relationship between overweight and coronary heart disease by estimating single nucleotide polymorphism (SNP)-exposure and SNP-outcome association based on Mendelian randomization analysis.

**Methods:**

All of the genetic data were obtained from publicly available GWAS summary data through the MR-BASE repository, genetic instruments for overweight were obtained from 158,855 participants of European ancestry. In a two-sample Mendelian randomization (MR), the exposure and outcome variables are estimated in non-overlapping European ancestry. The study was based on univariable Mendelian randomization and multivariable Mendelian randomization to estimate the total and direct effects of genetically predisposed overweight and coronary heart disease. The assumptions of MR are: instrument variable (IV) is associated with exposure, the IV should not be associated with any confounders of the exposure-outcome relationship, and it should be associated with the outcome variable through the exposure variable only. The inverse variance weighted (IVW) method was used for the randomization analysis, while MR-Egger is helpful for sensitivity analysis. The MR-Egger was used to rule out the chances of directional pleiotropy. Additionally, the MR-RAPS (Robust Adjusted Profile Score) was used to extreme outliers and maximizes the profile likelihood of the Wald ratio for univariable MR.

**Results:**

Based on univariable Mendelian randomization, we found that being overweight is significantly related to the increased risk of coronary heart disease (OR 1.21, 95% CI 1.08-1.34, p=0.0006). The study found a causal association between overweight and coronary heart disease. We discovered that a genetically inherited high predisposition toward overweight was strongly related to an elevated risk of coronary heart disease. The findings were substantiated by the absence of any directional horizontal pleiotropy for the outcome because the MR-Egger intercept was negative but non-significant (β=-0.003, p=0.862). To evaluate if the Mendelian randomization association between overweight and coronary heart disease is attributed to low-density lipoprotein, systolic blood pressure, triglyceride, and fasting blood glucose, multivariable Mendelian randomization was undertaken. The Mendelian randomization association between being overweight and coronary heart disease became weaker and did not reach statistical significance when low-density lipoprotein was included in the regression model with systolic blood pressure (β=0.102, p=0.138), fasting blood glucose (β=0.109, p=0.108), or triglyceride (β=0.004, p=0.952) was incorporated in the regression models. Thus, the multivariable Mendelian randomization analysis showed overweight independent causal pathways for coronary heart disease.

**Conclusion:**

In conclusion, we discovered that being overweight is substantially associated with coronary heart disease in European populations. However, genetic predispositions of being overweight and coronary heart disease is mediated by low-density lipoprotein, triglyceride, and systolic blood pressure. These findings imply that a dyslipidemia management plays a major impact in predicting illness risk or future health issues.

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**Keywords**: Mendelian randomizations; Overweight; Low-density lipoprotein; Systolic blood pressure; Fasting blood glucose; Triglycerides; Coronary heart disease

# I. INTRODUCTION

Overweight and obesity are metabolic diseases featured by the excess deposition of fats in the subcutaneous tissues. Obesity increases not only the risk of cardiovascular mortality and morbidity but also T2D that further precipitates the former.[23] BMI is the clinical measure for obesity and overweight. For example, a BMI higher than 26 kg/m$^2$ is overweight while that over 30 kg/m$^2$ is obese. More than 500 million individuals across the globe are overweight, while two-thirds of adults in the United States are overweight or obese.[1] Apart from lifestyle and dietary attributes, genetic mutations, and gene-environment interactions predispose the risk of being overweight or obese. The mutation susceptibility for higher BMI ranges between 40% and 85%.[2,22] Studies suggest that obesity not only increases the risk of cardiovascular mortality and CHD but also the risks for chronic obstructive pulmonary disease, T2D, and stroke.[24]

On the other hand, few randomized trials have provided data that can precisely delineate the underlying causal links between cardiometabolic characteristics and overweight. Because of confounding when a correlation does not suggest a causal link and reverse causality, statistical relationships between BMI and characteristics or illness occurrences are critical.[3] The illness process changes the exposure of focus.

According to the worldwide burden of sickness, more than 4 million people died in 2017 from obesity or overweight.[3] There is a distinction to be made between being overweight and being obese. Obesity refers to a considerably larger percentage of body fat than "overweight." Hypertension (high blood pressure) is caused by obesity and refers to the pressure that blood exerts on the inner walls of the arteries. Obesity is frequently mentioned as a risk influence for CHD.[1] A high BMI has been linked to elevated jeopardy of coronary heart illness in several epidemiology studies. Environmental confounding factors and measurement error, on the other hand, can lead to an underestimation of the proportion of effect mediated in epidemiology research.[2] Obesity is a significant risk factor for CHD progression and development. Approximately 80% of people suffering from CHD are obese or overweight. Weight loss is a wide risk response remedy, even though obesity is generally considered a "small" CHD risk factor.[3] Reductions in body weight could significantly impact different outcomes such as alcoholism, smoking, and dyslipidemia. Adiposity increases the risk of incident T2D, stroke, and CHD in epidemiological studies.[4]

Many inferential researchers claim similar relationships between overweight or obesity and CHD and selected adiposity variables; for instance, the risk influences found similar relations with various ischemic and CHD and central and general adiposity assessed by the hip to waist ratio and BMI for ischemic stroke and CHD.[3]

Polymorphism can be perpendicular due to many downstream influences that abide by the SNP impact the understanding of interest, but MR assumptions are not jeopardized. Pleiotropy can also be lateral, in which the instruments or SNP affect systems other than those of the exposure of interest, possibly contradicting the MR hypothesis that the SNP only influences the consequence through the sensitivity of interest and generating in skewed causal estimations.[4]

There seems to be a probability that pleiotropic influences will become balanced with multi-SNP detectors, allowing for reasoning about the exposure.[3] In the case of asymmetrical pleiotropy, MR-Egger modeling offers a criterion for it and a causal prediction of the treatment on the outcome. Studies also employ the subjective median model, which can produce mathematical equations even in the manifestation of lateral pleiotropy if at minimum half of the data in the analysis derives from legitimate device variations and has the improvement of keeping more correctness in the predictions than MR-Egger.[3]

The study by Dale is the most thorough examination of the causative role of adiposity in CHD, stroke, and T2D. It compares the causal influences of central adiposity against general adiposity overweight on several cardiovascular consequences: new CHD occurrences from current and future studies.[4]

The two-sample MR technique was utilized in this study, with causal estimates between prognostic factors produced by dividing the equipment correlation by the equipment association of each SNP. Following that, the inverse weighted correlation ratios are combined. For the primary MR analysis, we used the IVW approach. The study achieved the aims through the use of a two-sample Mendelian randomization model.

The objectives of the study are as follows:

1. To find causal estimates between overweight (with a BMI range from 25kg/m$^2$ to 29.9kg/m$^2$ and CHD by dividing the instrument-outcome association by the instrument-exposure association of each SNP. The BMI range selected is a standardized measure for nutritional status.[42] These association ratios are combined using the IVW for the main MR analysis.

2. Undertake MVMR for evaluating separate but correlated exposure variables by simultaneously estimating the effects of each on an outcome variable by using a genetic instrument with potentially overlapping genetic variants. So the causal effect assessed by MR and MVMR could differ because the former estimates the total causal effect of exposure on the outcome, while the latter evaluates the direct causal effect of each exposure on the outcome. Thus, MVMR estimates the mediating effects in a two-step MR, as it adjusts for possible pleiotropy (bias due to horizontal pleiotropy of a specific effect) or to adjust for potential confounders.[41]

# II. MATERIAL AND METHODS

## 1. Study population and Data Sources

The genetic data for this study were retrieved from GWAS summary data. The data is available in the MR-BASE repository. The repository was created by the Medical Research Council Integrative Epidemiology Unit, University of Bristol, for facilitating two-sample Mendelian randomization created the repository made repository. The GWAS outcomes depicted are insufficiently precise, which destabilize the effective application of this analysis.[6] The referred MR-BASE repository (http://www.mrbase.org) comprises 11 billion SNP-trait associations from 1,673 GWAS. The repository is updated regularly.

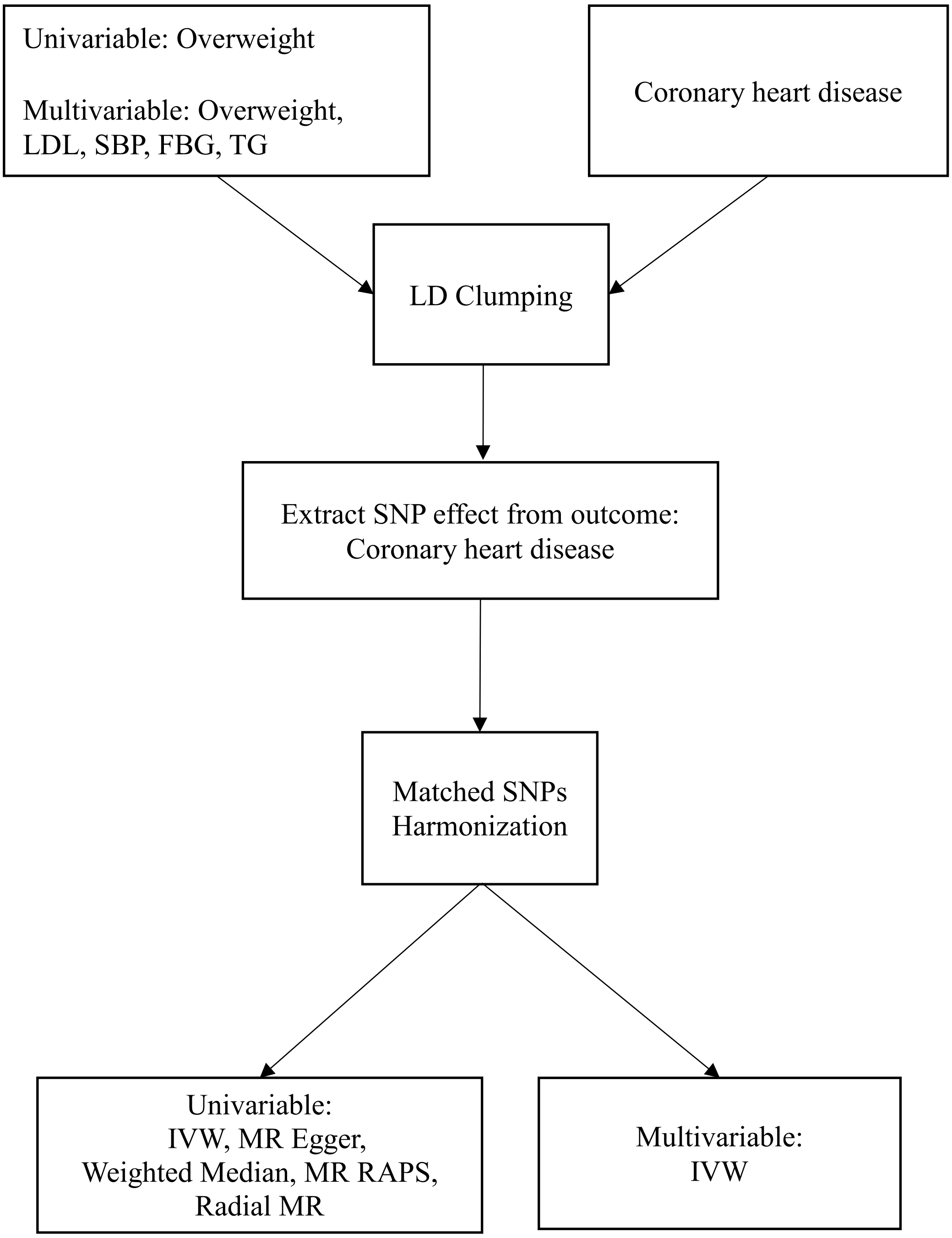



**Figure 1. Flow chart of mendelian randomization**

## 2. Assumptions of Mendelian randomization:

MR effect estimate to be valid, the instrument(s) must satisfy

***three key assumptions***:

IV1. The instrument(s) must be robustly associated with the exposure.

IV2. The instrument(s) must not be associated with any confounders of the exposure-outcome relationship.

IV3. The instrument(s) can only be associated with the outcome via the exposure and not via a different biological pathway independent of the exposure.

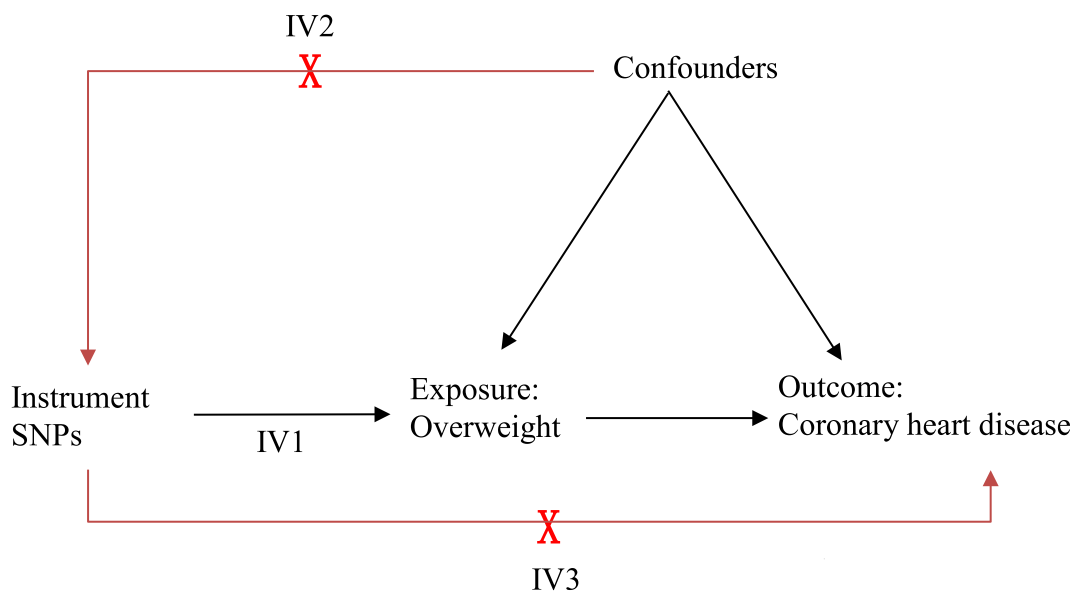



**Figure 2. Flow diagram of univariable two-sample mendelian randomization**

## 3. Statistical analysis

### (1) Inverse variance weighted

The Wald ratios for each genetics instrument were constructed by dividing the association outcome for each instrument by the exposure association for each instrument using a two-sample MR summary.[6] The IVW estimate was used to infer the causal effects in the regression of the Wald ratio sets. By balancing each of the estimates by IVW, MR estimates as Wald ratio estimates were derived.

### (2) MR Egger

Traditionally, the MR technique does not presume that pleiotropy has no effect on any SNP outcome relationships; therefore, all variations are permitted to be non-zero.[7] The assumption is that the size of pleiotropy effects is unaffected by respective instrument strengths. In other words, the size of the variants provides no information about the sizes of other variants, a situation known as InSIDE, MR egger, like the IVW approach, makes NOME assumptions. A regression of the SNP result relation on the SNP exposure relationship is used in this strategy.[6] This approach can only discover pleiotropy if it is 'directional,' meaning it has a non-zero average value.

### (3) MR Robust adjusted score profile (RAPS)

We used MR-RAPS technique to model the pleiotropic influence of genetic variations using a random-impact distribution.[7] It is worth noting the assumption made that pleiotropic influences are normally distributed about point zero with an unknown value of variance.[7] We used the profile-likelihood to estimate the variance and causal influence of the pleiotropic effect function.

### (4) Radial MR

The directional pleiotropy of each genetic instrument was determined using Radial MR regression.[5] Cochran's statistics were used to investigate the heterogeneity of the Wald ratio estimations. The Radial plot method was used to find single outlier SNPs that created substantial disparities. In Radial MR, the variance of the instrument's associated outcomes and the variance of the instrument's associated exposure were both used for weighting, but in two-sample MR, the variance of the instrument result association was used.[4]

**(5) Multivariable MR**

MVMR evaluates separate but correlated exposure variables by simultaneously estimating the effects of each on an outcome variable by using a genetic instrument with potentially overlapping genetic variants. The resultant MVMR estimate depicts the direct effect of each exposure on the outcome variable. MVMR estimates the mediating effects in a two-step MR.[43] They are also used to adjust for possible pleiotropy or to adjust for potential confounding. MR estimates the total causal effect of exposure on the outcome, while MVMR evaluates the direct causal effect of each exposure on the outcome. As a result, the MVMR estimate reflects the causal effect of one exposure after holding the other exposure variable at a constant level.

Functionally, UVMR and MVMR differ, despite the principles of the former being applied to the latter. UVMR is a powerful epidemiology tool that estimates the causal effect of a single exposure variable on an outcome in the presence of any confounding variable by utilizing such genetic variants that are IV for the referred exposure variable. MVMR estimates the causal effect of multiple exposure variables on a health outcome on two-sample summary data. When the genetic variants (usually the SNP) could reliably predict the exposure variable without having any effect on the outcome, then they are considered valid IVs. The UVMR is extended to MVMR when there is a violation of MR assumptions 2 and 3.[21] The analysis also helps to evaluate whether more than one exposure exerts a causal effect on the outcome or mediates the effect of each other on the outcome variable. MVMR requires a set of SNP, which are associated with the exposure variables but do not separately affect the outcome other than their effect through these variables. The MVMR analysis indicates that multiple causal relationships are possible in either direction or their absence. The causal connection between overweight, LDL, SBP, FBG, TG, and CHD was investigated using MVMR because they can have a direct influence on the same result (Figure 3).

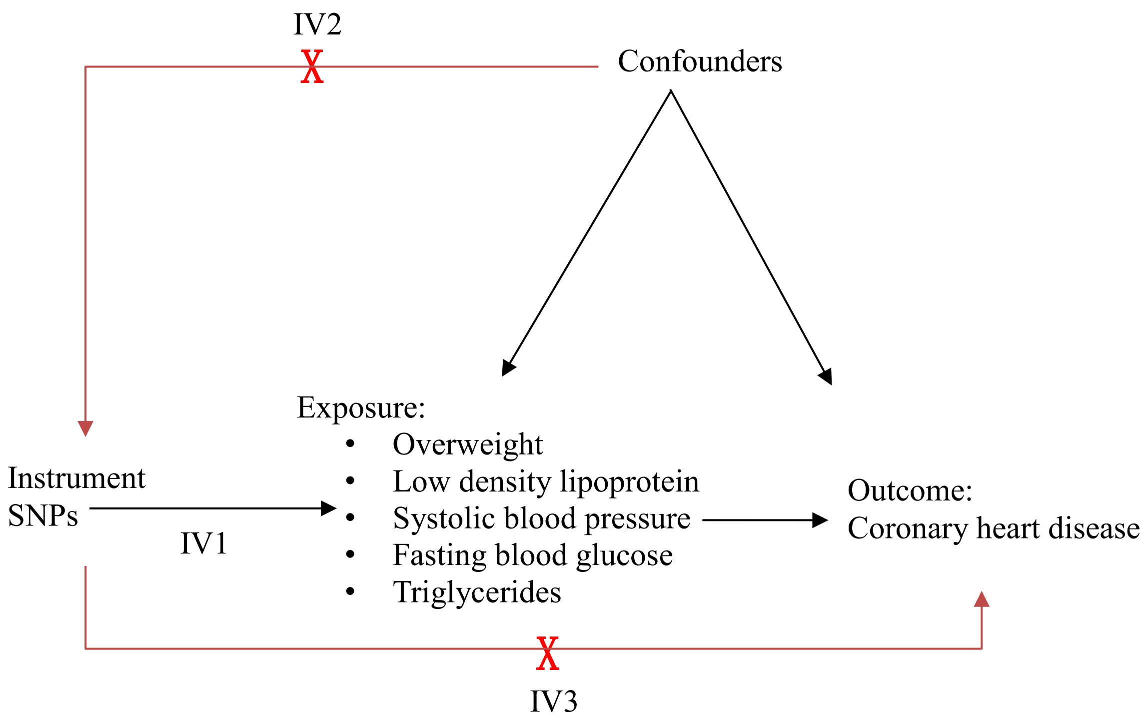



**Figure 3. Flow diagram of multivariable two-sample mendelian randomization**

In this study, all MR analyses were calculated using R packages in R version 3.6.1 from the R Core Team, based in Vienna, Austria.[1,5,8]

# III. RESULTS

## 1. GWAS consortium and study participants' characteristics

Table 1 depicts the sample sizes related to each GWAS dataset used in the MR analysis that investigated the effect of being overweight on CHD and its associated risk factors. For genetic instruments, overweight, SBP, and FBG (GWAS data) were obtained for European ancestry, while LDL and TG (GWAS data) were obtained for mixed ancestry. The proportion of non-European is about 4% (n=7,898). For the outcome variable CHD, the GWAS data were obtained from the CARDIoGRAM and GIANT consortium. Similarly, the GLGC and ICBP consortium were used to retrieve the GWAS data on lipid profile and blood pressure, respectively. The number of European participants with an overweight phenotype was 158,855, while that for CHD in the same population was 86,995, suggesting predisposition of overweight or obese phenotype to CHD. The GWAS data was retrieved from the MR-BASE repository. Table 2 depicts the mean age of the patients with CHD from the CARDIoGRAM consortium.

**Table 1. Description of GWAS consortium**

| Variable | Phenotype | Population | Sex | Age[a] | Sample size (cases) | Unit | Consortium | 1st Author | Journal (Year) |
|---|---|---|---|---|---|---|---|---|---|
| Exposure | Overweight | European | All | 54.3 yrs | 158,855 (93,015) | Log odds | GIANT[1] | Berndt SI | Nat Genet. (2013) |
| Exposure | LDL[2] | Mixed | All | 62.4 yrs | 173,082 | SD* | GLGC[2] | Willer CJ | Nat Genet. (2013) |
| Exposure | SBP[3] | European | All | 54.5 yrs | 300,194 | N/A | ICBP[6] | Evangelou, E | Nat Genet. (2018) |
| Exposure | FBG[4] | European | All | ** | 58,074 | mmol/L | MAGIC[7] | Manning AK | Nat Genet. (2012) |
| Exposure | TG[5] | Mixed | All | 62.4 yrs | 177,861 | SD(mg/dL) | GLGC[2] | Willer CJ | Nat Genet. (2013) |
| Outcome | Coronary heart disease | European | All | *** | 86,995 (22,233) | Log odds | CARDioGRAM[8] | Schunkert H | Nat Genet. (2011) |

[a]Age= Mean age
[1]GIANT=Genetic Investigation of Anthropometirc Traits,
[2]LDL cholesterol = low density lipoprotein cholesterol /GLGC=Global Lipid Genetics Consortium/The proportion of the non-European is about 4% (n=7,898),
[3]SBP=Systolic blood pressure, [4]FBG=Fasting blood glucose, [5]TG=Triglycerides,
[6]ICBP=International Consortium of Blood Pressure, [7]MAGIC=Meta-analyses of Glucose and Insulin-related traits Consortium,
[8]CARDIoGRAM=Coronary Artery Disease Genmoe wide Replication and Meta-analysis,
*Standard Deviation, **(male 56.23 years, female 55.52 years), *** See Table 2
These data were obtained from the refernece papers
(Berndt Si et al., Nat Genet. 2013 May;45(5):501-12., Willer CJ et al., Nat Genet. 2013 November; 45(5):1274-1285.,
Evangelou E et al., Nat Genet. 2018 Oct; 50(10): 1412–1425., Mannging AK et al. Nat Genet. 2012 May 13;44(6):659-69.)

**Table 2. Ages of GWAS Participants CARDioGRAM consortium**

| Coronary heart disease (n=86,995 (22,233 cases) | |
|---|---|
| Cohorts (n=case/controls) | Participants Mean age (case/controls) |
| ADVANCE (278/312) | 45.8/45.3 years |
| CaDomics(2078/2952) | 60.8/55.3 years |
| CHARGE (2287/22024) | 60.0/63.1 years |
| deCODE CAD (6640/27611) | 74.8/53.7 years |
| GERMIFS I (884/1604) | 50.2/62.6 years |
| GERMIFS II (1222/1287) | 51.4/51.2 years |
| GERMIFS III (KORA) (1157/1748) | 58.6/ 55.9 years |
| LURIC/AtheroRemo 1 (652/213) | 61.0/58.3 years |
| LURIC/AtheroRemo 2 (486/296) | 63.7/56.4 years |
| MedStar (874/447) | 48.9/59.7 years |
| MIGen(1274/1407) | 42.4/43.0 years* |
| OHGS1(1542/1455) | 48.7/75.0 years |
| PennCATH(933/468) | 52.7/61.7 years |
| WTCCC (1926/2938) | 49.8** |

* For cases age at diagnosis; for control age at recruitment
** WTCCC controls comprised of an equal number of subjects from the 1958 Birth Cohort and from the National Blood Service (NBS)
These data were obtained from the reference papers (Schunkert H et al., Nat Genet. 2011;43(4)333-8.)

## 2. Selection of genetic instruments

The results related to GWAS for overweight were obtained from a previous study. The total of 2,435,045 overweight SNPs were using a Bonferroni statistical threshold ($p<5x10^{-8}$). Linkage disequilibrium was used to identify the independent SNPs by using the $R^2$ threshold <0.005. After adjusting for correlated SNPs, 14 of them were selected as the genetic instruments for evaluating genetic predisposition to being overweight.

## 3. Harmonization of the univariable mendelian randomization

Once the genetic instruments were selected, the final set of harmonized data were completed by extracting information from the outcome GWAS matched to each instrument SNP. Overweight was used as exposure, while CHD was the outcome variable (Appendix 3).

### 4. The univariable mendelian randomization causal association between overweight and coronary heart disease

The IVW technique revealed that the OR at a confidence interval (CI) of 95% (1.08-1.34) was 1.205 per a single standard deviation (SD) increase with a *P* value of 0.0006 (Table 3). These results were in agreement with the weighted median approach (OR 1.24, 95% CI 1.06-1.44, p=0.006) and the MR-Egger methodological approach (OR 1.25, 95% CI 0.87-1.80, p=0.253). The MR RAPS causal estimate (OR 1.18, 95 % CI 1.50-1.32, p=0.004). The MR RAPS causal estimate predicted an effect size that was consistent with the IVW, MR-Egger, and weighted median findings. Based on the causal association analysis of the GWAS data using the MR's IVW technique, it was revealed that overweight was strongly associated with CHD and that the casual influence of overweight on the risk of development of CHD was true. Both the MR-Egger and IVW estimates showed heterogeneity in the 14 overweight SNPs, suggesting the causal effects that overweight had on CHD. As a result, the inclusion of possible SNPs could have been the chief cause of heterogeneity.

**Table 3. A causal relationship between overweight and coronary heart disease**

| Exposure | Outcome | Method | Nsnp[1] | β | SE[2] | OR (95% CI)[3] | *P* value |
|---|---|---|---|---|---|---|---|
| Overweight | Coronary Heart Disease | IVW[4] | 14 | 0.187 | 0.054 | 1.21(1.08-1.34) | 0.0006 |
| | | MR Egger | | 0.223 | 0.186 | 1.25(0.87-1.80) | 0.253 |
| | | Weighted median | | 0.212 | 0.076 | 1.24(1.06-1.44) | 0.006 |
| | | MR RAPS[5] | | 0.164 | 0.057 | 1.18(1.05-1.32) | 0.004 |

[1]Nsnp = Number of (Single Nucleotide polymorphism, SNP)
[2]SE = Standard Error
[3]OR = Odds Ratio (95% Confidence Intervals)
[4]IVW=Inverse variance weight
[5]MR RAPS= Mendelian Randomization Robust Adjusted Profile

Based on the two-sample MR randomization, it was revealed that a causal association between overweight and CHD existed. The MR slopes of the plots for the IVW and weighted median regression indicated positive direction plots and were statistically significant suggesting a causal association between the measurement variable SNP overweight on CHD (Figure 4). On the contrary, the MR-Egger regression indicated that the slope (causal effect) had no significant relationship with the outcome. This assumption suggests that there might be horizontal pleiotropy or significant outliers that violate the findings of the IVW, and weighted mean regarding the relationship between genetic predispositions to obesity and CHD. The (Figure 4) substantiated the assumption as the effect size on SNP-based outcome was lowest for MR-Egger.

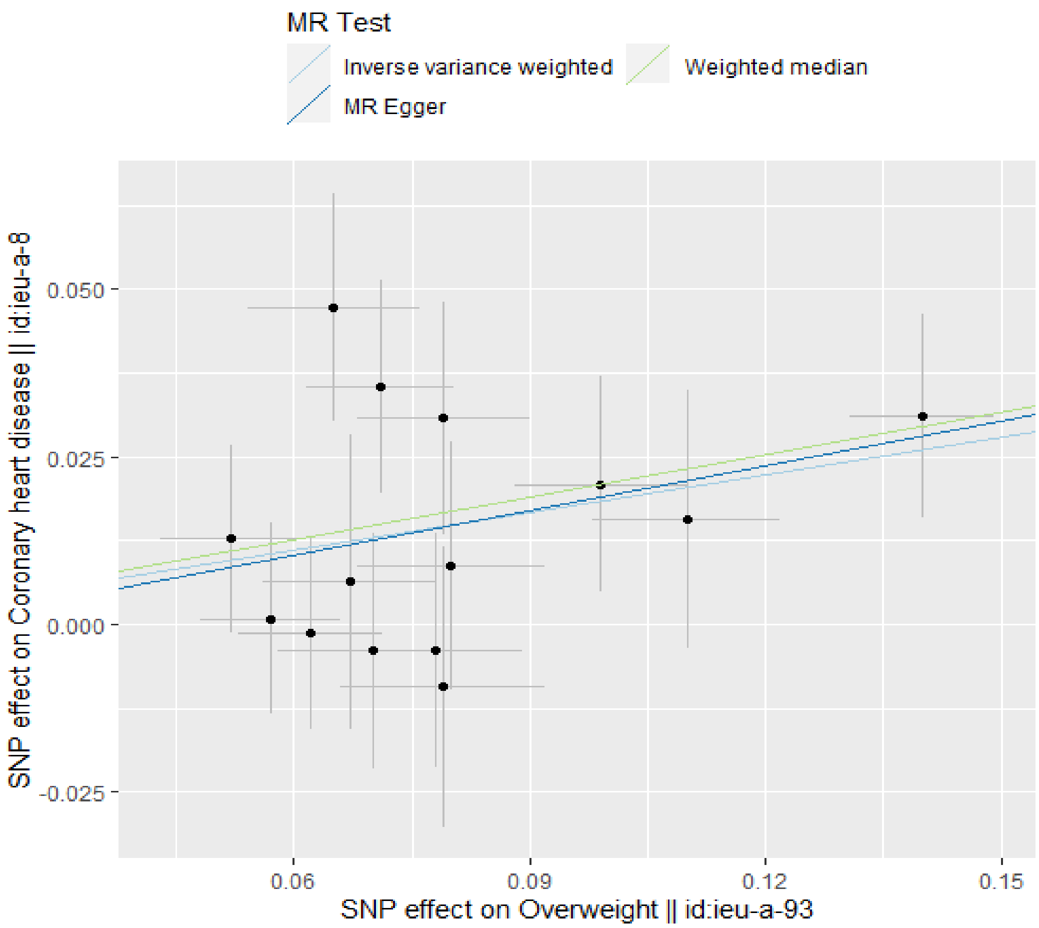



**Figure 4. A plot relating the effect sizes of the SNP overweight association and coronary heart disease**

The Forest plot of the causal effect of overweight on CHD estimated using each SNP singly using the Wald ratio (Figure 5) refelected the effect size of MR-Egger was more than IVW. However, the observation further suggested that the risk of CHD could be lower with genetic predisposed obesity in the MR Egger. This is not suprising because MR-Egger often produces an inflated effect due to Type I error. Such assumptions were ruled out when one of the SNPs were left out from the analysis (Figure 6). The respective SNP could be considered a potential outlier for the relationship between overweight and CHD. The funnel plot (Figure 7) showed that MR-Egger produced relatively more asymmetry for the effects of overweight on CHD compared to IVW. The asymmetry further contended the involvement of horizontal pleiotropy for the relationship between genetically predisposed overweight and CHD.

The (Figure 8) showed that modeling the estimates from invalid IV with MR RAPS including outliers for overweight and CHD had lower effect sizes compared to (Figure 9), SNP rs8028313 was removed. This means that invalid IVs (that might be outliers) are not robust estimates of the genetic predisposed relationship between being overweight and CHD development.

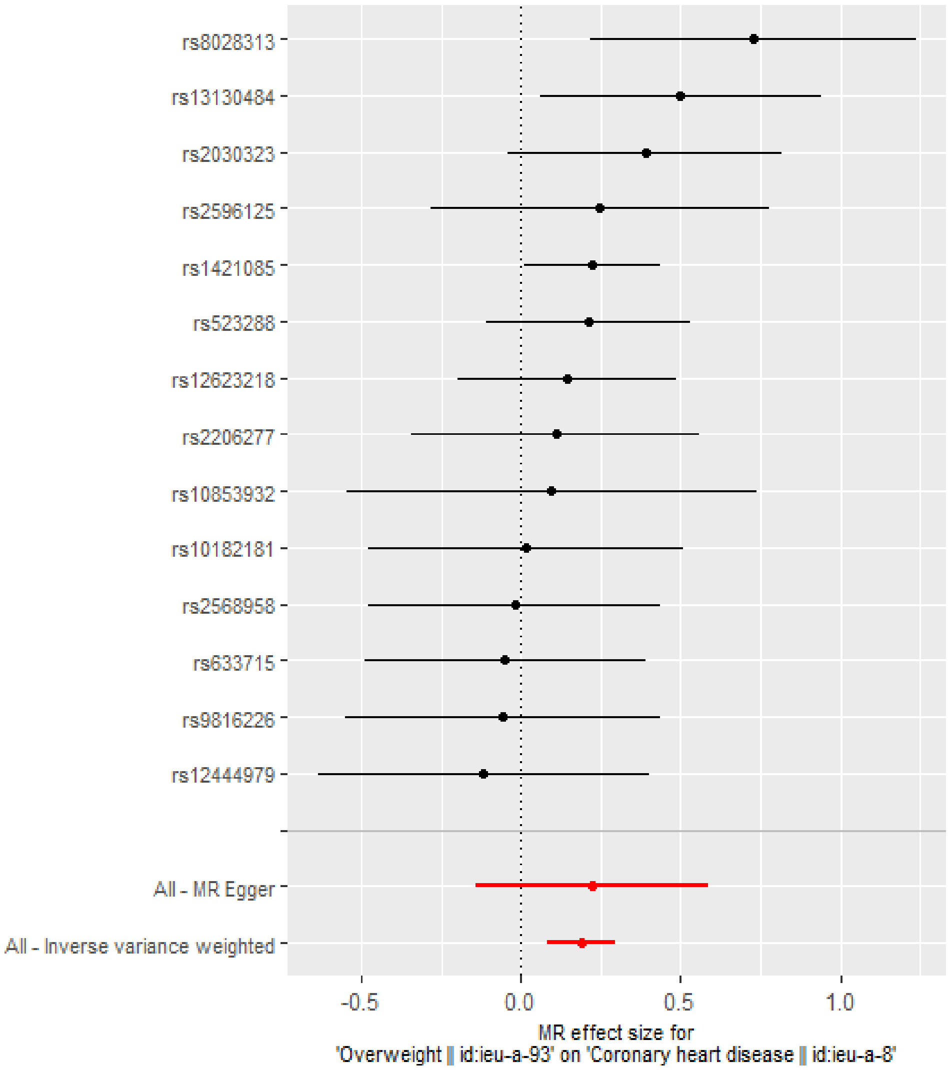



**Figure 5. Forest plot- the causal effect of overweight on coronary heart disease estimated using each SNP singly using the Wald ratio**

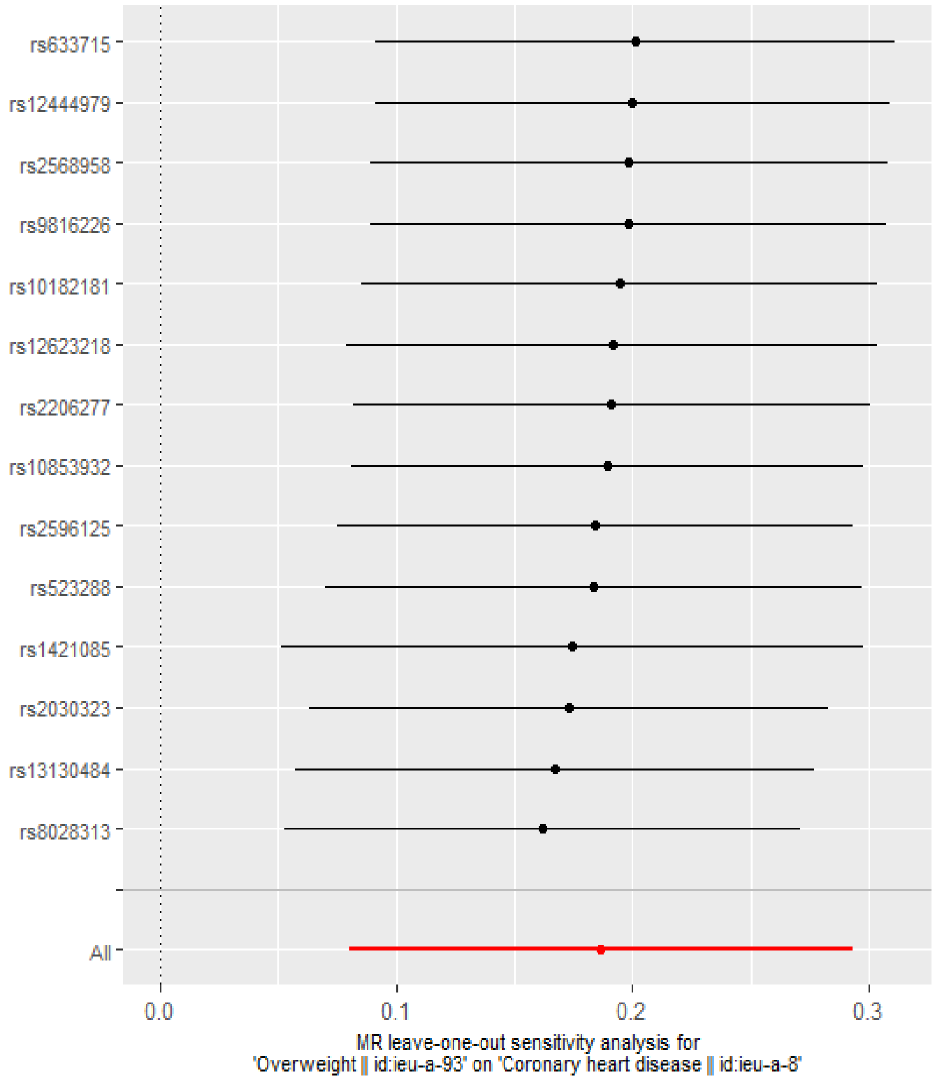



**Figure 6. Leave one out the sensitivity analysis plot-the causal effect of overweight on coronary heart disease**

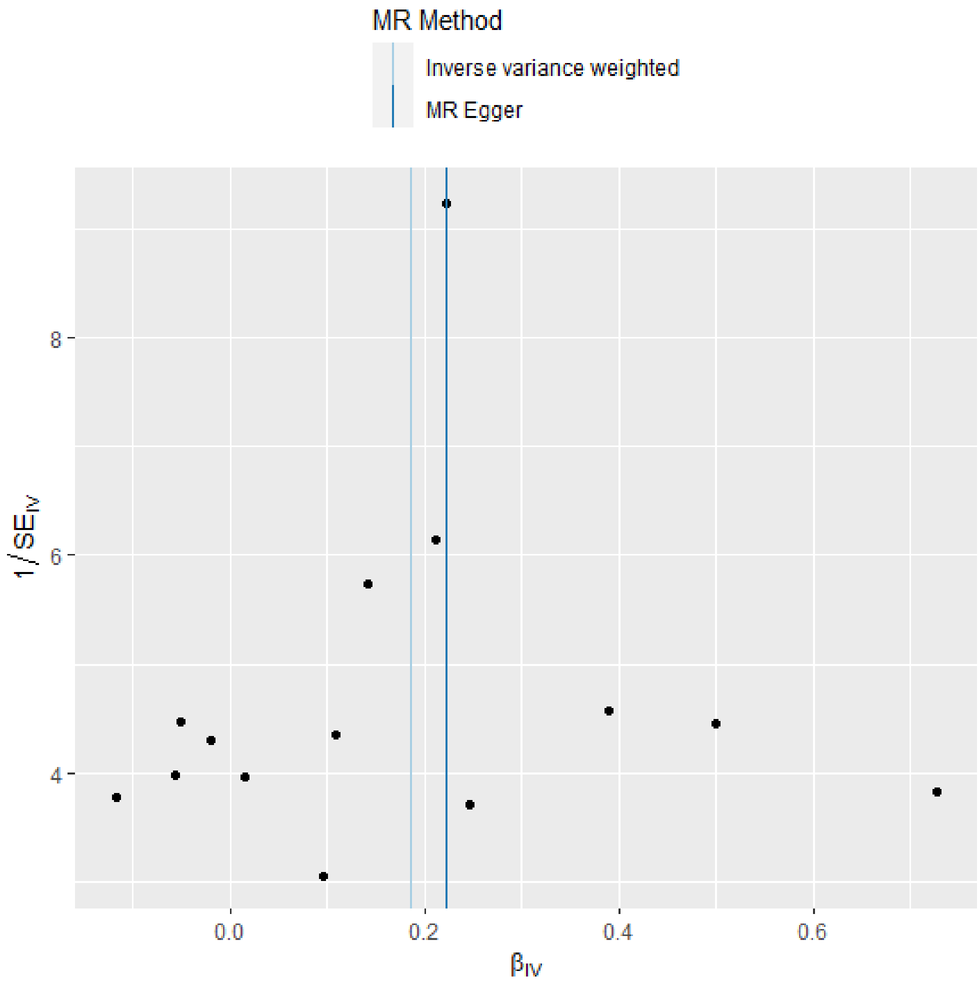
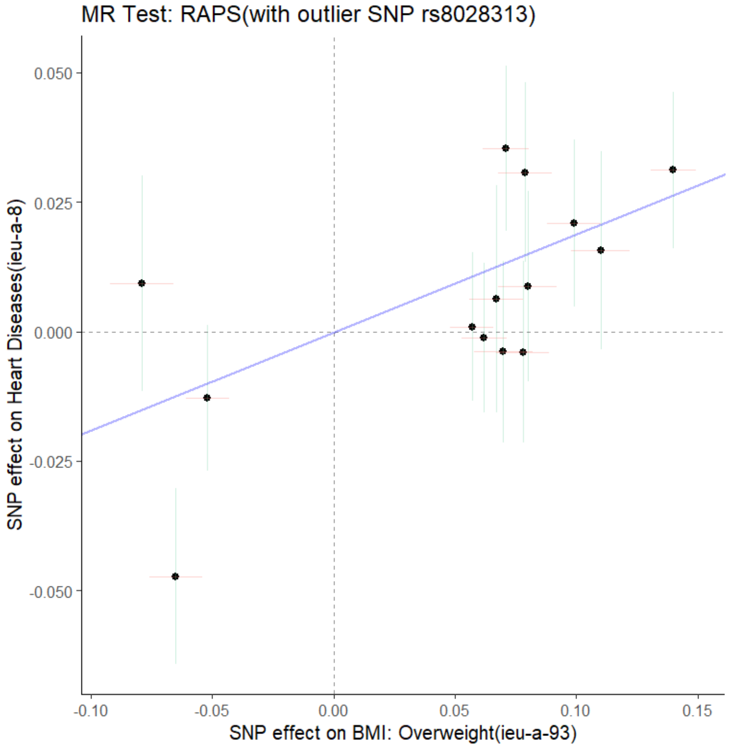



**Figure 7. Funnel plot showing the relationship between the cause-effect of overweight and coronary heart disease**



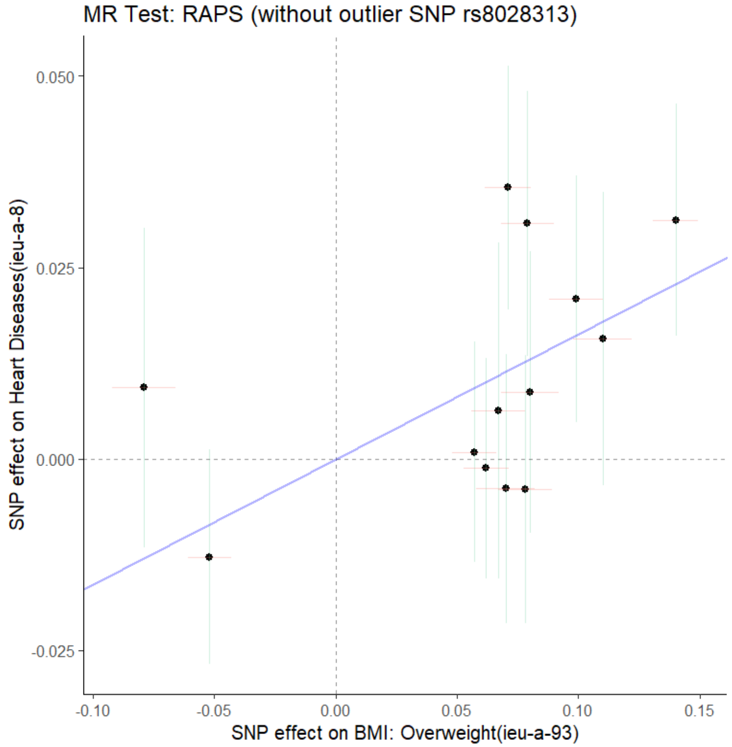




**Figure 8 (Left). MR Robust Adjusted Profile Score(RAPS) with outlier plot overweight and coronary heart disease**

**Figure 9 (Right). MR Robust Adjusted Profile Score(RAPS) without outlier plot overweight and coronary heart disease**

### (4-1) MR-Egger intercept

The MR-Egger estimator has the ability to correct for directional pleiotropic effects of genetic instruments in instrumental variable analysis. MR-Egger comprises three parts; a test that indicates both violations of the IV assumptions and bias in conventional IV analytics, a test for the causal effect, and estimates of the causal effect. The MR-Egger regression explores the association of the risk/exposure variable, genetic association with outcome, and the genetic variant. Thus, the genetic association with the outcome is decomposed into the sum of direct (pleiotropic) and indirect (causal) effects. The intercept of the regression represents the effect of the genetic variant on the outcome and is independent of the effect of the risk factor or exposure, and the slope represents the causal effect of the risk factor on the outcome. A genetic variant is pleiotropic if it is associated with more than one exposure factor on different causal pathways. Any pleiotropic effect is included in the intercept is not equal to zero. Pleiotropic genetic variants are not valid instrumental variables. However, the MR -Egger estimate also includes an error term (residual) in the simple linear regression model. Hence, the MR-Egger estimate equals the IVW estimate when the intercept is equal to zero. If the pleiotropic are independent of the genetic associations with exposure factors, it is referred to as the InSIDE.

Based on the InSIDE assumption, the intercept is interpreted as the average pleiotropic effect included in the analysis (which is also referred to as balanced pleiotropy), then IVW is a consistent estimate of the causal effect.[21] When the intercept from the MR-Egger analysis is not equal to zero, then it is assumed that the average pleiotropic effect differs from zero (also referred to as directional pleiotropy), including the violation of the InSIDE assumption or without it. Directional or horizontal pleiotropy occurs when the genetic variant has an effect on the outcome without its effect on the exposure variable in MR. Violation of the no horizontal pleiotropy could lead to severe bias in MR. The issue of horizontal pleiotropy is a significant concern in MR.[21]

The inclusion of pleiotropic effects could lead to biased causal effects and increase the probability of Type I error on the association between exposure and outcome. The acceptance of the horizontal pleiotropic effect also means that IV assumptions were violated, and the findings of MR are subjected to the same criticisms related to the small sample size in meta-analysis. Table 4 depicted that even the intercept was not equal to zero ($\beta$=-0.003, SE=0.152), directional horizontal pleiotropy cannot be accepted because the p-value of the MR-Egger intercept was greater than 0.05 (p=0.842). Thus, the analysis showed that genetically predicted obesity was positively associated with CHD and the causal influence of the former on the latter was true. Since the probability of directional pleiotropy was non-significant, genetic predisposition to obesity also increases the risk of CHD. Hence, the MR findings on the relationship between genetic predisposition to obesity and CHD are not biased.

**Table 4. Overweight and coronary heart disease egger intercept**

| Exposure | Outcome | MR Egger Intercept (Estimate) | SE[1] | *P* value |
|---|---|---|---|---|
| Overweight | Coronary Heart Disease | -0.003 | 0.152 | 0.842 |

[1]SE = Standard Error

### (4-2) Radial MR analysis for detection of outlier SNPs

For detecting individual outlier SNPs responsible for horizontal pleiotropy, the Radial MR analysis with the modified second-order weighting method was performed. The Radial IVW findings indicated a stronger positive relationship between overweight and CHD (OR 1.20, 95% CI 0.43-26.34, p=0.0000384) (Table 5). The Radial MR-Egger reflected that there was no significant association between overweight and CHD (OR 1.30, 95% CI 0.35-38.52, p=0.167) (Table 5). These findings suggested that there could be outliers for Radial MR-Egger or radial IVW. However, following the removal of the outlier, the positive association between overweight and CHD persisted (OR 1.18, 95% CI 0.42-25.16, p=0.0003) (Table 6), suggesting no significant detection of the outlier for radial IVW. On the contrary, removal of the outlier in the Radial MR-Egger established the positive relationship between overweight and CHD (OR 1.40, 95% CI 0.42-38.75, p=0.040). Thus, outlier SNPs for overweight and CHD was evident from the Radial MR-Egger. However, the Radial MR-Egger intercept reflected that horizontal pleiotropy did not influence the genetic predisposition of being overweight with CHD.

**Table 5. Radial MR regression overweight and coronary heart disease**

| Exposure | Outcome | Method | β [1] | SE [2] | OR(95%CI) | *P* values | Q-statistic for heterogeneity | *q* values |
|---|---|---|---|---|---|---|---|---|
| Overweight | Coronary Heart Disease | Radial IVW | 0.187 | 0.053 | 1.20 (0.43-26.34) | 0.0000384 | 11.97 | 0.53 |
| | | Radial MR-Egger | 0.266 | 0.18 | 1.30 (0.35-38.52) | 0.167 | 11.60 | 0.56 |

[1]β=Beta
[2]SE=Standard Error

**Table 6. Radial MR regression removed outlier overweight and coronary heart disease**

| Exposure | Outcome | Method | β[1] | SE[2] | OR(95%CI) | *P* value | Q-statistic for heterogeneity | *q* value |
|---|---|---|---|---|---|---|---|---|
| Overweight | Coronary Heart Disease | Radial IVW removed outlier | 0.162 | 0.044 | 1.18 (0.42-25.16) | 0.0003 | 7.584 | 0.816 |
| | | Radial MR-Egger removed outlier | 0.333 | 0.143 | 1.40 (0.42-38.75) | 0.040 | 6.425 | 0.893 |

[1]β=Beta
[2]SE=Standard Error

Radial estimates revealed a strong association between overweight and CHD with or without the outliers, as shown in (Figures 10 and 11). Data exhibiting two-sample MR are visualized with a scatter plot where the SNP outcome associations are plotted against SNP exposure associations to generate an immediate picture of the cause-and-effect estimate of the individual genetic variant. The scattergram is also helpful to overlay the standard IVW of the causal effect as the fitted slope, which analyzes whether individual SNPs support or contradict the overall assumption. However, the traditional scatter plot is not suitable to estimate such cause-and-effect relationships whenever varying degrees of precision are needed to evaluate SNP-outcome associations. The Radial plot or Radial MR regression is used under such conditions because it has several advantages. The major advantage is it removes the need for recoding the genetic data as it provides a straightforward detection of the significant outliers and data points that influence the magnitude and direction of the outcome variable. The Radial plot aids in the detection of a single outlying variant which is responsible for large differences between IVW and MR-Egger estimates. Thus, in the present study, when the outliers are removed, the IVW and MR-Egger exhibited the same causal relation between overweight and CHD. Thus, when the MR-Egger outlier was removed, the significant relationship between overweight and obesity was established.

On the other hand, the removal of the IVW outlier did not substantially impact the relationship between the two SNP associated variables. Therefore, the Radial plot analysis identified the single outliers in the MR-Egger regression that violated the causal effect of the IVW.

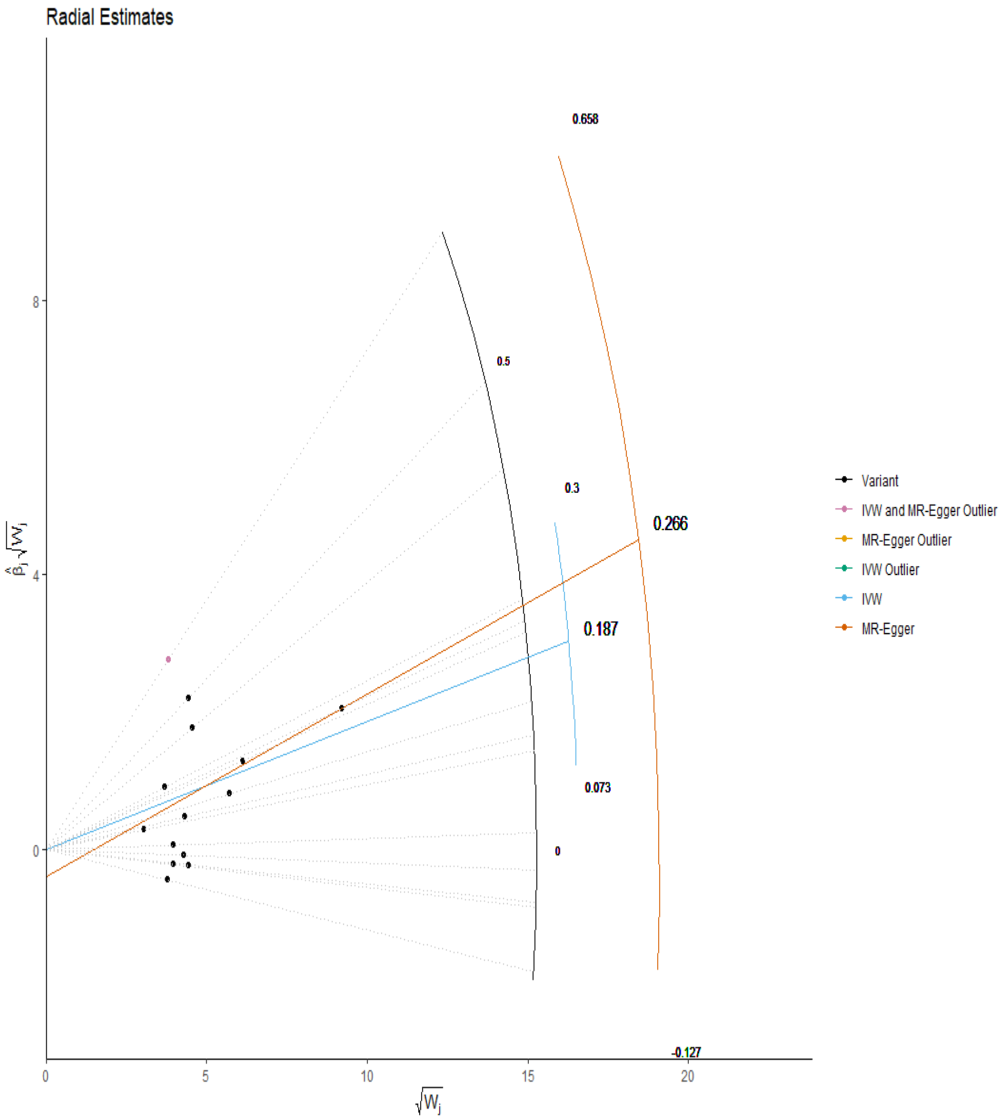



**Figure 10. Radial MR plot of the overweight and coronary heart disease with outlier**

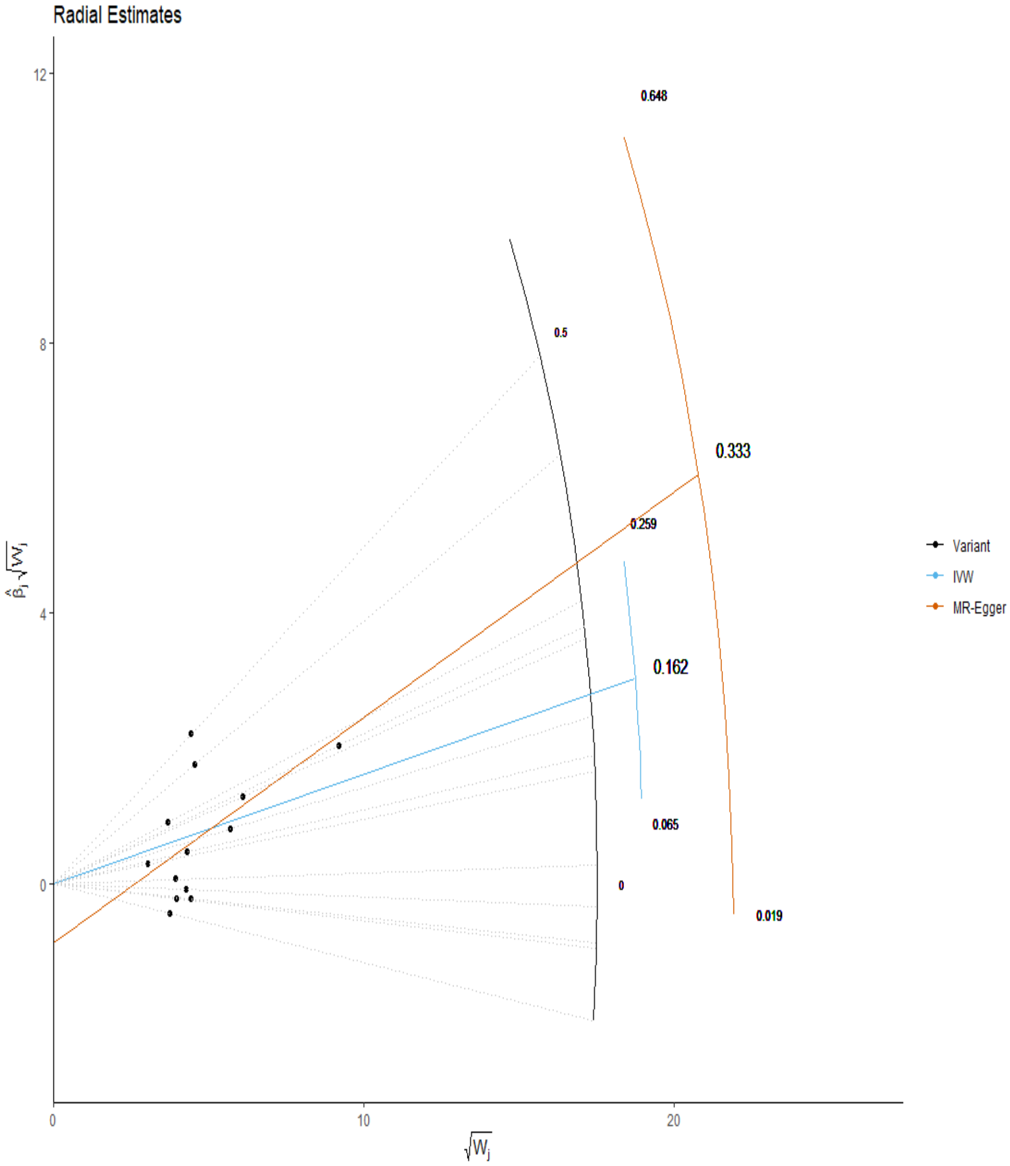



**Figure 11. Radial MR removes outliers plot of the overweight and coronary heart disease**

## 5. MVMR causal relationship between Overweight, LDL, SBP, TG, and coronary heart disease.

Based on the IVW analysis, it was contended that genetic predipsoition of being overweight was significantly associated with CHD as well as LDL, TG, and FBG (Table 7). To evaluate if the MR association between overweight and CHD is attributed to LDL, SBP, TG, and FBG, MVMR was undertaken. The MR association between being overweight and CHD became weaker and did not reach statistical significance when LDL was included in the regression model with SBP (β=0.102, p=0.138), FBG (β=0.109, p=0.108), or TG (β=0.466, p=0.952) was incorporated in the regression models. Thus, the MVMR analysis showed overweight independent causal pathways for CHD. The overweight independent causal pathways that were revealed include SBP, LDL, and TG because the p-values of the respective variables were less than 0.05. On the other hand, FBG did not influence CHD. The correlation between the exposure variables indicated that being overweight might predispose the risk of high FBG, but the latter is not an independent predictor of CHD. The connection between high BMI (overweight) and high LDL levels were reported by Klop et al.[25] However, they did not show whether obesity or LDL is the pathogenic factor for CHD.

**Table 7. Multivariable MR casual relationship between exposures and outcome**

| Model | Exposure | Outcome | β* | SE | t-value | *P* value |
|---|---|---|---|---|---|---|
| Model 1 | Overweight | Coronary Heart Disease | 0.102 | 0.069 | 1.489 | 0.138 |
| | LDL[1] | | 0.456 | 0.073 | 6.207 | 2.13E-09 |
| | SBP[2] | | 0.691 | 0.098 | 7.061 | 1.51E-11 |
| Model 2 | Overweight | Coronary Heart Disease | 0.109 | 0.067 | 1.619 | 0.108 |
| | LDL[1] | | 0.517 | 0.056 | 9.194 | 1.61E-15 |
| | FBG[3] | | 0.246 | 0.126 | 1.956 | 0.052 |
| Model 3 | Overweight | Coronary Heart Disease | 0.004 | 0.065 | 0.060 | 0.952 |
| | LDL[1] | | 0.348 | 0.074 | 4.678 | 6.27E-06 |
| | TG[4] | | 0.466 | 0.089 | 5.234 | 5.31E-07 |

[1]LDL=Low density lipoprotien cholesterol
[2]SBP=Systolic blood pressure
[3]FBG=Fasting glucose
[4]TG=Triglycerides
*β=Beta

# Ⅳ. DISCUSSION

## 1. Summary of findings

This study explored the causal relationship between overweight and CHD as a function of two-sample MR using suitable MR platforms. The MR-Egger estimate reflected the absence of horizontal pleiotropy on CHD as its intercept was negative but non-significant (β=-0.003, p=0.842). However, genetically predisposed overweight was significantly related to the increased risk of CHD as depicted by the IVW estimation (OR 1.32, 95% CI 1.21-1.44, p=0.001), and such effects were not mediated through horizontal pleiotropy as the intercept of the MR-Egger was not significant (p=0.842). This means that the genetic variants that influence overweight did not influence other risk factors for CHD. However, LDL and TG levels independently influenced CHD irrespective of their mediation on genetically predisposed overweight. These findings suggest that lifestyle habits, as well as genetic predisposition, could cause overweight-related effects on CHD.[22,23] The removal of the IVW outlier did not substantially impact the relationship between the two SNP associated variables. Hence, it could be concluded that the IVW outliers were not significant. Therefore, the Radial plot analysis identified the single outliers in the MR-Egger regression that violated the causal effect of the IVW.

## 2. Discussion of study results

MR is gaining high popularity in epidemiological studies because it helps to establish whether a modifiable exposure has a causal relationship with the pathophysiology of a disease.[20] Also, MR is increasingly used due to the availability of GWAS that provides an opportunity to use a large number of genetic variants in the referred analysis. If the variants in totality could explain a larger proportion of variance in the exposure variable, it would lead to more precise estimates of the causal effects. The precise estimation would increase the reliability of the cause-effect relationships with the referred variables. On the contrary, analysis conducted with an enlarged set of genetic variants is more likely to incorporate invalid instrument variables due to the violations of the assumptions of Mendelian randomization. One such set of variants are those causing horizontal pleiotropy. This is in contrast to vertical pleiotropy, where two traits that are biologically related are correlated irrespective of the gene or variant that is responsible for the effect. Being overweight is a well-known risk factor for CHD, but the genetic predisposition to the cause-and-effect relationship remains relatively unexplored. The study explored whether genetically predisposed obesity significantly increases the risk of CHD. The etiology governing overweight-mediated CHD might be through its effect on higher cholesterol and sugar levels. The deposition of cholesterol in extrahepatic tissues (such as the coronary blood vessels) prevents the flow of blood and oxygen to the myocardium, which increases the risk of CHD.[24] On the other hand, being overweight could lead to immobility and vascular stasis that could impede coronary circulation to increase the risk of CHD. It is contended that overweight and obesity might also prevent the upregulation of GLUT-4 transporter by reducing the fluidity of the plasma membrane. Since the GLUT-4 transporter transports glucose from the blood to the cells under the influence of insulin, the low turnover of these receptors predisposes the risk of hyperglycemia. Nevertheless, the present study did not show a causal relationship between FBG and CHD, despite the significant correlation between overweight and FBG. The paradox could be explained by the fact that a high FBG might not signify T2D, unless there is persistent hyperglycemia. On the contrary, the study showed that genetically predisposed overweight significantly increased the risk of CHD. The findings of the present study are aligned with those of Hu et al. The authors used the MR framework for determining the causal association between BMI and CHD. Hu et al. also evaluated if HbA1c (glycosylated hemoglobin), TC, TG, LDL, and HDL (High density lipoprotein cholesterol) serve as causal mediators from BMI to CHD. BMI was positively associated with HbA1c and TG and negatively associated with HDL.[18] However, there were no associations between BMI and TC or LDL. On the other hand, HbA1c, TC, LDL, and TG were positively associated with CHD. This finding is both comparable and contradictory to the present study because blood sugar did not affect CHD, while overweight was positively correlated to LDL. The contradictions with the Hu et al. study might stem from the differences in the study population because they selected participants from all BMI groups, while the present study had a cut-off from overweight. This means unless individuals are overweight, the LDL and TC might not be high. This finding again substantiates the genetic predisposition assumption of overweight to CHD. Dale et al., who showed that adiposity and body fat distribution are independent predictors of CHD, stroke, and T2D, also support the assumption[19]. However, the present study emphasized the need for dietary modifications and lifestyle habits to reduce the levels of TG and LDL. Obesity-related dyslipidemic profiles are evident as high TC, LDL, HDL, and TG levels compared to controls.[25] Studies further showed that the genetic predisposition to obesity, T2D, and dietary habits interact with each other in determining hyperlipidemia.[26] The findings of the MVMR contradict the findings of Capurso et al. [27] The latter showed that insulin resistance and T2D, along with abdominal obesity, lead to CHD. From this perspective, it may be considered that the present study evaluated FBG, which might not portray insulin resistance. However, the present study considered participants with FBG and not HbA1c, which could have helped to diagnose T2D in them. Flega et al. also reported that as CHD is a sequel of obesity, the biochemical pathways implicated in the development of obesity could also lead to the development of CHD.[28] Therefore, being overweight might stem from pathways that are also implicated in the genetic predisposition to CHD in the same population. Elevated levels of TG, LDL, and VLDL (Very low-density lipoprotein) are strongly correlated with obesity and are major risk factors for CHD.[29] Similarly, our study also showed that being overweight is associated with high FBG levels, TG, and LDL. These findings challenge the relationship between BMI and CHD because unless BMI falls within pathological levels, the risk of dyslipidemia might not be prevalent. Apart from BMI, the distribution of adiposity is related to insulin resistance. This is aligned with the findings that the lack of fluidity of the plasma membrane causes down regulation of the glucose transporters.[30] Simultaneously, studies reflected that dietary fatty acids might predispose the risk of metabolic syndrome.[31] This data could be used to extrapolate our findings that dyslipidemia (which is a part of the metabolic syndrome) would predispose the risk of CHD irrespective of the ethnicity of the participants. The assumptions are not surprising because atherogenic lipoprotein molecule subclasses remain a significant predictor of CHD by blocking coronary vasculature.[32] However, the study should have evaluated the correlation between being overweight and HDL level because some fractions in the latter are strongly associated with CHD.[33]

The present study showed no correlation between FBG and CHD, which contradicts the findings of Park et al.[34] These authors showed that low FBG levels (<70 mg/dl) increased the risk of all-cause stroke.[37] The J-shaped relationship between FBG and CHD was supported by this study because the risk of CHD is lower at FBG levels between 85 to 99 mg/dl.[35,36,38] These findings suggest that future studies should evaluate Hb1Ac as an exposure variable for CHD. Sherwani et al. reported that pathogenic Hb1Ac levels predicted the risk of CHD.[39] This is not surprising because Hb1Ac is a reliable marker for DM.[39,40] The lack of glucose within the cells might precipitate the effects of dyslipidemia on CHD.

## 3. Strengths and Limitations

The main strength of this study is that the causal relationship of genetically predisposed obesity and CHD were based on various MR methods, which ensured the reliability and reproducibility of the findings. The MR-Egger approach reduced the bias due to reverse causality and confounding. Finally, the construction of MVMR provided a detailed analysis regarding the ways various exposure variables are correlated with being overweight. The IVW coupled with MR-Egger increased the reliability and reproducibility of the study across different comorbid conditions related to CHD.

The major limitation of this study is that we only used the data from individuals of European descent. Hence, it should be cautious about generalizing our findings to other populations. Thus, the chances of Type I error cannot be ruled out in this study, considering data from Europeans only. The relation between being overweight genetically and the risk of developing CHD could not be extrapolated to populations other than Europeans. Moreover, no power estimations were conducted for selecting the sample size, which might have further reduced the reproducibility of the findings. Nevertheless, the limited availability of population-specific information on genetic associations, genetic instruments tend to show poor statistical power. On the contrary, different MR frameworks substantiated the causal relationship between the genetic predisposition of being overweight and CHD after removing the outliers. Such measures increased the reliability and validity of the findings of our study.

# V. CONCLUSIONS

We discovered that overweight is substantially associated with CHD risk in European populations using two-sample Mendelian randomization. However, the present study also showed that LDL and TG could also predispose the risk of CHD independently of being overweight genetically. As high LDL and TG levels are associated with poor dietary and lifestyle habits, and they could posit CHD risk in individuals who are not genetically overweight.

The study showed that both genetic predisposition and lifestyle behaviors might predispose the risk of CHD. This is aligned with the findings that individuals with an ideal lifestyle and high genetic risk are twice likely to develop CHD compared to those with an ideal lifestyle and low genetic risk. These findings imply that genetic predisposition to cardiovascular disease is moderated through lifestyle and dietary behaviors. Hence, individuals who are genetically predisposed to being overweight should refrain from poor dietary habits that increase the levels of LDL and TG.

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**Appendix Table 1. Overweight instrument variable**

| NO. | SNP | Position | Effect Allele | Effect Allele Frequency | Beta(β) | Standard error | *P* value |
|---|---|---|---|---|---|---|---|
| 1 | rs633715 | 1:177852580 | C | T | 0.078 | 0.011 | 4.00E-12 |
| 2 | rs2568958 | 1:72765116 | A | G | 0.062 | 0.009 | 1.10E-11 |
| 3 | rs12623218 | 2:632146 | A | T | 0.110 | 0.012 | 5.80E-22 |
| 4 | rs10182181 | 2:25150296 | G | A | 0.057 | 0.009 | 2.10E-10 |
| 5 | rs9816226 | 3:185834499 | T | A | 0.070 | 0.012 | 2.00E-09 |
| 6 | rs13130484 | 4:45175691 | T | C | 0.071 | 0.009 | 3.90E-14 |
| 7 | rs2206277 | 6:50798526 | T | C | 0.080 | 0.012 | 5.60E-12 |
| 8 | rs2596125 | 8:76642325 | T | C | -0.052 | 0.009 | 5.90E-09 |
| 9 | rs2030323 | 11:27728539 | C | A | 0.079 | 0.011 | 1.10E-12 |
| 10 | rs8028313 | 15:68043057 | G | C | -0.065 | 0.011 | 2.00E-09 |
| 11 | rs12444979 | 16:19933600 | T | C | -0.079 | 0.013 | 1.80E-09 |
| 12 | rs1421085 | 16:53800954 | C | T | 0.140 | 0.009 | 5.80E-50 |
| 13 | rs523288 | 18:57848369 | T | A | 0.099 | 0.011 | 1.70E-20 |
| 14 | rs10853932 | 19:34324709 | C | T | 0.067 | 0.011 | 1.30E-09 |

**Appendix Table 2. Coronary heart disease instrument variable**

| NO. | SNP | Position | Effect Allele | Effect Allele Frequency | Beta(β) | Standard error | *P* value |
|---|---|---|---|---|---|---|---|
| 1 | rs599839 | 1:177852580 | A | G | 0.107 | 0.017 | 2.89E-10 |
| 2 | rs17114036 | 1:56962821 | G | A | -0.145 | 0.026 | 1.43E-08 |
| 3 | rs2351524 | 2:203880992 | C | T | -0.139 | 0.021 | 1.76E-11 |
| 4 | rs7651039 | 3:15648004 | C | T | 0.142 | 0.025 | 1.85E-08 |
| 5 | rs2306374 | 3:138119952 | C | T | 0.108 | 0.020 | 3.34E-08 |
| 6 | rs10455872 | 6:161010118 | G | A | 0.278 | 0.038 | 3.08E-13 |
| 7 | rs9351814 | 6:72193707 | C | A | -0.080 | 0.014 | 2.02E-08 |
| 8 | rs4714955 | 6:12903435 | T | C | -0.100 | 0.015 | 6.03E-12 |
| 9 | rs12190287 | 6:134214525 | G | C | -0.103 | 0.016 | 4.64E-11 |
| 10 | rs11556924 | 7:129663496 | T | C | -0.091 | 0.015 | 2.22E-09 |
| 11 | rs1333045 | 9:22119195 | C | T | 0.226 | 0.019 | 4.63E-32 |
| 12 | rs964184 | 11:116648917 | C | G | -0.126 | 0.020 | 8.02E-10 |
| 13 | rs2219939 | 15:79029723 | A | G | -0.099 | 0.016 | 1.21E-09 |
| 14 | rs1122608 | 19:11163601 | T | G | -0.127 | 0.021 | 9.73E-10 |
| 15 | rs9982601 | 21:35599128 | T | C | 0.164 | 0.026 | 4.22E-10 |

**Appendix Table 3. Harmonized data of overweight and coronary heart disease**

| NO. | SNP | EA | OA | beta.exposure | beta.outcome | se.exposure | se.outcome | pval.exposure | pval.outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1 | rs10182181 | G | A | 0.057 | 0.001 | 0.009 | 0.014 | 2.10E-10 | 0.95 |
| 2 | rs10853932 | C | T | 0.067 | 0.006 | 0.011 | 0.022 | 1.30E-09 | 0.77 |
| 3 | rs12444979 | T | C | -0.079 | 0.009 | 0.013 | 0.021 | 1.80E-09 | 0.66 |
| 4 | rs12623218 | A | T | 0.110 | 0.016 | 0.012 | 0.019 | 5.80E-22 | 0.41 |
| 5 | rs13130484 | T | C | 0.071 | 0.035 | 0.009 | 0.016 | 3.90E-14 | 0.03 |
| 6 | rs1421085 | C | T | 0.140 | 0.031 | 0.009 | 0.015 | 5.80E-50 | 0.04 |
| 7 | rs2030323 | C | A | 0.079 | 0.031 | 0.011 | 0.017 | 1.10E-12 | 0.08 |
| 8 | rs2206277 | T | C | 0.080 | 0.009 | 0.012 | 0.018 | 5.60E-12 | 0.63 |
| 9 | rs2568958 | A | G | 0.062 | -0.001 | 0.009 | 0.014 | 1.10E-11 | 0.93 |
| 10 | rs2596125 | T | C | -0.052 | -0.013 | 0.009 | 0.014 | 5.90E-09 | 0.36 |
| 11 | rs523288 | T | A | 0.099 | 0.021 | 0.011 | 0.016 | 1.70E-20 | 0.19 |
| 12 | rs633715 | C | T | 0.078 | -0.004 | 0.011 | 0.017 | 4.00E-12 | 0.82 |
| 13 | rs8028313 | G | C | -0.065 | -0.047 | 0.011 | 0.017 | 2.00E-09 | 0.01 |
| 14 | rs9816226 | T | A | 0.070 | -0.004 | 0.012 | 0.018 | 2.00E-09 | 0.82 |

**Appendix Table 4. Overweight and coronary heart disease MR result**

| No. | SNP | Beta (β) | SE | *P* value |
|---|---|---|---|---|
| 1 | rs10182181 | -1.279 | 0.424 | 0.003 |
| 2 | rs10853932 | 0.281 | 0.312 | 0.368 |
| 3 | rs12444979 | -0.467 | 0.344 | 0.175 |
| 4 | rs12623218 | -0.363 | 0.225 | 0.108 |
| 5 | rs13130484 | -0.530 | 0.268 | 0.048 |
| 6 | rs1421085 | -0.753 | 0.137 | 0.000 |
| 7 | rs2030323 | 0.289 | 0.300 | 0.336 |
| 8 | rs2206277 | -0.954 | 0.314 | 0.002 |
| 9 | rs2568958 | -0.098 | 0.312 | 0.753 |
| 10 | rs2596125 | -0.699 | 0.369 | 0.058 |
| 11 | rs523288 | -0.144 | 0.226 | 0.524 |
| 12 | rs633715 | -0.184 | 0.301 | 0.541 |
| 13 | rs8028313 | -0.327 | 0.353 | 0.354 |
| 14 | rs9816226 | 0.780 | 0.376 | 0.038 |
| 15 | All - Inverse variance weighted | -0.395 | 0.122 | 0.001 |
| 16 | All - MR Egger | -0.820 | 0.410 | 0.069 |

**Appendix Table 5. Overweight and coronary heart disease leave one out sensitivity analysis**

| No. | SNP | β | SE | *P* value |
|---|---|---|---|---|
| 1 | rs10182181 | 0.194974353 | 0.055724 | 0.000467 |
| 2 | rs10853932 | 0.189228177 | 0.05531 | 0.000623 |
| 3 | rs12444979 | 0.200075969 | 0.0556 | 0.00032 |
| 4 | rs12623218 | 0.191386132 | 0.057435 | 0.000862 |
| 5 | rs13130484 | 0.167096395 | 0.056083 | 0.002888 |
| 6 | rs1421085 | 0.174410424 | 0.062947 | 0.005593 |
| 7 | rs2030323 | 0.173295703 | 0.05617 | 0.002034 |
| 8 | rs2206277 | 0.19120155 | 0.056041 | 0.000645 |
| 9 | rs2568958 | 0.198584861 | 0.055966 | 0.000388 |
| 10 | rs2596125 | 0.184091132 | 0.055753 | 0.00096 |
| 11 | rs523288 | 0.183497766 | 0.058007 | 0.00156 |
| 12 | rs633715 | 0.201491122 | 0.056088 | 0.000328 |
| 13 | rs8028313 | 0.1621159 | 0.055629 | 0.003565 |
| 14 | rs9816226 | 0.198529131 | 0.055731 | 0.000368 |
| 15 | All | 0.186622085 | 0.05441 | 0.000604 |

**Appendix Table 6. Harmonized data of low-density lipoprotein and coronary heart disease**

| NO. | SNP | EA | OA | beta.exposure | beta.outcome | se.exposure | se.outcome | pval.exposure | pval.outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1 | rs10195252 | C | T | -0.0238 | -0.0145 | 0.0039 | 0.0144 | 3.81E-08 | 0.313012 |
| 2 | rs10490626 | A | G | -0.0508 | -0.0430 | 0.0069 | 0.0267 | 1.70E-12 | 0.107487 |
| 3 | rs10832962 | T | C | 0.0320 | 0.0443 | 0.0040 | 0.0157 | 6.62E-14 | 0.004884 |
| 4 | rs10893499 | A | G | 0.0521 | 0.0535 | 0.0053 | 0.0220 | 3.86E-21 | 0.015163 |
| 5 | rs10903129 | G | A | 0.0328 | 0.0123 | 0.0037 | 0.0140 | 3.03E-17 | 0.380497 |
| 6 | rs10947332 | A | G | 0.0504 | 0.0251 | 0.0056 | 0.0221 | 6.97E-18 | 0.256018 |
| 7 | rs11563251 | T | C | 0.0345 | 0.0016 | 0.0062 | 0.0268 | 4.50E-08 | 0.951349 |
| 8 | rs1169288 | C | A | 0.0375 | 0.0702 | 0.0040 | 0.0151 | 6.45E-21 | 3.49E-06 |
| 9 | rs12066643 | T | C | -0.0389 | 0.0170 | 0.0064 | 0.0278 | 1.06E-08 | 0.539825 |
| 10 | rs1250229 | C | T | 0.0243 | -0.0337 | 0.0042 | 0.0184 | 3.13E-08 | 0.066655 |
| 11 | rs12721109 | A | G | -0.4462 | -0.1441 | 0.0183 | 0.0800 | 2.99E-122 | 0.071488 |
| 12 | rs12748152 | T | C | 0.0499 | 0.0415 | 0.0066 | 0.0239 | 3.21E-12 | 0.082456 |
| 13 | rs12916 | C | T | 0.0733 | 0.0407 | 0.0038 | 0.0146 | 7.79E-78 | 0.005326 |
| 14 | rs13206249 | A | G | -0.0378 | -0.0208 | 0.0062 | 0.0166 | 4.53E-08 | 0.212092 |
| 15 | rs13277801 | T | C | -0.0338 | 0.0081 | 0.0038 | 0.0145 | 3.99E-17 | 0.57527 |
| 16 | rs1367117 | A | G | 0.1186 | 0.0353 | 0.0040 | 0.0155 | 9.48E-183 | 0.023027 |
| 17 | rs1408272 | G | T | -0.0520 | -0.0311 | 0.0083 | 0.0317 | 3.68E-09 | 0.325866 |
| 18 | rs1564348 | C | T | 0.0481 | 0.0608 | 0.0050 | 0.0189 | 2.76E-21 | 0.001284 |
| 19 | rs16831243 | T | C | 0.0378 | -0.0118 | 0.0055 | 0.0213 | 9.06E-12 | 0.579439 |
| 20 | rs17404153 | T | G | -0.0336 | -0.0660 | 0.0054 | 0.0212 | 1.83E-09 | 0.001797 |
| 21 | rs174583 | T | C | -0.0522 | -0.0016 | 0.0038 | 0.0144 | 7.00E-41 | 0.911637 |
| 22 | rs1800961 | T | C | -0.0685 | 0.0304 | 0.0106 | 0.0442 | 6.03E-10 | 0.491232 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 23 | rs1883025 | T | C | -0.0296 | -0.0141 | 0.0044 | 0.0170 | 6.14E-11 | 0.406622 |
| 24 | rs2000999 | A | G | 0.0650 | 0.0402 | 0.0046 | 0.0185 | 4.22E-41 | 0.029767 |
| 25 | rs2030746 | T | C | 0.0214 | 0.0277 | 0.0038 | 0.0162 | 8.60E-09 | 0.087153 |
| 26 | rs2073547 | G | A | 0.0485 | 0.0207 | 0.0049 | 0.0263 | 1.92E-21 | 0.431464 |
| 27 | rs2228603 | T | C | -0.1040 | -0.1106 | 0.0072 | 0.0282 | 4.43E-44 | 8.97E-05 |
| 28 | rs2315065 | A | C | 0.1102 | 0.2560 | 0.0158 | 0.0561 | 5.23E-12 | 5.04E-06 |
| 29 | rs2328223 | C | A | 0.0299 | -0.0053 | 0.0050 | 0.0291 | 5.63E-09 | 0.85477 |
| 30 | rs2390536 | A | G | 0.0223 | 0.0148 | 0.0038 | 0.0146 | 2.04E-08 | 0.309586 |
| 31 | rs2419604 | G | A | -0.0302 | 0.0057 | 0.0040 | 0.0158 | 7.49E-14 | 0.715875 |
| 32 | rs247616 | T | C | -0.0547 | -0.0365 | 0.0041 | 0.0206 | 2.57E-37 | 0.077124 |
| 33 | rs2587534 | A | G | 0.0391 | -0.0006 | 0.0037 | 0.0140 | 8.06E-25 | 0.963704 |
| 34 | rs2642438 | G | A | 0.0352 | 0.0197 | 0.0042 | 0.0160 | 7.32E-16 | 0.218884 |
| 35 | rs267733 | G | A | -0.0331 | -0.0027 | 0.0053 | 0.0220 | 5.29E-09 | 0.9009 |
| 36 | rs2710642 | A | G | 0.0239 | 0.0166 | 0.0038 | 0.0146 | 6.09E-09 | 0.255491 |
| 37 | rs2737252 | A | G | -0.0314 | 0.0079 | 0.0041 | 0.0155 | 7.04E-14 | 0.61004 |
| 38 | rs2886232 | C | T | -0.0451 | -0.0630 | 0.0064 | 0.0350 | 3.88E-11 | 0.071623 |
| 39 | rs2954029 | T | A | -0.0564 | -0.0586 | 0.0036 | 0.0140 | 2.10E-50 | 2.79E-05 |
| 40 | rs2965157 | C | T | -0.1886 | -0.0896 | 0.0112 | 0.0442 | 7.29E-62 | 0.042695 |
| 41 | rs314253 | C | T | -0.0242 | -0.0104 | 0.0038 | 0.0151 | 3.44E-10 | 0.490563 |
| 42 | rs3184504 | C | T | 0.0268 | -0.0704 | 0.0038 | 0.0156 | 4.20E-12 | 6.35E-06 |
| 43 | rs364585 | G | A | 0.0249 | 0.0072 | 0.0038 | 0.0144 | 4.28E-10 | 0.614571 |
| 44 | rs3757354 | T | C | -0.0382 | -0.0182 | 0.0044 | 0.0206 | 2.09E-17 | 0.376032 |
| 45 | rs3780181 | G | A | -0.0445 | -0.0351 | 0.0074 | 0.0260 | 1.76E-09 | 0.177783 |
| 46 | rs4253776 | G | A | 0.0311 | 0.0337 | 0.0059 | 0.0240 | 3.35E-08 | 0.160715 |
| 47 | rs4530754 | A | G | 0.0275 | -0.0075 | 0.0036 | 0.0142 | 3.58E-12 | 0.594162 |
| 48 | rs4722551 | C | T | 0.0391 | 0.0332 | 0.0049 | 0.0273 | 3.95E-14 | 0.225026 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 49 | rs4942486 | C | T | -0.0243 | 0.0000 | 0.0037 | 0.0141 | 2.26E-11 | 0.999267 |
| 50 | rs4970712 | C | A | 0.0339 | 0.0123 | 0.0044 | 0.0171 | 2.46E-13 | 0.471551 |
| 51 | rs4970834 | T | C | -0.1503 | -0.1287 | 0.0047 | 0.0219 | 1.00E-200 | 4.25E-09 |
| 52 | rs5763662 | T | C | 0.0767 | -0.0097 | 0.0121 | 0.0502 | 1.19E-08 | 0.846522 |
| 53 | rs579459 | C | T | 0.0665 | 0.0981 | 0.0045 | 0.0185 | 2.42E-44 | 1.16E-07 |
| 54 | rs6016373 | G | A | -0.0349 | -0.0109 | 0.0037 | 0.0144 | 7.95E-19 | 0.448828 |
| 55 | rs6065311 | C | T | 0.0417 | 0.0193 | 0.0036 | 0.0140 | 1.66E-30 | 0.167658 |
| 56 | rs6504872 | T | C | 0.0274 | 0.0069 | 0.0037 | 0.0141 | 3.48E-13 | 0.626014 |
| 57 | rs6511720 | T | G | -0.2209 | -0.1253 | 0.0061 | 0.0332 | 1.00E-200 | 0.000161 |
| 58 | rs6544713 | C | T | -0.0806 | -0.0615 | 0.0041 | 0.0166 | 4.84E-83 | 0.000222 |
| 59 | rs6709904 | G | A | -0.0550 | -0.0622 | 0.0085 | 0.0264 | 4.58E-10 | 0.018499 |
| 60 | rs676388 | C | T | 0.0265 | 0.0058 | 0.0039 | 0.0162 | 1.31E-11 | 0.720324 |
| 61 | rs6818397 | G | T | -0.0224 | -0.0298 | 0.0040 | 0.0175 | 1.68E-08 | 0.088332 |
| 62 | rs6882076 | C | T | 0.0456 | 0.0215 | 0.0038 | 0.0149 | 3.31E-31 | 0.149584 |
| 63 | rs6909746 | T | C | -0.0263 | -0.0230 | 0.0037 | 0.0142 | 7.86E-11 | 0.105959 |
| 64 | rs7254892 | A | G | -0.4853 | -0.1360 | 0.0119 | 0.0803 | 1.00E-200 | 0.09033 |
| 65 | rs72902576 | G | T | -0.0933 | -0.0501 | 0.0133 | 0.0684 | 9.58E-12 | 0.464229 |
| 66 | rs7551981 | T | G | 0.0472 | 0.0262 | 0.0038 | 0.0161 | 1.36E-33 | 0.103138 |
| 67 | rs7640978 | T | C | -0.0392 | -0.0934 | 0.0069 | 0.0264 | 9.84E-09 | 0.000408 |
| 68 | rs7832643 | T | G | 0.0339 | -0.0111 | 0.0038 | 0.0143 | 2.67E-17 | 0.43824 |
| 69 | rs8017377 | A | G | 0.0303 | -0.0184 | 0.0038 | 0.0202 | 2.52E-15 | 0.36153 |
| 70 | rs964184 | C | G | -0.0855 | -0.1260 | 0.0078 | 0.0205 | 2.01E-26 | 8.02E-10 |
| 71 | rs9875338 | A | G | -0.0270 | -0.0181 | 0.0037 | 0.0144 | 2.21E-11 | 0.209173 |
| 72 | rs9987289 | G | A | 0.0714 | 0.0215 | 0.0066 | 0.0255 | 8.53E-24 | 0.399913 |

**Appendix Table 7. Harmonized data of systolic blood glucose and coronary heart disease**

| NO. | SNP | EA | OA | beta.exposure | beta.outcome | se.exposure | se.outcome | pval.exposure | pval.outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1 | rs1000423 | T | C | 0.41380 | -0.05189 | 0.03460 | 0.01702 | 6.50E-33 | 0.00230 |
| 2 | rs10045307 | G | C | 0.20240 | -0.00500 | 0.03620 | 0.01614 | 2.21E-08 | 0.75647 |
| 3 | rs10048404 | T | C | -0.26070 | -0.01523 | 0.03170 | 0.01518 | 1.91E-16 | 0.31570 |
| 4 | rs1006545 | T | G | 0.68460 | -0.00818 | 0.04800 | 0.02285 | 3.50E-46 | 0.72044 |
| 5 | rs10069690 | T | C | 0.30980 | -0.02000 | 0.03690 | 0.03300 | 4.47E-17 | 0.54447 |
| 6 | rs1010064 | C | A | -0.35710 | -0.02712 | 0.03870 | 0.01814 | 3.02E-20 | 0.13489 |
| 7 | rs1012089 | G | C | 0.19200 | -0.00210 | 0.03020 | 0.01393 | 1.95E-10 | 0.87990 |
| 8 | rs10188003 | T | C | 0.18830 | -0.01911 | 0.03070 | 0.01450 | 8.80E-10 | 0.18747 |
| 9 | rs10207726 | T | C | -0.21420 | -0.00698 | 0.03300 | 0.01525 | 8.06E-11 | 0.64709 |
| 10 | rs10224210 | C | T | 0.38310 | 0.00021 | 0.03400 | 0.01686 | 1.60E-29 | 0.99017 |
| 11 | rs1044822 | T | C | -0.24800 | 0.00114 | 0.04240 | 0.01922 | 5.16E-09 | 0.95285 |
| 12 | rs10460108 | G | A | -0.21410 | -0.00326 | 0.03010 | 0.01392 | 1.12E-12 | 0.81498 |
| 13 | rs1049212 | G | A | 0.29900 | 0.00006 | 0.03020 | 0.01412 | 4.59E-23 | 0.99660 |
| 14 | rs10501410 | A | G | 0.41220 | 0.01132 | 0.06070 | 0.02857 | 1.10E-11 | 0.69195 |
| 15 | rs1052501 | T | C | 0.22620 | 0.02649 | 0.04120 | 0.02117 | 4.14E-08 | 0.21092 |
| 16 | rs10749572 | T | G | -0.20300 | -0.02123 | 0.03020 | 0.01397 | 1.88E-11 | 0.12846 |
| 17 | rs10750441 | T | C | 0.17540 | 0.00416 | 0.03190 | 0.01475 | 3.74E-08 | 0.77768 |
| 18 | rs10776752 | T | G | 0.82110 | 0.07600 | 0.05760 | 0.03630 | 4.61E-46 | 0.03629 |
| 19 | rs10777213 | A | G | -0.17860 | 0.01211 | 0.02990 | 0.01408 | 2.45E-09 | 0.38957 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 20 | rs10782230 | A | G | 0.21060 | -0.00419 | 0.03020 | 0.01444 | 2.91E-12 | 0.77189 |
| 21 | rs10804330 | C | T | -0.23510 | -0.02061 | 0.03060 | 0.01426 | 1.62E-14 | 0.14835 |
| 22 | rs10914124 | C | T | -0.23400 | -0.00222 | 0.03120 | 0.01578 | 6.32E-14 | 0.88814 |
| 23 | rs11120093 | T | C | -0.17920 | -0.00899 | 0.03070 | 0.01408 | 5.13E-09 | 0.52309 |
| 24 | rs11159091 | A | G | 0.19780 | 0.01080 | 0.03030 | 0.01394 | 6.79E-11 | 0.43873 |
| 25 | rs111866816 | T | C | 0.35690 | -0.02058 | 0.05970 | 0.02741 | 2.29E-09 | 0.45278 |
| 26 | rs11191580 | C | T | -1.09950 | -0.10399 | 0.05500 | 0.02510 | 7.74E-89 | 0.00003 |
| 27 | rs11222084 | T | A | 0.33630 | -0.02402 | 0.03160 | 0.01480 | 1.80E-26 | 0.10463 |
| 28 | rs11241313 | T | C | -0.20710 | -0.01804 | 0.03260 | 0.01486 | 2.23E-10 | 0.22468 |
| 29 | rs112509803 | C | G | -0.26410 | -0.01420 | 0.04770 | 0.01917 | 3.18E-08 | 0.45886 |
| 30 | rs11252324 | T | G | -0.41640 | -0.03513 | 0.05730 | 0.02617 | 3.61E-13 | 0.17948 |
| 31 | rs113086489 | T | C | 0.32490 | -0.02715 | 0.03070 | 0.01682 | 3.80E-26 | 0.10637 |
| 32 | rs1154214 | G | T | 0.20310 | 0.01051 | 0.03060 | 0.01420 | 3.27E-11 | 0.45935 |
| 33 | rs11585169 | A | T | 0.17960 | 0.04435 | 0.03080 | 0.01426 | 5.34E-09 | 0.00187 |
| 34 | rs11592107 | A | G | 0.30240 | 0.00565 | 0.03260 | 0.01490 | 1.55E-20 | 0.70437 |
| 35 | rs11604357 | A | C | -0.27700 | 0.01877 | 0.04110 | 0.01950 | 1.60E-11 | 0.33557 |
| 36 | rs11636952 | C | T | -0.53130 | -0.00643 | 0.03280 | 0.01499 | 4.22E-59 | 0.66793 |
| 37 | rs11641374 | A | C | -0.19430 | -0.02396 | 0.03090 | 0.02119 | 3.26E-10 | 0.25829 |
| 38 | rs11655604 | T | C | -0.20330 | -0.03088 | 0.03330 | 0.02032 | 1.09E-09 | 0.12874 |
| 39 | rs11672660 | T | C | 0.22120 | -0.04559 | 0.03810 | 0.02360 | 6.32E-09 | 0.05334 |
| 40 | rs1169078 | G | C | 0.19710 | 0.01802 | 0.03270 | 0.01532 | 1.68E-09 | 0.23940 |
| 41 | rs11694601 | G | A | 0.19090 | 0.00166 | 0.03090 | 0.01420 | 6.41E-10 | 0.90716 |
| 42 | rs11874246 | T | C | 0.28560 | 0.00772 | 0.03280 | 0.01497 | 3.22E-18 | 0.60621 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 43 | rs11925504 | A | G | -0.29010 | -0.03822 | 0.03050 | 0.01398 | 1.78E-21 | 0.00627 |
| 44 | rs11960210 | C | T | -0.47270 | -0.02945 | 0.03130 | 0.01443 | 1.25E-51 | 0.04133 |
| 45 | rs11977526 | A | G | -0.32130 | -0.01126 | 0.03120 | 0.01516 | 6.62E-25 | 0.45796 |
| 46 | rs1199330 | G | A | 0.26540 | 0.10547 | 0.04700 | 0.02182 | 1.65E-08 | 0.00000 |
| 47 | rs1209384 | G | A | -0.25580 | -0.03632 | 0.03130 | 0.01417 | 2.85E-16 | 0.01036 |
| 48 | rs12136922 | A | G | 0.20270 | -0.00315 | 0.03040 | 0.01400 | 2.69E-11 | 0.82218 |
| 49 | rs12255372 | T | G | 0.23580 | 0.01138 | 0.03350 | 0.01558 | 1.94E-12 | 0.46512 |
| 50 | rs12258967 | G | C | -0.63270 | -0.03311 | 0.03370 | 0.01561 | 1.08E-78 | 0.03395 |
| 51 | rs12321 | C | G | -0.22920 | -0.00813 | 0.03030 | 0.01536 | 3.81E-14 | 0.59677 |
| 52 | rs12464602 | A | G | -0.24370 | -0.05015 | 0.03150 | 0.01868 | 1.02E-14 | 0.00725 |
| 53 | rs12509595 | C | T | 0.83670 | 0.00046 | 0.03340 | 0.02472 | 2.55E-138 | 0.98508 |
| 54 | rs12511987 | G | T | 0.23290 | 0.03029 | 0.03990 | 0.01924 | 5.39E-09 | 0.11540 |
| 55 | rs12596630 | T | C | 0.42780 | 0.02733 | 0.05470 | 0.03894 | 5.01E-15 | 0.48284 |
| 56 | rs12610654 | G | A | -0.23150 | -0.00159 | 0.03200 | 0.01689 | 4.41E-13 | 0.92518 |
| 57 | rs12627651 | A | G | 0.34980 | 0.03188 | 0.03410 | 0.02410 | 1.02E-24 | 0.18597 |
| 58 | rs12637573 | G | A | 0.17310 | -0.01238 | 0.03020 | 0.01394 | 9.95E-09 | 0.37443 |
| 59 | rs12643599 | G | A | -0.31340 | -0.04926 | 0.03130 | 0.01445 | 1.23E-23 | 0.00065 |
| 60 | rs12656497 | C | T | 0.63820 | 0.03395 | 0.03070 | 0.01416 | 7.14E-96 | 0.01648 |
| 61 | rs12657950 | T | C | 0.45500 | -0.01922 | 0.05900 | 0.02792 | 1.27E-14 | 0.49127 |
| 62 | rs12668436 | C | T | 0.21510 | 0.03274 | 0.03500 | 0.01605 | 7.88E-10 | 0.04141 |
| 63 | rs12693982 | T | C | 0.25750 | 0.05013 | 0.03090 | 0.01410 | 7.49E-17 | 0.00038 |
| 64 | rs12731646 | T | C | -0.18900 | -0.04143 | 0.03070 | 0.01440 | 7.21E-10 | 0.00401 |
| 65 | rs1275985 | T | C | -0.54110 | 0.01075 | 0.03080 | 0.01403 | 4.73E-69 | 0.44383 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 66 | rs12883810 | T | C | -0.23820 | -0.02424 | 0.04280 | 0.02253 | 2.70E-08 | 0.28194 |
| 67 | rs12885878 | G | A | 0.22910 | 0.06049 | 0.03670 | 0.02557 | 4.32E-10 | 0.01798 |
| 68 | rs12906962 | C | T | 0.26530 | 0.03975 | 0.03250 | 0.01854 | 3.28E-16 | 0.03206 |
| 69 | rs1290784 | T | C | 0.41240 | 0.02299 | 0.03030 | 0.01405 | 2.97E-42 | 0.10175 |
| 70 | rs12926550 | A | G | -0.25480 | -0.02185 | 0.03240 | 0.01540 | 3.43E-15 | 0.15587 |
| 71 | rs1293969 | C | T | 0.19880 | -0.01478 | 0.03470 | 0.01617 | 1.03E-08 | 0.36070 |
| 72 | rs13016772 | T | C | 0.25220 | -0.00963 | 0.03550 | 0.01669 | 1.23E-12 | 0.56374 |
| 73 | rs13091418 | G | C | 0.22340 | 0.00330 | 0.03250 | 0.01479 | 6.15E-12 | 0.82358 |
| 74 | rs13107261 | A | G | -0.17780 | 0.01552 | 0.03140 | 0.01419 | 1.57E-08 | 0.27408 |
| 75 | rs13107325 | T | C | -0.90860 | 0.00494 | 0.05920 | 0.04247 | 4.22E-53 | 0.90743 |
| 76 | rs13204703 | C | T | -0.19670 | 0.02380 | 0.03500 | 0.01574 | 1.94E-08 | 0.13049 |
| 77 | rs13253358 | T | C | 0.21270 | 0.03011 | 0.03300 | 0.01502 | 1.13E-10 | 0.04504 |
| 78 | rs1332813 | C | T | -0.22030 | -0.00869 | 0.03140 | 0.01437 | 2.32E-12 | 0.54527 |
| 79 | rs13358657 | G | A | 0.38800 | 0.00098 | 0.04450 | 0.02103 | 2.95E-18 | 0.96290 |
| 80 | rs13412750 | A | G | -0.28890 | 0.02503 | 0.03410 | 0.01578 | 2.32E-17 | 0.11266 |
| 81 | rs13420463 | G | A | -0.31430 | 0.00026 | 0.03600 | 0.01692 | 2.72E-18 | 0.98774 |
| 82 | rs1375564 | T | C | 0.25790 | 0.00742 | 0.03150 | 0.01436 | 2.84E-16 | 0.60536 |
| 83 | rs1382472 | A | G | -0.19170 | 0.01155 | 0.03070 | 0.01408 | 4.47E-10 | 0.41195 |
| 84 | rs1408945 | T | G | -0.31960 | -0.01912 | 0.03040 | 0.01409 | 8.33E-26 | 0.17476 |
| 85 | rs1410222 | T | C | 0.21730 | -0.01814 | 0.03880 | 0.01803 | 2.17E-08 | 0.31434 |
| 86 | rs141958336 | A | G | 0.78070 | -0.02496 | 0.07800 | 0.03469 | 1.36E-23 | 0.47188 |
| 87 | rs1422279 | T | C | 0.33100 | 0.01995 | 0.03090 | 0.01439 | 1.05E-26 | 0.16552 |
| 88 | rs1433121 | T | C | -0.22800 | 0.00140 | 0.03260 | 0.01495 | 2.66E-12 | 0.92528 |

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|---|---|---|---|---|---|---|---|---|---|
| 89 | rs1437649 | A | G | -0.21890 | 0.01988 | 0.03570 | 0.01631 | 8.57E-10 | 0.22290 |
| 90 | rs146550789 | C | T | 0.48240 | 0.00917 | 0.07780 | 0.03145 | 5.64E-10 | 0.77068 |
| 91 | rs148140538 | T | C | -0.32520 | -0.00835 | 0.05620 | 0.02838 | 7.39E-09 | 0.76868 |
| 92 | rs1493132 | C | T | 0.17660 | 0.00439 | 0.03180 | 0.01442 | 2.73E-08 | 0.76088 |
| 93 | rs1544861 | C | T | -0.19690 | 0.02820 | 0.03180 | 0.02546 | 5.66E-10 | 0.26803 |
| 94 | rs1551355 | T | C | 0.20980 | -0.00495 | 0.03560 | 0.02011 | 3.89E-09 | 0.80561 |
| 95 | rs1565440 | A | G | 0.17460 | 0.00038 | 0.03110 | 0.01449 | 1.94E-08 | 0.97914 |
| 96 | rs1575290 | T | C | 0.19730 | 0.00785 | 0.03010 | 0.01446 | 5.59E-11 | 0.58733 |
| 97 | rs1623474 | T | C | 0.38270 | 0.00738 | 0.03210 | 0.01530 | 7.66E-33 | 0.62937 |
| 98 | rs1630736 | T | C | -0.17060 | 0.03162 | 0.03090 | 0.01578 | 3.52E-08 | 0.04501 |
| 99 | rs1664781 | A | G | 0.26430 | 0.03260 | 0.03260 | 0.01473 | 5.69E-16 | 0.02693 |
| 100 | rs17010957 | C | T | 0.53400 | 0.00578 | 0.04300 | 0.02105 | 1.78E-35 | 0.78368 |
| 101 | rs17035181 | G | T | -0.30740 | -0.03498 | 0.04290 | 0.01966 | 7.61E-13 | 0.07516 |
| 102 | rs17080102 | C | G | -0.80850 | -0.06970 | 0.05940 | 0.02810 | 3.52E-42 | 0.01314 |
| 103 | rs17245822 | C | A | 0.18990 | 0.00311 | 0.03120 | 0.01419 | 1.15E-09 | 0.82651 |
| 104 | rs17249754 | A | G | -0.84460 | 0.04477 | 0.04030 | 0.01807 | 1.25E-97 | 0.01322 |
| 105 | rs17257081 | G | A | -0.22740 | 0.00942 | 0.03920 | 0.01836 | 6.35E-09 | 0.60789 |
| 106 | rs17562391 | T | C | 0.19670 | 0.08518 | 0.03060 | 0.01667 | 1.35E-10 | 0.00000 |
| 107 | rs17608766 | C | T | 0.69030 | 0.08802 | 0.04330 | 0.02042 | 2.48E-57 | 0.00002 |
| 108 | rs177551 | A | C | 0.37300 | 0.04663 | 0.04420 | 0.01951 | 3.47E-17 | 0.01681 |
| 109 | rs17760259 | C | T | 0.26540 | 0.02116 | 0.03040 | 0.01401 | 2.25E-18 | 0.13100 |
| 110 | rs17762 | A | G | 0.41170 | 0.01407 | 0.05710 | 0.02677 | 5.60E-13 | 0.59923 |
| 111 | rs17812022 | T | C | -0.36130 | 0.03492 | 0.05250 | 0.02534 | 5.65E-12 | 0.16817 |

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|---|---|---|---|---|---|---|---|---|---|
| 112 | rs1786345 | C | A | -0.20730 | -0.00152 | 0.03070 | 0.01420 | 1.34E-11 | 0.91462 |
| 113 | rs1814951 | A | G | -0.32310 | 0.00242 | 0.04660 | 0.02123 | 3.91E-12 | 0.90929 |
| 114 | rs1821002 | G | C | -0.37940 | -0.03175 | 0.03070 | 0.01484 | 5.19E-35 | 0.03246 |
| 115 | rs1848994 | A | G | 0.20120 | -0.02400 | 0.03340 | 0.01576 | 1.79E-09 | 0.12790 |
| 116 | rs1871190 | T | G | 0.19540 | 0.02562 | 0.03240 | 0.01940 | 1.66E-09 | 0.18674 |
| 117 | rs1882212 | G | A | -0.27530 | 0.00779 | 0.03630 | 0.01737 | 3.34E-14 | 0.65398 |
| 118 | rs1882961 | T | C | 0.24430 | 0.04876 | 0.03260 | 0.01533 | 6.69E-14 | 0.00147 |
| 119 | rs1889785 | A | G | 0.17820 | -0.01666 | 0.03040 | 0.01732 | 4.35E-09 | 0.33629 |
| 120 | rs1906672 | A | G | 0.29660 | -0.00833 | 0.03580 | 0.01658 | 1.20E-16 | 0.61535 |
| 121 | rs1957563 | T | C | 0.36290 | 0.02896 | 0.03420 | 0.01551 | 2.32E-26 | 0.06182 |
| 122 | rs1984195 | A | G | 0.24090 | 0.02478 | 0.03030 | 0.01388 | 1.77E-15 | 0.07421 |
| 123 | rs1994158 | G | A | -0.25130 | -0.02028 | 0.03910 | 0.01753 | 1.23E-10 | 0.24741 |
| 124 | rs2014408 | T | C | 0.51690 | -0.00885 | 0.03730 | 0.01793 | 1.26E-43 | 0.62161 |
| 125 | rs2024385 | A | T | -0.26420 | 0.00815 | 0.03060 | 0.01450 | 5.88E-18 | 0.57386 |
| 126 | rs2111557 | T | C | 0.17640 | 0.00660 | 0.03020 | 0.01422 | 5.22E-09 | 0.64269 |
| 127 | rs2126474 | T | G | -0.26010 | 0.01753 | 0.03060 | 0.01412 | 1.87E-17 | 0.21456 |
| 128 | rs2129869 | T | A | 0.26430 | 0.01111 | 0.03610 | 0.01681 | 2.44E-13 | 0.50869 |
| 129 | rs2161967 | G | T | -0.28360 | -0.03187 | 0.03070 | 0.01623 | 2.87E-20 | 0.04962 |
| 130 | rs2177843 | T | C | 0.43940 | 0.02860 | 0.04320 | 0.01963 | 2.80E-24 | 0.14518 |
| 131 | rs2238787 | A | G | 0.25520 | 0.02932 | 0.03320 | 0.01653 | 1.45E-14 | 0.07614 |
| 132 | rs2249105 | G | A | -0.29270 | 0.00537 | 0.03130 | 0.01427 | 7.63E-21 | 0.70671 |
| 133 | rs2276153 | G | C | -0.32960 | -0.01564 | 0.03510 | 0.01656 | 6.56E-21 | 0.34487 |
| 134 | rs2283500 | C | A | -0.31060 | -0.01675 | 0.04810 | 0.02205 | 1.08E-10 | 0.44759 |

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|---|---|---|---|---|---|---|---|---|---|
| 135 | rs2291434 | T | G | -0.26220 | -0.01596 | 0.03030 | 0.01394 | 5.10E-18 | 0.25232 |
| 136 | rs2291516 | A | G | 0.37080 | 0.00230 | 0.05050 | 0.03220 | 2.17E-13 | 0.94307 |
| 137 | rs2353940 | C | T | 0.20750 | 0.04521 | 0.03580 | 0.02298 | 6.85E-09 | 0.04916 |
| 138 | rs2354862 | C | A | -0.25070 | -0.00251 | 0.03170 | 0.01429 | 2.42E-15 | 0.86053 |
| 139 | rs2392929 | G | T | 0.75070 | 0.02474 | 0.03790 | 0.01975 | 1.96E-87 | 0.21044 |
| 140 | rs246973 | T | C | 0.24790 | -0.00617 | 0.03350 | 0.01586 | 1.45E-13 | 0.69725 |
| 141 | rs2470004 | T | C | -0.34540 | 0.00066 | 0.03920 | 0.01761 | 1.28E-18 | 0.97024 |
| 142 | rs2493134 | C | T | 0.37360 | 0.04754 | 0.03090 | 0.01415 | 1.10E-33 | 0.00078 |
| 143 | rs2493296 | T | C | 0.41830 | 0.07896 | 0.04420 | 0.02330 | 3.14E-21 | 0.00070 |
| 144 | rs2498323 | A | G | 0.31710 | 0.06681 | 0.05170 | 0.02667 | 8.51E-10 | 0.01223 |
| 145 | rs2580350 | A | G | 0.17690 | 0.00745 | 0.03070 | 0.01621 | 8.39E-09 | 0.64566 |
| 146 | rs2589218 | C | T | 0.22580 | 0.01206 | 0.03390 | 0.01596 | 2.54E-11 | 0.45005 |
| 147 | rs2598 | G | A | -0.16800 | 0.02735 | 0.03030 | 0.01539 | 2.87E-08 | 0.07548 |
| 148 | rs2610990 | G | A | 0.29030 | 0.06052 | 0.03430 | 0.01554 | 2.86E-17 | 0.00010 |
| 149 | rs2627313 | T | C | 0.32080 | 0.02236 | 0.03030 | 0.01399 | 3.55E-26 | 0.11000 |
| 150 | rs263532 | C | T | -0.17980 | -0.02918 | 0.03070 | 0.01618 | 4.72E-09 | 0.07126 |
| 151 | rs2652812 | T | C | -0.25160 | -0.01783 | 0.03530 | 0.01637 | 1.03E-12 | 0.27605 |
| 152 | rs2724377 | G | A | -0.19380 | -0.00359 | 0.03010 | 0.01391 | 1.29E-10 | 0.79663 |
| 153 | rs2760748 | A | T | 0.36260 | 0.06445 | 0.05090 | 0.02321 | 1.05E-12 | 0.00549 |
| 154 | rs2776037 | C | T | 0.18510 | 0.01420 | 0.03090 | 0.01624 | 2.15E-09 | 0.38173 |
| 155 | rs2801008 | G | T | 0.18760 | 0.00065 | 0.03240 | 0.01556 | 7.37E-09 | 0.96667 |
| 156 | rs2833834 | A | C | 0.21770 | 0.00139 | 0.03380 | 0.01532 | 1.22E-10 | 0.92783 |
| 157 | rs28572357 | C | A | 0.27330 | 0.02661 | 0.03080 | 0.01403 | 6.34E-19 | 0.05780 |

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|---|---|---|---|---|---|---|---|---|---|
| 158 | rs28650790 | T | C | 0.22870 | 0.05357 | 0.03870 | 0.01815 | 3.30E-09 | 0.00315 |
| 159 | rs28866311 | G | T | 0.27620 | 0.01619 | 0.03020 | 0.01407 | 5.45E-20 | 0.24973 |
| 160 | rs2904315 | G | A | 0.20810 | 0.02498 | 0.03250 | 0.01517 | 1.58E-10 | 0.09976 |
| 161 | rs2913920 | T | C | 0.24180 | 0.02645 | 0.03590 | 0.01794 | 1.62E-11 | 0.14030 |
| 162 | rs2957688 | A | G | 0.34720 | 0.01482 | 0.03040 | 0.01433 | 2.74E-30 | 0.30085 |
| 163 | rs3098186 | T | C | -0.24220 | 0.01426 | 0.03030 | 0.01397 | 1.41E-15 | 0.30738 |
| 164 | rs3104552 | C | T | -0.24490 | 0.01491 | 0.03030 | 0.01428 | 6.31E-16 | 0.29633 |
| 165 | rs34025993 | G | A | -0.22300 | 0.00014 | 0.03080 | 0.01440 | 4.71E-13 | 0.99241 |
| 166 | rs34072724 | A | G | -0.24220 | -0.04243 | 0.03030 | 0.01382 | 1.37E-15 | 0.00214 |
| 167 | rs34727427 | C | T | 0.23530 | 0.00978 | 0.03240 | 0.01578 | 4.02E-13 | 0.53534 |
| 168 | rs34917849 | C | G | 0.31240 | 0.05326 | 0.04540 | 0.02013 | 5.97E-12 | 0.00817 |
| 169 | rs34941092 | A | G | -0.32250 | -0.01141 | 0.04250 | 0.02317 | 3.23E-14 | 0.62244 |
| 170 | rs35098810 | C | A | -0.19670 | -0.00344 | 0.03560 | 0.01620 | 3.20E-08 | 0.83183 |
| 171 | rs35444 | G | A | -0.43680 | 0.00500 | 0.03100 | 0.01579 | 3.47E-45 | 0.75138 |
| 172 | rs35783704 | A | G | -0.46190 | -0.04343 | 0.05070 | 0.02388 | 8.81E-20 | 0.06904 |
| 173 | rs365990 | G | A | -0.22500 | -0.02253 | 0.03120 | 0.02079 | 5.95E-13 | 0.27848 |
| 174 | rs3735533 | C | T | 0.91000 | 0.01270 | 0.05770 | 0.02729 | 5.29E-56 | 0.64158 |
| 175 | rs3764400 | C | T | -0.37480 | -0.01855 | 0.04450 | 0.02295 | 3.69E-17 | 0.41910 |
| 176 | rs3772219 | C | A | -0.27330 | -0.02852 | 0.03240 | 0.01743 | 3.10E-17 | 0.10187 |
| 177 | rs3802517 | A | T | 0.25270 | 0.01139 | 0.03010 | 0.01384 | 4.65E-17 | 0.41053 |
| 178 | rs3807925 | G | A | 0.18590 | 0.00320 | 0.03190 | 0.02001 | 5.39E-09 | 0.87297 |
| 179 | rs3815460 | G | C | 0.28500 | 0.01778 | 0.05000 | 0.02400 | 1.21E-08 | 0.45887 |
| 180 | rs3819532 | C | T | 0.18750 | 0.02781 | 0.03060 | 0.01416 | 9.44E-10 | 0.04947 |

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|---|---|---|---|---|---|---|---|---|---|
| 181 | rs3828282 | G | C | -0.18570 | -0.02300 | 0.03180 | 0.02280 | 5.29E-09 | 0.31300 |
| 182 | rs3845811 | G | C | 0.29420 | 0.00652 | 0.03090 | 0.01572 | 1.88E-21 | 0.67856 |
| 183 | rs3860770 | A | G | -0.26630 | -0.01000 | 0.03330 | 0.01494 | 1.20E-15 | 0.50335 |
| 184 | rs3950627 | A | C | 0.18510 | 0.00995 | 0.03080 | 0.02105 | 1.82E-09 | 0.63638 |
| 185 | rs3980686 | T | G | -0.49980 | -0.03015 | 0.04870 | 0.02166 | 1.03E-24 | 0.16392 |
| 186 | rs4143175 | C | T | -0.21870 | -0.02241 | 0.03520 | 0.01638 | 5.10E-10 | 0.17116 |
| 187 | rs4245599 | G | A | 0.17940 | -0.00156 | 0.03050 | 0.01397 | 4.03E-09 | 0.91103 |
| 188 | rs4260863 | G | C | -0.19110 | -0.02502 | 0.03140 | 0.01433 | 1.17E-09 | 0.08077 |
| 189 | rs4284362 | A | C | -0.22560 | -0.01299 | 0.03380 | 0.01567 | 2.61E-11 | 0.40704 |
| 190 | rs4408839 | G | A | 0.23010 | -0.07056 | 0.03450 | 0.01622 | 2.42E-11 | 0.00001 |
| 191 | rs4440615 | A | G | -0.22010 | 0.00864 | 0.03120 | 0.01422 | 1.87E-12 | 0.54331 |
| 192 | rs4499560 | T | A | 0.21990 | 0.00395 | 0.03260 | 0.01526 | 1.46E-11 | 0.79553 |
| 193 | rs4511593 | T | C | -0.28810 | 0.00212 | 0.03180 | 0.01765 | 1.28E-19 | 0.90448 |
| 194 | rs4577304 | C | T | 0.17670 | 0.00974 | 0.03020 | 0.01397 | 4.99E-09 | 0.48578 |
| 195 | rs4651224 | T | C | 0.19860 | -0.02033 | 0.03060 | 0.01409 | 9.00E-11 | 0.14885 |
| 196 | rs4734868 | G | A | 0.18440 | -0.03945 | 0.03210 | 0.01483 | 9.22E-09 | 0.00780 |
| 197 | rs4784541 | C | T | 0.20150 | -0.01132 | 0.03070 | 0.01671 | 4.93E-11 | 0.49834 |
| 198 | rs483071 | T | C | 0.27090 | -0.01445 | 0.03130 | 0.01837 | 5.09E-18 | 0.43168 |
| 199 | rs4834792 | A | T | 0.19730 | 0.03434 | 0.03030 | 0.01391 | 7.24E-11 | 0.01357 |
| 200 | rs4873492 | T | C | 0.34310 | 0.04636 | 0.04030 | 0.01817 | 1.61E-17 | 0.01075 |
| 201 | rs488834 | T | C | -0.37990 | -0.05034 | 0.03650 | 0.02490 | 2.35E-25 | 0.04323 |
| 202 | rs4888408 | A | G | 0.36530 | 0.05432 | 0.03070 | 0.01467 | 1.42E-32 | 0.00021 |
| 203 | rs4925159 | A | G | 0.21740 | -0.02959 | 0.03050 | 0.01423 | 9.66E-13 | 0.03761 |

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|---|---|---|---|---|---|---|---|---|---|
| 204 | rs4952609 | G | A | -0.21240 | -0.00921 | 0.03470 | 0.01602 | 9.60E-10 | 0.56523 |
| 205 | rs4955575 | C | A | -0.21580 | 0.02664 | 0.03480 | 0.01628 | 5.63E-10 | 0.10174 |
| 206 | rs4957026 | G | A | -0.19820 | 0.00269 | 0.03230 | 0.01477 | 8.12E-10 | 0.85539 |
| 207 | rs4961293 | T | C | 0.22680 | -0.00539 | 0.03030 | 0.01392 | 7.35E-14 | 0.69876 |
| 208 | rs4980379 | T | C | 0.57640 | 0.00466 | 0.03200 | 0.02085 | 2.47E-72 | 0.82317 |
| 209 | rs509833 | G | A | -0.32900 | -0.00912 | 0.04400 | 0.02049 | 7.08E-14 | 0.65616 |
| 210 | rs55732192 | T | G | -0.33580 | -0.04229 | 0.05210 | 0.02488 | 1.15E-10 | 0.08917 |
| 211 | rs56288724 | G | A | 0.21780 | -0.01329 | 0.03100 | 0.01981 | 2.01E-12 | 0.50220 |
| 212 | rs571689 | T | C | 0.22800 | 0.00087 | 0.03040 | 0.01587 | 6.77E-14 | 0.95642 |
| 213 | rs573455 | G | A | -0.19940 | -0.00205 | 0.03030 | 0.01433 | 4.77E-11 | 0.88635 |
| 214 | rs5742643 | C | T | 0.22330 | -0.00945 | 0.03490 | 0.01565 | 1.53E-10 | 0.54589 |
| 215 | rs57946343 | C | T | -0.71600 | -0.06321 | 0.04260 | 0.02047 | 2.10E-63 | 0.00201 |
| 216 | rs60191654 | G | A | 0.23820 | 0.00205 | 0.03850 | 0.01869 | 5.88E-10 | 0.91259 |
| 217 | rs6026578 | G | C | 0.18500 | -0.01539 | 0.03160 | 0.01492 | 4.59E-09 | 0.30218 |
| 218 | rs6026744 | T | A | 0.71310 | 0.05876 | 0.04610 | 0.02154 | 7.00E-54 | 0.00637 |
| 219 | rs604723 | C | T | 0.65500 | 0.01634 | 0.03390 | 0.01554 | 2.55E-83 | 0.29301 |
| 220 | rs6054139 | A | G | 0.20940 | -0.00095 | 0.03060 | 0.01415 | 8.23E-12 | 0.94646 |
| 221 | rs6058088 | G | T | -0.28320 | -0.01188 | 0.04170 | 0.02083 | 1.14E-11 | 0.56851 |
| 222 | rs6062324 | A | G | -0.32940 | -0.02142 | 0.03630 | 0.01771 | 1.18E-19 | 0.22646 |
| 223 | rs6078093 | A | G | -0.18490 | -0.00991 | 0.03040 | 0.01397 | 1.20E-09 | 0.47803 |
| 224 | rs6090907 | A | G | -0.38540 | -0.08817 | 0.04250 | 0.03595 | 1.29E-19 | 0.01420 |
| 225 | rs60909079 | C | G | -0.21140 | 0.00292 | 0.03510 | 0.01603 | 1.73E-09 | 0.85526 |
| 226 | rs60991988 | G | T | -0.37890 | -0.03036 | 0.04980 | 0.02327 | 2.82E-14 | 0.19208 |

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|---|---|---|---|---|---|---|---|---|---|
| 227 | rs6108787 | G | T | 0.42740 | 0.04049 | 0.03000 | 0.01796 | 5.38E-46 | 0.02412 |
| 228 | rs61772592 | G | A | 0.31810 | 0.06876 | 0.04550 | 0.02102 | 2.86E-12 | 0.00107 |
| 229 | rs62076622 | G | A | -0.23630 | 0.02262 | 0.03770 | 0.01697 | 3.79E-10 | 0.18250 |
| 230 | rs62082230 | A | T | -0.18840 | -0.02378 | 0.03450 | 0.05101 | 4.69E-08 | 0.64110 |
| 231 | rs62309747 | A | G | -0.22440 | -0.02387 | 0.03040 | 0.01413 | 1.59E-13 | 0.09111 |
| 232 | rs62512914 | G | A | -0.20660 | -0.00851 | 0.03060 | 0.01404 | 1.42E-11 | 0.54457 |
| 233 | rs6271 | T | C | -0.55470 | -0.00407 | 0.06110 | 0.03999 | 1.18E-19 | 0.91893 |
| 234 | rs6438857 | C | T | -0.27360 | -0.02158 | 0.03050 | 0.01411 | 3.13E-19 | 0.12630 |
| 235 | rs6445583 | A | G | 0.27740 | 0.02183 | 0.03490 | 0.01726 | 1.90E-15 | 0.20609 |
| 236 | rs6452769 | A | G | -0.31430 | 0.00016 | 0.03770 | 0.01982 | 7.82E-17 | 0.99354 |
| 237 | rs6490019 | G | A | 0.28970 | 0.01336 | 0.03090 | 0.01406 | 6.61E-21 | 0.34203 |
| 238 | rs6504213 | C | T | 0.29820 | 0.04231 | 0.03120 | 0.01501 | 1.25E-21 | 0.00482 |
| 239 | rs6540119 | T | A | -0.20160 | -0.02074 | 0.03220 | 0.01473 | 3.93E-10 | 0.15911 |
| 240 | rs658780 | G | T | 0.20280 | -0.01715 | 0.03470 | 0.01705 | 5.29E-09 | 0.31424 |
| 241 | rs665445 | A | C | -0.19090 | 0.02645 | 0.03340 | 0.01503 | 1.15E-08 | 0.07835 |
| 242 | rs66864335 | A | G | -0.39630 | -0.03804 | 0.03650 | 0.01836 | 1.79E-27 | 0.03826 |
| 243 | rs6699618 | G | C | -0.91150 | -0.02498 | 0.04100 | 0.01881 | 1.68E-109 | 0.18430 |
| 244 | rs6731373 | A | G | 0.19130 | 0.00042 | 0.03260 | 0.01864 | 4.18E-09 | 0.98214 |
| 245 | rs6732123 | C | G | -0.17370 | -0.03045 | 0.03070 | 0.01465 | 1.52E-08 | 0.03763 |
| 246 | rs6737318 | G | A | -0.23480 | -0.02936 | 0.03640 | 0.01701 | 1.13E-10 | 0.08433 |
| 247 | rs6788907 | A | G | 0.22100 | 0.00065 | 0.03390 | 0.01586 | 7.31E-11 | 0.96719 |
| 248 | rs6788984 | G | A | -0.29990 | -0.06264 | 0.04320 | 0.01972 | 3.81E-12 | 0.00149 |
| 249 | rs68085857 | T | C | 0.27400 | -0.01738 | 0.03570 | 0.01790 | 1.68E-14 | 0.33163 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 250 | rs6870654 | C | T | -0.21360 | -0.01300 | 0.03470 | 0.02033 | 7.58E-10 | 0.52251 |
| 251 | rs6892983 | A | C | 0.34270 | -0.00016 | 0.03070 | 0.01422 | 7.11E-29 | 0.99083 |
| 252 | rs6921291 | T | C | 0.35750 | -0.05247 | 0.03850 | 0.01780 | 1.58E-20 | 0.00321 |
| 253 | rs6961048 | G | C | 0.53040 | 0.04664 | 0.04970 | 0.02171 | 1.43E-26 | 0.03171 |
| 254 | rs7012866 | G | T | 0.23250 | 0.01350 | 0.03010 | 0.01407 | 1.21E-14 | 0.33711 |
| 255 | rs702395 | T | C | 0.23180 | -0.00654 | 0.03050 | 0.01837 | 3.24E-14 | 0.72170 |
| 256 | rs7026176 | T | G | -0.18690 | -0.02796 | 0.02990 | 0.02620 | 4.01E-10 | 0.28587 |
| 257 | rs7045409 | A | T | -0.18620 | 0.01011 | 0.03130 | 0.01414 | 2.55E-09 | 0.47469 |
| 258 | rs7093894 | A | C | 0.23600 | 0.04325 | 0.04270 | 0.02074 | 3.16E-08 | 0.03707 |
| 259 | rs7134677 | T | C | -0.38510 | 0.01183 | 0.03320 | 0.01548 | 4.46E-31 | 0.44458 |
| 260 | rs7154723 | A | G | 0.25300 | 0.04809 | 0.03090 | 0.01416 | 2.72E-16 | 0.00068 |
| 261 | rs7186298 | T | C | -0.23150 | -0.02562 | 0.03020 | 0.01402 | 1.88E-14 | 0.06766 |
| 262 | rs7211535 | G | A | 0.17790 | -0.00337 | 0.03040 | 0.01440 | 4.61E-09 | 0.81499 |
| 263 | rs7213273 | A | G | -0.40000 | 0.01517 | 0.03150 | 0.01458 | 6.24E-37 | 0.29810 |
| 264 | rs72719160 | T | A | 0.22430 | 0.03829 | 0.03240 | 0.01471 | 4.34E-12 | 0.00926 |
| 265 | rs72742507 | T | C | -0.20530 | -0.00222 | 0.03280 | 0.01540 | 3.80E-10 | 0.88532 |
| 266 | rs7278003 | C | T | 0.18760 | 0.04260 | 0.03040 | 0.01421 | 6.63E-10 | 0.00271 |
| 267 | rs72847885 | G | A | -0.24130 | -0.01838 | 0.03180 | 0.01482 | 3.08E-14 | 0.21470 |
| 268 | rs73103937 | C | T | -0.20510 | -0.05455 | 0.03440 | 0.01641 | 2.36E-09 | 0.00089 |
| 269 | rs7310615 | G | C | -0.58500 | -0.06983 | 0.03060 | 0.01556 | 1.32E-81 | 0.00001 |
| 270 | rs7331680 | T | G | 0.41010 | 0.04410 | 0.04230 | 0.02107 | 3.35E-22 | 0.03639 |
| 271 | rs73855810 | A | G | 0.27320 | 0.09004 | 0.04340 | 0.02009 | 3.04E-10 | 0.00001 |
| 272 | rs740746 | A | G | 0.45570 | 0.00636 | 0.03420 | 0.01868 | 1.42E-40 | 0.73345 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 273 | rs743395 | T | C | 0.25970 | 0.01167 | 0.03170 | 0.01693 | 2.55E-16 | 0.49076 |
| 274 | rs7439567 | T | C | 0.25370 | 0.03967 | 0.03090 | 0.01566 | 2.31E-16 | 0.01131 |
| 275 | rs7463212 | A | T | -0.27530 | -0.00620 | 0.03050 | 0.01427 | 1.81E-19 | 0.66389 |
| 276 | rs7491248 | A | G | 0.21630 | 0.00931 | 0.03620 | 0.01698 | 2.37E-09 | 0.58336 |
| 277 | rs7493678 | T | A | 0.18900 | 0.01743 | 0.03160 | 0.01481 | 2.31E-09 | 0.23907 |
| 278 | rs75016974 | T | C | -0.25130 | -0.06012 | 0.04390 | 0.02158 | 1.05E-08 | 0.00533 |
| 279 | rs75461554 | T | C | -0.30160 | -0.02286 | 0.03770 | 0.01678 | 1.18E-15 | 0.17318 |
| 280 | rs7555285 | C | G | 0.22940 | 0.01468 | 0.03760 | 0.01758 | 1.05E-09 | 0.40372 |
| 281 | rs75961402 | A | G | 0.26590 | 0.01350 | 0.04180 | 0.01943 | 1.95E-10 | 0.48713 |
| 282 | rs7615099 | G | A | -0.18910 | -0.01720 | 0.03210 | 0.01545 | 3.90E-09 | 0.26541 |
| 283 | rs7618284 | C | G | -0.18910 | 0.02482 | 0.03310 | 0.02082 | 1.10E-08 | 0.23322 |
| 284 | rs7683728 | T | C | -0.36540 | -0.03257 | 0.03040 | 0.01401 | 2.43E-33 | 0.02004 |
| 285 | rs7703560 | G | A | 0.22460 | 0.03721 | 0.03330 | 0.01606 | 1.51E-11 | 0.02050 |
| 286 | rs7722243 | A | G | -0.20480 | -0.03724 | 0.03020 | 0.01408 | 1.21E-11 | 0.00819 |
| 287 | rs7725413 | T | C | -0.19850 | -0.01425 | 0.03590 | 0.01654 | 3.07E-08 | 0.38909 |
| 288 | rs77375686 | G | A | 0.34670 | 0.00438 | 0.04850 | 0.02366 | 8.38E-13 | 0.85319 |
| 289 | rs7744902 | A | G | -0.40880 | -0.03231 | 0.05930 | 0.03186 | 5.64E-12 | 0.31053 |
| 290 | rs7763558 | A | G | 0.33630 | 0.00103 | 0.03210 | 0.01487 | 1.17E-25 | 0.94455 |
| 291 | rs7765526 | G | A | -0.20100 | 0.00623 | 0.03070 | 0.01426 | 5.88E-11 | 0.66210 |
| 292 | rs778124 | A | G | 0.29650 | 0.00175 | 0.03110 | 0.01441 | 1.45E-21 | 0.90356 |
| 293 | rs7796 | G | C | -0.33850 | -0.00681 | 0.03140 | 0.01384 | 5.00E-27 | 0.62273 |
| 294 | rs7821832 | G | T | -0.42220 | -0.00944 | 0.03480 | 0.01593 | 6.67E-34 | 0.55354 |
| 295 | rs78474310 | G | A | 0.46990 | 0.08911 | 0.07340 | 0.08439 | 1.51E-10 | 0.29102 |

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|---|---|---|---|---|---|---|---|---|---|
| 296 | rs786923 | T | C | -0.30820 | -0.04166 | 0.03100 | 0.01469 | 2.82E-23 | 0.00458 |
| 297 | rs78998485 | G | C | 0.24490 | -0.02803 | 0.03460 | 0.01576 | 1.48E-12 | 0.07533 |
| 298 | rs7912283 | A | G | -0.21440 | -0.01143 | 0.03220 | 0.01520 | 2.94E-11 | 0.45181 |
| 299 | rs7926110 | G | T | -0.26030 | -0.00289 | 0.03210 | 0.01486 | 5.71E-16 | 0.84600 |
| 300 | rs79384779 | T | C | 0.31790 | -0.01631 | 0.04280 | 0.02096 | 1.08E-13 | 0.43653 |
| 301 | rs7963801 | C | T | 0.23620 | -0.00571 | 0.03110 | 0.01979 | 2.87E-14 | 0.77309 |
| 302 | rs7980644 | G | A | -0.26410 | -0.01683 | 0.04040 | 0.02001 | 6.30E-11 | 0.40019 |
| 303 | rs8003103 | A | G | -0.17550 | 0.00982 | 0.03190 | 0.01492 | 3.60E-08 | 0.51054 |
| 304 | rs8044992 | C | T | -0.21380 | 0.00060 | 0.03310 | 0.02830 | 1.07E-10 | 0.98302 |
| 305 | rs8180684 | T | C | 0.21340 | 0.01987 | 0.03350 | 0.01773 | 1.80E-10 | 0.26257 |
| 306 | rs869396 | A | C | -0.21150 | -0.04381 | 0.03050 | 0.01531 | 4.12E-12 | 0.00423 |
| 307 | rs871004 | A | G | 0.23360 | 0.00121 | 0.03170 | 0.01497 | 1.65E-13 | 0.93574 |
| 308 | rs908951 | T | C | -0.22610 | 0.00510 | 0.03150 | 0.01708 | 7.14E-13 | 0.76510 |
| 309 | rs9285476 | G | C | -0.18440 | -0.07959 | 0.03330 | 0.01549 | 3.07E-08 | 0.00000 |
| 310 | rs9302885 | G | A | -0.22420 | -0.04057 | 0.03020 | 0.01534 | 1.03E-13 | 0.00818 |
| 311 | rs9327297 | G | C | -0.27470 | -0.01796 | 0.03190 | 0.01476 | 8.07E-18 | 0.22381 |
| 312 | rs9349379 | G | A | -0.26640 | 0.09298 | 0.03120 | 0.01772 | 1.31E-17 | 0.00000 |
| 313 | rs9361836 | T | C | 0.21960 | 0.01932 | 0.03240 | 0.01417 | 1.25E-11 | 0.17283 |
| 314 | rs9368222 | A | C | 0.22810 | 0.03260 | 0.03390 | 0.01586 | 1.84E-11 | 0.03976 |
| 315 | rs9401913 | A | G | 0.52020 | 0.00375 | 0.03050 | 0.01407 | 3.66E-65 | 0.78960 |
| 316 | rs9486916 | T | C | 0.26570 | -0.01491 | 0.03850 | 0.01772 | 5.42E-12 | 0.40009 |
| 317 | rs9508495 | T | C | -0.35570 | 0.03509 | 0.03530 | 0.02127 | 6.34E-24 | 0.09907 |
| 318 | rs9526707 | A | G | -0.20390 | -0.00840 | 0.03230 | 0.01713 | 2.77E-10 | 0.62410 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 319 | rs961764 | G | C | 0.19090 | 0.02829 | 0.03050 | 0.01406 | 3.74E-10 | 0.04430 |
| 320 | rs9848170 | C | G | 0.32310 | 0.00945 | 0.03070 | 0.01449 | 7.01E-26 | 0.51433 |
| 321 | rs9869437 | A | C | -0.20010 | 0.00550 | 0.03180 | 0.01478 | 3.22E-10 | 0.70971 |
| 322 | rs9876694 | T | C | 0.47130 | -0.05361 | 0.06510 | 0.03351 | 4.64E-13 | 0.10968 |
| 323 | rs9880098 | A | G | 0.30810 | 0.03268 | 0.03080 | 0.01426 | 1.59E-23 | 0.02189 |
| 324 | rs9899540 | T | A | -0.20110 | -0.02851 | 0.03160 | 0.01424 | 1.87E-10 | 0.04528 |

**Appendix Table 8. Harmonized data of triglyceride and coronary heart disease**

| NO. | SNP | EA | OA | beta.exposure | beta.outcome | se.exposure | se.outcome | pval.exposure | pval.outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1 | rs10401969 | C | T | -0.1210 | -0.1081 | 0.0065 | 0.0294 | 9.70E-70 | 0.0002 |
| 2 | rs10440120 | A | C | -0.0306 | -0.0180 | 0.0044 | 0.0198 | 5.34E-11 | 0.3617 |
| 3 | rs10501321 | C | T | -0.0216 | -0.0188 | 0.0035 | 0.0145 | 1.41E-08 | 0.1929 |
| 4 | rs10761762 | C | T | -0.0270 | 0.0137 | 0.0033 | 0.0140 | 1.06E-17 | 0.3289 |
| 5 | rs11057408 | T | G | -0.0258 | -0.0396 | 0.0035 | 0.0146 | 2.05E-12 | 0.0068 |
| 6 | rs11613352 | T | C | -0.0280 | -0.0007 | 0.0039 | 0.0157 | 9.40E-14 | 0.9656 |
| 7 | rs11974409 | G | A | -0.0899 | 0.0100 | 0.0042 | 0.0180 | 1.36E-100 | 0.5771 |
| 8 | rs12280753 | T | C | 0.1931 | 0.0562 | 0.0064 | 0.0279 | 1.22E-179 | 0.0440 |
| 9 | rs1260326 | C | T | -0.1148 | -0.0239 | 0.0034 | 0.0145 | 1.00E-200 | 0.1006 |
| 10 | rs12676857 | C | T | 0.0332 | 0.0667 | 0.0046 | 0.0198 | 7.29E-12 | 0.0008 |
| 11 | rs12678919 | G | A | -0.1702 | -0.0873 | 0.0056 | 0.0238 | 1.82E-199 | 0.0002 |
| 12 | rs12748152 | T | C | 0.0372 | 0.0415 | 0.0059 | 0.0239 | 1.10E-09 | 0.0825 |
| 13 | rs1321257 | A | G | -0.0402 | -0.0294 | 0.0034 | 0.0145 | 5.99E-31 | 0.0433 |
| 14 | rs13389219 | T | C | -0.0271 | -0.0135 | 0.0034 | 0.0142 | 2.60E-15 | 0.3427 |
| 15 | rs16948098 | A | G | 0.0800 | 0.0898 | 0.0089 | 0.0343 | 4.84E-17 | 0.0088 |
| 16 | rs174535 | C | T | 0.0470 | -0.0069 | 0.0034 | 0.0145 | 1.73E-41 | 0.6335 |
| 17 | rs17513135 | T | C | 0.0220 | 0.0147 | 0.0039 | 0.0162 | 1.63E-08 | 0.3649 |
| 18 | rs1832007 | G | A | -0.0327 | 0.0138 | 0.0047 | 0.0201 | 1.72E-12 | 0.4931 |
| 19 | rs2043085 | C | T | -0.0327 | -0.0127 | 0.0034 | 0.0150 | 7.81E-20 | 0.3965 |
| 20 | rs2068888 | A | G | -0.0241 | -0.0329 | 0.0034 | 0.0200 | 1.68E-11 | 0.0991 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 21 | rs2239520 | A | G | -0.0236 | 0.0269 | 0.0037 | 0.0144 | 4.14E-10 | 0.0618 |
| 22 | rs2247056 | C | T | 0.0378 | 0.0300 | 0.0039 | 0.0159 | 3.86E-21 | 0.0582 |
| 23 | rs2250802 | A | G | 0.0230 | 0.0081 | 0.0037 | 0.0156 | 1.21E-10 | 0.6065 |
| 24 | rs247616 | T | C | -0.0393 | -0.0365 | 0.0037 | 0.0206 | 1.12E-25 | 0.0771 |
| 25 | rs2665357 | C | A | 0.0212 | 0.0518 | 0.0033 | 0.0139 | 8.33E-10 | 0.0002 |
| 26 | rs287621 | C | T | -0.0222 | -0.0340 | 0.0037 | 0.0159 | 7.67E-09 | 0.0322 |
| 27 | rs2954022 | A | C | -0.0780 | -0.0561 | 0.0033 | 0.0139 | 2.23E-113 | 0.0001 |
| 28 | rs2972146 | T | G | 0.0281 | 0.0507 | 0.0034 | 0.0143 | 2.97E-15 | 0.0004 |
| 29 | rs3198697 | T | C | -0.0198 | -0.0171 | 0.0034 | 0.0142 | 2.21E-08 | 0.2287 |
| 30 | rs3760627 | C | T | 0.0189 | -0.0172 | 0.0034 | 0.0160 | 5.29E-09 | 0.2840 |
| 31 | rs3761445 | A | G | 0.0232 | -0.0268 | 0.0034 | 0.0143 | 8.06E-12 | 0.0614 |
| 32 | rs38855 | G | A | -0.0187 | -0.0204 | 0.0033 | 0.0141 | 2.11E-08 | 0.1465 |
| 33 | rs439401 | C | T | 0.0659 | 0.0087 | 0.0038 | 0.0289 | 1.42E-66 | 0.7635 |
| 34 | rs442177 | T | G | 0.0309 | 0.0281 | 0.0033 | 0.0141 | 1.32E-18 | 0.0463 |
| 35 | rs4587594 | A | G | -0.0694 | 0.0166 | 0.0035 | 0.0147 | 3.50E-82 | 0.2596 |
| 36 | rs4719841 | G | A | 0.0232 | -0.0128 | 0.0034 | 0.0165 | 8.86E-11 | 0.4361 |
| 37 | rs4738684 | G | A | -0.0205 | 0.0041 | 0.0035 | 0.0152 | 8.82E-09 | 0.7866 |
| 38 | rs4810479 | T | C | -0.0474 | 0.0301 | 0.0038 | 0.0165 | 2.07E-34 | 0.0682 |
| 39 | rs588136 | T | C | -0.0495 | -0.0140 | 0.0041 | 0.0176 | 3.37E-30 | 0.4274 |
| 40 | rs6029143 | T | C | -0.0388 | -0.0696 | 0.0071 | 0.0327 | 4.93E-08 | 0.0335 |
| 41 | rs634869 | C | T | -0.0272 | -0.0377 | 0.0033 | 0.0140 | 1.78E-14 | 0.0072 |
| 42 | rs645040 | T | G | 0.0293 | 0.0246 | 0.0040 | 0.0168 | 1.83E-12 | 0.1432 |
| 43 | rs676210 | A | G | -0.0733 | -0.0297 | 0.0039 | 0.0168 | 3.28E-71 | 0.0768 |
| 44 | rs6831256 | G | A | 0.0258 | 0.0255 | 0.0035 | 0.0201 | 1.60E-12 | 0.2048 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 45 | rs6882076 | C | T | 0.0286 | 0.0215 | 0.0035 | 0.0149 | 1.51E-15 | 0.1496 |
| 46 | rs6995541 | G | A | 0.0265 | -0.0354 | 0.0037 | 0.0158 | 1.34E-12 | 0.0252 |
| 47 | rs719726 | T | C | 0.0199 | 0.0097 | 0.0035 | 0.0150 | 2.49E-08 | 0.5179 |
| 48 | rs7248104 | A | G | -0.0222 | -0.0057 | 0.0034 | 0.0139 | 5.04E-10 | 0.6821 |
| 49 | rs731839 | A | G | -0.0224 | -0.0209 | 0.0036 | 0.0163 | 2.65E-09 | 0.2008 |
| 50 | rs7350481 | C | T | -0.2254 | -0.1240 | 0.0066 | 0.0279 | 1.00E-200 | 0.0000 |
| 51 | rs749671 | A | G | -0.0211 | -0.0054 | 0.0034 | 0.0141 | 6.11E-10 | 0.6996 |
| 52 | rs8077889 | C | A | 0.0252 | -0.0300 | 0.0042 | 0.0183 | 9.88E-09 | 0.1019 |
| 53 | rs948690 | C | T | -0.0306 | -0.0107 | 0.0052 | 0.0154 | 6.57E-09 | 0.4869 |
| 54 | rs9686661 | T | C | 0.0379 | 0.0536 | 0.0044 | 0.0181 | 2.54E-16 | 0.0032 |
| 55 | rs998584 | A | C | 0.0293 | 0.0481 | 0.0037 | 0.0184 | 3.42E-15 | 0.0090 |

## 국 문 요 약 (Korean Abstract)

### 과체중과 관상동맥질환의 인과 관계: MR-BASE 플랫폼을 사용한

### Two sample Mendelian Randomization

연세대학교 대학원 보건학과
김조이스

**배경 및 목적**:

생활습관 및 환경적 요인은 과체중이 될 위험성을 증가시킨다. 그러나 유전적 요인이 40%에서 85%를 차지한다. 본 연구는 멘델 무작위 분석법 (Mendelian Randomization)을 토대로 독립변수인 과체중 단일 핵산염기 다형현상(Single Nucleotide Polymorphism, SNP)과 종속변수인 관상동맥질환 단일 핵산염기 다형현상 (SNP)를 추정하여 과제중과 관상동맥지로한과의 인과적 관련성을 평가하고자 하였다.

**연구 방법:**

모든 유전 데이터는 MR-BASE 데이터베이스를 통해 일반에 공개된 GWAS (Genome-wide association study) 이차 데이터를 활용하였다. 멘델 무작위 분석에서 독립변수는 과체중으로 정하였고, 종속변수는 관상동맥질환으로 하였다. 대상자는 유럽인으로 총 158,855 이였다. 본 연구는 단변수 및 다변수 멘델 무작위 분석법을 토대로 유전적 요인이 있는 과체중 및 관상동맥질환의 총 효과 및 직접효과를 추정하였다. MR 의 가정은 다음과 같다: 도구 변수(IV)는 독립변수와 관련이 있고, IV 는 독립변수-종속변수

관계의 어떠한 교란 변수와도 연관되어서는 안 되며, 독립변수만을 통해서 종속변수와 연관 지어야 한다. Inverse-variance weighted (IVW)를 주요 분석으로 사용되었으며, MR-Egger 와 Weighted median 을 민감성 분석으로 사용하였다. MR-Egger 분석법은 민감도 분석에 도움이 되는 반면, 무작위 분석을 위해 역분산 가중법이 사용되었다. 방향성 다면 발현 가능성(Pleiotropy)을 배제시키기 위해 MR-Egger 분석법을 사용하였다.

**연구 결과:**

단변수 멘델 무작위 분석법을 토대로 하여 과체중이 관상동맥질환 위험성의 증가와 크게 관련이 있음을 확인하였다 (OR 1.21, 95% CI 1.08-1.34, p=0.0006). 이 연구를 통해 과체중 및 관상동맥질환과의 인과적 연관성을 확인하였다. 또한 유전적으로 가지고 태어난 높은 과체중 요인이 관상동맥질환 위험의 상승과 크게 연관되어 있음을 발견하였다. MR-Egger 절편분석 결과 음의 관련성이지만 통계적으로 유의하지 않기 때문에 (β=-0.003, p=0.862) 결과에 대한 방향성 수평적 다면 발현이 없음을 입증되었다. 과체중과 관상동맥질환 간의 멘델 무작위 분석 연관성이 저밀도 지질단백질, 수축기 혈압, 중성지방, 그리고 공복혈당에 기인하는지 평가하기 위해 다변수 멘델 무작위 분석을 진행하였다. 수축기 혈압 (β=0.102, p=0.138), 공복혈당 (β=0.109, p=0.108), 그리고 중성지방 (β=0.004, p=0.952)이 포함된 회귀 모형에 저밀도 지질단백질을 포함시켰을 때 과체중과 관상동맥질환 사이의 멘델 무작위 분석 연관성이 약해졌고 통계적 유의하지 않았다. 따라서 다변수 멘델 무작위 분석법으로 관상동맥질환에 대한 과체중의 독립된 인과적 경로를 보여주었다.

**결론 및 고찰:**

결론적으로, 유럽인에서 과체중은 관상동맥질환와 상당한 연관성이 있음을 발견하였다. 그러나 과체중과 관상동맥질환의 유전적 요인은 저밀도 지질단백질, 중성지방, 그리고 수축기 혈압에 영향을 받는다. 본 연구는 질병 위험성이나 향후 건강 문제를 예측하는 데 있어서 이상지질혈증 관리가 큰 영향을 미치다는 것을 밝혔다는데 큰 의미가 있다.

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**핵심어:** 멘델 무작위 분석법; 통합 변수; 과체중; 저밀도 지질단백질; 수축기 혈압; 공복혈당; 중성지방; 관상동맥질환