Sex differences in the risk of coronary heart disease associated with type 2 diabetes: a Mendelian Randomization analysis

| Complete List of Authors: | Peters, Tricia; Lady Davis Institute for Medical Research; McGill University Faculty of Medicine, Division of Endocrinology, Department of Medicine, The Jewish General Hospital
Holmes, Michael V; University of Oxford, National Institute for Health Research, Oxford Biomedical Research Centre; University of Oxford, Medical Research Council Population Health Research Unit; University of Oxford, Clinical Trial Service Unit & Epidemiological Studies Unit, Nuffield Department of Population Health; University of Bristol, Medical Research Council Integrative Epidemiology Unit
Richards, Brent; McGill University, Medicine and Human Genetics; Lady Davis Institute for Medical Research, Centre for Clinical Epidemiology
Palmer, Tom; University of Bristol, Bristol Medical School; University of Bristol, Medical Research Council Integrative Epidemiology Unit
Forgetta, Vincenzo; Lady Davis Institute for Medical Research, Centre for Clinical Epidemiology
Lindgren, Cecilia; University of Oxford, Wellcome trust centre for human genetics; Oxford University, Big Data Institute, Li Ka Shing Center for Health Information and Discovery; Broad Institute, Program in Medical and Population Genetics
Asselbergs, Folkert; Utrecht University, Department of Cardiology, Division Heart & Lungs, University Medical Center Utrecht; Utrecht University, Institute of Cardiovascular Science, Faculty of Population Health Sciences; University College London, Institute of Cardiovascular Science, Faculty of Population Health Sciences
Nelson, Christopher; University of Leicester, Department of Cardiovascular Sciences; National Institute for Health Research Leicester Biomedical Research Centre, Glenfield Hospital
Samani, Nilesh; University of Leicester, Department of Cardiovascular Science; National Institute for Health Research Leicester Biomedical Research Centre, Glenfield Hospital
McCarthy, Mark; Oxford University, Wellcome Centre for Human Genetics; Oxford University Hospitals NHS Trust, Oxford National Institute for Health Research Biomedical Research Centre; Oxford University, Oxford Centre for Diabetes, Endocrinology and Metabolism
Mahajan, Anubha; University of Oxford, Oxford Centre for Diabetes, Endocrinology and Metabolism; University of Oxford, Wellcome Centre for Human Genetics, Nuffield Department of Medicine
Davey-Smith, George; University of Bristol, Medical Research Council |

	Integrative Epidemiology Unit; University of Bristol, School of Social and Community Medicine
	Woodward, Mark; George Institute, Professorial Unit; Oxford University, The George Institute for Global Health; Johns Hopkins University, Department of Epidemiology
	O'Keeffe, Linda; University College Cork, School of Public Health; University of Bristol, Medical Research Council Integrative Epidemiology Unit
	Peters, Sanne; Utrecht University, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht; University of Oxford, George Institute for Global Health; George Institute for Global Health

Sex differences in the risk of coronary heart disease associated with type 2 diabetes: a Mendelian Randomization analysis

Sex differences in diabetes and heart disease

Tricia M. Peters, MD, PhD, Michael V. Holmes, MBBS, PhD, J. Brent Richards, MD, MSc, Tom Palmer, PhD, Vincenzo Forgetta, MSc, Cecilia M. Lindgren, PhD, Folkert W. Asselbergs, MD, PhD, Christopher P. Nelson, PhD, Nilesh J. Samani, MD, Mark I. McCarthy, MB, BChir, MD[1], Anubha Mahajan, PhD[1], George Davey Smith, MD, BChir, MSc, Mark Woodward, MSc, PhD, Linda M. O'Keeffe, PhD*, Sanne A.E. Peters, PhD*

*Denotes equal contribution

Affiliations

Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research, Montreal, QC (T.M.P., J.B.R., V.F.)

Division of Endocrinology, Department of Medicine, The Jewish General Hospital, McGill University, Montreal, QC (T.M.P., J.B.R.)

Medical Research Council Population Health Research Unit, University of Oxford, Roosevelt Drive, Oxford, UK (M.V.H.)

Clinical Trial Service Unit & Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK (M.V.H.)

National Institute for Health Research, Oxford Biomedical Research Centre, Oxford University Hospital, Oxford, UK (M.V.H.)

Medical Research Council Integrative Epidemiology Unit, University of Bristol, Oakfield House, Oakfield Grove, Bristol, UK (M.V.H., T.P., G.D.S., L.M.O.K.)

Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK (T.P.)

Big Data Institute, Li Ka Shing Center for Health Information and Discovery, Oxford University, Oxford, UK (C.M.L.)

Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK (C.M.L, A.M., M.I.M.)

Program in Medical and Population Genetics, Broad Institute, Boston, MA, USA (C.M.L.)

Department of Cardiology, Division Heart & Lungs, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands (F.W.A.)

Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, United Kingdom (F.W.A.)

Health Data Research UK and Institute of Health Informatics, University College London, London, United Kingdom (F.W.A.)

Department of Cardiovascular Sciences, University of Leicester, Leicester, UK (C.P.N., N.J.S.)

National Institute for Health Research Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, UK (C.P.N., N.J.S.)

Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Churchill Hospital, University of Oxford, Oxford, UK (M.I.M., A.M.)

Oxford National Institute for Health Research Biomedical Research Centre, Oxford University Hospitals Trust, Oxford, UK (M.I.M.)

School of Social and Community Medicine, University of Bristol, Bristol, UK (G.D.S.)

The George Institute for Global Health, University of Oxford, Oxford, UK (M.W., S.A.E.P.)

The George Institute for Global Health, University of New South Wales, Sydney, Australia (M.W., S.A.E.P.)

Department of Epidemiology, Johns Hopkins University, Baltimore MD, USA (M.W.)

School of Public Health, University College Cork, Ireland (L.M.O.K.)

Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht,

The Netherlands (S.A.E.P.)

[1]Current address: Genentech, 1 DNA Way, South San Francisco, CA 94080

Contact for correspondence:

Dr. Tricia M. Peters

Centre for Clinical Epidemiology, Room H-450

Lady Davis Institute, Jewish General Hospital

3755 Cote Ste Catherine

Montreal, Quebec H3T 1E2

CANADA

Telephone number: 514-340-8222 x 28391

Fax number: 514-340-7529

Email address: tricia.peters@mcgill.ca

Total word count: 3689

3 Tables

1 Supplementary Figure, 3 Supplementary Tables

Abstract

Objective: Observational studies have demonstrated that type 2 diabetes is a stronger risk factor for coronary heart disease (CHD) in women compared with men. However, it is not clear whether this reflects a sex differential in the causal effect of diabetes on CHD risk or results from sex-specific residual confounding.

Methods: Using 270 single nucleotide polymorphisms (SNPs) for type 2 diabetes identified in a type 2 diabetes genome-wide association study, we performed a sex-stratified Mendelian randomization (MR) study of type 2 diabetes and CHD using individual participant data in UK Biobank (N=251,420 women and 212,049 men). Weighted-median, MR Egger, MR-PRESSO and radial MR from summary-level analyses were used for pleiotropy assessment.

Results: MR analyses showed that genetic risk of type 2 diabetes increased the odds of CHD for women (odds ratio [OR] 1.13, 95% confidence interval [CI] 1.08-1.18 per 1-log unit increase in odds of type 2 diabetes) and men (OR 1.21, 95% CI 1.17-1.26 per 1-log unit increase in odds of type 2 diabetes). Sensitivity analyses showed some evidence of directional pleiotropy, however, results were similar after correction for outlier SNPs.

Conclusions: This MR analysis supports a causal effect of genetic liability to type 2 diabetes on risk of CHD that is not stronger for women than men. Assuming a lack of bias, these findings suggest that the prevention and management of type 2 diabetes for CHD risk reduction is of equal priority in both sexes.

4

Introduction

Type 2 diabetes is a major risk factor for coronary heart disease (CHD)(1). Meta-analysis of observational studies demonstrates that type 2 diabetes is associated with a 44% greater relative risk of CHD in women compared with men(2). However, whether this reflects sex differences in the causal effect of type 2 diabetes on CHD or arises from confounding in observational studies is not well understood. Most observational studies adjust for traditional cardiovascular risk factors, yet novel biomarkers, social and behavioral factors, or women-specific risk factors, such as gestational diabetes, are not generally adjusted for and may explain some of the sex difference(3–5). Sex differences in screening for and treatment of type 2 diabetes might also contribute to the greater excess risk of CHD conferred by type 2 diabetes among women relative to men(6).

Mendelian randomization (MR) analysis exploits the natural random allocation of genetic variants at conception and is an increasingly utilized approach that can limit potential confounding in human research(7). Under the assumption that differences in the risk of disease arising from genotype mimic changes in the risk of disease acquired during life, MR can be used to detect causal effects. Recent MR studies support a causal relationship between genetic predisposition to type 2 diabetes and CHD(8,9). However, these studies did not evaluate sex differences in the causal role of type 2 diabetes in CHD risk. If type 2 diabetes has a stronger causal effect on CHD risk in women compared with men, randomly allocated genetic variants that are risk alleles for type 2 diabetes should also be more strongly associated with the risk of CHD in women than in men. Therefore, in this study we conducted a MR analysis to examine the sex-specific causal effect of the genetic risk of type 2 diabetes on CHD.

Methods

Data sources and study participants

Data from the UK Biobank and a consortium of genome-wide association studies (GWAS) for type 2 diabetes were used. The UK Biobank is a large prospective study of over 500,000 individuals(10). Baseline data collection in the UK Biobank was conducted between 2006 and 2010 across 22 assessment centers. Participants aged 37 to 73 completed touchscreen questionnaires, were interviewed by trained research nurses, had physical measurements taken and blood samples extracted and frozen. The presence of type 2 diabetes and CHD was self-reported at study baseline and confirmed by a trained nurse. Genotyping was performed using the Affymetrix UK BiLEVE Axiom array or the Affymetrix UK Biobank Axiom® array. A combined reference panel including UK10K samples was used for imputation(11). In accordance with the National Research Ethics Service and the governing Research Ethics Committee of UK Biobank, generic Research Tissue Bank approval was obtained, and study participants provided written informed consent(10).

For the present study, we included individual-participant data on 463,469 UK Biobank participants who had concordant genetic and self-reported sex, who clustered with the Great Britain population in 1000 Genomes(12), whose genetic data was of sufficient quality(13), and who provided data on type 2 diabetes and CHD at baseline. Individuals with self-reported type 1 diabetes, gestational diabetes only, or a diabetes diagnosis prior to the age of 18 were excluded. CHD was defined as self-reported history of angina or myocardial infarction, and linkage with hospital admissions data and the national death register was used to also identify incident diagnoses of CHD after the baseline visit using international classification of disease (ICD) 9 or 10 codes (ICD9 410-414, ICD10 I20-I25) using follow-up data from recruitment through the end of February 2016 (mean 5.3 [SD 2.4] years), with N=3453 incident cases of CHD for women and

N=7420 incident cases for men. Myocardial infarction was also defined using the UK Biobank algorithm (https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/alg_outcome_mi.pdf).

Sex-specific summary-level data (ß-coefficients and standard errors) for the genetic contribution of type 2 diabetes risk were obtained from the European DIAMANTE (DIAbetes Meta-Analysis of Trans-Ethnic association studies) GWAS of type 2 diabetes cases (N=30,053 women and 41,846 men) and controls (N=434,336 women and 383,767 men) of European descent(14). The UK Biobank was excluded from GWAS estimates used in our analyses to avoid sample overlap.

Mendelian randomization and selection of SNPs for analyses

Mendelian randomization studies exploit the random assortment and independent inheritance of genetic variants in the population, which removes bias due to reverse causation and, if conducted appropriately, greatly reduces bias from residual or unmeasured confounding(15). However, three key assumptions must be met for genetic variants to serve as instrumental variables of an exposure in MR analyses (Supplemental Figure 1)(16). First, the variants must be associated with the exposure of interest; second, they must not be associated with confounders of the relationship between the exposure and the outcome; third, they must be independent of the outcome except for their association via the exposure. This third assumption relates to the issue of horizontal pleiotropy, in which one or more variants used in the instrumental variable influences the outcome via a pathway other than the exposure of interest. When horizontal pleiotropy has a net effect to bias the properties of the genetic instrument, the summary MR estimate can be biased either towards or away from the null. In this situation, horizontal pleiotropy leads to bias of the underlying 'true' causal effect and it is termed unbalanced horizontal, or directional, pleiotropy.

In this study, we used data from the UK Biobank for individual-participant MR analysis. SNPs with significant associations ($p<5x10^{-8}$) with type 2 diabetes from the sex-combined European DIAMANTE GWAS were selected (Supplemental Table 1). We assessed linkage disequilibrium (LD; $r^2>0.2$) using PLINK[17] on a reference panel consisting of a random selection of 50,000 individuals from UK Biobank. Of 291 genome-wide significant SNPs from the European DIAMANTE GWAS, 270 were found in UK Biobank that were bi-allelic, were not in LD, and were not derived from GWAS that adjusted for body mass index. The SNPs were aligned to the same effect allele, and effect allele frequencies were checked for concordance. These 270 SNPs were used to generate sex-specific weighted genetic risk scores as the instrumental variable for analyses[18]. Individual SNPs were coded as 0, 1, or 2 depending on the number of type 2 diabetes risk alleles. Each SNP was weighted by the corresponding sex-specific ß-coefficient obtained from the European DIAMANTE GWAS and then summed for all SNPs. This method reduces the risk of false positive results and bias toward the confounded observational association that may occur when all data (SNPs, exposure, outcome) are obtained from a single sample[19].

Statistical analysis

The strength of the genetic risk score as an instrument for type 2 diabetes was assessed using the F-statistic, where an F-statistic greater than 10 provides evidence against the possibility of bias arising due to a weak instrument[20]. The association of sex-specific genetic risk scores with potential confounders was evaluated to assess the validity of the second assumption of MR (i.e., the genetic instrument is not associated with potential confounders) and was also compared with the observational association of type 2 diabetes status with potential confounders.

Two-stage residual inclusion estimation using logistic regression at the second stage[21] and Terza standard errors[22] evaluated the association of the genetic risk scores for type 2

diabetes with CHD to estimate the odds of CHD per 1-log unit increase in the odds of type 2 diabetes. This method includes first-stage residuals to correct for endogeneity(21), since application of traditional instrumental variable estimation approaches can be problematic for models including a binary exposure and a binary outcome(23). Models were adjusted for age, genotype array, and the first four principal components of ancestry.

To assess and account for potential directional horizontal pleiotropy, we also performed summary-level MR analyses using SNP to type 2 diabetes estimates from DIAMANTE and SNP to CHD estimates in UK Biobank. For summary-level analyses, we obtained odds ratios (ORs) and 95% confidence intervals (CI) for the causal effect of a 1-log unit increase in the odds of genetic liability to type 2 diabetes on the odds of CHD using the weighted-median, MR Egger, Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO), and radial MR methods(24–27). The weighted-median method calculates a median of the SNP-specific causal estimates from the ratio method for each SNP(25). It has been shown to yield consistent estimates when the weights of up to half the instruments are not valid. The MR Egger method is equivalent to an inverse-variance weighted method but does not constrain the intercept to zero, and as such, the MR Egger estimate is the slope of the modified linear regression equation and the intercept represents the average pleiotropic effect across SNPs(24). A non-zero intercept provides evidence of unbalanced horizontal pleiotropy, and the slope of the regression coefficient should provide an estimate that is free from bias induced by unbalanced horizontal pleiotropy. Analyses were conducted using the 'MendelianRandomization' package in R Studio version 1.2.1206. The MR-PRESSO test detects and corrects for horizontal pleiotropy and was performed using the 'MRPRESSO' package in R(26). The first part of the test (MR-PRESSO global test) identifies the presence of horizontal pleiotropy, the second part corrects the causal estimate for identified

pleiotropy via outlier removal, and the third part (MR-PRESSO distortion test) tests whether the causal estimate significantly differs before and after correction. Additional analyses for pleiotropy assessment used radial MR Egger models to identify outliers in the UK Biobank analysis using the 'WSpiller/RadialMR' package in R with modified second order weights(27), and analyses were repeated after exclusion of sex-specific outliers. P-values for the test of interaction for estimates from separate analyses was used to assess interaction by sex for each analysis(28).

Results

Characteristics of the UK Biobank participants are presented in Table 1 and Supplemental Table 3. The mean age was 57 (standard deviation [SD] = 8) years and 46% of participants were men. The prevalence of type 2 diabetes was 4% in women and 8% in men. CHD was documented among 5% of women (N=12 716) and 12% of men (N=26 344), with myocardial infarction diagnosed in 1.5% of women (N=3807) and 6% of men (N=12 871). Both women and men with CHD were more likely to have traditional CHD risk factors (older age, type 2 diabetes, history of smoking, dyslipidemia, and hypertension) (Supplemental Table 3).

The sex-specific 270-SNP genetic risk score showed a strong association with type 2 diabetes in both sexes (F-statistic 683 for women and 1005 for men, Supplemental Table 2), thus satisfying the first assumption of MR that the genetic instrument is associated with the exposure. We evaluated whether the apparent difference in instrument strength by sex was due to sex differences in the prevalence of type 2 diabetes. In a random subset of UK Biobank participants with 750 cases of type 2 diabetes for both women (N=18 493) and men (N=9100), the adjusted F statistic of 47 (R-squared 0.02) for women, and adjusted F statistic 45 (R-squared 0.03) for men were similar (data not shown). Thus, because the difference in instrument strength by sex is a

product of greater prevalence of type 2 diabetes in men, it is not likely to appreciably affect the comparative validity of estimates derived from MR analyses.

Potential confounders were similarly distributed across quartiles of the genetic risk score for both women and men (Table 2). Conversely, conventional observational analyses showed that type 2 diabetes status was strongly associated with all potential confounders assessed (Table 2), highlighting the need for instrumental variables in this setting.

Individual-participant results from TSRI analyses in UK Biobank showed similar effects of genetic risk of type 2 diabetes on CHD for each sex (OR 1.13, 95% CI 1.08-1.18 for women; OR 1.21, 95% CI 1.17-1.26 for men, Table 3). Sensitivity analyses using the weighted median method showed attenuated results (OR 1.04, 95% CI 1.00-1.08 for women; OR 1.06, 95% CI 1.03-1.09 for men, Table 3). Using MR Egger, evidence of directional pleiotropy was observed in women (OR 1.01, 95% CI 0.96-1.06 and intercept 0.004, 95% CI 0.000 to 0.008, Table 3) and men (OR 1.00, 95% CI 0.96-1.04 and intercept 0.008, 95% CI 0.004 to 0.011, Table 3). Results from MR-PRESSO after outlier correction were slightly attenuated compared with those from TSRI analyses for both women (three outliers removed, OR 1.08, 95% CI 1.05-1.13) and men (five outliers removed, OR 1.13, 95% CI 1.10-1.17, Table 3). Analyses excluding SNPs from the genetic instrument that were identified as outliers by radial MR showed similar effect estimates as the TSRI results: OR 1.09, 95% CI 1.05-1.14 for women; OR 1.24, 95% CI 1.20-1.29 for men (Table 3). We employed additional measures to assess for heterogeneity based on MR-Egger regression, including the Cochran Q-test and I-squared statistic. The Q-test showed evidence of heterogeneity in the effect of type 2 diabetes SNPs on CHD for both women (Q-statistic 395.8) and men (Q-statistic 666.0). The I-squared (I^2) statistic measures heterogeneity in the genetic associations with the exposure, and results (I^2 84.7% for women and 87.1% men) showed some evidence of

heterogeneity in the associations of SNPs with type 2 diabetes. Such heterogeneity could be reflective of multiple causal pathways between type 2 diabetes and risk of CHD.

Discussion

In this MR study of the sex-specific effect of type 2 diabetes on CHD, we found that genetic predisposition to type 2 diabetes does not confer a greater excess risk of CHD for women than for men. While our results are consistent with previous sex-combined MR studies providing support for a causal role of type 2 diabetes in CHD risk(8,9), the finding that the causal effect of genetic liability to type 2 diabetes on CHD risk is not stronger for women than men is novel and differs from sex-specific estimates from the accumulated observational evidence(2). This includes a recent analysis in the UK Biobank, which showed a stronger association of type 2 diabetes with CHD for women than men(29).

There are several potential explanations for the differences between the findings of our MR study and the observational evidence. As with any observational study, studies of sex differences in the association of type 2 diabetes with CHD may not have controlled for all relevant confounders or may have controlled for confounders that were poorly measured, leading to residual confounding. If this residual confounding differs between the sexes, a sex difference in the observational association of type 2 diabetes with CHD could arise. For example, men are typically at higher absolute risk of CHD, and the prevalence of many cardiovascular risk factors is higher for men than for women(1). However, cardiovascular risk factors including type 2 diabetes appear to confer a greater relative CHD risk for women than for men in observational analyses(29). Furthermore, among individuals with type 2 diabetes compared to those without type 2 diabetes, several studies have shown that the differences in cardiovascular risk factors including blood pressure, dyslipidemia, and particularly anthropometric variables are greater among women than

men(3,6). Although women generally display a more favorable cardiometabolic risk profile than men, this favorable risk profile declines and ultimately reverses as glycemic control deteriorates(30).

Yet observational evidence of sex differences in the association of other major risk factors with CHD is not universally observed, suggesting mechanisms other than confounding alone may be involved. An alternative explanation is that sex differences in the effect of diabetes on CHD risk seen in observational studies reflect the more adverse deterioration in cardiovascular risk profile along the glucose intolerance spectrum in women than men. A recent MR study showed that the association of BMI with the risk of diabetes was stronger for women than men(31). Accordingly, a pathway of type 2 diabetes progression and glycemic dysregulation that leads to more adverse complications of diabetes for women than men may underpin the observational findings, rather than a direct sex difference in the effect of diabetes on CHD risk.

Furthermore, women may be perceived as having lower cardiovascular risk and consequently, type 2 diabetes and comorbid cardiovascular risk factors may be treated less aggressively(32,33). Guidelines for the diagnosis and treatment of type 2 diabetes and CHD are not sex-specific; our results of a similar causal association of type 2 diabetes with CHD by sex would support the notion that for a given state of glycemic dysregulation and burden of cardiovascular risk factors, prevention and management of type 2 diabetes for the reduction of CHD risk should be of equal priority for both women and men. In addition, sex-specific confounders, such as reproductive factors including gestational diabetes, are rarely adjusted for in observational studies that include both sexes; this could inflate the association of type 2 diabetes with CHD in women if the cumulative duration of the exposure to diabetes is greater, on average, among women than men. Sex-specific residual confounding may therefore explain some of the

discrepancy between the MR and observational evidence. Alternatively, the discrepancy might arise if the MR analysis does not account for genetic variation in the risk of type 2 diabetes that derives from sex chromosomes, as the GWAS data includes only autosomal SNPs. For example, a recent MR study observed a causal association of genetically determined testosterone (X chromosome) with increased type 2 diabetes risk for women but not for men(34). Multiple other mechanisms could also play a role in conferring higher CHD risks for women with type 2 diabetes compared with men independent of glucose dysregulation or diabetes, including sex differences in microvasculature such as vascular responsivity to aldosterone(35).

The diagnosis of type 2 diabetes is defined by a cut-point along a continuum of glycemia that is based on the risk of associated complications such as retinopathy(36). Accordingly, an individual with borderline glycemia who is not yet diagnosed with type 2 diabetes may display phenotypic and genetic similarity when compared to an individual with diagnosed diabetes. Exposure misclassification of this type would tend to bias individual-participant MR estimates toward the null, leading to underestimation of the MR results. In our individual-participant MR, this scenario would only affect our conclusion when pre-diabetes affected a differential proportion of women and men in the study population. Of note, this should not influence summary-level MR results as the exposure is fully defined by genotype.

There are several strengths of our study, including the use of MR, which under specific assumptions can be used to test the hypothesis that a particular risk factor is causal for an outcome(16). In accordance with the first assumption of MR, the sex-specific genetic risk scores were very strong instruments for type 2 diabetes for both women and men. Meeting the second and third assumptions of MR, the genetic risk scores were shown to be broadly independent of measured potential confounding factors. Furthermore, for both women and men, results of

sensitivity analyses after correction for outliers were similar to initial results. However, there are also limitations of our study. Although the genetic risk scores were strong instruments for type 2 diabetes, our instruments may have been underpowered to detect modest differences in sex-specific causal effects. Furthermore, our analysis used genetic risk scores derived from 270 genome-wide significant type 2 diabetes SNPs in the sex-combined European DIAMANTE GWAS(14). Genetic instruments obtained from the SNPs that are associated with type 2 diabetes in sex-specific GWAS could also have been constructed. However, the European DIAMANTE GWAS observed only one significant sex-differentiated SNP(14) and thus, the impact of the use of a sex-combined instrument is unlikely to have changed our results substantially. Moreover, such an instrument would not permit direct comparison of sex differences in the overall genetic predisposition to type 2 diabetes, but instead compares the causal effect of two distinct sex-specific instruments on CHD risk.

SNPs included in the genetic instruments for type 2 diabetes may affect CHD risk via pathways separate from their effect on type 2 diabetes risk, and these pathways could differ by sex. For example, there was some evidence of directional pleiotropy using MR Egger. However, the intercept for both men and women neared zero and MR-Egger generally lacks power. Moreover, results from outlier-robust sensitivity analyses were more similar to the overall results. This suggests that our primary results are in fact robust and that MR Egger results may have been influenced by sensitivity of this method to extreme outliers(37).

These results might reflect multiple different scenarios(38), some of which may have downstream effects on type 2 diabetes risk and may differentially affect CHD risk by sex. Taken together, we cannot exclude a sex-specific causal effect via other pathways not captured in our genetic instrument. Of note, our instrumental variables for type 2 diabetes were derived from the

DIAMANTE GWAS effect estimates without adjustment for BMI since the influence of BMI on type 2 diabetes risk may be sex-differential(31). Considering the important role of BMI in type 2 diabetes risk, adjusting for measures of adiposity in the type 2 diabetes GRS could bias a true differential effect of type 2 diabetes on CHD to the null. In addition, the UK Biobank and the European DIAMANTE GWAS used for our analyses include primarily European populations, and therefore, we cannot assess sex differences in the causal effect of type 2 diabetes with CHD across ethnicities. Furthermore, despite the large sample size of the UK Biobank, a low overall response rate of ~5.5% limits the generalizability of our results. Considering that the participating population is unlikely representative of the general UK population, as recently demonstrated(39), it is possible that our findings might be biased if there is a sex-specific selection bias that is associated with both the exposure and the outcome. Finally, a recent study demonstrated an association of autosomal loci with sex, which may introduce bias due to sex differences in study participation(40). If risk alleles for type 2 diabetes were associated with study participation in a sex-specific manner, this may have resulted in an inability to consistently detect a sex difference in the causal effect of type 2 diabetes with CHD in our MR analyses.

Conclusion

The present MR analysis supports a causal effect of type 2 diabetes on the risk of CHD, with similar effects seen between women and men. In the absence of bias, these findings suggest that the prevention and management of type 2 diabetes for the reduction of CHD risk should be of equal priority for both women and men.

Acknowledgments

Sources of Funding

Disclosures

Author Contributions

References

1.   Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Executive
        Summary: Heart Disease and Stroke Statistics—2016 Update. Circulation
        2016;133(4):447–54.

2.   Peters SAE, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart
        disease in women compared with men: a systematic review and meta-analysis of 64
        cohorts including 858,507 individuals and 28,203 coronary events. Diabetologia
        2014;57(8):1542–51.

3.   Peters SAE, Bots SH, Woodward M. Sex Differences in the Association Between
        Measures of General and Central Adiposity and the Risk of Myocardial Infarction: Results
        From the UK Biobank. J Am Heart Assoc 2018;7(5).

4.   Li J, Song C, Li C, Liu P, Sun Z, Yang X. Increased risk of cardiovascular disease in
        women with prior gestational diabetes: A systematic review and meta-analysis. Diabetes
        Res Clin Pract 2018;140:324–38.

5.   Peters TM, Pelletier R, Behlouli H, Rossi AM, Pilote L. Excess psychosocial burden in
        women with diabetes and premature acute coronary syndrome. Diabet Med
        2017;34(11):1568–74.

6.   Juutilainen A, Kortelainen S, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Gender
        difference in the impact of type 2 diabetes on coronary heart disease risk. Diabetes Care
        2004;27(12):2898–904.

7.   Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal
        inference in epidemiological studies. Hum Mol Genet 2014;23(R1):R89–98.

8.   Ross S, Gerstein HC, Eikelboom J, Anand SS, Yusuf S, Paré G. Mendelian randomization
        analysis supports the causal role of dysglycaemia and diabetes in the risk of coronary

artery disease. Eur Heart J 2015;36(23):1454–62.

9.   Ahmad OS, Morris JA, Mujammami M, Forgetta V, Leong A, Li R, et al. A Mendelian

         randomization study of the effect of type-2 diabetes on coronary heart disease. Nat

         Commun 2015;6:7060.

10.   Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK Biobank: An

         Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases

         of Middle and Old Age. PLOS Med 2015;12(3):e1001779.

11.   UK10K Consortium, Walter K, Min JL, Huang J, Crooks L, Memari Y, et al. The UK10K

         project identifies rare variants in health and disease. Nature 2015;526(7571):82–90.

12.   Kemp JP, Morris JA, Medina-Gomez C, Forgetta V, Warrington NM, Youlten SE, et al.

         Identification of 153 new loci associated with heel bone mineral density and functional

         involvement of GPC6 in osteoporosis. Nat Genet 2017;49(10):1468–75.

13.   UK Biobank. Genotyping and quality control of UK Biobank, a large-scale, extensively

         phenotyped prospective resource, 2015. Available from: http://www.ukbiobank.ac.uk/wp-

         content/uploads/2014/04/UKBiobank_genotyping_QC_documentation-web.pdf

14.   Mahajan A, Taliun D, Thurner M, Robertson NR, Torres JM, Rayner NW, et al. Fine-

         mapping type 2 diabetes loci to single-variant resolution using high-density imputation

         and islet-specific epigenome maps. Nat Genet 2018;50(11):1505–13.

15.   Evans DM, Davey Smith G. Mendelian Randomization: New Applications in the Coming

         Age of Hypothesis-Free Causality. Annu Rev Genomics Hum Genet 2015;16(1):327–50.

16.   Lawlor DA, Harbord RM, Sterne JAC, Timpson N, Davey Smith G. Mendelian

         randomization: Using genes as instruments for making causal inferences in epidemiology.

         Stat Med 2008;27(8):1133–63.

17. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. Gigascience 2015;4(1):7.

18. Burgess S, Thompson SG. Use of allele scores as instrumental variables for Mendelian randomization. Int J Epidemiol 2013; 42(4):1134–44.

19. Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample Mendelian randomization. Genet Epidemiol 2016;40(7):597–608.

20. Stock J, Yogo M, Wright J. A Survey of Weak Instruments and Weak Identification in Generalized Method of Moments. Journal of Business and Economic Statistics. 2002. Vol. 20, p. 518 – 529.

21. Palmer TM, Holmes M V, Keating BJ, Sheehan NA. Correcting the Standard Errors of 2-Stage Residual Inclusion Estimators for Mendelian Randomization Studies. Am J Epidemiol 2017;186(9):1104–14.

22. Terza J V. Simpler Standard Errors for Two-stage Optimization Estimators. Stata J Promot Commun Stat Stata 2016;16(2):368–85.

23. Burgess S, Thompson SG, CRP CHD Genetics Collaboration. Methods for meta-analysis of individual participant data from Mendelian randomisation studies with binary outcomes. Stat Methods Med Res 2016;25(1):272–93.

24. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 2015;44(2):512–25.

25. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. Genet Epidemiol 2016;40(4):304–14.

26.   Verbanck M, Chen C-Y, Neale B, Do R. Detection of widespread horizontal pleiotropy in

        causal relationships inferred from Mendelian randomization between complex traits and

        diseases. Nat Genet 2018;50(5):693–8.

27.   Bowden J, Spiller W, Del Greco M F, Sheehan N, Thompson J, Minelli C, et al.

        Improving the visualization, interpretation and analysis of two-sample summary data

        Mendelian randomization via the Radial plot and Radial regression. Int J Epidemiol

        2018;47(4):1264–78.

28.   Altman DG, Bland JM. Interaction revisited: The difference between two estimates. BMJ

        2003;326(7382):219.

29.   Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial

        infarction: cohort study of UK Biobank participants. BMJ 2018;363:k4247.

30.   Peters SAE, Huxley RR, Sattar N, Woodward M. Sex Differences in the Excess Risk of

        Cardiovascular Diseases Associated with Type 2 Diabetes: Potential Explanations and

        Clinical Implications. Curr Cardiovasc Risk Rep 2015;9(7):36.

31.   Censin JC, Peters SAE, Bovijn J, Ferreira T, Pulit SL, Mägi R, et al. Causal relationships

        between obesity and the leading causes of death in women and men. PLoS Genet.

        2019;15(10).

32.   Eapen ZJ, Liang L, Shubrook JH, Bauman MA, Bufalino VJ, Bhatt DL, et al. Current

        quality of cardiovascular prevention for Million Hearts: An analysis of 147,038

        outpatients from The Guideline Advantage. Am Heart J 2014;168(3):398–404.

33.   Zhao M, Vaartjes I, Graham I, Grobbee D, Spiering W, Klipstein-Grobusch K, et al. Sex

        differences in risk factor management of coronary heart disease across three regions.

        Heart 2017;103(20):1587–94.

34. Ruth KS, Day FR, Tyrrell J, Thompson DJ, Wood AR, Mahajan A, et al. Using human genetics to understand the disease impacts of testosterone in men and women. Nat Med 2020;26(2):252–8.

35. Haas A V., Rosner BA, Kwong RY, Rao AD, Garg R, Di Carli MF, et al. Sex differences in coronary microvascular function in individuals with type 2 diabetes. Diabetes 2019;68(3):631–6.

36. Colagiuri S, Lee CMY, Wong TY, Balkau B, Shaw JE, Borch-Johnsen K, et al. Glycemic Thresholds for Diabetes-Specific Retinopathy: Implications for diagnostic criteria for diabetes. Diabetes Care 2011;34(1):145–50.

37. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. Eur J Epidemiol 2017;32(5):377–89.

38. Holmes M V, Davey Smith G. Can Mendelian Randomization Shift into Reverse Gear? Clin Chem 2019;65(3):363–6.

39. Batty GD, Gale CR, Kivimäki M, Deary IJ, Bell S. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. BMJ. 2020;368:m131.

40. Pirastu N, Cordioli M, Nandakumar P, Mignogna G, Abdellaoui A, Hollis B, et al. Genetic analyses identify widespread sex-differential participation bias. bioRxiv 2020 Jan 1;2020.03.22.001453. Available from: http://biorxiv.org/content/early/2020/03/23/2020.03.22.001453.abstract

Table 1. Population Characteristics, UK Biobank (N=463 469)

	Women (N=251 420)		Men (N=212 049)	
Age, mean (SD*), years	56.6	(7.95)	57.0	(8.12)
Array type, No. (%)				
BiLEVE	24 920	(9.9)	24 897	(11.7)
Axiom	226 489	(90.1)	187 147	(88.3)
Type 2 diabetes, No. (%)	9964	(4.0)	16 917	(8.0)
Body mass index, mean (SD), kg/m^2	27.0	(5.1)	27.9	(4.2)
Waist circumference, mean (SD), cm	84.6	(12.5)	97.1	(11.4)
Smoking history, No. (%)				
Never	146 521	(58.3)	102 139	(48.2)
Previous	81 252	(32.3)	82 970	(39.1)
Current	22 574	(9.0)	26 011	(12.3)
Dyslipidemia, No. (%)	25 549	(10.2)	33 843	(16.0)
Hypertension, No. (%)	57 721	(23.0)	64 668	(30.5)
Systolic BP†, mean (SD), mmHg	135.3	(19.1)	141.1	(17.4)
Diastolic BP, mean (SD), mmHg	80.5	(9.9)	84.0	(9.9)
Coronary heart disease, No. (%)	12 716	(5.1)	26 344	(12.4)
Myocardial infarction, No. (%)	3807	(1.5)	12 871	(6.0)
Angina, No. (%)	4864	(1.9)	10 219	(4.8)

*SD: standard deviation; †BP: blood pressure

Table 2. Association of sex-specific genetic risk scores (270 SNPs*) for type 2 diabetes, by quartile, with potential confounders, and association of observational type 2 diabetes with potential confounders in the UK Biobank.

Women

	Genetic type 2 diabetes risk (Quartiles of genetic risk score)				Type 2 diabetes diagnosis (Observational association)	
Quartile range	Q1	Q2	Q3	Q4	No Diabetes	Diabetes
	13.82-<15.94	15.94-<16.31	16.31-<16.68	16.68-<18.71		
No. participants	62 856	62 854	62 855	62 855	241 456	9964
Height, mean (SD†), cm	162.8 (6.2)	162.6 (6.3)	162.5 (6.2)	162.5 (6.3)	162.7 (6.2)	161.4 (6.3)
Weight, mean (SD), kg	70.8 (13.8)	71.3 (13.9)	71.6 (14.0)	72.0 (14.1)	70.9 (13.5)	84.6 (18.2)
Body mass index, mean (SD), kg/m²	26.7 (5.1)	27.0 (5.1)	27.1 (5.2)	27.3 (5.2)	26.8 (5.0)	32.5 (6.6)
Waist, mean (SD), cm	83.7 (12.3)	84.3 (12.4)	84.8 (12.5)	85.5 (12.7)	84.0 (12.0)	99.1 (14.8)
Current smoking, N (%)	5543 (8.8)	5564 (8.9)	5755 (9.2)	5781 (9.2)	21 585 (8.9)	1058 (10.6)
Dyslipidemia, N (%)	5796 (9.2)	6108 (9.7)	6497 (10.3)	7148 (11.4)	51 833 (21.5)	5888 (59.1)
Hypertension, N (%)	13 190 (21.0)	14 032 (22.3)	14 769 (23.5)	15 730 (25.0)	22 024 (9.1)	3525 (35.4)
Type 2 diabetes, N (%)	1204 (1.9)	1898 (3.0)	2560 (4.1)	4302 (6.8)		
Coronary heart disease, N (%)	3008 (4.8)	3077 (5.0)	3247 (5.2)	3348 (5.3)	10 823 (4.5)	1893 (19.0)

Men

	Genetic type 2 diabetes risk (Quartiles of genetic risk score)				Type 2 diabetes diagnosis (Observational association)	
Quartile range	Q1	Q2	Q3	Q4	No Diabetes	Diabetes
	14.58-<16.67	16.67-<17.05	17.05-<17.43	17.43-19.54		
No. participants	53 014	53 011	53 012	53 012	195 132	16 917
Height, mean (SD), cm	176.0 (6.8)	175.8 (6.8)	175.8 (6.8)	175.7 (6.8)	175.9 (6.8)	174.7 (6.8)
Weight, mean (SD), kg	85.9 (14.4)	86.0 (14.3)	86.3 (14.3)	86.5 (14.2)	85.4 (13.7)	95.4 (17.5)
Body mass index, mean (SD), kg/m²	27.7 (4.3)	27.8 (4.3)	27.9 (4.3)	28.0 (4.2)	27.6 (4.0)	31.2 (5.2)
Waist, mean (SD), cm	96.8 (11.5)	96.9 (11.4)	97.2 (11.3)	97.4 (11.2)	96.2 (10.8)	106.3 (13.2)
Current smoking, N (%)	6417 (12.1)	6492 (12.2)	6670 (12.6)	6555 (12.4)	23 931 (12.3)	2203 (13.0)

Diabetes Care

Dyslipidemia, N (%)	7925 (14.9)	8349 (15.7)	8473 (16.0)	9096 (17.2)	Dyslipidemia, N (%)	27 627 (14.2)	10 749 (63.5)
Hypertension, N (%)	15 205 (28.7)	15 784 (29.8)	16 386 (30.9)	17 293 (32.6)	Hypertension, N (%)	53 919 (27.6)	6216 (36.7)
Type 2 diabetes, N (%)	2157 (4.1)	3248 (6.1)	4495 (8.5)	7017 (13.2)	Type 2 diabetes, N (%)		
Coronary heart disease, N (%)	6136 (11.6)	6512 (12.3)	6663 (12.6)	7033 (13.3)	Coronary heart disease, N (%)	21 132 (10.8)	5212 (30.8)

*SNP: single nucleotide polymorphism; †SD: standard deviation

Table 3. Mendelian randomization analysis of type 2 diabetes and risk of coronary heart disease, by sex, in UK Biobank*. Results indicate the increased risk of coronary heart disease per 1-log unit increase in genetic risk of type 2 diabetes (odds ratio [OR] and 95% confidence interval [CI]).

	Women		Men	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Two-stage residual inclusion estimation[†]	1.13 (1.08-1.18)	5.84×10^{-08}	1.21 (1.17-1.26)	2.31×10^{-24}
Weighted-median[‡.]	1.04 (1.00-1.08)	0.067	1.06 (1.03-1.09)	<0.001
MR-Egger[‡]	1.01 (0.96-1.06)	0.81	1.00 (0.96-1.04)	0.99
MR PRESSO (outlier-corrected)[‡]	1.08 (1.05-1.13)	3.11×10^{-05}	1.13 (1.10-1.17)	1.57×10^{-12}
Sex-specific outliers removed[†‡§]	1.09 (1.05-1.14)	6.76×10^{-05}	1.24 (1.20-1.29)	2.78×10^{-27}
	Intercept (95% CI)	p-value	Intercept (95% CI)	p-value
MR-Egger (intercept)[‡]	0.002 (0.000-0.008)	0.027	0.008 (0.004, 0.011)	<0.001
Q-test[‡]	395.8		666.0	
I-squared[‡]	84.7%		87.1%	

*Genetic instrument comprised of N=270 SNPs for type 2 diabetes identified in European DIAMANTE GWAS.

[†]Results from two-stage residual inclusion estimation using individual participant data and weighted genetic risk score in UK Biobank. Adjusted for age, genotype array, principle components of ancestry. P-value for interaction=0.02.

‡Results from summary-level analyses using SNP-type 2 diabetes estimates from DIAMANTE GWAS (excluding UK Biobank) and SNP-CHD estimates from UK Biobank. P-values for interaction: weighted median 0.43; MR-Egger 0.76; MR-PRESSO 0.07.

§Analysis with type 2 diabetes genetic instrument comprised of N=258 SNPs for women and N=245 SNPs for men, after SNPs identified as sex-specific outliers using radial MR excluded from genetic instrument. P-value for interaction <0.001.

Supplemental Figure 1.
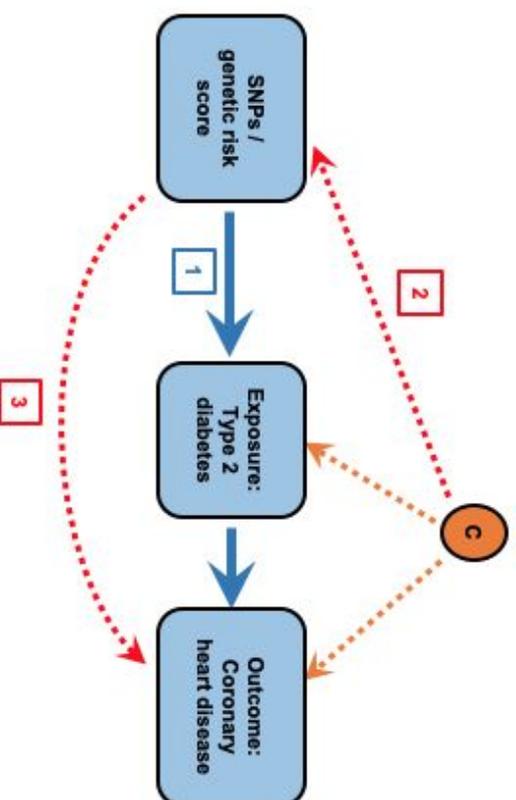
Assumptions of Mendelian randomization: 1) The variants must be associated with the exposure of interest; 2) The variants must not be associated with confounders of the relationship between the exposure and the outcome; 3) The variants must be independent of the outcome except for their association via the exposure. SNP: single nucleotide polymorphism; C: Confounders

Supplemental Table 1. Details of the 270 single nucleotide polymorphisms (SNP) used as a genetic instrument for type 2 diabetes in Mendelian randomization analyses. Beta coefficients and standard errors (SE) for the association of each SNP with type 2 diabetes from the European DIAMANTE genome-wide association study. Outlier SNPs identified using radial MR.

SNP*	Locus	Chr†	Effect Allele	Non-effect Allele	WOMEN		MEN		OUTLIER‡
					Beta	SE	Beta	SE	
rs1005752	HMG20A	15	A	C	0.082	0.013	0.076	0.012	W,M
rs1096633	LPL	8	C	T	0.086	0.019	0.056	0.017	W
rs10097617	TP53INP1	8	T	C	0.05	0.012	0.043	0.011	
rs10193538	BNIPL	2	T	G	0.025	0.012	0.033	0.011	
rs10195252	GRB14/COBLL1	2	T	C	0.066	0.012	0.036	0.011	
rs10228066	DGKB	7	T	C	0.058	0.012	0.061	0.011	
rs10406327	PEPD	19	C	G	0.01	0.012	0.043	0.011	
rs10406431	GIPR	19	A	G	0.041	0.012	0.06	0.011	W
rs1042725	HMGA2	12	T	C	0.053	0.012	0.04	0.011	
rs1061810	HSD17B12	11	A	C	0.041	0.013	0.078	0.012	
rs10750397	ETS1	11	A	G	0.031	0.013	0.053	0.012	
rs1057283	CDKN2A/B	9	T	C	0.017	0.012	0.029	0.011	
rs1830963	MTNR1B	11	G	C	0.1	0.013	0.1	0.013	
rs1842994	KLHDC5	12	C	T	0.079	0.015	0.089	0.014	
rs1882101	HHEX/IDE	10	T	C	0.1	0.012	0.11	0.011	
rs1893829	ETS1	11	T	C	0.022	0.017	0.06	0.016	
rs1908278	HNF1B	17	T	A	0.052	0.012	0.083	0.011	
rs10937721	WFS1	4	C	G	0.071	0.012	0.096	0.011	
rs10938398	GNPDA2	4	A	G	0.056	0.012	0.042	0.011	
rs10954772	PURG	8	T	C	0.037	0.013	0.026	0.012	
rs10962	HNF1B	17	C	G	0.021	0.015	0.053	0.014	
rs10974438	GLIS3	9	C	A	0.035	0.013	0.055	0.012	

Diabetes Care

rs1042596	INS/IGF2	11	G	T	0.057	0.013	0.032	0.012	
rs11063028	CCND2	12	C	T	0.046	0.016	0.057	0.015	M
rs11070332	LTK	15	A	G	0.045	0.013	0.044	0.012	
rs1137820	MTND2P8	9	C	G	0.026	0.012	0.059	0.011	
rs11257655	CDC123/CAMK1D	10	T	C	0.08	0.014	0.09	0.013	
rs127215	PTGFRN	1	C	T	0.048	0.012	0.046	0.011	
rs11496066	FBXL13	7	T	C	0.049	0.016	0.037	0.015	
rs11505614	PAM	5	T	C	0.15	0.029	0.17	0.026	M
rs1642430	FAM57B	16	G	C	0.034	0.012	0.048	0.011	
rs11680058	FAM49A	2	A	G	0.049	0.019	0.056	0.018	
rs11688682	GLI2	2	G	C	0.072	0.014	0.036	0.013	
rs1699802	CEBPB	20	C	T	0.037	0.012	0.041	0.011	
rs17001013	YWHAH	22	C	T	0.07	0.022	0.03	0.02	
rs11708067	ADCY5	3	A	G	0.1	0.015	0.08	0.014	
rs1709077	PPARG	3	G	A	0.11	0.019	0.11	0.017	
rs17483894	TCF12	15	G	A	0.12	0.031	0.077	0.029	
rs1759026	CENPW	6	G	A	0.062	0.014	0.059	0.013	W
rs1820019	CCND1	11	T	C	0.1	0.04	0.15	0.038	
rs1842871	HMGB1	13	G	T	0.051	0.014	0.028	0.013	
rs1926707	KIF9	3	C	T	0.048	0.013	0.029	0.012	
rs11967262	VEGFA	6	G	C	0.035	0.013	0.039	0.011	W
rs2001437	UBAP2	9	C	T	0.047	0.012	0.043	0.011	
rs2048743	DSTYK	1	G	C	0.043	0.012	0.039	0.011	
rs2140153	PATJ	1	G	T	0.065	0.021	0.039	0.02	
rs12454712	BCL2A	18	T	C	0.051	0.013	0.045	0.012	
rs260326	GCKR	2	C	T	0.047	0.012	0.062	0.012	
rs2640250	LCORL	4	C	A	0.054	0.013	0.035	0.013	
rs2680028	TRHR	8	C	G	0.042	0.012	0.023	0.011	
rs2719778	BOP1	8	T	C	0.028	0.012	0.031	0.011	
rs2811407	FBRSL1	12	A	G	0.05	0.014	0.043	0.013	
rs12910825	PRC1	15	G	A	0.053	0.013	0.055	0.012	
rs12920022	SPG7	16	A	T	0.051	0.017	0.042	0.016	

rs1296328	PABPC4L	4	A	C	0.02	0.012	0.034	0.011	
rs13024606	GRB14/COBLL1	2	T	C	0.05	0.029	0.074	0.028	
rs13041756	NKX2.2	20	C	T	0.088	0.019	0.063	0.018	
rs13085136	SHOI	3	C	T	0.05	0.025	0.058	0.023	
rs316776	DMGDH	5	C	A	0.041	0.013	0.059	0.012	M
rs13426680	CYTIP	2	A	G	0.13	0.026	0.034	0.023	
rs1359790	SPRY2	13	G	A	0.057	0.013	0.085	0.013	
rs1737	PTPN9	15	G	T	0.04	0.014	0.044	0.014	
rs377807	ZZEF1	17	C	G	0.059	0.013	0.054	0.012	W
rs140242150	TCF7L2	10	A	G	0.25	0.11	0.22	0.11	
rs426371	WSCD2	12	G	A	0.059	0.014	0.035	0.013	
rs45678014	QSER1	11	G	T	0.15	0.032	0.1	0.029	M
rs41521721	PDE3B	11	A	C	0.11	0.04	0.085	0.039	
rs412234	LINGO2	9	C	T	0.061	0.013	0.032	0.012	
rs45904381	FAM63A	1	T	C	0.11	0.061	0.3	0.056	
rs49364428	CPQ	8	A	G	0.27	0.061	0.18	0.058	
rs1493694	NOTCH2	1	T	C	0.084	0.019	0.087	0.018	M
rs531583	PCGF3	4	T	G	0.11	0.028	0.095	0.026	
rs561927	PVT1	8	C	T	0.038	0.013	0.046	0.013	
rs562396	KLF14	7	G	A	0.081	0.013	0.029	0.012	
rs580278	SLC9B1	4	C	A	0.052	0.012	0.029	0.011	
rs7013314	UBE2E2	3	G	A	0.13	0.033	0.12	0.031	
rs1708302	JAZF1	7	C	T	0.086	0.012	0.097	0.011	
rs7122772	SLC7A7	14	G	C	0.038	0.015	0.043	0.014	
rs7168486	DGKB	7	T	C	0.052	0.015	0.07	0.014	
rs7250977	ANKH	5	G	A	0.12	0.034	0.099	0.033	M
rs7261179	ITGA1	5	T	C	0.038	0.012	0.041	0.011	
rs7522122	AKAP6	14	T	G	0.031	0.012	0.045	0.011	
rs7684074	WDR7	18	G	C	0.033	0.014	0.046	0.013	M
rs7689007	MSRA	8	G	A	0.056	0.012	0.037	0.011	
rs17045	NEUROG3	10	G	A	0.064	0.013	0.054	0.012	

SNP	Gene	Chr							
rs1772814	CASC11	8	G	A	0.081	0.024	0.12	0.022	
rs1791513	TLE4	9	A	G	0.094	0.025	0.12	0.022	
rs1802463	DTNB	2	G	T	0.037	0.014	0.043	0.013	
rs1819328	PPARG	3	G	T	0.035	0.012	0.029	0.011	
rs1783541	MAP3K11	11	T	C	0.076	0.015	0.036	0.014	
rs17836088	NRXN3	14	C	G	0.058	0.015	0.049	0.014	
rs1796330	TSPAN8/LGR5	12	G	C	0.049	0.012	0.062	0.011	
rs1800574	HNF1A	12	T	C	0.16	0.036	0.18	0.033	
rs1800961	HNF4A	20	T	C	0.17	0.032	0.11	0.029	
rs1801645	PIM3	22	C	T	0.041	0.014	0.045	0.013	
rs184509201	TCF7L2	10	C	G	0.18	0.052	0.15	0.048	
rs1903002	FAM13A	4	G	C	0.032	0.012	0.05	0.011	
rs2028150	CEP68	2	C	G	0.045	0.012	0.059	0.011	
rs2066827	CDKN1B	12	G	T	0.022	0.016	0.055	0.015	
rs2102278	USP46	4	G	A	0.038	0.013	0.011	0.012	
rs2197973	USP44	12	T	C	0.031	0.012	0.02	0.011	
rs2237895	KCNQ1	11	C	A	0.068	0.013	0.098	0.012	
rs2237897	KCNQ1	11	C	T	0.16	0.033	0.19	0.029	
rs2238689	GIPR	19	C	T	0.04	0.013	0.037	0.012	
rs2249105	CEP68	2	A	G	0.046	0.013	0.057	0.012	W
rs2258238	HMGA2	12	T	A	0.13	0.02	0.084	0.019	
rs2268078	RALY	20	A	G	0.029	0.013	0.051	0.012	M
rs2272163	ROBO2	3	C	A	0.044	0.012	0.033	0.012	
rs2280141	PLEKHA1	10	T	G	0.039	0.012	0.071	0.011	
rs2283220	KCNQ1	11	A	G	0.041	0.014	0.024	0.012	
rs2307111	POC5	5	T	C	0.07	0.012	0.039	0.011	
rs231349	KCNQ1	11	T	C	0.078	0.02	0.053	0.019	
rs231361	KCNQ1	11	A	G	0.052	0.014	0.06	0.013	M
rs243024	BCL11A	2	A	G	0.044	0.012	0.068	0.011	
rs2431115	ANKRD55	5	A	G	0.024	0.012	0.026	0.011	
rs2456530	ONECUT1	15	T	C	0.028	0.018	0.042	0.017	
rs2581787	RFT1	3	T	G	0.043	0.012	0.039	0.011	

rsID	Gene	Chr	A1	A2					
rs2642588	NEUROG3	10	G	T	0.042	0.013	0.066	0.012	
rs2767036	PDHX	11	C	A	0.032	0.013	0.044	0.012	
rs2796441	TLE1	9	G	A	0.034	0.012	0.069	0.011	
rs279744	ARL15	5	C	A	0.049	0.013	0.03	0.012	
rs2800733	SOG43	6	A	G	0.028	0.014	0.061	0.013	
rs2820446	LYPLAL1	1	C	G	0.068	0.013	0.057	0.012	M
rs28505901	GPSM1	9	G	A	0.076	0.016	0.086	0.015	
rs2872246	ABCC5	3	A	C	0.03	0.012	0.029	0.011	
rs2819812	PDGFC	4	C	A	0.032	0.015	0.05	0.014	
rs291367	GNG4	1	G	A	0.058	0.014	0.045	0.013	
rs2925979	CMIP	16	T	C	0.094	0.013	0.039	0.012	
rs2972144	IRS1	2	G	A	0.089	0.013	0.11	0.012	M
rs3111316	FARSA	19	A	G	0.053	0.012	0.025	0.011	
rs3217792	CCND2	12	C	T	0.08	0.024	0.1	0.022	
rs3217860	CCND2	12	G	A	0.042	0.014	0.051	0.013	
rs329122	PHF15	5	A	G	0.024	0.012	0.041	0.011	
rs340874	PROX1	1	C	T	0.049	0.012	0.07	0.011	
rs3298980	LRFN2	6	T	C	0.035	0.013	0.024	0.012	
rs34454109	TSHZ2	20	A	T	0.054	0.014	0.047	0.013	W
rs34584161	RNF6	13	A	G	0.025	0.014	0.068	0.013	M
rs34715063	RASGRP1	15	C	T	0.043	0.02	0.066	0.018	M
rs348330	ABCB10	1	G	A	0.032	0.013	0.058	0.012	
rs34855406	MLX	17	C	G	0.047	0.013	0.035	0.013	
rs34855922	TCF7L2	10	A	G	0.017	0.014	0.044	0.013	
rs34965774	KSR2	12	A	G	0.039	0.017	0.069	0.016	
rs3352848	UBE2E2	3	T	C	0.056	0.015	0.052	0.014	
rs35895680	TTLL6	17	C	A	0.05	0.013	0.05	0.012	M
rs35913461	TMEM18	2	C	T	0.06	0.016	0.042	0.015	
rs35999103	PABPC1P2	2	T	C	0.047	0.016	0.019	0.015	
rs362307	HTT	4	T	C	0.092	0.023	0.044	0.021	
rs3751837	CLUAP1	16	T	C	0.058	0.015	0.029	0.013	
rs3768321	MACF1	1	T	G	0.086	0.015	0.084	0.014	

Diabetes Care

rs3772071	RBMS1	2	T	C	0.055	0.013	0.044	0.013	
rs3774723	PSMD6	3	G	A	0.046	0.017	0.052	0.015	
rs3798519	TFAP2B	6	C	A	0.057	0.015	0.036	0.014	
rs3802177	SLC30A8	8	G	A	0.1	0.013	0.11	0.012	
rs3810291	ZC3H4	19	A	G	0.042	0.013	0.05	0.012	M
rs3811978	ITGA1	5	G	A	0.028	0.016	0.054	0.015	M
rs3845281	ANKH	5	G	A	0.068	0.021	0.058	0.019	
rs3887925	ST6GAL1	3	T	C	0.052	0.012	0.051	0.011	
rs39328	RELN	7	T	C	0.033	0.012	0.024	0.011	M
rs4148856	MPHOSPH9	12	C	G	0.053	0.015	0.049	0.014	
rs429358	TOMM40/APOE	19	T	C	0.079	0.018	0.1	0.016	W, M
rs457053	ZBED3	5	G	A	0.065	0.013	0.067	0.012	
rs465002	ANKRD55	5	C	T	0.068	0.014	0.069	0.013	
rs4281707	FTO	16	G	A	0.028	0.012	0.029	0.011	
rs4279506	IGF2BP3	7	G	C	0.028	0.012	0.04	0.011	
rs4238013	CCND2	12	C	T	0.062	0.015	0.059	0.014	
rs4486471	LPP	3	C	T	0.058	0.012	0.047	0.011	
rs4688760	RBM6	3	T	C	0.027	0.013	0.039	0.012	
rs4709746	QKI	6	C	T	0.059	0.018	0.051	0.017	
rs474513	SLC22A3	6	A	G	0.043	0.012	0.032	0.011	W
rs4776970	MAP2K5	15	A	T	0.05	0.013	0.058	0.012	
rs4804833	MAP2K7	19	A	G	0.045	0.013	0.04	0.012	
rs4810426	HNF4A	20	T	C	0.092	0.019	0.072	0.018	
rs4925109	RAI1	17	A	G	0.066	0.013	0.038	0.012	
rs4929965	INS/IGF2	11	A	G	0.066	0.013	0.056	0.012	
rs4932265	AP3S2	15	T	C	0.052	0.013	0.078	0.013	
rs4946812	BEND3	6	G	A	0.038	0.013	0.036	0.012	
rs4977213	BOP1	8	C	T	0.05	0.013	0.044	0.012	
rs505922	ABO	9	C	T	0.066	0.013	0.056	0.012	
rs5213	KCNJ11	11	C	T	0.083	0.012	0.058	0.011	
rs523288	MC4R	18	T	A	0.037	0.014	0.041	0.013	
rs52835091	WDR72	15	G	C	0.31	0.078	0.27	0.075	

rs539515	SEC16B	1	C	A	0.082	0.015	0.028	0.014	
rs55759341	INS/IGF2	11	C	G	0.32	0.1	0.32	0.099	
rs55653563	ZNF169	9	A	C	0.042	0.013	0.048	0.013	
rs56337234	MAEA	4	C	T	0.067	0.013	0.039	0.012	
rs56348580	HNF1A	12	G	C	0.069	0.013	0.085	0.012	M
rs57235767	MTNR1B	11	C	T	0.038	0.013	0.046	0.012	
rs57327348	XKR6	8	A	T	0.068	0.015	0.043	0.014	
rs5758223	EP300	22	A	G	0.04	0.013	0.028	0.012	
rs576674	KL	13	G	A	0.061	0.016	0.061	0.015	
rs58432198	FAF1	1	C	T	0.041	0.019	0.061	0.018	
rs58730668	ACSL1	4	T	C	0.074	0.017	0.072	0.016	
rs601945	MHC	6	G	A	0.077	0.016	0.074	0.015	
rs6027648	ACE	17	T	C	0.042	0.018	0.061	0.017	
rs6063048	EYA2	20	G	A	0.044	0.013	0.039	0.013	
rs6070625	GNAS	20	G	C	0.03	0.012	0.041	0.011	
rs6167547	BPTF	17	C	G	0.05	0.015	0.082	0.014	
rs6207683	MARK3	14	G	T	0.035	0.013	0.031	0.012	
rs6080313	COMMD9	18	C	T	0.06	0.018	0.053	0.018	
rs62107261	TMEM18	2	T	C	0.13	0.032	0.071	0.029	
rs62271373	TSC22D2	3	A	T	0.12	0.028	0.052	0.026	
rs62492368	AOC1	7	A	G	0.044	0.013	0.037	0.012	
rs6458354	VEGFA	6	C	T	0.039	0.013	0.07	0.012	
rs6459733	MNX1	7	G	C	0.057	0.013	0.057	0.012	M
rs649961	SLC12A8	3	T	C	0.022	0.012	0.054	0.011	
rs6518681	MTMR3/ASCC2	22	G	A	0.096	0.023	0.09	0.021	
rs6545714	BNIPL	2	G	A	0.04	0.012	0.022	0.011	
rs660191	ITFG3	16	T	C	0.062	0.016	0.06	0.015	
rs6708643	THADA	2	A	G	0.032	0.012	0.037	0.011	
rs67232546	ETS1	11	T	C	0.059	0.015	0.049	0.014	
rs6821438	SMARCAD1	4	A	G	0.048	0.012	0.044	0.011	M
rs6884702	MRPS30	5	G	A	0.05	0.012	0.045	0.011	
rs6885132	ANKH	5	C	G	0.051	0.021	0.055	0.02	

Diabetes Care

rs6976111	CTTNBP2	7	A	C	0.033	0.015	0.03	0.014	
rs7022807	HAUS6	9	G	A	0.056	0.012	0.023	0.011	
rs702634	ARL15	5	A	G	0.056	0.013	0.054	0.012	
rs703972	ZMIZ1	10	G	C	0.061	0.012	0.059	0.011	
rs715753	CRY2	11	A	G	0.03	0.012	0.039	0.011	
rs7124681	ELF1	11	A	C	0.047	0.012	0.02	0.011	
rs7137253	NF1	17	C	T	0.045	0.025	0.11	0.024	
rs7178762	USP3	15	C	T	0.028	0.012	0.045	0.011	
rs718314	ITPR2	12	G	A	0.05	0.014	0.034	0.013	
rs7222481	GLP2R	17	C	G	0.044	0.013	0.03	0.012	
rs7240767	LAMA1	18	C	T	0.045	0.012	0.025	0.012	
rs7249758	UHRF1	19	A	G	0.044	0.015	0.04	0.014	
rs7280342	BCAR1	16	C	A	0.088	0.023	0.14	0.022	W
rs72926932	TCF4	18	C	A	0.085	0.021	0.087	0.02	
rs73226260	HNF1A	12	G	A	0.084	0.037	0.097	0.034	
rs738408	PNPLA3	22	T	C	0.037	0.014	0.066	0.013	
rs74452128	MC4R	18	C	A	0.17	0.042	0.14	0.038	
rs74653713	MBNL1	3	C	A	0.083	0.03	0.091	0.027	
rs75253922	INSR	19	C	T	0.041	0.015	0.029	0.015	
rs76263492	CACNA2D3	3	T	G	0.047	0.029	0.11	0.028	
rs7629630	EGFEM1P	3	A	T	0.041	0.017	0.065	0.016	
rs7645517	ST6GAL1	3	A	G	0.011	0.026	0.066	0.025	
rs76549217	ANKH	5	T	C	0.11	0.041	0.074	0.039	
rs7669833	TMEM154	4	T	A	0.044	0.013	0.07	0.012	
rs7689563	CCND2	12	T	G	0.42	0.056	0.51	0.052	
rs7719891	RASA1	5	G	A	0.034	0.014	0.046	0.013	
rs7744186	CENTD2/ARAP1	11	A	C	0.09	0.017	0.1	0.015	
rs7756992	CDKAL1	6	G	A	0.15	0.013	0.14	0.012	M
rs77864822	RMST	12	A	G	0.075	0.025	0.065	0.023	
rs78020297	FTO	16	A	G	0.041	0.028	0.038	0.025	
rs7867635	FOCAD	9	C	T	0.029	0.012	0.041	0.011	
rs7918400	TCF7L2	10	C	T	0.0092	0.012	0.021	0.011	

SNP	Gene	Chr							
rs7968284	PROX1	1	C	G	0.15	0.035	0.17	0.033	
rs7987740	IRS2	13	T	C	0.042	0.012	0.013	0.011	
rs8010382	SMEK1	14	G	A	0.042	0.013	0.035	0.012	
rs80147536	THADA	2	A	T	0.08	0.021	0.16	0.02	
rs8017808	CLEC14A	14	G	T	0.043	0.014	0.015	0.013	
rs8032939	RASGRP1	15	C	T	0.058	0.014	0.026	0.013	
rs8037894	C2CD4A/B	15	G	C	0.046	0.012	0.051	0.011	
rs8046545	ATP2A1	16	G	A	0.033	0.013	0.028	0.012	
rs8107974	TM6SF2	19	T	A	0.061	0.022	0.11	0.021	M
rs862320	NFAT5	16	C	T	0.028	0.012	0.023	0.011	
rs878521	GCK	7	A	G	0.065	0.014	0.072	0.013	W
rs917195	CRHR2	7	C	T	0.055	0.015	0.052	0.014	
rs9379084	RREB1	6	G	A	0.099	0.02	0.051	0.019	
rs9430095	SRGAP2	1	C	G	0.015	0.012	0.043	0.011	
rs9494624	SLC35D3	6	A	G	0.041	0.013	0.059	0.012	
rs9505097	RREB1	6	C	T	0.032	0.015	0.054	0.014	
rs9537803	PCDH17	13	C	T	0.03	0.013	0.03	0.013	
rs9563615	SRGAP2D	13	A	T	0.032	0.013	0.023	0.012	
rs963740	DLEU1	13	A	T	0.024	0.013	0.056	0.013	
rs9687832	ANKRD55	5	A	G	0.076	0.015	0.041	0.014	
rs9828772	TMCC1	3	C	G	0.057	0.021	0.071	0.019	
rs9860730	ADAMTS9	3	A	G	0.067	0.013	0.066	0.012	M
rs9873618	SLC2A2	3	G	A	0.056	0.013	0.095	0.013	M
rs9957145	GRP	18	G	A	0.036	0.016	0.037	0.015	

*SNP: single nucleotide polymorphism
†Chr: Chromosome
‡Outliers identified using radial MR; W: women; M: men

Supplemental Table 2. Association of sex-specific genetic risk scores for type 2 diabetes with type 2 diabetes[*]. Genetic risk score comprised of 270 SNPs from the European DIAMANTE genome-wide association study.

	Women		Men	
F statistic	683		1077	
R-squared	0.02		0.03	
Odds ratio (95% confidence interval)[†]	1.70	(1.66-1.73)	1.70	(1.67-1.73)

[*]Adjusted for age, genotype array, and four principal components of ancestry.
[†]Odds ratios for the risk of type 2 diabetes per standard deviation increase in type 2 diabetes genetic risk score.

Supplemental Table 3: Population Characteristics, UK Biobank (N=463 469), stratified by sex

and coronary heart disease status.

	Women (N=251 420)				Men (N=212 049)			
	Without CHD (N=238 704)		With CHD (N=12 716)		Without CHD (N=185 705)		With CHD (N=26 344)	
Age, mean (SD*), years	56.3	(8.0)	61.6	(6.1)	56.3	(8.2)	61.5	(6.2)
Array type, No. (%)								
BiLEVE	23 257	(9.7)	1663	(13.1)	21 256	(11.4)	3641	(13.8)
Axiom	215 436	(90.3)	11 053	(86.9)	164 446	(88.9)	22 701	(86.2)
Type 2 diabetes, No. (%)	8071	(3.3)	1893	(14.9)	11 705	(6.3)	5212	(19.8)
Body mass index, mean (SD), kg/m^2	26.9	(5.1)	29.3	(5.8)	27.7	(4.2)	29.1	(4.6)
Waist circumference, mean (SD), cm	84.2	(12.3)	90.8	(13.8)	96.5	(11.1)	100.9	(12.0)
Smoking history, No. (%)								
Never	140 460	(58.8)	6061	(47.7)	93 156	(51.8)	8983	(34.1)
Previous	76 325	(32.0)	4927	(38.7)	69 566	(37.5)	13 404	(50.9)
Current	20 937	(8.8)	1637	(12.9)	22 237	(12.0)	3774	(14.3)
Dyslipidemia, No. (%)	21 515	(9.0)	4034	(31.7)	24 773	(13.3)	9070	(34.4)
Hypertension, No. (%)	51 335	(21.5)	6386	(50.2)	51 029	(27.5)	13 639	(51.8)
Systolic BP†, mean (SD), mmHg	135.1	(19.1)	140.1	(19.7)	141.0	(17.2)	141.4	(18.7)
Diastolic BP, mean (SD), mmHg	80.6	(9.9)	79.8	(10.5)	84.3	(9.8)	81.7	(10.6)

*SD: standard deviation; †BP: blood pressure