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Type 2 Diabetes, Metabolic traits and Risk of Heart Failure: a Mendelian Randomization study

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Short Title: Genetic Liability to Type 2 Diabetes and Heart Failure

ABSTRACT

Objective

The aim of this study was to use Mendelian randomization (MR) techniques to estimate the causal relationships between genetic liability to type 2 diabetes, glycaemic traits and risk of HF.

Research Design and Methods

Summary-level data were obtained from genome-wide association studies (GWAS) of type 2 diabetes, insulin resistance (IR), glycated haemoglobin, fasting insulin and glucose and HF. MR was conducted using the inverse variance weighted (IVW) method. Sensitivity analyses included MR-Egger, weighted median and mode methods, and multivariable MR conditioning on potential mediators.

Results

Genetic liability to type 2 diabetes was causally related to higher risk of HF (OR: 1.13 per 1 log-unit higher risk of type 2 diabetes; 95% CI 1.11-1.14, $p < 0.001$), however sensitivity analysis revealed evidence of directional pleiotropy. The relationship between type 2 diabetes and HF was attenuated when adjusted for coronary disease, body mass index, LDL-cholesterol and blood pressure. Genetically-instrumented higher IR was associated with higher risk of HF (OR 1.19 per 1 log-unit higher risk of IR; 95% CI 1.00-1.41, $p = 0.041$). There were no notable associations identified between fasting insulin, glucose or glycated haemoglobin and risk of HF. Genetic liability to HF was causally linked to higher risk of type 2 diabetes (OR 1.49; 95% CI 1.01-2.19, $p = 0.042$) though again with evidence of pleiotropy.

Conclusions

These findings suggest a causal role of type 2 diabetes and IR in HF aetiology, though both the presence of bidirectional effects and directional pleiotropy highlight potential sources of bias that need to be considered.

Type 2 diabetes and heart failure (HF) are increasingly common scourges. The worldwide prevalence of type 2 diabetes is almost 10%(1) while the estimated prevalence of HF is 2.2% in the United States.(2) While type 2 diabetes and HF frequently co-exist, their causal inter-relationship is poorly understood. Observational studies have shown that patients with type 2 diabetes have a 2 to 3-fold increased risk of developing HF compared to individuals without type 2 diabetes independent of other risk factors such as coronary heart disease; the prevalence of HF at baseline in recent type 2 diabetes clinical trials has ranged from 10-30%.(3) Glycaemic traits related to type 2 diabetes, such as insulin resistance (IR)(4; 5) and glycated haemoglobin (HbA1c)(6) have also been independently associated with incident HF. There is some suggestion that the relationship might be bidirectional with HF being associated with higher likelihood of type 2 diabetes development, although this has been less easy to evaluate given confounding. HF patients appear to have a higher prevalence of type 2 diabetes than the general population (3) and a higher prevalence of IR.(7)

Observational analyses cannot provide evidence of causality and whether type 2 diabetes causes heart failure remains uncertain. Randomised controlled trials of interventions of glucose-lowering therapies have reported inconsistent effects on incident HF, and until recently, with sodium-glucose co-transporter 2 (SGLT2) inhibitors, treatment of type 2 diabetes had not been shown to reduce HF risk(8). It is possible that observational associations between type 2 diabetes and HF simply reflect associations with other prevalent upstream risk factors such as coronary heart disease, obesity and hypertension.

Mendelian randomisation (MR) uses data from genetic studies to estimate the unconfounded relationships between exposures and outcomes. By using genetic variants associated with exposures, the causal effect of the exposure on an outcome excluding confounders can be estimated.(9; 10) Multivariable MR techniques can also be used to take into account potential pleiotropic effects of genetic variants to estimate direct effects.(11)

The aim of this study was to use MR techniques to shed light on the relationships of metabolic risk factors and type 2 diabetes with risk of HF.

METHODS

Data Sources

Two-sample MR was performed using published summary-level data from GWASs of the traits of interest in predominantly European individuals. Details of the GWAS datasets are given in

Supplementary Table 1. Exposures of interest were type 2 diabetes, insulin resistance, HbA1c, fasting insulin, fasting glucose and HF. For type 2 diabetes, we used two GWAS datasets. First, we selected 529 variants significantly (at $p < 5 \times 10^{-8}$) associated with type 2 diabetes from a GWAS from the DIAMANTE consortium of 228,499 type 2 diabetes cases and 1,178,783 controls (**Supplementary Table 2**).⁽¹²⁾ T2D cases were variably defined using physician diagnosis, self-reported use of T2D medications, elevated fasting glucose or glycated haemoglobin or ICD coding, either alone or in combination, as described in the main GWAS papers. We were unable to obtain summary-level data for the DIAMANTE GWAS, so in order to perform multivariable MR analyses we used an earlier T2D GWAS from the DIAGRAM consortium of 74,124 T2D cases and 824,006 controls of European ancestry, selecting 234 variants associated with T2D at GWAS significance (**Supplementary Table 3**).⁽¹³⁾ Variants associated with insulin resistance were obtained from a GWAS of 188,577 individuals published by the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC).⁽¹⁴⁾ In the MAGIC GWAS, the authors identified variants associated with the combined phenotype of higher fasting insulin and triglyceride levels and lower HDL-cholesterol. Because this study did not publish beta estimates and standard errors for the association of each SNP with a combined IR phenotype, these were obtained from a subsequent MR study (**Supplementary Table 4**).⁽¹⁵⁾ Variants associated with the individual traits fasting insulin, fasting glucose and HbA1c were also obtained from GWAS published by the MAGIC investigators (**Supplementary Table 5-7**).^(16; 17)

Variants associated with HF were obtained from a GWAS of 47,309 cases and 930,014 controls published by the Heart Failure Molecular Epidemiology for Therapeutic Targets (HERMES) consortium (**Supplementary Table 8**).⁽¹⁸⁾ This GWAS included HF samples from population cohorts and case-

control studies. The full details of each contributing cohort have been published previously. To identify HF cases, of the 25 participating studies, physician diagnosis of HF was used by 18 cohorts, ICD coding for HF by 12, imaging by 15, HF treatment by 8 and natriuretic peptides by one cohort. 20 of the 25 cohorts used a combination of at least two of these diagnostic criteria, while the remaining 5 studies used ICD coding alone.

An observational estimate of the association between type 2 diabetes and incident HF was performed using individual level data from the Genetics of Diabetes Audit and Research Tayside Scotland (GoDARTS) study, the details of which have been published previously.⁽¹⁹⁾ Briefly, GoDARTS is a cohort study including 10,149 patients with type 2 diabetes and 8,157 controls without type 2 diabetes. All patients provided a blood sample for genotyping at the recruitment to the study and consented for follow-up using electronic health record linkage. Diagnosis of HF cases was made where the ICD-10 code for HF (I50) was present within the first three causes of death or hospitalisation.⁽²⁰⁾ Deaths and hospitalisations were obtained from the General Register Office for Scotland (GRO) and the Scottish Morbidity Record (SMR) 01 respectively. This was supplemented by echocardiographic data from the electronic health record showing reduced left ventricular systolic function (where this had been performed for clinical reasons) and the requirement for loop diuretic treatment.

MR in the reverse direction was also performed to evaluate the association between HF and type 2 diabetes. For this analysis, SNPs associated with HF at GWAS significance in the HERMES GWAS were used as the exposure. Variants from the DIAGRAM GWAS were used as the outcome for the estimate of the association between HF and type 2 diabetes.⁽¹³⁾

Individuals participating in each of the GWAS consortia provided ethical approval to take part in the contributing studies as such no specific ethical approval was required for this study. Summary-level data from the majority of consortia are freely available for download.

Statistical Analyses

First, an observational analysis was performed using data from the GoDARTS study to determine the association between type 2 diabetes and HF incidence. We performed multivariable Cox proportional hazards regression with adjustment for age, sex, systolic blood pressure, body mass index (BMI), smoking status, prior history of MI, aspirin and statin use and total and HDL cholesterol (as LDL cholesterol is not routinely reported in this cohort). A mediation analysis was also performed using the *psych* R package to determine how much of the association between T2D and HF was mediated via prior MI, systolic blood pressure, HDL cholesterol, BMI, age and sex.

We performed MR studies to determine the association between glycaemic traits and the development of HF, and in the reverse direction to evaluate the association between HF and development of type 2 diabetes. Genetic variants associated with the exposure of interest at GWAS significance were selected as genetic instruments for each exposure. Variants were harmonized such that the effect allele was consistent across all datasets and was positively associated with the exposure traits. We pruned the genetic variants for those in linkage disequilibrium ($r^2 > 0.01$) by only including the variant with the strongest association with the exposure trait of interest. Palindromic variants were identified and corrected using allele frequencies where possible, with exclusion of variants where the major allele frequency was $> 45\%$ and thus strand orientation could not be reliably ascertained.

Throughout the manuscript, the MR estimate is expressed as an odds ratio with 95% confidence intervals. The primary analysis was performed using the inverse variance-weighted (IVW) method, whereby the genetic variant to outcome estimate is regressed on the variant to exposure estimate. IVW can give a biased estimate if the genetic instrument is invalid,(21) hence we also performed sensitivity tests using 1. The MR-Egger method, which is valid even if all variants are invalid, 2. The weighted median method, which provides a consistent estimate even when up to 50% of the information is from invalid instrumental variables and; 3. The weighted mode which produces robust estimates when the largest number of similar individual-instrument causal effect estimates arise from valid instruments, even if the most are invalid.(21-23) We also performed additional tests using the Lasso method which removes significant

outliers, and the MR-Pleiotropy Residual Sum and Outlier (PRESSO) method which downgrades outliers.(24) We performed a leave-one-out analysis to determine whether any one single variant was driving the association between T2D and HF. Previous GWAS of IR have identified that although the majority of genetic variants contribute equally to the insulin resistance phenotype, rs1011685 (near the *LPL* gene) has a much weaker effect on fasting insulin when adjusted for BMI, therefore we also performed a sensitivity analysis excluding the variant in our genetic instrument for the effect of IR on HF.(15) To formally assess the risk of bias due to sample overlap we performed a formal calculation of the F statistic using the method proposed by Burgess et al (<https://sb452.shinyapps.io/overlap>).(25)

To further explore potential pleiotropic effects of the exposure on the outcome, we also conducted a multivariable MR analysis.(11) This method takes into account the association of variants with multiple exposures to clarify the direct effects (i.e. the effects that are not mediated by other traits included in the model) of exposures on outcomes. We performed multivariable MR using the IVW method for the association between type 2 diabetes and HF adjusted for effects of variants associated with BMI (26), LDL-cholesterol (27), systolic blood pressure (SBP) (28) and coronary heart disease (CHD).(29) We also performed sensitivity analyses using multivariable median and multivariable MR-Egger methods. Power calculations for our main analyses were performed using the method of Brion et al.(30) Overall, the DIAMANTE GWAS found genetic variants accounting for around 20% of the estimated heritability of T2D. As we only used genetic variants reaching GWAS significance for our MR analyses (as opposed to the whole genome), we conservatively estimated that our MR instrument would account for half of this (i.e. 10% proportion of variance in T2D risk). For the association from T2D to HF, we had >99% power to detect an association with an odds ratio of 1.1 at an alpha of 0.05. Even at a more conservative proportion of variance estimate of 2.5%, we still had >90% to detect an association with an odds ratio of 1.1. For the association from HF to T2D, based on HF variants explaining 8.8% of the risk of HF, we also had >99% power to detect an association with an odds ratio of 1.1 at an alpha of 0.05. **Supplementary**

Figure 1 gives a visual representation of power calculations for a range of possible exposure instruments and odds ratios.

All analyses were performed using R version 3.5.1. (R Foundation for Statistical Computing, Vienna, Austria) and the packages “MendelianRandomization” and “TwoSampleMR”.

RESULTS

Observational Association between Type 2 Diabetes and Heart Failure

12,919 individuals were evaluated from the GoDARTS study including 8,329 (64.5%) with type 2 diabetes. Baseline characteristics are summarised in **Supplementary Table 9**. Over a median follow-up of 10 years there were 1,293 incident HF events. The incidence of HF was higher in type 2 diabetes individuals than in controls without type 2 diabetes (13.4% vs. 3.9%). After adjustment for clinical variables including age, sex, systolic blood pressure, prior history of MI, BMI, aspirin and statin use and total and HDL cholesterol, type 2 diabetes was associated with a higher risk of developing HF (HR 1.40; 95% CI 1.04-1.89, $p=0.028$). In mediation analysis approximately 35% of the association between T2D and HF was mediated via age, sex, history of prior MI, BMI, SBP and HDL cholesterol.

Genetic Association between Type 2 Diabetes and Heart Failure

Univariable MR analysis supported a causal role for liability to type 2 diabetes in the development of HF (IVW: DIAMANTE: 1.13 per 1 log-unit higher risk of type 2 diabetes; 95% CI 1.11-1.14, $p<0.001$; DIAGRAM: OR 1.06; 95% CI 1.03-1.09, $p<0.001$), however under sensitivity analyses, some estimates were attenuated: weighted median (DIAMANTE: OR 1.05; 95% CI 1.03-1.07, $p=0.014$; DIAGRAM: OR 1.03; 95% CI 0.99-1.07, $p=0.13$), weighted mode (DIAMANTE: OR 1.03; 95% CI 1.00-1.06, $p=0.30$; DIAGRAM: OR 1.01; 95% CI 0.98-1.05, $p=0.46$), Lasso method (DIAMANTE: OR 1.12; 95% CI 1.09-1.14, $p<0.001$; tuning parameter 0.08; DIAGRAM: OR 1.05; 95% CI 1.03-1.07, $p<0.001$; tuning parameter 0.11). The estimate from MR-Egger (DIAMANTE: OR 0.99; 95% CI 0.96-1.01, $p=0.60$; DIAGRAM: OR 0.99; 95% CI 0.94-1.04, $p=0.62$) was imprecise and provided additional evidence that

the variants used to instrument type 2 diabetes demonstrated unbalanced horizontal pleiotropy (intercept beta DIAMANTE: 0.006, se 0.001, $p < 0.001$; DIAGRAM: 0.005, se 0.002, $p < 0.001$) (**Figure 1 and Supplementary Figure 2**), also seen using the MR-PRESSO (DIAMANTE: estimate 1.13; 95% CI 1.10-1.14, $p < 0.001$; global test $p < 0.001$), although there were no outliers. Using the CAUSE model also suggested that there was pleiotropy (causal model OR 1.04; 95% CI 1.00-1.08, $p = 0.07$, difference in fit between causal model and sharing model -0.35, $p = 0.43$). Leave-one-out analysis did not suggest that any one single variant was driving the association between T2D and HF (**Supplementary Table 10**). Formal assessment revealed minimal risk of relative bias (< 0.01 regardless of overlap proportion), with an F statistic of 44.35.

Despite this evidence of horizontal pleiotropy, we explored the extent to which the IVW estimate was driven by shared risk factors. Multivariable MR revealed that the association between genetic liability to type 2 diabetes and HF was most attenuated when adjusted for CHD but persisted (OR 1.04; 95% CI 1.01-1.07, $p = 0.004$). The association between type 2 diabetes and HF was similar to the unadjusted estimate when adjusted for BMI (OR 1.06; 95% CI 1.03-1.09, $p < 0.001$); SBP (OR 1.05; 95% CI 1.02-1.07, $p < 0.001$) or LDL-cholesterol alone (OR 1.06; 95% CI 1.03-1.09, $p = 0.001$). In a full model including the type 2 diabetes variants associations with CHD, SBP, BMI and LDL-cholesterol in multivariable MR, there was attenuation of the association between type 2 diabetes and HF (OR 1.03; 95% CI 1.00-1.06, $p = 0.038$), suggesting that around half of the genetic association between type 2 diabetes and HF was explained via the association between type 2 diabetes and these traits (**Figure 2, Supplementary Table 11**). As with the univariable estimate, in sensitivity analyses there was some evidence of pleiotropy using the multivariable median method (OR 1.02; 95% CI 0.99-1.05, $p = 0.18$). Using the multivariable MR-Egger the estimate was in the same direction as the IVW estimate (OR 1.02; 95% CI 0.98-1.06, $p = 0.33$), with no evidence of horizontal pleiotropy (intercept beta 0.001; 95% CI -0.001-0.003, $p = 0.29$).

Genetic Association between Insulin Resistance, Glycaemic Traits and Heart Failure

MR results for the association of IR with HF are summarized in **Figure 2**. In univariate analysis genetically instrumented IR was related to a higher risk of HF using (IVW OR per 1-standard deviation higher IR 1.19; 95% CI 1.00-1.41, $p=0.041$), which remained the case using the weighted median method: OR 1.31; 95% CI 1.08-1.59, $p=0.006$). Consistent estimates were derived using the mode-based method (OR 1.21; 95% CI 0.99-1.50, $p=0.06$) and MR-Egger (OR 1.40; 95% CI 0.95-1.98, $p=0.053$) with no evidence of pleiotropy (intercept beta -0.004, 95% CI -0.012–0.013, p value 0.29) (**Figure 2 and Supplementary Figure 3**). In the sensitivity analysis excluding rs1011685 the IVW estimate for the causal association of IR on HF was attenuated (though directionally similar; OR 1.15; 95% CI 0.94-1.39, $p=0.17$).

We identified no convincing evidence of causal relationships between genetically-instrumented fasting insulin and HF (IVW: OR 0.87 per 1-log unit increase in mmol/l fasting insulin; 95% CI 0.63-1.19, $p=0.38$); fasting glucose and HF (IVW: OR 0.99 per 1-log unit increase in mmol/l fasting glucose; 95% CI 0.66-1.51, $p=0.98$) or HbA1c and HF (IVW: OR 1.00 per 1-log-unit % higher HbA1c; 95% CI 0.80-1.25, $p=0.99$).

Genetic Association between Heart Failure and Type 2 Diabetes

Using the IVW method, genetic liability to HF was related to a higher risk of type 2 diabetes (OR 1.49 per 1-log unit increase in the relative odds of HF; 95% CI 1.01-2.19, $p=0.042$). Consistent measures of effect were identified using weighted median (OR 1.31; 95% CI 1.15-1.51, $p<0.001$) but more weakly using the mode-based estimate (OR 1.15; 95% CI 0.98-1.35, $p=0.08$). MR-Egger demonstrated potential evidence of horizontal pleiotropy, with imprecise causal estimates and a reversal of the point estimate (OR 0.57; 95% CI 0.20-1.64, $p=0.30$, intercept beta 0.064, $p=0.059$) (**Supplementary Figure 4**).

DISCUSSION

In this Mendelian randomization study, we found evidence in potential support of causal roles of genetic liability to type 2 diabetes and insulin resistance with HF. In both cases, the relationships attenuated when

we included CAD in the analyses, suggesting that the causal effects, if real, might be partially mediated by CAD. We found potential evidence of a bidirectional relationship between HF and risk of type 2 diabetes, which, together with evidence of directional pleiotropy potentially undermines the strength and presence of this relationship. We did not find any association between genetic determinants of fasting insulin, fasting glucose or HbA1c and HF. These findings shed additional light on the relationships between type 2 diabetes, IR and HF and support the importance of the prevention of CAD in patients with type 2 diabetes to prevent development of HF.

Several observational studies have reported an association between type 2 diabetes and HF.(31) Similarly, IR has also been associated with HF in observational studies.(4) Our MR study has shown that there is a relationship between genetic variants predisposing to type 2 diabetes and HF. Although in univariate analysis we did show presence of causal effects between both type 2 diabetes and IR and risk of HF, this association was attenuated when we adjusted for the genetic association with coronary heart disease. We also found evidence of directional pleiotropy in the relationship between genetic variants associated with type 2 diabetes and HF within our analyses. This may reflect the shared pathophysiological pathways between type 2 diabetes and CHD, and CHD and HF, and/or suggests the potential presence of bias in our MR analysis. It is notable that in our multivariable MR analysis the MR-Egger intercept included zero, suggesting that inclusion of genetic variants associated with CHD, systolic blood pressure, BMI and LDL-cholesterol at least in part explain some of this directional pleiotropy. Genetic variants associated with type 2 diabetes are strongly associated with CHD(32), while genetic variants associated with CHD are strongly associated with HF.(18) If CHD is the primary cause of HF in these patients then this would explain the attenuation of the results, reflecting the shared pathophysiological pathways between type 2 diabetes, CHD and HF. We also found an association between IR and HF, and no evidence of directional pleiotropy, although this was driven by a variant near the *LPL* gene (rs1011685). The associations between type 2 diabetes and HF may, at least in part, be indirect, mediated by the associations between metabolic disease and coronary heart disease.

We recognise that CHD risk is already elevated before T2D develops. Indeed, we recently showed that people with pre-diabetes had a higher cardiovascular risk profile than those with normal glycaemic control.(33) By taking BMI, SBP and LDL cholesterol into account, we have considered most of the relevant factors in our analyses. The presence of pleiotropy in our results does however mean that we cannot be completely certain that genetic associations between HF and T2D are not mediated via alternative, non-direct pathways.

We found that the relationship between type 2 diabetes and HF was attenuated by SBP. Hypertension is particularly prevalent in patients with insulin resistance(34), and both type 2 diabetes and IR are associated with development of left ventricular hypertrophy, a precursor of HF. The fact that the genetic relationship between type 2 diabetes and HF was only partially attenuated by SBP might reflect our increasing understanding that T2D is actually comprised of distinct clusters of patients in whom IR is not always the underlying pathophysiological problem.(35) In addition, IR is in part downstream of other processes, such as ectopic fat deposition.(36)

We found no evidence for a causal relationship between fasting insulin, fasting glucose or HbA1c and risk of HF. It is probable that dysglycaemia alone does not explain the increased incidence of HF in type 2 diabetes patients. It is likely that the benefits of type 2 diabetes therapies such as SGLT2 inhibitors on HF are by mechanisms other than improved glycaemic control.(37) Importantly however the genetic variants associated with fasting insulin and glucose and glycated haemoglobin we used in our analyses only account for a small proportion of the variance in these parameters and so we may have been underpowered to detect a smaller but significant effect, such has been seen in traditional observational data.

Our finding that genetic liability to HF is associated with type 2 diabetes risk is also of interest. Although the presence of HF as a risk factor for incident type 2 diabetes per se has not been previously evaluated, HF patients have a high prevalence of type 2 diabetes and dysglycaemia (although this could reflect the causal role of type 2 diabetes in HF). In HF clinical trial populations the prevalence of type 2 diabetes was

up to 40%.(3) In the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial 7.8% of patients developed new onset type 2 diabetes over the median 2.8 year follow-up period.(38) Observational data suggest that HF patients with more severe symptoms are more likely to develop type 2 diabetes.(39) HF has also been strongly associated with generalised insulin resistance, however whether this association is simply a reflection of the high prevalence of type 2 diabetes and prediabetes in HF populations(40) is unclear. Our findings might lend support to a causal relationship between liability to HF and increased risk of type 2 diabetes.

There are some limitations with our study. First, this analysis was conducted with summary-level data, limiting our ability to perform subgroups analysis, for example by age or sex. Second, we cannot exclude non-linear relationships between (for example) glycated haemoglobin and HF, as has been reported in previous observational studies.(6) The genetic variants selected in our MR analyses may not account for all of the genetic variation in examined traits and we may have been underpowered to find a small but statistically significant effect, for example in relation to the association between fasting insulin levels and HF, as the fasting insulin GWAS only included a few genetic variants and likely only accounts for a small proportion of the variation of fasting insulin levels. Nevertheless, we were adequately powered for our main analyses. Third, we did not have any HF subtype data available, for example HF with reduced versus preserved ejection fraction, or ischaemic versus non-ischaemic aetiology. It is likely that the relationship between T2D and HF is different between aetiologies or across the left ventricular ejection fraction spectrum, and this should be the focus of further work. Similarly, recent studies have identified genetic variants relating to specific clusters of pathophysiological subtypes of T2D (e.g. beta cell function, obesity). At present these clusters have only included 20-30 variants for each subtype and so have limited power in MR studies, however as more genetic variants are discovered and these clusters become larger it may be possible to determine whether specific clusters of T2D variants are differentially associated with HF. Finally, the majority of patients in the GWAS used for this analysis were Caucasian, and so we cannot extrapolate these results to other populations.

CONCLUSION

Our results suggest that genetic liability to type 2 diabetes and IR play a causal role in the aetiology of HF, and that CAD, in particular, might mediate this relationship. Presence of directional pleiotropy is however a concern and might be a source of bias. Further MR studies with sequential incidence of disease onset (between type 2 diabetes, CAD and HF) and HF subtypes e.g. preserved vs. reduced ejection fraction, will help to establish the exact nature of this relationship.

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Authorship Contributions: Conception and design, analysis and interpretation of data: IM, MV, CCL.

Drafting of the manuscript: IM, MH. Critical revision: RTL, CP, EP, NS, CCL

Conflict of Interest: NS has consulted for Amgen, Astrazeneca, Boehringer Ingelheim, Eli-Lilly, Novo Nordisk, Novartis, Pfizer and Sanofi. All other authors report no conflicts of interest relevant to this article.

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REFERENCES

1. IDF Diabetes Atlas [article online], 2019. Available from <https://www.diabetesatlas.org/en/>. Accessed 5th March 2020
2. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS, American Heart Association Council on E, Prevention Statistics C, Stroke Statistics S. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation* 2019;139:e56-e528
3. Seferovic PM, Petrie MC, Filippatos GS, Anker SD, Rosano G, Bauersachs J, Paulus WJ, Komajda M, Cosentino F, de Boer RA, Farmakis D, Doehner W, Lambrinou E, Lopatin Y, Piepoli MF, Theodorakis MJ, Wiggers H, Lekakis J, Mebazaa A, Mamas MA, Tschope C, Hoes AW, Seferovic JP, Logue J, McDonagh T, Riley JP, Milinkovic I, Polovina M, van Veldhuisen DJ, Lainscak M, Maggioni AP, Ruschitzka F, McMurray JJV. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;20:853-872
4. Banerjee D, Biggs ML, Mercer L, Mukamal K, Kaplan R, Barzilay J, Kuller L, Kizer JR, Djousse L, Tracy R, Zieman S, Lloyd-Jones D, Siscovick D, Carnethon M. Insulin resistance and risk of incident heart failure: Cardiovascular Health Study. *Circ Heart Fail* 2013;6:364-370
5. Vardeny O, Gupta DK, Claggett B, Burke S, Shah A, Loehr L, Rasmussen-Torvik L, Selvin E, Chang PP, Aguilar D, Solomon SD. Insulin resistance and incident heart failure the ARIC study (Atherosclerosis Risk in Communities). *JACC Heart Fail* 2013;1:531-536
6. Parry HM, Deshmukh H, Levin D, Van Zuydam N, Elder DH, Morris AD, Struthers AD, Palmer CN, Doney AS, Lang CC. Both high and low HbA1c predict incident heart failure in type 2 diabetes mellitus. *Circ Heart Fail* 2015;8:236-242
7. Witteles RM, Tang WH, Jamali AH, Chu JW, Reaven GM, Fowler MB. Insulin resistance in idiopathic dilated cardiomyopathy: a possible etiologic link. *J Am Coll Cardiol* 2004;44:78-81
8. Castagno D, Baird-Gunning J, Jhund PS, Biondi-Zoccai G, MacDonald MR, Petrie MC, Gaita F, McMurray JJ. Intensive glycaemic control has no impact on the risk of heart failure in type 2 diabetic patients: evidence from a 37,229 patient meta-analysis. *Am Heart J* 2011;162:938-948 e932
9. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Hum Mol Genet* 2014;23:R89-98
10. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ* 2018;362:k601
11. Burgess S, Thompson SG. Multivariable Mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects. *Am J Epidemiol* 2015;181:251-260
12. Vujkovic M, Keaton JM, Lynch JA, Miller DR, Zhou J, Tcheandjieu C, Huffman JE, Assimes TL, Lorenz K, Zhu X, Hilliard AT, Judy RL, Huang J, Lee KM, Klarin D, Pyarajan S, Danesh J, Melander O, Rasheed A, Mallick NH, Hameed S, Qureshi IH, Afzal MN, Malik U, Jalal A, Abbas S, Sheng X, Gao L, Kaestner KH, Susztak K, Sun YV, DuVall SL, Cho K, Lee JS, Gaziano JM, Phillips LS, Meigs JB, Reaven PD, Wilson PW, Edwards TL, Rader DJ, Damrauer SM, O'Donnell CJ, Tsao PS, Consortium H, Regeneron Genetics C, Program VAMV, Chang KM, Voight BF, Saleheen D. Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis. *Nat Genet* 2020;52:680-691
13. Mahajan A, Taliun D, Thurner M, Robertson NR, Torres JM, Rayner NW, Payne AJ, Steinthorsdottir V, Scott RA, Grarup N, Cook JP, Schmidt EM, Wuttke M, Sarnowski C, Magi R, Nano J, Gieger C, Trompet S,

Lecoeur C, Preuss MH, Prins BP, Guo X, Bielak LF, Below JE, Bowden DW, Chambers JC, Kim YJ, Ng MCY, Petty LE, Sim X, Zhang W, Bennett AJ, Bork-Jensen J, Brummett CM, Canouil M, Ec Kardt KU, Fischer K, Kardia SLR, Kronenberg F, Lall K, Liu CT, Locke AE, Luan J, Ntalla I, Nylander V, Schonherr S, Schurmann C, Yengo L, Bottinger EP, Brandslund I, Christensen C, Dedoussis G, Florez JC, Ford I, Franco OH, Frayling TM, Giedraitis V, Hackinger S, Hattersley AT, Herder C, Ikram MA, Ingelsson M, Jorgensen ME, Jorgensen T, Kriebel J, Kuusisto J, Ligthart S, Lindgren CM, Linneberg A, Lyssenko V, Mamakou V, Meitinger T, Mohlke KL, Morris AD, Nadkarni G, Pankow JS, Peters A, Sattar N, Stancakova A, Strauch K, Taylor KD, Thorand B, Thorleifsson G, Thorsteinsdottir U, Tuomilehto J, Witte DR, Dupuis J, Peyser PA, Zeggini E, Loos RJF, Froguel P, Ingelsson E, Lind L, Groop L, Laakso M, Collins FS, Jukema JW, Palmer CNA, Grallert H, Metspalu A, Dehghan A, Kottgen A, Abecasis GR, Meigs JB, Rotter JI, Marchini J, Pedersen O, Hansen T, Langenberg C, Wareham NJ, Stefansson K, Gloyn AL, Morris AP, Boehnke M, McCarthy MI. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet* 2018;50:1505-1513

14. Lotta LA, Gulati P, Day FR, Payne F, Ongen H, van de Bunt M, Gaulton KJ, Eicher JD, Sharp SJ, Luan J, De Lucia Rolfe E, Stewart ID, Wheeler E, Willems SM, Adams C, Yaghootkar H, Forouhi NG, Khaw KT, Johnson AD, Semple RK, Frayling T, Perry JR, Dermizakis E, McCarthy MI, Barroso I, Wareham NJ, Savage DB, Langenberg C, O'Rahilly S, Scott RA. Integrative genomic analysis implicates limited peripheral adipose storage capacity in the pathogenesis of human insulin resistance. *Nat Genet* 2017;49:17-26

15. Wang Q, Holmes MV, Davey Smith G, Ala-Korpela M. Genetic Support for a Causal Role of Insulin Resistance on Circulating Branched-Chain Amino Acids and Inflammation. *Diabetes Care* 2017;40:1779-1786

16. Scott RA, Lagou V, Welch RP, Wheeler E, Montasser ME, Luan J, Magi R, Strawbridge RJ, Rehnberg E, Gustafsson S, Kanoni S, Rasmussen-Torvik LJ, Yengo L, Lecoeur C, Shungin D, Sanna S, Sidore C, Johnson PC, Jukema JW, Johnson T, Mahajan A, Verweij N, Thorleifsson G, Hottenga JJ, Shah S, Smith AV, Sennblad B, Gieger C, Salo P, Perola M, Timpson NJ, Evans DM, Pourcain BS, Wu Y, Andrews JS, Hui J, Bielak LF, Zhao W, Horikoshi M, Navarro P, Isaacs A, O'Connell JR, Stirrups K, Vitart V, Hayward C, Esko T, Mihailov E, Fraser RM, Fall T, Voight BF, Raychaudhuri S, Chen H, Lindgren CM, Morris AP, Rayner NW, Robertson N, Rybin D, Liu CT, Beckmann JS, Willems SM, Chines PS, Jackson AU, Kang HM, Stringham HM, Song K, Tanaka T, Peden JF, Goel A, Hicks AA, An P, Muller-Nurasyid M, Franco-Cereceda A, Folkersen L, Marullo L, Jansen H, Oldehinkel AJ, Bruinenberg M, Pankow JS, North KE, Forouhi NG, Loos RJ, Edkins S, Varga TV, Hallmans G, Oksa H, Antonella M, Nagaraja R, Trompet S, Ford I, Bakker SJ, Kong A, Kumari M, Gigante B, Herder C, Munroe PB, Caulfield M, Antti J, Mangino M, Small K, Miljkovic I, Liu Y, Atalay M, Kiess W, James AL, Rivadeneira F, Uitterlinden AG, Palmer CN, Doney AS, Willemsen G, Smit JH, Campbell S, Polasek O, Bonnycastle LL, Hercberg S, Dimitriou M, Bolton JL, Fowkes GR, Kovacs P, Lindstrom J, Zemunik T, Bandinelli S, Wild SH, Basart HV, Rathmann W, Grallert H, Replication DIG, Meta-analysis C, Maerz W, Kleber ME, Boehm BO, Peters A, Pramstaller PP, Province MA, Borecki IB, Hastie ND, Rudan I, Campbell H, Watkins H, Farrall M, Stumvoll M, Ferrucci L, Waterworth DM, Bergman RN, Collins FS, Tuomilehto J, Watanabe RM, de Geus EJ, Penninx BW, Hofman A, Oostra BA, Psaty BM, Vollenweider P, Wilson JF, Wright AF, Hovingh GK, Metspalu A, Uusitupa M, Magnusson PK, Kyvik KO, Kaprio J, Price JF, Dedoussis GV, Deloukas P, Meneton P, Lind L, Boehnke M, Shuldiner AR, van Duijn CM, Morris AD, Toenjes A, Peyser PA, Beilby JP, Korner A, Kuusisto J, Laakso M, Bornstein SR, Schwarz PE, Lakka TA, Rauramaa R, Adair LS, Smith GD, Spector TD, Illig T, de Faire U, Hamsten A, Gudnason V, Kivimaki M, Hingorani A, Keinanen-Kiukaanniemi SM, Saaristo TE, Boomsma DI, Stefansson K, van der Harst P, Dupuis J, Pedersen NL, Sattar N, Harris TB, Cucca F, Ripatti S, Salomaa V, Mohlke KL, Balkau B, Froguel P, Pouta A, Jarvelin MR, Wareham NJ, Bouatia-Naji N, McCarthy MI, Franks PW, Meigs JB, Teslovich TM, Florez JC, Langenberg C, Ingelsson E, Prokopenko I, Barroso I. Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways. *Nat Genet* 2012;44:991-1005

17. Wheeler E, Leong A, Liu CT, Hivert MF, Strawbridge RJ, Podmore C, Li M, Yao J, Sim X, Hong J, Chu AY, Zhang W, Wang X, Chen P, Maruthur NM, Porneala BC, Sharp SJ, Jia Y, Kabagambe EK, Chang LC, Chen WM, Elks CE, Evans DS, Fan Q, Giulianini F, Go MJ, Hottenga JJ, Hu Y, Jackson AU, Kanoni S, Kim YJ, Kleber ME, Ladenvall C, Lecoeur C, Lim SH, Lu Y, Mahajan A, Marzi C, Nalls MA, Navarro P, Nolte IM, Rose LM, Rybin DV, Sanna S, Shi Y, Stram DO, Takeuchi F, Tan SP, van der Most PJ, Van Vliet-Ostaptchouk JV, Wong A, Yengo L, Zhao W, Goel A, Martinez Larrad MT, Radke D, Salo P, Tanaka T, van Iperen EPA, Abecasis G, Afaq S, Alizadeh BZ, Bertoni AG, Bonnefond A, Bottcher Y, Bottinger EP, Campbell H, Carlson OD, Chen CH, Cho YS, Garvey WT, Gieger C, Goodarzi MO, Grallert H, Hamsten A, Hartman CA, Herder C, Hsiung CA, Huang J, Igase M, Isono M, Katsuya T, Khor CC, Kiess W, Kohara K, Kovacs P, Lee J, Lee WJ, Lehne B, Li H, Liu J, Lobbens S, Luan J, Lyssenko V, Meitinger T, Miki T, Miljkovic I, Moon S, Mulas A, Muller G, Muller-Nurasyid M, Nagaraja R, Nauck M, Pankow JS, Polasek O, Prokopenko I, Ramos PS, Rasmussen-Torvik L, Rathmann W, Rich SS, Robertson NR, Roden M, Roussel R, Rudan I, Scott RA, Scott WR, Sennblad B, Siscovick DS, Strauch K, Sun L, Swertz M, Tajuddin SM, Taylor KD, Teo YY, Tham YC, Tonjes A, Wareham NJ, Willemssen G, Wilsgaard T, Hingorani AD, Consortium E-C, Consortium EP-I, Lifelines Cohort S, Egan J, Ferrucci L, Hovingh GK, Jula A, Kivimaki M, Kumari M, Njolstad I, Palmer CNA, Serrano Rios M, Stumvoll M, Watkins H, Aung T, Bluher M, Boehnke M, Boomsma DI, Bornstein SR, Chambers JC, Chasman DI, Chen YI, Chen YT, Cheng CY, Cucca F, de Geus EJC, Deloukas P, Evans MK, Fornage M, Friedlander Y, Froguel P, Groop L, Gross MD, Harris TB, Hayward C, Heng CK, Ingelsson E, Kato N, Kim BJ, Koh WP, Kooner JS, Korner A, Kuh D, Kuusisto J, Laakso M, Lin X, Liu Y, Loos RJF, Magnusson PKE, Marz W, McCarthy MI, Oldehinkel AJ, Ong KK, Pedersen NL, Pereira MA, Peters A, Ridker PM, Sabanayagam C, Sale M, Saleheen D, Saltevo J, Schwarz PE, Sheu WHH, Snieder H, Spector TD, Tabara Y, Tuomilehto J, van Dam RM, Wilson JG, Wilson JF, Wolffenbuttel BHR, Wong TY, Wu JY, Yuan JM, Zonderman AB, Soranzo N, Guo X, Roberts DJ, Florez JC, Sladek R, Dupuis J, Morris AP, Tai ES, Selvin E, Rotter JI, Langenberg C, Barroso I, Meigs JB. Impact of common genetic determinants of Hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: A transethnic genome-wide meta-analysis. *PLoS Med* 2017;14:e1002383

18. Shah S, Henry A, Roselli C, Lin H, Sveinbjornsson G, Fatemifar G, Hedman AK, Wilk JB, Morley MP, Chaffin MD, Helgadottir A, Verweij N, Dehghan A, Almgren P, Andersson C, Aragam KG, Arnlov J, Backman JD, Biggs ML, Bloom HL, Brandimarto J, Brown MR, Buckbinder L, Carey DJ, Chasman DI, Chen X, Chen X, Chung J, Chutkow W, Cook JP, Delgado GE, Denaxas S, Doney AS, Dorr M, Dudley SC, Dunn ME, Engstrom G, Esko T, Felix SB, Finan C, Ford I, Ghanbari M, Ghasemi S, Giedraitis V, Giulianini F, Gottdiener JS, Gross S, Guethbjartsson DF, Gutmann R, Haggerty CM, van der Harst P, Hyde CL, Ingelsson E, Jukema JW, Kavousi M, Khaw KT, Kleber ME, Kober L, Koekemoer A, Langenberg C, Lind L, Lindgren CM, London B, Lotta LA, Lovering RC, Luan J, Magnusson P, Mahajan A, Margulies KB, Marz W, Melander O, Mordi IR, Morgan T, Morris AD, Morris AP, Morrison AC, Nagle MW, Nelson CP, Niessner A, Niiranen T, O'Donoghue ML, Owens AT, Palmer CNA, Parry HM, Perola M, Portilla-Fernandez E, Psaty BM, Regeneron Genetics C, Rice KM, Ridker PM, Romaine SPR, Rotter JI, Salo P, Salomaa V, van Setten J, Shalaby AA, Smelser DT, Smith NL, Stender S, Stott DJ, Svensson P, Tammesoo ML, Taylor KD, Teder-Laving M, Teumer A, Thorgeirsson G, Thorsteinsdottir U, Torp-Pedersen C, Trompet S, Tyl B, Uitterlinden AG, Veluchamy A, Volker U, Voors AA, Wang X, Wareham NJ, Waterworth D, Weeke PE, Weiss R, Wiggins KL, Xing H, Yerges-Armstrong LM, Yu B, Zannad F, Zhao JH, Hemingway H, Samani NJ, McMurray JJV, Yang J, Visscher PM, Newton-Cheh C, Malarstig A, Holm H, Lubitz SA, Sattar N, Holmes MV, Cappola TP, Asselbergs FW, Hingorani AD, Kuchenbaecker K, Ellinor PT, Lang CC, Stefansson K, Smith JG, Vasan RS, Swerdlow DI, Lumbers RT. Genome-wide association and Mendelian randomisation analysis provide insights into the pathogenesis of heart failure. *Nat Commun* 2020;11:163

19. Hebert HL, Shepherd B, Milburn K, Veluchamy A, Meng W, Carr F, Donnelly LA, Tavendale R, Leese G, Colhoun HM, Dow E, Morris AD, Doney AS, Lang CC, Pearson ER, Smith BH, Palmer CNA. Cohort Profile:

Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS). *Int J Epidemiol* 2018;47:380-381j

20. Mordi IR, Pearson ER, Palmer CNA, Doney ASF, Lang CC. Differential Association of Genetic Risk of Coronary Artery Disease With Development of Heart Failure With Reduced Versus Preserved Ejection Fraction. *Circulation* 2019;139:986-988

21. 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;40:304-314

22. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol* 2015;44:512-525

23. Gan W, Clarke RJ, Mahajan A, Kulohoma B, Kitajima H, Robertson NR, Rayner NW, Walters RG, Holmes MV, Chen Z, McCarthy MI. Bone mineral density and risk of type 2 diabetes and coronary heart disease: A Mendelian randomization study. *Wellcome Open Res* 2017;2:68

24. Slob EAW, Burgess S. A comparison of robust Mendelian randomization methods using summary data. *Genet Epidemiol* 2020;44:313-329

25. Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample Mendelian randomization. *Genet Epidemiol* 2016;40:597-608

26. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S, Buchkovich ML, Yang J, Croteau-Chonka DC, Esko T, Fall T, Ferreira T, Gustafsson S, Kutalik Z, Luan J, Magi R, Randall JC, Winkler TW, Wood AR, Workalemahu T, Faul JD, Smith JA, Zhao JH, Zhao W, Chen J, Fehrmann R, Hedman AK, Karjalainen J, Schmidt EM, Absher D, Amin N, Anderson D, Beekman M, Bolton JL, Bragg-Gresham JL, Buyske S, Demirkan A, Deng G, Ehret GB, Feenstra B, Feitosa MF, Fischer K, Goel A, Gong J, Jackson AU, Kanoni S, Kleber ME, Kristiansson K, Lim U, Lotay V, Mangino M, Leach IM, Medina-Gomez C, Medland SE, Nalls MA, Palmer CD, Pasko D, Pechlivanis S, Peters MJ, Prokopenko I, Shungin D, Stancakova A, Strawbridge RJ, Sung YJ, Tanaka T, Teumer A, Trompet S, van der Laan SW, van Setten J, Van Vliet-Ostaptchouk JV, Wang Z, Yengo L, Zhang W, Isaacs A, Albrecht E, Arnlöv J, Arscott GM, Attwood AP, Bandinelli S, Barrett A, Bas IN, Bellis C, Bennett AJ, Berne C, Blagieva R, Bluher M, Bohringer S, Bonnycastle LL, Bottcher Y, Boyd HA, Bruinenberg M, Caspersen IH, Chen YI, Clarke R, Daw EW, de Craen AJM, Delgado G, Dimitriou M, Doney ASF, Eklund N, Estrada K, Eury E, Folkersen L, Fraser RM, Garcia ME, Geller F, Giedraitis V, Gigante B, Go AS, Golay A, Goodall AH, Gordon SD, Gorski M, Grabe HJ, Grallert H, Grammer TB, Grassler J, Gronberg H, Groves CJ, Gusto G, Haessler J, Hall P, Haller T, Hallmans G, Hartman CA, Hassinen M, Hayward C, Heard-Costa NL, Helmer Q, Hengstenberg C, Holmen O, Hottenga JJ, James AL, Jeff JM, Johansson A, Jolley J, Juliusdottir T, Kinnunen L, Koenig W, Koskenvuo M, Kratzer W, Laitinen J, Lamina C, Leander K, Lee NR, Lichtner P, Lind L, Lindstrom J, Lo KS, Lobbens S, Lorbeer R, Lu Y, Mach F, Magnusson PKE, Mahajan A, McArdle WL, McLachlan S, Menni C, Merger S, Mihailov E, Milani L, Moayyeri A, Monda KL, Morken MA, Mulas A, Muller G, Muller-Nurasyid M, Musk AW, Nagaraja R, Nothen MM, Nolte IM, Pilz S, Rayner NW, Renstrom F, Rettig R, Ried JS, Ripke S, Robertson NR, Rose LM, Sanna S, Scharnagl H, Scholtens S, Schumacher FR, Scott WR, Seufferlein T, Shi J, Smith AV, Smolonska J, Stanton AV, Steinthorsdottir V, Stirrups K, Stringham HM, Sundstrom J, Swertz MA, Swift AJ, Syvanen AC, Tan ST, Tayo BO, Thorand B, Thorleifsson G, Tyrer JP, Uh HW, Vandenput L, Verhulst FC, Vermeulen SH, Verweij N, Vonk JM, Waite LL, Warren HR, Waterworth D, Weedon MN, Wilkens LR, Willenborg C, Wilsgaard T, Wojczynski MK, Wong A, Wright AF, Zhang Q, Brennan EP, Choi M, Dastani Z, Drong AW, Eriksson P, Franco-Cereceda A, Gadin JR, Gharavi AG, Goddard ME, Handsaker RE, Huang J, Karpe F, Kathiresan S, Keildson S, Kiryluk K, Kubo M, Lee JY, Liang L, Lifton RP, Ma B, McCarroll SA, McKnight AJ, Min JL, Moffatt MF, Montgomery GW, Murabito JM, Nicholson G, Nyholt DR, Okada Y, Perry JRB, Dorajoo R, Reinmaa E, Salem RM, Sandholm N, Scott RA, Stolk L, Takahashi A, Tanaka T, van 't Hooft FM, Vinkhuyzen AAE, Westra HJ, Zheng W, Zondervan KT, Heath AC, Arveiler D, Bakker SJL, Beilby J, Bergman RN, Blangero J, Bovet P, Campbell H, Caulfield MJ, Cesana G, Chakravarti A, Chasman DI, Chines PS, Collins FS, Crawford DC, Cupples LA, Cusi D, Danesh J, de Faire U, den Ruijter

HM, Dominiczak AF, Erbel R, Erdmann J, Eriksson JG, Farrall M, Felix SB, Ferrannini E, Ferrieres J, Ford I, Forouhi NG, Forrester T, Franco OH, Gansevoort RT, Gejman PV, Gieger C, Gottesman O, Gudnason V, Gyllensten U, Hall AS, Harris TB, Hattersley AT, Hicks AA, Hindorf LA, Hingorani AD, Hofman A, Homuth G, Hovingh GK, Humphries SE, Hunt SC, Hypponen E, Illig T, Jacobs KB, Jarvelin MR, Jockel KH, Johansen B, Jousilahti P, Jukema JW, Jula AM, Kaprio J, Kastelein JJP, Keinanen-Kiukkaanniemi SM, Kiemenev LA, Knekt P, Kooner JS, Kooperberg C, Kovacs P, Kraja AT, Kumari M, Kuusisto J, Lakka TA, Langenberg C, Marchand LL, Lehtimaki T, Lyssenko V, Mannisto S, Marette A, Matise TC, McKenzie CA, McKnight B, Moll FL, Morris AD, Morris AP, Murray JC, Nelis M, Ohlsson C, Oldehinkel AJ, Ong KK, Madden PAF, Pasterkamp G, Peden JF, Peters A, Postma DS, Pramstaller PP, Price JF, Qi L, Raitakari OT, Rankinen T, Rao DC, Rice TK, Ridker PM, Rioux JD, Ritchie MD, Rudan I, Salomaa V, Samani NJ, Saramies J, Sarzynski MA, Schunkert H, Schwarz PEH, Sever P, Shuldiner AR, Sinisalo J, Stolk RP, Strauch K, Tonjes A, Tregouet DA, Tremblay A, Tremoli E, Virtamo J, Vohl MC, Volker U, Waeber G, Willemsen G, Witteman JC, Zillikens MC, Adair LS, Amouyel P, Asselbergs FW, Assimes TL, Bochud M, Boehm BO, Boerwinkle E, Bornstein SR, Bottinger EP, Bouchard C, Cauchi S, Chambers JC, Chanock SJ, Cooper RS, de Bakker PIW, Dedoussis G, Ferrucci L, Franks PW, Froguel P, Groop LC, Haiman CA, Hamsten A, Hui J, Hunter DJ, Hveem K, Kaplan RC, Kivimaki M, Kuh D, Laakso M, Liu Y, Martin NG, Marz W, Melbye M, Metspalu A, Moebus S, Munroe PB, Njolstad I, Oostra BA, Palmer CNA, Pedersen NL, Perola M, Perusse L, Peters U, Power C, Quertermous T, Rauramaa R, Rivadeneira F, Saaristo TE, Saleheen D, Sattar N, Schadt EE, Schlessinger D, Slagboom PE, Snieder H, Spector TD, Thorsteinsdottir U, Stumvoll M, Tuomilehto J, Uitterlinden AG, Uusitupa M, van der Harst P, Walker M, Wallaschofski H, Wareham NJ, Watkins H, Weir DR, Wichmann HE, Wilson JF, Zanen P, Borecki IB, Deloukas P, Fox CS, Heid IM, O'Connell JR, Strachan DP, Stefansson K, van Duijn CM, Abecasis GR, Franke L, Frayling TM, McCarthy MI, Visscher PM, Scherag A, Willer CJ, Boehnke M, Mohlke KL, Lindgren CM, Beckmann JS, Barroso I, North KE, Ingelsson E, Hirschhorn JN, Loos RJF, Speliotes EK. Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015;518:197-206

27. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang HY, Demirkan A, Den Hertog HM, Do R, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkila K, Hypponen E, Isaacs A, Jackson AU, Johansson A, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lyytikainen LP, Magnusson PKE, Mangino M, Mihailov E, Montasser ME, Muller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen AK, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney ASF, Doring A, Elliott P, Epstein SE, Ingi Eyjolfsson G, Gigante B, Goodarzi MO, Grallert H, Gravito ML, Groves CJ, Hallmans G, Hartikainen AL, Hayward C, Hernandez D, Hicks AA, Holm H, Hung YJ, Illig T, Jones MR, Kaleebu P, Kastelein JJP, Khaw KT, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimaki T, Lin SY, Lindstrom J, Loos RJF, Mach F, McArdle WL, Meisinger C, Mitchell BD, Muller G, Nagaraja R, Narisu N, Nieminen TVM, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stancakova A, Stirrups K, Swift AJ, Tirit L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemsen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen YI, Collins FS, Cooper RS, Danesh J, Dedoussis G, de Faire U, Feranil AB, Ferrieres J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V, Gyllensten U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Jarvelin MR, Jula A, Kahonen M, Kaprio J, Kesaniemi A, Kivimaki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L,

Lindgren CM, Martin NG, Marz W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe PB, Njolstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PEH, Sheu WH, Shuldiner AR, Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BHR, Ordovas JM, Boerwinkle E, Palmer CNA, Thorsteinsdottir U, Chasman DI, Rotter JI, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P, Kathiresan S, Mohlke KL, Ingelsson E, Abecasis GR. Discovery and refinement of loci associated with lipid levels. *Nat Genet* 2013;45:1274-1283

28. Evangelou E, Warren HR, Mosen-Ansorena D, Mifsud B, Pazoki R, Gao H, Ntritsos G, Dimou N, Cabrera CP, Karaman I, Ng FL, Evangelou M, Witkowska K, Tzani E, Hellwege JN, Giri A, Velez Edwards DR, Sun YV, Cho K, Gaziano JM, Wilson PWF, Tsao PS, Kovesdy CP, Esko T, Magi R, Milani L, Almgren P, Boutin T, Debette S, Ding J, Giulianini F, Holliday EG, Jackson AU, Li-Gao R, Lin WY, Luan J, Mangino M, Oldmeadow C, Prins BP, Qian Y, Sargurupremraj M, Shah N, Surendran P, Theriault S, Verweij N, Willems SM, Zhao JH, Amouyel P, Connell J, de Mutsert R, Doney ASF, Farrall M, Menni C, Morris AD, Noordam R, Pare G, Poulter NR, Shields DC, Stanton A, Thom S, Abecasis G, Amin N, Arking DE, Ayers KL, Barbieri CM, Batini C, Bis JC, Blake T, Bochud M, Boehnke M, Boerwinkle E, Boomsma DI, Bottinger EP, Braund PS, Brumat M, Campbell A, Campbell H, Chakravarti A, Chambers JC, Chauhan G, Ciullo M, Cocca M, Collins F, Cordell HJ, Davies G, de Borst MH, de Geus EJ, Deary IJ, Deelen J, Del Greco MF, Demirkale CY, Dorr M, Ehret GB, Elosua R, Enroth S, Erzurumluoglu AM, Ferreira T, Franberg M, Franco OH, Gandin I, Gasparini P, Giedraitis V, Gieger C, Girotto G, Goel A, Gow AJ, Gudnason V, Guo X, Gyllenstein U, Hamsten A, Harris TB, Harris SE, Hartman CA, Havulinna AS, Hicks AA, Hofer E, Hofman A, Hottenga JJ, Huffman JE, Hwang SJ, Ingelsson E, James A, Jansen R, Jarvelin MR, Joehanes R, Johansson A, Johnson AD, Joshi PK, Jousilahti P, Jukema JW, Jula A, Kahonen M, Kathiresan S, Keavney BD, Khaw KT, Knekt P, Knight J, Kolcic I, Kooner JS, Koskinen S, Kristiansson K, Kutalik Z, Laan M, Larson M, Launer LJ, Lehne B, Lehtimaki T, Liewald DCM, Lin L, Lind L, Lindgren CM, Liu Y, Loos RJF, Lopez LM, Lu Y, Lytikainen LP, Mahajan A, Mamasoula C, Marrugat J, Marten J, Milanesechi Y, Morgan A, Morris AP, Morrison AC, Munson PJ, Nalls MA, Nandakumar P, Nelson CP, Niiranen T, Nolte IM, Nutile T, Oldehinkel AJ, Oostra BA, O'Reilly PF, Org E, Padmanabhan S, Palmas W, Palotie A, Pattie A, Penninx B, Perola M, Peters A, Polasek O, Pramstaller PP, Nguyen QT, Raitakari OT, Ren M, Rettig R, Rice K, Ridker PM, Ried JS, Riese H, Ripatti S, Robino A, Rose LM, Rotter JI, Rudan I, Ruggiero D, Saba Y, Sala CF, Salomaa V, Samani NJ, Sarin AP, Schmidt R, Schmidt H, Shrine N, Siscovick D, Smith AV, Snieder H, Sober S, Sorice R, Starr JM, Stott DJ, Strachan DP, Strawbridge RJ, Sundstrom J, Swertz MA, Taylor KD, Teumer A, Tobin MD, Tomaszewski M, Toniolo D, Traglia M, Trompet S, Tuomilehto J, Tzourio C, Uitterlinden AG, Vaez A, van der Most PJ, van Duijn CM, Vergnaud AC, Verwoert GC, Vitart V, Volker U, Vollenweider P, Vuckovic D, Watkins H, Wild SH, Willemsen G, Wilson JF, Wright AF, Yao J, Zemunik T, Zhang W, Attia JR, Butterworth AS, Chasman DI, Conen D, Cucca F, Danesh J, Hayward C, Howson JMM, Laakso M, Lakatta EG, Langenberg C, Melander O, Mook-Kanamori DO, Palmer CNA, Risch L, Scott RA, Scott RJ, Sever P, Spector TD, van der Harst P, Wareham NJ, Zeggini E, Levy D, Munroe PB, Newton-Cheh C, Brown MJ, Metspalu A, Hung AM, O'Donnell CJ, Edwards TL, Psaty BM, Tzoulaki I, Barnes MR, Wain LV, Elliott P, Caulfield MJ, Million Veteran P. Genetic analysis of over 1 million people identifies 535 new loci associated with blood pressure traits. *Nat Genet* 2018;50:1412-1425

29. Nelson CP, Goel A, Butterworth AS, Kanoni S, Webb TR, Marouli E, Zeng L, Ntalla I, Lai FY, Hopewell JC, Giannakopoulou O, Jiang T, Hamby SE, Di Angelantonio E, Assimes TL, Bottinger EP, Chambers JC, Clarke R, Palmer CNA, Cubbon RM, Ellinor P, Ermel R, Evangelou E, Franks PW, Grace C, Gu D, Hingorani AD, Howson JMM, Ingelsson E, Kastrati A, Kessler T, Kyriakou T, Lehtimaki T, Lu X, Lu Y, Marz W, McPherson R, Metspalu A, Pujades-Rodriguez M, Ruusalepp A, Schadt EE, Schmidt AF, Sweeting MJ, Zalloua PA, AlGhalayini K, Keavney BD, Kooner JS, Loos RJF, Patel RS, Rutter MK, Tomaszewski M, Tzoulaki I, Zeggini E, Erdmann J, Dedoussis G, Bjorkegren JLM, Consortium E-C, CardioGramplusC4D,

group UKBCCCw, Schunkert H, Farrall M, Danesh J, Samani NJ, Watkins H, Deloukas P. Association analyses based on false discovery rate implicate new loci for coronary artery disease. *Nat Genet* 2017;49:1385-1391

30. Brion MJ, Shakhbazov K, Visscher PM. Calculating statistical power in Mendelian randomization studies. *Int J Epidemiol* 2013;42:1497-1501

31. Aune D, Schlesinger S, Neuenschwander M, Feng T, Janszky I, Norat T, Riboli E. Diabetes mellitus, blood glucose and the risk of heart failure: A systematic review and meta-analysis of prospective studies. *Nutr Metab Cardiovasc Dis* 2018;28:1081-1091

32. Ross S, Gerstein HC, Eikelboom J, Anand SS, Yusuf S, Pare G. Mendelian randomization analysis supports the causal role of dysglycaemia and diabetes in the risk of coronary artery disease. *Eur Heart J* 2015;36:1454-1462

33. Welsh C, Welsh P, Celis-Morales CA, Mark PB, Mackay D, Ghouri N, Ho FK, Ferguson LD, Brown R, Lewsey J, Cleland JG, Gray SR, Lyall DM, Anderson JJ, Jhund PS, Pell JP, McGuire DK, Gill JMR, Sattar N. Glycated Hemoglobin, Prediabetes, and the Links to Cardiovascular Disease: Data From UK Biobank. *Diabetes Care* 2020;43:440-445

34. Zhou MS, Wang A, Yu H. Link between insulin resistance and hypertension: What is the evidence from evolutionary biology? *Diabetol Metab Syndr* 2014;6:12

35. Ahlqvist E, Storm P, Karajamaki A, Martinell M, Dorkhan M, Carlsson A, Vikman P, Prasad RB, Aly DM, Almgren P, Wessman Y, Shaat N, Spegel P, Mulder H, Lindholm E, Melander O, Hansson O, Malmqvist U, Lernmark A, Lahti K, Forsen T, Tuomi T, Rosengren AH, Groop L. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol* 2018;6:361-369

36. Taylor R, Al-Mrabeh A, Sattar N. Understanding the mechanisms of reversal of type 2 diabetes. *Lancet Diabetes Endocrinol* 2019;7:726-736

37. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia* 2018;61:2108-2117

38. Preiss D, Zetterstrand S, McMurray JJ, Ostergren J, Michelson EL, Granger CB, Yusuf S, Swedberg K, Pfeffer MA, Gerstein HC, Sattar N. Predictors of development of diabetes in patients with chronic heart failure in the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) program. *Diabetes Care* 2009;32:915-920

39. Tenenbaum A, Motro M, Fisman EZ, Leor J, Freimark D, Boyko V, Mandelzweig L, Adler Y, Sherer Y, Behar S. Functional class in patients with heart failure is associated with the development of diabetes. *Am J Med* 2003;114:271-275

40. Kristensen SL, Preiss D, Jhund PS, Squire I, Cardoso JS, Merkely B, Martinez F, Starling RC, Desai AS, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, McMurray JJ, Packer M. Risk Related to Pre-Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction: Insights From Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial. *Circ Heart Fail* 2016;9

FIGURE LEGEND

1. Summary of Mendelian Randomization Analyses of the Relationship between Type 2 Diabetes and Heart Failure.

Univariate MR analyses of the association between genetically-instrumented liability to type 2 diabetes and HF using variants from both the DIAMANTE and DIAGRAM GWAS.

2. Summary of Multivariable Mendelian Randomization Analyses of the Relationship between Type 2 Diabetes and Heart Failure.

Multivariable MR analyses (IVW and MR-Egger) of the association between genetically-instrumented liability to type 2 diabetes and HF using variants from DIAGRAM GWAS.

Figure 1.

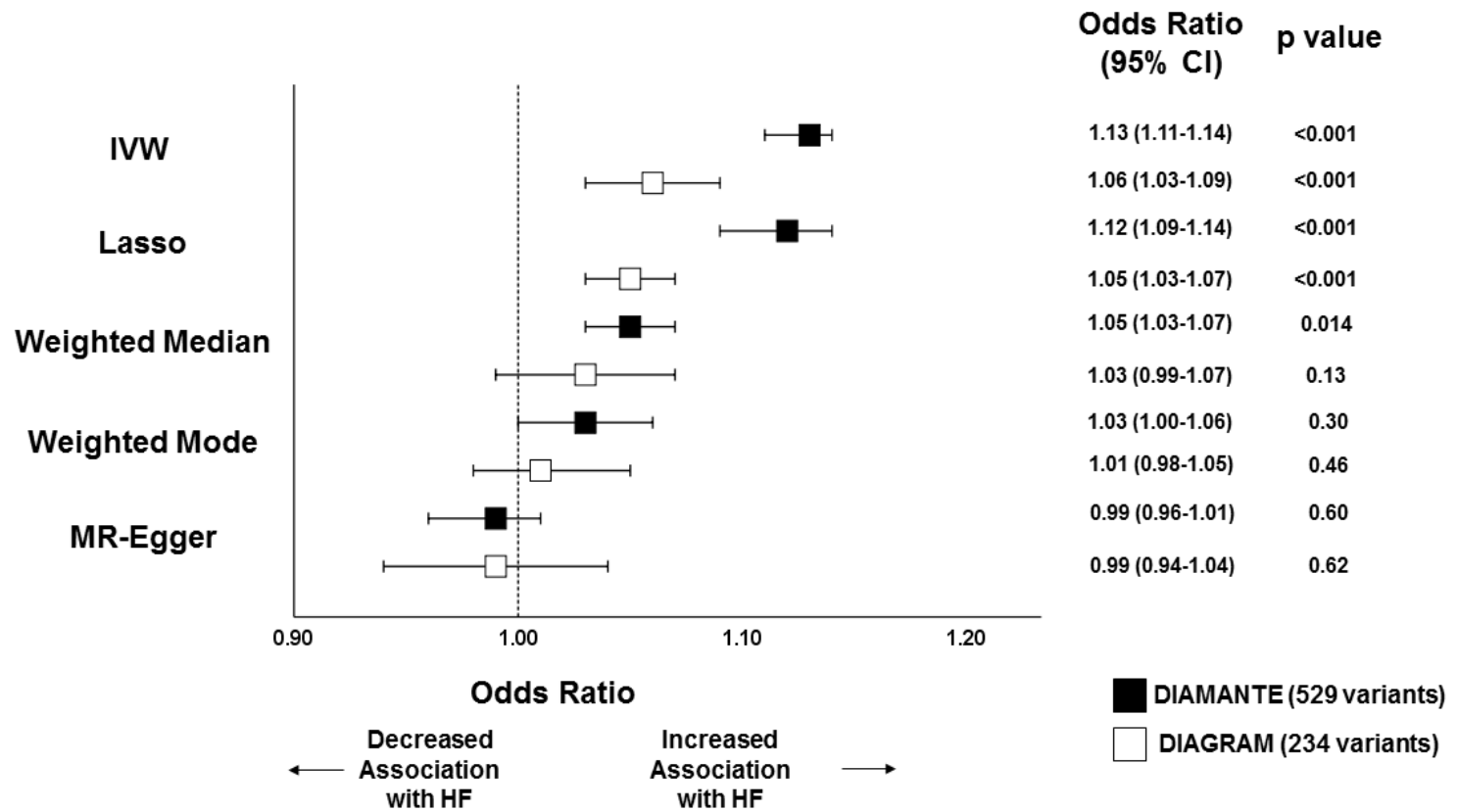


Figure 2.

