



# Type 2 Diabetes, Metabolic Traits, and Risk of Heart Failure: A Mendelian Randomization Study

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## 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 (T2D), glycemic traits, and risk of heart failure (HF).

## RESEARCH DESIGN AND METHODS

Summary-level data were obtained from genome-wide association studies of T2D, insulin resistance (IR), glycated hemoglobin, fasting insulin and glucose, and HF. MR was conducted using the inverse-variance weighted method. Sensitivity analyses included the MR-Egger method, weighted median and mode methods, and multivariable MR conditioning on potential mediators.

## RESULTS

Genetic liability to T2D was causally related to higher risk of HF (odds ratio [OR] 1.13 per 1-log unit higher risk of T2D; 95% CI 1.11–1.14;  $P < 0.001$ ); however, sensitivity analysis revealed evidence of directional pleiotropy. The relationship between T2D and HF was attenuated when adjusted for coronary disease, BMI, LDL cholesterol, and blood pressure in multivariable MR. 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 hemoglobin and risk of HF. Genetic liability to HF was causally linked to higher risk of T2D (OR 1.49; 95% CI 1.01–2.19;  $P = 0.042$ ), although again with evidence of pleiotropy.

## CONCLUSIONS

These findings suggest a possible causal role of T2D and IR in HF etiology, although the presence of both bidirectional effects and directional pleiotropy highlights potential sources of bias that must be considered.

Type 2 diabetes (T2D) and heart failure (HF) are increasingly common burdens. The worldwide prevalence of T2D is almost 10% (1), and the estimated prevalence of HF is 2.2% in the U.S. (2). While T2D and HF frequently coexist, their causal interrelationship is poorly understood. Observational studies have shown that patients with T2D have a two- to threefold increased risk of developing HF compared with individuals without T2D independent of other risk factors such as coronary heart disease; the prevalence of HF at baseline in recent T2D clinical trials has ranged

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\*A complete list of HERMES Consortium Executive Committee members can be found in the APPENDIX.

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from 10 to 30% (3). Glycemic traits related to T2D, such as insulin resistance (IR) (4,5) and glycosylated hemoglobin (HbA<sub>1c</sub>) (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 T2D development, although this has been less easy to evaluate owing to potential sources of error, such as confounding. Patients with HF seem to have a higher prevalence of T2D than the general population (3) and a higher prevalence of IR (7).

Observational analyses cannot provide evidence of causality, and whether T2D causes HF remains uncertain. Randomized controlled trials of interventions of glucose-lowering therapies have reported inconsistent effects on incident HF, and until recently, with sodium–glucose cotransporter 2 inhibitors, treatment of T2D had not been shown to reduce HF risk (8). It is possible that observational associations between T2D and HF simply reflect associations with other prevalent upstream risk factors such as coronary heart disease, obesity, and hypertension.

Mendelian randomization (MR) uses data from genetic studies to estimate the unconfounded relationships between exposures and outcomes. By using genetic variants associated with an exposure, the causal effect of the exposure on an outcome excluding confounders can potentially be estimated (9,10). Multivariable MR techniques can also be used to take into account potential pleiotropic effects of genetic instruments 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 T2D with risk of HF.

## RESEARCH DESIGN AND METHODS

### Data Sources

Two-sample MR was performed using published summary-level data from genome-wide association studies (GWAS) of the traits of interest in predominantly European individuals. Details of the GWAS data sets are given in Supplementary Table 1. Exposures of interest were T2D, IR, HbA<sub>1c</sub>, fasting insulin, fasting glucose, and HF. For T2D, we used two GWAS data sets. First, we selected 529 variants significantly (in

this manuscript we refer to GWAS significance as variants associated with a trait at  $P < 5 \times 10^{-8}$ ) associated with T2D from a GWAS from the DIAMANTE consortium of 228,499 T2D cases and 1,178,783 controls (12) (Supplementary Table 2). T2D cases were variably defined using physician diagnosis, self-reported use of T2D medications, elevated fasting glucose or HbA<sub>1c</sub>, or ICD coding, either alone or in combination, as described in the main GWAS articles. We were unable to obtain summary-level data for the DIAMANTE GWAS, so 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 (13) (Supplementary Table 3). Variants associated with IR were obtained from a GWAS of 188,577 individuals published by the MAGIC (Meta-Analyses of Glucose and Insulin-Related Traits) Consortium (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 or SEs for the association of each single nucleotide polymorphism with a combined IR phenotype, these were obtained from a subsequent MR study (15) (Supplementary Table 4). Variants associated with the individual traits of fasting insulin, fasting glucose, and HbA<sub>1c</sub> were also obtained from GWAS published by the MAGIC investigators (16,17) (Supplementary Tables 5–7).

Variants associated with HF were obtained from a GWAS of 47,309 cases and 930,014 controls published by the HERMES (Heart Failure Molecular Epidemiology for Therapeutic Targets) Consortium (18) (Supplementary Table 8). This GWAS included HF samples from population cohorts and case-control studies. The full details of each contributing cohort have been published previously (18). 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 eight, and natriuretic peptides by one; 20 of the 25 cohorts used a combination of at least two of these diagnostic criteria, while the remaining five studies used ICD coding alone.

An observational estimate of the association between T2D and incident HF was performed using individual-level

data from the GoDARTS (Genetics of Diabetes Audit and Research Tayside Scotland) study, the details of which have been published previously (19). Briefly, GoDARTS is a cohort study including 10,149 patients with T2D and 8,157 controls without T2D. All patients provided a blood sample for genotyping at 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 hospitalization (20). Deaths and hospitalizations were obtained from the General Register Office for Scotland and the Scottish Morbidity Record 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 T2D. For this analysis, single nucleotide polymorphisms 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 T2D (13).

Individuals participating in each of the GWAS consortia provided ethical approval to take part in the contributing studies, because such no specific ethical approval was required for this study. Summary-level data from a 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 T2D and HF incidence. We performed multivariable Cox proportional hazards regression with adjustment for age, sex, systolic blood pressure, BMI, smoking status, history of myocardial infarction (MI), aspirin and statin use, and total and HDL cholesterol (because 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 attenuated by prior MI, systolic blood

pressure, HDL cholesterol, BMI, age, and sex.

We performed MR studies to explore the association between glycemic traits and the development of HF and, in the reverse direction, to evaluate the association between HF and development of T2D. 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 data sets and was positively associated with the exposure traits. We pruned the genetic variants for those in linkage disequilibrium ( $r^2 > 0.01$ ) by including only 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 (OR) with 95% CI. The primary analysis was performed using the inverse-variance weighted (IVW) method, whereby the estimate of the genetic variant to outcome is regressed on the variant-to-exposure estimate. IVW can give a biased estimate if the genetic instrument is invalid (21); therefore, we also performed sensitivity tests using 1) the MR-Egger method, which can give reliable estimates of effect, in the absence of violation of the InSIDE rule (22), 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 most are invalid (21,23,24). We also performed additional tests using the Lasso method, which removes outliers, and the MR-pleiotropy residual sum and outlier method, which downgrades outliers (25). 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 a majority of genetic variants contribute equally to the IR 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 resulting from sample overlap, we performed a calculation of bias and type 1 error rate using the method proposed by Burgess et al. (26) (<https://sb452.shinyapps.io/overlap>).

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 T2D and HF adjusted for the effects of variants associated with BMI (27), LDL cholesterol (28), systolic blood pressure (SBP) (29), and coronary heart disease (CHD) (30). 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. (31). Overall, the DIAMANTE GWAS found genetic variants accounting for  $\sim 20\%$  of the estimated heritability of T2D. Because 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 OR 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 OR 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 OR of 1.1 at an  $\alpha$  of 0.05. Supplementary Figure 1 provides a visual representation of power calculations for a range of possible exposure instruments and ORs.

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

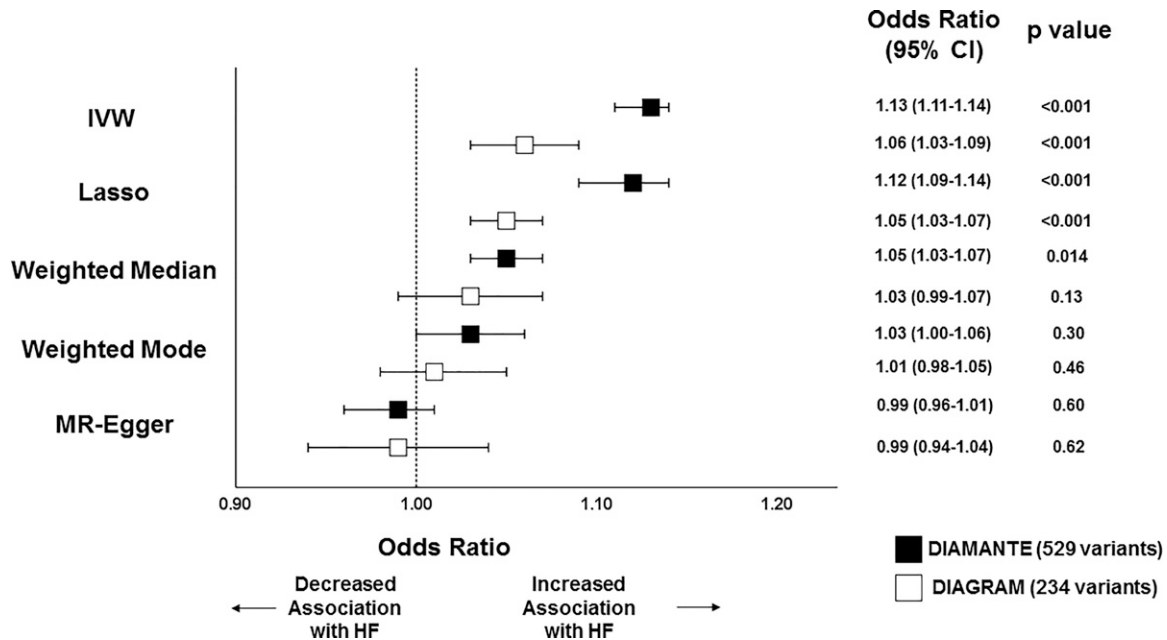
## RESULTS

### Observational Association Between T2D and HF

From the GoDARTS study, 12,919 individuals were evaluated, including 8,329 (64.5%) with T2D. Baseline characteristics are summarized 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 individuals with T2D than in controls without T2D (13.4% vs. 3.9%). After adjustment for clinical variables including age, sex, SBP, history of MI, BMI, aspirin and statin use, and total and HDL cholesterol, T2D was associated with a higher risk of developing HF (hazard ratio 1.40; 95% CI 1.04–1.89;  $P = 0.028$ ). In mediation analysis,  $\sim 35\%$  of the association between T2D and HF was mediated via age, sex, history of MI, BMI, SBP, and HDL cholesterol.

### Genetic Association Between T2D and HF

Univariable MR analysis supported a causal role for liability to T2D in the development of HF (IVW: DIAMANTE: OR 1.13 per 1-log unit higher odds of T2D; 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;  $P = 0.46$ ), and 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 T2D demonstrated unbalanced horizontal pleiotropy (DIAMANTE: intercept  $\beta$  0.006; SE 0.001;  $P < 0.001$ ; DIAGRAM: intercept  $\beta$  0.005; SE 0.002;  $P < 0.001$ ) (Fig. 1 and Supplementary Fig. 2), also seen using the MR-pleiotropy residual sum and outlier method (DIAMANTE: estimate 1.13; 95% CI 1.10–1.14;  $P < 0.001$ ; global test  $P < 0.001$ ), although there were no outliers. Use of the Causal Analysis Using Summary



**Figure 1**—Summary of MR analyses of the relationship between T2D and HF. Univariate MR analyses of the association between genetically instrumented liability to T2D and HF using variants from both the DIAMANTE and DIAGRAM GWAS.

Effect 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 bias from sample overlap ( $<0.01$ , regardless of overlap proportion), with an F statistic of 44.35.

Despite this evidence of unbalanced 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 T2D 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 T2D and HF was similar to the unadjusted estimate when additional traits were included in the multivariable MR model including: 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 T2D, CHD, SBP, BMI, and LDL cholesterol in multivariable MR, there was attenuation of the association between T2D and HF (OR 1.03; 95% CI 1.00–1.06;  $P = 0.038$ ), suggesting

that approximately half of the genetic association between T2D and HF in univariable IVW analysis was explained via these traits (Fig. 2 and Supplementary Table 11). As with the univariable estimate, in sensitivity analyses, there was 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 method applied to the fully fitted model, the estimate was in the same direction as the IVW multivariable 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  $-0.001$  to 0.003;  $P = 0.29$ ).

#### Genetic Association Between IR, Glycemic Traits, and HF

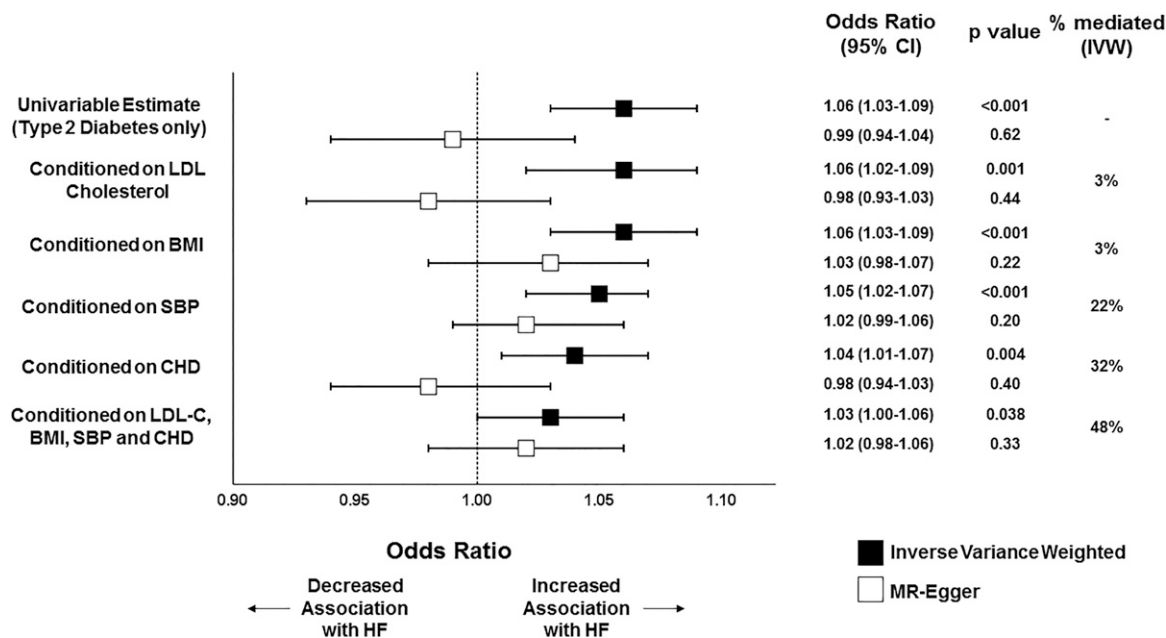
In univariate analysis, genetically instrumented IR was related to a higher risk of HF using IVW (OR 1.19 per 1-SD higher IR; 95% CI 1.00–1.41;  $P = 0.041$ ), which remained the case using the weighted median method (OR 1.31; 95% CI 1.08–1.59;  $P = 0.006$ ). Consistent estimates were derived using the mode-based method (OR 1.21; 95% CI 0.99–1.50;  $P = 0.06$ ) and MR-Egger method (OR 1.40; 95% CI 0.95–1.98;  $P = 0.053$ ), with no evidence of pleiotropy (intercept  $\beta$   $-0.004$ ; 95% CI  $-0.012$  to 0.013;  $P = 0.29$ ) (Supplementary Fig. 3). In the sensitivity analysis excluding rs1011685,

the IVW estimate for the causal relationship of IR with HF was attenuated, although 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 HbA<sub>1c</sub> and HF (IVW: OR 1.00 per 1-log-unit % higher HbA<sub>1c</sub>; 95% CI 0.80–1.25;  $P = 0.99$ ).

#### Genetic Association Between HF and T2D

Using the IVW method, genetic liability to HF was related to a higher risk of T2D (OR 1.49 per 1-log unit increase in the 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;  $P = 0.08$ ). The MR-Egger method 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 Fig. 4).



**Figure 2**—Summary of multivariable MR analyses of the relationship between T2D and HF. Multivariable MR analyses (IVW and MR-Egger) of the association between genetically instrumented liability to T2D and HF using variants from the DIAGRAM GWAS.

**CONCLUSIONS**

In this MR study, we found evidence in potential support of causal roles of genetic liability to T2D and IR with HF. For the association between T2D and HF, the relationship attenuated when we included coronary heart disease (CHD) in the analyses, suggesting that the causal effects, if real, might be partially mediated by CHD. We found potential strong evidence of a bidirectional relationship between HF and risk of T2D, which, together with strong evidence of directional pleiotropy, threatens to undermine the strength and presence of this relationship. We did not find any association between genetic determinants of fasting insulin, fasting glucose, or HbA<sub>1c</sub> and HF. These findings shed additional light on the relationships between T2D, IR, and HF and support the importance of the prevention of CHD in patients with T2D to prevent development of HF.

Several observational studies have reported an association between T2D and HF (32). 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 T2D and HF. Although in univariate analysis we did show presence of causal effects between both T2D and IR and risk of HF, this association was attenuated when we adjusted for the genetic

association with CHD. We also found strong evidence of directional pleiotropy in the relationship between genetic variants associated with T2D and HF within our analyses. This may reflect the shared pathophysiological pathways between T2D and CHD, and CHD and HF, and/or suggest 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, SBP, BMI, and LDL cholesterol at least in part potentially explains some of this directional pleiotropy. Genetic variants associated with T2D are strongly associated with CHD (33), while genetic variants associated with CHD are strongly associated with HF (18). If CHD is the primary cause of HF in these patients, this could explain the attenuation of the results, reflecting the shared pathophysiological pathways between T2D, CHD, and HF. We also found an association between IR and HF and no evidence of directional pleiotropy, although the association was driven by a variant near the *LPL* gene (rs1011685). The associations between T2D and HF may, at least in part, be indirect, mediated by the associations between metabolic disease and CHD.

We recognize that CHD risk is already elevated before T2D develops. Indeed, we recently showed that people with prediabetes had a higher cardiovascular risk profile than those with normal

glycemic control (34). By taking BMI, SBP, and LDL cholesterol into account, we have considered many of the relevant factors in our analyses. However, the presence of pleiotropy in our results does mean that we cannot be completely certain that genetic associations between HF and T2D are not due to alternative pathways.

We found that the relationship between T2D and HF was attenuated by SBP. Hypertension is particularly prevalent in patients with IR (35), and both T2D and IR are associated with development of left ventricular hypertrophy, a precursor of HF. The fact that the genetic relationship between T2D and HF was only partially attenuated by SBP might reflect our increasing understanding that T2D actually comprises distinct clusters of patients in whom IR is not always the underlying pathophysiological problem (36). In addition, IR is in part downstream of other processes, such as ectopic fat deposition (37).

We found no evidence for a causal relationship between fasting insulin, fasting glucose, or HbA<sub>1c</sub> and risk of HF. It is probable that dysglycemia alone does not explain the increased incidence of HF in patients with T2D. It is likely that the benefits of T2D therapies such as sodium–glucose cotransporter 2 inhibitors with regard to HF occur via mechanisms other than improved glycemic control



(38). Importantly, however, the genetic variants associated with fasting insulin and glucose and HbA<sub>1c</sub> we used in our analyses only account for a small proportion of the variance in these parameters, so we may have been underpowered to detect a smaller effect, as has been seen in traditional observational data.

Our finding that genetic liability to HF is associated with T2D risk is also of interest. Although the presence of HF as a risk factor for incident T2D per se has not been previously evaluated, patients with HF have a high prevalence of T2D and dysglycemia (although this could reflect the causal role of T2D in HF). In HF clinical trial populations, the prevalence of T2D was up to 40% (3). In the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) trial, 7.8% of patients developed new-onset T2D over the median 2.8-year follow-up period (39). Observational data suggest that patients with HF with more severe symptoms are more likely to develop T2D (40). HF has also been strongly associated with generalized IR; however, whether this association is simply a reflection of the high prevalence of T2D and prediabetes in HF populations (41) is unclear.

There are some limitations with our study. First, this analysis was conducted with summary-level data, limiting our ability to perform subgroup analysis, for example, by age or sex. Second, we cannot exclude nonlinear relationships between, for example, HbA<sub>1c</sub> 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 magnitude of effect, for example, in relation to the association between fasting insulin levels and HF, because the fasting insulin GWAS included only 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 ischemic versus nonischemic etiology. It is likely that the relationship between T2D and HF is different between etiologies 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, a majority of patients in the GWAS used for this analysis were Caucasian, so we cannot extrapolate these results to other populations.

In conclusion, our results suggest that genetic liability to T2D and IR plays a causal role in the etiology of HF and that CHD, in particular, might mediate this relationship. However, presence of directional pleiotropy is a concern and might be a source of bias. Additional MR studies with sequential incidence of disease onset (between T2D, CHD, 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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**Duality of Interest.** M.V.H. has consulted for Boehringer Ingelheim and in accordance with the CTSU University of Oxford policy, did not accept any payment or honoraria. N.S. has consulted for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Novartis, Pfizer, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** I.R.M. and M.V.H. drafted the manuscript. I.R.M., M.V.H., and C.C.L. were responsible for conception and design and analysis and interpretation of data. R.T.L., C.N.A.P., E.R.P., N.S., and C.C.L. performed critical revision. I.R.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## APPENDIX

The HERMES Consortium Executive Committee members are Folkert Asselbergs, Thomas P. Cappola, Marie-Pierre Dube, Michael Dunn, Patrick Ellinor, Aroon D. Hingorani, Quinn Wells, J. Gustav Smith, Ramachandran S. Vasan, Nilesh Samani, and Daniel I. Swerdlow.

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