Insulin resistance and incident heart failure: a meta-analysis

Mechanistic studies have shown that insulin resistance (IR) is a key pathogenic feature in diabetes-related cardiac dysfunction. Population-based studies have described the relation between IR and incident heart failure (HF), but the findings have been inconclusive, and available data have not been adequately synthesized. Therefore, we conducted a meta-analysis to evaluate the association of IR and incident HF.

We searched PubMed and EMBASE from inception up to 31 July 2021. We included prospective cohort studies of incident HF in relation to IR, assessed using the homeostasis model assessment for insulin resistance (HOMA-IR) index. Studies reporting on other IR measures and HF were too few to perform a separate meta-analysis. A Mendelian randomization study of IR and HF was not included, as it provided insufficient data to be pooled with other studies (i.e. no IR measurement method reported, no relative risk (RR) estimate for the IR and incident HF association).

Two investigators (S.E. and J.B.E.T.) independently abstracted data from eligible studies on study characteristics (setting, period, design), participant characteristics (demographics and clinical variables), duration of follow-up, incident HF definition, and

Figure 1 Overall relative risk (RR) (95% confidence interval [CI]) of incident heart failure associated with insulin resistance for: comparison of the top versus bottom tertiles of the distribution of the homeostasis model assessment for insulin resistance (HOMA-IR) index. (A) Minimally adjusted (unadjusted or age- and sex-adjusted) RR. (B) Maximally adjusted RR. Each standard deviation (SD) change in HOMA-IR index. (C) Minimally adjusted (unadjusted or age- and sex-adjusted) RR. (D) Maximally adjusted RR.

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RR for HF. For each study, wherever possible, we abstracted two RR estimates of the IR and HF association (i) from the minimally (model with lowest number of covariates, usually unadjusted or age- and sex-adjusted models) and (ii) from maximally (model with highest number of covariates)-adjusted models. We also abstracted the unit of comparison (e.g. a doubling of HOMA-IR) and the adjustment variables.

For consistency across studies, we calculated the RR using 1 standard deviation (SD) in HOMA-IR as the unit of comparison, assuming a log-linear association between HOMA-IR and HF risk, and a normal distribution of HOMA-IR or its log-transformation. We detected no significant heterogeneity across studies, and no publication bias (p-value for Egger test =0.20).

Our meta-analysis shows that higher levels of IR are associated with a higher risk of developing HF after accounting for traditional risk factors. This association was present in studies comprising individuals with and without diabetes. Although we only perform meta-analysis of studies using HOMA-IR, the association likely exists with other IR measures, as evidenced by the results from studies that also examined OGTT- or hyperinsulinaemic-euglycaemic-based IR measures.\(^{1,7}\) HF ascertainment was mainly based on hospital discharge records; hence, HF incidence may have been underestimated by missing asymptomatic or undiagnosed HF. Thus, the observed

### Table 1  Characteristics of prospective cohort studies of the association between insulin resistance and incident heart failure

| Author | Study name | Country | Study years | Sample size | Male (%) | White (%) | Av. age (years) | Av. BMI (kg/m\(^2\)) | DM (%) | HTN (%) | Prior CAD (%) | HF identification | Av. follow-up (years) | HF cases | Adjustment variables |
|--------|------------|---------|-------------|-------------|----------|------------|----------------|-------------------|--------|--------|---------------|-------------------|-------------------|----------|-------------------|
| Ingelsson,\(^{6}\) 2005 | ULSAM | Sweden | 1970–1974 | 1187 | 100 100 70 | 26.3 | 10.6 74.4 | NR | 8.9 | 104 | ICD discharge code plus adjudication by an expert committee | | |
| Bahrami,\(^{3}\) 2008 | MESA | US | 2000–2002 | 6814 | 47 38 65.4 | 28.4 | 14.2 47.7 | 0 | 4 | 79 | Hospitalization and death records, plus adjudication by an expert committee | | |
| Kalogeropoulou,\(^{4}\) 2009 | Health ABC | US | 1997–1998 | 2386 | 39.6 62.5 73 | 26.3 | 4 44 15.3 | | 7.2 | 185 | Hospitalization records and death certificate, plus adjudication by an expert committee | | |
| Banerjee,\(^{2}\) 2013 | CHS | US | 1989–1993 | 4425 | 47.5 86.6 72.7 | NR | 0 NR NR | | 12 | 1216 | Hospitalization records and death certificate, plus adjudication by an expert committee | | |
| Vardany,\(^{5}\) 2013 | ARIC | US | 1987–1989 | 12606 | 44 76.3 54 | 26.9 | 0 28.9 0 | | 20.6 | 1453 | ICD discharge code and death certificate | | |
| Wolniak,\(^{7}\) 2013 | UKPDS | UK | 1977–1991 | 4344 | 59 81 52.5 | 28.8 | 100 36.8 | NR | 16.4 | 235 | ICD code on hospital discharge records | | |
| Pooled estimate | – | – | – | 3176 | 48.4 70 60.9 | 27.5 | 17.4 38.1 | – | 14 | 3274 | | | | |

ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CAD, coronary artery disease; cIMT, carotid intima-media thickness; CHS, Cardiovascular Health Study; DM, diabetes mellitus; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; Hba\(_1c\), glycosylated haemoglobin; Health ABC, Health, Aging, and Body Composition; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HTN, hypertension; ICD, international classification of diseases; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; MRI, magnetic resonance imaging; NR, not reported; PA, physical activity; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; SBP, systolic blood pressure; UKPDS, United Kingdom Prospective Diabetes Study; ULSAM, Uppsala Longitudinal Study of Adult Men; WHR, waist-to-hip ratio; WC, waist circumference.

\(^{1}\) The RR for the highest versus lowest tertile of HOMA-IR was 1.45 (95% confidence interval [CI] 1.25, 1.56; Figure 1A). The corresponding maximally adjusted RR for HF was 1.15 (95% CI 1.08, 1.22; Figure 1B).

The pooled minimally adjusted RR for HF 1 SD change in log HOMA-IR was 1.26 (95% CI 1.20, 1.33; Figure 1C). The corresponding maximally adjusted RR for HF was 1.08 (95% CI 1.04, 1.11; Figure 1D and Table 1). We detected no significant heterogeneity (\(I^2 = 43\%\), \(p = 0.13\) across studies, and no publication bias (p-value for Egger test =0.20).

Our meta-analysis shows that higher levels of IR are associated with a higher risk of developing HF after accounting for traditional risk factors. This association was present in studies comprising individuals with and without diabetes. Although we only perform meta-analysis of studies using HOMA-IR, the association likely exists with other IR measures, as evidenced by the results from studies that also examined OGTT- or hyperinsulinaemic-euglycaemic-based IR measures.\(^{1,7}\) HF ascertainment was mainly based on hospital discharge records; hence, HF incidence may have been underestimated by missing asymptomatic or undiagnosed HF. Thus, the observed

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The extent of adjustment for confounders varied across studies, hence the possibility of residual confounding. Our results suggest a possible causal association between IR and HF, which is corroborated by results of a Mendelian randomization study showing that genetically instrumented higher IR was associated with higher risk of HF.\textsuperscript{3} The possible mechanistic pathways linking IR and HF include hyperinsulinaemia, sodium retention, sympathetic nervous system activation, increased response to angiotensin II, and IR-related metabolic alterations.\textsuperscript{1}

The effect of IR on incident HF may also be indirect, partly mediated by its effect on HF precursors, including cardiovascular risk factors and coronary heart disease (CHD). However, the persistence of the IR and HF association after adjustment for the intermediate cardiovascular risk factors, suggests direct IR effect on the myocardium. Study-level data did not allow us to explore the role of CHD, as an intermediate factor, in the IR and HF association. These aspects would need clarification in larger prospective studies.

Our findings point to the need for investigating potential interventions that counteract IR to reduce the HF burden. Such interventions include lifestyle changes, bariatric surgery, and drugs such as metformin, thiazolidinediones, and glucagon-like peptide-1 receptor agonists, and possibly sodium–glucose cotransporter 2 inhibitors. This meta-analysis has some limitations. The HF diagnostic criteria and the extent of adjustment for potential confounders varied across studies, which could account for different HF risk estimates. The studies were mainly US-based, included limited data on non-White populations, and did not include HF subtypes. Most studies lacked IR measures based on dynamic tests such as OGTT or hyperinsulinaemic-euglycaemic clamp, which more effectively capture the extent of IR.\textsuperscript{10}

The number and design of the studies limited our ability to conduct relevant subgroups analyses by sex, race/ethnicity, CHD status, diabetes status, or other comorbidities. Our study has strengths including the examination of IR across different populations including men and women across age groups, which improved the statistical power to detect smaller effects.

Our data show a significantly higher HF risk among individuals with higher IR independent of traditional risk factors. Additional large-scale prospective studies including IR measures based on dynamic testing and HF subtypes, are warranted to further characterize the IR and HF association.

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Conflict of Interest: G.C.F. reports consulting for Abbott, Amgen, AstraZeneca, Bayer, Cytokinetics, Janssen, Medtronic, Merck, and Novartis. All other authors have nothing to disclose.

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