doi:10.1002/ejhf.2531
Online publish-ahead-of-print 16 May 2022

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.[1] 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.[2] 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,[3] 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

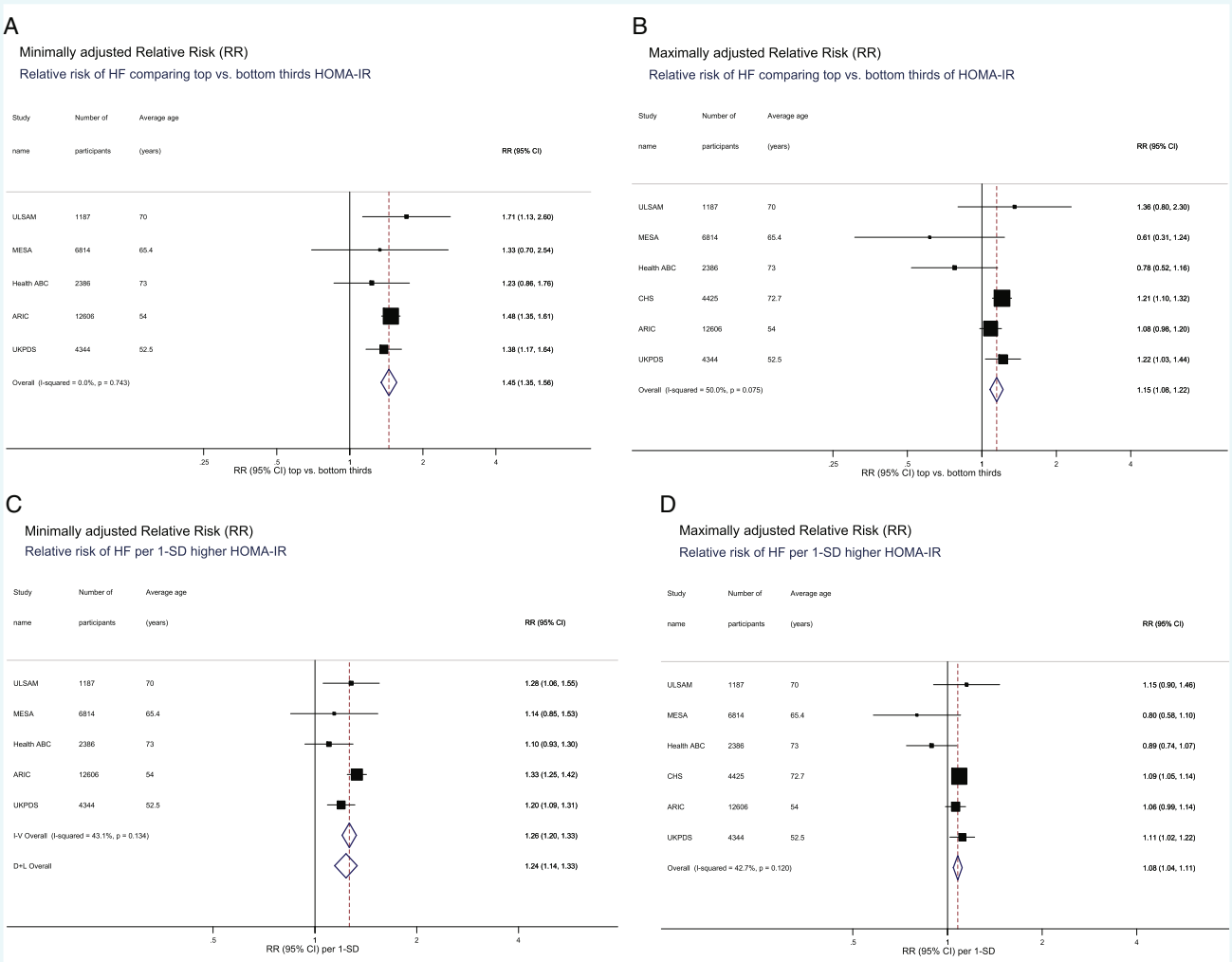

Figure 1 Overall relative risk (RR) (95% confidence interval [CI]) of incident heart failure associated with insulin resistance for: comparison of the top versus bottom tertiles of the distribution of the homeostasis model assessment for insulin resistance (HOMA-IR) index. (*A*) Minimally adjusted (unadjusted 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.

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,[4] 2005	ULSAM	Sweden	1970–1974	1187	100	100	70	26.3	10.6	74.4	NR	ICD discharge code plus adjudication by an expert committee	8.9	104	DM, HTN, smoking, TC, prior MI, LVH on ECG
Bahrami,[5] 2008	MESA	US	2000–2002	6814	47	38	65.4	28.4	14.2	47.7	0	Hospitalization and death records, plus adjudication by an expert committee	4	79	Age, sex, smoking, HTN, DM, obesity, TC, LVH, LVEF by MRI
Kalegoropoulos,[6] 2009	Health ABC	US	1997–1998	2386	39.6	62.5	73	26.5	4	44	15.5	Hospitalization records and death certificate, plus adjudication by an expert committee	7.2	185	Age, smoking, prior CAD, BMI, SBP, LVH on ECG, serum creatinine, serum albumin
Banerjee,[7] 2013	CHS	US	1989–1993	4425	47.5	86.6	72.7	NR	0	NR	NR	Hospitalization records and death certificate, plus adjudication by an expert committee	12	1216	Age, sex, race/ethnicity, centre, PA, smoking, alcohol, HDL-C, TC, SBP, WC, cIMT, major ECG abnormality
Vardeny,[8] 2013	ARIC	US	1987–1989	12 606	44	76.3	54	26.9	0	28.9	0	ICD discharge code and death certificate	20.6	1455	Age, sex, BMI, HTN, smoking, centre, incident MI
Walmil,[9] 2021	UKPDS	UK	1977–1991	4344	59	81	52.5	28.8	100	36.8	NR	ICD code on hospital discharge records	16.4	235	Age, sex, race/ethnicity, smoking, BMI, HbA_{1c}, FPG, WHR, SBP, TC, LDL-C, TG, eGFR, atrial fibrillation, microalbuminuria
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; ULSM, Uppsala Longitudinal Study of Adult Men; WHR, waist-to-hip ratio; WC, waist circumference.

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 calculated the RR comparing individual in the highest versus lowest tertiles of HOMA-IR distribution. We pooled RRs across studies using fixed-effects model meta-analysis, after showing a low heterogeneity across studies using the I^2 statistic (I^2 >75% indicates high heterogeneity). The small number of studies precluded subgroup analyses. We assessed publication bias using the Egger regression test *p*-value for funnel-plot asymmetry. Analyses were conducted using Stata version 15 (StataCorp, College Station, TX, USA).

The six prospective studies (four US-based) included,[4–9] comprised 31 762 participants without prevalent HF at baseline, with an average age ranging by study from 53 to 71 years (weighted average 61 years), 0%–60% women (weighted average 52%), 38%–100% Whites (weighted average 70%). Across studies, the average body mass index was 26–29 kg/m^2 (weighted average 27.5 kg/m^2), 0% to 100% (weighted average 17%) of participants had diabetes, and 29% to 74% (weighted average 38%) had hypertension.[4–9] All studies assessed IR using HOMA-IR, while three studies also examined fasting insulin,[4,6,7] and two studies additionally used IR indices derived from the hyperinsulinaemic-euglycaemic clamp or oral glucose tolerance (OGTT) tests.[4,7] Over follow-up (duration: 4 to 21 years, weighted average 14 years), 3247 incident HF events occurred.

The pooled minimally adjusted RR for HF comparing 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.[4,7] 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

association may have been underestimated. 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.[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.[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.[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.

Acknowledgements

The authors thank the United Kingdom Prospective Diabetes Study (UKPDS) staff for providing us with the requested data.

Funding

Dr. Echouffo-Tcheugui was supported by NIH/NHLBI grant K23 HL153774. Dr. Erqou is supported by Department of Veterans Affairs, Veterans Health Administration, VISN 1 Career Development Award. Prof. Adler is supported in part by the NIHR Oxford Biomedical Research Centre.

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.

Sebhat Erqou[1], Amanda I. Adler[2], Azariyas A. Challa[3], Gregg C. Fonarow[4], and Justin B. Echouffo-Tcheugui[5]*

[1]Division of Cardiovascular Medicine, Department of Medicine, Providence VA Medical Center and Alpert Medical School of Brown University, Providence, RI, USA; [2]Diabetes Trials Unit, University of Oxford, Oxford, UK; [3]Division of Cardiovascular Medicine, Department of Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, OH, USA; [4]Ahmanson-UCLA Cardiomyopathy Center, Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA; and [5]Division of Endocrinology, Diabetes & Metabolism, Department of Medicine, Johns Hopkins University, Baltimore, MD, USA
*Email: jechouf1@jhmi.edu

References

1. Aroor AR, Mandavia CH, Sowers JR. Insulin resistance and heart failure: molecular mechanisms. *Heart Fail Clin*. 2012;**8**:609–17.
2. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;**28**:412–9.
3. Mordi IR, Lumbers RT, Palmer CNA, Pearson ER, Sattar N, Holmes MV, et al. Type 2 diabetes, metabolic traits, and risk of heart failure: a Mendelian randomization study. *Diabetes Care*. 2021;**44**:1699–705.
4. Ingelsson E, Sundström J, Ärnlöv J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. *JAMA*. 2005;**294**:334–41.
5. Bahrami H, Bluemke DA, Kronmal R, Bertoni AG, Lloyd-Jones DM, Shahar E, et al. Novel metabolic risk factors for incident heart failure and their relationship with obesity. *J Am Coll Cardiol*. 2008;**51**:1775–83.
6. Kalogeropoulos A, Georgiopoulou V, Harris TB, Kritchevsky SB, Bauer DC, Smith AL, et al.; Health ABC Study. Glycemic status and incident heart failure in elderly without history of diabetes mellitus: the Health, Aging, and Body Composition study. *J Card Fail*. 2009;**15**:593–9.
7. Banerjee D, Biggs ML, Mercer L, Mukamal K, Kaplan R, Barzilay J, et al. Insulin resistance and risk of incident heart failure: Cardiovascular Health Study. *Circ Heart Fail*. 2013;**6**:364–70.
8. Vardeny O, Gupta DK, Claggett B, Burke S, Shah A, Loehr L, et al. Insulin resistance and incident heart failure. The ARIC study (Atherosclerosis Risk in Communities). *JACC Heart Fail*. 2013;**1**:531–6.
9. Wamil M, Coleman RL, Adler AI, McMurray JJV, Holman RR. Increased risk of incident heart failure and death is associated with insulin resistance in people with newly diagnosed type 2 diabetes: UKPDS 89. *Diabetes Care*. 2021;**44**:1877–84.
10. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. *Am J Physiol Endocrinol Metab*. 2008;**294**:E15–26.