

Increased Risk of Incident Heart Failure and Death is Associated with Insulin Resistance in People with Newly-Diagnosed Type 2 Diabetes: UKPDS nn (*number to be added in proof*)

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Abstract

OBJECTIVE

Insulin resistance (IR) may mediate heart failure (HF) development. We examined whether IR in people with newly-diagnosed type 2 diabetes (T2D) increased their risk of a composite outcome of HF or death, or HF alone.

RESEARCH DESIGN AND METHODS

Homeostasis Model Assessment insulin resistance (HOMA2_IR) values for UKPDS participants were derived from paired fasting plasma glucose (FPG) and insulin measures. Kaplan Meier survival curves and multivariable survival models were used to evaluate associations between HOMA2_IR and HF/death or HF alone. We adjusted for potential confounders by including variables with univariate associations ($P < 0.1$), and by requiring a multivariable P value < 0.05 .

RESULTS

Of 5,102 UKPDS participants with newly-diagnosed T2D, 4,344 had HOMA2_IR measurements. At enrollment they were mean (SD) age 52.5 (87) years, with HbA_{1c} 7.2 (1.8) %, body mass index 28.8 (5.5) kg/m², and median (IQR) HOMA2_IR 1.6 (1.1–2.2). HF/death occurred in 1,974 (45.4%) participants (first events: 235 HF, 1,739 deaths) over median 16.4 years follow-up. Multivariable independent associations with HF/death were: higher age, body mass index, HOMA2_IR, FPG, waist-to-hip ratio, systolic blood pressure, LDL-cholesterol, heart rate, as well as sex, race, smoking status, prior AF, and microalbuminuria. A doubling of HOMA2_IR was associated with a 5% greater risk of HF/death (relative risk [RR] 1.05, 95% CI 1.01–1.12, $P = 0.0029$) and a 14% greater risk of HF (RR 1.14, 95% CI 1.02–1.27, $P = 0.017$).

CONCLUSIONS

Insulin resistant patients with newly-diagnosed T2D were more likely to develop HF or die than those more sensitive to insulin.

Clinical Trial Registration: ISRCTN75451837

Several studies have shown a relationship between measures of higher insulin resistance (IR) and the development of HF in people with diabetes (1-3) and obesity.(4) Both conditions are associated with IR, which is correlated with adverse cardiac remodelling (cardiac fibrosis, myocardial hypertrophy, and steatosis of the myocardium).(5, 6) Additionally, severe IR is a feature of lipodystrophy, a rare genetic disorder characterised by redistribution of body fat, and associated with a three-fold increase in myocardial triglyceride content and cardiomyopathy.(7) The link between IR and HF is also supported by the observation that IR is associated with HF in patients without diabetes.(2) In addition, the Strong Heart Study in Native Americans demonstrated that abnormalities of left ventricle size and systolic function correlated with fasting plasma insulin values, and predated the development of diabetes.(8)

In this *post hoc* observational analysis of the UK Prospective Diabetes Study (UKPDS)(9) and its ten-year post-trial monitoring study,(10) we sought to examine possible associations between IR and the incidence of adjudicated HF or death, or HF alone, in patients with newly-diagnosed type 2 diabetes (T2D), and whether this was independent of a relationship with body mass index (BMI). We also evaluated the impact on HF/death and on HF alone of the glucose-lowering therapies allocated at random in the UKPDS.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The UKPDS protocol, design, methods and impact on diabetic complications of a more intensive glycemic strategy, compared with a conventional glycemic strategy, have been reported in detail.(9, 11) The UKPDS recruited individuals with newly-diagnosed T2D aged 25–65 years between 1977 and 1991. Those with fasting plasma glucose (FPG) concentrations >6 and <15 mmol/L following a 3-4 month dietary run-in period were assigned randomly to a conventional glycemic control strategy (primarily with diet), or to an intensive glycemic control strategy, primarily using sulfonylurea, insulin, or metformin (only in those >120% ideal body weight) monotherapy, and then followed quarterly in UKPDS clinics.

When the interventional trial closed out on 30th September 1997, all surviving participants were entered into a 10-year post-trial monitoring study,(10) with no attempt made to maintain them on their previously randomized therapies. Participants were returned to usual care, but seen annually for the first 5 years in UKPDS clinics to facilitate continued standardized collection of outcome data, as well as measurements of FPG, glycated hemoglobin (HbA_{1c}), blood pressure, plasma creatinine and urinary albumin. For the second 5 years, participants were followed remotely via questionnaires. Members of the UKPDS end-point committee who were unaware of assignments to study groups adjudicated all predefined clinical outcomes during the trial, including HF and death, as detailed previously (9). Post-trial outcomes were adjudicated in exactly the same way.(10)

Microalbuminuria was defined in the UKPDS as a urinary albumin concentration >50 mg/L due to initial storage of urine samples at –20°C between 1979 and 1988.(11) Hypertension at baseline was diagnosed if the mean of the two and nine month blood pressure measurements exceeded 160 mmHg systolic and/or 90 mmHg diastolic, or if the participant was already taking antihypertensive therapy.(12)

The UKPDS was performed according to the Declaration of Helsinki and all participants gave written informed consent to participate. The study protocol was approved by the ethics committees from all 23 UKPDS clinical centres.

Estimating Insulin Resistance

Insulin resistance at baseline for each participant was estimated using the Homeostasis Model Assessment (HOMA) Calculator v2.(13) HOMA uses a structural mathematical model that incorporates the physiological glucose/insulin feedback system, including pancreatic beta-cell function and peripheral (muscle) plus hepatic insulin sensitivity, to estimate an individual's insulin resistance (HOMA2_IR) and beta cell function (HOMA2_%B).(14) The HOMA model compares favourably with other models used to estimate insulin resistance, and has the advantage of requiring only a single fasting plasma sample to be assayed for insulin and glucose.(15, 16) We compared UKPDS participants with higher, versus lower,

HOMA2_IR values split by the median value.

Clinical Outcomes

We defined the primary outcome as a composite of incident HF (ICD-9 codes 411 to 428.1) or death, with death included as it is a competing risk. Secondary outcomes were incident HF (first instance), and the impact of the randomly-allocated glucose-lowering therapies used in the UKPDS on HF/death or HF alone.

Statistical Analysis

Continuous baseline variables were summarized as mean (SD) or median (IQR). Categorical variables were summarized as counts and percentages. Comparisons between those with high and low baseline HOMA2_IR values were performed using Student's t-test, Wilcoxon signed rank test or Chi-squared tests as appropriate. We used Kaplan Meier estimates and, as the assumptions required for proportional-hazards models were not met, multivariable accelerated failure time (AFT) models assuming a Weibull distribution to evaluate possible associations between HOMA2_IR and HF/death or HF alone.

For analysis of the primary HF/death outcome, participants were censored if alive without HF at the end of follow-up, or when lost to follow-up. For the secondary analysis of HF alone, participants without HF were censored at the end of follow-up, when lost to follow-up, or when they died. We adjusted for potential confounders by including variables with univariate associations ($P < 0.1$), and by requiring a multivariable P value < 0.05 for retention in the full model. Potential confounders included age, BMI, systolic blood pressure (SBP), heart rate in beats per minute, fasting plasma triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol, plasma creatinine, hemoglobin and HbA_{1c} as continuous variables, and ethnicity, sex, smoking status, prior cardiovascular events, atrial fibrillation (AF) and microalbuminuria as categorical variables.

To examine the relationship of obesity to any associations identified between

HOMA2_IR and HF/death or HF, we performed a sensitivity analysis, with conventional BMI cut-offs as defined by the World Health Organisation (17) (normal weight ≥ 18.5 -25, overweight ≥ 25 -30, obese ≥ 30 kg/m²) and waist-to-hip ratio (WHR) split by tertiles.

To evaluate the impact of the randomly allocated diet, sulfonylurea, insulin and metformin glucose-lowering monotherapies used in the UKPDS on HF/death or HF alone, we performed a sensitivity analysis examining the Kaplan-Meier estimates for each therapy. (18)

All analyses were conducted using SAS v9.4 (SAS Institute North Carolina). Univariate analyses were performed in complete case datasets. As 20% of participants had missing data for at least one candidate variable, missing data were assigned mean or mode values for the AFT models with results compared to complete case models. For multivariate statistical comparisons we used two-sided tests at the 0.05 level of significance, with no adjustment for multiple testing.

RESULTS

Participant Characteristics

Of the 5,102 participants enrolled into the UKPDS, 4,344 had the simultaneous fasting plasma insulin and FPG measures required to estimate HOMA2_IR values and were included in these analyses. At baseline, 59% were male and 81% were White Caucasian with mean (SD) age 52.5 (8.7) years, HbA_{1c} 7.2 (1.8) %, BMI 28.8 (5.5) kg/m², WHR 0.91 (0.08) and median (IQR) HOMA2_IR 1.6 (1.1–2.2) (**Table 1**). History of HF at baseline was assessed by study physicians. There were 4,317 (99.4%) participants with no history of heart failure, 5 (0.1%) thought to have probable/definite heart failure, 22 (0.5%) for whom this information was not recorded, and 45 (1.0%) who were on diuretic therapy. The diuretic therapy and a history of HF categories were not mutually exclusive.

At baseline, participants with higher HOMA2_IR values (≥ 1.6 , n=2245), compared

with those with lower values (<1.6 , $n=2099$), were younger (mean 51.9 vs. 53.2 years, $P<0.0001$), more likely to be female (47 vs. 34%, $P<0.0001$) and Asian-Indian (12 vs. 7%, $P<0.0001$). They had higher mean BMI (30.6 vs. 26.8 kg/m², $P<0.0001$), HbA_{1c} (7.3 vs. 7.0 %, $P<0.0001$), urinary albumin values (9 vs. 7 mg/L, $P<0.0001$) and median triglycerides (1.74 vs. 1.26 mmol/L, $P<0.0001$), and were also more likely to be hypertensive (**Table 1**).

Risk Factors for HF/death and HF Alone

Over a median follow-up period of 16.4 years the primary composite HF/death outcome occurred in 1,974 (45.4%) participants, triggered by 235 first HF events and 1,739 deaths, equating to an incidence rate of 29.6 *per* 1000 person-years. Variables found to be associated independently with HF/death in the multivariate analysis were higher age, BMI, HOMA2_IR, FPG, WHR, SBP, heart rate, LDL-cholesterol, and sex, race, smoking, prior history of AF and microalbuminuria. In the secondary HF alone analysis, independent associations were found for age, BMI, HOMA2_IR, SBP, prior AF and microalbuminuria. Baseline HbA_{1c} values did not predict the composite HF/death outcome.

Association of HOMA2_IR with HF/death and HF Alone

During the study there were 145 (6.5%) HF events and 1,095 (48.8%) HF/death events in individuals with baseline HOMA2_IR ≥ 1.6 , compared with 90 (4.3%) HF events and 879 (41.9%) HF/death events in those with HOMA2_IR <1.6 . The unadjusted relative risks (RR) for HF/death and HF alone for participants with HOMA2_IR ≥ 1.6 were 1.09 (95%CI 1.04–1.15) and 1.32 (1.10–1.58) respectively. Unadjusted RRs using log₂ HOMA_IR as a continuous variable were 1.08 (1.05–1.11) and 1.24 (1.11–1.39) respectively, suggesting that a two-fold increase in HOMA_IR is associated with corresponding risk increases of 8% for HF/death and 24% for HF alone. The corresponding adjusted RRs in the multivariable analysis were 1.05 (1.01–1.12) for HF/death and 1.14 (1.02–1.27) for HF alone, suggesting that a two-fold increase in HOMA_IR is associated with risk increases of 5% and 14%

respectively (**Table 2**). Kaplan-Meier estimates confirmed a significant association (Logrank $P<0.0001$) between baseline HOMA2_IR and HF/death and HF alone (**Figure 1**).

Relationship to Obesity

We found no heterogeneity for the association of HOMA2_IR with HF/death between normal-weight, overweight and obese individuals (P for interaction=0.16), but between thirds of WHR we found possible evidence suggesting a stronger association of HOMA2_IR with the composite outcome of heart failure or death in those with a lower waist-to-hip ratio ($P=0.049$, **Figure 2**).

Impact of Randomly-assigned Glucose-lowering Therapies on HF/death

The Kaplan-Meier analysis of the probability of HF/death event-free survival in four groups of participants assigned randomly to a conventional glycemic control strategy with diet (reference group), or to an intensive glucose control strategy with sulfonylurea (RR 0.96, 95% CI 0.90–1.02), insulin (RR 0.94, 95% CI 0.88–1.01) or metformin (RR 0.92, 95% CI 0.83–1.02) showed no between-group differences over five years (**Figure 3**; Logrank $P=0.24$).

DISCUSSION

In this large prospective study of patients with newly-diagnosed T2D, the incidence of the HF/death composite outcome was higher in those who were more insulin resistant than in those who were less insulin resistant. This association was independent of different BMI categories, but not thirds of waist-to-hip ratio. Specifically, we found that a doubling of HOMA2_IR values was associated with a 5% higher adjusted relative risk for HF/death, and a 14% higher adjusted relative risk for incident HF. The somewhat higher risk ratios for incident HF than for HF/death suggest that death may act as a dilutional factor, as might be expected if HF-specific events were driving the observed associations.

We also found that higher HOMA2_IR values were associated independently with

HF/death, as were higher age, BMI, FPG, waist-to-hip ratio, SBP, heart rate, LDL-cholesterol, as well as sex, race, smoking, prior history of AF and microalbuminuria. Higher HOMA2_IR values were also associated independently with incident HF alone, as were higher age, BMI, SBP, as well as prior AF and microalbuminuria. Our findings confirm that HOMA2_IR, assessed at the time T2D is diagnosed, can help predict the future risk of HF/death, as has been shown for IR and incident HF in people with established T2D.(1, 19, 20)

Our demonstration that the association between HOMA2_IR and HF/death is independent of BMI, is consistent with prior reports.(1, 3) Of note, we showed that the association of HOMA_IR with composite HF/death outcome was stronger for participants in the lowest waist-to-hip ratio category. We cannot, however, exclude that obesity and insulin resistance are on the same causal pathway.

In previous UKPDS reports, we have shown a lack of association between baseline fasting hyperinsulinemia and macrovascular disease, and specifically ischemic heart disease,(21) and have also demonstrated that measuring insulin sensitivity (estimated as HOMA_%S, the reciprocal of HOMA_IR) at the time of diagnosis of T2D provides no additional value with respect to predicting the future risk of myocardial infarction.(22) We did not, however, examine HF outcomes in these previous reports, although others have reported that among participants without antecedent myocardial infarction higher fasting insulin levels are associated with HF risk.(2) Accordingly, it may be that promoting insulin sensitisation early in the course of T2D could play a role in preventing the development of HF although we did not see any risk reduction for HF/death in the overweight UKPDS participants randomised to metformin despite a 22% reduction in their median (IQR) fasting plasma insulin from 15.6 (9.3–25.9) mU/L at baseline to 12.1 (7.2–20.1) mU/L at six years (P<0.01) as reported previously.(23)

A causal relationship between IR and the development of heart failure has not been confirmed so far in clinical trials with any insulin-sensitising agent. Thiazolidinediones,

despite their well-documented specific effect on peripheral insulin resistance, cause fluid retention and therefore their use in a non-selected population has been associated with an increased risk of HF hospitalisation.(24)

Several possible mechanisms explaining an increased risk of HF in non-diabetic subjects with IR have been proposed previously. These include the link between hyperinsulinemia and sodium retention,(25) sympathetic nervous system activation (26) and increased pressor response to angiotensin II.(27) Additionally, the metabolic alterations defining IR have been shown to have a direct effect on myocardial structure and function. Studies utilising various cardiac imaging modalities described concentric left ventricular hypertrophy and increased LV mass in otherwise healthy subjects with IR.(19, 28) Moreover, IR and dysglycemia have been correlated with an adverse LV remodelling after myocardial infarction.(19, 29) Nevertheless, the implicated mechanism requires further studies.

Lastly, we would like to highlight the potential utility and relatively low cost of using HOMA-IR for early risk stratification of people with newly-diagnosed diabetes which could facilitate targeting patients with IR (and at high risk of HF) with treatments particularly effective at reducing HF, e.g. sodium-glucose co-transporter-2 inhibitors. HOMA2_IR estimates have been validated against euglycemic clamp measures, the acute insulin response from the intravenous glucose tolerance test, and the insulinogenic index from oral glucose tolerance testing (16). Estimating IR by HOMA2_IR requires measuring only paired concentrations of fasting insulin and FPG, and could therefore be used in clinical practice, in addition to epidemiological studies.

Our study has several limitations. Firstly, information about left ventricular ejection fraction was not collected routinely in the UKPDS, so it is difficult to draw any conclusions regarding the aetiology of the HF events that occurred. The UKPDS based the diagnosis of HF primarily on clinical judgement rather than current imaging or biomarker criteria and therefore does not fully represent a contemporary definition of HF. Information about left ventricular ejection fraction was not collected routinely in the UKPDS so it is difficult to draw any conclusions regarding the aetiology of the HF events that occurred. It is also possible

that HF preserved ejection fraction, which is frequently observed in people with diabetes, may not have been fully captured in the UKPDS. Secondly, the number of adjudicated HF events in UKPDS is relatively small compared with the number of deaths. We also evaluated a composite endpoint of HF or death to account for the competing risk of death and present the analysis separately to visualise the HF-specific risk. Thirdly, the substantially increased risk for HF/death events in the 0.7% of UKPDS participants with prior AF needs to be evaluated further in a much larger cohort, although it is noteworthy that AF has been included consistently in HF risk score models developed from various large clinical trials.(30, 31) Finally, we are not able to exclude that the association we found between higher HOMA2_IR values and the future risk of HF/death risk reflects residual confounding. IR is a feature of a spectrum of cardio-metabolic disorders, many of which increase cardiovascular mortality.

In conclusion, this large post-hoc cohort analysis showed that participants with insulin resistance and newly-diagnosed T2D were more likely to develop HF or die than those who were more insulin sensitive. These associations were independent of their BMI. Accordingly, we propose that HOMA2_IR measured at the time of the diagnosis of T2D could be an important additional predictor of the future risk of HF and death in people with T2D.

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Disclosures

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Author Contributions

M.W. and R.R.H. designed the study. R.L.C. performed the analyses. M.W. wrote the manuscript. R.L.C., A.I.A., J.J.V.M., and R.R.H. reviewed and edited the manuscript. R.R.H. 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.

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1 **Figure Legends**

2 **Figure 1.** Cumulative incidence plot for time to heart failure or death (Panel A), and for heart
3 failure alone (Panel B), split by the median HOMA2_IR value with unadjusted relative risks
4 (RR) and Logrank P values.

5 **Figure 2.** Subgroup analyses of the association of HOMA2_IR with the composite outcome
6 of heart failure or death, split by body mass index categories and by tertiles of waist-to-hip
7 ratio.

8 **Figure 3.** Cumulative incidence plot for time to the composite outcome of heart failure or
9 death, split by the four randomly allocated glucose-lowering therapies and Logrank P value
10 with diet as the reference group.

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1 **Table 1:** Baseline characteristics of UKPDS participants analysed

	All N = 4344	HOMA2_IR<1.6 N = 2099	HOMA2_IR ≥1.6 N = 2245	P-value
Age (years)	52.5 (8.72)	53.2 (8.5)	51.9 (8.8)	<0.0001
Sex				<0.0001
Male	2578 (59%)	1388 (66%)	1190 (53%)	
Female	1766 (41%)	711 (34%)	1055 (47%)	
Race				<0.0001
• White	3537 (81.4%)	1737 (82.8%)	1800 (80.2%)	
• Afro-Caribbean	343 (7.9%)	181 (8.6%)	162 (7.2%)	
• Asian-Indian	431 (9.9%)	162 (7.7%)	269 (12.0%)	
• Other	33 (0.8%)	19 (0.9%)	14 (0.6%)	
HbA _{1c} (%)	7.2 (1.8)	7.0 (1.7)	7.3 (1.8)	<0.0001
Fasting plasma glucose (mmol/L)	8.7 (2.9)	8.3 (2.7)	9.2 (3.1)	<0.0001
Fasting plasma insulin (mU/L)	14.1 (8.1)	8.6 (3.1)	19.3 (7.9)	<0.0001
HOMA2_IR	1.6 (1.1–2.2)	1.1 (0.8–1.3)	2.2 (1.8–2.8)	-
Waist-to-hip ratio	0.91 (0.08)	0.90 (0.07)	0.92 (0.08)	<0.0001
Body mass index (kg/m ²)	28.8 (5.5)	26.8 (4.2)	30.6 (5.9)	<0.0001
Systolic blood pressure (mmHg)	135.3 (19.4)	133.6 (19.4)	136.9 (19.2)	<0.0001
Heart rate (bpm)	71 (13.3)	70 (13.0)	72 (13.6)	<0.0001
Atrial fibrillation	30 (0.7%)	12 (0.6%)	18 (0.8%)	0.36
Fasting triglycerides (mmol/L)	1.5 (1.1–2.1)	1.3 (1.0–1.7)	1.7 (1.3–2.4)	<0.0001
Total cholesterol (mmol/L)	5.4 (1.1)	5.3 (1.1)	5.5 (1.1)	<0.0001
HDL-cholesterol (mmol/L)	1.07 (0.24)	1.10 (0.25)	1.04 (0.23)	<0.0001
LDL-cholesterol (mmol/L)	3.5 (1.0)	3.5 (1.0)	3.5 (1.0)	0.031
Smoking status				0.16
• Current	1339 (30.8%)	653 (31.1%)	686 (30.6%)	
• Ex	1463 (33.7%)	730 (34.8%)	733 (32.7%)	
• Never	1541 (35.5%)	716 (34.1%)	825 (36.8%)	
eGFR (ml/min/1.73 m ²)	81 (23)	78 (22)	84 (23)	<0.0001
Urinary albumin (mg/L)	9 (4–20)	7 (4–15)	9 (4–25)	<0.0001
Microalbuminuria	462 (11.9%)	165 (8.7%)	297 (15.0%)	<0.0001
Hypertension	1597 (36.8%)	702 (33.6%)	895 (39.9%)	<0.0001
Baseline medication				
• Aspirin	834 (19.2%)	371 (17.7%)	463 (20.6%)	0.014
• Diuretics	389 (9.4%)	167 (8.3%)	222 (10.5%)	0.017

	All N = 4344	HOMA2_IR<1.6 N = 2099	HOMA2_IR ≥1.6 N = 2245	P-value
• Corticosteroids	9 (0.2%)	3 (0.1%)	6 (0.3%)	0.37
• Digoxin	45 (1.0%)	14 (0.7%)	31 (1.4%)	0.020
• Anti-hypertensives	513 (11.8%)	242 (11.5%)	271 (12.1%)	0.57
• Lipid-lowering	11 (0.3%)	6 (0.3%)	5 (0.2%)	0.68

1 Data are mean (SD), median (IQR) or N (%).
2 Up to 10% of data were missing for HbA_{1C}, BP, HR, microalbuminuria

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Table 2. Multivariable analysis of all risk factors with a univariate *P* value <0.1 association with the composite outcome of heart failure or death, and with heart failure alone.

Variable	Heart failure or death (1974 events)			Heart Failure (235 events)		
	Relative Risk	95% Confidence Interval	p-value	Relative Risk	95% Confidence Interval	p - value
Age (per year)	1.04	(1.03–1.04)	<0.0001	1.05	(1.06–1.11)	<0.0001
Female sex (vs. Male)	0.86	(0.81– 0.91)	<0.0001	0.96	(0.79–1.12)	0.52
Afro-Caribbean (vs. White Caucasian)	0.81	(0.74– 0.90)	<0.0001	0.84	(0.59–1.20)	0.32
Asian-Indian (vs. White Caucasian)	0.88	(0.80– 0.98)	0.011	0.81	(0.55–1.21)	0.28
Current smoker (Yes vs. No)	1.24	(1.18– 1.30)	<0.0001	N/A	N/A	N/A
Body mass index (kg/m ²)	1.01	(1.01–1.01)	0.0003	1.03	(1.03–1.08)	<0.0001
HOMA2_IR (log ₂)	1.05	(1.01–1.12)	0.0029	1.14	(1.02–1.27)	0.017
HbA _{1c} (per 1%)	1.00	(0.98–1.02)	0.78	N/A	N/A	N/A
Fasting plasma glucose (per 1 mmol/L)	1.02	(1.02–1.03)	<0.0001	1.01	(0.99–1.04)	0.36
Waist-to-hip ratio	1.74	(1.22–2.58)	0.0039	2.36	(0.81–6.90)	0.12
Systolic blood pressure (per 10 mmHg)	1.05	(1.04–1.07)	<0.0001	1.05	(1.01–1.19)	0.038
Heart rate (per 5 bpm)	1.02	(1.01–1.03)	<0.0001	1.03	(1.00–1.06)	0.081
LDL-cholesterol (mmol/l)	1.03	(1.01–1.06)	0.0096	N/A	N/A	N/A
HDL-cholesterol (mmol/l)	N/A	N/A	N/A	0.75	(0.52–1.08)	0.12
Fasting triglycerides (Log ₂ mmol/L)	1.03	(0.99–1.07)	0.13	1.03	(0.91–1.16)	0.65

eGFR (per 10 ml/min/1.73 m ²)	1.00	(1.00–1.00)	0.11	N/A	N/A	N/A
Atrial fibrillation (Yes vs. No)	1.84	(1.52–2.25)	<0.0001	3.70	(9.48–50.18)	<0.0001
Microalbuminuria (Yes vs. No)	1.15	(1.07–1.30)	0.0001	1.44	(1.22–2.79)	0.0027

N/A: univariate association ≥ 0.1

Figure 1.

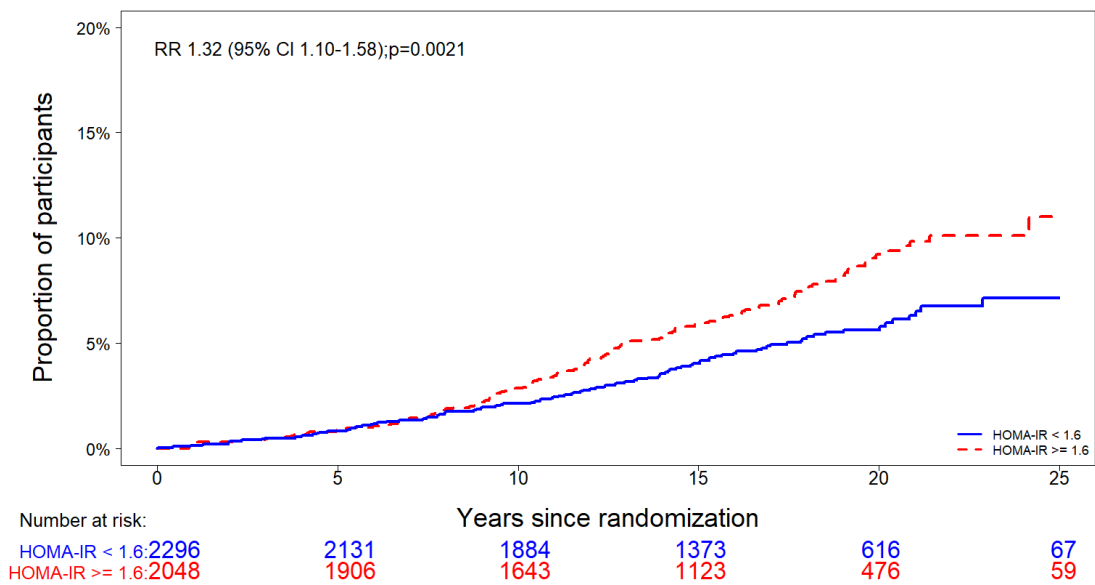
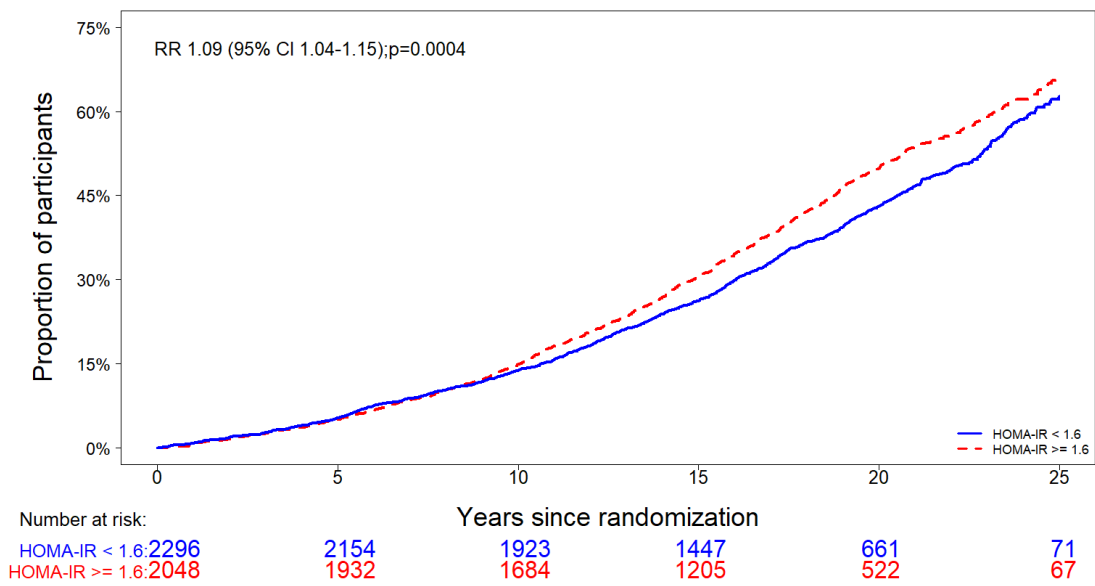


Figure 2

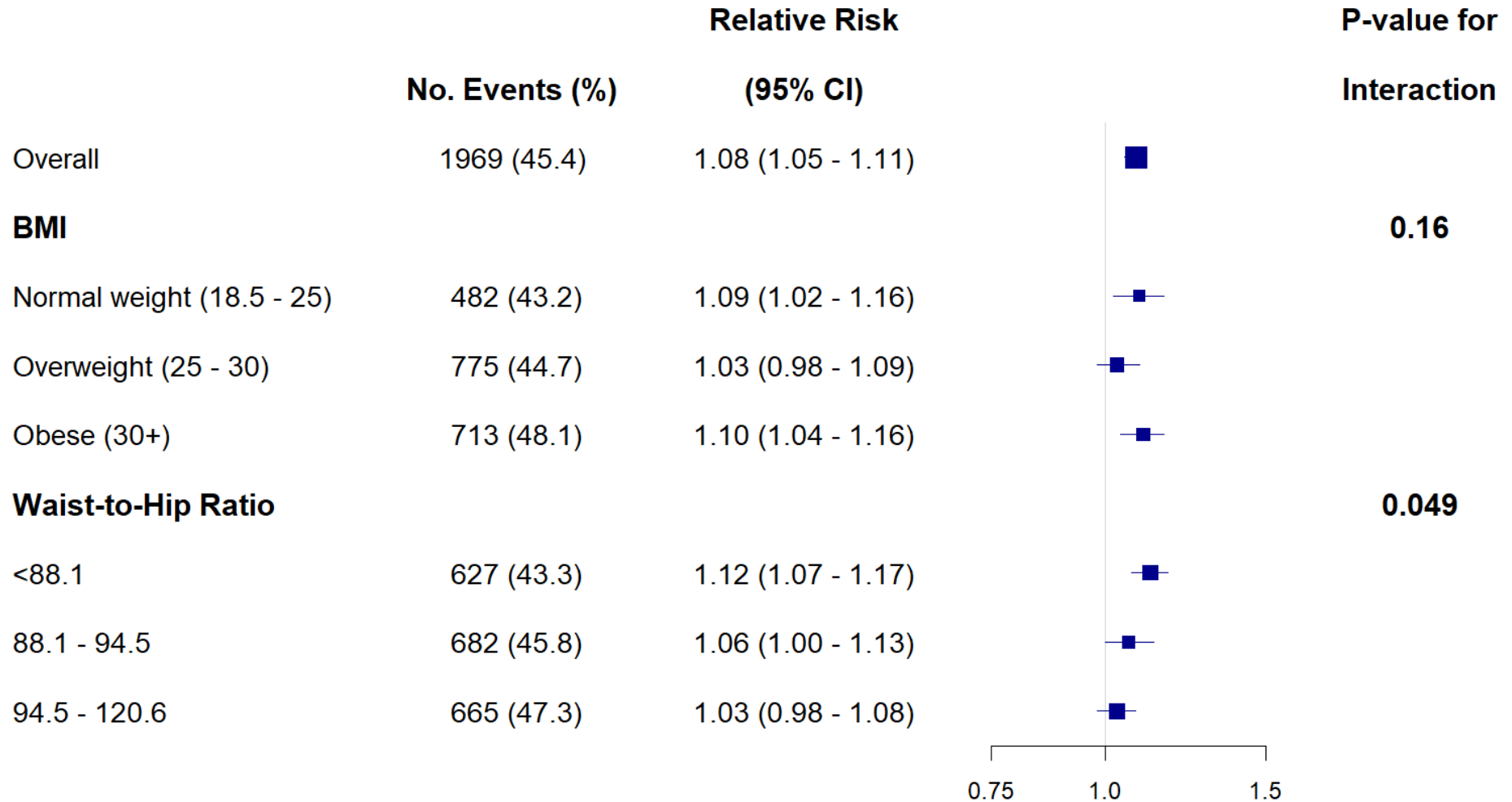


Figure 3.

