International Journal of Cardiology 379 (2023) 66–75

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Metabolic syndrome and risk of incident heart failure in non-diabetic patients with established cardiovascular disease

Pascal M. Burger [a], Stefan Koudstaal [b], Jannick A.N. Dorresteijn [a], Gianluigi Savarese [c], Manon G. van der Meer [d], Gert J. de Borst [e], Arend Mosterd [f], Frank L.J. Visseren [a,*], on behalf of the UCC-SMART study group

[a] Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, the Netherlands
[b] Department of Cardiology, Green Heart Hospital, Gouda, the Netherlands
[c] Department of Medicine, Karolinska Institutet, Stockholm, Sweden
[d] Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands
[e] Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, the Netherlands
[f] Department of Cardiology, Meander Medical Center, Amersfoort, the Netherlands

ARTICLE INFO

Keywords:
Heart failure
Metabolic syndrome
Insulin resistance
Obesity
Atherosclerotic vascular disease
Coronary artery disease

ABSTRACT

Background: In patients with established cardiovascular disease (CVD), the relation between metabolic syndrome (MetS) and incident heart failure (HF) in the absence of diabetes mellitus (DM) is largely unknown. This study assessed this relation in non-diabetic patients with established CVD.

Methods: Patients from the prospective UCC-SMART cohort with established CVD, but without DM or HF at baseline were included ($n = 4653$). MetS was defined according to the Adult Treatment Panel III criteria. Insulin resistance was quantified using the homeostasis model of insulin resistance (HOMA-IR). The outcome was a first hospitalization for HF. Relations were assessed using Cox proportional hazards models adjusted for established risk factors: age, sex, prior myocardial infarction (MI), smoking, cholesterol, and kidney function.

Results: During a median follow-up of 8.0 years, 290 cases of incident HF were observed (0.81/100 person years). MetS was significantly related to an increased risk of incident HF independent of established risk factors (hazard ratio [HR] 1.32; 95% confidence interval [CI] 1.04–1.68, HR per criterion 1.17; 95% CI 1.06–1.29), as was HOMA-IR (HR per standard deviation [SD] 1.15; 95% CI 1.03–1.29). Of the individual MetS components, only higher waist circumference independently increased the risk of HF (HR per SD 1.34; 95% CI 1.17–1.53). Relations were independent of the occurrence of interim DM and MI, and were not significantly different for HF with reduced vs preserved ejection fraction.

Conclusion: In CVD patients without a current diagnosis of DM, MetS and insulin resistance increase the risk of incident HF independent of established risk factors.

1. Introduction

Obesity is an increasing global health issue, with nearly a third of the world's population now classified as overweight or obese [1]. At the same time, there has been an emerging heart failure (HF) epidemic. The current worldwide prevalence of HF in the general adult population is estimated to be 1–2% [2]. The rising number of patients with HF is thought to be related to the growing burden of obesity-related diseases. Several factors have been identified as potential links between obesity and HF. Diabetes mellitus (DM) is an established and widely recognized risk factor of incident HF [3]. But in individuals without DM, other less commonly appreciated metabolic risk factors such as abdominal obesity, hypertension, lipid disturbances, and impaired glucose metabolism (clustered as part of the metabolic syndrome [MetS]) might also contribute to an elevated risk of HF [4].

MetS and insulin resistance increase the risk of incident HF in apparently healthy people and individuals with DM [5–13]. In non-diabetic patients with established cardiovascular disease (CVD), i.e. coronary artery disease (CAD), cerebrovascular disease (CeVD), peripheral artery disease (PAD), or abdominal aortic aneurysm (AAA),

* Corresponding author at: University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands.
E-mail address: F.L.J.Visseren@umcutrecht.nl (F.L.J. Visseren).

https://doi.org/10.1016/j.ijcard.2023.03.024
Received 9 January 2023; Received in revised form 2 March 2023; Accepted 7 March 2023
Available online 11 March 2023

metabolic risk factors have been shown to be strongly related to atherosclerotic CVD events, but their relation with incident HF is largely unknown [14,15]. This while the incidence of HF in these patients is considerably higher than in the general population, and interventions targeting (components of) the MetS may therefore be more (cost-) effective [16,17]. Establishing the relation between metabolic risk factors and incident HF in patients with established CVD may reveal potential treatment targets to reduce the incidence of HF in this high-risk population.

This study aimed to determine the relation between MetS (and its components), insulin resistance, and the risk of incident HF in CVD patients without a current diagnosis of DM.

2. Methods

2.1. Study population

Patients were from the Utrecht Cardiovascular Cohort-Second Manifestations of ARTerial disease (UCC-SMART) study, an ongoing prospective cohort study of patients with established CVD at the University Medical Centre Utrecht, the Netherlands. A detailed description of the study protocol has been published elsewhere [18]. The Medical Ethics Committee approved the study, and all participants gave their written informed consent. For the current study, all patients with established CVD, i.e. CAD (prior myocardial infarction [MI], cardiac arrest, or coronary revascularization), CeVD (prior transient ischemic attack, or ischemic or hemorrhagic stroke), PAD (symptomatic obstruction of distal arteries of the leg with ankle-brachial index ≤0.90, prior percutaneous transluminal angioplasty or bypass surgery of the leg, or amputation), and/or AAA (prior abdominal aortic surgery or an abdominal aortic anteroposterior diameter of ≥3 cm), without a history of HF, and without DM at baseline (self-reported diagnosis, use of antidiabetic medication, or fasting glucose ≥126 mg/dL at screening), who were enrolled in the cohort between July 2003 and January 2019 were included ($n = 4653$). Patients were enrolled in the cohort at least two months after the qualifying CVD event.

2.2. Data collection

Information on medical history, and physical examination and laboratory measurements were obtained at baseline based on a standardized screening protocol [18]. Waist circumference was measured halfway between the lower rib and the iliac crest. Hip circumference was measured at the largest circumference around the buttocks. Visceral and total abdominal fat were measured by ultrasonography. Systolic blood pressure (SBP) was measured twice in both arms, and the highest mean of the measurements in one arm was used. Total cholesterol, high-density lipoprotein cholesterol (HDL-c), triglycerides, creatinine, plasma glucose, and plasma insulin were measured in blood samples collected after an overnight fast. Non-HDL-c was calculated as total cholesterol minus HDL-c. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Smoking and medication use were self-reported. Missing data (<3.0% for all variables) were imputed by single imputation using predictive mean matching.

MetS was defined according to the Adult Treatment Panel (ATP) III criteria [19]. MetS was considered present in patients meeting at least three of the following criteria: waist circumference ≥40 in. (≥102 cm) in men and ≥35 in. (≥88 cm) in women, SBP ≥130 mmHg or DBP ≥85 mmHg, triglycerides ≥150 mg/dL (≥1.7 mmol/L), HDL-c <40 mg/dL (<1.04 mmol/L) in men and <50 mg/dL (<1.29 mmol/L) in women, and fasting glucose ≥100 mg/dL (≥5.6 mmol/L). Patients with a history of hypertension who were currently on antihypertensive drug treatment were considered to meet the criterion for elevated blood pressure.

Insulin resistance was quantified using the homeostasis model of insulin resistance (HOMA-IR): HOMA-IR = fasting glucose (mmol/L) × fasting insulin (mIU/L) / 22.5 [20]. HOMA-IR correlates well with more direct, but complicated and expensive measurements of insulin resistance, i.e. the euglycemic clamp technique, and therefore provides a reliable and feasible method for estimating insulin resistance in large epidemiological studies [21]. In a sensitivity analysis, HOMA-IR was replaced by other measures of insulin resistance, i.e. the quantitative insulin sensitivity check index (QUICKI = 1/(log(insulin [mIU/L] × glucose [mg/dL]))), and the triglyceride-glucose index (TyG = ln(triglycerides [mg/dL] × glucose [mg/dL] / 2)) [22].

2.3. Outcomes

The outcome of interest was incident HF, which was defined as a first hospitalization for HF. Outcomes were retrieved through linkage of UCC-SMART data to the national hospitalization registry from Statistics Netherlands. This registry continuously collects causes of hospitalization for all hospitalizations in the Netherlands. Cause of hospitalization is coded using the International Classification of Diseases (ICD), 9th (1995–2012) and 10th revision (2013-present). Hospitalization for HF was defined as any hospitalization with ICD-9 codes 428.0–428.4 or 428.9, or ICD-10 codes I50.1-I50.4 or I50.9. Outcomes were divided in HF with reduced ejection fraction (HFrEF; i.e. left ventricular ejection fraction [LVEF] ≤50%) and preserved ejection fraction (HFpEF; i.e. LVEF >50%), using echocardiography reports retrieved from medical records. MI and DM were assessed as interim outcomes (i.e. outcomes occurring during follow-up but before an HF event). These outcomes were available in the UCC-SMART cohort, and were based on hospital and general practitioner's data, and adjudicated by three independent physicians.

2.4. Data analyses

Baseline characteristics were presented stratified by number of MetS criteria, and HOMA-IR quartiles. Kaplan-Meier curves for incident HF were plotted stratified by number of MetS criteria, HOMA-IR quartiles, and CVD location.

Cox proportional hazards models were derived to assess the relation of MetS and HOMA-IR with incident HF. MetS was analyzed as a dichotomous variable (based on the ATP III definition), and in terms of the number of MetS criteria (both categorically and continuously). The relations of HOMA-IR and the individual MetS components with incident HF were analyzed continuously (per SD increase) and in quartiles. HOMA-IR was winsorized at the 1st and 99th percentile to limit the effect of outliers. The models were progressively adjusted for potential confounders. First, models were adjusted for age and sex. Then, models were additionally adjusted for established risk factors of HF, i.e. smoking, non-HDL-c, and eGFR, including CVD locations, i.e. CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA. Finally, to assess whether the effect of one metabolic risk factor on the risk of incident HF was mediated by another, models were additionally adjusted for all metabolic risk factors. The analyses were also performed stratified for HFrEF and HFpEF. Whether there was a differential effect of metabolic risk factors on the risk of HFrEF vs HFpEF was formally tested using the Lunn-McNeil method [23]. The proportional hazards assumption, assessed using Schoenfeld residuals, was not violated. Visual inspection of restricted cubic splines revealed no violations of the linearity assumption, except for SBP. A series of sensitivity analyses evaluating the influence of antihypertensive therapy, history of hypertension, and blood pressure cut points was performed to further explore the relation between hypertension and incident HF.

Influence of medication use was evaluated in an exploratory model adjusted for baseline use of statins, antiplatelet therapy, and

Table 1
Baseline characteristics stratified by number of metabolic syndrome criteria.

Characteristic	No metabolic syndrome, $n = 2674$ (57%)		Metabolic syndrome, $n = 1979$ (43%)	
	0–1 ATP III criteria, $n = 1283$ (28%)	2 ATP III criteria, $n = 1391$ (30%)	3 ATP III criteria, $n = 1106$ (24%)	4–5 ATP III criteria, $n = 873$ (19%)
Age (years)	58.2 ± 11.0	60.7 ± 10.2	61.1 ± 9.9	59.9 ± 9.7
Sex (male)	885 (69%)	1033 (74%)	795 (72%)	634 (73%)
Smoking status				
Former	580 (45%)	662 (48%)	532 (48%)	405 (46%)
Current	354 (28%)	364 (26%)	310 (28%)	283 (32%)
CVD locations				
Coronary artery disease	734 (57%)	883 (64%)	729 (66%)	596 (68%)
Prior myocardial infarction	407 (32%)	438 (32%)	375 (34%)	334 (38%)
Cerebrovascular disease	452 (35%)	421 (30%)	325 (29%)	222 (25%)
Peripheral artery disease	152 (12%)	168 (12%)	141 (13%)	138 (16%)
Abdominal aortic aneurysm	73 (6%)	78 (6%)	86 (8%)	80 (9%)
History of hypertension	420 (33%)	761 (55%)	710 (64%)	637 (73%)
Body-mass index (kg/m^2)	24.4 ± 2.8	25.9 ± 3.2	28.1 ± 3.9	29.9 ± 4.0
Metabolic syndrome				
Waist circumference (inch)	34.3 ± 3.9	36.2 ± 4.0	39.0 ± 4.3	41.3 ± 4.0
Systolic blood pressure (mmHg)	130 ± 19	139 ± 20	139 ± 19	142 ± 19
Diastolic blood pressure (mmHg)	78 ± 11	82 ± 11	82 ± 11	84 ± 11
Triglycerides (mg/dL)	89 ± 35	106 ± 53	151 ± 97	204 ± 106
HDL-cholesterol (mg/dL)	54 ± 15	50 ± 14	46 ± 12	39 ± 8
Fasting glucose (mg/dL)	95 ± 7	105 ± 11	106 ± 12	112 ± 13
Insulin resistance				
Fasting insulin (mU/L), median (IQR)	7.0 (5.0–9.7)	8.6 (6.0–12.0)	11.0 (8.0–16.0)	14.0 (10.0–20.0)
HOMA-IR, median (IQR)	1.6 (1.1–2.3)	2.2 (1.6–3.0)	2.9 (2.0–4.2)	3.9 (2.7–5.8)
HOMA-IR ≥2.0, n (%)[a]	414 (32%)	802 (58%)	832 (75%)	787 (90%)
HOMA-IR ≥2.5, n (%)[a]	247 (19%)	530 (38%)	661 (60%)	697 (80%)
QUICKI, median (IQR)	0.36 (0.34–0.38)	0.34 (0.32–0.36)	0.33 (0.31–0.34)	0.31 (0.30–0.33)
TyG, median (IQR)	8.3 (8.1–8.6)	8.5 (8.3–8.8)	8.8 (8.5–9.1)	9.2 (9.0–9.5)
Other laboratory values				
CRP (mg/L), median (IQR)	1.2 (0.6–2.8)	1.6 (0.8–3.2)	2.1 (1.1–4.2)	2.6 (1.3–5.3)
LDL-cholesterol (mg/dL)	101 ± 35	102 ± 36	104 ± 39	106 ± 40
Non-HDL-cholesterol (mg/dL)	116 ± 35	120 ± 39	131 ± 42	143 ± 44
eGFR (mL/min/1.73 m^2)	81 ± 16	78 ± 17	78 ± 17	77 ± 18
Medication use				
Statin	943 (74%)	1090 (78%)	881 (80%)	671 (77%)
Antiplatelet therapy	1040 (81%)	1164 (84%)	920 (83%)	718 (82%)
Antihypertensive agent	836 (65%)	1065 (77%)	913 (83%)	741 (85%)

All data in n (%) or mean ± SD, unless otherwise specified.
Abbreviations: ATP = Adult Treatment Panel, CRP = C-reactive protein, CVD = cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, HOMA-IR = homeostasis model of insulin resistance, IQR = interquartile range, LDL = low-density lipoprotein, MetS = metabolic syndrome, QUICKI = quantitative insulin sensitivity check index, SD = standard deviation, TyG = triglyceride-glucose index.
[a] Commonly used thresholds for insulin resistance.

antihypertensive agents. Mediation through the occurrence of DM or MI during follow-up was assessed by adjusting the model for interim DM and MI as time-varying covariates. To assess the effects of metabolic risk factors in complete absence of DM (both at baseline and during follow-up), a sensitivity analysis was performed in which patients with interim DM were excluded. Reverse causality was assessed by repeating the analyses after excluding patients who had incident HF within the first 1, 2, and 5 years of follow-up. Effect modification by age, sex, and CVD location was evaluated by testing interaction terms of these factors with metabolic risk factors, and by performing stratified analyses. In a sensitivity analysis, the relation of QUICKI and TyG with incident HF was assessed and compared to the main analysis with HOMA-IR. The effects of waist circumference were compared to other measures of obesity by replacing it by body-mass index (BMI), waist-to-hip ratio, visceral fat, and contribution of visceral fat to total abdominal fat. The combined effects of the presence of both metabolic and established risk factors were assessed by determining the effects of combinations of MetS with prior MI and/or current smoking, on the risk of incident HF.

All analyses were conducted with R statistical software V.4.0.3 (www.r-project.org).

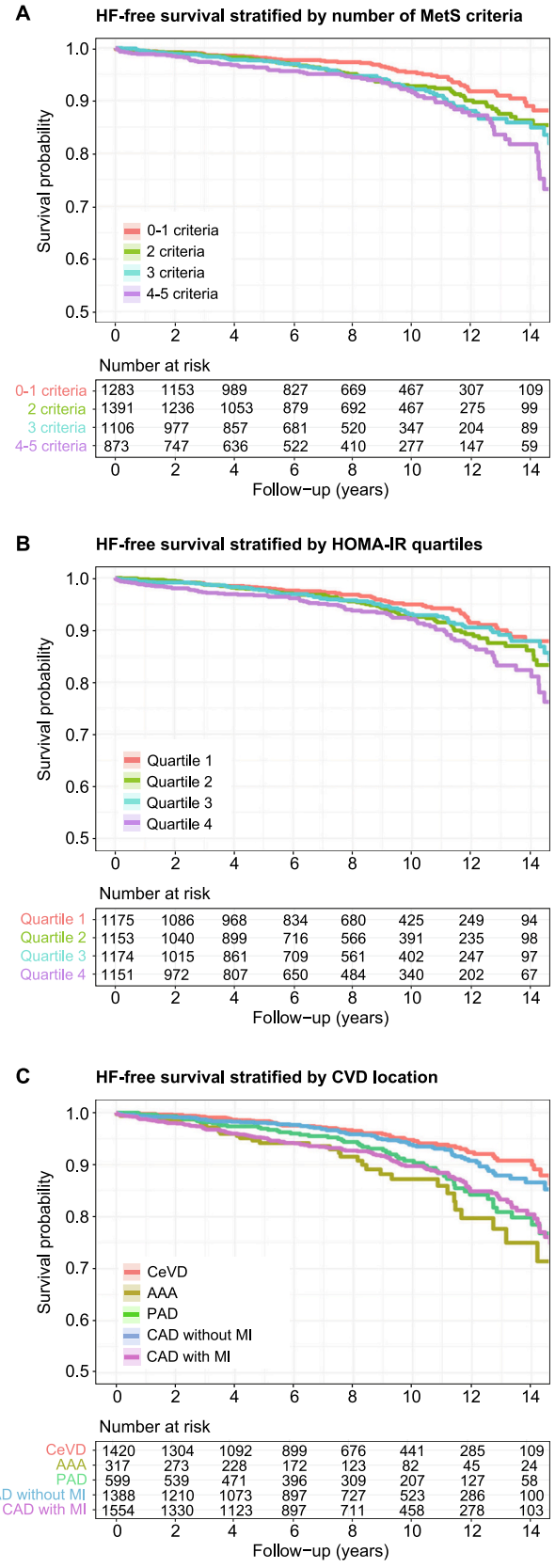
3. Results

3.1. Baseline characteristics

In the total study population, 1979 patients (42.5%) had MetS, and median HOMA-IR was 2.4 (interquartile range [IQR] 1.6–3.6). Baseline characteristics are presented stratified by number of MetS criteria in Table 1, and HOMA-IR quartiles in Table S1. Levels of HOMA-IR and other measures of insulin resistance, the individual MetS components, and BMI increased with an increasing number of MetS criteria, while age, sex, smoking status, and statin and antiplatelet use remained relatively stable. Similar trends were observed across HOMA-IR quartiles.

3.2. Incidence of HF

During a median follow-up of 8.0 years (IQR 4.3–11.4) incident HF was observed in 290 patients (6.2%; event rate: 0.81 / 100 person years). This included 114 (39.3%) cases of HFrEF, 102 (35.2%) cases of HFpEF, and 74 (25.5%) cases with unknown LVEF. The crude incidence of HF was higher in patients with compared to without MetS (0.98 vs.



(caption on next column)

Fig. 1. Unadjusted HF-free survival stratified by the number of MetS criteria (A), HOMA-IR quartiles (B), and CVD location (C).
Quartiles of HOMA-IR, median (range): Quartile 1, 1.18 (0.39–1.58); Quartile 2, 1.96 (1.59–2.36); Quartile 3, 2.88 (2.37–3.64); Quartile 4, 4.95 (3.65–30.80).
Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CVD = cardiovascular disease, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, MetS = metabolic syndrome, MI = myocardial infarction, PAD = peripheral artery disease.

0.69 / 100 person years), and increased with an increasing number of MetS criteria (Fig. 1A). A similar trend was observed across HOMA-IR quartiles, but the incidence in the second and third quartiles was almost equal (Fig. 1B). HF incidence was lowest in patients with CeVD, followed by patients with CAD without prior MI (Fig. 1C). The incidence in patients with PAD and AAA was comparable to patients with a prior MI.

3.3. Relation of MetS and HOMA-IR with incident HF

MetS was significantly related to an increased risk of incident HF, independent of established risk factors (hazard ratio [HR] 1.32; 95% confidence interval [CI] 1.04–1.68) (Table 2). There was a significant continuous relation between the number of MetS criteria and incident HF (HR per 1 criterion 1.17; 95% CI 1.06–1.29), with an especially high relative risk for patients with 4–5 criteria (HR vs. 0–1 criteria 1.69; 95% CI 1.18–2.41). Higher HOMA-IR was also significantly related to an increased risk of incident HF independent of established risk factors (HR per SD [= 1.91] increase 1.15; 95% CI 1.03–1.29). Especially values within the highest quartile of HOMA-IR (>3.6) were associated with a high relative risk (HR vs. lowest quartile 1.55; 95% CI 1.11–2.17). Additional adjustment for medication use hardly changed the results (Table S2).

The relation between MetS and incident HF was attenuated and no longer statistically significant after additional adjustment for HOMA-IR, indicating that the effect of MetS on the risk of HF is partially mediated by increases in insulin resistance (Table 2). However, the relation of the number of MetS criteria and the presence of 4–5 criteria with incident HF remained significant, implying that metabolic disturbances also contribute to an elevated risk of HF through other pathways than insulin resistance. The relation between HOMA-IR and incident HF was almost completely attenuated by adjustment for waist circumference, SBP, triglycerides, and HDL-c, indicating that the effect of insulin resistance on HF risk is largely mediated by changes in these components of the MetS.

3.4. Individual components of the MetS

The ATP III criteria for high waist circumference, high triglycerides, and low HDL-c were significantly related to an increased risk of incident HF when adjusted for age and sex (Table 3). These components and fasting glucose also had a significant continuous relation with HF adjusted for age and sex. Only waist circumference remained significantly related to incident HF after adjustment for established risk factors (HR per SD [= 4.7 in./12.0 cm] increase 1.34; 95% CI 1.17–1.53). Especially a waist circumference in the highest quartile (>40.9 in. [>104 cm] for men, and > 37.4 in. [>95 cm] for women) was related to an increased risk (HR vs. lowest quartile 2.10; 95% CI 1.49–2.97). After adjustment for the other MetS components and HOMA-IR, the relation between waist circumference and incident HF was only marginally attenuated, suggesting that waist circumference increases the risk of HF independent of other metabolic risk factors. The full model containing all established and metabolic risk factors is presented in Table S3.

Blood pressure was not related to incident HF based on the ATP III criterion, nor when the relation between SBP and HF was assessed linearly (Table 3). However, restricted cubic splines revealed a non-linear

Table 2
Relation of metabolic syndrome and HOMA-IR with incident HF.

	Events/ Patients	Event rate (events/100 PY)	Unadjusted, HR (95% CI)	Adjusted for age and sex, HR (95% CI)	Adjusted for established risk factors[a], HR (95% CI)	Adjusted for metabolic risk factors[b], HR (95% CI)
Metabolic syndrome						
ATP III definition	290/4653	0.81	1.46 (1.16–1.83)	1.39 (1.11–1.75)	1.32 (1.04–1.68)	1.21 (0.93–1.57)
No. of criteria						
Continuous (per 1 criterion)	290/4653	0.81	1.22 (1.11–1.33)	1.20 (1.09–1.32)	1.17 (1.06–1.29)	1.13 (1.01–1.27)
Continuous (per SD = 1.25 criteria)	290/4653	0.81	1.28 (1.14–1.43)	1.26 (1.12–1.42)	1.21 (1.07–1.37)	1.17 (1.02–1.34)
0–1	60/1283	0.58	Ref	Ref	Ref	Ref
2	85/1391	0.79	1.40 (1.00–1.94)	1.19 (0.85–1.69)	1.14 (0.82–1.59)	1.10 (0.78–1.54)
3	74/1106	0.88	1.57 (1.12–2.21)	1.30 (0.92–1.83)	1.25 (0.88–1.77)	1.16 (0.80–1.67)
4–5	71/873	1.10	1.97 (1.40–2.78)	1.89 (1.34–2.66)	1.69 (1.18–2.41)	1.51 (1.02–2.26)
Insulin resistance						
HOMA-IR						
Continuous (per 1 unit)	290/4653	0.81	1.10 (1.04–1.16)	1.10 (1.04–1.16)	1.08 (1.02–1.14)	1.02 (0.96–1.10)
Continuous (per SD = 1.91 units)	290/4653	0.81	1.19 (1.07–1.33)	1.20 (1.07–1.33)	1.15 (1.03–1.29)	1.05 (0.92–1.19)
Quartile 1	60/1175	0.61	Ref	Ref	Ref	Ref
Quartile 2	75/1153	0.83	1.34 (0.96–1.88)	1.27 (0.91–1.79)	1.29 (0.92–1.81)	1.15 (0.81–1.63)
Quartile 3	68/1174	0.76	1.21 (0.85–1.71)	1.20 (0.85–1.69)	1.09 (0.77–1.56)	0.91 (0.63–1.32)
Quartile 4	87/1151	1.07	1.80 (1.29–2.50)	1.68 (1.21–2.34)	1.55 (1.11–2.17)	1.15 (0.78–1.69)

Hazard ratios (95% CI) for the relation of metabolic syndrome and HOMA-IR with incident HF.
Quartiles of HOMA-IR, median (range): Quartile 1, 1.18 (0.39–1.58); Quartile 2, 1.96 (1.59–2.36); Quartile 3, 2.88 (2.37–3.64); Quartile 4, 4.95 (3.65–30.80).
Abbreviations: AAA = abdominal aortic aneurysm, ATP = Adult Treatment Panel, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, No. = number, PAD = peripheral artery disease, PY = person years, Ref = reference, SD = standard deviation.
[a] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.
[b] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus HOMA-IR (only in the analyses with metabolic syndrome and its criteria), or waist circumference, systolic blood pressure, triglycerides, and HDL-c (only in the analyses with HOMA-IR). The analyses with HOMA-IR were not adjusted for fasting glucose, as fasting glucose is in the HOMA-IR formula.

relation between SBP and incident HF, with both low (<130 mmHg) and high (>160 mmHg) levels of SBP related to an increased risk of HF (Fig. S1A). A similar shape was observed for other measures of blood pressure (Fig. S1B—D). Alternative indicators of hypertension were related to an increased risk of incident HF, i.e. history of hypertension (HR 1.33; 95% CI 1.04–1.70), and number of antihypertensive drugs used at baseline (HR per one drug 1.26; 95% CI 1.12–1.42), as was SBP dichotomized at a threshold of 160 mmHg (HR 1.33; 95% CI 1.00–1.77) (Table S4). There was a trend towards an increased risk of HF with higher levels of SBP and DBP in patients without antihypertensive therapy at baseline, and patients with SBP ≥120 mmHg, while opposite trends were observed in patients with antihypertensive therapy or SBP <120 mmHg (Table S5).

3.5. Relation between metabolic risk factors and HF subtypes

There was a trend towards a relation between MetS, higher HOMA-IR, and an increased risk of both HFrEF and HFpEF (Table 4; individual MetS components in Table S6). Every additional MetS criterion significantly increased the risk of HFrEF (HR 1.16; 95% CI 1.00–1.35), and HFpEF (HR 1.18; 95% CI 1.00–1.39). Overall, effect sizes were greater for HFpEF as compared to HFrEF (except for triglycerides and HDL-c), but differences were not significant (Lunn-McNeil tests: $p > 0.05$). Similar results were obtained for unclassified HF cases.

3.6. Influence of interim MI and DM

Interim MI and DM were observed in 237 patients (event rate: 0.67 / 100 person years) and 316 patients (event rate: 0.92 / 100 person years) respectively, of whom 31 (13.1%) and 23 (7.3%) patients went on to have incident HF later during follow-up. Adjusted for established risk factors, MetS and HOMA-IR were not significantly related to interim MI, but very strongly related to interim DM (Table S7). Interim MI significantly increased the risk of subsequent incident HF (HR 2.55; 95% CI 1.74–3.74), while interim DM did not (Table S8). Adjustment for interim MI and DM hardly altered the relation of MetS and HOMA-IR with incident HF (Table S9). Results also remained largely unchanged after excluding patients with interim DM (Table S10).

3.7. Other measures of insulin resistance and obesity

Replacing HOMA-IR by QUICKI and TyG yielded largely comparable results, although the relation between these other measures of insulin resistance and incident HF was no longer significant after adjustment for established risk factors (Table S11). Waist-to-hip ratio, visceral fat, and contribution of visceral to total abdominal fat all had similar relations with incident HF as waist circumference (Table S12). Waist circumference and the other measures of abdominal obesity were more strongly related to incident HF than BMI.

3.8. Reverse causality and effect modification

Repeating the analyses after excluding patients who had incident HF within the first 1, 2, and 5 years of follow-up yielded largely consistent results (Table S13). The relation between HOMA-IR and incident HF was slightly attenuated by excluding patients with an event in the first year. The relation between metabolic risk factors and incident HF was not significantly modified by age, sex, or CVD location (Table S14). There was a non-significant trend towards a stronger effect of MetS and HOMA-IR in women as compared to men.

3.9. Combined effects of metabolic and established risk factors

MetS increased the risk of incident HF on top of established risk factors, i.e. prior MI and current smoking (Fig. 2). The combined presence of all three risk factors was associated with the highest relative risk of incident HF (compared to none of the three risk factors: HR 5.42; 95% CI 3.35–8.78), exceeding relative risks associated with prior MI alone

Table 3
Relation between individual components of the metabolic syndrome and incident HF.

	Events/ Patients	Event rate (events/100 PY)	Unadjusted, HR (95% CI)	Adjusted for age and sex, HR (95% CI)	Adjusted for established risk factors[a], HR (95% CI)	Adjusted for metabolic risk factors[b], HR (95% CI)
Waist circumference						
ATP III criterion, ≥40/ ≥35 in. (M/F)	290/4653	0.81	1.68 (1.34–2.12)	1.70 (1.35–2.15)	1.60 (1.27–2.03)	1.52 (1.18–1.95)
Continuous (per SD = 4.7 in.)	290/4653	0.81	1.41 (1.26–1.58)	1.38 (1.21–1.57)	1.34 (1.17–1.53)	1.31 (1.13–1.52)
Quartile 1	50/1189	0.53	Ref	Ref	Ref	Ref
Quartile 2	73/1248	0.73	1.35 (0.94–1.93)	1.19 (0.83–1.71)	1.16 (0.81–1.66)	1.14 (0.79–1.64)
Quartile 3	69/1145	0.78	1.46 (1.02–2.11)	1.30 (0.90–1.87)	1.22 (0.85–1.76)	1.18 (0.80–1.72)
Quartile 4	98/1071	1.26	2.45 (1.74–3.44)	2.27 (1.61–3.19)	2.10 (1.49–2.97)	1.98 (1.36–2.88)
Blood pressure						
ATP III criterion, ≥130/ ≥85 mmHg	290/4653	0.81	1.18 (0.88–1.60)	0.88 (0.65–1.19)	0.94 (0.69–1.27)	0.85 (0.62–1.16)
Continuous, SBP (per SD = 20 mmHg)	290/4653	0.81	1.15 (1.03–1.28)	0.96 (0.85–1.07)	0.96 (0.86–1.08)	0.95 (0.84–1.06)
Quartile 1	71/1198	0.82	Ref	Ref	Ref	Ref
Quartile 2	53/1153	0.62	0.75 (0.53–1.07)	0.67 (0.47–0.96)	0.70 (0.49–1.00)	0.68 (0.48–0.97)
Quartile 3	78/1181	0.83	0.94 (0.68–1.29)	0.72 (0.52–1.00)	0.76 (0.55–1.06)	0.72 (0.51–0.99)
Quartile 4	88/1121	0.93	1.04 (0.76–1.43)	0.62 (0.45–0.85)	0.65 (0.47–0.90)	0.62 (0.45–0.87)
Triglycerides						
ATP III criterion, ≥150 mg/dL	290/4653	0.81	1.12 (0.87–1.44)	1.33 (1.04–1.72)	1.21 (0.91–1.61)	1.08 (0.80–1.46)
Continuous (per SD = 87 mg/dL)	290/4653	0.81	1.03 (0.92–1.14)	1.11 (1.00–1.22)	1.06 (0.94–1.20)	1.00 (0.87–1.16)
Quartile 1	69/1232	0.73	Ref	Ref	Ref	Ref
Quartile 2	75/1134	0.86	1.11 (0.80–1.54)	1.11 (0.80–1.54)	1.01 (0.73–1.41)	0.95 (0.68–1.33)
Quartile 3	66/1124	0.75	0.93 (0.67–1.31)	1.01 (0.72–1.42)	0.90 (0.63–1.28)	0.78 (0.54–1.12)
Quartile 4	80/1163	0.88	1.09 (0.79–1.51)	1.36 (0.98–1.89)	1.15 (0.79–1.66)	0.93 (0.62–1.40)
HDL-cholesterol						
ATP III criterion, <40/ <50 mg/dL (M/F)	290/4653	0.81	1.20 (0.95–1.53)	1.39 (1.09–1.77)	1.26 (0.99–1.61)	1.14 (0.88–1.47)
Continuous (per SD = 14 mg/dL)	290/4653	0.81	0.88 (0.78–0.99)	0.85 (0.74–0.97)	0.91 (0.80–1.04)	0.98 (0.85–1.13)
Quartile 1	84/1198	0.90	Ref	Ref	Ref	Ref
Quartile 2	64/1174	0.72	0.81 (0.58–1.11)	0.75 (0.54–1.04)	0.81 (0.58–1.12)	0.88 (0.63–1.22)
Quartile 3	64/1128	0.74	0.80 (0.58–1.11)	0.70 (0.50–0.97)	0.78 (0.56–1.09)	0.86 (0.61–1.20)
Quartile 4	78/1150	0.85	0.91 (0.67–1.24)	0.72 (0.53–0.98)	0.85 (0.62–1.17)	1.03 (0.73–1.44)
Fasting glucose						
ATP III criterion, ≥100 mg/dL	290/4653	0.81	1.48 (1.17–1.88)	1.15 (0.90–1.47)	1.12 (0.88–1.43)	1.02 (0.80–1.31)
Continuous (per SD = 12 mg/dL)	290/4653	0.81	1.26 (1.14–1.39)	1.12 (1.01–1.25)	1.10 (0.98–1.22)	1.04 (0.93–1.17)
Quartile 1	69/1226	0.66	Ref	Ref	Ref	Ref
Quartile 2	69/1337	0.66	1.06 (0.76–1.48)	0.88 (0.63–1.23)	0.89 (0.64–1.25)	0.84 (0.60–1.17)
Quartile 3	66/1041	0.85	1.41 (1.01–1.98)	1.05 (0.74–1.47)	0.99 (0.71–1.39)	0.90 (0.64–1.27)
Quartile 4	86/1049	1.16	1.97 (1.44–2.71)	1.37 (0.99–1.89)	1.29 (0.93–1.78)	1.10 (0.79–1.54)

Hazard ratios (95% CI) for the relation of the individual components of the metabolic syndrome with incident HF. Waist circumference and HDL-c quartiles are sex-specific (e.g. the highest waist circumference quartile includes the 25% of men with the highest waist circumference and the 25% of women with the highest waist circumference).

Quartiles, median (range): Waist circumference (M/F, inch): Quartile 1, 34 (25–35) / 29 (23−31); Quartile 2, 37 (36–38) / 33 (32–34); Quartile 3, 40 (39–41) / 36 (35–37); Quartile 4, 43 (42–63) / 40 (38–55); SBP (mmHg): Quartile 1, 116 (85–123); Quartile 2, 130 (124–134); Quartile 3, 140 (135–148); Quartile 4, 160 (149–227); Triglycerides (mg/dL): Quartile 1, 69 (18–80); Quartile 2, 97 (81–106); Quartile 3, 126 (107–157); Quartile 4, 204 (158–1311); HDL-c (M/F, mg/dL): Quartile 1, 34 (6–38) / 41 (19–47); Quartile 2, 41 (39–44) / 51 (48–55); Quartile 3, 48 (45–52) / 60 (56–66); Quartile 4, 60 (53–135) / 75 (67–152); Fasting glucose (mg/dL): Quartile 1, 92 (54–95); Quartile 2, 100 (96–103); Quartile 3, 107 (104–110); Quartile 4, 117 (111–125).

Abbreviations: AAA = abdominal aortic aneurysm, ATP = Adult Treatment Panel, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, eGFR = estimated glomerular filtration rate, F = female, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, M = male, MI = myocardial infarction, PY = person years, Ref = reference, SD = standard deviation.

[a] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.

[b] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus all other components of the metabolic syndrome and HOMA-IR. The analyses with fasting glucose were not adjusted for HOMA-IR, as the HOMA-IR formula includes fasting glucose.

(HR 1.84; 95% CI 1.24–2.73), current smoking alone (HR 1.31; 95% CI 0.77–2.22), and the combination of prior MI and current smoking (HR 3.10; 95% CI 1.82–5.28).

4. Discussion

In this study of 4653 CVD patients without a current diagnosis of DM, MetS and insulin resistance (measured by HOMA-IR) were related to an increased risk of incident HF independent of established risk factors. Effects mostly appeared to be greater for HFpEF as compared to HFrEF, but differences were not significant. The relation between insulin resistance and incident HF was largely mediated through changes in the MetS components, while the degree of metabolic disturbances in the context of the MetS also increased the risk of HF independent of insulin resistance. Of the individual components, abdominal obesity appeared to be the major driver of HF risk.

Several mechanisms may explain the relation between MetS, insulin resistance, and incident HF. First of all, in the setting of insulin resistance, the myocardium uses more free fatty acids instead of glucose, which increases vulnerability to pressure overload and ischemia [24].

Table 4
Relation of metabolic syndrome and HOMA-IR with HF subtypes.

	HFrEF (n = 114 [39.3%])		HFpEF (n = 102 [35.2%])		HF unclassified[a] (n = 74 [25.5%])	
	Adjusted for established risk factors[b], HR (95% CI)	Adjusted for metabolic risk factors[c], HR (95% CI)	Adjusted for established risk factors[b], HR (95% CI)	Adjusted for metabolic risk factors[c], HR (95% CI)	Adjusted for established risk factors[b], HR (95% CI)	Adjusted for metabolic risk factors[c], HR (95% CI)
Metabolic syndrome						
ATP III definition	1.28 (0.87–1.89)[d]	1.19 (0.78–1.82)	1.35 (0.90–2.03)[d]	1.24 (0.79–1.95)	1.33 (0.82–2.15)	1.21 (0.71–2.05)
No. of criteria						
Continuous (per 1 criterion)	1.16 (1.00–1.35)[d]	1.12 (0.94–1.33)	1.18 (1.00–1.39)[d]	1.14 (0.93–1.39)	1.17 (0.96–1.43)	1.14 (0.91–1.42)
Continuous (per SD = 1.25 criteria)	1.20 (1.00–1.46)	1.15 (0.93–1.43)	1.23 (1.00–1.51)	1.18 (0.91–1.51)	1.22 (0.95–1.56)	1.18 (0.89–1.55)
Insulin resistance						
HOMA-IR						
Continuous (per 1 unit)	1.06 (0.97–1.16)	1.01 (0.90–1.13)	1.10 (1.00–1.21)	1.04 (0.93–1.17)	1.09 (0.96–1.23)	1.02 (0.88–1.19)
Continuous (per SD = 1.91 units)	1.12 (0.94–1.33)[d]	1.02 (0.82–1.26)	1.20 (1.00–1.44)[d]	1.08 (0.87–1.35)	1.18 (0.92–1.48)	1.04 (0.78–1.39)

Hazard ratios (95% CI) for the relation of metabolic syndrome and HOMA-IR with HF subtypes.
Abbreviations: AAA = abdominal aortic aneurysm, ATP = Adult Treatment Panel, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-c = high-density lipoprotein cholesterol, HF = heart failure, HFrEF = heart failure with reduced ejection fraction, HFpEF = heart failure with preserved ejection fraction, HOMA-IR = homeostasis model of insulin resistance, HR = hazard ratio, MI = myocardial infarction, No. = number, PAD = peripheral artery disease, PY = person years, Ref = reference, SD = standard deviation.
[a] Cases for which LVEF was unknown.
[b] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA.
[c] Adjusted for age, sex, smoking, non-HDL-c, eGFR, CAD with prior MI, CAD without prior MI, CeVD, PAD, and AAA, plus HOMA-IR (only in the analyses with metabolic syndrome and its criteria), or waist circumference, systolic blood pressure, triglycerides, and HDL-c (only in the analyses with HOMA-IR). The analyses with HOMA-IR were not adjusted for fasting glucose, as fasting glucose is in the HOMA-IR formula.
[d] Hazard ratios compared for HFrEF vs HFpEF using the Lunn-McNeil method. This showed no significant differences ($p > 0.05$).

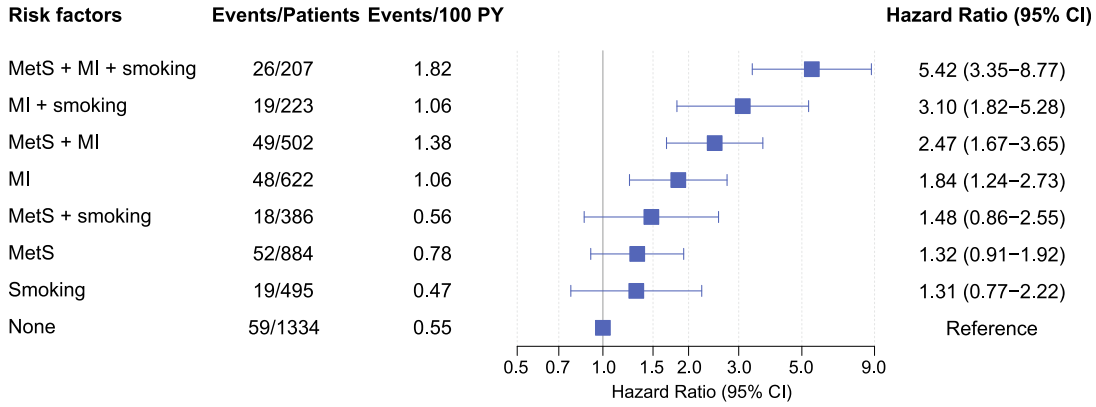


Fig. 2. Hazard ratios (95% CI) for the combined effects of MetS, MI, and current smoking on the risk of incident HF. Hazard ratios are adjusted for age, sex, non-HDL-c, eGFR, CAD without MI, CeVD, PAD, and AAA. The reference group includes non-smoking patients without MetS and without a prior MI. When a risk factor is not included in the description of the subgroup, it means the risk factor is absent (e.g. 'MetS + smoking' indicates current smokers with MetS, but without a prior MI). Abbreviations: AAA = abdominal aortic aneurysm, CAD = coronary artery disease, CeVD = cerebrovascular disease, CI = confidence interval, HF = heart failure, MetS = metabolic syndrome, MI = myocardial infarction, PAD = peripheral artery disease, PY = person years.

Second, insulin may act as a growth factor, leading to increased myocardial mass and reduced cardiac output [25]. Dysfunctional adipose tissue causes sodium retention, activation of the sympathetic nervous system, and an increased response to angiotensin II, which contribute to volume expansion, increased peripheral vascular resistance, and myocardial hypertrophy and fibrosis [26,27]. Independent of insulin resistance, MetS may lead to incident HF through hypertension [5]. However, in the current study there was no significant continuous relation between SBP and incident HF. This is likely explained by the study population consisting of patients with established CVD, in whom the relation between SBP and HF appears to be non-linear, with both low and high levels of SBP related to an increased risk. A low SBP may be related to a higher risk of HF because it can be an early sign of systolic dysfunction leading up to HF, which may be common in a population in which 63% of patients had a history of CAD. Also, 54% had a history of hypertension, and 76% used at least one antihypertensive drug. Therefore, a low SBP may also be indicative of the use of (multiple) antihypertensive drugs, which may reflect a history of (severe) hypertension and/or a high presumed risk of CVD events. As shown in this study, a history of hypertension and a larger number of antihypertensive drugs at baseline were both related to an increased risk of HF. Moreover, antihypertensive therapy and patients' adherence to this therapy may change during follow-up, potentially diluting the relation between baseline SBP and outcomes. Finally, blood pressure was based on office measurements, which may not represent the average blood pressure during the day. Another explanation of how MetS may lead to incident HF independent of insulin resistance, is through its association with inflammation. It has been shown that inflammatory markers such as

CRP, IL-6, and TNF-α are associated with progressive systolic dysfunction and cardiac remodelling [28]. Finally, MetS and insulin resistance may lead to MI or DM, which then increase the risk of subsequent HF. But as shown in this study, metabolic risk factors are related to incident HF independent of interim MI and DM.

The results of this study extend prior work in people without a history of CVD. In line with the current study, previous population-based studies in America and Europe have shown that MetS is related to an increased risk of incident HF independent of established risk factors, with hazard ratios ranging from 1.32 to 1.74 [10–12]. As in the current study, abdominal obesity was strongly related to HF [5,7,10,11,13]. But in contrast with the current findings in patients with CVD, hypertension, low HDL-cholesterol, and high triglycerides were also identified as independent risk factors in some studies [7,10–13]. This difference might be explained by the fact that most patients with established CVD are treated with blood pressure- and lipid-lowering medication, potentially distorting the relation between these modifiable risk factors and incident HF. Previous studies have also demonstrated that insulin resistance is independently related to incident HF in people without a history of CVD [6–8,13]. But differences in the measures used to quantify insulin resistance complicate a direct comparison. One previous study assessed the relation between metabolic risk factors and the risk of HFrEF vs HFpEF [13]. In line with the current study, HOMA-IR and waist circumference were more strongly related to HFpEF, and lipids to HFrEF, although differences were larger and significant for HOMA-IR in the previous study. To our knowledge, no previous studies assessed the relation between metabolic risk factors and incident HF in patients with established CVD.

When evaluating metabolic risk factors and the risk of incident HF, a distinction between individuals with and without a history of CVD might be important for several reasons. First of all, many previous studies have demonstrated an obesity paradox in patients with established CVD, with the overweight having a better prognosis than their leaner counterparts [29]. This has casted doubts over the potential benefits of weight loss in this population. Second, the prevalence of MetS is considerably higher in patients with established CVD (42.5% in our cohort) as compared to the general population (7.0–26.9% in Western countries based on the ATP III definition) [30]. The median HOMA-IR of 2.4 in our cohort, indicates that almost half/more than half of all patients with established CVD meet commonly used thresholds for insulin resistance (HOMA-IR $\geq$2.0/$\geq$2.5) [6,20]. At the same time, the incidence of HF is also considerably higher in patients with established CVD, with an event rate of 0.81 per 100 person years in our cohort as compared to approximately 0.12 per 100 person years in a Dutch population-based cohort [31]. As shown in this study, not only patients with a prior MI or other manifestations of CAD, but also patients with non-coronary vascular disease are at high risk of HF. The prognosis associated with HF is poor with 5-year mortality rates exceeding 50%, and it imposes a huge economic burden estimated at a global expenditure of over $100 billion per year [32]. Besides HF, previous studies have shown that MetS and insulin resistance also increase the risk of other major adverse cardiovascular events in patients with established CVD [14,15]. This illustrates the scale and importance of both metabolic disturbances and the risk of HF in patients with a history of CVD, and highlights the need for interventions targeting these metabolic risk factors to reduce HF risk, especially in these high-risk patients.

In contrast with the obesity paradox observed in previous studies in patients with established CVD, abdominal obesity was the major driver of HF risk in the current study. Waist circumference was strongly related to incident HF independent of established and other metabolic risk factors. This suggests that weight loss might be an effective way to lower the risk of HF in these patients. Weight loss naturally reduces abdominal obesity, and also has positive effects on the other components of the MetS and insulin resistance. A meta-analysis of four cohort studies of patients with CAD has shown that intentional weight loss through lifestyle interventions reduced the risk of major adverse cardiovascular events by 33% [33]. Previous studies have also demonstrated that weight loss decreases left ventricular mass and lowers arterial and cardiac filling pressures, and may therefore reduce the risk of incident HF as well [34]. Randomized clinical trials assessing the effects of weight loss interventions (e.g. dietary interventions or exercise programs) on the risk of incident HF (and other CVD events) in patients with established CVD may be warranted. In addition, we propose that incident HF should be among the outcomes routinely presented in all future trials in this population, in an attempt to identify new therapies that can reduce the high risk of HF in these patients. Based on current knowledge, intensification of preventive therapy in CVD patients with MetS and/or insulin resistance may already be considered.

Strengths of this study are the practice-based cohort with prospective design, long follow-up, and low proportions of missing data. Study limitations should be considered. This is an observational study, thus subject to possible residual confounding. Insulin resistance was quantified by HOMA-IR instead of the euglycemic clamp technique, usually considered as the gold standard. However, HOMA-IR correlates well with clamp-measured insulin resistance and is more suitable for large epidemiological studies [21]. Echocardiography was not part of the baseline screening, so data on LVEF and other parameters of systolic and diastolic function at study entry were not available. Therefore, the influence of baseline cardiac function on the study results could not be assessed. HF outcomes were based on ICD codes. Registration of ICD codes by clinicians in routine clinical care might be imperfect, but a previous study in another Dutch cohort found that only 3.3% of patients with a presumed HF hospitalization based on ICD codes were misclassified [35]. Also, 74% of HF cases in this study could be confirmed and classified as either HFrEF or HFpEF based on echocardiography reports retrieved from medical records. For 26% of cases, information on LVEF was not available, so these remained unclassified. As outcomes were based on hospitalizations only, out-patient diagnoses of HF were missed. Specifically, the number of HFpEF cases may be underestimated, as HFpEF less frequently leads to hospitalization.

In conclusion, this study showed that in CVD patients without a current diagnosis of DM, MetS and insulin resistance are independent risk factors of incident HF. Abdominal obesity was identified as a major driver of HF risk, supporting the importance of weight loss in this population.

Funding

The UCC-SMART study was financially supported by a grant of the University Medical Center Utrecht. The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The authors did not receive any specific funding for the current study.

CRediT authorship contribution statement

Pascal M. Burger: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft, Writing – review & editing. **Stefan Koudstaal:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Jannick A.N. Dorresteijn:** Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – review & editing. **Gianluigi Savarese:** Investigation, Methodology, Validation, Writing – review & editing. **Manon G. van der Meer:** Investigation, Methodology, Validation, Writing – review & editing. **Gert J. de Borst:** Investigation, Methodology, Validation, Writing – review & editing. **Arend Mosterd:** Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – review & editing. **Frank L.J. Visseren:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Conflict of interest

Dr. Savarese reported grants and personal fees from Vifor, grants and non-financial support from Boehringer Ingelheim, grants and personal fees from AstraZeneca, personal fees from Roche, personal fees from Servier, grants and personal fees from Novartis, grants and personal fees from Cytokinetics, personal fees from Medtronic, grants from Boston Scientific, grants and personal fees from Pharmacosmos, grants from Merck, grants from Bayer, personal fees from Edwards, and funding through the Horizon 2022 program, outside the submitted work. Other authors declared no conflicts of interest.

Data availability statement

Results are based on calculations by the authors using non-public microdata from Statistics Netherlands. Under certain conditions, these microdata are accessible for statistical and scientific research. For further information: microdata@cbs.nl.

Acknowledgements

We gratefully acknowledge the contribution of the participants, the research nurses, R. van Petersen (data manager), A. Vandersteen (study manager), and the members of the UCC-SMART study group: M.J. Cramer, M.G. van der Meer, and H.M. Nathoe, Department of Cardiology; G.J. de Borst, Department of Vascular Surgery; M.L. Bots, Julius Center for Health Sciences and Primary Care; M.H. Emmelot-Vonk, Department of Geriatrics; P.A. de Jong, Department of Radiology; A.T. Lely, Department of Gynecology and Obstetrics; N.P. van der Kaaij, Department of Cardiothoracic Surgery; L.J. Kappelle and Y.M. Ruigrok, Department of Neurology; M.C. Verhaar, Department of Nephrology & Hypertension; F.L.J. Visseren (chair) and J.A.N. Dorresteijn, Department of Vascular Medicine, University Medical Center Utrecht and Utrecht University.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.03.024.

References

[1] Y.C. Chooi, C. Ding, F. Magkos, The epidemiology of obesity, Metabolism. 92 (2019) 6–10, https://doi.org/10.1016/j.metabol.2018.09.005.
[2] A. Groenewegen, F.H. Rutten, A. Mosterd, A.W. Hoes, Epidemiology of heart failure, Eur. J. Heart Fail. 22 (8) (2020) 1342–1356, https://doi.org/10.1002/ejhf.1858.
[3] S.M. Dunlay, M.M. Givertz, D. Aguilar, et al., Type 2 diabetes mellitus and heart failure a scientific statement from the American Heart Association and the Heart Failure Society of America, Circulation. 140 (7) (2019) E294–E324, https://doi.org/10.1161/CIR.0000000000000691.
[4] T.B. Horwich, G.C. Fonarow, Glucose, obesity, metabolic syndrome, and diabetes. Relevance to incidence of heart failure, J. Am. Coll. Cardiol. 55 (4) (2010) 283–293, https://doi.org/10.1016/j.jacc.2009.07.029.
[5] H. Bahrami, D.A. Bluemke, R. Kronmal, et al., Novel metabolic risk factors for incident heart failure and their relationship with obesity. The MESA (multi-ethnic study of atherosclerosis) study, J. Am. Coll. Cardiol. 51 (18) (2008) 1775–1783, https://doi.org/10.1016/j.jacc.2007.12.048.
[6] O. Vardeny, D.K. Gupta, B. Claggett, et al., Insulin resistance and incident heart failure. The ARIC study (atherosclerosis risk in communities), JACC Heart Fail. 1 (6) (2013) 531–536, https://doi.org/10.1016/j.jchf.2013.07.006.
[7] E. Ingelsson, J. Sundström, J. Ärnlöv, B. Zethelius, L. Lind, Insulin resistance and risk of congestive heart failure, J. Am. Med. Assoc. 294 (3) (2005) 334–341, https://doi.org/10.1001/jama.294.3.334.
[8] D. Banerjee, M.L. Biggs, L. Mercer, et al., Insulin resistance and risk of incident heart failure cardiovascular health study, Circ. Heart Fail. 6 (3) (2013) 364–370, https://doi.org/10.1161/CIRCHEARTFAILURE.112.000022.
[9] M. Wamil, R.L. Coleman, A.I. Adler, J.J.V. McMurray, R.R. Holman, 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 44 (8) (2021) 1877–1884, https://doi.org/10.2337/dc21-0429.
[10] T. Suzuki, R. Katz, N.S. Jenny, et al., Metabolic syndrome, inflammation, and incident heart failure in the elderly: the cardiovascular health study, Circ. Heart Fail. 1 (4) (2008) 242–248, https://doi.org/10.1161/CIRCHEARTFAILURE.108.785485.
[11] J. Wang, K. Sarnola, S. Ruotsalainen, et al., The metabolic syndrome predicts incident congestive heart failure: a 20-year follow-up study of elderly finns, Atherosclerosis. 210 (1) (2010) 237–242, https://doi.org/10.1016/j.atherosclerosis.2009.10.042.
[12] E. Ingelsson, J. Ärnlöv, L. Lind, J. Sundström, Metabolic syndrome and risk for heart failure in middle-aged men, Heart. 92 (10) (2006) 1409–1413, https://doi.org/10.1136/hrt.2006.089011.
[13] N. Savji, W.C. Meijers, T.M. Bartz, et al., The Association of Obesity and Cardiometabolic Traits with Incident HFpEF and HFrEF, JACC Heart Fail. 6 (8) (2018) 701–709, https://doi.org/10.1016/j.jchf.2018.05.018.
[14] A.M.J. Wassink, Y. Van Der Graaf, J.K. Olijhoek, F.L.J. Visseren, Metabolic syndrome and the risk of new vascular events and all-cause mortality in patients with coronary artery disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm, Eur. Heart J. 29 (2) (2008) 213–223, https://doi.org/10.1093/eurheartj/ehm582.
[15] S.N. Verhagen, A.M.J. Wassink, Y. van der Graaf, P.M. Gorter, F.L.J. Visseren, Insulin resistance increases the occurrence of new cardiovascular events in patients with manifest arterial disease without known diabetes. The SMART study, Cardiovasc. Diabetol. (2011) 10, https://doi.org/10.1186/1475-2840-10-100.
[16] M.D. Samsky, A. Hellkamp, W.R. Hiatt, et al., Association of heart failure with outcomes among patients with peripheral artery disease: insights from EUCLID, J. Am. Heart Assoc. 10 (12) (2021), https://doi.org/10.1161/JAHA.120.018684.
[17] B.M. Everett, J.H. Cornel, M. Lainscak, et al., Anti-inflammatory therapy with canakinumab for the prevention of hospitalization for heart failure, Circulation. 139 (10) (2019) 1289–1299, https://doi.org/10.1161/CIRCULATIONAHA.118.038010.
[18] M.C. Castelijns, M.A.G. Helmink, S.H.J. Hageman, et al., Cohort profile: the Utrecht Cardiovascular Cohort–Second Manifestations of Arterial Disease (UCC-SMART) Study–an ongoing prospective cohort study of patients at high cardiovascular risk in the Netherlands, BMJ Open 13 (2) (2023), e066952, https://doi.org/10.1136/bmjopen-2022-066952.
[19] S.M. Grundy, J.I. Cleeman, S.R. Daniels, et al., Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement, Circulation. 112 (17) (2005) 2735–2752, https://doi.org/10.1161/CIRCULATIONAHA.105.169404.
[20] D.R. Matthews, J.P. Hosker, A.S. Rudenski, B.A. Naylor, D.F. Treacher, R.C. Turner, Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man, Diabetologia. 28 (7) (1985) 412–419, https://doi.org/10.1007/BF00280883.
[21] E. Bonora, G. Targher, M. Alberiche, et al., Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity, Diabetes Care 23 (1) (2000) 57–63, https://doi.org/10.2337/diacare.23.1.57.
[22] Minh H. Van, H.A. Tien, C.T. Sinh, et al., Assessment of preferred methods to measure insulin resistance in Asian patients with hypertension, J. Clin. Hypertens. 23 (3) (2021) 529–537, https://doi.org/10.1111/jch.14155.
[23] M. Lunn, D. McNeil, Applying cox regression to competing risks, Biometrics 51 (2) (1995) 524–532, https://doi.org/10.2307/2532940.
[24] R.M. Witteles, M.B. Fowler, Insulin-resistant cardiomyopathy. clinical evidence, mechanisms, and treatment options, J. Am. Coll. Cardiol. 51 (2) (2008) 93–102, https://doi.org/10.1016/j.jacc.2007.10.021.
[25] M.K. Rutter, H. Parise, E.J. Benjamin, et al., Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham heart study, Circulation. 107 (3) (2003) 448–454, https://doi.org/10.1161/01.CIR.0000045671.62860.98.
[26] R.A. DeFronzo, C.R. Cooke, R. Andres, G.R. Faloona, P.J. Davis, The effect of insulin on renal handling of sodium, potassium, calcium, and phosphate in man, J. Clin. Investig. 55 (4) (1975) 845–855, https://doi.org/10.1172/JCI107996.
[27] E.A. Anderson, R.P. Hoffman, T.W. Balon, C.A. Sinkey, A.L. Mark, Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans, J. Clin. Investig. 87 (6) (1991) 2246–2252, https://doi.org/10.1172/JCI115260.
[28] G. Torre-Amione, S. Kapadia, C. Benedict, H. Oral, J.B. Young, D.L. Mann, Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the studies of left ventricular dysfunction (SOLVD), J. Am. Coll. Cardiol. 27 (5) (1996) 1201–1206, https://doi.org/10.1016/0735-1097(95)00589-7.
[29] A. Elagizi, S. Kachur, C.J. Lavie, et al., An overview and update on obesity and the obesity paradox in cardiovascular diseases, Prog. Cardiovasc. Dis. 61 (2) (2018) 142–150, https://doi.org/10.1016/j.pcad.2018.07.003.
[30] R.H. Eckel, S.M. Grundy, P.Z. Zimmet, The metabolic syndrome, Lancet. 365 (2005) 1415–1428, https://doi.org/10.1016/S0140-6736(05)66378-7.
[31] A. Uijl, S. Koudstaal, I. Vaartjes, et al., Risk for heart failure: the opportunity for prevention with the American Heart Association's Life's simple 7, JACC Heart Fail. 7 (8) (2019) 637–647, https://doi.org/10.1016/j.jchf.2019.03.009.

[32] C. Cook, G. Cole, P. Asaria, R. Jabbour, D.P. Francis, The annual global economic burden of heart failure, Int. J. Cardiol. 171 (3) (2014) 368–376, https://doi.org/10.1016/j.ijcard.2013.12.028.
[33] Q.R. Pack, J.P. Rodriguez-Escudero, R.J. Thomas, et al., The prognostic importance of weight loss in coronary artery disease: a systematic review and meta-analysis, Mayo Clin. Proc. 89 (10) (2014) 1368–1377, https://doi.org/10.1016/j.mayocp.2014.04.033.
[34] P. Poirier, T.D. Giles, G.A. Bray, et al., Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association scientific statement on obesity and heart disease from the obesity Committee of the Council on nutrition, physical activity, and metabolism, Circulation 113 (6) (2006) 898–918, https://doi.org/10.1161/CIRCULATIONAHA.106.171016.
[35] J. Buddeke, G.B. Valstar, I. Van Dis, et al., Mortality after hospital admission for heart failure: improvement over time, equally strong in women as in men, BMC Public Health 20 (1) (2020), https://doi.org/10.1186/s12889-019-7934-3.