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Waist-hip ratio and Mortality in Heart Failure

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ABSTRACT

Aims: A higher body mass index (BMI) is associated with better survival in heart failure (HF) patients, also known as the obesity paradox. However, BMI does not account for body composition. We therefore analysed the association between abdominal fat, measured via waist-hip ratio (WHR), BMI and all-cause mortality in patients with HF.

Methods: For this analysis 1738 patients from The Scottish BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) validation study were included. Patients without waist and hip measurements were excluded. WHR was defined as waist circumference/hip circumference, divided into tertiles and split for sex. A linear regression of principal components from an extensive panel of biomarkers was performed to provide insight in the pathophysiology behind a higher WHR.

Results: In total, 1479 patients with were included, of which 33% were female and mean age was 75±11 years. A higher WHR was independently associated with a higher BMI, a higher prevalence of diabetes and higher functional NYHA class. There was a significant interaction between sex and WHR on its association with mortality (P<0.001). In women, a higher WHR was associated with a higher mortality risk (HR 2.23; 95% confidence interval (CI) 1.37-3.63, P=0.001), whereas no significant association was found in men (HR 0.87, 95% CI 0.63-1.20, P=0.409). We found a strong association between a higher WHR and elevated markers of inflammation and MAPK cascade in women, while in men these associations were less profound.

Conclusions: A higher WHR was associated with a higher risk of death in female, but not in male HF patients. These findings challenge the obesity paradox, and suggest that fat deposition is pathophysiologically harmful and may be a target for therapy in female patients with HF.

Keywords: heart failure, obesity, waist-hip ratio, body mass index, mortality

INTRODUCTION

Obesity a risk factor for the development of heart failure (HF), but in patients with established HF a higher body mass index (BMI) is associated with a lower risk of death.(1-4) This so-called obesity paradox describes improved survival rates in HF patients, with a BMI between 25-35 kg/m^2 compared with normal or underweight HF patients. Although this paradox has been widely described, the precise mechanisms behind this paradox are not well understood. The most commonly used measurement to define obesity is BMI. However, patients with a high BMI might be misclassified as HF due to dyspnoea, and BMI fails to account for body composition, including fat distribution and fluid in the third space. Specifically, BMI may neglect the effects of abdominal fat, which has been identified as a potential risk factor in the onset of HF and is known to be associated with mortality in the general population.(5-7) Abdominal fat is better reflected by measuring waist to hip ratio (WHR). However, nothing is known about the association between WHR and clinical outcome in patients with established HF. We therefore examined the association between abdominal fat, measured via WHR, BMI and all-cause mortality.

METHODS

Study population

For the current analysis, we used data from BIOSTAT-CHF (A systems BIOlogy Study to Tailored Treatment in Chronic Heart Failure). BIOSTAT-CHF is a multicentre, prospective observational study.(8-10) For this study, the BIOSTAT-CHF cohort from Scotland was used, since only in this cohort WHR was routinely measured (n=1738). Main inclusion criteria were documented HF and patients had to be treated with at least 20mg furosemide or equivalent per day and were anticipated to be up titrated with ACE inhibitors/ARBs and/or beta-blockers. The complete list of inclusion and exclusion criteria has been previously published elsewhere.(8) The study complied with the Declaration of Helsinki, local ethics committee has approved the research protocol and all patients signed informed consent . WHR was calculated as waist circumference (WC) divided by hip circumference (HC). WC and hip circumference (HC) were measured according to the World Health Organization (WHO) recommendations. The subject was asked to stand relaxed with arms at the sides, feet positioned close together and weight evenly distributed across feet. WC was measured midway between the lowest rib and the superior border of iliac crest. HC was measured at the level of widest portion of buttocks (trochanters). All measurements were in centimetres (cm) to the nearest 0.1 cm. Body mass index was calculated as weight in kilograms (kg) divided by squared length in meters (m). Obesity based on both BMI ($\geq$30 kg/m^2) and WHR (for men $\geq$0.90, for women $\geq$0.85) was defined according to the World Health Organisation guidelines. Patients were divided into sex specific tertiles of WHR, since fat metabolism and deposition differs with sex. HF with reduced ejection fraction was defined as an left ventricular ejection fraction (LVEF) <40%, HF with mid-range ejection fraction as a LVEF between 40 and 50% and HF with preserved ejection fraction as a LVEF equal or above 50%, according to the most recent ESC HF guidelines.(11)

Laboratory analysis

Additional analyses were performed using a high-throughput technique using the Olink Proseek® Multiplex INF I96 96 kit, which measures 92 selected cardiovascular-related proteins simultaneously in 1µl plasma samples.(12) The amplicons are subsequently quantified using a Fluidigm BioMark™

HD real-time PCR platform. The platform provides normalized protein expression (NPX) data where a high protein value corresponds to a high protein concentration, but not an absolute quantification. These proteins were divided by Olink into thirteen domains; Inflammation, Catabolic process, Angiogenesis/blood vessel morphogenesis, Cell adhesion, Chemotaxis, Coagulation, mitogen-activated protein kinase (MAPK) cascade, Platelet activation, Proteolysis, Hypoxia, Response to peptide hormone, Wound healing and other (online supplementary ***Table S1***). The manufacturer of the protein assay, Olink Bioscience (Uppsala, Sweden), had no input on the study design, analysis or manuscript preparation.

Statistical analysis

Normally distributed data is shown as means and standard deviation, whereas not normally distributed data as medians and 25^{th} until 75^{th} percentile, and categorical variables as percentages and frequencies. Differences between variables were tested using one-way ANOVA for normal distributed data; skewed data was tested using Chi-squared test or Kruskal-Wallis test when appropriate. Linear regression was performed to assess associated variables with WHR and BMI. Univariable significant variables ($P<0.1$) were entered in a multivariable backward selection. The final backward multivariable model contained demographics, clinical variables and laboratory measurements. All non-normally distributed variables were transformed accordingly prior to adding them to the multivariable models. Kaplan-Meier curves were drafted to show differences in survival between tertiles of WHR groups. Cox proportional hazard analysis was performed to determine hazard ratios for the different groups. Restricted cubic splines were used to explore the functional association between WHR on a continuous level and all-cause mortality. Results were summarized by adjusted hazard ratios of the general model (solid line), and confidence intervals based on restricted cubic splines. To assess an independent contribution, all multivariable models were adjusted for a previously published prognostic model within BIOSTAT-CHF, BMI when appropriate for the use of statins, and sex-specific confounders.(13) When WHR is corrected for BMI it has been shown to be a proper surrogate measurement of abdominal obesity. (14)

To assess each of the pathophysiological domains with WHR, principal component analysis was

performed with the markers in each disease domain. The first principal component was used as a linear variable and the association with WHR was univariably assessed with a linear regression and the standardized betas were plotted. P-values were corrected for multiple testing by dividing 0.05 by the number of biomarkers within each of the domains. Interaction between sex and WHR on the risk of death was assessed by modelling WHR on a continuous scale.

All analyses were performed using IBM SPSS Statistics version 23 and R: a Language and Environment for Statistical Computing, version 3.4.2. (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Patients with measured WHR were included (n=1479), of which 997 were men (67%) and 482 women (33%). Baseline characteristics are depicted in ***Table 1***. Mean WHR in women was 0.93±0.09, and mean WHR in men was 1.00±0.08. Distribution of WHR in the total population is displayed in the online supplementary ***Figure S1***.

Associates of WHR and BMI

Table 2 shows the associates of WHR or BMI in women and men. In both women and men a higher WHR was associated with a higher body weight (P=0.001 and P<0.003 respectively), higher glucose levels (P=0.004 and P=0.001 respectively) and lower serum iron levels (P=0.021 and P=0.020 respectively). In women a higher WHR was also associated with less use of betablocker (β=-0.130, P=0.018) and higher NT-proBNP (β=0.156, P=0.007). In men a higher WHR was also associated with a lower height (β=-0.104, P=0.006) and a higher age (β=0.073, P=0.046).

BMI was in both women and men associated with higher waist and hip circumference, lower NT-proBNP levels, lower age, and more edema. In women the only other variable associated with a higher BMI was a history of hypertension (β=0.103, P=0.003). In men, variables associated with a higher BMI were a higher diastolic blood pressure (β=0.055, P=0.033), higher TSH levels (β=0.051, P=0.045) and the presence of diabetes (β=0.051, P=0.050).

Biomarkers associated with WHR

Standardized betas of the principal components of the different domains and WHR were plotted in ***Figure 1***. In women the strongest associations of WHR were found with inflammation ($\beta = 0.181$, $P<0.001$) and MAPK cascade ($\beta = 0.162$, $P<0.001$), while in men these associations were less profound and non-significant after correction for multiple testing ($\beta = 0.081$, $P=0.011$ and $\beta = 0.082$, $P=0.010$ respectively).

Mortality

We found a significant interaction between sex and WHR on the risk of death (P for interaction<0.001).

During a median follow-up of 21 months, 34% of women had died, ranging from 22% in the lowest tertile to 45% in the highest WHR tertile (P<0.001). As shown in ***Figure* 2**, women with a BMI < 30 kg/m^2 had higher mortality rates compared to women with a BMI > 30 kg/m^2 (P=0.042). However, women with a WHR below the mean had a significantly better survival (P<0.001). In women, patients in the highest WHR tertile had a significantly higher multivariable adjusted risk of death compared to women in the lowest WHR tertile, as seen in ***Table 3*** (Hazard ratio (HR) 2.23, [95% Confidence interval (CI) 1.37-3.63], P=0.001). The HR was plotted on a continuous scale in ***Figure 3***. For women, a linear increase of HR was seen with an increasing WHR.

During a median follow up of 21 months, 33% of the male patients had died, ranging from 31% in the lowest WHR tertile to 37% in the highest WHR tertile. There was no significant difference in a WHR above or below the mean (P=0.059)**.** Furthermore, there was no significant difference in HR between the WHR tertiles in men (***Table 3***).

The online supplementary ***Table S2*** *and* ***Figure S2*** shows the HR for all-cause mortality by tertiles of WHR and separated for men and women within HFrEF, HFmrEF and HFpEF. There was no significant interaction found between LVEF on a continuous scale and WHR, or between HF category and WHR. Separate data on waist circumference alone and hip circumference alone in women and men is depicted in ***Figure S3***.

DISCUSSION

This is the first study to show an association between a higher WHR, reflecting abdominal obesity, and an increased risk of death in female patients with HF, but not in male patients. Patients with a lower BMI and a higher WHR had the highest all-cause mortality risks in both women and men.

Waist-hip ratio, BMI and mortality

We found a significant interaction between sex and the association of WHR and the risk of death. The complex relationship between fat distribution and outcome has been an on-going topic throughout the past years, where a recent study has even hinted that patients with a higher waist circumference might benefit more from eplerenone treatment.(15) Koster et al. have recently shown that in men intermuscular fat was associated with higher mortality, while in woman visceral fat was associated with increased mortality risks.(16) Adipose tissue is known to be a secreting organ of multiple adipokines. Gluteofemoral fat is known to secrete more favourable adipokines and thus can be associated with better outcome, while visceral fat is known to be associated with a worse outcome.(17,18) One of the explanations for the difference seen in women and men in our study could be that fat distributes differently in both sexes. While men are known to accumulate more visceral fat, and therefore have a higher WHR, women often store fat subcutaneously in the gluteofemoral region.(19) If WHR increases substantially in women, this might therefore supersede the beneficial effects of subcutaneous fat and significantly increase mortality rates. We also found a higher WHR in women to be more strongly associated with markers of inflammation and MAPK cascade. As is known, the MAPK cascade is often involved in cardiac remodelling and vascular disease.(20) A variety of different cascades play a role in hypertrophy and pathological remodelling, and are known to be associated with worse outcomes.(21) The same holds true for the process of inflammation, which is known to be associated with HF, especially HFpEF.(22,23) Inflammation is also known to be associated with adverse cardiac remodelling, and worse outcome in HF.(24) The stronger associations

within women with a higher WHR and these processes might (partially) explain the worse outcome we found in women.

Obesity paradox

Several studies have previously shown that patients with HF and with higher BMI levels had a lower mortality risk compared to HF patients with normal of a low BMI.(4,25) There are however multiple limitations on the use of BMI as a measurement for obesity. BMI does not provide an indication of the fat distribution in the body, and could also be raised with more decompensated HF patients due to fluid accumulation. Furthermore, BMI has the limitation that it does not differ between fat and muscle mass, and therefore might not differ between fitness and fatness. In a recent analysis, Piepoli et al. have shown that exercise tolerance matters, and after correction for cardiorespiratory fitness the protective effect of BMI disappeared.(26)

Previous studies using solely waist circumference as a measurement of abdominal obesity showed contradicting results with our study, where in patients with HFrEF a higher waist circumference was associated with lower mortality rates Tsujimoto et al found a higher waist circumference in patients with HFpEF to be associated with higher mortality rates in a multivariable analysis.(6,27,28) Part of the difference could be explained by the fact that we used WHR instead of waist circumference alone. When assessing WHR, not only waist circumference is used, but by using WHR one might discriminate more accurately between abdominal fat (large waist circumference, normal/small hip circumference) and merely a larger body size (large waist circumference and large hip circumference). In the present study, we showed that fat distribution matters, where an increase in WHR in patients with HF is associated with a gradual increase in risk of death, and that this was more pronounced in women.

The risk associated with abdominal obesity in the general population was previously shown in a paper by Pischon et al., which showed a U-shaped risk for mortality with BMI, but abdominal obesity was associated with an increasing mortality risk.(29) Although the underlying mechanisms are unknown, one can speculate about possible contributing factors. A high WHR is known to be associated with a high burden of atherosclerosis, where the association between BMI and atherosclerosis is less

pronounced. Therefore central obesity might play a role in the initiation and progress of atherosclerosis.(30) Although this might hold true for the general population, it was unknown whether the same risk was associated with mortality in patients with HF.

Metabolic syndrome

We showed a higher prevalence of diabetes mellitus, higher glucose levels and lower HDL cholesterol with increasing WHR. A higher WHR is known to be associated and incorporated within the definition of the metabolic syndrome.(31,32) This syndrome consists of multiple factors, some of which are associated with increased survival (such as obesity), or are known to worsen onset and/or progression of HF.(33,34) Most likely the metabolic syndrome induces a pro-inflammatory state, where abdominal adiposity plays a pivotal role. Consistent with these results, we found higher levels of inflammatory markers in the upper tertiles of WHR. An altered balance in adipokines and increasing insulin resistance are most likely responsible for the association with worse outcome for patients with metabolic syndrome, together with accompanying comorbidities such as hypertension and dyslipidaemia.(35) Besides these systemic effects of central adiposity, there is also an association with adverse cardiac mechanisms such as worse global longitudinal strain and early diastolic strain rate. This association was found for both abdominal obesity and WHR.(36,37) To the best of our knowledge, we are the first to show this increased risk for female patients and a higher WHR in a HF population.

Strengths and limitations

This study is limited by its retrospective nature. Secondly, in patients with HF and a large abdominal mass, it is difficult to distinguish between fat and fluid. Thirdly, WHR measurements were performed by different individuals, although they were provided with clear instructions.

CONCLUSION

A higher WHR was associated with higher mortality in female, but not in male HF patients. This might be explained by a higher inflammatory status with a higher WHR in woman, but not in men.

This association was independent of BMI. These findings challenge the obesity paradox, and suggest that abdominal fat deposition is pathophysiologically harmful and maybe a target for therapy in (female) patients with HF.

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Table 1; Baseline characteristics

Sex	Women				Men			
Waist-hip-ratio	**1st tertile**	**2nd tertile**	**3rd tertile**	**P-value**	**1st tertile**	**2nd tertile**	**3rd tertile**	**P-value**
N =	171	151	160		360	282	355	
Waist-hip-ratio	0.84±0.05	0.93±0.02	1.02±0.05	<0.001	0.92±0.04	0.99±0.02	1.08±0.07	<0.001
Age (years)	76±11	77±11	77±11	0.539	75±11	76±10	75±10	0.856
Systolic Blood Pressure (mmHg)	125±22	129±26	125±24	0.207	126±21	125±22	126±22	0.689
Diastolic Blood Pressure (mmHg)	68±13	67±15	68±14	0.558	71±12	68±11	71±13	0.039
Heart Rate (beats/min)	73±15	75±16	78±17	0.009	72±16	72±17	73±15	0.739
Clinical profile								
LVEF (%)	43±13	43±14	44±13	0.695	39±13	40±11	39±12	0.865
HFrEF (%)	61 (39)	62 (44)	53 (37)	0.659	169 (51)	135 (51)	182 (55)	0.130
HFmrEF (%)	43 (27)	30 (21)	36 (25)		89 (27)	81 (30)	71 (21)	
HFpEF (%)	53 (34)	49 (35)	54 (38)		71 (22)	51 (19)	80 (24)	
Peripheral edema present (%)	89 (59)	95 (66)	107 (74)	0.020	155 (48)	158 (63)	203 (61)	<0.001
Rales present (%)	51 (32)	67 (46)	85 (54)	0.001	122 (36)	116 (43)	149 (43)	0.103
Elevated JVP (%)	38 (26)	46 (34)	37 (26)	0.255	90 (29)	82 (32)	90 (29)	0.629
Height (cm)	159±7	159±7	158±8	0.489	173±8	173±8	173±9	0.579
Weight (kg)	68.8±18.2	76.2±18.2	75.2±17.8	<0.001	80.3±15.6	86.1±17.6	92.4±20.9	<0.001
Body mass index (kg/m2)	25.7 [22.9-30.8]	29.6 [25.1-33.7]	29.6 [25.2-35.2]	<0.001	26.2 [23.5-29.7]	28.8 [25.1-31.8]	30.7 [26.5-34.4]	<0.001
Medical History								
Hypertension (%)	95 (56)	92 (61)	102 (64)	0.360	188 (52)	150 (53)	222 (63)	0.010
Myocardial Infarction (%)	71 (42)	49 (33)	73 (46)	0.053	180 (50)	163 (58)	191 (54)	0.130
PCI (%)	24 (14)	27 (18)	31 (19)	0.409	69 (19)	72 (26)	55 (16)	0.006
CABG (%)	15 (9)	12 (8)	15 (9)	0.905	75 (21)	65 (23)	81 (23)	0.759
Diabetes mellitus (%)	40 (23)	43 (29)	58 (37)	0.033	92 (26)	82 (29)	153 (43)	<0.001
Stroke (%)	28 (17)	22 (15)	32 (20)	0.448	66 (18)	44 (16)	72 (21)	0.321
Atrial Fibrillation (%)	74 (44)	54 (36)	65 (41)	0.363	177 (50)	124 (44)	160 (45)	0.307

Sex		Women				Men			
Waist-hip-ratio		**1st tertile**	**2nd tertile**	**3rd tertile**	**P-value**	**1st tertile**	**2nd tertile**	**3rd tertile**	**P-value**
N =		171	151	160		360	282	355	
COPD (%)		29 (17)	27 (18)	41 (26)	0.110	57 (16)	48 (17)	60 (17)	0.891
Peripheral arterial disease (%)		28 (17)	40 (27)	35 (23)	0.070	79 (23)	73 (26)	78 (23)	0.484
NYHA Class					<0.001				<0.001
	1	1 (0.6)	0 (0)	0 (0)		8 (2.2)	1 (0.4)	5 (1.4)	
	2	83 (48.5)	48 (32.0)	43 (26.9)		200 (55.6)	127 (45.0)	139 (39.2)	
	3	69 (40.4)	74 (49.3)	74 (46.3)		129 (35.8)	130 (46.1)	160 (45.1)	
	4	18 (10.5)	28 (18.7)	43 (26.9)		23 (6.4)	24 (8.5)	51 (14.4)	
Beta blocker (%)		122 (71)	97 (64)	104 (65)	0.321	277 (77)	212 (75)	260 (73)	0.519
MRA (%)		52 (30)	51 (34)	46 (29)	0.622	115 (32)	91 (32)	119 (34)	0.895
Diuretics (%)		170 (99)	149 (99)	156 (98)	0.342	353 (98)	280 (99)	352 (99)	0.269
ACE-i/ARB (%)		130 (76)	97 (64)	102 (64)	0.025	269 (75)	209 (74)	258 (73)	0.817
Statins (%)		95 (56)	87 (58)	97 (61)	0.645	218 (61)	187 (66)	232 (65)	0.249
Laboratory values									
Glucose (mmol/L)		5.5 [4.8-7.0]	6.1 [5.1-8.1]	6.7 [5.7-8.7]	<0.001	5.8 [5.0-7.3]	6.2 [5.3-8.3]	6.8 [5.6-10.2]	<0.001
HDL cholesterol		1.32 [1.03-1.64]	1.25 [1.03-1.53]	1.20 [0.96-1.49]	0.211	1.08 [0.89-1.37]	1.05 [0.85-1.28]	1.02 [0.84-1.22]	0.002
NT-proBNP (ng/L)		1027 [383-2594]	1142 [364-2907]	1758 [528-4953]	0.029	1391 [554-3177]	1299 [508-2937]	1240 [486-3289]	0.665
FABP4		6.04 [5.36-6.79]	6.45 [5.72-7.53]	6.57 [5.68-7.38]	<0.001	5.37 [4.75-6.12]	5.65 [4.98-6.32]	5.88 [5.23-6.74]	<0.001
TNF-R1		5.32 [4.92-5.88]	5.54 [5.01-6.12]	5.56 [5.09-6.06]	0.015	5.29 [4.89-5.73]	5.40 [5.01-5.89]	5.46 [5.02-6.15]	<0.001
Outcome									
All-cause mortality (%)		38 (22.2)	47 (31.3)	72 (45.0)	<0.001	112 (31.1)	92 (32.9)	130 (36.9)	0.245
Hospitalization (%)		50 (29.4)	69 (46.0)	73 (45.6)	0.002	131 (36.4)	82 (29.3)	136 (38.7)	0.040

Values are given as means ± standard deviation, median (25th to 75th percentiles) or percentage and frequency

LVEF = Left ventricular ejection fraction; HFrEF = Heart failure with reduced ejection fraction; HFmrEF = Heart failure with mid-range ejection fraction; HFpEF = Heart failure with preserved ejection fraction; JVP = Jugular venous pressure; PCI = Percutaneous coronary intervention; CABG = Coronary artery bypass surgery; COPD = Chronic obstructive pulmonary disease; NYHA = New York Heart Association; MRA = Mineralocorticoid receptor antagonist; ACE-i/ARB = ACE-inhibitor/Angiotensin II receptor blocker; HDL = High density lipoprotein; NT-proBNP = N-terminal pro brain natriuretic peptide; KCCQ = Kansas city Cardiomyopathy Questionnaire; VAS = Visual analog scale

Table 2; Multivariable linear regression for waist-hip ratio and body mass index

WHR	Women	R^2=0.11		Men	R^2=0.18	
Variable	**β**	**t-value**	**p-value**	**β**	**t-value**	**p-value**
Weight	0.170	3.00	0.003	0.426	10.9	<0.001
Glucose	0.157	2.87	0.004	0.115	3.24	0.001
NT-proBNP	0.156	2.71	0.007			
Betablocker	-0.130	-2.37	0.018			
Iron, serum	-0.126	-2.32	0.021	-0.082	-2.33	0.020
Height				-0.104	-2.76	0.006
Age				0.073	2.00	0.046

BMI	Women	R^2=0.66		Men	R^2=0.62	
Variable	**β**	**t-value**	**p-value**	**β**	**t-value**	**p-value**
Waist circumference	0.385	6.43	<0.001	0.447	10.7	<0.001
Hip circumference	0.366	6.05	<0.001	0.279	6.69	<0.001
Age	-0.136	-3.66	<0.001	-0.109	-4.11	<0.001
History of hypertension	0.103	2.96	0.003			
Edema	0.095	2.66	0.008	0.052	1.99	0.047
NT-proBNP	-0.080	-2.18	0.030	-0.118	-4.20	<0.001
Diastolic blood pressure				0.055	2.14	0.033
TSH				0.051	2.01	0.045
Diabetes				0.051	1.96	0.050

All univariable significant variables (P<0.1) where entered in a multivariable backward selection. WHR = Waist-hip ratio; BMI = Body mass index; HDL = High density lipoprotein; NT-proBNP = N-terminal pro brain natriuretic peptide; TSH = thyroid stimulation hormone

Table 3; Hazard ratio for tertiles of Waist-hip ratio and all-cause mortality

All-cause mortality Women	Hazard ratio°	P-value	Hazard ratio*	P-value
Waist-hip ratio 1st tertile	Ref		Ref	
Waist-hip ratio 2nd tertile	1.49 [0.97-2.29]	0.068	1.11 [0.66-1.89]	0.692
Waist-hip ratio 3rd tertile	2.40 [1.62-3.56]	<0.001	2.23 [1.37-3.63]	0.001
All-cause mortality Men	**Hazard ratio°**	**P-value**	**Hazard ratio×**	**P-value**
Waist-hip ratio 1st tertile	Ref		Ref	
Waist-hip ratio 2nd tertile	1.12 [0.85-1.48]	0.419	0.92 [0.66-1.27]	0.596
Waist-hip ratio 3rd tertile	1.24 [0.97-1.60]	0.091	0.87 [0.63-1.20]	0.409

° Univariable model
*** Corrected for age, BMI, Urea, NT-proBNP, hemoglobin, use of beta-blocker, heart rate, presence of rales, NYHA class, history of diabetes, ACE/ARB use, glucose, FABP4 and use of statins**
× Corrected for age, BMI, Urea, NT-proBNP, hemoglobin, use of beta-blocker, diastolic blood pressure, presence of peripheral edema, NYHA class, history of hypertension, history of diabetes, HDL levels, glucose, FABP4 and use of statins
P for interaction <0.001 between sex and waist-hip ratio for all-cause mortality

Figure legends:

Figure 1; Linear regression for different domains with Waist-hip ratio in women and men

Figure 2; Kaplan-Meier for obesity based on BMI in women (A) and men (B). At the bottom for waist-hip ratio in women (C) and men (D), according to the WHO guidelines

Figure 3; Hazard ratio for Waist-hip ratio on a continuous scale for women and men. All corrected for age, Urea, NT-proBNP, hemoglobin, use of beta-blocker, statins and BMI

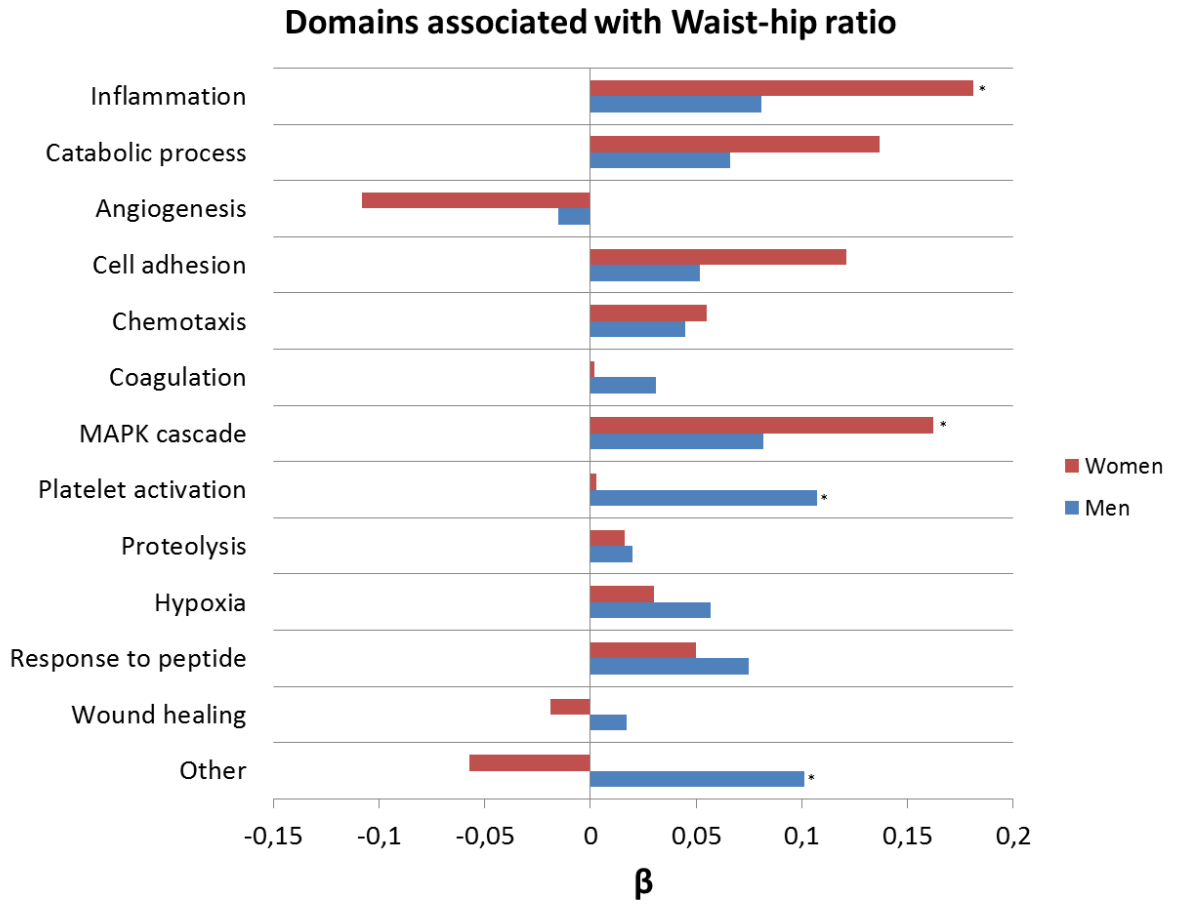

Figure 1; Linear regression for different domains with Waist-hip ratio in women and men *=significant p-value after correction for multiple testing

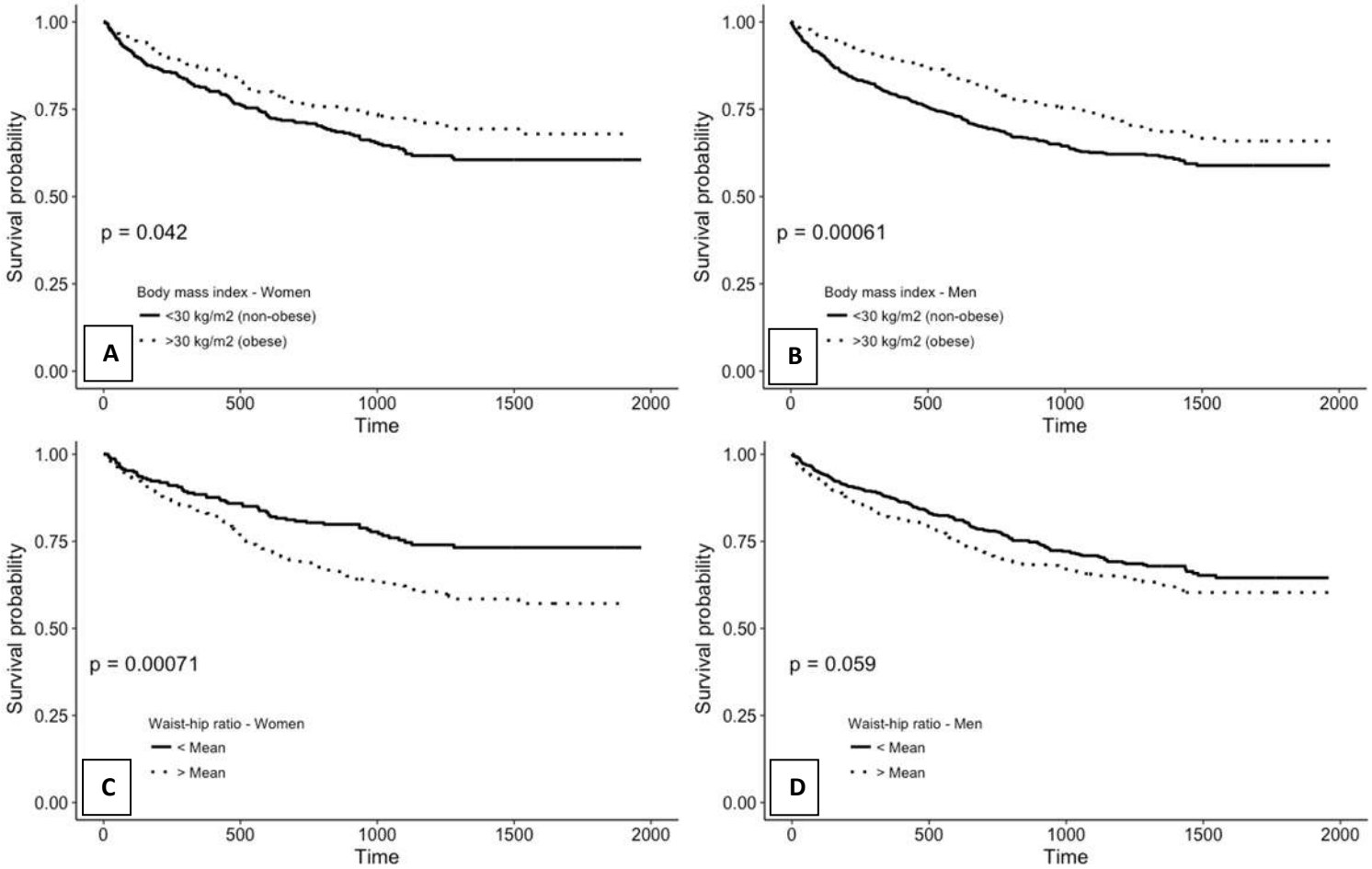

Figure 2; Kaplan-Meier for obesity based on BMI in women (A) and men (B). At the bottom for waist-hip ratio in women (C) and men (D), split on the population mean.

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Figure 3; Adjusted effect of WHR on hazard ratio for all-cause mortality. Solid line shows estimated linear relation of WHR, while the dotted lines are 95% confidence intervals for a more general relation using restricted cubic splines. Corrected for age, Urea, NT-proBNP, hemoglobin, use of beta-blocker, statins, heart rate, presence of rales, NYHA class, history of diabetes, ACE/ARB use, glucose levels, FABP4 and BMI for women.
Corrected for age, BMI, Urea, NT-proBNP, hemoglobin, use of beta-blocker, diastolic blood pressure, presence of peripheral edema, NYHA class, history of hypertension, history of diabetes, HDL levels, glucose, FABP4 and use of statins for men.
Overall P-value within women P<0.001 and men P=0.136

SUPPLEMENTARY MATERIAL

Supplementary Table 1; Olink biomarkers and domains

Domain	Markers
Inflammation	AZU1, CCL15, CCL16, CCL22, CCL24, CHI3L1, SELE, FABP4, ITGB2, IL-1RT1, IL-17RA, IL2-RA, IL6-RA, JAM-A, LTBR, MCP-1, OPN, SELP, PGLYRP1, PAI, RARRES2, CD163, ST2, TR-AP, TR, TNF-R1, TNF-R2, TNFRSF10C, TNFRSF14, FAS, AXL
Catabolic process	AP-N, CASP-3, CTSD, CTSZ, CHIT1, COL1A1, CD93, EGFR, FABP4, KLK6, LDL receptor, MMP-2, MMP-3, MMP-9, TIMP4, PRTN3, MPO, PON3, PGLYRP1, PLC, PCSK9, RARRES2, TNF-R2
Angiogenesis/blood vessel morphogenesis	AP-N, CCL24, CHI3L1, 4EPHB4, ITGB2, MMP-2, MCP-1, NOTCH3, PLC, PAI, PDGF subunit A, uPA
Cell adhesion	AZU1, CDH5, CASP-3, ALCAM, COL1A1, CD93, CNTN1, SELE, 4EPHB4, EGFR, Ep-Cam, Gal-3, Gal-4, IGFBP-2, IGFBP-7, ITGB2, ICAM-2, IL2-RA, MCP-1, OPN, SELP, PAI, PECAM-1, PSP-D, SPON1, TR-AP, TLT-2, TNFRSF14, FAS, AXL, SHPS-1, uPA, vWF
Chemotaxis	AZU1, CCL15, CCL16, CCL22, CCL24, CXCL16, ALCAM, Gal-3, ITGB2, IL6-RA, MCP-1, PAI, PSP-D, RARRES2, uPA
Coagulation	COL1A1, PRTN3, SELP, PAI, PDGF subunit A, TFPI, t-PA, AXL, U-PAR, uPA, vWF
MAPK cascade	CCL15, CCL16, CCL22, CCL24, CHI3L1, EGFR, GDF-15, IL2-RA, IL6-RA, LTBR, MCP-1, OPG, PDGF subunit A, TNF-R2, TNFRSF14, FAS
Platelet activation	COL1A1, SELP, PDGF subunit A, AXL, vWF
Proteolysis	AZU1, BLM hydrolase, CPA1, CASP-3, CTSZ, CSTB, KLK6, MMP-2, MMP-3, MMP-9, TIMP4, PAI, PCSK9, t-PA, TNF-R2, FAS, U-PAR, uPA
Hypoxia	CASP-3, MMP-2, MCP-1, MB, PDGF subunit A, t-PA, TR, FAS, uPA
Response to peptide hormone	COL1A1, IGFBP-1, TIMP4, MCP-1, PCSK9, RETN, RARRES2, FAS
Wound healing	CASP-3, COL1A1, IGFBP-1, KLK6, PRTN3, SELP, PAI, PDGF subunit A, TFPI, t-PA, AXL, U-PAR, uPA, vWF
Other	CPB1, PI3, GRN, IL-1RT2, IL-18BP, MEPE, NT-proBNP, DLK-1, SCGB3A2, TFF3, TNFSF13B

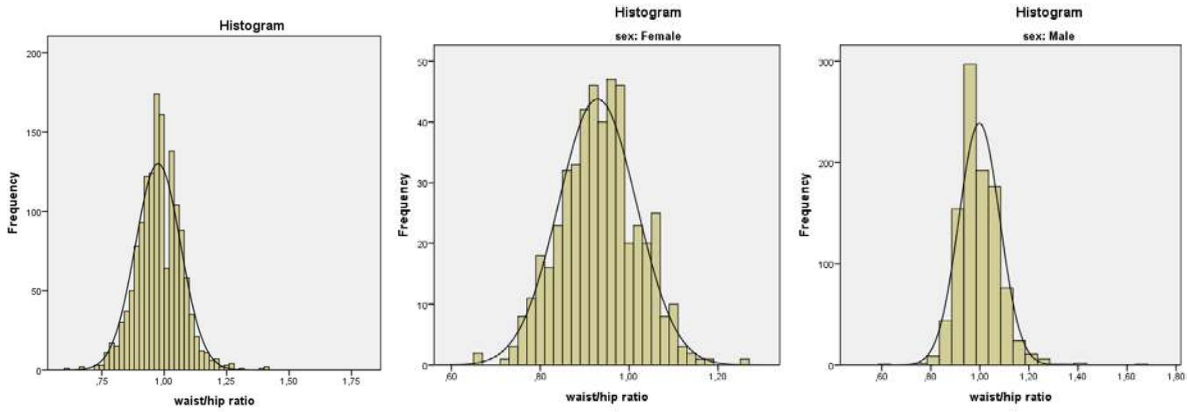
ALCAM = CD166 antigen; AP-N = Aminopeptidase N; AXL = Tyrosine-proteinkinase receptor UFO; AZU1 = Azurocidin; BLM hydrolase = Bleomycin hydrolase; CASP-3 = Caspase-3; CCL15 = C-C motif chemokine 15; CCL16 = C-C motif chemokine 16; CCL22 = C-C motif chemokine 22; CCL24 = C-C motif chemokine 24; CD163 = Scavenger receptor cysteine-rich type 1 protein m130; CD93 = Complement component C1q receptor; CDH5 = Cadherin-5; CHI3L1 = Chitinase-3-like protein 1; CHIT1 = Chitoriosidase-1; CNTN1 = Contactin-1; COL1A1 = Collagen alpha-1 (I) chain; CPA1 = Carboxypeptidase A1; CPB1 = Carboxypeptidase B; CSTB = Cystatin-B; CTSD = Cathepsin D; CTSZ = Cathepsin Z; CXCL16 = C-X-C motif chemokine 16; DLK-1 = Protein delta homolog 1; EGFR = Epidermal growth factor receptor; Ep-Cam = Epithelial cell adhesion molecule; EPHB4 = Ephrin type-B receptor 4; FABP4 = Fatty acid-binding protein, adipocyte; FAS = Tumor necrosis factor receptor superfamily member 6; Gal-3 = Galectin-3; Gal-4 = Galectin-4; GDF-15 = Growth/differentiation factor 15; GRN = Granulins; ICAM-2 = Intercellular adhesion molecule 2; IGFBP-1 = Insulin-like growth factor-binding protein 1; IGFBP-2 = Insulin-like growth factor-binding protein 2; IGFBP-7 = Insulin-like growth factor-binding protein 7; IL-17RA = Interleukin-17 receptor A; IL-18BP = Interleukin-18 binding protein; IL-1RT1 = Interleukin-1 receptor type 1; IL-1RT2 = Interleukin-1 receptor type 2; IL2-RA = Interleukin-2 receptor subunit Alpha; IL6-RA = Interleukin-6 receptor subunit Alpha; ITGB2 = Integrin beta-2; JAM-A = Junctional adhesion molecule A; KLK6 = Kallikrein-6; LDL receptor = Low-density lipoprotein receptor; LTBR = Lympotoxin-beta receptor; MB = Myoglobin; MCP-1 = Monocypte chemotactic protein 1; MEPE = Matrix extracellular phosphoglycoprotein; MMP-2 = Matrix metalloproteinase-2; MMP-3 = Matrix metalloproteinase-3; MMP-9 = Matrix metalloproteinase-9; MPO = Myeloperoxidase; NOTCH3 = Neurogenic locus notch homolog protein 3; NT-proBNP = N-terminal pro b-type natriuretic peptide; OPG = Osteoprotegerin (OPG); OPN = Osteopontin; PAI = Plasminogen activator inhibitor 1; PCSK9 = Proprotein convertase subtillisin/kexin type 9; PDGF subunit A = Platelet-derived growth factor subunit A; PECAM-1 = Platelet endothelial cell adhesion molecule; PGLYRP1 = Peptidoglycan recognition protein 1; PI3 = Elafin; PLC = Perlecan; PON3 = Paraoxnase; PRTN3 = Myeloblastin; PSP-D = Pulmonary surfactant-associated protein D; RARRES2 = Retinoic acid receptor responder protein 2; RETN = Resistin; SCGB3A2 = Secretoglobin family 3A member 2; SELE = E-selectin; SELP = P-selectin; SHPS-1 = Tyrosine-protein phosphatase non-receptor type substrate 1; SPON1 = Spondin-1; ST2 = ST2 protein; TFF3 = Trefoil factor 3; TFPI = Tissue factor pathway inhibitor; TIMP4 = Metalloproteinase inhibitor 4; TLT-2 = Trem-like transcript 2 protein; TNF-R1 = Tumor necrosis factor receptor 1; TNF-R2 = Tumor necrosis factor receptor 2; TNFRSF10C = Tumor necrosis factor receptor superfamily member 10C; TNFRSF14 = Tumor necrosis factor receptor superfamily member 14; TNFSF13B = Tumor necrosis factor ligand superfamily member 13B; t-PA = Tissue-type plasminogen activator; TR = Trassferrin receptor protein 1; TR-AP = Tartrate-resistant acid phosphatase type 5; uPA = Urokinase-type plasminogen activator; U-PAR = Urokinase plasminogen activator surface receptor; vWF; von Willebrand factor

Supplementary Table 2; Hazard ratio for tertiles of Waist-hip ratio in different HF subgroups and all-cause mortality

All-cause mortality HFrEF	Hazard ratio°	P-value	Hazard ratio*	P-value
Waist-hip ratio 1st tertile	Ref		Ref	
Waist-hip ratio 2nd tertile	1.27 [0.90-1.79]	0.181	0.92 [0.63-1.34]	0.654
Waist-hip ratio 3rd tertile	1.64 [1.19-2.26]	0.002	1.34 [0.95-1.89]	0.099
All-cause mortality HFmrEF	**Hazard ratio°**	**P-value**	**Hazard ratio***	**P-value**
Waist-hip ratio 1st tertile	Ref		Ref	
Waist-hip ratio 2nd tertile	0.89 [0.56-1.40]	0.613	0.93 [0.58-1.49]	0.753
Waist-hip ratio 3rd tertile	1.33 [0.85-2.06]	0.210	1.41 [0.87-2.26]	0.162
All-cause mortality HFpEF	**Hazard ratio°**	**P-value**	**Hazard ratio***	**P-value**
Waist-hip ratio 1st tertile	Ref		Ref	
Waist-hip ratio 2nd tertile	1.25 [0.81-1.94]	0.322	1.46 [0.91-2.34]	0.120
Waist-hip ratio 3rd tertile	1.47 [0.96-2.24]	0.076	2.08 [1.30-3.33]	0.002

° Univariable model

*** All are corrected for age, sex, Urea, NT-proBNP, hemoglobin, use of beta-blocker and statins**



Supplementary Figure 1; Histogram of distribution of WHR in the total population (left), in women (middle) and in men (right).

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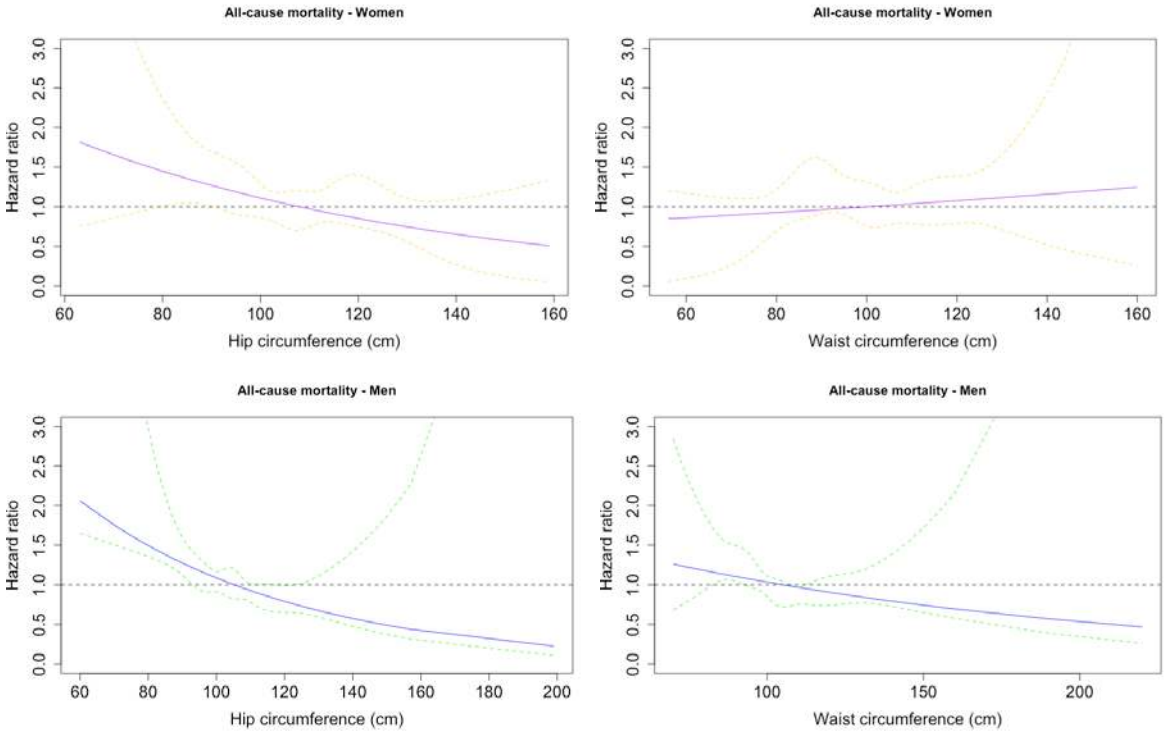
Supplementary Figure 2; Hazard ratio for Waist-hip ratio separated for women (left) and men (right) in HFrEF , HFmrEF and HFpEF . Corrected for age, Urea, NT-proBNP, hemoglobin, use of beta-blocker and statins



Supplementary Figure 3; Hazard ratio for Waist and Hip circumference in women (top) and men (bottom).