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Confirmatory factor analysis including MRI-derived adipose tissues quantification improves associations of metabolic dysregulation to diastolic dysfunction

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ABSTRACT

Aims: To quantify metabolic impairment via a one-factor approach with confirmatory factor analysis (CFA) including MRI-derived visceral and subcutaneous adipose tissues and to associate it with diastolic dysfunction.
Methods: In this cross-sectional analysis, 916 participants (53% female, mean age (SD): 56 (6)) underwent abdominal and cardiovascular MRI. With CFA a metabolic-load factor of metabolic-syndrome variables and visceral and subcutaneous adipose tissues was constructed. A piecewise structural equation model approach with adjustment for confounding factors was used to determine associations with left-ventricular diastolic function, cardiac morphology and hemodynamics.
Results: Model fitting excluding blood pressure and waist circumference but including visceral and subcutaneous adipose tissues, fasting glucose, HDL-c and triglycerides was used to construct the metabolic-load factor. Evaluating measurement invariance demonstrated sex-specificity. Change in mitral early/late peak filling rate ratio was −0.12 for both males [−0.20; −0.05, $p > 0.05$] and females [−0.17; −0.07, $p > 0.001$] per SD of metabolic-load factor. Change in deceleration time of mitral early filling was −11.83ms only in females [−17.38; −6.27, $p > 0.001$] per SD of metabolic-load factor.
Conclusion: A single latent metabolic-load factor via CFA including MRI-derived adipose tissues increased sensitivity for metabolic impairment obsoleting waist circumference and is associated with a decreased left-ventricular diastolic function, more apparent in females than in males.

1. Introduction

Currently the metabolic syndrome (MetS) is commonly defined by a cluster of medical conditions with categorized variables indicating certain pathogenesis.[1] Generally, a consensus exists on the definition of MetS, which consists of waist circumference, systolic and diastolic blood pressure, glucose, high-density lipoproteins (HDL-c) cholesterol and triglycerides. However it is still controversial which pathogenesis is the

Abbreviations: CFA, confirmatory factor analysis; E/A ratio, ratio of the mitral early and late peak filling rates; *E*-DT, deceleration time of mitral early filling; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle; MetS, metabolic syndrome; MLF, metabolic load factor; SAT, subcutaneous adipose tissue; SEM, structural equation model; VAT, visceral adipose tissue.

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primary actor in MetS.[2–4] Additionally, severity of metabolic impairment can vary given the same MetS diagnosis due to fixed cut-off values. These methodological limitations can potentially be resolved with confirmatory factor analysis (CFA), which uses full continuous information of each single indicator.[2,3]

MRI is increasingly recognized as the modality-of-choice for accurate assessment of body fat distribution, including differentiation of subcutaneous adipose tissue (SAT) from visceral adipose tissue (VAT) with the latter being more metabolically active.[5,6] Adipose tissue quantification by MRI along with the other MetS variables via a one-factor CFA approach could potentially determine metabolic impairment more accurately, as waist-circumference is a less specific measure for metabolically active adiposity. Therefore, we investigated whether addition of MRI-derived VAT and SAT results in improved model-fit and associations as opposed to the use of surrogate measures of abdominal obesity such as waist circumference.

Construction of such a single latent factor of metabolic load which uses full continuous information would in addition provide the opportunity to investigate important MetS -associated clinical conditions that are otherwise limited by multicollinearity problems in multiple regression analysis. Heart failure with preserved ejection fraction (HFpEF) is a poorly understood clinical syndrome that has been associated with adverse physiological changes that occur in obesity, and is often investigated with multiple regression analysis including the MetS.[7] Diastolic dysfunction provoked by metabolic dysregulation is considered to play a central role in the pathophysiology of HFpEF,[8–10] however the role of the MetS in LV diastolic dysfunction remains unclear.

Because many factors and comorbidities contribute to HFpEF, population-based studies are needed to identify the importance and associations of the various factors involved. Most of such studies assess cardiac function by echocardiography,[11–14] which is a fast and cost-effective imaging modality suitable for large cohort studies. However, echocardiography is considered less accurate than cardiac MRI for routine cardiac parameters such as volumes, mass and ejection fraction.[15–17]

The aim of this study was therefore to construct one latent factor via CFA, characterizing metabolic load, using continuous information of MetS variables in a large study sample of an obese sample. Complementary, MRI- derived VAT and SAT were included to investigate if the explained variance of the observed variables by the metabolic load factor (MLF) would be augmented compared to using waist circumference. Moreover a piecewise structural equation model (SEM) was used to examine the associations of MLF with left ventricular (LV) diastolic function and cardiac morphology and hemodynamics. We hypothesized that in particular VAT plays a prominent role in the MLF whereas SAT and waist circumference are involved to a lesser extent. Additionally, we hypothesize that the MLF is associated with LV diastolic dysfunction.

2. Materials & methods

2.1. Study design and population

The current study is a cross-sectional observational analysis of data from the Netherlands Epidemiology of Obesity (NEO) study. Men and women aged 45 to 65 years living in the Leiden area in the Netherlands, where prospectively included. Overweight or obese individuals were found eligible to participate and oversampled. A reference group, men and women aged 45 to 65 years irrespective of their BMI, was sampled from the Leiderdorp area. Anthropometry data, as well as fasting blood and urine samples were acquired. General questionnaires were used to report demographic, lifestyle, and clinical information. A comprehensive overview of study design can be found in.[18]

Exclusion criteria were use of systemic immunosuppressive medication (corticosteroids, lumiracoxib or naproxen) and a history of cardiovascular disease (myocardial infarction, stable angina, congestive heart failure, stroke, or peripheral vascular disease). After excluding individuals not eligible for imaging determined by MRI contraindications (claustrophobia or metallic implants), a random subset underwent abdominal and cardiac MRI. The final study group illustrated in Fig. 1 was determined after excluding poor MRI image quality and missing relevant data (complete case analysis).

The Medical Ethical Committee of the Leiden University Medical Center approved the design of the study (Protocol number: P08.109, date of approval: 04-08-2008) and all individuals gave their written informed consent. The study was carried out according to the ethical standards of the Helsinki Declaration of 1975, as revised in 2013.

2.2. Data collection

Participating individuals reported sex (female/male), ethnicity (white/other), tobacco smoking (never/former/current), and education (high/other). The MetS variables, according to the joint statement of Grundy et al. (2004), consisted of glucose, triglycerides, HDL-c, diastolic and systolic blood pressure and where derived from fasting blood samples and physical examination.[1]

2.3. Magnetic resonance imaging

MRI was performed on a 1.5 T MRI scanner (Philips Medical Systems, Best, the Netherlands) with a 16-channel phased array coil. Details on the image acquisition settings are provided as Supplementary Material. Representative examples of segmentations required to derive functional parameters are shown in Fig. 1.

2.3.1. Diastolic function

To analyze LV diastolic function, we included the deceleration time of mitral early filling rate (*E*-DT) and the ratio of the mitral early and late peak filling rates (E/A ratio). The E-DT and E/A ratio were determined using an electrocardiographically (ECG) retrospectively gated gradient echo sequence with velocity encoding over the mitral valve and 40 cardiac phases.

2.3.2. Cardiac morphology and hemodynamics

To analyze cardiac morphology and hemodynamics, we included LV mass, quantified in the end-diastolic phase, and LV end-diastolic volume. The LV mass/LV end-diastolic volume ratio has been added as a more sensitive measure of ventricular remodeling. LV mass and LV end-diastolic volume were determined from ECG retrospectively gated breath-hold balanced steady-state free precession (bSSFP) CINE movies covering the whole heart in short axis orientation.

2.3.3. Adiposity

To analyze adiposity we included abdominal VAT and SAT, which were determined from 3 slices acquired at the level of the fifth lumbar vertebra with a turbo-spin-echo T1-weighted sequence. VAT and SAT areas (unit cm^2) were determined by averaging the 3 slices using in-house developed software (MASS, Leiden, the Netherlands).

2.4. Statistical analyses

2.4.1. Measurement model via confirmatory factor analysis

In the NEO study, individuals with a BMI of 27 kg/m^2 or higher were oversampled. To correctly represent baseline associations in the general population,[19] adjustments for the oversampling of individuals with a BMI $\geq$27 kg/m^2 were made. This was done by weighting all participants toward the BMI distribution of participants from the Leiderdorp municipality,[20] whose BMI distribution is similar to the BMI distribution of the general Dutch population.[21] All results were based on weighted analyses. Consequently, the results apply to a population-based study without oversampling of individuals with a BMI $\geq$27 kg/m^2. CFA was used as a measurement model to construct a MLF, whereby the concept of the MetS was applied.[1] Firstly, all of the MetS variables and MRI-

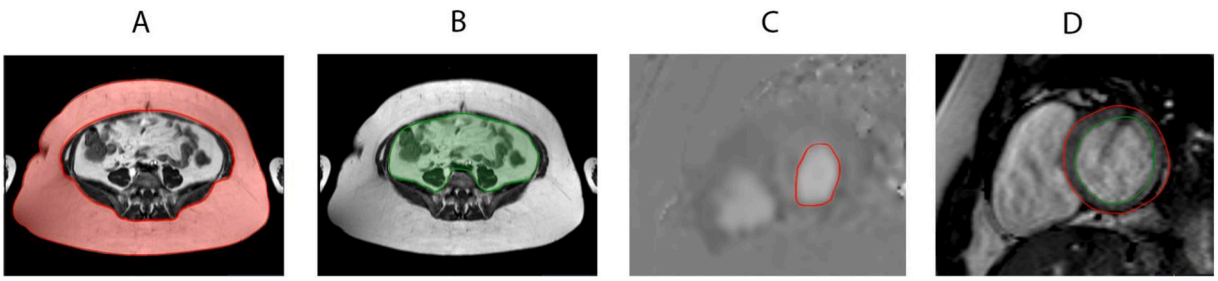

Fig. 1. Example segmentations to quantify MRI-derived variables [unpublished data].
(A) Adipose tissue depots SAT and (B) VAT were determined on transverse slices at the level of the fifth lumbar vertebra. (C) LV diastolic function was determined by calculating the ratio of the early and late diastolic flow rates across the mitral valve, using velocity-encoded MRI (right panel), resulting in the E/A ratio and E-DT. (D) LV morphology and hemodynamic variables were quantified from short-axis cine MRI. VAT = visceral adipose tissue, SAT = subcutaneous adipose tissue, E-DT = E-wave deceleration time, LV = left ventricular.

derived abdominal VAT and SAT were included to analyze the individual factor loadings. Consequently, a selection of included variables which loaded significantly was made ($p < 0.05$), defining indicators of a MLF. Model fits were assessed using a comparative fit index (CFI), the root mean square error of approximation (RMSEA) and the standardized root mean square residual (SRMR). Indication of goodness of model fitting was CFI $\geq$ 0.95, RMSEA$\leq$0.05 and SRMR$\leq$0.05. Stepwise exclusion of indicators with lowest loading was carried out till model fit did not improve further. An evaluation of measurement invariance was carried out to examine presence of sex-specific difference on loadings of each single indicator of the MLF.[22]

2.4.2. *Piecewise structural equation model (SEM)*

A SEM is the combination of a measurement model and path model where the joint variance-covariance matrix is analyzed of the observed variables. We used a piecewise SEM approach, combining individual models with estimated paths merged to construct the causal model.[23] Hereby we examined associations between the MLF, diastolic function and cardiac morphology and hemodynamics. Regression coefficients were calculated with 95% confidence intervals (95%CI). After checking for normality, variables were transformed into *Z*-scores standardized to a mean of zero with and standard deviation (SD) of 1. The crude model, which included solely the MLF, was adjusted for the potential confounding factors age, ethnicity, education and tobacco smoking. To evaluate whether the MLF was a more comprehensive factor to determine cardiovascular health, we also examined associations between the MetS, diastolic function and cardiac morphology and hemodynamics. *P*-values were adjusted according to the false discovery rate (FDR) method as proposed by Benjamini and Hochberg.[24] For all statistical analyses R version 4.0.2 was used.

3. Results

3.1. *Baseline characteristics*

The entire population of the NEO study included 6671 participants. After random selection, 1207 participants underwent cardiovascular MRI. After exclusion of (i) $n = 88$ due to technical errors in the E/A ratio,

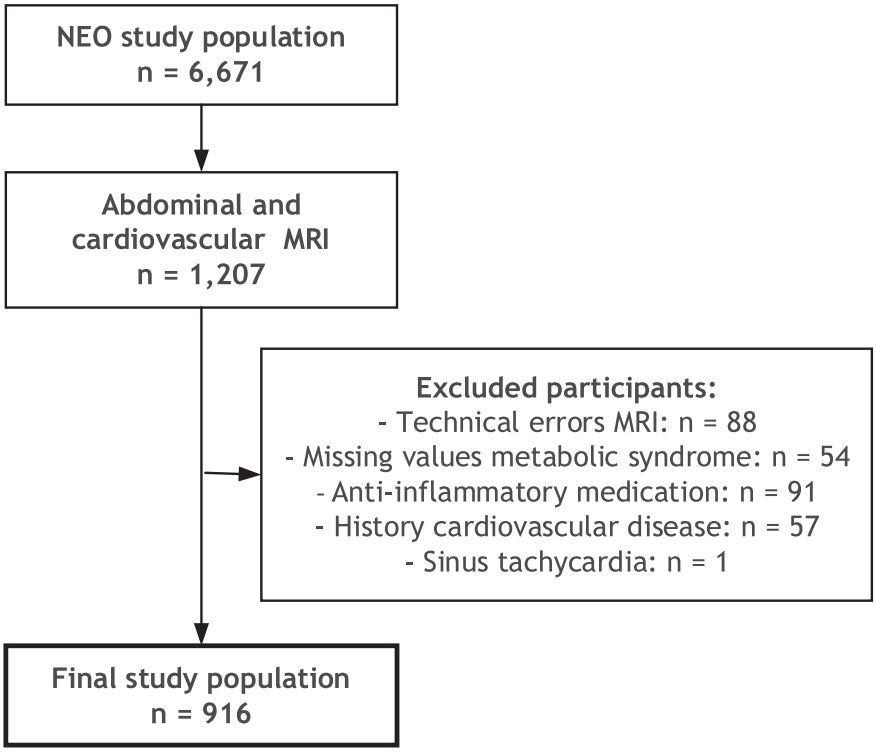

Fig. 2. Study flowchart.

E-DT, LV mass, LV end-systolic and end-diastolic volume, VAT and SAT quantification, (ii) $n = 54$ due to missing data in one of the MetS variables, heart rate, or confounders, (iii) $n = 91$ due to usage of systemic inflammation-lowering medication, (iv) $n = 57$ due to a history of cardiovascular disease and (v) $n = 1$ due to sinus tachycardia,[25] the final number of included participants was 916 (Fig. 2).

Mean age (±SD) was 56 (6) years (53% female), BMI 26 (4) kg/m^2, E/A ratio 1.3 (0.5), *E*-DT 182.9 (47.2) ms, VAT 88.1 (53.9) cm^2, SAT 235.3 (95). Sex-specific differences were found between previous mentioned variables except for the E/A ratio, E-DT an all of the MetS variables except triglycerides. Participant characteristics are presented in Tables 1 and 2. Participant characteristics where not different from the total group (56% female, mean age (SD): 56 (6), BMI: 26 (4) kg/m^2). Correlations of variables used in current study are presented in Fig. 3.

3.2. Metabolic load construction via CFA

CFA model 1 included all of the MetS variables, as well as VAT and SAT which were allowed to correlate. CFA model fit 1 was moderate: (CFI = 0.535; RMSEA = 0.208; SRMR = 0.148). All indicators loaded significantly ($p < 0.05$) on the MLF (standardized estimates: waist circumference = 0.115, VAT = 0.457, SAT = 0.528, systolic blood pressure = 0.036, diastolic blood pressure = 0.023, glucose = 0.374, HDL-c = −0.238 and triglycerides = 0.351). However factor loadings of waist circumference, systolic and diastolic blood pressure were considered low and therefore excluded in CFA model 2. CFA model fit 2 was good and improved compared to CFA model 1: (CFI = 0.949; RMSEA = 0.073; SRMR = 0.039). All indicators loaded significantly (standardized estimates: VAT = 0.373, SAT = 0.182, glucose = 0.411, HDL-c = −0.300, triglycerides = 0.503). The measurement of invariance test showed that chosen indicators to define metabolic load where different between sexes. After constraining the factor loadings to be equal across groups, model fit was not preserved thereby failing metric invariance (difference in robust CFI = −0.021, $p < 0.001$). The standardized estimates divided by sex are shown in Fig. 4.

Table 1
Baseline characteristics.

Characteristics	Total population	Men (47%)	Women (53%)	p-value
Age (years)	56 (6)	55 (7)	56 (6)	0.84
Education (% High)	46	50	43	–
Ethnicity (% white)	97	96	98	–
Weight (kg)	78.2 (14.8)	86.6 (12.6)	70.9 (12.5)	<0.001
Body mass index, (kg/m2)	26 (4.0)	27 (3.4)	25 (4.3)	<0.001
Waist circumference (cm)	91.2 (12.4)	97.2 (9.6)	85.9 (12.2)	<0.001
Waist/hip ratio	0.9 (0.1)	0.9 (0.1)	0.8 (0.1)	<0.001
Smoking				
Current (%)	13	13	12	–
Previous (%)	44	44	45	–
Never (%)	43	43	44	–
Systolic blood pressure (mmHg)	130.5 (17.7)	134.7 (15.8)	126.8 (18.5)	<0.001
Diastolic blood pressure (mmHg)	83.5 (10.7)	85.2 (10.4)	82.0 (10.7)	0.004
Diabetes mellitus (%)	2.9	3.9	2.0	–
Fasting glucose (mmol/l)	5.5 (1.0)	5.6 (1.1)	5.3 (0.8)	<0.001
Total cholesterol (mmol/l)	5.8 (1.0)	5.6 (1.0)	5.9 (1.0)	0.008
LDL c (mmol/l)	3.7 (0.9)	3.7 (0.9)	3.7 (1.0)	0.95
HDL c (mmol/l)	1.5 (0.4)	1.3 (0.3)	1.7 (0.4)	<0.001
Triglycerides (mmol/l)	1.0 (0.8–1.5)	1.2 (0.9–1.7)	0.9 (0.7–1.4)	0.82
Central Obese (%)	36	32	40	–
Hypertension (%)	61	69	55	–
Hypertriglyceridemia (%)	19	23	15	–
Low-HDL-c (%)	16	17	14	–
Disturbed glucose metabolism (%)	30	37	23	–
Metabolic syndrome (%)	23	27	19	–

Results were weighted toward the BMI distribution of the general population. Data are presented as mean (SD) for continuous variables with a normal distribution, median (25th, 75th percentile) for continuous variables with a non-normal distribution or percentage (number). LDL-c = low-density lipoproteins cholesterol, HDL-c = high-density lipoproteins cholesterol. Unpaired comparisons between sex were examined via *t*-tests or Mann-Whitney tests. P < 0.05 was considered significant and p-values were controlled for the FDR.

Table 2
Cardiovascular parameters.

Imaging measurements	Total population	Men	Women	p-value
Diastolic function				
E/A ratio	1.3 (0.5)	1.3 (0.5)	1.4 (0.5)	0.10
E-DT(ms)	182.9 (47.2)	182.3 (48.4)	183.5 (46.1)	0.82
Cardiac morphology & hemodynamic				
LV mass (g)	99.5 (25.7)	118.5 (22.0)	82.9 (15.1)	<0.001
LV mass index (g/m^2)	51.1 (10.2)	57.0 (9.3)	46.0 (7.9)	<0.001
LV end-systolic volume, (ml)	54.2 (16.5)	61.4 (17.6)	47.9 (12.4)	<0.001
LV end-diastolic volume (ml)	148.0 (33.0)	165.3 (33.0)	132.8 (24.4)	<0.001
LV stroke volume (ml)	93.8 (21.0)	103.9 (21.6)	84.9 (15.8)	<0.001
LV ejection fraction (%)	63.6 (5.9)	63.0 (6.3)	64.2 (5.4)	0.04
Cardiac output (l/min)	6.2 (1.4)	6.8 (1.4)	5.6 (1.1)	<0.001
Adiposity				
VAT (cm^2)	88.1 (53.9)	111.9 (55.8)	67.3 (42.4)	<0.001
SAT (cm^2)	235.0 (95.0)	205.8 (74.5)	260.6 (103.4)	<0.001

Results were weighted toward the BMI distribution of the general population. Data are presented as mean (SD) for continuous variables with a normal distribution. *E*-DT = E-wave deceleration time, LV = left ventricle, VAT = visceral adipose tissue, SAT = subcutaneous adipose tissue. Unpaired comparisons between sex were examined via t-tests. P < 0.05 was considered significant and p-values were controlled for the FDR.

3.3. Associations of metabolic load with diastolic function via piecewise SEM

Table 3 and Fig. 4 present sex-specific crude and adjusted associations between the MLF (per 1 SD change) and diastolic parameters. In the unadjusted model, the MLF was significantly associated to the E/A ratio for both males (β = −0.12; 95% CI = [−0.19; −0.04]) and females (β = −0.16; 95% CI = [−0.22; −0.10]). After adjusting, this negative relationship sustained (males/females: β = −0.12/−0.12; 95% CI = [−0.20; −0.05]/[−0.17; −0.07]). For *E*-DT, the MLF was only negatively associated in females with a decrease of 12.27 ms (95% CI = [−17.86; −6.68]) in the unadjusted model. After adjusting, this relationship sustained with an E-DT decrease of −11.83 ms (95% CI = [−17.38, −6.27]).

3.4. Associations of metabolic load with cardiac morphology & hemodynamics via piecewise SEM

Table 3 also presents sex-specific crude and adjusted associations between the MLF (per 1 SD change) and cardiac morphology and hemodynamics parameters. For the unadjusted model in males, LV mass (β = 3.97 g; 95% CI = [1.12; 6.87]) and LV mass/LV end-diastolic volume ratio (β = 0.02 g; 95% CI = [0.00; 0.04]) were associated to the MLF. In females, the LV mass index (β = −1.65 g; 95% CI = [−2.84; −0.47]) and LV mass/LV end-diastolic volume ratio (β = 0.02 g; 95% CI = [0.00; 0.04]) were associated. These relationships sustained for the adjusted models in males: LV mass (β = 3.61 g; 95% CI = [0.72; 6.50]), LV mass/

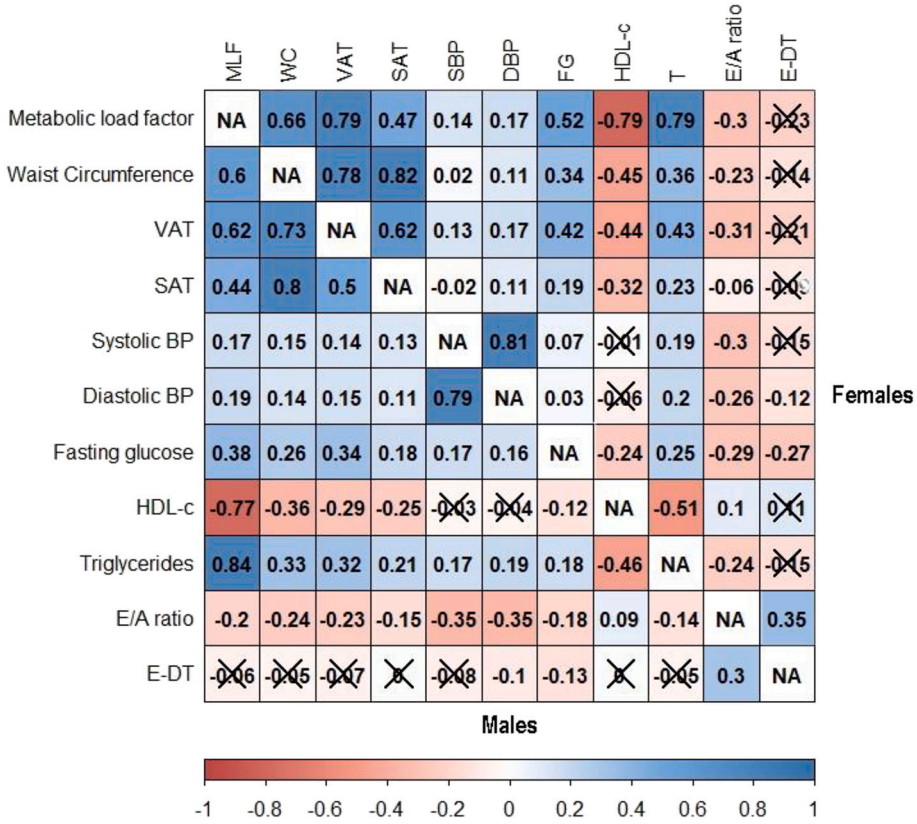

Fig. 3. Intercorrelations of variables under study. Females are shown above, males below in the figure. MLF = MLF, WC = waist circumference, VAT = visceral adipose tissue, SAT = subcutaneous adipose tissue. SBP = systolic blood pressure, DBP = diastolic blood pressure, FG = fasting glucose, HDL-c = high-density lipoproteins cholesterol, T = triglycerides, E-DT = E-wave deceleration time. $P < 0.05$ was considered significant and are depicted with colored squares. Crossed depicted squares are non-significant. *P*-values were controlled for the FDR.

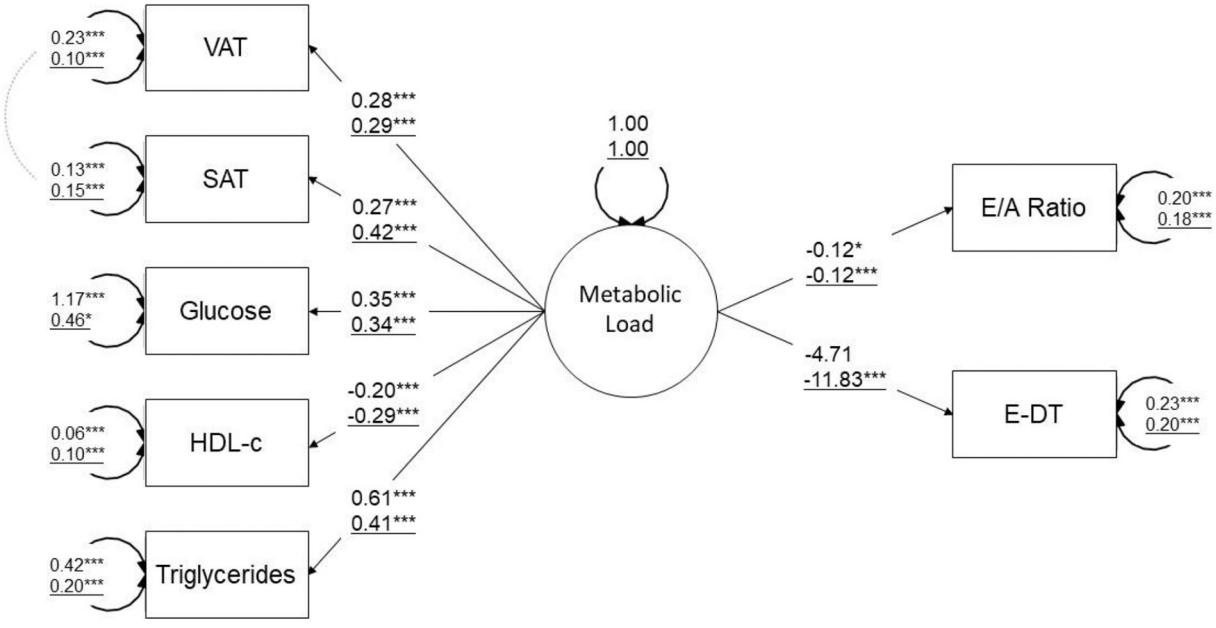

Fig. 4. Graphical representation of a piecewise SEM including the MLF regressed on diastolic function.
Proposed sex-specific one-factor structure of metabolic load regressed on diastolic parameters E/A ratio and E deceleration time (E-DT). Adjusting for potential confounding was made by including age, ethnicity, education and tobacco smoking. Standardized parameter estimates representing factor loadings and regression coefficients are shown on paths left and right of the MLF respectively. Upper numbers on paths refer to the male (above) and female (below and underline) group. Double headed arrows presenting covariance and error terms of indicators respectively. Coefficients are significant at $*p > 0.05$, $**p > 0.01$, $***p > 0.001$. VAT = visceral adipose tissue, SAT = subcutaneous adipose tissue, HDL-c = high-density lipoproteins cholesterol.

LV end-diastolic volume ratio (β = 0.02; 95% CI = [0.00; 0.04]) and LV cardiac output (LV CO) (β = 0.21 L/min; 95% CI = [0.05; 0.37]) and females: LV mass index (β = −1.78 g; 95% CI = [−2.97; −0.59]) and LV mass/LV end-diastolic volume ratio (β = 0.02; 95% CI = [0.00; 0.04]).

Table 3
Associations of the MLF with cardiac outcomes.

	Males			Females		
Parameter	β	95% CI	p-value	β	95% CI	p-value
Diastolic function						
E/A ratio						
Crude	−0.12	−0.19, −0.04	0.04	−0.16	−0.22, −0.10	<0.001
Adjusted	−0.12	−0.20, −0.05	0.04	−0.12	−0.17, −0.07	<0.001
DT (ms)						
Crude	−3.60	−9.54, 2.33	0.50	−12.27	−17.86, −6.68	<0.001
Adjusted	−4.71	−10.93, 1.51	0.35	−11.83	−17.38, −6.27	<0.001
Cardiac morphology						
LV mass (g)						
Crude	3.97	1.12, 6.87	0.04	1.36	−0.91, 3.63	0.43
Adjusted	3.61	0.72, 6.50	0.05	1.37	−0.83, 3.58	0.43
LV mass index (g/m^2)						
Crude	−0.60	−1.71, 0.50	0.51	−1.65	−2.84, −0.47	0.02
Adjusted	−0.67	−1.82, 0.47	0.50	−1.78	−2.97, −0.59	0.01
LV mass/LV end-diastolic volume ratio						
Crude	0.02	0.00, 0.04	0.03	0.02	0.00, 0.04	0.005
Adjusted	0.02	0.00, 0.04	0.03	0.02	0.00, 0.04	0.01
Cardiac hemodynamics						
LV end-systolic volume (ml)						
Crude	−0.20	−2.65, 2.26	0.93	−0.13	−1.89, 1.63	0.89
Adjusted	−0.56	−2.84, 1.72	0.81	0.12	−1.58, 1.82	0.89
LV end-diastolic volume (ml)						
Crude	0.79	−4.18, 5.75	0.85	−1.58	−5.50, 2.35	0.60
Adjusted	0.01	−4.46, 4.48	0.99	−1.00	−4.59, 2.60	0.70
LV stroke volume (ml)						
Crude	1.00	−2.20, 4.17	0.75	−1.45	−4.11, 1.21	0.46
Adjusted	0.57	−2.34, 3.48	0.84	−1.12	−3.53, 1.29	0.54
Ejection Fraction (%)						
Crude	0.37	−0.46, 1.20	0.57	−0.19	−1.01, 0.63	0.74
Adjusted	0.39	−0.42, 1.21	0.56	−0.23	−1.04, 0.58	0.70
Cardiac output (L/min)						
Crude	0.21	0.03, 0.39	0.06	0.14	0.04, 0.31	0.29
Adjusted	0.21	0.05, 0.37	0.05	0.16	0.00, 0.32	0.15

Results represents linear regression coefficients and 95% CI, weighted toward the BMI distribution of the general population. Regression coefficients reflects the change in outcome per 1 SD change of MLF. Crude models where adjusted for age, sex, smoking, ethnicity and education. CI = confidence interval, *E*-DT = E-wave deceleration time, LV = left ventricle. P < 0.05 was considered significant and p-values were controlled for the FDR.

3.5. Associations of the metabolic syndrome with diastolic function

Table 4 presents crude and adjusted associations between the MetS (present or not) and diastolic parameters. In the unadjusted model, the MetS was significantly associated to the E/A ratio (β = −0.28; 95% CI = [−0.35, −0.20]). After adjusting, this negative relationship remained (β = −0.23; 95% CI = [−0.29, −0.16]). For the *E*-DT, the MetS was also negatively associated with a decrease of 13.27 ms (95% CI = [−21.70, −4.85]) in the unadjusted model. After adjusting, this relationship sustained with E-DT decrease of 13.28 ms (95% CI = [−22.05, −4.51]).

3.6. Associations of the MetS with cardiac morphology & hemodynamics

Table 4 also presents crude and adjusted associations between the MetS (present or not) and cardiac morphology and hemodynamics parameters. For the unadjusted model the LV mass, LV mass/LV end-diastolic volume ratio and cardiac output were associated to the MetS (all $p < 0.001$). For the adjusted models, these associations with the MetS remained: LV mass (β = 5.42 g; 95% CI = [2.02, 8.83]), LV mass/LV end-diastolic volume ratio (β = 0.03; 95% CI = [0.01; 0.05]) and cardiac output (β = −0.38 L/min; 95% CI = [0.16, 0.61]).

4. Discussion

Our main aim was to construct a latent factor via CFA that characterizes metabolic load, using continuous information of the MetS variables. Importantly, we wanted to investigate whether addition of MRI-derived VAT and SAT resulted in improved model-fit and associations as opposed to the use of surrogate measures of abdominal obesity such as waist circumference.

In agreement with our hypothesis, this work indeed revealed that a one-factor structure of metabolic load could be described with MRI-derived VAT and SAT. As far as we are aware this is the first time that accurate adipose tissue quantification with MRI has been included in a CFA model regarding metabolic impairment. Moreover, our findings confirm that waist circumference becomes obsolete once VAT and SAT are included. Surprisingly, no difference in factor loading was found between VAT and SAT in males. SAT described metabolic load better than VAT in females. Despite various studies argued that VAT is the predominant contributor to metabolic impairment,[5,9,10] other studies showed the importance of SAT.[26,27] It seems that the large SAT regions were associated with a higher burden of unfavorable risk factors such as leptin, which has been linked to vascular dysfunction. Moreover, sex-specific differences in adiposity distributions are well known, where males tend to have more VAT per body surface area whereas women have more SAT.[26,28] Consequently, our study confirms additional support of sex specific development of metabolic impairment which was also apparent in triglycerides.[29]

Further analysis showed that blood pressure did not contribute to the metabolic factor regarding its low loadings. Though some studies showed differently, this is in good agreement with previous findings.[2,3] In the current analysis it seems that blood pressure is a consequence of other MetS mechanisms such as insulin resistance and lipid metabolism.[30] This has been confirmed in a multi-factor study which showed that blood pressure is more related to a glucose metabolism specific factor.[3]

In our final analyses, we aimed to test the predictive power of the MLF to primarily LV diastolic function and, secondarily LV cardiac morphology and hemodynamics. Though the observed effects on diastolic function were small, there is a distinct proof that the MLF was associated with reduced diastolic function determined by a lower E/A ratio. A reduced diastolic function was more apparent in females than males determined by a shorter E-DT, possibly highlighting impaired LV

Table 4
Associations of the metabolic syndrome with cardiac outcomes.

Parameter	β	95% CI	p-value
Diastolic function			
E/A ratio			
Crude	−0.28	−0.35, −0.20	<0.001
Adjusted	−0.23	−0.29, −0.16	<0.001
DT (ms)			
Crude	−13.27	−21.70, −4.85	0.005
Adjusted	−13.28	−22.05, −4.51	0.007
Cardiac morphology			
LV mass (g)			
Crude	9.57	4.93, 14.20	<0.001
Adjusted	5.42	2.02, 8.83	0.005
LV mass index (g/m^2)			
Crude	0.20	−1.49, 1.88	0.82
Adjusted	−1.24	−2.69, 0.22	0.18
LV mass/LV end-diastolic volume ratio			
Crude	0.045	0.02, 0.07	<0.001
Adjusted	0.030	0.01, 0.05	0.003
Cardiac hemodynamics			
LV end-systolic volume (ml)			
Crude	2.59	−0.41, 5.58	0.18
Adjusted	1.20	−1.51, 3.90	0.53
LV end-diastolic volume (ml)			
Crude	4.65	−1.62, 10.92	0.24
Adjusted	1.58	−3.63, 6.80	0.64
LV stroke volume (ml)			
Crude	2.07	−1.92, 6.04	0.46
Adjusted	0.39	−2.96, 3.73	0.82
Ejection Fraction (%)			
Crude	−0.44	−1.52, 0.64	0.55
Adjusted	−0.31	−1.40, 0.77	0.64
Cardiac output (L/min)			
Crude	0.49	0.21, 0.58	<0.001
Adjusted	0.38	0.16, 0.61	<0.001

Results represents linear regression coefficients and 95% CI, weighted toward the BMI distribution of the general population. Regression coefficients reflects the change in outcome per 1 SD change of MLF. Crude models where adjusted for age, sex, smoking, ethnicity and education. CI = confidence interval, E-DT = E-wave deceleration time, LV = left ventricle. $P < 0.05$ was considered significant and p-values were controlled for the FDR.

filling due to increased LV stiffness.[7] Though controversial, an explanation could be that elevated levels of hepatic free fatty acid delivery resulting from lipolysis in VAT is more present in females than males contributing to adverse risk factors.[31] Furthermore, there was a minor increase in LV mass in males to none in females though both increased the LV mass/LV end-diastolic volume ratio, indicating a decrease in diastolic function develops with LV remodeling. Also, LV CO increased primarily in males suggesting an increased metabolic demand when metabolic load is elevated. Lastly, the categorical nature of the MetS overestimate cardiac associations. A possible explanation could be that blood pressure is included, which is not part of the MLF. Moreover, the MetS cannot capture severity of metabolic impairment and lacks sex-specific sensitivity of underlying metabolic impairments.

Finally, a number of potential limitations need to be considered. First, while evidence is growing that obesity has detrimental effects on the cardiac health, causal inference is hindered by the cross-sectional design of this observational study. Second, to improve the assessment of diastolic (dys-)function, additional cardiac functional variables should be included. In echocardiography, a multiparametric approach is recommended where distinct algorithms should be used in subjects with normal LV ejection fraction or depressed LV ejection fraction/patients with myocardial disease.[32] Besides these limitations, we emphasize that various studies proposed multiple latent factors in metabolic dysregulation.[3,33] Yet these studies included considerably more metabolic variables making a multiple factor approach possible. Our proposed one-factor structure was well supported by its fit indices and was stable across sexes.

Our study has highlighted the importance of adipose tissue quantification by MRI to determine metabolic impairment accurately along with the other metabolic syndrome variables via a one-factor confirmatory factor analysis approach. Specifically, visceral adipose tissue and subcutaneous adipose tissue are both of importance where the latter is most prominent in females. Clinically used surrogate variables like waist circumference do less accurately describe metabolic dysregulation worse in combination with other metabolic syndrome variables. Besides MRI derived adipose tissue quantification, deep learning by artificial neural networks using waist circumference among others as input to estimate visceral adipose tissue may be beneficial.[34] Additionally, we have showed that a one-factor structure of metabolic load is associated with a decreased diastolic function, which was more apparent in females than in males with only modest to no increases in left ventricular mass.

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Declaration of competing interest

The authors have nothing to disclose.

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Appendix A. Supplementary data

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