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Impaired Metabolic Health and Low Cardiorespiratory Fitness Independently Associate With Subclinical Atherosclerosis in Obesity

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Abstract

Context: For a given body mass index (BMI), both impaired metabolic health (MH) and reduced cardiorespiratory fitness (CRF) associate with increased risk of cardiovascular disease (CVD).

Objective: It remains unknown whether both risk phenotypes relate to CVD independently of each other, and whether these relationships differ in normal weight, overweight, and obese subjects.

Methods: Data from 421 participants from the Tübingen Diabetes Family Study, who had measurements of anthropometrics, metabolic parameters, CRF (maximal aerobic capacity [VO_{2max}]) and carotid intima-media thickness (cIMT), an early marker of atherosclerosis, were analyzed. Subjects were divided by BMI and MH status into 6 phenotypes.

Results: In univariate analyses, older age, increased BMI, and a metabolic risk profile correlated positively, while insulin sensitivity and VO_{2max} negatively with cIMT. In multivariable analyses in obese subjects, older age, male sex, lower VO_{2max} (std. ß −0.21, $P = 0.002$) and impaired MH (std. ß 0.13, $P = 0.02$) were independent determinants of increased cIMT. After adjustment for age and sex, subjects with metabolically healthy obesity (MHO) had higher cIMT than subjects with metabolically healthy normal weight (MHNW; 0.59 ± 0.009 vs 0.52 ± 0.01 mm; $P < 0.05$). When VO_{2max} was additionally included in this model, the difference in cIMT between MHO and MHNW groups became statistically nonsignificant (0.58 ± 0.009 vs 0.56 ± 0.02 mm; $P > 0.05$).

Conclusion: These data suggest that impaired MH and low CRF independently determine increased cIMT in obese subjects and that low CRF may explain part of the increased CVD risk observed in MHO compared with MHNW.

Key Words: Metabolically healthy obesity, cardiorespiratory fitness, subclinical atherosclerosis, obesity, carotid intima-media thickness, cardiovascular disease

Abbreviations: BMI, body mass index; BW, body weight; cIMT, carotid intima-media thickness; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; HPA, habitual physical activity; MH, metabolic health; MHNW, metabolically healthy normal weight; MHO, metabolically healthy obesity; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MUH, metabolically unhealthy; MUHNW, metabolically unhealthy normal weight; MUHO, metabolically unhealthy obesity; OGTT, oral glucose tolerance test; TDFS, Tübingen Diabetes Family Study; VO_{2max}, maximal aerobic capacity

Compared to subjects with a normal body mass index (BMI) people with a higher BMI have increased morbidity and an elevated risk of all-cause and cardiovascular mortality (1). However, the research into the causes and consequences of metabolically healthy obesity (MHO) revealed that for a given BMI the risk of cardiometabolic diseases and death may vary substantially among obese subjects. Furthermore, there is a relatively large variability of these risks over a broad range of BMI and subjects with metabolically unhealthy normal weight (MUHNW) also have an increased risk of cardiometabolic diseases (2-10).

During recent years there has been much discussion about how metabolic health (MH) should be defined and to what extent MH is sustained during a longer period of follow-up (11-16). Important findings emerged showing that subjects with MHO still have a ~25% higher risk of all-cause

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mortality and/or cardiovascular disease (CVD), compared to subjects with metabolically healthy normal weight (MHNW). However, this risk is much higher in subjects with metabolically unhealthy obesity (MUHO) and in subjects with metabolically unhealthy normal weight (MUHNW) (2-10). Thus, achieving and sustaining MH in obesity is considered a first step toward a lower risk of cardiometabolic diseases (9, 10, 17). For this purpose, low-calorie diets with different amounts of fat, carbohydrates, and protein (17-19) or precision dietary management approaches (20-22) are being tested.

In the search of the main characteristics of MH the absence of a lipodystrophic phenotype in MHNW (23) and of visceral obesity and fatty liver in MHO (24-27), were identified. Furthermore, besides MH, high cardiorespiratory fitness (CRF), has been associated with lower mortality and risk of cardiometabolic diseases, independently of other important risk markers, in obese individuals (28-30). However, it remains so far unclear if CRF may explain part of the elevated risk of mortality/CVD that is observed in subjects with MHO relative to subjects with MHNW. Therefore, we investigated the relationship of CRF with MH and with carotid intima-media thickness (cIMT), which is an independent predictor of CVD (31, 32).

Methods

Data were analyzed from a total of 421 participants from the Tübingen Diabetes Family Study (TDFS) (23), for whom measurements of (1) body fat mass and distribution and of liver fat content; (2) cIMT; and (3) CRF were available. Subjects were included into the TDFS when their risk of cardiometabolic diseases was increased based on the following criteria: a family history of type 2 diabetes, a BMI ≥ 27 kg/m^2, previous gestational diabetes in women, prediabetes or suspected nonalcoholic fatty liver disease (NAFLD). Participants were considered healthy according to results of a physical examination and routine laboratory tests. Informed written consent was obtained from all participants and the Ethics Committee of the University of Tübingen had approved the protocol.

Simple Anthropometrics, Oral Glucose Tolerance Test, and Blood Pressure

BMI was calculated as weight divided by the square of height (kg/m^2). Waist circumference was measured in the upright position at the midpoint between the lateral iliac crest and the lowest rib. Hip circumference was taken at the widest point over the greater trochanters. Subjects underwent a frequently sampled 2-hour, 75-g oral glucose tolerance test (OGTT). Venous plasma samples were obtained at 0, 30, 60, 90, and 120 minutes for determination of plasma glucose and insulin levels. Whole-body insulin sensitivity was calculated from glucose and insulin values during the OGTT as proposed by Matsuda and DeFronzo (33). The blood pressure measurement was performed at the dominant arm (unless there was a deformity), using a sphygmomanometer and a stethoscope to auscultate the Korotkoff sounds. Blood pressure was measured in duplicate, and the mean value of both measurements was calculated.

Total Body Fat Mass, Body Fat Distribution, Skeletal Muscle Mass, and Liver Fat Content

Measurements of total body and visceral fat mass, and of skeletal muscle mass of the upper lower extremities were performed applying a T1-weighted axial magnetic resonance imaging (MRI) technique on a 1.5 T whole-body scanner (Magnetom Sonata, Siemens Healthineers, Erlangen, Germany). Liver fat content was measured by localized proton magnetic resonance spectroscopy (^{1}H-MRS) as previously described (34).

Carotid Intima-Media Thickness

The cIMT was measured in the fasting state using a high-resolution ultrasound system (AU5 idea, Esaote Biomedica, Munich, Germany) with an integrated electrocardiography package as previously described (35).

Habitual Physical Activity

All individuals completed a standardized self-administered and validated questionnaire to measure physical activity and a habitual physical activity (HPA) score was calculated (36).

Cardiorespiratory Fitness

For the measurement of CRF, the maximal aerobic capacity (VO_{2max}) was determined. The individuals underwent a continuous, incremental exercise test to volitional exhaustion using a cycle ergometer. The cycle ergometer test was performed on an electromagnetically braked cycle ergometer (Ergometrics 800 S; Ergoline, Bitz, Germany). Oxygen consumption was measured using a spiroergometer (MedGraphics System Breese Ex 3.02 A; MedGraphics) (37). The VO_{2max} data are presented as mL/min/kg body weight (BW) and as mL/min/kg skeletal muscle (SM) mass.

Analytical Procedures

Blood glucose was determined using a bedside glucose analyzer (glucose-oxidase method; YSI, Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin was determined on an ADVIA Centaur XP and all other blood parameters on an ADVIA XPT clinical chemistry system (Siemens Healthineers systems, Eschborn, Germany).

Metabolic Health

Subjects were considered metabolically healthy when fewer than 2 parameters of the metabolic syndrome, as defined by the National Cholesterol Education Program Adult Treatment Panel III in 2005 (38), except accounting for waist circumference, were present. The risk parameters were (1) triglycerides ≥ 150 mg/dL, or pharmacological treatment for elevated triglycerides; (2) HDL cholesterol < 50 mg/dL for women and < 40 mg/dL for men, or pharmacological treatment for elevated total- and LDL cholesterol or reduced HDL cholesterol; (3) blood pressure ≥ 130/85 mmHg or pharmacological antihypertensive treatment; and (4) fasting glucose ≥ 100 mg/dL or pharmacological treatment of elevated glucose. Subjects were also categorized in different BMI strata (normal weight [BMI 18.5–24.9 kg/m^2], overweight [BMI 25.0–29.9 kg/m^2], and obese [BMI ≥ 30 kg/m^2]).

Statistical Analyses

Values are presented as means ± SD or means ± standard error of means (SEM). Data that were not normally distributed (Shapiro-Wilk *W* test) were logarithmically transformed. For statistical testing Pearson's correlations, multivariable linear

regression analyses, and ANOVA, followed by Student's *t* test, were used. For statistical testing, the analysis program JMP 14.2.0 of SAS was used.

Results

The characteristics of the subjects are shown in Table 1. Subjects (260 women, 161 men) had a mean age of 44 years and a mean BMI of 30.4 kg/m^2. Among the 421 subjects, 43 had normal weight, 173 were overweight, and 205 were obese. A total of 283 subjects were metabolically healthy, while 138 subjects were metabolically unhealthy. The percentage of males was higher in the metabolically unhealthy subjects and, except for habitual physically activity, the metabolically unhealthy subjects had higher anthropometric and cardiometabolic risk parameters compared with the metabolically healthy subjects. As it has been suggested that estimates of body composition should be adjusted for height squared to make them better comparable among groups, we also show the respective data.

Univariate Relationships of Anthropometrics and Cardiometabolic Risk Factors with cIMT

First, we investigated the relationships of anthropometrics and cardiometabolic risk factors with cIMT. In univariate analyses, male sex; age; body weight; BMI; waist and hip circumferences; visceral fat mass; liver fat content; fasting and 2-hour glycemia; total-, HDL- and LDL cholesterol levels; blood pressure; high-sensitivity C-reactive protein (hs-CRP) levels; and the metabolically unhealthy (MUH) phenotype correlated positively with cIMT, while insulin sensitivity and VO_{2max} correlated negatively with cIMT (Table 2).

Table 1. Subject characteristics

Parameter	All (N = 421)	MH (N = 283)	MUH (N = 138)	*P*
Gender (males/females)	161/260	95/188	66/72	0.005
Age (years)	44 (12)	42 (12)	48 (11)	<0.0001
Body weight (kg)	88.9 (16.6)	86.8 (16.9)	93.1 (15.2)	<0.0001
Height (m)	1.71 (0.09)	1.71 (0.09)	1.71 (0.09)	0.77
Body mass index (kg/m^2)	30.4 (4.8)	29.8 (4.9)	31.8 (4.2)	<0.0001
Waist circumference (cm)	97.9 (12.9)	95.5 (12.9)	102.9 (11.5)	<0.0001
Waist circumference/height^2	33.7 (4.7)	32.9 (4.5)	35.4 (4.7)	<0.0001
Hip circumference (cm)	109.4 (10.2)	108.6 (10.4)	111.0 (9.7)	0.02
Hip circumference/height^2	37.9 (5.4)	37.6 (5.2)	38.4 (5.8)	0.20
Waist-to-hip ratio	0.90 (0.09)	0.88 (0.09)	0.93 (0.09)	<0.0001
Waist-to-hip ratio/height^2	0.31 (0.03)	0.30 (0.03)	0.32 (0.03)	<0.0001
Total body fat $_{MRI}$ (kg)	29.8 (11.3)	29.1 (11.6)	31.3 (10.4)	0.009
Total body fat/height^2	10.3 (4.0)	10.1 (4.1)	10.8 (3.9)	<0.04
Visceral fat $_{MRI}$ (kg)	3.4 (2.1)	2.9 (1.9)	4.3 (2.0)	<0.0001
Visceral fat/height^2	1.14 (0.65)	0.99 (0.60)	1.45 (0.62)	<0.0001
UE + LE skeletal muscle $_{MRI}$ (kg)	30.4 (6.4)	29.7 (6.2)	31.6 (6.6)	0.004
UE + LE skeletal muscle/height^2	10.3 (1.4)	10.1 (1.4)	10.7 (1.5)	<0.0001
Liver fat $_{H\text{-}MRS}$(%)	6.5 (6.9)	4.9 (5.1)	10.0 (8.6)	<0.0001
Fasting glucose (mM)	5.3 (0.5)	5.1 (0.4)	5.5 (0.6)	<0.0001
2-hour glucose (mM)	6.7 (1.4)	6.5 (1.3)	7.2 (1.6)	<0.0001
IS_{OGTT} (arbitrary units)	10.8 (6.3)	12.4 (6.5)	7.5 (4.1)	<0.0001
Total cholesterol (mg/dL)	196 (36)	192 (36)	204 (34)	0.0002
HDL cholesterol (mg/dL)	52 (13)	56 (13)	45 (9)	<0.0001
LDL cholesterol (mg/dL)	121 (31)	116 (30)	130 (31)	<0.0001
Triglycerides (mg/dL)	127 (94)	104 (66)	174 (122)	<0.0001
Blood pressure, systolic (mmHg)	126 (16)	121 (15)	136 (15)	<0.0001
Blood pressure, diastolic (mmHg)	79 (11)	76 (11)	85 (11)	<0.0001
hs-CRP (mg/dL)	0.26 (0.34)	0.25 (0.34)	0.29 (0.35)	0.005
cIMT (mm)	0.57 (0.13)	0.55 (0.12)	0.62 (0.12)	<0.0001
VO_{2max} (mL/min/kgBW)	22.5 (6.5)	23.4 (6.7)	20.7 (5.6)	<0.0001
VO_{2max} (mL/min/kgSM_{UE+LE})	65.0 (13.8)	67.1 (13.7)	60.6 (12.9)	<0.0001
HPA score	7.9 (1.2)	8.0 (1.2)	7.8 (1.1)	0.08

Data are means (SD). *P* from χ^2-test or Student's *t* test.
Abbreviations: BW, body weight; cIMT, carotid intima-media thickness; HDL, high-density lipoprotein; H-MRS, proton magnetic resonance spectroscopy; HPA, habitual physical activity; hs-CRP, high-sensitivity C-reactive protein; IS, insulin sensitivity; LDL, low-density lipoprotein; LE, lower extremities, MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; SM, skeletal muscle mass; UE, upper extremities; $VO2_{max}$, maximal aerobic capacity.

Table 2. Univariate relationships of anthropometrics and cardiometabolic risk factors with cIMT

Parameter	r	*P*
Males	0.16	0.001
Age	0.61	<0.0001
Body weight	0.14	0.003
Height	-0.05	0.34
Body mass index	0.20	<0.0001
Waist circumference	0.33	<0.0001
Waist circumference/height^2	0.35	<0.0001
Hip circumference	0.11	0.03
Hip circumference/height^2	0.11	0.03
Waist-to-hip ratio	0.32	<0.0001
Waist-to-hip ratio/height^2	0.36	<0.0001
Total body fat $_{MRI}$	0.08	0.08
Total body fat/height^2	0.09	0.06
Visceral fat $_{MRI}$	0.43	<0.0001
Visceral fat/height^2	0.45	<0.0001
UE + LE Skeletal muscle mass $_{MRI}$	0.11	0.02
UE + LE Skeletal muscle/height^2	0.20	<0.0001
Liver fat $_{H\text{-}MRS}$	0.28	<0.0001
Fasting glucose	0.27	<0.0001
2-hour glucose	0.12	0.01
IS_{OGTT}	-0.22	<0.0001
Total cholesterol	0.23	<0.0001
HDL cholesterol	-0.10	0.03
LDL cholesterol	0.16	0.0009
Triglycerides	0.18	0.0002
Blood pressure, systolic	0.28	<0.0001
Blood pressure, diastolic	0.21	<0.0001
hs-CRP	0.12	0.02
VO_{2max} (mL/min/kgBW)	-0.30	<0.0001
VO_{2max} (mL/min/kgSM_{UE+LE})	-0.38	<0.0001
HPA score	0.04	0.44
MUH phenotype	0.24	<0.0001

Abbreviations: BW, body weight; cIMT, carotid intima-media thickness; HDL, high-density lipoprotein; H-MRS, proton magnetic resonance spectroscopy; HPA, habitual physical activity; hs-CRP, high-sensitivity C-reactive protein; IS, insulin sensitivity; LDL, low-density lipoprotein; LE, lower extremities, MRI, magnetic resonance imaging; MUH, metabolically unhealthy; OGTT, oral glucose tolerance test; SM, skeletal muscle mass; UE, upper extremities; $VO2_{max}$, maximal aerobic capacity.

Anthropometrics and Cardiometabolic Risk Phenotypes in Metabolically Healthy and Unhealthy Phenotypes in Different BMI Categories

Second, we asked the question how cIMT and VO_{2max} relates to MH in subjects with normal weight, overweight, and obesity (Table 3). The percentage of males was higher in the MUH phenotypes and, in general, subjects with the MUH phenotypes were older and had a higher cardiometabolic risk profile. The cIMT was higher in the MUH phenotypes in the normal weight and obese groups, but no difference in cIMT was observed between the MH and MUH phenotypes in the overweight group. VO_{2max} was lower in the MUH phenotypes.

To investigate whether and to what extent total body fat mass, visceral fat mass, and skeletal muscle mass independently contribute to the MH phenotype and VO_{2max} (mL/min/kgBW) we ran multivariate models including these parameters, as well as sex and age. In these models, only high visceral fat mass independently determined the MH phenotype, while younger age, lower total body and visceral fat mass, and higher skeletal muscle mass independently determined higher VO_{2max} (Table 4).

Selected Variables as Possible Independent Determinants of cIMT in Subjects With Obesity

Third, we investigated independent determinants of cIMT. Because we predominantly recruited subjects with a higher BMI, the overweight and the normal weight groups had lower sample sizes than the obese group. Therefore, we only performed these analyses in obese subjects. To focus on the impact of the MUH phenotype and low VO_{2max} (mL/min/kgBW), we generated a parsimonious statistical model. Here, we included the variables that are not used to define MH, such as sex, age, BMI, waist circumference, and LDL cholesterol levels, in the multivariable linear regression model. Among the variables sex, age, BMI, waist circumference, and LDL cholesterol levels, only older age associated with increased cIMT (Table 5, Model 1). After additional inclusion of VO_{2max} in this model, a low VO_{2max} was also associated with higher cIMT (Table 5, Model 2). When VO_{2max} was replaced by the MUH phenotype, this phenotype also associated with higher cIMT (Table 5, Model 3). When VO_{2max} and the MUH phenotype were included in the statistical model, both a low VO_{2max} and the MUH phenotype were found to associate with higher cIMT (Table 5, Model 4). The results were not considerably affected by replacing waist circumference by waist circumference/(height)^2 in the statistical models. Furthermore, replacing VO_{2max} (mL/min/kgBW) by VO_{2max} (mL/min/kg skeletal muscle mass $[SM]_{UE+LE}$) did not change the relationships (eg, in the Model 4), except for the relationship of sex with cIMT, which became statistically not significant (for males: from std. ß 0.19, $P = 0.02$ to std. ß 0.11, $P = 0.12$).

Replacement of BMI and waist circumference by visceral fat and liver fat content also revealed similar results.

cIMT of Subjects With MH and MUH Phenotypes in Different BMI Categories

Finally, in an exploratory approach, we investigated the differences in cIMT among 6 BMI/MH phenotypes. In a multivariable regression model including the independent determinants of cIMT, identified in the BMI categories—age, sex, and MUH phenotype—subjects with MHO had a higher cIMT than subjects with MHNW (0.59 ± 0.009 mm vs 0.52 ± 0.01 mm, $P < 0.05$; Fig. 1, panel A). When $VO2_{max}$ was additionally included in this statistical model, the difference in cIMT between the MHO and MHNW groups became statistically nonsignificant (0.58 ± 0.009 mm vs 0.56 ± 0.02 mm; Fig. 1, panel B).

Discussion

A high CRF might mitigate the detrimental effects of excess body weight on CVD and CVD mortality, termed the "fat but fit" paradox (39). On the other hand, MH, that is, as widely used, the absence of hyperglycemia, low HDL cholesterol levels, high triglyceride levels, and hypertension, or the prevalence of fewer than 2 of these risk factors, associates with no or only a moderately increased risk of CVD and

Table 3. Characteristics of 6 phenotypes based on the BMI and metabolic health categories

Parameter	MHNW	MUHNW	MHOW	MUHOW	MHO	MUHO
Gender (males/females)	5/32	2/4	53/76	24/20	37/80	40/48
Age (years)	42 (12)	54 (6)	42 (12)	47 (11)	43 (12)	48 (12)
Body weight (kg)	64.4 (8.0)	69.5 (2.4)	82.8 (9.7)	82.4 (10.0)	98.3 (16.2)	100.0 (13.1)
Height (m)	1.69 (0.08)	1.71 (0.03)	1.72 (0.10)	1.71 (0.10)	1.70 (0.08)	1.71 (0.09)
Body mass index ($kg \cdot m^{-2}$)	22.6 (1.8)	23.8 (0.7)	27.9 (1.3)	28.1 (1.3)	34.0 (4.0)	34.2 (3.2)
Waist circumference (cm)	78.3 (6.7)	81.3 (10.3)	93.0 (8.1)	94.9 (7.5)	103.7 (12.1)	108.4 (8.9)
Waist circumference/height^2	27.6 (2.8)	27.9 (3.6)	31.5 (2.8)	32.5 (2.3)	36.1 (4.1)	37.3 (4.5)
Hip circumference (cm)	95.4 (5.2)	94.8 (4.6)	105.2 (5.7)	103.8 (4.7)	116.7 (9.1)	115.7 (8.4)
Hip circumference/height^2	33.7 (3.2)	32.5 (2.0)	35.9 (4.4)	35.8 (4.0)	40.8 (4.9)	40.1 (6.1)
Waist-to-hip ratio	0.82 (0.06)	0.86 (0.12)	0.89 (0.09)	0.92 (0.08)	0.89 (0.09)	0.94 (0.10)
Total body fat $_{MRI}$ (kg)	15.0 (5.2)	14.7 (5.7)	24.6 (5.9)	23.0 (5.4)	38.4 (10.5)	36.5 (8.6)
Total body fat/height^2	5.3 (1.9)	5.1 (2.0)	8.4 (2.3)	8.0 (2.1)	13.4 (3.6)	12.7 (3.4)
Visceral fat $_{MRI}$ (kg)	1.0 (0.6)	1.6 (0.3)	2.7 (1.5)	3.4 (1.6)	3.8 (2.1)	4.9 (1.9)
Visceral fat/height^2	0.35 (0.21)	0.54 (0.10)	0.90 (0.45)	1.14 (0.49)	1.28 (0.65)	1.67 (0.59)
UE + LE Skeletal muscle mass $_{MRI}$	24.7 (3.9)	26.8 (3.1)	29.8 (6.0)	29.7 (5.9)	31.2 (6.1)	32.9 (6.8)
UE + LE Skeletal muscle/height^2	8.6 (0.8)	9.2 (0.9)	10.0 (1.2)	10.1 (1.2)	10.8 (1.3)	11.2 (1.4)
Liver fat $_{H\text{-}MRS}$(%)	1.6 (1.5)	3.0 (1.9)	4.3 (4.3)	6.7 (7.7)	6.5 (5.8)	12.1 (8.6)
Fasting glucose (mM)	5.0 (0.5)	5.4 (0.4)	5.1 (0.4)	5.4 (0.5)	5.2 (0.4)	5.6 (0.6)
2-hour glucose (mM)	6.9 (1.6)	6.7 (0.7)	6.4 (1.2)	6.8 (1.5)	6.7 (1.4)	7.4 (1.7)
IS_{OGTT} (arbitrary units)	17.5 (5.6)	14.3 (6.2)	13.2 (6.7)	9.1 (4.0)	9.8 (5.4)	6.3 (3.2)
Total cholesterol (mg/dL)	196 (41)	212 (44)	192 (39)	201 (34)	190 (32)	205 (35)
HDL cholesterol (mg/dL)	64 (15)	53 (18)	55 (12)	45 (7)	54 (12)	44 (9)
LDL cholesterol (mg/dl)	116 (37)	140 (26)	117 (29)	134 (33)	115 (28)	127 (30)
Triglycerides (mg/dL)	89 (32)	115 (37)	108 (86)	142 (60)	103 (45)	194 (143)
Blood pressure, systolic (mmHg)	115 (15)	129 (13)	120 (14)	131 (16)	124 (15)	138 (13)
Blood pressure, diastolic (mmHg)	73 (10)	83 (12)	75 (10)	82 (11)	79 (11)	87 (11)
hs-CRP (mg/dL)	0.15 (0.26)	0.20 (0.25)	0.19 (0.26)	0.18 (0.19)	0.35 (0.40)	0.36 (0.39)
cIMT (mm)	0.50 (0.11)	0.62 (0.11)	0.55 (0.13)	0.58 (0.12)	0.57 (0.12)	0.64 (0.12)
VO_{2max} (mL/min/kgBW)	28.7 (8.3)	23.9 (8.0)	24.8 (6.2)	22.7 (6.2)	20.1 (5.0)	19.4 (4.7)
VO_{2max} (mL/min/kgSM_{UE+LE})	74.1 (16.2)	61.2 (16.3)	69.0 (13.1)	63.2 (14.9)	63.0 (12.1)	59.3 (11.5)
HPA score	8.4 (1.1)	8.3 (1.3)	8.2 (1.1)	7.5 (1.2)	7.5 (1.3)	7.9 (1.0)

Data are means (SD).
Abbreviations: BW, body weight; cIMT, carotid intima-media thickness; HDL, high-density lipoprotein; H-MRS, proton magnetic resonance spectroscopy; HPA, habitual physical activity; hs-CRP, high-sensitivity C-reactive protein; IS, insulin sensitivity; LDL, low-density lipoprotein; LE, lower extremities, MHNW, metabolically healthy normal weight; MHO, metabolically healthy obesity; MHOW, metabolically healthy overweight; MRI, magnetic resonance imaging; MUHNW, metabolically unhealthy normal weight; MUHO, metabolically unhealthy obesity; MUHOW, metabolically unhealthy overweight; OGTT, oral glucose tolerance test; SM, skeletal muscle mass; UE, upper extremities; $VO2_{max}$, maximal aerobic capacity.

Table 4. Selected variables as possible independent determinants of the MUH phenotype and of $VO2_{max}$ in multivariate analyses

	MUH phenotype		$VO2_{max}$ (mL/min/kgBW)			MUH phenotype		$VO2_{max}$ (mL/min/kgBW)	
	ß	*P*	std. ß	*P*		ß	*P*	std. ß	*P*
Intercept	-2.45	0.58	**0**	**<0.0001**	**Intercept**	-4.59	0.23	**0**	**<0.0001**
Males	-0.27	0.31	0.07	0.32	**Males**	-0.32	0.19	0.06	0.35
Age	0.63	0.20	**-0.17**	**<0.0001**	**Age**	0.63	0.19	**-0.17**	**<0.0001**
Total body fat	-0.51	0.30	**-0.60**	**<0.0001**	**Total body fat/height^2**	-0.56	0.26	**-0.63**	**<0.0001**
Visceral fat	**1.63**	**<0.0001**	**-0.21**	**<0.0001**	**Visceral fat/height^2**	**1.57**	**<0.0001**	**-0.20**	**0.001**
UE + LE Skeletal muscle mass	-0.23	0.83	**0.37**	**<0.0001**	**UE + LE Skeletal muscle mass/height^2**	1.12	0.38	**0.28**	**<0.0001**

Abbreviations: BW, body weight; LE, lower extremities; MUH, metabolically unhealthy; UE, upper extremities; $VO2_{max}$, maximal aerobic capacity.

CVD mortality in obesity, when compared to MH in normal weight (2-10). There is little information whether high CRF and MH independently associate with a lower CVD risk. Studying subjects from the TDFS who had measurements of anthropometrics, metabolic parameters, CRF, and cIMT, an early marker of atherosclerosis, we found that, besides other

Table 5. Selected variables as possible independent determinants of cIMT in multivariate analyses in subjects with obesity

	Model 1		Model 2		Model 3		Model 4	
	std. ß	*P*	std. ß	*P*	std. ß	*P*	std. ß	*P*
Intercept	0	0.001	0	0.33	0	0.009	0	0.55
Males	−0.09	0.24	**−0.20**	**0.02**	−0.09	0.26	**0.19**	**0.02**
Age	**0.61**	**<0.0001**	**0.57**	**<0.0001**	**0.59**	**<0.0001**	**0.55**	**<0.0001**
BMI	0.08	0.37	0.04	0.66	0.09	0.31	0.05	0.57
Waist circumference	0.10	0.33	0.06	0.57	0.07	0.51	0.03	0.76
LDL cholesterol	−0.01	0.83	-0.006	0.92	−0.03	0.58	−0.02	0.67
VO_{2max} (mL/min/kgBW)	-	-	**−0.22**	**0.001**	-	-	**−0.21**	**0.002**
MUH phenotype	-	-	-	-	**0.14**	**0.01**	**0.13**	**0.02**

Abbreviations: BMI, body mass index; BW, body weight; LDL, low-density lipoprotein; MUH, metabolically unhealthy; VO_{2max}, maximal aerobic capacity.

risk factors, low CRF and the MUH phenotype associated with increased cIMT. When we investigated independent relationships of low CRF and the MUH phenotype with cIMT in obese subjects, besides older age and male sex, also low CRF and the MUH phenotype were identified as independent determinants of increased cIMT. These findings suggest that, in addition to a high CRF, a healthy metabolic profile may be important to protect from early atherosclerosis in obese subjects.

Considering Jonathan Well's capacity-load model (ie, a possible mismatch between fat mass and fat-free mass as a risk factor of metabolic and cardiovascular health) (40), we also investigated to what extent fat mass, visceral obesity, and skeletal muscle mass determine the MUH phenotype and low CRF. We found that only high visceral fat mass independently determined the MH phenotype, while younger age, lower total body and visceral fat mass, and higher skeletal muscle mass independently determined higher VO_{2max}.

An interesting question is whether the differences in CVD risk observed between subjects with MHNW and MHO are due to differences in adiposity levels or CRF (41). It has been well established that subjects with MHNW have higher CRF compared to subjects with MHO (39). In a meta-analysis of 10 studies accounting for physical activity, which generally associates with high CRF, physical activity was found to strongly reduce/eliminate the elevated risk of all-cause mortality and CVD mortality/morbidity in subjects with MHO, compared to subjects with MHNW (42). However, as CRF is not only determined by physical activity, but also by genetics (43, 44), it is unclear to what extent CRF may have been the underlying variable explaining the relationship of physical activity with all-cause mortality and CVD mortality/morbidity in that analysis. So far, only 1 study investigated the role of CRF in the CVD risk in subjects with MHO. In that study the differences in the risks of all-cause mortality and CVD mortality/morbidity between subjects with MHO and MHNW were largely explained by differences in CRF between the 2 phenotypes (45). Thus, our data not only support the conclusion of that study but highlight that such relationships may already be observed in early states of atherosclerosis. Consequently, it can be hypothesized that improvement of CRF in subjects with MHO may be effective to reduce their elevated risk of CVD.

Our study has the strength that we could study subjects who underwent precise measurements of body fat mass and distribution, glucose and lipid metabolism, CRF and cIMT; however, it has the limitation that we could only study a small number of subjects with normal weight and overweight. Furthermore, because we excluded patients with diabetes from our study, we could not determine metabolic health based on our most recently proposed empirically derived definition of metabolically healthy obesity (46). In addition, the exclusion of patients with diabetes, as well as of patients with other chronic diseases, resulted in more obese patients with MHO than MUHO, which differs from the relationship of these phenotypes observed in many other studies (11). On the other hand, this procedure allowed us to exclude the impact of diabetes-associated hyperglycemia and other chronic diseases on the phenotypes studied. Finally, the differences of mean (SD) cIMT between our subjects with MHO (0.57 [0.12] mm) and MUHO (0.64 [0.12] mm), although statistically significant, were small. Nevertheless, in the Framingham Offspring Study a similarly higher cIMT at baseline (0.59 [0.13] mm vs 0.66 [0.15] mm) was found to associate with a higher risk of incident CVD, independently of established CVD risk markers (31).

In conclusion, impaired MH and low CRF independently determine increased cIMT in obese subjects. Furthermore, a low CRF may explain part of the increased risk of CVD that is observed in subjects with MHO, when compared to subjects with MHNW.

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Author Contributions

Angela Lehn-Stefan: Methodology, validation, formal analysis, investigation, writing-original draft, writing-review and editing, visualization. Andreas Peter: Investigation, resources, writing-review and editing. Jürgen Machann: Investigation, resources, data curation. Fritz Schick: Validation, resources. Elko Randrianarisoa: Investigation, data curation. Martin Heni: Data curation, writing-review and editing. Robert Wagner: Writing-review and editing. Andreas L. Birkenfeld: Data curation, supervision, project administration. Andreas Fritsche: Data curation, writing-review and editing. Matthias B. Schulze: Validation, formal analysis,

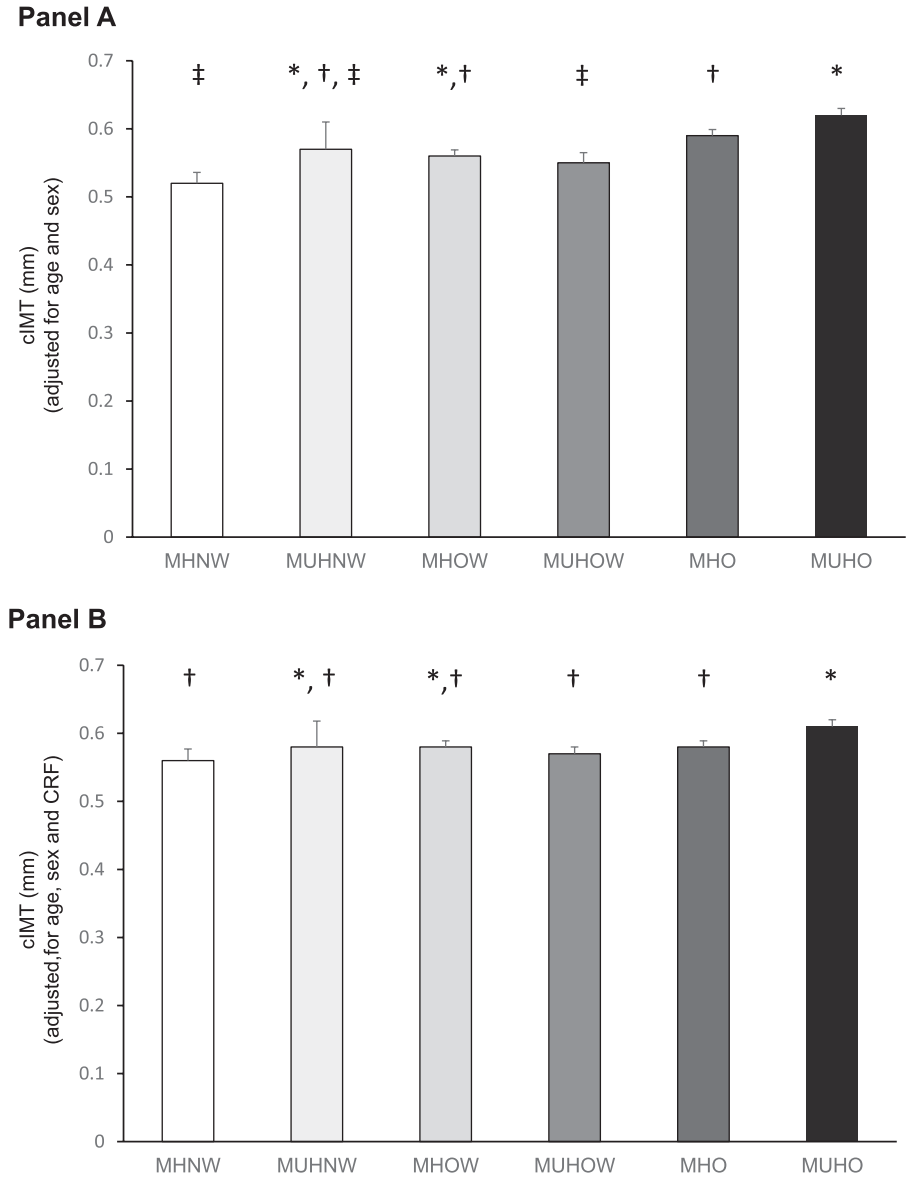

Figure 1. Carotid intima-media thickness (cIMT), adjusted for age and sex (panel A) and for age, sex, and cardiorespiratory fitness (CRF) (panel B), in subjects with metabolically healthy (MHNW) and unhealthy (MUHNW) normal weight, metabolically healthy (MHOW) and unhealthy (MUHOW) overweight, and metabolically healthy (MHO) and unhealthy (MUHO) obesity. Values (means and SEM) that are not connected by the same symbol (*, †, ‡) are statistically different from each other.

writing-review and editing, visualization. Norbert Stefan: Conceptualization, methodology, validation, formal analysis, data curation, writing-original draft, writing-review and editing, visualization, supervision. Konstantinos Kantartzis: Methodology, validation, formal analysis, data curation, investigation, writing-original draft, writing-review and editing, visualization.

Disclosures

All authors declare that they have no conflict of interest to disclose.

Data Availability

All data generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References

1. Bhaskaran K, Dos-Santos-Silva I, Leon DA, Douglas IJ, Smeeth L. Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3.6 million adults in the UK. *Lancet Diabetes Endocrinol*. 2018;6(12):944-953.
2. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis. *Ann Intern Med*. 2013;159(11):758-769.
3. Hamer M, Stamatakis E. Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. *J Clin Endocrinol Metab*. 2012;97(7):2482-2488.
4. Eckel N, Meidtner K, Kalle-Uhlmann T, Stefan N, Schulze MB. Metabolically healthy obesity and cardiovascular events: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2016;23(9):956-966.
5. Lassale C, Tzoulaki I, Moons KGM, *et al*. Separate and combined associations of obesity and metabolic health with coronary heart disease: a pan-European case-cohort analysis. *Eur Heart J*. 2018;39(5):397-406.

6. Yang HK, Han K, Kwon HS, *et al*. Obesity, metabolic health, and mortality in adults: a nationwide population-based study in Korea. *Sci Rep*. 2016;6:30329. doi:10.1038/srep30329
7. Bell JA, Hamer M, Sabia S, Singh-Manoux A, Batty GD, Kivimaki M. The natural course of healthy obesity over 20 years. *J Am Coll Cardiol*. 2015;65(1):101-102.
8. Caleyachetty R, Thomas GN, Toulis KA, *et al*. Metabolically healthy obese and incident cardiovascular disease events among 3.5 million men and women. *J Am Coll Cardiol*. 2017;70(12):1429-1437.
9. Appleton SL, Seaborn CJ, Visvanathan R, *et al*. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. *Diabetes Care*. 2013;36(8):2388-2394.
10. Eckel N, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study. *Lancet Diabetes Endocrinol*. 2018;6(9):714-724.
11. Stefan N, Haring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. *Lancet Diabetes Endocrinol*. 2013;1(2):152-162.
12. Samocha-Bonet D, Dixit VD, Kahn CR, *et al*. Metabolically healthy and unhealthy obese--the 2013 Stock Conference report. *Obes Rev*. 2014;15(9):697-708.
13. Magkos F. Metabolically healthy obesity: what's in a name? *Am J Clin Nutr*. 2019;110(3):533-539.
14. Schulze MB. Metabolic health in normal-weight and obese individuals. *Diabetologia*. 2019;62(4):558-566.
15. Bluher M. Metabolically healthy obesity. *Endocr Rev*. 2020;41(3):405-420. doi:10.1210/endrev/bnaa004
16. Smith GI, Mittendorfer B, Klein S. Metabolically healthy obesity: facts and fantasies. *J Clin Invest*. 2019;129(10):3978-3989.
17. Stefan N, Haring HU, Schulze MB. Metabolically healthy obesity: the low-hanging fruit in obesity treatment? *Lancet Diabetes Endocrinol*. 2018;6(3):249-258.
18. Magkos F, Fraterrigo G, Yoshino J, *et al*. Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. *Cell Metab*. 2016;23(4):591-601.
19. Ludwig DS, Ebbeling CB, Heymsfield SB. Improving the quality of dietary research. *JAMA*. 2019;322(16):1549-1550.
20. Wang DD, Hu FB. Precision nutrition for prevention and management of type 2 diabetes. *Lancet Diabetes Endocrinol*. 2018;6(5):416-426.
21. Magkos F, Hjorth MF, Astrup A. Diet and exercise in the prevention and treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2020;16(10):545-555.
22. Schulze MB, Minihane AM, Saleh RNM, Riserus U. Intake and metabolism of omega-3 and omega-6 polyunsaturated fatty acids: nutritional implications for cardiometabolic diseases. *Lancet Diabetes Endocrinol*. 2020;8(11):915-930.
23. Stefan N, Schick F, Haring HU. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. *Cell Metab*. 2017;26(2):292-300.
24. Stefan N. Causes, consequences, and treatment of metabolically unhealthy fat distribution. *Lancet Diabetes Endocrinol*. 2020;8(7):616-627.
25. Neeland IJ, Ross R, Despres JP, *et al*. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. *Lancet Diabetes Endocrinol*. 2019;7(9):715-725.
26. Stefan N, Haring HU, Cusi K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies. *Lancet Diabetes Endocrinol*. 2019;7(4):313-324.
27. Goossens GH, Jocken JWE, Blaak EE. Sexual dimorphism in cardiometabolic health: the role of adipose tissue, muscle and liver. *Nat Rev Endocrinol*. 2021;17(1):47-66.
28. McAuley PA, Artero EG, Sui X, *et al*. The obesity paradox, cardiorespiratory fitness, and coronary heart disease. *Mayo Clin Proc*. 2012;87(5):443-451.
29. Lavie CJ, McAuley PA, Church TS, Milani RV, Blair SN. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. *J Am Coll Cardiol*. 2014;63(14):1345-1354.
30. Kennedy AB, Lavie CJ, Blair SN. Fitness or fatness: which is more important? *JAMA*. 2018;319(3):231-232.
31. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. *N Engl J Med*. 2011;365(3):213-221.
32. Willeit P, Tschiderer L, Allara E, *et al*. Carotid intima-media thickness progression as surrogate marker for cardiovascular risk: meta-analysis of 119 clinical trials involving 100 667 patients. *Circulation*. 2020;142(7):621-642.
33. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care*. 1999;22(9):1462-1470.
34. Stefan N, Kantartzis K, Machann J, *et al*. Identification and characterization of metabolically benign obesity in humans. *Arch Intern Med*. 2008;168(15):1609-1616.
35. Balletshofer BM, Haap M, Rittig K, Stock J, Lehn-Stefan A, Haring HU. Early carotid atherosclerosis in overweight nondiabetic individuals is associated with subclinical chronic inflammation independent of underlying insulin resistance. *Horm Metab Res*. 2005;37(5):331-335.
36. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr*. 1982;36(5):936-942.
37. Kantartzis K, Thamer C, Peter A, *et al*. High cardiorespiratory fitness is an independent predictor of the reduction in liver fat during a lifestyle intervention in non-alcoholic fatty liver disease. *Gut*. 2009;58(9):1281-1288.
38. Grundy SM, Cleeman JI, Daniels SR, *et al*. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112(17):2735-2752.
39. Ortega FB, Ruiz JR, Labayen I, Lavie CJ, Blair SN. The Fat but Fit paradox: what we know and don't know about it. *Br J Sports Med*. 2018;52(3):151-153.
40. Wells JCK. Body composition and susceptibility to type 2 diabetes: an evolutionary perspective. *Eur J Clin Nutr*. 2017;71(7):881-889.
41. Lavie CJ, Laddu D, Arena R, Ortega FB, Alpert MA, Kushner RF. Healthy weight and obesity prevention: JACC Health Promotion Series. *J Am Coll Cardiol*. 2018;72(13):1506-1531.
42. Ortega FB, Cadenas-Sanchez C, Migueles JH, *et al*. Role of physical activity and fitness in the characterization and prognosis of the metabolically healthy obesity phenotype: a systematic review and meta-analysis. *Prog Cardiovasc Dis*. 2018;61(2):190-205.
43. Rankinen T, Bouchard C. Invited commentary: physical activity, mortality, and genetics. *Am J Epidemiol*. 2007;166(3):260-262.
44. Stefan N, Thamer C, Staiger H, *et al*. Genetic variations in PPARD and PPARGC1A determine mitochondrial function and change in aerobic physical fitness and insulin sensitivity during lifestyle intervention. *J Clin Endocrinol Metab*. 2007;92(5):1827-1833.
45. Ortega FB, Lee DC, Katzmarzyk PT, *et al*. The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. *Eur Heart J*. 2013;34(5):389-397.
46. Zembic A, Eckel N, Stefan N, Baudry J, Schulze MB. An empirically derived definition of metabolically healthy obesity based on risk of cardiovascular and total mortality. *JAMA Netw Open*. 2021;4(5):e218505.