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Association between cardiorespiratory fitness and metabolic health in overweight and obese adults

Cardiorespiratory fitness and metabolic health

Eero A. HAAPALA^{1,2*}, Tanja SJÖROS³, Saara LAINE³, Taru GARTHWAITE³, Petri KALLIO⁶, Maria SAARENHOVI⁶, Henri VÄHÄ-YPYÄ⁴, Eliisa LÖYTTYNIEMI⁵, Harri SIEVÄNEN⁴, Noora HOUTTU⁷, Kirsi LAITINEN⁷, Kari KALLIOKOSKI³, Juhani KNUUTI³, Tommi VASANKARI^{4,8}, Ilkka H. A. HEINONEN^{3,9}

¹ Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

² Institute of Biomedicine, School of Medicine, University of Eastern Finland, Kuopio, Finland

³ Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland ⁴ The UKK Institute for Health Promotion Research, Tampere, Finland

⁵ Department of Biostatistics, University of Turku, Turku, Finland

⁶ Department of Clinical Physiology and Nuclear Medicine, University of Turku and Turku University Hospital, Turku, Finland

⁷ Institute of Biomedicine, University of Turku, Turku, Finland

⁸ Faculty of Medicine and Health Technology, Tampere University, Finland

⁹ Rydberg Laboratory of Applied Sciences, University of Halmstad, Halmstad, Sweden

^{*} Eero Haapala, PhD, Sports and Exercise Medicine, Faculty of Sport and Health Sciences, University of Jyväskylä, PO Box 35, FI-40014, Jyväskylä, Finland; E-mail: eero.a.haapala@jyu.fi; OrcID: 0000-0001-5096-851X.

BACKGROUND: Cardiorespiratory fitness (CRF) has been inversely associated with insulin resistance and clustering of cardiometabolic risk factors among overweight and obese individuals. However, most previous studies have scaled CRF by body mass (BM) possibly inflating the association between CRF and cardiometabolic health. We investigated the associations of peak oxygen uptake ($\dot{V}O_{2peak}$) and peak power output (W_{peak}) scaled either by BM⁻¹, fat free mass (FFM⁻¹), or by allometric methods with individual cardiometabolic risk factors and clustering of cardiometabolic risk factors in 55 overweight or obese adults with metabolic syndrome.

METHODS: VO_{2peak} and W_{peak} were assessed by a maximal cycle ergometer exercise test. FFM was measured by air displacement plethysmograph and glucose, insulin, HbA1c, triglycerides, and total, LDL, and HDL cholesterol from fasting blood samples. HOMA-IR and metabolic syndrome score (MetS) were computed.

RESULTS: $\dot{V}O_{2peak}$ and W_{peak} scaled by BM⁻¹ were inversely associated with insulin (β =-0.404 to -0.372, 95% CI=-0.704 to -0.048), HOMA-IR (β =-0.442 to -0.440, 95% CI=-0.762 to -0.117), and MetS (β =-0.474 to -0.463, 95% CI's=-0.798 to -0.127). Other measures of CRF were not associated with cardiometabolic risk factors.

CONCLUSIONS: Our results suggest that using BM⁻¹ as a scaling factor confounds the associations between CRF and cardiometabolic risk in overweight/obese adults with the metabolic syndrome.

Key words: aerobic fitness, metabolic syndrome, insulin resistance, allometry

Introduction

Insulin resistance and the metabolic syndrome form a significant burden of disease increasing the risk of type 2 diabetes, cardiovascular disease, dementia, and all-cause mortality^{1,2}. Overweight and obesity, especially abdominal obesity, are strong determinants of insulin resistance and the metabolic syndrome¹. Furthermore, low cardiorespiratory fitness (CRF) has been suggested to be an integral feature of cardiometabolic diseases and their risk factors in children and adults^{3,4} while high CRF has been suggested to reduce cardiometabolic risk also in obese individuals^{5,6}. However, most evidence of the latter is based on studies utilizing either a direct measure of respiratory gas exchange as maximal oxygen uptake ($\dot{V}O_{2max}$) scaled by total body mass (BM⁻¹) or indirect field tests to estimate endurance capacity.

 $\dot{V}O_{2max}$ is considered the reference method for measuring CRF 4 . $\dot{V}O_{2max}$ describes the integrated ability of cardiopulmonary and vascular systems to transport oxygen and working skeletal muscles to use oxygen in energy metabolism. Ideally, to allow interindividual comparison, absolute $\dot{V}O_{2max}$ should be considered by taking into account the physiological skeletal muscle mass of the working muscles $^{7-9}$. Skeletal muscle tissue is mostly responsible for increased oxygen consumption during exercise and physical activity and it also contributes to increased left-ventricular end-diastolic volume, left-ventricular stroke volume and cardiac output, and thereby $\dot{V}O_{2max}^{10,11}$. Nevertheless, for practical reasons, lean body mass or fat free mass (FFM) are often used instead of skeletal muscle mass, as these consists mostly of muscle mass.

Traditionally, absolute $\dot{V}O_{2max}$ has been divided by absolute body mass (BM^{-1}) . However, scaling of $\dot{V}O_{2max}$ by BM^{-1} has some shortcomings. First, $\dot{V}O_{2max}$ scaled by BM^{-1} often

demonstrates a statistically significant inverse association with BM suggesting the inability of this approach to remove the effect of body size on $\dot{V}O_{2max}^{12,13}$. Second, BM includes fat mass that does not contribute to $\dot{V}O_{2max}$ or cardiac output ¹⁴. $\dot{V}O_{2max}$ scaled by BM⁻¹ is thereby affected by adiposity and underestimates CRF in overweight and obese people ^{11,12,15}. This underestimation of CRF in overweight and obese people is mostly due to their larger fat mass rather than limitations in integrated functions of cardiopulmonary, vascular, and skeletal muscle metabolic systems ^{9,11}. Therefore, because higher fat mass is strongly associated with increased cardiometabolic risk ¹, scaling CRF by BM⁻¹ may inflate the associations between CRF and cardiometabolic risk factors in adults, especially among those with higher levels of adiposity, as previously shown in children ^{16,17}.

In the present study, we first investigated the associations of $\dot{V}O_{2max}$ scaled either by BM⁻¹ or FFM⁻¹ with individual cardiometabolic risk factors and clustering of risk factors in overweight or obese adults with the metabolic syndrome. Second, we also studied the effect of log-linear allometric scaling of CRF^{13,18} on these associations to provide a comprehensive picture of the role of different scaling approaches on the associations between CRF and cardiometabolic risk factors. Third, we also report the results regarding peak power output (W_{peak}), which is a common measure of CRF even though it also reflects anaerobic capacity and neuromuscular performance^{4,19}, because direct respiratory gas analyses are not commonly available in clinical practice.

Materials and methods

Study design and population

This cross-sectional study was conducted between April 2017 and August 2019 at Turku PET Centre (Turku, Finland) as part of a larger intervention study²⁰. A total of 64 participants were included in the primary study sample at baseline. Of them, 55 participants had maximal cycle ergometer data and 54 participants had valid respiratory gas exchange data. The reasons for premature exercise test termination included knee pain (n=4), hip pain (n=1), dyspnea (n=1), abnormal rise in exercise blood pressure (n=2), and cramp of the calf muscles (n=1). Those who were excluded from the final study sample were likely to be men, taller, heavier, and have more fat mass and higher fasting insulin (p<0.05).

All participants gave written informed consent before enrolment in the study, and the study was conducted according to good clinical practice and the Declaration of Helsinki, and approved by the Ethics Committee of the Hospital District of Southwest Finland (TO5/026/17). The study is registered at Clinicaltrials.gov with an identifier NCT03101228.

The participants were recruited from the local community by advertisements in newspapers and bulletin leaflets. The inclusion criteria were age 40-65 years; physically inactive (< 120 min/week of moderate to vigorous physical activity according to self-report); device-measured daily sitting time \geq 10 h or 60 % of accelerometer wear time; BMI 25-40 kg/m²; blood pressure < 160/100 mmHg; fasting plasma glucose < 7.0 mmol/l; and fulfilment of the metabolic syndrome criteria according to Alberti et al.²¹ including three of the following symptoms: central obesity (waist circumference \geq 94 cm for men

and ≥ 80 cm for women), triglycerides ≥ 1.7 mmol/l, HDL < 1.0 mmol/l for men and < 1.3 mmol/l for women, systolic blood pressure ≥ 130 and/or diastolic blood pressure ≥ 85 mmHg, or fasting glucose > 5.6 mmol/l. The exclusion criteria were history of a cardiac event; insulin- or medically treated diabetes; abundant use of alcohol; use of narcotics; cigarette smoking or consumption of snuff tobacco; diagnosed depressive or bipolar disorder; previous PET imaging or considerable exposure to radiation; presence of ferromagnetic objects that would make MR imaging contraindicated; and any chronic disease or condition that could create a hazard to the participant safety, endanger the study procedures, or interfere with the interpretation of study results.

Assessment of body size and composition

Total BM, body volume, and body density were measured by air displacement plethysmography and an electronic scale (the Bod Pod system, COSMED, Inc., Concord, CA, USA) after at least four hours of fasting and FFM and body fat percentage (BF%) were calculated using the equation provided by Siri²². Body density measured by the Bod Pod has been reported to have a good agreement with body density estimated by the gold standard underwater weighing in overweight and obese adults²³. BF% assessed by the Bod Pod has been found to have an acceptable short term repeatability as indicated by the coefficient of variation of 1.7 to 4.5%²⁴. Body height was measured barefooted with a standard wall-mounted stadiometer. Body mass index (BMI) was calculated using measured weight and height (kg/m²). Waist circumference was measured midway between the iliac crest and the lowest rib with a flexible measuring tape. Two measurements were performed, or until the same measurement was obtained twice, and all measurements were performed by the same outcome assessor.

Assessment of cardiorespiratory fitness

Peak oxygen uptake (VO_{2peak}) and W_{peak} were assessed by maximal cycle ergometry test (eBike EL Ergometer + CASE v6.7, GE Medical Systems Information Technologies, Inc. Milwaukee, WI, USA) with direct respiratory gas measurements (Vyntus CPX, CareFusion, Yorba Linda, CA, USA). In this study, we used peak values because we did not perform a confirmation test to investigate whether the participants achieved their true maximal aerobic capacity²⁵. $\dot{V}O_{2peak}$ was determined as the average of three consequent highest values in ml/kg/min. Exercise intensity started at 25 W and was increased by 25 W every three minutes until volitional exhaustion, and participants were instructed to maintain a pace of 65 rpm throughout the test. W_{peak} was defined as the highest power output at last completed three minute step + computed workload from the next incomplete step. Perceived exertion on Borg scale and blood pressure were measured every three minutes. The exercise test was considered maximal if the primary and secondary objectives and subjective criteria indicated maximal effort and maximal cardiorespiratory capacity (a plateau of $\dot{V}O_2$ regardless of increasing workload, peak heart rate +/- 10 beat/min of predicted, or respiratory exchange ratio > 1.0), and the research staff supervising the exercise test considered the test maximal.

 $\dot{V}O_{2peak}$ was defined as $\dot{V}O_{2peak}$ (mL/kg BM⁻¹/min⁻¹) and $\dot{V}O_{2peak}$ (mL/kg FFM⁻¹/min⁻¹) and W_{peak} as W_{peak} /kg BM⁻¹ and W_{peak} /kg FFM⁻¹. Because $\dot{V}O_{2peak}$ expressed mL/kg BM⁻¹/min⁻¹, mL/kg FFM⁻¹/min⁻¹ and W_{peak} /kg BM⁻¹ and W_{peak} /kg FFM⁻¹ had statistically significant (p<0.05) inverse associations with their denominators suggesting the inability of ratio scaling to remove the effect of body size on $\dot{V}O_{2peak}$ and W_{peak} , we also utilized log-linear allometric modelling and equation $\ln y = \ln a + b \cdot \ln x^{13,18}$ to identify appropriate exponent and to create sample specific power function ratios. Using power function ratios, $\dot{V}O_{2max}$

was expressed as mL/kg BM $^{-0.39}$ /min $^{-1}$ and mL/kg FFM $^{-0.70}$ /min $^{-1}$ and W_{peak} as W_{peak}/kg BM $^{-0.18}$ and W_{peak}/kg FFM $^{-0.52}$. None of these power function ratios were statistically significantly associated with their denominators indicating their validity in scaling of CRF.

Assessment of cardiometabolic risk factors

Venous blood samples were drawn after at least 10 hours of fasting and samples were analyzed at the Turku University Hospital Laboratory. Plasma insulin was measured by electrochemiluminescence immunoassay (Cobas 8000 e801, Roche Diagnostics GmbH, Mannheim, Germany) and plasma glucose was determined by enzymatic reference method with hexokinase GLUC3 (Cobas 8000 c702, Roche Diagnostics GmbH, Mannheim, Germany). HbA1c was measured by turbidimetric inhibition immunoassay (Cobas 6000 c501, Roche Diagnostics GmbH, Mannheim, Germany). Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index was calculated from insulin and glucose values with a formula: *insulin* (*mU/ml*) *x glucose* (*mmol/l*)/22.5²⁶. Plasma triglycerides, total, LDL and HDL cholesterol were measured by enzymatic colorimetric tests (Cobas 8000 c702, Roche Diagnostics GmbH, Mannheim, Germany). Blood pressure was measured by a digital blood pressure monitor (Apteq AE701f, Rossmax International LtD, Taipei, Taiwan) in a seated position after at least 10 minutes of resting. Measure was taken 2–3 times and the mean of repeated measures was used.

We calculated continuous metabolic syndrome score (MetS) using the formula waist circumference + insulin + glucose + atherogenic index of plasma (triacylglycerol/HDL-cholesterol ratio) + the average of systolic blood pressure and diastolic blood pressure as

described previously²⁷. A higher MetS score indicates a less favorable metabolic risk profile.

Statistical methods

Statistical analyses were performed by SPSS statistical software, version 26.0 (IBM Corp. Armonk, NY, USA). Basic characteristics between men and women were compared using the Student's t-test for normally distributed continuous variables, the Mann-Whitney Utest for continuous variables with skewed distributions, or the χ^2 -test for categorical variables. Associations of the measures of CRF with glucose, insulin, HbA1c, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, systolic blood pressure, diastolic blood pressure, HOMA-IR, MetS, and BF%, were investigated using multiple regression analyses adjusted for age and sex. Furthermore, we investigated the associations of BF% with glucose, insulin, HbA1c, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, systolic blood pressure, diastolic blood pressure, HOMA-IR, and MetS using were investigated multiple regression analyses adjusted for age and sex. The data on the associations of CRF and BF% with cardiometabolic risk factors were further adjusted for blood pressure or cholesterol medication use.

Previous studies have reported correlation coefficients varying from 0.27 to 0.49 between CRF and cardiometabolic risk factors^{17,28,29}. A total of 105 and 30 observations was needed to observe the correlation of 0.27 and 0.49, respectively, at the power of 0.80 when two tailed statistical significance level was set at P<0.05.

Results

Basic characteristics

Women were shorter, lighter, had a smaller waist circumference and higher BF%, more fat mass and less FFM than men (Table 1). Women also had higher total cholesterol and HDL cholesterol, and lower HOMA-IR than men. Furthermore, women had lower absolute $\dot{V}O_{2peak}$ (mL/min⁻¹) and $\dot{V}O_{2peak}$ (mL/kg BM⁻¹/min⁻¹), and they achieved lower W_{peak} than men.

Associations of cardiorespiratory fitness with individual cardiometabolic risk factors $\dot{V}O_{2peak}$ expressed as mL/kg BM⁻¹/min⁻¹ was inversely associated with insulin (R²_{adj}=0.072, Table 2) and BF% (β :-0.553, 95% CI: 0.766 to -0.340, p<0.001, R²_{adj}=0.186) after adjustment for age and sex. Higher $\dot{V}O_{2peak}$ expressed as mL/kg BM^{-0.39}/min⁻¹ was associated with lower BF% (β :-0.416, 95% CI:0.732 to -0.100, p=0.011, R²_{adj}=0.058). Similarly, W_{peak}/kg BM⁻¹ was inversely associated with insulin (R²_{adj}=0.102, Table 2) and BF% (β :-0.549, 95% CI:0.739 to -0.359, p<0.001, R²_{adj}=0.210) and higher W_{peak}/BM^{-0.18} was associated with lower BF% (β :-0.366, 95% CI:0.659 to -0.074, p=0.015, R_{2adj}=0.051). Further adjustment for blood pressure and cholesterol medication had no effect on the magnitude of these associations. Other measures of CRF had no statistically significant associations with individual cardiometabolic risk factors.

Associations of cardiorespiratory fitness with HOMA-IR and continuous metabolic syndrome score

Higher $\dot{V}O_{2peak}$ expressed as mL/kg BM⁻¹/min⁻¹ was associated with lower HOMA-IR (β:-0.440, 95% CI:-0.762 to -0.117, p=0.009, R_{2adj}=0.106) and lower MetS (β:-0.463, 95% CI:-0.798 to -0.127, p=0.008, R_{2adj}=0.118) after adjustment for age and sex. Higher

 $W_{peak}/kg~BM^{-1}$ was associated with lower HOMA-IR (β :-0.442, 95% CI:-0.733 to -0.150, p=0.004, R_{2adj}=0.128) and lower MetS (β :-0.474, 95% CI:-0.769 to -0.163, p=0.003, R_{2adj}=0.144) after adjustment for age and sex. Further adjustment for blood pressure and cholesterol medication had no effect on the magnitude of these associations. Other measures of CRF had no statistically significant associations with HOMA-IR and MetS (data not shown).

Associations of body fat percentage with individual cardiometabolic risk factors, HOMA-IR, and continuous metabolic syndrome score

BF% was positively associated with insulin (β :0.706, 95% CI:0.403 to 1.010, p<0.001, R_{2adj}=0.264), systolic blood pressure (β :0.411, 95% CI:0.058 to 0.765, p=0.023, R_{2adj}=0.075), diastolic blood pressure (β :0.558, 95% CI:0.204 to 0.912, p=0.003, R_{2adj}=0.152), HOMA-IR (β :0.777, 95% CI:0.489 to 1.066, p<0.001, R_{2adj}=0.326) and MetS (β :0.831, 95% CI:0.535 to 1.127, p<0.001, R_{2adj}=0.375). Further adjustment for blood pressure and cholesterol medication had no effect on the magnitude of these associations.

Discussion

We found that $\dot{V}O_{2peak}$ scaled by FFM⁻¹, FFM^{-0.70}, and BM^{-0.18} were not associated with cardiometabolic risk factors in overweight or obese adults with the metabolic syndrome. However, overweight or obese adults with higher $\dot{V}O_{2peak}$ scaled by BM⁻¹ had lower insulin resistance and MetS than those with lower $\dot{V}O_{2peak}$. Similarly, only W_{max} scaled by BM⁻¹ was inversely associated with cardiometabolic risk factors. Furthermore, BF% had strong positive associations with blood pressure, insulin resistance, and MetS. Therefore,

our results suggest that CRF is not strongly associated with cardiometabolic risk once body size and composition are partitioned out from the measure of CRF using FFM.

Our results on the inverse association between $\dot{V}O_{2peak}$ scaled by BM⁻¹ and cardiometabolic risk are in line with available evidence suggesting a beneficial role of CRF in cardiometabolic health among adults^{4,30–32}. However, when we partitioned out the influence of body size and body composition on CRF using FFM and allometry, CRF had very weak and statistically non-significant associations with cardiometabolic risk factors in overweight and obese adults with the metabolic syndrome suggesting that increased body adiposity is more important determinant of cardiometabolic risk than CRF. These present findings are similar to previous observations in children showing that CRF scaled by BM⁻¹ is strongly and inversely associated with insulin resistance and MetS, but the associations attenuate remarkably when other scaling approaches are applied^{16,17,33}.

Increased body adiposity is a strong determinant of insulin resistance, the metabolic syndrome, and type 2 diabetes^{34–36}. Increased adiposity may increase insulin resistance by impairing downstream insulin signaling in the skeletal muscle and increasing systemic inflammation and free fatty acids in plasma, and negatively affecting adiponectin secretion ^{35,36}. Therefore, the inverse association of $\dot{V}O_{2peak}$ scaled by BM⁻¹ with insulin resistance observed in our study may share the same mechanisms than increased adiposity because $\dot{V}O_{2peak}$ scaled by BM⁻¹ includes body adiposity. $\dot{V}O_{2peak}$ scaled by BM⁻¹ may therefore reflect a combination of genetics, body composition, caloric intake, dietary quality, and physical activity in addition to the cardiopulmonary functions. These observations plausibly explain why the associations of CRF with insulin resistance and MetS were also attenuated when the effect of adiposity on CRF was reduced by expressing $\dot{V}O_{2max}$ either

scaled by FFM or allometric approaches. Thereby, because CRF is a representation of the capacity of pulmonary and cardiovascular systems, it is not surprising that the associations of CRF with insulin resistance and MetS were weak when we used methodology reducing the effect of adiposity on CRF³⁷. Accordingly, some evidence suggests that CRF, even when scaled by FFM, is more strongly related to cardiovascular diseases and cardiovascular mortality^{38–40} than to type 2 diabetes mellitus³⁷.

The strengths of the present study include valid and reproducible measurement of $\dot{V}O_{2peak}$ using an exercise test until volitional exhaustion with respiratory gas analysis, body composition using air-displacement plethysmography, and cardiometabolic risk factors using standardised measures. Our sample also included inactive overweight or obese adults with the metabolic syndrome and therefore our study provides evidence and understanding on the role of CRF among those at the highest risk of cardiometabolic diseases. However, the sample size was relatively small, and the results may not be generalized to other populations. Because of relatively small sample size, we were only able to observe associations with moderate to high effect sizes. We also had several statistical models and therefore it is possible that some associations were observed by chance. We did not investigate whether an exposure to a long sedentary lifestyle influenced observed associations and further studies are warranted to investigate the role of physical activity level in these associations. Furthermore, in further studies it is important to consider the most crucial physiological factors limiting $\dot{V}O_{2max}$ in health and disease. Although arterial oxygen content also contributes^{41,42}, it is well established that the most critical factor for $\dot{V}O_{2max}$ is cardiac output 41,43, which was not measured in the present study. Especially healthy skeletal muscle is well capable of extracting oxygen from the arterial blood and its extraction is usually not a limiting factor⁴⁴. It is of

importance also to distribute oxygen supply precisely to working skeletal muscle fibers 45,46 and further studies should focus to investigate this distribution, as especially in diseased and aging states also these peripheral factors can contribute to the limitations in $\dot{V}O_{2max}$ among humans 47. In addition, we cannot completely rule out the possibility that the medication used by the participants influences the associations between CRF and cardiometabolic risk factors. Our study was cross-sectional, so no causal inferences can be drawn and prospective studies are warranted to assess the value of allometrically scaled CRF with respect to disease outcomes. Moreover, we used only a proxy of whole-body insulin resistance so it is possible that CRF has different associations with whole body insulin resistance determined by gold standard hyperinsulinemic euglycemic clamp method, or in different organs or organ systems. Finally, we investigated the associations of CRF with traditional cardiometabolic biomarkers and therefore more research on the associations between CRF scaled by different approaches and vascular outcomes, such as endothelial functions and sub-clinical atherosclerosis, are needed.

Conclusions

In conclusion, we found that $\dot{V}O_{2max}$ scaled by FFM or allometric modeling had weak if any associations with cardiometabolic risk factors, but that $\dot{V}O_{2max}$ scaled by BM⁻¹ was inversely associated with insulin and HOMA-IR. These results suggest that using BM⁻¹ as a scaling factor inflate the associations between CRF and cardiometabolic risk in overweight or obese adults with the metabolic syndrome.

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Conflicts of interest. The authors declare no conflicts of interest

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TABLES

Table I. Characteristics of participants

	All (55)	Women (35)	Men (20)	р
Age†	61 (52 to 64)	61 (51 to 64)	61 (53 to 63)	0.958
Height	170.3 (7.9)	166.0 (5.7)	177.8 (5.3)	<.0.001
Body mass	90.7 (14.3)	87.5 (13.5)	96.5 (14.3)	0.023
Body mass index	31.3 (4.3)	31.7 (4.3)	30.5 (4.4)	0.355
Waist circumference (cm)	109.6 (10.6)	107.5 (9.2)	113.2 (12.4)	0.056
Normal weight (n, %)	2, (3.6)	1, (2.9)	1 (5.0)	0.614
Overweight (body mass index $\geq 25 < 30$) (n, %)	22, (40.0)	12, (34.3)	10, (50.0)	
Obese (body mass index $\geq 30 < 35$) (n, %)	19, (34.5)	13, (13)	6, (30.0)	
Obese (body mass index ≥35) (n, %)	12, (21.8)	9, (25.7)	3, (15.0)	
Fat mass (kg) †	38.1 (32.9 to 47.8)	39.4 (35.2 to 51.2)	32.7 (27.2 to 46.0)	0.014
Body fat percentage †	44.6 (39.2 to 49.3)	47.3 (44.1.6 to 51.5)	36.1 (31.6 to 42.1)	< 0.001
Fat free mass (kg) †	49.5 (45.4 to 69.6)	47.1 (41.6 to 48.9)	62.3 (56.2 to 68.1)	< 0.001
Systolic blood pressure (mmHg)	141 (15)	143 (15)	139 (15)	0.324
Diastolic blood pressure (mmHg)	88 (8)	88 (7)	87 (10)	0.638
Plasma glucose (mmol/L)†	5.7 (5.5 to 6.0)	5.7 (5.5 to 6.0)	5.9 (5.5 to 6.3)	0.098
Plasma insulin (mU/L)†	9 (7 to 14)	8 (7 to 12)	13 (7 to 24)	0.075
Plasma triglycerides (mmol/L)†	1.2 (0.8 to 1.7)	1.2 (0.8 to 1.6)	1.2 (1.0 to 1.7)	0.575
Plasma total cholesterol (mmol/L)	4.7 (0.9)	4.9 (1.0)	4.4 (0.7)	0.038
Plasma LDL cholesterol (mmol/L)	3.0 (0.8)	3.2 (0.8)	2.8 (0.7)	0.139
Plasma HDL cholesterol (mmol/L)	1.37 (0.34)	1.43 (0.32)	1.25 (0.36)	0.049
HbA1c	37 (3)	36 (3)	37 (3)	0.260
Homeostatic model assessment for insulin resistance;	0.9 (0.6)	0.8 (0.5)	1.2 (0.7)	0.018
Metabolic syndrome score	0.0 (1.0)	-0.18 (0.9)	0.30 (1.2)	0.121
Peak oxygen uptake (mL/min ⁻¹)	2074 (468)	1817 (352)	2512 (272)	< 0.001
Peak oxygen uptake (mL/kg FFM ⁻¹ /min ⁻¹)	40.4 (5.6)	40.0 (6.1)	41.2 (4.7)	0.466
Peak oxygen uptake (mL/kg BM ⁻¹ /min ⁻¹)	23.0 (4.6)	21.1 (3.7)	26.2 (4.1)	< 0.001
Peak power output (W)	130.7 (30.7)	115.8 (26.1)	156.7 (18.4)	< 0.001
Peak power output (W _{max} /kg FFM ⁻¹)	2.5 (0.4)	2.5 (0.5)	2.6 (0.4)	0.733
Peak power output (W _{max} /kg BM ⁻¹)	1.5 (0.3)	1.3 (0.3)	1.7 (0.3)	< 0.001
Peak respiratory exchange ratio	1.12 (0.1)	1.13 (0.1)	1.11 (0.1)	0.321
Peak heart rate	156 (15.6)	157 (14.2)	156 (18.0)	0.775
% of predicted peak heart rate	88.4 (8.3)	88.6 (7.4)	88.1 (9.9)	0.841
Plateau in oxygen uptake (n, %)	23.6 (13)	31.4 (11)	10.0 (2)	0.125
Exercise test duration (min:ss)	16:36 (13:03 to 18:15)	13:41 (12:05 to 16:36)	18:15 (18:00 to 20:10)	< 0.001
Cholesterol medication (n, %)	13 (23.6)	7 (20.0)	6 (30.0)	0.401
Blood pressure medication (n, %)	29 (52.7)	13 (37.1)	16 (80.0)	0.002

Values are means and standard deviations or †medians and interquartile ranges. P-values are from independent samples t test for variables with normal distributions or Mann-Whitney U test for variables with skewed distribution and chi-square test for categorical variables. Bolded values indicate statistically significant associations between women and men (P<0.05). FFM, fat free mass; BM, body mass. ‡ Homeostatic model assessment for insulin resistance was logarithmically transformed.

Table II. Associations of the measures of cardiorespiratory fitness with individual cardiometabolic risk factors

	Glucose (mmol/L)	Insulin (mU/L)	HbA1c	triglycerides (mmol/L)	Total cholesterol (mmol/L)	HDL cholesterol (mmol/L)	LDL cholesterol (mmol/L)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)
VO _{2peak} (mL/kg	0.01 (-0.31 to	0.04 (-026 to	0.07 (-0.24 to	0.08 (-0.24 to	0.09 (-0.22 to 0.39)	-0.15 (-0.45 to	0.13 (-0.18 to	0.22 (-0.08 to 0.52)	0.20 (-0.12 to 0.51)
FFM ^{-1.0} /min ⁻¹)	0.33)	0.35)	0.37)	0.40)		0.15)	0.44)		
VO _{2peak} (mL/kg	-0.00 (-0.37 to	0.13 (-0.21 to	0.08 (-0.27 to	0.14 (-0.21 to	0.07 (-0.27 to 0.42)	-0.26 (-0.59 to	0.15 (-0.20 to	0.22 (-0.12 to 0.56)	0.23 (-0.13 to 0.58)
FFM ^{-0.70} /min ⁻¹)	0.36)	0.47)	0.42)	0.50)		0.07)	0.50)		
VO _{2peak} (mL/kg	-0.06 (-0.42 to	-0.37 (-0.70 to -	-0.11 (-0.46	0.08 (-0.28 to	0.12 (-0.22 to 0.47)	-0.10 (-0.44 to	0.10 (-0.25 to	-0.01 (-0.36 to 0.34)	-0.10 (-0.46 to 0.27)
BM ⁻¹ /min ⁻¹)	0.30)	0.05)*	to 0.24)	0.44)		0.24)	0.46)		
VO _{2peak} (mL/kg	-0.05 (-0.52 to	-0.01 (-0.45 to	-0.06 (-0.51	0.21 (-0.25 to	0.08 (-0.36 to 0.53)	-0.35 (-0.77 to	0.16 (-0.29 to	-0.07 (-0.38 to 0.51)	-0.06 (-0.41 to 0.52)
BM ^{-0.39} /min ⁻¹)	0.43)	0.43)	to 0.38)	0.67)		0.08)	0.61)		
Wpeak (W/kg	-0.04 (-0.35 to	-0.06 (-0.35 to	0.15 (-0.14 to	0.12 (-0.19 to	0.09 (-0.20 to 0.39)	-0.18 (-0.46 to	0.11 (-0.19 to	0.10 (-0.20 to 0.40)	0.18 (-0.12 to 0.49)
FFM ⁻¹)	0.27)	0.23)	0.45)	0.43)		0.11)	0.42)		
Wpeak (W/kg	-0.06 (-0.42 to	0.01 (-0.33 to	0.16 (-0.18 to	0.20 (-0.16 to	0.08 (-0.27 to 0.42)	-0.32 (-0.64 to	0.13 (-0.23 to	0.10 (-0.25 to 0.44)	0.21 (-0.15 to 0.56)
FFM ^{-0.52})	0.31)	0.35)	0.50)	0.55)		0.01)	0.48)		
Wpeak (W/kg BM	-0.06 (-0.39 to	-0.40 (-0.70 to -	-0.02 (-0.34	0.08 (-0.25 to	0.12 (-0.20 to 0.44)	-0.08 (-0.40 to	0.09 (-0.24 to	-0.10 (-0.42 to 0.23)	-0.10 (-0.44 to 0.24)
1)	0.27)	0.11)**	to 0.30)	0.42)		0.23)	0.42)		•
Wpeak (W/kg BM	-0.09 (-0.52 to	-0.01 (-0.42 to	0.11 (-0.30 to	0.25 (-0.17 to	0.07 (0.34 to 0.48)	-0.38 (-0.77 to	0.12 (-0.30 to	0.03 (-0.38 to 0.44)	0.14 (-0.29 to 0.56)
0.18)	0.34)	0.39)	0.51)	0.67)		0.01)	0.54)	•	

Data are standardised regression coefficient and their 95% confidence intervals adjusted for age and sex. *p<0.05, **p<0.01, There were 54 participants in the analyses on $\dot{V}O_{2peak}$ and 55 participants in the analyses on Wpeak.