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ORIGINAL ARTICLE

Obesity-associated metabolic changes influence resting and peak heart rate in women and men

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Abstract

Objectives: To study the relationship between obesity and heart rate (HR) in women and men. *Design:* We studied 241 overweight and obese subjects without known heart disease. All subjects underwent ergospirometry during maximal exercise testing on treadmill and recording of body composition, electrocardiogram and clinic and ambulatory blood pressure. *Results:* Women ($n = 132$) were slightly older and had higher fat mass, but lower weight, blood pressure and prevalence of metabolic syndrome (MetS) than men ($n = 109$) (all $p < 0.05$), while prevalences of obesity and hypertension did not differ. A significant interaction between sex and HR was demonstrated ($p < 0.05$). In multivariate analysis, female sex ($\beta = 0.99$, $p < 0.01$) predicted higher resting HR independent of confounders. Higher resting HR was particularly associated with presence of MetS, hypertension, higher insulin resistance and lower relative muscle mass in men (all $p < 0.05$). Female sex also predicted higher peak exercise HR ($\beta = 0.48$, $p < 0.01$) independent of confounders. Higher peak exercise HR was particularly associated with higher exercise capacity and lower age and self-reported physical activity in men, while lower HbA_{1c} and absence of obesity were the main covariates in women in multivariate analyses (all $p < 0.05$). *Conclusions:* In our study population, obesity and obesity-associated metabolic changes influenced both resting and peak exercise HR.

Key words: *Exercise capacity, Heart rate, Obesity, Sex*

Introduction

Resting heart rate (HR) is a well-known predictor of cardiovascular morbidity and mortality both in women and men (1–3). Obesity may increase HR through sympathetic nervous system disturbances and insulin resistance (4,5). In addition, clustering of cardiometabolic risk factors, often referred to as metabolic syndrome (MetS), has been shown to be associated with higher resting HR (6). However, in clinical studies, some studies have documented an association between increasing body mass index (BMI) and higher resting HR (7,8), while others have not (9). Similar discrepancy has been reported for peak exercise HR. Some studies have found that overweight and obesity are associated with lower peak exercise HR (9,10), possibly related to poorer sympathetic response to exercise (9) or lower level of physical fitness, while others found no association between peak exercise HR and BMI (11). Finally, several studies in general population have documented that women have higher resting HR than men (11,12). The aim of this study was to add to current knowledge about the association of overweight and obesity with HR at rest and during peak exercise using sex-specific analyses.

Materials and Methods

Study population

Women and men aged 30–65 years with BMI > 27 kg/m^2 were included in the FAT associated CardiOvasculaR dysfunction (FATCOR) study at Haukeland University Hospital in Bergen, Norway. Subjects were included at the collaborating general practice centre (Alfahelse AS), which prospectively

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invited subjects from the practice that fulfilled the inclusion criteria. Exclusion criteria were gastrointestinal disorder, severe psychiatric disorder, previous myocardial infarction and inability to understand Norwegian. The present analysis includes the 241 participants with completed examinations and results registered in the database recruited from October 2009 to November 2012. The FATCOR study was performed in accordance with the declaration of Helsinki from 1983, and approved by the Regional Ethics Committee. All participants signed written informed consent.

Measurements

A standardised clinical examination was performed by the general practitioner, including measurement of clinic blood pressure and resting HR following guideline recommendations (13) as well as body composition analysis by bioimpedance (Tanita TBF-300A, Tanita Corporation of America, Arlington Heights, USA). All participants filled in a standardised questionnaire for self-reported health, use of any medication and level of physical activity (hours/week).

All participants underwent a maximal exercise capacity test on treadmill (Schiller CS-200, Schiller AG, Baar, Switzerland) using the standardised Chronotropic Assessment Exercise Protocol (CAEP). Peak exercise HR was measured from the electrocardiogram (ECG) at maximal exercise. Peak oxygen uptake (VO_2max) and the respiratory exchange ratio (RER) between CO_2 and O_2 were measured with ergospirometry. Metabolic equivalents (METs), a measure of physical capacity independent of body weight, were calculated (14). The test was observed by qualified personnel to detect critical arrhythmias or signs of ischaemia on the ECG. A peripheral venous cannula was introduced beforehand for safety reasons. The participants were instructed to continue until exhaustion or presentation of any discomfort or symptoms like chest pain, strong dyspnoea or fatigue.

A 24-hour ambulatory blood pressure (ABP) recording was performed on the non-dominant arm (Diasys Integra II, Novacor, Cedex, France), with measurements every 20 minutes at daytime and every 30 minutes at night. The participants were instructed to have normal daily activity and to relax the arm during measurements (13).

Fasting venous blood samples were drawn for measurement of serum lipid profile, fasting serum glucose and serum creatinine. All non-diabetic patients underwent a glucose tolerance test.

Classification of overweight and obesity follow the guidelines of the World Health Organization, where overweight is classified as BMI ≥ 25 kg/m^2 and obesity as BMI ≥ 30 kg/m^2 (15).

We used the American Heart Association/National Heart, Lung, and Blood Institute criteria to identify presence of MetS (16). Persons were considered to have MetS if at least three of the following five criteria at baseline were fulfilled: waist circumference ≥ 88 cm in women and ≥ 102 cm in men; blood pressure $\geq 130/85$ mmHg; fasting serum glucose ≥ 100 mg/dl; serum triglycerides ≥ 1.7 mmol/l; and serum high-density-lipoprotein (HDL) cholesterol < 1.3 mmol/l in women and < 1.03 mmol/l in men (16).

Diabetes mellitus was defined as previously known diabetes, use of anti-diabetic treatment, or fasting blood glucose ≥ 7 mmol/L, impaired glucose tolerance as blood glucose 7.8–11.0 mmol/L 2 hours after oral intake of 75 g of glucose, and insulin resistance from homeostatic model assessment (HOMA-IR), respectively (17).

Statistical analyses

The SPSS statistical software (version 21) was used for all statistical analyses and data management. We performed analysis on the whole study population, and for women and men separately. Groups were compared by Student's t-test for continuous variables and by Chi-Square test for categorical variables and the results were presented as mean $\pm$ standard deviation and percentages, respectively. Univariate analyses were performed with Pearson's correlation and univariate linear regression analysis for the whole group and for women and men separately. Multivariate linear regression with collinearity tools were used to find independent variables of resting HR and peak exercise HR in the whole group, and separately for women and men, including variables significant in univariate analyses as well as known confounders from the literature. A sex–HR interaction term was included in the models assessing the total study population. Results presented are the standardised correlation coefficients (ß) and p values for the individual variables and multiple R^2 for the overall models. Level of significance was set to $p < 0.05$ for all statistical analyses.

Results

Clinical characteristics

The study population included 132 women (54.8%) and 109 men, on average 49 ± 9 years old with an average BMI of 32.2 ± 4.3 kg/m^2. Obesity was present in 65.1% and MetS in 40.1% of the study population (Table I). Women were slightly older and had higher fat mass, despite lower body weight and waist

Table I. Clinical characteristics of the study population and in women and men separately.

Variable	All ($n = 241$)	Women ($n = 132$)	Men ($n = 109$)
Age (years)	49 ± 9	50 ± 9*	48 ± 9
Weight (kg)	96.5 ± 16.4	90.7 ± 15.2†	103.6 ± 15.0
Height (cm)	173 ± 10	166.8 ± 6.5†	180.3 ± 7.0
BMI (kg/m^2)	32.2 ± 4.3	32.6 ± 4.6	31.8 ± 3.8
Obesity (%)	65.1	65.9	64.2
Metabolic syndrome (%)	40.1	32.5*	49.1
Hypertension (%)	41.2	43.0	39.0
Diabetes mellitus (%)	11.9	11.4	12.6
Impaired glucose tolerance (%)	7.5	8.0	6.8
HOMA-IR (units)	4.8 ± 8.9	4.1 ± 5.1	5.6 ± 11.9
Use of anti-hypertensive drugs (%)	61.1	55.6	68.3
Current smoking (%)	14.4	12.1	17.3
Heart rate (beats/minute)	69 ± 11	70 ± 10	68 ± 12
Systolic blood pressure (mmHg)	132 ± 16	130 ± 17*	134 ± 14
Diastolic blood pressure (mmHg)	84 ± 9	82 ± 9*	85 ± 9
Systolic ABP (mmHg)	123 ± 12	121 ± 13†	125 ± 11
Diastolic ABP (mmHg)	78 ± 8	76 ± 8†	80 ± 7
Mean ABP (mmHg)	93 ± 9	92 ± 9†	95 ± 7
Physical activity/week (hours)	3.8 ± 2.7	3.9 ± 2.7	3.6 ± 2.6
Waist circumference (cm)	108.1 ± 10.9	105.9 ± 11.2†	110.9 ± 9.9
Hip circumference (cm)	114.6 ± 11.1	117.7 ± 12.8†	110.8 ± 6.9
Fat mass (kg)	35.3 ± 10.8	38.5 ± 9.8†	31.2 ± 10.7
Muscle mass (kg)	57.4 ± 12.2	49.2 ± 5.9†	67.6 ± 10.1
Relative muscle mass (%)	60 ± 8	55 ± 4†	66 ± 9
Fasting serum glucose (mmol/L)	5.6 ± 1.2	5.4 ± 1.0*	5.8 ± 1.4
Triglycerides (mmol/L)	1.6 ± 1.0	1.3 ± 0.8†	1.8 ± 1.0
Serum cholesterol (mmol/L)	5.4 ± 1.0	5.5 ± 1.0	5.4 ± 1.1
Serum HDL-cholesterol (mmol/L)	1.2 ± 0.3	1.4 ± 0.3†	1.1 ± 0.2
Serum LDL-cholesterol (mmol/L)	3.7 ± 1.0	3.6 ± 0.9	3.8 ± 1.0
HbA_{1c} (%)	5.6 ± 0.6	5.6 ± 0.5	5.7 ± 0.7
Haemoglobin (g/dL)	14.5 ± 1.3	13.7 ± 0.8†	15.4 ± 1.0
Serum creatinine (μmol/L)	72.8 ± 13.3	65.6 ± 9.3†	81.4 ± 12.1

*$p < 0.05$; †$p < 0.01$: difference between women and men.
BMI, Body mass index; HOMA-IR, insulin resistance from homeostatic model assessment; ABP, Ambulatory blood pressure; HDL, High-density lipoprotein; LDL, Low-density-lipoprotein; HbA_{1c}, Haemoglobin A_{1c}.

circumference than men (all $p < 0.05$), while prevalences of obesity and hypertension did not differ between sexes (Table I). In contrast, clinic blood pressure, muscle mass and prevalence of MetS were all higher in men (all $p < 0.05$) (Table I).

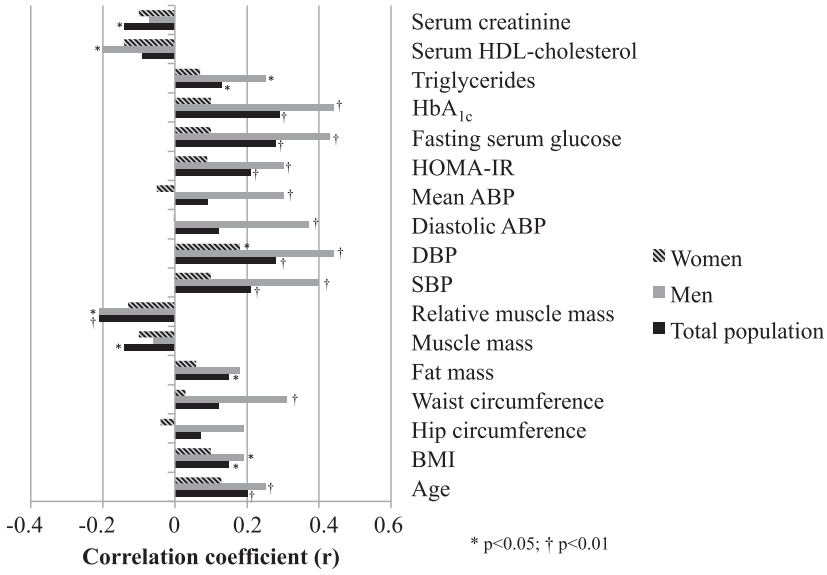
Correlates of resting HR in uni- and multivariate analyses

In the total study population, having diabetes (ß = 0.21), hypertension (ß = 0.23), MetS (ß = 0.26) and being treated for hypertension (ß = 0.21) were all significantly associated with higher resting HR in univariate analyses (all $p < 0.01$), while female sex was not (ß = 0.12, $p = 0.07$). Also higher fat mass and fasting serum glucose were associated with higher resting HR (both $p < 0.05$) (Figure 1a). Although mean resting HR did not differ between women and men, a significant interaction between sex and resting HR was demonstrated in multivariate analysis, and female sex was independently associated with higher resting HR (multiple $R^2 = 0.39$, $p < 0.01$) after adjusting for important confounders (Table II).

Sex-specific analyses identified the same covariates of resting HR in men as described for the total study population above, while for women only diastolic blood pressure was identified as a significant covariate of resting HR (Figure 1a), revealing a pronounced sex difference. In multivariate analyses, presence of MetS and hypertension, in addition to lower relative muscle mass and higher HOMA-IR, were the key covariates of higher resting HR in men (multiple $R^2 = 0.46$, $p < 0.01$), while no model could be constructed in women (Table II).

Correlates of peak exercise HR in uni- and multivariate analyses

In the total study population, not having either diabetes (ß = −0.17), hypertension (ß = −0.24) or



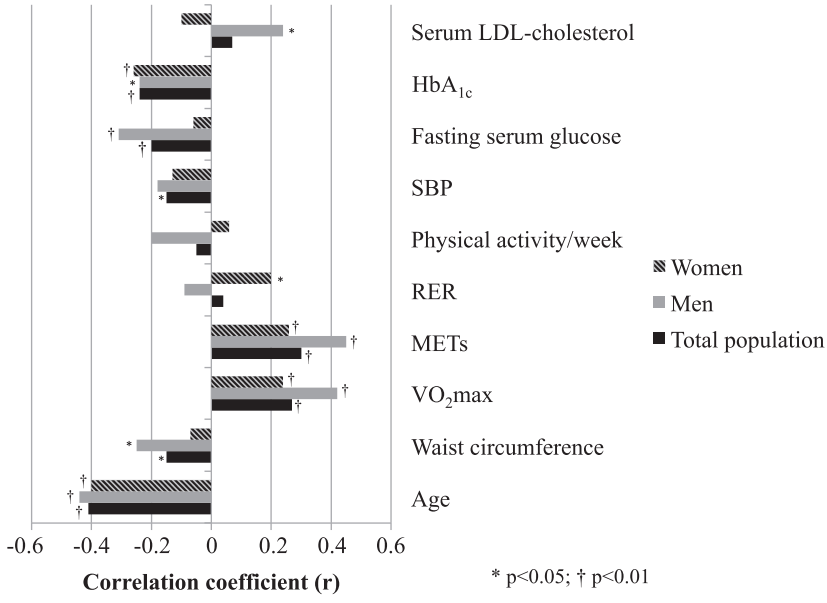


Figure 1. (upper panel) Univariate correlations of higher resting HR in the total population and in women and men separately. (lower panel) Univariate correlations of higher peak exercise HR in the total population and in women and men separately. HDL, High-density-lipoprotein; HbA_{1c}, Haemoglobin A_{1c}; HOMA-IR, insulin resistance from homeostatic model assessment; ABP, Ambulatory blood pressure; DBP, Diastolic blood pressure; SBP, Systolic blood pressure; BMI, Body mass index; LDL, Low-density-lipoprotein; RER, Respiratory exchange ratio; METs, Metabolic equivalents; VO_2max, peak oxygen uptake

being treated for hypertension (ß = −0.29) were all associated with higher peak exercise HR (all $p < 0.05$). Although mean peak exercise HR during maximal treadmill testing did not differ between women and men (Table III), a significant interaction between sex and peak exercise HR was demonstrated in multivariate analysis, and female sex was independently associated with higher peak exercise HR in multivariate regression analysis (multiple $R^2 = 0.23$, $p < 0.01$) (Table IV).

In sex-specific analyses, not having either diabetes (ß = −0.25), hypertension (ß = −0.31), MetS (ß = −0.20) or being treated for hypertension (ß = −0.44) were all associated with higher peak exercise HR in men in univariate analyses (all $p < 0.05$), while not having hypertension was associated with higher peak exercise HR in women (ß = −0.20, $p < 0.05$). Also lower HbA_{1c} was associated with higher peak exercise HR in women ($p < 0.01$) (Figure 1b). In multivariate regression analysis, higher peak exercise HR was independently associated with higher exercise capacity and lower age and self-reported physical activity in men (multiple $R^2 = 0.36$, $p < 0.01$), while lower HbA_{1c} and absence of obesity were independently associated with higher peak exercise HR in women (multiple $R^2 = 0.30$, $p < 0.01$) (Table IV).

Table II. Multivariate regression analyses of resting HR in the total study population and in women and men separately.

	Total population		Women		Men	
Variable	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Multiple R^2 for model		0.39		0.05		0.46
HOMA-IR (units)	0.21†	0.14*			0.30†	0.25*
HbA_{1c} (%)	0.29†	0.11				
Fat mass (kg)	0.15*	−0.01				
Metabolic syndrome	0.26†	0.20†	0.15	0.17	0.41†	0.30†
Hypertension	0.23†	0.16†			0.32†	0.29†
Female sex	0.12	0.99†				
Age (years)			0.13	0.16	0.25†	0.15
Relative muscle mass (%)					−0.21*	−0.20*
Diabetes mellitus					0.30†	0.16
Sex–HR interaction term		0.89†				

*$p < 0.05$; †$p < 0.01$.
Coefficients represent the change in outcome for 1 beats/minutes change in HR at rest.
HOMA-IR, insulin resistance from homeostatic model assessment; HbA_{1c}, Haemoglobin $A_{1c.}$

Discussion

This study demonstrates several interactions of obesity and obesity-associated metabolic changes with resting and peak exercise HR. Average values for resting and peak exercise HR were similar between women and men, but a significant interaction between sex and HR was demonstrated in multivariate analyses, and female sex was independently associated with both higher resting and peak exercise HR when adjusted for confounders.

Some studies in obesity have found resting HR to increase in parallel with BMI (7), which may be secondary to obesity-associated autonomic disturbances like increased sympathetic activity, reduced vagal activity and increased insulin resistance (4,5). In our study we found a positive univariate association between BMI and resting HR in the total study population and in men, but this was not confirmed in multivariate models. In contrast, higher insulin resistance and presence of MetS were associated with higher resting HR, particularly in men, reflecting that subjects with the MetS, impaired glucose tolerance, insulin resistance and diabetes may also have enhanced sympathetic activity secondary to relative metabolic stress. This adds to previous findings from the large European Global Cardiometabolic Risk Profile in Patients with hypertension disease (GOOD) survey, documenting higher resting HR in hypertensive subjects with MetS (6). Compared to the prevalence of MetS in the Health Study in North Trøndelag (HUNT3), where 12.8% of the general population had MetS, our finding of MetS in 32.5% of women and 49.1% of men was considerably higher, reflecting the close association between obesity and clustering of cardiovascular risk factors (18). Others have found MetS to be associated with hypertension as well as left ventricle hypertrophy and systolic dysfunction in general population (19), all known factors affecting exercise capacity (20). However, echocardiography was not included in the present study.

We also discovered a pronounced difference in covariates of resting HR as well as peak exercise HR between women and men. Having MetS, hypertension and higher HOMA-IR were all associated with

Table III. Characteristics from exercise testing in the total study population and in women and men separately.

Variable	Total population	Women	Men
Heart rate (beats/minute)	69 ± 11	70 ± 10	68 ± 12
Peak heart rate (beats/minute)	179 ± 19	179 ± 19	179 ± 19
METs	8.8 ± 2.3	7.8 ± 1.7†	10.0 ± 2.3
VO_2max (ml/kg/min)	31.2 ± 7.7	27.5 ± 5.6†	35.6 ± 7.6
RER (VCO_2/VO_2)	1.3 ± 0.4	1.3 ± 0.3	1.4 ± 0.4
Systolic BP before start (mmHg)	141 ± 17	141 ± 18	141 ± 17
Systolic BP at peak exercise (mmHg)	188 ± 25	185 ± 23	191 ± 28

*$p < 0.05$; †$p < 0.01$: difference between women and men.
METs, Metabolic equivalents; VO_2max, peak oxygen uptake; RER, Respiratory exchange ratio; BP, blood pressure.

Table IV. Multivariate regression analyses of peak HR in the total study population and in women and men separately.

	Total population		Women		Men	
Variable	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Multiple R^2 for model		0.23		0.30		0.36
VO_2max (ml/kg/min)	0.27†	0.27†			0.42†	0.37†
Female sex	0.02	0.48†				
Age (years)	−0.41†	−0.32†	−0.40†	−0.42†	−0.44†	−0.30†
Hypertension	−0.24†	−0.08				
HbA_{1c} (%)			−0.26†	−0.19*		
Systolic ABP (mmHg)			−0.14	0.17		
Obesity			0.15	−0.18*		
RER (VCO_2/VO_2)			0.20*	0.16		
Heart rate (beats/minute)			0.05	0.08	−0.06	0.11
Physical activity/week (hours)					−0.20	−0.21*
Metabolic syndrome					−0.20*	−0.09
Sex–HR interaction term		0.27*				

*$p < 0.05$; †$p < 0.01$.
Coefficients represent the change in outcome for 1 beats/minutes change in HR at peak.
VO_2max, peak oxygen uptake; HbA_{1c}, Haemoglobin A_{1c}; ABP, Ambulatory blood pressure; RER, Respiratory exchange ratio.

higher resting HR in men, but these associations were not found in women, although women had higher fat mass. Absence of obesity was particularly associated with higher peak exercise HR in women. This finding in women adds to the results in the study by Gondoni et al. (9), demonstrating lower peak exercise HR in trained and unfit obese subjects without heart disease compared to normal and overweight subjects. In contrast, lower self-reported physical activity and higher exercise capacity were particularly associated with higher peak exercise HR in men.

It is well demonstrated by others that resting HR increases in parallel with age (21). Gondoni et al. reported that age alone explained 36% of the variance in peak exercise HR (9). Age was also the strongest covariate of peak exercise HR in the present study.

As demonstrated, average values of resting HR and peak exercise HR were comparable in women and men. However, in multivariate analysis, female sex independently predicted higher resting HR, in line with previous reports in healthy subjects (11,12). Ogawa et al. studied healthy sedentary and trained women and men of different age, and could not find differences in peak exercise HR between sexes, independent of training status and age (22). In contrast, results from the HUNT Fitness Study, investigating a Norwegian healthy adult population, demonstrated a slightly lower peak HR in women when adjusted for age (23).

In our study population, the peak oxygen uptake was 23% lower in women than men, a slightly larger difference than the results from the HUNT Fitness Study (24), reflecting the lower muscle mass in women. Of note, the protocol used for exercise testing in our study, the CAEP protocol, is probably superior to the Bruce protocol in overweight and obese subjects with low expected physical capacity. The CAEP protocol has smaller increase in exercise load between stages, probably resulting in a more accurate test in sedate and obese subjects with lower exercise capacity, as pointed out by Bratberg et al. (25).

Our study has several potential limitations. The FATCOR study prospectively included women and men aged 30–65 years with BMI > 27.0 kg/m^2, thus age and BMI were truncated by design, and this may have influenced the prevalence of metabolic syndrome in the study population, which in particular was high among men. Projection of results to individuals with age and BMI values outside our range should be done with caution. Both health status and physical activity were self-reported in a standardised questionnaire. Although the information was quality assured by the general practitioner, we cannot exclude that health problems may have been underreported.

Conclusions

Among overweight and obese women and men without known cardiovascular disease participating in the FATCOR study, obesity and obesity-associated metabolic disturbances influenced both resting and peak exercise HR. In particular absence of obesity and lower HbA_{1c} were associated with higher peak exercise HR in women and presence of MetS, hypertension and higher insulin resistance with higher resting HR in men in sex-specific multivariate analyses.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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