Peak Oxygen Uptake and Cardiovascular Risk Factors in 4631 Healthy Women and Men

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ABSTRACT

ASPENES, S. T., T. I. L. NILSEN, E.-A. SKAUG, G. F. BERTHEUSSEN, Ø. ELLINGSEN, L. VATTEN, and U. WISLØFF. Peak Oxygen Uptake and Cardiovascular Risk Factors in 4631 Healthy Women and Men. *Med. Sci. Sports Exerc.*, Vol. 43, No. 8, pp. 1465–1473, 2011. **Introduction**: Many studies suggest that cardiorespiratory fitness, measured as peak oxygen uptake ($\dot{V}O_{2peak}$), may be the single best predictor of cardiovascular morbidity and premature cardiovascular mortality. However, current reference values are either estimates of oxygen uptake or come from small studies, mainly of men. Therefore, the aims of this study were to directly measure $\dot{V}O_{2peak}$ in healthy adult men and women and to assess the association with cardiovascular risk factor levels. **Methods**: A cross-sectional study of 4631 volunteering, free-living Norwegian men (n = 2368) and women (n = 2263) age 20–90 yr. The data collection was from June 2007 to June 2008. Participants were free from known pulmonary or cardiovascular disease. $\dot{V}O_{2peak}$ was measured by ergospirometry during treadmill running. Associations (odds ratios, OR) with unfavorable levels of cardiovascular risk factors and a cluster of cardiovascular risk factors were assessed by logistic regression analysis. **Results**: Overall, mean $\dot{V}O_{2peak}$ was 40.0 ± 9.5 mL·kg^{-1}·min^{-1}. Women below the median $\dot{V}O_{2peak}$ (<35.1 mL·kg^{-1}·min^{-1}) were five times (OR = 5.4, 95% confidence interval = 2.3–12.9) and men below the median (<44.2 mL·kg^{-1}·min^{-1}) were eight times (OR = 7.9, 95% confidence interval = 3.5–18.0) more likely to have a cluster of cardiovascular risk factors compared to those in the highest quartile of $\dot{V}O_{2peak}$ (≥40.8 and ≥50.5 mL·kg^{-1}·min^{-1} in women and men, respectively). Each 5-mL·kg^{-1}·min^{-1} lower $\dot{V}O_{2peak}$ corresponded to ~56% higher odds of cardiovascular risk factor clustering. **Conclusions**: These data represent the largest reference material of objectively measured $\dot{V}O_{2peak}$ in healthy men and women age 20–90 yr. Even in people considered to be fit, $\dot{V}O_{2peak}$ was clearly associated with levels of conventional cardiovascular risk factors. **Key Words:** OXYGEN CONSUMPTION, PHYSICAL ACTIVITY, CARDIOVASCULAR RISK, HYPERTENSION, EPIDEMIOLOGY

There is accumulating evidence that cardiorespiratory fitness has an independent protective effect against cardiovascular morbidity and cardiovascular and all-cause mortality, both in the general population and in people with increased risk of cardiovascular disease (5,9,17,19,22,23,30,31,35). Most recently, Lee et al. (25) found that following the recommendations for physical activity had no effect on mortality as long as the fitness was poor, whereas those who had a high degree of fitness were protected whether they adhered to the recommendations or not.

Several methods have been used to measure fitness (16), but the best measure seems to be maximal oxygen uptake ($\dot{V}O_{2max}$) (4). However, reference values for $\dot{V}O_{2max}$ have either been indirect or based on small, selected, or undescribed populations (2,3,8,11,14,15,24,26,28,32,37) or taken from a meta-analysis (36). The only study (38) that provided results from directly measured $\dot{V}O_{2max}$ in a healthy adult population with more than 1000 participants of both genders and a full age range focused primarily on physical activity and did not include analyses of whether risk factors relevant for cardiovascular health could be associated with fitness.

Despite the clinical importance of $\dot{V}O_{2max}$ (16,19), there are no large studies showing the distribution of directly measured $\dot{V}O_{2max}$ in a heterogeneous healthy population. The objectives of the present study were to examine the distribution of $\dot{V}O_{2max}$ across age and gender in a large population-based sample in Norway and to assess the association of cardiorespiratory fitness with the prevalence of unfavorable levels of cardiovascular risk factors.

METHODS

Study participants. The third wave of the Nord–Trøndelag Health Study (the HUNT Study (13,20)) in Norway was carried out between October 2006 and June

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2008. All inhabitants of Nord–Trøndelag County 20 yr and older (n = 94,194) were invited, and 50,821 individuals (54%) accepted the invitation.

The Fitness Study was designed to obtain measures of $\dot{V}O_{2max}$ in a healthy population and was conducted between June 2007 and June 2008 in three communities within the main HUNT Study. To be eligible, participants had to be free from cancer, obstructive lung disease, and cardiovascular disease; were not using blood pressure medication; and had to pass a brief medical interview to enter the $\dot{V}O_{2max}$ testing (Fig. 1). On the basis of self-reported information, 30,513 participants were potentially eligible for the Fitness Study (Table 1), and 12,609 of them were residents in the three townships that were selected for the Fitness Study. Among eligible participants, 5633 volunteered to participate, and a total of 4631 individuals completed a $\dot{V}O_{2max}$ test (Fig. 1).

The study was approved by the regional committee for medical research ethics, the Norwegian Data Inspectorate, and the National Directorate of Health. The study is in conformity with Norwegian laws and the Helsinki Declaration; all participants signed a document of informed consent.

Oxygen uptake and peak HR. An individualized protocol, previously published (33), was applied to measure $\dot{V}O_{2max}$ using mixing chamber gas analyzer ergospirometry (Cortex MetaMax II; Cortex, Leipzig, Germany). Each test subject was familiarized with treadmill walking during a warm-up of 8–10 min, also to ensure safety and avoid handrail grasp when this was not necessary. Briefly, the test was initiated from the inclination and speed was derived from warm-up with the participants wearing a tight facemask (Hans Rudolph, Germany) connected to the MetaMax II. When the participant reached an oxygen consumption that was stable during 30 s, inclination (1%–2% each step) or velocity (0.5–1 km·h^{-1}) on the treadmill was increased depending on the appearance of and feedback from the participant until exhaustion. Combined with a respiratory exchange ratio of 1.05 or higher, a maximal test was

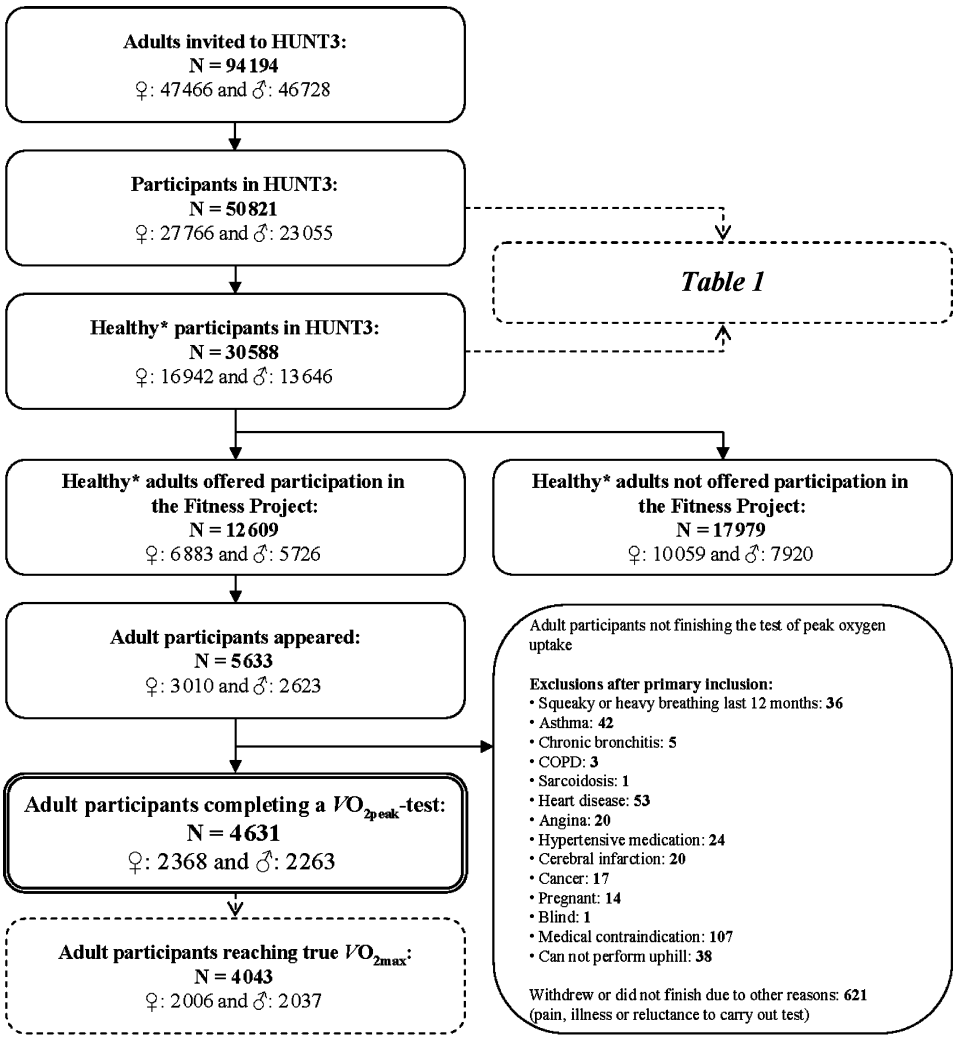

FIGURE 1—Flowchart of participation in the HUNT Fitness Study. *Has not had squeaky or heavy breathing for the past 12 months and never had asthma, chronic bronchitis, chronic obstructive pulmonary disease, sarcoidosis, heart disease, angina, cancer or cerebral infarction, never used hypertensive medication.

TABLE 1. Characteristics of the Fitness Study population compared to the total HUNT population and HUNT participants without known cardiovascular disease, lung disease, or cancer.

		Fitness Study Population		Healthy[a] HUNT Population		Total HUNT Population	
Women	Number of participants	2368		16,909		27,766	
	Age (yr)	48.0	(13.7)	47.6	(14.9)	52.2	(16.4)
	Height (m)	1.66	(0.06)	1.65	(0.07)	1.65	(0.07)
	Weight (kg)	69.8	(11.2)	71.5	(12.8)	72.9	(13.7)
	BMI ($kg \cdot m^{-2}$)	25.4	(3.9)	26.1	(4.4)	26.9	(4.9)
	Waist circumference (m)	0.86	(0.11)	0.88	(0.12)	0.90	(0.13)
	Hip circumference (m)	1.01	(0.08)	1.03	(0.09)	1.04	(0.09)
	Waist-to-hip ratio	0.85	(0.07)	0.86	(0.07)	0.87	(0.07)
	SBP (mm Hg)	123.5	(15.6)	124.3	(18.0)	128.0	(19.7)
	DBP (mm Hg)	69.7	(9.8)	69.8	(10.4)	70.7	(10.8)
	MAP (mm Hg)	87.6	(10.7)	88.0	(11.9)	89.7	(12.5)
	Cholesterol ($mmol \cdot L^{-1}$)	5.44	(1.11)	5.52	(1.14)	5.56	(1.14)
	HDL ($mmol \cdot L^{-1}$)	1.53	(0.35)	1.48	(0.35)	1.46	(0.35)
	Glucose, median (range) ($mmol \cdot L^{-1}$)	5.1	(16.1)	5.1	(28.6)	5.2	(31.4)
Men	Number of participants	2263		13,604		23,055	
	Age (yr)	48.9	(13.5)	48.1	(14.3)	53.1	(15.6)
	Height (m)	1.79	(0.06)	1.79	(0.07)	1.78	(0.07)
	Weight (kg)	85.6	(11.5)	86.2	(12.7)	86.9	(13.3)
	BMI ($kg \cdot m^{-2}$)	26.6	(3.2)	27.0	(3.5)	27.5	(3.8)
	Waist circumference (m)	0.95	(0.09)	0.96	(0.10)	0.97	(0.11)
	Hip circumference (m)	1.03	(0.06)	1.03	(0.06)	1.04	(0.07)
	Waist-to-hip ratio	0.92	(0.06)	0.92	(0.06)	0.94	(0.07)
	SBP (mm Hg)	131.9	(14.2)	131.4	(15.6)	133.5	(17.0)
	DBP (mm Hg)	76.2	(10.2)	75.4	(10.8)	76.2	(11.0)
	MAP (mm Hg)	94.7	(10.5)	94.1	(11.4)	95.3	(11.8)
	Cholesterol ($mmol \cdot L^{-1}$)	5.48	(1.01)	5.50	(1.04)	5.42	(1.08)
	HDL ($mmol \cdot L^{-1}$)	1.25	(0.29)	1.23	(0.29)	1.21	(0.30)
	Glucose, median (range) ($mmol \cdot L^{-1}$)	5.3	(27.9)	5.3	(39.3)	5.4	(39.4)

Data are presented as mean (SD), except otherwise noted.

[a] Has not had squeaky or heavy breathing for the past 12 months and never had asthma, chronic bronchitis, chronic obstructive pulmonary disease, sarcoidosis, heart disease, angina, cancer or cerebral infarction, and never used hypertensive medication.

DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

considered achieved when the oxygen uptake did not increase >2 $mL \cdot kg^{-1} \cdot min^{-1}$ despite increased workload. As 12.6% of the participants did not achieve $\dot{V}O_{2max}$, the term $\dot{V}O_{2peak}$ was used. HR was measured by radio telemetry (Polar S610i; Polar Electro Oy, Kempele, Finland).

Questionnaire-based information. All participants filled in a self-administered questionnaire that was included with the invitation letter. The questionnaire contained three items on physical activity: Question 1: "How frequently do you exercise?," with the following response options: "never" (0), "less than once a week" (0), "once a week" (1), "2–3 times per week" (2.5) and "almost every day" (5). Question 2: "If you exercise as frequently as once or more times a week, how hard do you push yourself?" with the following response options: "I take it easy without breaking a sweat or losing my breath" (1), "I push myself so hard that I lose my breath and break into sweat" (2), and "I push myself to near exhaustion" (3). Question 3: "How long does each session last?," with the following response options: "Less than 15 min" (0.1), "15–29 min" (0.38), "30 min to 1 h" (0.75), and "more than 1 h" (1.0). Each participant's response to the above three questions (i.e., numbers in parentheses) was weighted to calculate a physical activity index score. Because the second and third questions only addressed people who exercised at least once a week, both "never" and "less than once a week" yielded an index score of zero. Participants with a zero score were categorized as inactive, and the other participants were classified into three equally sized groups (tertiles) based on the sex-specific distribution of score values (i.e., low, medium, or high physical activity score). Among the 4631 participants in the Fitness Study, 29 women and 24 men had missing data on physical activity and were therefore excluded from the analyses.

Clinical measures. Resting HR was the lowest HR registered by three-point echocardiography (GE Healthcare) lying supine on a bench for 10 min in a dimly lit quiet room. Blood pressure was measured while sitting (Critikon Dinamap 845XT; GE Medical Systems) and followed established guidelines (27). Blood was drawn nonfasting immediately after blood pressure measurement, and total serum cholesterol, HDL-cholesterol, and glucose were measured from serum according to previous investigations (13).

Risk factors were classified as follows: hypertension as diastolic blood pressure ≥90 mm Hg and/or systolic blood pressure ≥140 mm Hg (27), high waist circumference as wider than 102 cm in men and wider than 88 cm in women (18), obesity as body mass index (BMI) ≥30.0 $kg \cdot m^{-2}$, and hyperglycemia as glucose >6.0 $mmol \cdot L^{-1}$ (34). In participants younger than 30 yr, total serum cholesterol >6.1 $mmol \cdot L^{-1}$ was defined as elevated, whereas levels >6.9 $mmol \cdot L^{-1}$ and >7.8 $mmol \cdot L^{-1}$ were defined as elevated in participants 30–49 and 50 yr or older, respectively (34). HDL-cholesterol <1.0 $mmol \cdot L^{-1}$ was defined as reduced (34). Cardiovascular risk factor clustering was defined as waist circumference of 94 cm or wider in men and 80 cm or wider in women, combined with HDL-cholesterol <1.0 $mmol \cdot L^{-1}$ in men and <1.3 $mmol \cdot L^{-1}$ in women, and systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg, on the basis of the definition of the metabolic syndrome (1,39). Resting HR >70 beats·min^{-1} was considered elevated, as this approximated mean HR plus 1 SD in both genders.

Weight and height were measured (Model DS-102; Arctic Heating AS, Nøtterøy, Norway), and BMI was calculated. Waist circumference was measured with a steel band to the nearest 1 cm horizontally at the height of the umbilicus.

Statistical analysis. $\dot{V}O_{2peak}$, respiratory quotient (RQ), and ventilation were categorized into 10-yr age groups (20–29, 30–39, …, 60–69, ≥70 yr).

In a general linear model, we estimated the mean difference (with 95% confidence interval (CI)) in $\dot{V}O_{2peak}$ between categories of physical activity, using the inactive group as reference. We also assessed the association of $\dot{V}O_{2peak}$ with the prevalence of unfavorable conventional cardiovascular risk factors. In a logistic regression analysis, we calculated the odds ratio (OR) for having a risk factor within each quartile category of $\dot{V}O_{2peak}$, using the highest quartile as the reference (i.e., those with highest cardiovascular fitness). All analyses were adjusted for age, and in an additional multivariable analysis, we also adjusted for the potential confounding effect of physical activity, smoking status (never, former, current occasional, and current daily smoker), mean arterial pressure (except hypertension and cardiovascular risk factor clustering models), waist circumference (except high waist circumference, obesity, and cardiovascular risk factor clustering models), cholesterol (except cholesterol, HDL, and cardiovascular risk factor clustering models), and glucose (except glucose model). In a separate analysis, we assessed the linear associations of a 5-mL·kg^{-1}·min^{-1} increase in $\dot{V}O_{2peak}$ with the prevalence of hypertension and cardiovascular risk factor clustering.

All statistical tests were two-sided, and all analyses were conducted using the statistical package SPSS, version 16.0 (SPSS, Inc., Chicago, IL).

RESULTS

The HUNT Fitness Study included 4631 participants with a complete $\dot{V}O_{2peak}$ test (Fig. 1). We compared the HUNT Fitness population with the total HUNT Study population and with the proportion of the total HUNT population that was considered healthy on the basis of questionnaire information (Fig. 1). The HUNT Fitness participants weighed less, had lower waist circumference, and lower waist-to-hip ratio, as well as higher HDL-cholesterol compared with

TABLE 2. Distribution of peak oxygen uptake stratified by gender and age.

		Women		Men	
20–29 yr	Number of participants	247		210	
	Normalized $\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	42.9	(7.6)	54.0	(8.7)
	Absolute $\dot{V}O_{2peak}$ (L·min^{-1})	2.77	(0.47)	4.30	(0.73)
	RQ[a]	1.15	(0.06)	1.15	(0.05)
	Ventilation[a] (L·min^{-1})	92.4	(16.4)	142.2	(25.6)
	Percent who reached $\dot{V}O_{2max}$ (%)	96.0		97.1	
30–39 yr	Number of participants	411		344	
	Normalized $\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	39.8	(6.8)	48.8	(7.7)
	Absolute $\dot{V}O_{2peak}$ (L·min^{-1})	2.74	(0.47)	4.22	(0.64)
	RQ[a]	1.15	(0.06)	1.15	(0.06)
	Ventilation[a] (L·min^{-1})	92.0	(15.8)	137.2	(22.2)
	Percent who reached $\dot{V}O_{2max}$ (%)	93.9		95.3	
40–49 yr	Number of participants	610		594	
	Normalized $\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	37.9	(7.0)	46.7	(7.9)
	Absolute $\dot{V}O_{2peak}$ (L·min^{-1})	2.63	(0.45)	4.01	(0.62)
	RQ[a]	1.13	(0.07)	1.14	(0.06)
	Ventilation[a] (L·min^{-1})	87.9	(14.8)	132.2	(22.0)
	Percent who reached $\dot{V}O_{2max}$ (%)	89.7		93.9	
50–59 yr	Number of participants	590		580	
	Normalized $\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	33.7	(5.7)	42.1	(7.6)
	Absolute $\dot{V}O_{2peak}$ (L·min^{-1})	2.35	(0.38)	3.62	(0.60)
	RQ[a]	1.11	(0.07)	1.13	(0.06)
	Ventilation[a] (L·min^{-1})	77.3	(13.6)	119.0	(21.6)
	Percent who reached $\dot{V}O_{2max}$ (%)	82.9		90.2	
60–69 yr	Number of participants	376		401	
	Normalized $\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	30.6	(5.1)	38.5	(7.0)
	Absolute $\dot{V}O_{2peak}$ (L·min^{-1})	2.15	(0.36)	3.23	(0.57)
	RQ[a]	1.09	(0.08)	1.11	(0.07)
	Ventilation[a] (L·min^{-1})	70.6	(14.9)	109.1	(21.3)
	Percent who reached $\dot{V}O_{2max}$ (%)	74.5		83.0	
≥70 yr	Number of participants	137		132	
	Normalized $\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	26.5	(4.7)	34.1	(7.0)
	Absolute $\dot{V}O_{2peak}$ (L·min^{-1})	1.79	(0.35)	2.71	(0.54)
	RQ[a]	1.04	(0.07)	1.07	(0.08)
	Ventilation[a] (L·min^{-1})	58.4	(16.1)	90.6	(20.8)
	Percent who reached $\dot{V}O_{2max}$ (%)	50.4		67.4	

Data are presented as mean (SD), except otherwise noted.

[a] Measured at $\dot{V}O_{2peak}$.

RQ, respiratory quotient; Ventilation, pulmonary ventilation; $\dot{V}O_{2peak}$, peak oxygen uptake.

both reference populations (Table 1). Among HUNT Fitness participants, 14.1% reported to be inactive (defined as no activity or exercising less than once per week) compared with 21.4% in the total HUNT Study population and 20.6% among the healthy participants of the HUNT population. In the HUNT Fitness study, 3.7% of the men and 1.3% of the women reported never to engage in physical exercise, and the corresponding proportions in the HUNT Study population that were regarded healthy were 6.1% and 2.7%. In the total HUNT Study population, the prevalence of cardiovascular risk factor clustering was 6.4% as compared with 5.6% in the HUNT Fitness study population ($P < 0.001$).

Table 2 shows mean $\dot{V}O_{2peak}$ among Fitness Study participants, stratified by sex and age group. The overall mean $\dot{V}O_{2peak}$ was 40.0 $mL \cdot kg^{-1} \cdot min^{-1}$ (±9.5 $mL \cdot kg^{-1} \cdot min^{-1}$, SD), with lower values for women (35.9 $mL \cdot kg^{-1} \cdot min^{-1}$) than for men (44.3 $mL \cdot kg^{-1} \cdot min^{-1}$). $\dot{V}O_{2peak}$ was consistently higher in men than in women across age groups, and the level of $\dot{V}O_{2peak}$ expressed relative to body mass declined by approximately 6.2% (95% CI = 5.9%–6.6%) per 10-yr increase in age both in women and men.

In all age groups (Table 3), there was a higher proportion of men than women who reported to be inactive (all $P < 0.001$). The largest difference was in the age group 40–49 yr, where 23.1% of men and 7.7% of women reported to be inactive (Table 3). Irrespective of age, $\dot{V}O_{2peak}$ was consistently lower in people who reported low physical activity. For example, $\dot{V}O_{2peak}$ in inactive participants aged 20–29 yr was nearly identical with that of highly active participants age 50–59 yr. The correlations between self-reported physical activity and $\dot{V}O_{2peak}$ were 0.38 and 0.34 (both $P < 0.001$) for men and women, respectively.

As shown in Table 4, compared to participants in the highest quartile of $\dot{V}O_{2peak}$, those in the lowest quartile had higher odds of having elevated resting HR (OR = 1.8, 95% CI = 1.1–3.2 in women and OR = 5.8, 95% CI = 2.8–12.0 in men), high waist circumference (OR = 15.0, 95% CI = 10.2–21.9 in women and OR = 56.6, 95% CI = 30.0–107.0 in men), obesity (OR = 78.8, 95% CI = 33.6–184.6 in women and OR = 58.7, 95% CI = 28.1–122.7 in men), and cardiovascular risk factor clustering (OR = 5.4, 95% CI = 2.30–12.9 in women and OR = 7.9, 95% CI = 3.5–18.0 in men). The prevalence of cardiovascular risk factor clustering among inactive participants in the age group 20–29 yr (4.6%) was similar to the prevalence among physically active participants age 50–59 yr who had similar $\dot{V}O_{2peak}$ (4.2%).

In another subanalysis, we compared the cardiovascular risk factor levels of those who were obese (BMI > 30 $kg \cdot m^{-2}$) but in the highest fitness quarter (fat-but-fit, $n = 19$) to subjects who had a normal body weight (BMI < 25 $kg \cdot m^{-2}$) but was in the poorest quarter of fitness ($n = 243$). There were no differences in blood pressure (systolic, diastolic, or mean arterial), resting HR, or blood glucose, but there were significant differences in serum cholesterol (5.3 vs 5.9 $mmol \cdot L^{-1}$ in favor of the fat-but-fit, $P < 0.05$) and HDL-cholesterol (1.2 vs 1.5 $mmol \cdot L^{-1}$ in disfavor of the fat-but-fit, $P < 0.001$). Because this analysis includes few subjects only, this should be interpreted cautiously.

In analyses that assessed the odds of having hypertension based on a 5-$mL \cdot kg^{-1} \cdot min^{-1}$ difference in $\dot{V}O_{2peak}$, we observed an 11% (95% CI = 1%–22%) higher odds of hypertension in men associated with a 5-$mL \cdot kg^{-1} \cdot min^{-1}$

TABLE 3. $\dot{V}O_{2peak}$ according to usual physical activity (PA)[a] level stratified by age and sex.

	Women				Men			
	Inactive	Low PA	Medium PA	High PA	Inactive	Low PA	Medium PA	High PA
20–29 yr								
Number of participants	28	72	74	72	42	55	56	55
$\dot{V}O_{2peak}$[b]	36.7 (7.7)	39.1 (6.1)	43.5 (5.8)	48.5 (6.6)	46.9 (9.1)	51.4 (7.0)	56.1 (7.1)	59.8 (6.5)
Difference (95% CI)	(reference)	2.4 (−0.4–5.2)	6.8 (4.0–9.6)	11.8 (9.0–14.6)	(reference)	4.5 (1.5–7.4)	9.2 (6.2–12.1)	12.9 (9.9–15.9)
30–39 yr								
Number of participants	55	116	117	116	76	89	90	89
$\dot{V}O_{2peak}$[b]	36.0 (5.2)	37.8 (6.5)	39.4 (5.5)	43.8 (7.1)	44.3 (6.7)	47.2 (7.0)	48.9 (7.1)	54.1 (6.8)
Difference (95% CI)	(reference)	1.8 (−0.2–3.8)	3.4 (1.4–5.4)	7.8 (5.8–9.8)	(reference)	2.9 (0.7–5.0)	4.6 (2.5–6.7)	9.8 (7.7–11.9)
40–49 yr								
Number of participants	47	187	187	187	136	151	152	151
$\dot{V}O_{2peak}$[b]	34.1 (6.0)	35.5 (6.0)	37.9 (6.1)	41.4 (7.6)	42.0 (6.6)	45.3 (6.8)	47.4 (8.1)	51.9 (6.9)
Difference (95% CI)	(reference)	1.4 (−0.7–3.5)	3.8 (1.6–5.9)	7.3 (5.1–9.4)	(reference)	3.3 (1.6–4.9)	5.4 (3.8–7.1)	9.9 (8.3–11.6)
50–59 yr								
Number of participants	57	175	176	175	96	159	159	159
$\dot{V}O_{2peak}$[b]	31.3 (3.8)	31.8 (4.9)	33.4 (4.9)	36.9 (6.2)	38.3 (6.1)	39.1 (6.3)	42.8 (6.1)	46.7 (8.4)
Difference (95% CI)	(reference)	0.5 (−1.1–2.0)	2.1 (0.5–3.6)	5.6 (4.0–7.1)	(reference)	0.8 (−0.9–2.6)	4.5 (2.8–6.3)	8.4 (6.7–10.1)
60–69 yr								
Number of participants	36	110	110	110	58	113	113	113
$\dot{V}O_{2peak}$[b]	27.9 (3.8)	29.5 (4.7)	29.8 (4.3)	33.5 (5.5)	34.5 (6.0)	36.4 (6.0)	40.8 (6.6)	40.5 (7.3)
Difference (95% CI)	(reference)	1.6 (−0.2–3.4)	1.9 (0.1–3.7)	5.6 (3.8–7.4)	(reference)	1.9 (−0.1–4.0)	6.3 (4.3–8.4)	6.0 (3.9–8.1)
≥70 yr								
Number of participants	8	41	42	41	12	38	39	38
$\dot{V}O_{2peak}$[b]	21.4 (3.1)	24.7 (3.8)	26.9 (4.3)	29.0 (4.7)	30.2 (6.7)	31.8 (4.7)	34.8 (7.0)	37.5 (7.6)
Difference (95% CI)	(reference)	3.3 (0.1–6.5)	5.5 (2.3–8.7)	7.6 (4.4–10.8)	(reference)	1.8 (−2.7–5.9)	4.6 (0.4–8.9)	7.3 (3.0–11.7)

$\dot{V}O_{2peak}$ is presented as mean (SD).
[a] The physical activity summary score combines information on frequency, duration, and intensity.
[b] Measured as milliliters per kilogram per minute.

TABLE 4. Fitness status (low vs high) associated with the prevalence (OR) of unfavorable cardiovascular risk factor levels.[a]

Outcome Variable and Fitness Category	Women: Risk Factor (*n*) No	Women: Risk Factor (*n*) Yes	Women: Age-Adjusted OR	Women: Multiadjusted[c] OR (95% CI)	Men: Risk factor (*n*) No	Men: Risk factor (*n*) Yes	Men: Age-Adjusted OR	Men: Multiadjusted[c] OR (95% CI)
Hypertension[a]								
Fourth quarter (high fitness)	567	23	1.0	1.0 (reference)	484	79	1.0	1.0 (reference)
Third quarter	538	53	1.3	1.1 (0.6–1.9)	451	114	1.3	1.1 (0.8–1.6)
Second quarter	472	119	2.4	1.7 (1.0–2.9)	379	181	2.0	1.5 (1.0–2.2)
First quarter (low fitness)	413	179	2.2	1.3 (0.7–2.4)	306	259	2.6	1.8 (1.2–2.8)
Elevated resting HR[a]								
Fourth quarter (high fitness)	504	37	1.0	1.0 (reference)	498	19	1.0	1.0 (reference)
Third quarter	495	68	1.9	1.6 (1.0–2.5)	497	28	1.8	1.5 (0.8–2.8)
Second quarter	462	98	3.1	2.1 (1.3–3.4)	482	50	4.1	2.6 (1.3–5.0)
First quarter (low fitness)	462	96	3.3	1.8 (1.1–3.2)	424	89	10.8	5.8 (2.8–12.0)
High waist circumference[a]								
Fourth quarter (high fitness)	502	88	1.0	1.0 (reference)	549	16	1.0	1.0 (reference)
Third quarter	391	202	3.1	3.0 (2.2–4.1)	505	61	4.4	4.0 (2.2–7.4)
Second quarter	287	302	6.8	6.3 (4.5–8.8)	414	152	16.7	15.0 (8.2–27.2)
First quarter (low fitness)	181	411	16.7	15.0 (10.2–21.9)	302	263	59.5	56.6 (30.0–107.0)
Obesity[a]								
Fourth quarter (high fitness)	584	7	1.0	1.0 (reference)	553	12	1.0	1.0 (reference)
Third quarter	570	23	3.7	4.0 (1.7–9.6)	521	45	5.5	5.3 (2.6–10.8)
Second quarter	503	89	20.4	22.4 (9.9–50.9)	468	98	17.0	16.3 (8.1–32.8)
First quarter (low fitness)	407	185	67.0	78.8 (33.6–184.6)	402	164	58.2	58.7 (28.1–122.7)
High serum glucose[a]								
Fourth quarter (high fitness)	536	33	1.0	1.0 (reference)	485	62	1.0	1.0 (reference)
Third quarter	513	56	1.5	1.5 (0.9–2.4)	459	92	1.3	1.2 (0.8–1.7)
Second quarter	486	84	2.0	1.8 (1.1–3.0)	438	117	1.6	1.3 (0.8–1.9)
First quarter (low fitness)	472	101	2.1	1.7 (0.94–3.00)	376	170	2.2	1.6 (1.0–2.6)
High total cholesterol[a]								
Fourth quarter (high fitness)	565	4	1.0	1.0 (reference)	536	11	1.0	1.0 (reference)
Third quarter	554	15	2.7	2.3 (0.71–7.24)	517	34	5.1	3.8 (1.6–8.8)
Second quarter	547	23	4.8	3.6 (1.1–11.3)	531	24	5.7	3.2 (1.2–8.3)
First quarter (low fitness)	542	31	5.7	3.8 (1.1–13.1)	527	19	6.2	2.6 (0.9–8.2)
Low HDL[a]								
Fourth quarter (high fitness)	559	10	1.0	1.0 (reference)	509	38	1.0	1.0 (reference)
Third quarter	560	9	1.3	0.7 (0.2–1.9)	494	57	2.4	1.6 (1.0–2.7)
Second quarter	553	17	3.4	1.2 (0.5–3.4)	470	85	4.9	2.4 (1.4–4.1)
First quarter (low fitness)	559	14	3.4	0.6 (0.2–2.3)	444	102	9.3	3.1 (1.7–5.7)
CV-RF clustering[a]								
Fourth quarter (high fitness)	560	8	1.0	1.0 (reference)	536	10	1.0	1.0 (reference)
Third quarter	555	13	1.3	1.2 (0.5–3.1)	537	14	1.8	1.5 (0.7–3.6)
Second quarter	526	42	4.6	4.6 (2.1–10.4)	519	36	4.5	3.7 (1.7–8.1)
First quarter (low fitness)	515	58	5.7	5.4 (2.3–12.9)	484	61	10.2	7.9 (3.5–18.0)

[a] Hypertension was diastolic pressure ≥90 mm Hg and/or systolic pressure ≥140 mm Hg (30); high waist circumference was >1.02 m in men and >0.88 m in women (31); obesity was BMI ≥30.0 kg·m^{-2}; elevated serum glucose was >6.0 mmol·L^{-1} (32); elevated total serum cholesterol was >6.1 mmol·L^{-1} in participants younger than 30 yr, >6.9 mmol·L^{-1} in participants 30–49 yr, and >7.8 mmol·L^{-1} in participants 50 yr or older (32); elevated HDL-cholesterol was <1.0 mmol·L^{-1} (32); cardiovascular risk factor clustering was a waist circumference ≥0.94 m in men and ≥0.80 m in women, combined with HDL-cholesterol <1.0 mmol·L^{-1} in men and <1.3 mmol·L^{-1} in women and a systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg (33,34); elevated resting HR was >70 beats·min^{-1}.

[b] Fitness quartiles were classified from the $\dot{V}O_{2peak}$ values as <30.44, 30.44–35.14, 35.15–40.82, and >40.82 mL·kg^{-1}·min^{-1} in the females and <37.37, 37.37–44.22, 44.23–50.56, and >50.56 mL·kg^{-1}·min^{-1} in the males.

[c] Adjusted for age, physical activity, habitual smoking, mean arterial pressure (except hypertension and cardiovascular risk factor clustering models), waist circumference (except high waist circumference, obesity, and cardiovascular risk factor clustering models), cholesterol (except cholesterol, HDL, and cardiovascular risk factor clustering models), and glucose (except glucose model).

CV-RF clustering, cardiovascular risk factor clustering.

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lower $\dot{V}O_{2peak}$, whereas no such association was observed in women. In similar analyses, we found that each 5-mL·kg^{-1}·min^{-1} lower $\dot{V}O_{2peak}$ corresponded to 54% (95% CI = 27%–88%) higher odds for cardiovascular risk factor clustering in men and a 58% (95% CI = 35%–85%) higher odds in women.

DISCUSSION

At present, the HUNT Fitness Study provides the largest database in which cardiorespiratory fitness, objectively measured as $\dot{V}O_{2peak}$, is associated with detailed information on standard cardiovascular risk factors and self-reported physical activity in healthy women and men across the ages of 20–90 yr.

Given the absence of self-reported health problems in the study population, it may be surprising that relatively lower levels of $\dot{V}O_{2peak}$ were consistently associated with unfavorable levels of cardiovascular risk factors. Our data show that, in a population that is healthier and more fit than the populations of previous studies, $\dot{V}O_{2peak}$ was clearly associated with cardiovascular health, as assessed by cardiovascular risk factors. Compared with other studies, it is noteworthy that the average $\dot{V}O_{2peak}$ among women in our study was higher than the previously observed average in men (8,14,19,26,30,36,37). Our data suggest that a $\dot{V}O_{2peak}$

of 44.2 mL·kg^{-1}·min^{-1} in men and 35.1 mL·kg^{-1}·min^{-1} in women may represent thresholds, below which an unfavorable cardiovascular risk profile is apparent. Thus, it seems useful to assess $\dot{V}O_{2peak}$ by sex in studies of fitness and cardiovascular risk factors. Our findings also vaguely support previous suggestions that $\dot{V}O_{2peak}$ should be included in the definition of metabolic syndrome (12). We observed that the prevalence of cardiovascular risk factor clustering was nearly identical in physically active participants age 50–59 yr and inactive participants age 20–29 yr, given similar levels of $\dot{V}O_{2peak}$. This finding suggests that physical activity may be important in limiting the age-dependent decline in $\dot{V}O_{2peak}$ and, possibly, that cardiovascular risk factor levels may remain fairly constant with increasing age among people who regularly engage in physical exercise. This observation may translate into extended longevity, as well as extended independent living and improved quality of life (15,17).

We observed that each 5-mL·kg^{-1}·min^{-1} decrement in $\dot{V}O_{2peak}$ corresponded to ~56% higher prevalence of cardiovascular risk factor clustering in both genders. These results add to the observation of Keteyian et al. (17), who showed that each 1-mL·kg^{-1}·min^{-1} increase in $\dot{V}O_{2peak}$ was associated with a ~15% lower risk of death from all causes and from cardiovascular causes in men and women with coronary heart disease. Similarly, Myers et al. (30) observed that each 1-MET (i.e., 3.5 mL·kg^{-1}·min^{-1}) increase in fitness among men with cardiovascular disease was associated with 12% improved survival.

Physical fitness is a modifiable factor; and it is well established that exercise training substantially improves fitness and that fitness is associated with reduced mortality from all causes and, specifically, from cardiovascular disease (6). In a study of men and women with metabolic syndrome, we recently observed that moderate- and high-intensity exercise training three times per week during a 16-wk period increased $\dot{V}O_{2peak}$ by 5 and 11 mL·kg^{-1}·min^{-1}, respectively, and that 37% and 46% of the patients no longer qualified as having metabolic syndrome after the intervention period (39). Of interest, both men and women with cardiovascular risk factor clustering or the metabolic syndrome at baseline (pretest) (39) had a $\dot{V}O_{2peak}$ below the sex-specific $\dot{V}O_{2peak}$ thresholds from where the unfavorable cardiovascular risk profile was apparent in the present study. After the intervention (posttest), individuals who no longer classified as having metabolic syndrome had a $\dot{V}O_{2peak}$ above these thresholds.

Previous studies have also shown strong associations of fitness with cardiovascular risk factor levels in less fit populations. Lakka et al. (21) determined the association of directly measured $\dot{V}O_{2peak}$ with the prevalence of metabolic syndrome in 1609 men age 42–60 yr. They reported that men with a $\dot{V}O_{2peak}$ <29.1 mL·kg^{-1}·min^{-1} were almost seven times more likely to have metabolic syndrome than men with a $\dot{V}O_{2peak}$ >35.5 mL·kg^{-1}·min^{-1}. Similar results were observed in a study of 1294 middle-age (42–60 yr) men with an average $\dot{V}O_{2peak}$ of 32.3 mL·kg^{-1}·min^{-1} (23). Also, Myers et al. (30) reported an estimated $\dot{V}O_{2peak}$ of 33.3 mL·kg^{-1}·min^{-1} (9.5 METs) in 2534 healthy men (55 ± 12 yr) who were referred to exercise testing for suspected or manifest cardiovascular disease and that the level of $\dot{V}O_{2peak}$ was inversely associated with all-cause and cardiovascular mortality. Although participants in the latter two studies were defined as healthy at baseline, substantial proportions of the participants had a history of hypertension (20%–24%) and were on antihypertensive medication. These characteristics are probably also reflected in the relatively low level of $\dot{V}O_{2peak}$ of the participants in these studies. The largest study to date that estimated fitness and assessed the association with unfavorable cardiovascular risk factor levels in healthy individuals is The Aerobic Center Longitudinal Study (10,40). A recent study from that database that involved 9007 men and 2826 women age 20–84 yr who were free from any known disease suggested that estimated cardiorespiratory fitness was inversely associated with the prevalence of metabolic syndrome (10). Despite its large sample size, it is a weakness of the study that estimated fitness is a less accurate measure than direct measures of $\dot{V}O_{2peak}$ (29).

The high level of $\dot{V}O_{2peak}$ associated with low prevalence of unfavorable cardiovascular risk factor levels that we found may only partly be attributed to relatively high levels of self-reported physical activity. There was a relatively low but highly significant correlation between self-reported physical activity and $\dot{V}O_{2peak}$ levels in both men (R = 0.38) and women (R = 0.34), and therefore, self-reported activity may account for only ~13% (R^2 for both genders combined = 0.13) of the observed variance in $\dot{V}O_{2peak}$. This is somewhat higher than previously reported from a study of healthy men and women age 20–68 yr (~5%) (37) but in line (~12%) with the results of a study that included men and women from 18 to 95 yr (36).

The proportion of inactive (defined as no activity or exercising less than once weekly) participants was low in our study, and the proportion of inactivity did not increase with increasing age as has been observed in most other studies (7,24,37,38). The high activity level among the participants in our study is likely to contribute to higher levels of $\dot{V}O_{2peak}$ compared to those observed in other studies (8,28). In contrast to previous studies (7,11,37), a larger proportion of men than women (17.7% vs 9.7%) were inactive across all age groups, with the greatest gender difference in the age group 40–49 yr (23.1% and 7.7% inactive men and women, respectively).

Strengths and limitations. There are several strengths to this study. Previously, direct measurements of $\dot{V}O_{2peak}$ have been conducted in smaller or selected populations, whereas the present population is larger and consists of a less selected sample of participants than other studies. The assessments of conventional cardiovascular risk factors were conducted using standardized protocols and provided detailed information.

The most obvious limitation is the cross-sectional study design that, in principle, does not allow us to suggest causal pathways between $\dot{V}O_{2peak}$ and the prevalence of unfavorable levels of cardiovascular risk factors. The physical activity questionnaire has been validated, and it seems to provide a reasonable assessment of physical activity level. Nonetheless, it is still a subjective measure, and results related to physical activity should be interpreted with caution. The lipid measurements were nonfasting, and the approximation to the metabolic syndrome (currently defined as cardiovascular risk factor clustering) was therefore based on three conventional criteria, and not three out of five, as recommended (1). However, most likely this would underestimate the prevalence of the metabolic syndrome in this population. Finally, the homogenous Norwegian population strengthens the internal validity of the findings, but limits the generalizability to other populations.

CONCLUSIONS

In this large population of healthy adults, having a low level (below the median) of $\dot{V}O_{2peak}$ was associated with much higher prevalence of cardiovascular risk factor clustering, including obesity, hypertension and unfavorable levels of blood lipids compared with having $\dot{V}O_{2peak}$ at the median or higher. Together with the evidence from clinical experimental studies, these cross-sectional data suggest that, by increasing $\dot{V}O_{2peak}$, the risk of cardiovascular disease may be reduced.

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