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Peak oxygen uptake and incident coronary heart disease in a healthy population: the HUNT Fitness Study

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Aims The majority of previous research on the association between cardiorespiratory fitness (CRF) and cardiovascular disease (CVD) is based on indirect assessment of CRF in clinically referred predominantly male populations. Therefore, our aim was to examine the associations between VO_{2peak} measured by the gold-standard method of cardiopulmonary exercise testing and fatal and non-fatal coronary heart disease (CHD) in a healthy and fit population.

Methods and results Data on VO_{2peak} from 4527 adults (51% women) with no previous history of cardiovascular or lung disease, cancer, and hypertension or use of antihypertensive medications participating in a large population-based health-study (The HUNT3 Study), were linked to hospital registries and the cause of death registry. Average VO_{2peak} was 36.0 mL/kg/min and 44.4 mL/kg/min among women and men, and 83.5% had low 10-year risk of CVD at baseline. Average follow-up was 8.8 years, and 147 participants reached the primary endpoint. Multi-adjusted Cox-regression showed 15% lower risk for the primary endpoint per one-MET (metabolic equivalent task) higher VO_{2peak} [hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.77–0.93], with similar results across sex. The highest quartile of VO_{2peak} had 48% lower risk of event compared with the lowest quartile (multi-adjusted HR 0.52, 95% CI 0.33–0.82). Oxygen pulse and ventilatory equivalents of oxygen and carbon dioxide also showed significant predictive value for the primary endpoint.

Conclusion VO_{2peak} was strongly and inversely associated with CHD across the whole fitness continuum in a low-risk population sample. Increasing VO_{2peak} may have substantial benefits in reducing the burden of CHD.

Keywords Cardiorespiratory fitness • Oxygen uptake • Coronary heart disease • Cardiopulmonary exercise testing • Primary prevention

Introduction

Despite the decline in mortality from coronary heart disease (CHD),[1] CHD is still responsible for one-third of all deaths in the adult population.[2] As much as 50% of the decline in mortality from myocardial infarction has been attributed to lower case-fatality, probably due to enhanced treatment options such as percutaneous coronary interventions (PCI) and optimized medical treatment.[3] The prevalence of CHD in the population therefore remains relatively unchanged.[1] Hence, there is great potential for further lowering the burden of CHD by early risk detection and preventive strategies.[4]

Cardiorespiratory fitness (CRF) is strongly associated with all-cause and cardiovascular mortality,[5–7] and might even be an important predictor of mortality beyond traditional risk factors such as hypertension, diabetes, cholesterol levels, and smoking.[8] A more limited number of studies also suggest that moderate to high CRF in

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apparently healthy people is associated with delayed CHD progression and reduced non-fatal events.[9] Hence, a recent statement from the American Heart Association argued for routine implementation of CRF measurements in clinical practice in order to improve risk classification and optimize prevention.[8]

Most of the evidence, however, is based on studies from a limited number of cohorts including individuals referred to exercise testing for clinical reasons,[10,11] and the majority of the mortality risk burden has been associated with CRF levels below a threshold of 5–6 metabolic equivalents (METs).[12] Furthermore, women are lacking or underrepresented in most studies,[6,9,11,13] and the generalizability of findings to apparently healthy, free-living populations is uncertain. Moreover, CRF levels in population studies are commonly predicted from submaximal or peak workload on a treadmill or cycle ergometer as opposed to the gold-standard method of cardiopulmonary exercise testing (CPET) by direct gas-analysis of peak oxygen uptake (VO_{2peak}).[5] To our knowledge only two relatively small cohorts,[13,14] including middle-aged men, has examined the association between direct measurements of VO_{2peak} and risk of cardiovascular events, showing an inverse relationship.

The aim of this study was to examine the prospective associations of VO_{2peak} measured by CPET with fatal or non-fatal CHD events or coronary revascularization, in a healthy low-risk cohort of both men and women. Secondary, we aimed to assess the associations separately for acute and chronic CHD, and mortality, as well as the prognostic value of other CPET measures such as ventilatory equivalents and oxygen pulse.

Materials and methods

Study design and participants

The prospective cohort study involved participants from the HUNT3 Fitness Study, a sub-study of the third wave of the Nord-Trøndelag Health Study (HUNT3). In 2006–2008, all inhabitants in Nord-Trøndelag county in mid-Norway were invited to participate in HUNT3. Of 93 860 eligible adults, 50 807 inhabitants participated (54.1%).[15] Participants from four pre-selected municipalities with no previous history of cardiovascular and lung disease, cancer, sarcoidosis, and hypertension or use of antihypertensive medications were invited to CPET ($n = 12\ 609$). Of these, 5633 showed up for exercise testing, and a total of 4527 completed the exercise test as well as having no other missing variables for the main analyses. The study was approved by the Regional Committee for Medical Research Ethics, and the Norwegian Data Inspectorate approved the HUNT Study. All subjects gave their informed consent.

Self-reported and clinical measurements

Smoking status (current, former, occasional, and never smoker) and pack-years of cigarettes, snuffing status (currently using/not using) alcohol consumption (frequency of alcohol intake per week over the last 12 months), family history of cardiovascular disease (CVD) (myocardial infarction or stroke in first degree relative), and leisure-time physical activity was gathered from self-reported questionnaires. Physical activity was dichotomized to adherence or non-adherence to physical activity guidelines (see Supplementary material online, *Methods*). Clinical examinations were performed by trained personnel measuring weight to nearest half kilogram, and height and waist circumference to nearest centimetre in standing position. An oscillometry-based Dinamap 845XT (Critikon) was used for measuring resting heart rate and blood pressure. Blood samples were analysed for non-fasting serum-levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, creatinine, and C-reactive protein (CRP). Non-HDL cholesterol was calculated by subtracting HDL cholesterol from total cholesterol. Dyslipidaemia was defined as total-cholesterol over 7.0, HDL under 1.3 and 1.0 for men and women, respectively, or triglycerides over 1.7. Further information on measurement of clinical variables in HUNT3 has been described elsewhere.[15]

Cardiopulmonary exercise testing

Participants were given a 10-min warm-up and acclimatization to treadmill before initiating an individualized ramp-protocol wearing a face-covering mask and heart rate monitor. Continuous gas analysis was done by using a mixing chamber gas analyser (MetaMax II; Cortex Biophysik Gmbh, Leipzig, Germany). Routine gas and volume calibration were performed at standardized intervals several times per day. Further details are available in Supplementary material online, *Methods*. Comprehensive data of the reliability of the measurements has been previously published.[16] Test–retest correlation of oxygen uptake was 0.99 ($P < 0.001$) and the coefficient of variation was 1.8%. The test was defined as reaching VO_{2max} if measurements showed a plateau in oxygen consumption as well as a respiratory exchange ratio above 1.05. In this study, both tests meeting criteria for VO_{2max} and tests classified as VO_{2peak} are labelled VO_{2peak}. Oxygen pulse was calculated as maximal oxygen consumption in millilitres divided by heart-rate at peak exercise. Ventilatory efficiency equivalents was calculated as minute ventilation divided by CO_2 ventilation ($EqVCO_2$) or O_2 consumption ($EqVO_2$) in litres per minute at peak and steady state submaximal exercise.

Follow-up and information on endpoints

Follow-up was ensured by linking baseline data from The HUNT3 Study to a local, validated hospital database (Nord-Trøndelag Hospital Trust myocardial infarction registry), the regional health trust database on diagnoses and procedures, and the Norwegian Cause of Death Registry (NCDR). We used ICD-10 (International Classification of Disease-10) codes I20, I21, I24, I25 to define endpoints of CHD. Information on coronary revascularization including PCI and coronary artery bypass graft surgery (CABG) was based on relevant codes from Nomesco classification of surgical and radiological procedures (NCSP and NCRP). Information on cause and date of death was gathered from the NCDR. Death from CHD was based ICD-10 codes I20–I25. Primary endpoint was defined as diagnosis of, or death from, CHD, or coronary revascularization (PCI or CABG), whichever came first.

Statistical analyses

Ten-year risk of CVD was calculated and classified as low, medium, or high based on the recently published NORRISK2 risk prediction model (see Supplementary material online, *Methods*).[17] The Cox proportional hazards model was employed with attained age as the time scale, thus inherently adjusting analyses for age. Time under risk was calculated as time since participation in the HUNT3 Fitness Study (ranging from 14 June 2007 until 19 June 2008) until censoring (death of non-coronary cause), event, or end of follow-up (31 December 2016). The proportional hazards assumption was investigated by testing Schoenfeld residuals. Analyses were performed with VO_{2peak} expressed as a continuous variable by METs (one MET equals ~3.5 mL/kg/min) and by comparing quartiles of VO_{2peak}. Age- and sex-specific quartiles of VO_{2peak} was made by generating percentiles of VO_{2peak} in sex-split deciles of age before merging these into quartiles of VO_{2peak} (Q1 to Q4). Main analyses were adjusted for sex in Model 1, and in addition, smoking status, alcohol intake, and family history of CVD in Model 2. We performed sensitivity

analyses adjusted for several cardiovascular risk factors; body mass index (BMI), systolic blood pressure, dyslipidaemia, CRP, snuffing status, and diabetes. Adjustment for BMI was included in sub-analyses performed on exercise variables not being weight scaled. We examined evidence of interaction with VO_{2peak} expressed as METs and quartiles of VO_{2peak} across covariates in Model 1 and 2, age, and physical activity adherence. Stratified analyses by sex and age groups (<45, 45–65, >65 years), respectively, were performed to further examine potential effect modification. Test for linear trend across categories Q1 to Q4 was performed by tests for log-linearity of the hazard ratios (HRs). Results are presented as HR for effect estimates and 95% confidence intervals (95% CIs) for evaluation of precision. We also calculated net reclassification improvement (NRI), integrated discrimination improvement (IDI), and Harrell's *C* statistics by adding VO_{2peak} to the variables from NORRISK2 to examine whether VO_{2peak} could improve risk prediction of CHD.[18,19] NRI analyses were performed with modified NORRISK2 risk cut-offs of 5% and 10% due to different risk categories per age-group in the original model. Analyses were performed using STATA15.1 (StataCorp, TX, USA).

Results

Characteristics of the population

Baseline characteristics of the 4527 participants are shown in *Table 1*. Mean age was 48.2 [standard deviation (SD) 13.5, range 19–89] years, and gender distribution was balanced (51% women). Average VO_{2peak} was 36.0 mL/kg/min and 44.4 mL/kg/min among women and men, respectively. The pre-defined VO_{2max} criteria were reached in 80% of participants. Cut-offs of VO_{2peak} for Q1 to Q4 across sex and 10-year age groups are shown in Supplementary material online, *Table S1*. Levels of cardiovascular risk-factors were consistently decreasing from Q1 through Q4, except alcohol use being higher in higher quartiles of VO_{2peak} (Supplementary material online, *Table S2*). Clustering of cardiovascular risk at baseline was generally low, as 83.5% had low 10-year risk of CVD and CVD mortality measured by the NORRISK2 risk model.

Peak oxygen uptake and primary endpoint

During a total follow-up time of 40 060 person-years (mean 8.8, SD 1.0) 147 participants (3.3%) reached the composite primary endpoint of diagnosis of or death from CHD, or coronary revascularization. Incidence rate of primary endpoint was 3.7 events per 1000 person-years. In the combined analyses of men and women, the risk for primary endpoint was 16% (95% CI 8–23) lower per one MET higher VO_{2peak} after adjustment for sex (Model 1), and 15% (95% CI 7–23) when additionally adjusted for smoking status, alcohol use, and family history of CVD in the multi-adjusted Model 2 (*Table 2*). The same direction and comparable magnitude of effects were seen in analyses stratified by sex. The Kaplan–Meier graph (*Figure 1*) illustrates the higher event-free survival from the primary composite endpoint for the higher quartiles of VO_{2peak}. Analyses by quartiles of VO_{2peak} showed 48% (95% CI 18–67) lower risk in Q4 compared with Q1 and testing for trend across quartiles of VO_{2peak} showed a significant linear trend ($P < 0.005$ for Model 1 and 2 in combined analyses). Further, when subdivided by baseline VO_{2peak} level, participants in the highest quartiles had similar protective effect per one MET higher VO_{2peak}. There was no evidence of statistical interaction of VO_{2peak}

Table 1 Baseline characteristics of the study population stratified by sex

	Women	Men
n	2316	2211
Age (years), mean (SD)	47.7 (13.6)	48.8 (13.5)
Physical measurements		
Waist circumference (cm), mean (SD)	85.8 (10.6)	94.6 (9.1)
Body mass index (kg/cm^2), mean (SD)	25.4 (3.9)	26.6 (3.2)
Systolic blood pressure (mmHg), mean (SD)	123.5 (15.4)	132.0 (14.3)
Diastolic blood pressure (mmHg), mean (SD)	69.9 (9.8)	76.4 (10.3)
Resting heart rate (b.p.m.), mean (SD)	67.5 (10.0)	64.6 (10.9)
Biochemical measurements		
Total cholesterol (mmol/L), mean (SD)	5.43 (1.11)	5.48 (1.02)
HDL cholesterol (mmol/L), mean (SD)	1.53 (0.34)	1.25 (0.29)
Non-HDL cholesterol (mmol/L), mean (SD)	3.91 (1.07)	4.23 (1.03)
Triglycerides (mmol/L), mean (SD)	1.23 (0.67)	1.79 (1.12)
Glucose, non-fasting (mmol/L), mean (SD)	5.21 (1.01)	5.53 (1.51)
Creatinine (μmol/L), mean (SD)	72.2 (10.7)	85.8 (11.4)
C-reactive protein (mg/L), median (IQR)	0.80 (1.40)	0.90 (1.20)
Behavioural		
Regular alcohol intake[a] (%)	15.2	21.2
Pack years of cigarettes (*n*), median (IQR)	6.4 (11.7)	8.4 (15.6)
Smoker (%)	19.3	18.0
Snuff user (%)	3.7	27.7
Physically active (%)[b]	26.2	29.5
Disease in first-degree relative		
Cardiovascular disease (%)	19.4	17.7
Cardiovascular risk[c]		
Low	94.3	72.3
Moderate	2.9	9.9
High	2.8	17.9
Exercise testing variables		
VO_{2peak} (mL/min/kg), mean (SD)	36.0 (7.8)	44.4 (9.2)
VO_{2max} criteria met (%)	76.9	83.3
RER_{peak}, mean (SD)	1.12 (0.07)	1.12 (0.07)
Heart $rate_{peak}$ (b.p.m.), mean (SD)	179 (15)	180 (16)
Oxygen $pulse_{peak}$ (mL/heart beat)	13.9 (2.6)	20.9 (3.9)
$EqVCO_{2peak}$	24.5 (2.8)	24.5 (2.9)
$EqVO_{2peak}$	33.3 (4.7)	33.3 (4.7)

$EqVCO_2$, ventilatory equivalent for carbon dioxide; $EqVO_2$, ventilatory equivalent for oxygen; IQR, interquartile range; HDL, high-density lipoprotein; RER, respiratory exchange ratio; SD, standard deviation.
[a]Regular alcohol intake over once per week.
[b]Adherence to physical activity guidelines.
[c]Ten-year cardiovascular risk assessed by NORRISK2 risk prediction model.

Table 2 Hazard ratios for primary endpoint[a] per one MET higher VO_{2peak}, and by quartiles of VO_{2peak}

				Model 1		Model 2	
		n	Events (*n*)	HR	95% CI	HR	95% CI
Total	Per 1-MET	4527		0.84	0.77–0.92	0.85	0.77–0.93
	Q1	1136	58	1	—	1	—
	Q2	1134	34	0.58	0.38–0.88	0.58	0.38–0.90
	Q3	1131	27	0.46	0.29–0.73	0.48	0.30–0.76
	Q4	1126	28	0.49	0.31–0.78	0.52	0.33–0.82
Men	Per 1-MET	2211		0.82	0.75–0.91	0.83	0.75–0.92
	Q1	555	44	1	—	1	—
	Q2	554	23	0.50	0.30–0.83	0.51	0.31–0.85
	Q3	552	20	0.43	0.26–0.74	0.46	0.27–0.79
	Q4	550	18	0.40	0.23–0.70	0.43	0.24–0.75
Women	Per 1-MET	2316		0.89	0.74–1.08	0.88	0.73–1.08
	Q1	581	14	1	—	1	—
	Q2	580	11	0.79	0.36–1.74	0.76	0.35–1.69
	Q3	579	7	0.51	0.21–1.28	0.49	0.20–1.22
	Q4	576	10	0.79	0.35–1.78	0.77	0.34–1.77

Model 1: adjusted for sex.
Model 2: Model 1 + smoking status, alcohol use, and family history of CVD.
CI, confidence interval; HR, hazard ratio; Q1–Q4, age- and sex-specific quartiles of VO_{2peak} 1–4.
[a]Diagnosis or death from coronary heart disease, or coronary revascularization.

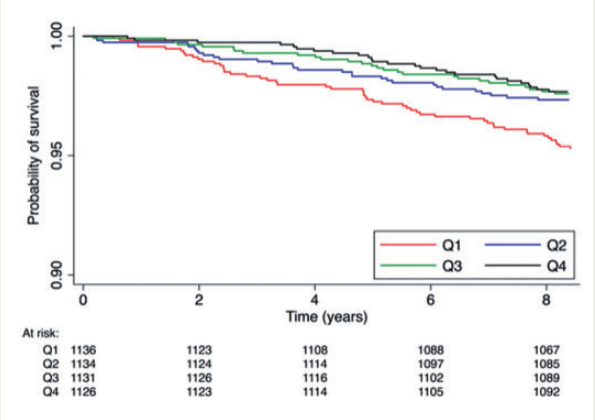


Figure 1 Kaplan–Meier curve for survival from primary endpoint according to age- and sex-specific quartiles of VO_{2peak} (Q1–Q4).

(quartiles and METs) and age, physical activity adherence and the covariates in Model 1 and 2. Stratified analyses by age (<45, 45–65, >65 years) showed comparable effect estimates (Supplementary material online, *Table S3*).

Sub-analyses

Analyses with myocardial infarction, chronic ischaemic heart disease, coronary revascularization, and mortality as endpoints are presented in *Table 3*. In general, the effect estimates were in line with findings in the main analyses. However, the association with all-cause mortality was weak, with a 6% (95% CI -5 to 16) lower risk per one MET higher VO_{2peak} in the multi-adjusted model. Mortality incidence rate was 2.2 per 1000 person-years (91 deaths of any cause). Malignant disease was the leading cause of death (48%), while cardiovascular and respiratory disease accounted for only 20% and 3% of deaths during follow-up, respectively.

Net reclassification improvement analyses showed improved risk prediction when adding VO_{2peak} to the risk factors from the NORRISK2 model (NRI 0.066, $P = 0.044$), as shown in *Table 4*. Among those with CHD 15 participants were correctly reclassified to a higher risk category, while six were reclassified down. The IDI was estimated at 0.004 ($P = 0.019$), while Harrell's *C* statistic did not improve by adding VO_{2peak} (ΔHarrell's $C = 0.003$, $P = 0.428$).

One percent higher 10-year cardiovascular risk was associated with 12% (95% CI 8–16) higher risk of the primary endpoint.

Oxygen pulse showed 8% (95% CI 2–13) lower risk for primary endpoint per unit higher value. $EqVO_2$ and $EqVCO_2$ at peak exercise was associated with 3% (95% CI 0–6, $n = 4497$) and 4% (95% CI 0–8, $n = 4495$) increased risk for the primary endpoint, respectively. Results on submaximal values were similar (Supplementary material online, *Table S4*). Having values of $EqVCO_2$ above the upper normal limit of 30 was associated with 39% (95% CI -6 to 106) higher risk of the primary endpoint.

Sensitivity analyses

In analysis for the primary endpoint after adjusting for BMI, systolic blood pressure, dyslipidaemia, CRP, snuffing status, and diabetes in addition to the variables in Model 1 and 2 the HR was slightly attenuated to 0.90 (95% CI 0.81–0.99, $n = 4349$). Findings were also consistent across groups stratified by estimated 10-year risk of CVD ($n = 4149$) with 14% (95% CI 2–24) and 16% (95% CI 0–29) lower risk per one MET higher VO_{2peak} for the low-medium and high-risk

Table 3 Hazard ratio per one MET higher VO_{2peak} for secondary endpoints

		Model 1		Model 2	
	Events (*n*)	HR	95% CI	HR	95% CI
Myocardial infarction	74	0.80	0.70–0.90	0.80	0.70–0.91
Chronic ischaemic heart disease	74	0.89	0.79–1.01	0.90	0.79–1.02
Coronary revascularization	85	0.83	0.74–0.93	0.83	0.74–0.94
All-cause mortality	91	0.90	0.80–1.01	0.94	0.84–1.05
Cardiovascular mortality	18	0.73	0.54–0.98	0.78	0.58–1.04

Model 1: adjusted for sex.
Model 2: Model 1 + smoking status, alcohol use, and family history of CVD.
CI, confidence interval; HR, hazard ratio; MET, metabolic equivalent task.

Table 4 Reclassification of CHD risk by adding VO_{2peak} to traditional risk factors (NORRISK2)

		NORRISK2 + VO_{2peak}				
		<5%	5–10%	≥10%	Total	Net correctly reclassified
NORRISK2	CHD					
	<5%	43	7		50	6.4%
	5–10%	4	36	8	48	
	≥10%		2	40	42	
	Total	47	45	48	140	
	No CHD					
	<5%	3326	75		3401	0.2%
	5–10%	99	401	41	541	
	≥10%		25	231	256	
	Total	3425	501	272	4198	
						NRI 0.066 (*P* = 0.04)

CHD, coronary heart disease; NRI, net reclassification improvement.

group, respectively (multi-adjusted model). Analyses for the primary endpoint excluding first 2 years of follow-up showed similar results as the main analyses, HR 0.89 (95% CI 0.81–0.98) per one MET higher VO_{2peak} (multi-adjusted model). Analyses with pack-years of smoking replacing the dichotomous smoking variable did not change of effect estimates (multi-adjusted model: HR per one MET 0.85, 95% CI 0.74–0.97, *n* = 1913).

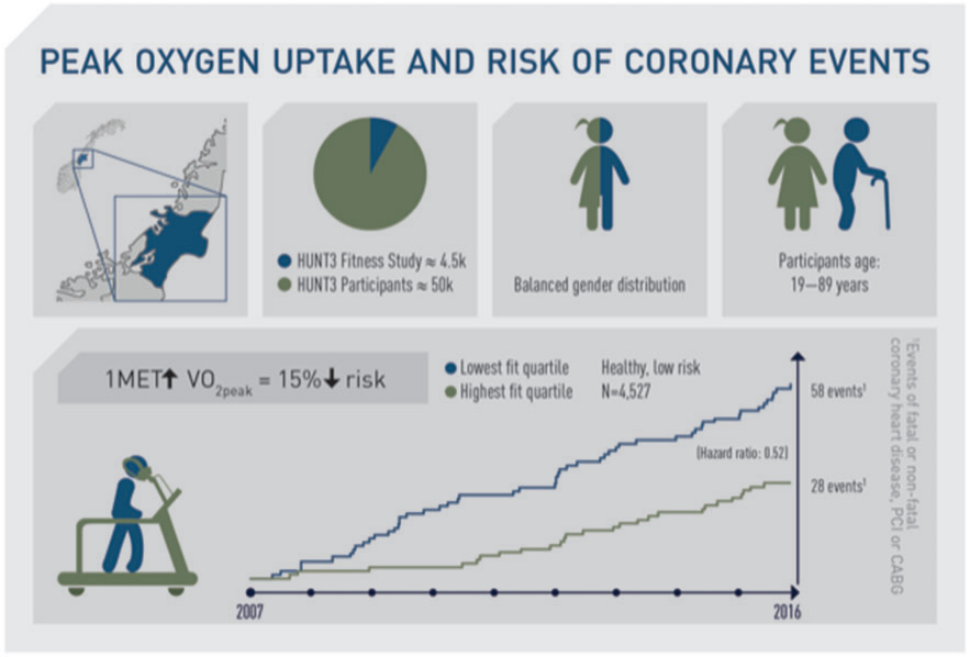
Discussion

Our results show that VO_{2peak} is inversely related to the risk of CHD in healthy men and women. The influence of VO_{2peak} was similar for acute diagnoses such as myocardial infarction and chronic diagnoses such as angina pectoris, and the reduced risk with higher VO_{2peak} was similar both in fit and unfit sub-populations. Further, ventilatory equivalents and oxygen pulse were also associated with incident CHD.

VO_{2peak} and coronary heart disease

Our main finding of 17% (men) and 12% (women) lower adjusted risk of CHD per one MET higher VO_{2peak} is in line with the large meta-analysis from 2009 estimating a 15% lower risk per one MET higher exercise capacity.[7] In general, our findings support several earlier studies describing an inverse relationship between CRF and fatal[11,20,21] and non-fatal[9,22] CHD. Even though precision was lower in women, the consistent size and direction of estimates makes erroneous conclusions less likely. Plausibility of our results is also strengthened by several biological pathways connecting CRF and CHD such as genetical background, obesity, and physical activity adherence with its effects on cardiac structure and function, inflammation, metabolism, atherosclerosis, and endothelial function.[8,23] CRF is in fact a measure of function involving several organ systems—thus signifying its potential as a marker of present and future health.

The association between VO_{2peak} and CHD was strong despite the fit population sample in this study. In fact, the average VO_{2peak} among women in this study was higher than the average among men in other studies.[9,13] The average 60-year-old man in our study had roughly the same fitness level as the group with highest estimated fitness in the meta-analysis by Kodama *et al.*[7] A 28% higher VO_{2peak} compared with the normal material from the US FRIEND cohort[24] further confirms the fit sample of participants. Test for trend across the quartiles of VO_{2peak} showed a significant linear relationship, and when analysing within the highest-fit quartile of VO_{2peak} we found the



Take home figure In 4527 health-survey participants without preexisting cardiovascular disease and predominantly low calculated cardiovascular risk, VO_{2peak} was a strong predictor of coronary heart disease.

same association per one MET higher VO_{2peak}, indicating that higher CRF is protective with no apparent upper threshold (*Take home figure*). Cut-offs of CRF for risk reduction have, however, been recommended earlier. Exercise capacity <5 METs has been proposed as a single threshold of increased risk,[12] as well as cut-offs of 8 and 6 METs for 50-year-old men and women, respectively, in another study.[7] Our results suggest that there is still a large potential for risk-reduction even when having CRF beyond such thresholds, and implicitly, thresholds may vary between populations.

The associations of VO_{2peak} to all-cause mortality was not statistically significant, and the effect estimates were somewhat lower than in a meta-analysis on CRF and mortality.[7] The low mortality from CVD and respiratory diseases may partially explain these weak associations.

Our results showed a clear predictive value of oxygen pulse, a less studied CPET variable, for future CHD. Similar findings was recently shown in a publication from the Kuopio Ischaemic Heart Disease cohort.[25] The oxygen pulse trajectory is included for judgement of myocardial ischaemia as a non-invasive measure of stroke volume,[26] and our findings support its prognostic value, even without assessing the trajectory during test. $EqVO_2$ and $EqVCO_2$ at peak exercise also showed predictive value of CHD.

Strengths and limitations

Our study has several methodological strengths. Firstly, CRF was measured by direct assessment of VO_{2peak} during maximal exercise, and this study is the first to use this gold-standard method in a healthy sample of the general population to evaluate associations with cardiovascular events and mortality. The precise measurements of exposure may have compensated somewhat for the relatively few endpoints accumulated over the follow-up period. Definition of endpoints by linkage to hospital databases and national registries ensured high-quality data with negligible loss to follow-up. We did not have specific information on emigration during follow-up, however emigration from the county is known to be very low.[15] The healthy population also reduced the risk of reverse confounding from clinical or subclinical disease as an explanation for the association. Sensitivity analyses with exclusion of participants with events during the first 2 years of follow-up supported this assumption.

Participating in voluntary exercise testing introduces the possibility of self-selection towards more active participants, which may reduce external validity. However, an earlier study compared the HUNT3 Fitness population with the healthy part of the total HUNT3 population and found a similar cardiovascular risk profile in men and women, but the Fitness study participants were slightly more active, weighed less and had lower waist circumference. The prevalence of cardiovascular risk factors was slightly lower in the Fitness population compared with the general HUNT3 population (5.6% vs. 6.4%).[27]

Clinical implications

The update on clinical recommendations for CPET from 2016 highlighted the potential for risk-stratification and prevention of non-communicable disease among apparently healthy individuals.[28] Our results confirm that the level of CRF predicts CHD, with a preventive influence of higher values, in a healthy free-living population. Higher VO_{2peak} was protective against both chronic and acute ischaemic

heart disease. Although submaximal and maximal exercise testing and non-exercise prediction equations is deemed to be feasible and has been shown to have prognostic value,[5,8] the additional clinical information and higher external validity due to superior precision obtained from CPET favours implementation of directly assessed VO_{2peak}.[8,24] For example, a study from the FRIEND database showed significant differences between CRF reference data based on direct measurement of VO_{2peak}, and VO_{2peak} estimated from exercise test data,[24] especially in the extremes of CRF. Our analyses showed slightly improved risk prediction when adding VO_{2peak} to an established risk prediction model. The results were not conclusive, however, as the relatively low number of events in this low-risk population sample limited the analyses. Further studies should therefore follow this issue, as well as investigate how VO_{2peak} measured by CPET performs compared with indirect CRF measurements in terms of risk prediction and classification.

Exercise is associated with healthy living, increased cardiorespiratory fitness, and reduced morbidity, and the potential for primary prevention is great, and not fully exploited.[29] Taking full advantage of exercise as (preventive) medicine is important as the evidence show great health-impact of as little as one MET higher CRF. Such a modest increase in CRF is easily achieved over a few months of regular exercise,[8] and thus, exercise may be an efficient way of reducing cardiovascular risk.

Conclusion

VO_{2peak} was strongly and inversely related to CHD in a large cohort of apparently healthy and low-risk men and women. These findings support that VO_{2peak} has predictive value along the whole fitness continuum, and future studies should further pursue integration of VO_{2peak} in risk prediction algorithms. Increasing VO_{2peak} may have substantial benefits in reducing the burden of CHD.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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References

1. Bhatnagar P, Wickramasinghe K, Wilkins E, Townsend N. Trends in the epidemiology of cardiovascular disease in the UK. *Heart* 2016;**102**:1945–1952.
2. Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. *Ann Transl Med* 2016;**4**:256.
3. Smolina K, Wright FL, Rayner M, Goldacre MJ. Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study. *BMJ* 2012;**344**:d8059.
4. Ford ES, Capewell S. Proportion of the decline in cardiovascular mortality disease due to prevention versus treatment: public health versus clinical care. *Annu Rev Public Health* 2011;**32**:5–22.
5. Harber MP, Kaminsky LA, Arena R, Blair SN, Franklin BA, Myers J, Ross R. Impact of cardiorespiratory fitness on all-cause and disease-specific mortality: advances since 2009. *Prog Cardiovasc Dis* 2017;**60**:11–20.
6. Blair SN, Kohl HW, Paffenbarger RS, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA* 1989;**262**:2395–2401.
7. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone H. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* 2009;**301**:2024–2035.
8. Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BA, Haskell WL, Kaminsky LA, Levine BD, Lavie CJ, Myers J, Niebauer J, Sallis R, Sawada SS, Sui X, Wisloff U; American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Cardiovascular and Stroke Nursing; Council on Functional Genomics and Translational Biology; Stroke Council. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation* 2016;**134**:e653–e699.
9. Khan H, Jaffar N, Rauramaa R, Kurl S, Savonen K, Laukkanen JA. Cardiorespiratory fitness and nonfatalcardiovascular events: a population-based follow-up study. *Am Heart J* 2017;**184**:55–61.
10. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002;**346**:793–801.
11. Kokkinos PF, Faselis C, Myers J, Narayan P, Sui X, Zhang J, Lavie CJ, Moore H, Karasik P, Fletcher R. Cardiorespiratory fitness and incidence of major adverse cardiovascular events in US Veterans: a cohort study. *Mayo Clin Proc* 2017;**92**:39–48.
12. Kokkinos P, Myers J, Faselis C, Panagiotakos DB, Doumas M, Pittaras A, Manolis A, Kokkinos JP, Karasik P, Greenberg M, Papademetriou V, Fletcher R. Exercise capacity and mortality in older men: a 20-year follow-up study. *Circulation* 2010;**122**:790–797.
13. Laukkanen JA, Lakka TA, Rauramaa R, Kuhanen R, Venalainen JM, Salonen R, Salonen JT. Cardiovascular fitness as a predictor of mortality in men. *Arch Intern Med* 2001;**161**:825–831.
14. Talbot LA, Morrell CH, Metter EJ, Fleg JL. Comparison of cardiorespiratory fitness versus leisure time physical activity as predictors of coronary events in men aged < or = 65 years and > 65 years. *Am J Cardiol* 2002;**89**:1187–1192.
15. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, Bratberg G, Heggland J, Holmen J. Cohort profile: the HUNT study, Norway. *Int J Epidemiol* 2013;**42**:968–977.
16. Loe H, Rognmo O, Saltin B, Wisloff U. Aerobic capacity reference data in 3816 healthy men and women 20-90 years. *PLoS One* 2013;**8**:e64319.
17. Selmer R, Igland J, Ariansen I, Tverdal A, Njolstad I, Furu K, Tell GS, Klemsdal TO. NORRISK 2: a Norwegian risk model for acute cerebral stroke and myocardial infarction. *Eur J Prev Cardiol* 2017;**24**:773–782.
18. Sundstrom J, Byberg L, Gedeborg R, Michaelsson K, Berglund L. Useful tests of usefulness of new risk factors: tools for assessing reclassification and discrimination. *Scand J Public Health* 2011;**39**:439–441.
19. Newson RB. Comparing the predictive powers of survival models using Harrell's C or Somers' D. *Stata J* 2010;**10**:339–358.
20. Farrell SW, Finley CE, Barlow CE, Willis BL, DeFina LF, Haskell WL, Vega GL. Moderate to high levels of cardiorespiratory fitness attenuate the effects of triglyceride to high-density lipoprotein cholesterol ratio on coronary heart disease mortality in men. *Mayo Clin Proc* 2017;**92**:1763–1771.
21. Gander JC, Sui X, Hebert JR, Hazlett LJ, Cai B, Lavie CJ, Blair SN. Association of cardiorespiratory fitness with coronary heart disease in asymptomatic men. *Mayo Clin Proc* 2015;**90**:1372–1379.
22. Berry JD, Pandey A, Gao A, Leonard D, Farzaneh-Far R, Ayers C, DeFina L, Willis B. Physical fitness and risk for heart failure and coronary artery disease. *Circ Heart Fail* 2013;**6**:627–634.
23. Myers J, McAuley P, Lavie CJ, Despres JP, Arena R, Kokkinos P. Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: their independent and interwoven importance to health status. *Prog Cardiovasc Dis* 2015;**57**:306–314.

24. Kaminsky LA, Arena R, Myers J. Reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing: data from the fitness registry and the importance of exercise national database. *Mayo Clin Proc* 2015;**90**: 1515–1523.
25. Laukkanen JA, Araujo CGS, Kurl S, Khan H, Jae SY, Guazzi M, Kunutsor SK. Relative peak exercise oxygen pulse is related to sudden cardiac death, cardiovascular and all-cause mortality in middle-aged men. *Eur J Prev Cardiol* 2018;**25**:772–782.
26. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, Arena R, Fletcher GF, Forman DE, Kitzman DW, Lavie CJ, Myers J; EACPR; AHA. EACPR/AHA Joint Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Eur Heart J* 2012; **33**:2917–2927.
27. Aspenes ST, Nilsen TI, Skaug EA, Bertheussen GF, Ellingsen O, Vatten L, Wisloff U. Peak oxygen uptake and cardiovascular risk factors in 4631 healthy women and men. *Med Sci Sports Exerc* 2011;**43**:1465–1473.
28. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Eur Heart J* 2018;**39**:1144–1161.
29. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL., Cooney MT., Corra U., Cosyns B., Deaton C., Graham I., Hall MS., Hobbs FD., Lochen ML., Lollgen H., Marques-Vidal P., Perk J., Prescott E., Redon J., Richter DJ., Sattar N., Smulders Y., Tiberi M., van der Worp HB., van Dis I., Verschuren WM. 2016 European guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2016;**37**:2315–2381.