Clinical research

The predictive value of cardiorespiratory fitness for cardiovascular events in men with various risk profiles: a prospective population-based cohort study

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Aims Few data exist to show if the prognostic value of peak exercise oxygen consumption (VO_{2peak}) for fatal and non-fatal coronary events is different among men with low and high pre-test probability for cardiovascular disease (CVD). Our objective was to determine whether VO_{2peak} could predict fatal and non-fatal cardiac events in 2361 men aged 42–60 years with and without conventional risk predictors of CVD or with documented CVD during a 13-year follow-up.

Methods and Results Maximal oxygen consumption (ml/kg/min) was measured directly by using respiratory gas exchange in a cycle ergometer exercise test. Of 204 CVD deaths, 153 were due to coronary disease and 51 were due to other CVDs. A total of 323 non-fatal coronary events occurred during the follow-up. One metabolic equivalent (MET) increment in VO_{2peak} was related to a decreased risk of coronary death in both healthy (RR=0.82, 95% CI 0.66–0.99) and unhealthy (RR=0.72, 95% CI 0.63–0.82) men. VO_{2peak} was predictive of non-fatal and fatal cardiac events among men with or without known risk factors. In subjects with or without common risk factors, one MET increment amounted to an average decrease of 17–29% in non-fatal and 28–51% in fatal cardiac events, after adjustment for age. VO_{2peak} and smoking represented two strongest independent and consistent risk predictors.

Conclusions VO_{2peak} can be used as a very powerful predictor of future fatal cardiac events beyond that predicted by many conventional risk factors. On the prognostic consideration, unfit men with unfavourable risk profiles or underlying chronic disease are the risk groups that will benefit most from preventive measures.
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Introduction

Physical inactivity[1,2] and low physical fitness[3-6] have been found to be as important predictors of mortality as conventional risk factors, such as smoking, hypercholesterolaemia, hypertension, overweight and diabetes. Recent evidence proposed that exercise capacity represents the most powerful predictor of total mortality in a clinical population,[6] but very little is known about the predictive value of peak exercise oxygen consumption (VO_{2peak}) in a general population of men with different pre-test probability (e.g., risk profile) with regard to both fatal and non-fatal cardiovascular events. Furthermore, the traditional cardiovascular risk factors interact with one another, but the interaction of physical fitness with traditional risk factors has not been investigated. Second, the level of physical fitness was not taken into account while estimating the prognostic value of conventional risk factors.

The objective of the present study was to determine whether directly measured VO_{2peak}, an accurate and reproducible measure of cardiorespiratory fitness,[7] may predict morbidity and mortality from cardiovascular causes in a population-based random sample of men as related to conventional risk factors, medications or underlying chronic disease.

Methods

Participants

The present report is based on participants of the Kuopio Ischaemic Heart Disease Risk Factor Study, an ongoing population study to investigate risk factors including physical fitness for cardiovascular disease (CVD) and atherosclerotic vascular diseases.[5,8,9] The study population is a representative random sample of eastern Finnish men who were 42–60 years of age at baseline examinations between March 1984 and December 1989. Of 3235 eligible men, 2682 (83%) participated in the study and those with complete data on VO_{2peak} (2361 men) were included in the analyses. The unhealthy subgroup included those with a history of coronary heart disease (CHD) or typical angina pectoris, cardiac insufficiency, claudication, stroke, cardiomyopathy, arrhythmias, chronic obstructive pulmonary disease, pulmonary tuberculosis, bronchial asthma or cancer (Table 1). The study was approved by the research ethics committee of the University of Kuopio, Kuopio, Finland. Each participant gave written informed consent.

Assessment of cardiorespiratory fitness

A maximal symptom-limited exercise tolerance test was performed between 8:00 a.m. and 10:00 a.m. during a cycle ergometer.[5,8,9] The standardised testing protocol comprised of an increase in the workload of 20 W/min with the direct analyses of respiratory gases. For safety reasons, and to obtain reliable information on exercise test variables, the tests were supervised by an experienced physician with the assistance of an experienced nurse. The electrocardiogram (ECG), blood pressure and heart rate (HR) were registered during the exercise test.[8]

VO_{2peak} was used as a measure of cardiorespiratory fitness. VO_{2peak} was defined as the highest value for or the plateau in oxygen uptake. If the plateau in oxygen uptake could not be reached despite an increase in the workload of exercise, the highest value of oxygen uptake was used as VO_{2peak}. A detailed description of the measurement of VO_2 has been given elsewhere.[9] In short, respiratory-gas exchange was measured for the first 622 men by the mixing-chamber method (Mijnhart Oxycon 4 analyzer, Mijnhardt, Odijk, The Netherlands), and for the other 1739 men by a breath-by-breath method (MGC 2001 analyzer, Medical Graphics, St. Paul, MN, USA). The Mijnhardt Oxycon 4 analyzer expressed the oxygen uptake as the average of values recorded over a 30 s period, whereas the MCG 2001 analyzer expressed it as the average of values recorded over 8 s. Pearson's coefficient for the correlation between simultaneous Mijnhardt Oxycon 4 and MCG measurements in 13 men was 0.97.

The most common reasons for stopping the exercise test were leg fatigue ($n=1191$), exhaustion ($n=366$), breathlessness ($n=322$), and pain in the leg muscles, joints, or back ($n=121$). The test was discontinued because of cardiorespiratory symptoms or abnormalities for 261 men. These included angina pectoris ($n=85$), arrhythmias ($n=73$), a marked change in systolic or diastolic blood pressure ($n=53$) or ischaemic ECG changes ($n=36$) or dizziness ($n=14$).

Assessment of risk factors

The lifelong exposure to smoking (cigarette pack-years) was estimated as the product of the number of years smoking and the number of tobacco products smoked daily at the time of examination.[10] Resting blood pressure was measured between 8:00 and 10:00 a.m. by one nurse with a random-zero sphygmomanometer.[9,10] The measuring protocol included, after a supine rest of 5 min, three measurements in supine, one in standing, and two in sitting position with 5 min intervals. The use of medications and the diagnosis of diseases were collected at baseline examination by an internist.

Alcohol consumption was assessed using the Nordic Alcohol Consumption Inventory.[11] Leisure-time physical activity was assessed from a 12-month Leisure-Time Physical Activity Questionnaire.[9] The collection of blood specimens and the measurement of serum lipids and lipoproteins, insulin, plasma fibrinogen, and glucose have been described elsewhere.[10,11,12]

Outcomes

Every resident of Finland has a unique personal identifier (PID) that is used in registers. All deaths that occurred between the study entry (March, 1984 to December, 1989) and 31 December, 2000 were included. There were no losses to follow-up. Deaths were ascertained by linkage to the national causes of Death Register using the PIDs. Causes of deaths were coded according to the Ninth International Classification of Disease (ICD) codes and the Tenth ICD codes.

Data on non-fatal and fatal coronary events from the beginning of study to the end of 2000 were obtained by computer linkage to the national hospital discharge and death certificate registers. Diagnostic information was collected from hospitals and classified using identical diagnostic criteria. If a subject had multiple non-fatal coronary events during the follow-up, the first event after baseline was defined as an outcome event. Each suspected coronary event (ICD-9 codes 410–414 and ICD-10 codes I20–I25) was classified into (1) a definite acute myocardial infarction, (2) a probable acute myocardial infarction, (3) a typical acute chest pain episode of more than 20 min indicating CHD, (4) an ischaemic cardiac arrest with successful resuscitation, (5) no acute coronary event or (6) an unclassifiable fatal

Table 1 Characteristics of the study population according to baseline health status

	Mean (SD)		p for statistical significance
	Healthy men (n = 1294)	Unhealthy men (n = 1057)	
Characteristics			
Age (years)	51.8 (5.4)	54.2 (4.2)	<0.001
Body mass index (kg/m^2)	26.6 (3.4)	27.1 (3.6)	0.001
Waist-to-hip ratio	0.94 (0.06)	0.96 (0.06)	<0.001
Smokers (%)	31.4	32.6	0.537
Cigarette smoking (pack-years)[a]	7.95 (16.0)	8.98 (17.1)	0.138
Alcohol consumption (g/week)	70.9 (109.4)	79.8 (139.3)	0.255
Physical activity (kcal/week)[b]	982.2 (1151.1)	972.3 (1306.4)	0.848
Mean intensity of physical activity, METs[b]	5.98 (1.80)	5.53 (1.75)	<0.001
Serum total cholesterol (mmol/l)	5.86 (1.02)	5.96 (1.12)	0.024
Serum LDL[c] cholesterol (mmol/l)	4.01 (0.97)	4.09 (1.06)	0.064
Serum HDL[c] cholesterol (mmol/l)	1.31 (0.30)	1.27 (0.31)	0.001
Serum triglycerides (mmol/l)	1.23 (0.76)	1.36 (0.88)	<0.001
Systolic blood pressure (mmHg)	133.8 (16.1)	134.4 (17.8)	0.392
Diastolic blood pressure (mmHg)	88.8 (10.4)	88.9 (10.6)	0.803
Blood glucose (mmol/l)	4.70 (0.89)	4.85 (1.45)	0.004
Serum insulin (mU/l)	10.8 (5.6)	12.6 (8.2)	<0.001
Diagnosed diseases			
Coronary heart disease (%)		23.8	
History of myocardial infarction (%)		7.4	
Family history of coronary heart disease (%)	44.8	54.9	<0.001
History of hypertension (%)	24.0	38.0	<0.001
Family history of hypertension (%)	45.1	50.1	0.01
Cardiac insufficiency (%)		6.6	
Cardiomyopathy (%)		2.1	
Cerebrovascular disease (%)		2.4	
Claudication (%)		3.8	
Arrhythmias (%)[d]		15.8	
Any pulmonary disease[e] (%)		12.4	
Chronic bronchitis (%)		7.0	
Bronchial asthma (%)		3.3	
Pulmonary tuberculosis (%)		3.8	
Cancer (%)		1.6	
Diabetes (%)	4.6	7.6	0.001
Abnormal resting ECG findings (%)	7.3	13.3	<0.001
Coronary bybass surgery (%)		0.6	
Regular use of medications			
Anti-hypertensive medication (%)	10.4	34.3	<0.001
Medication for hypercholesterolaemia (%)	1.5	1.1	0.002
Any β-blockers (%)	7.8	29.1	<0.001
Aspirin (%)	5.2	9.1	<0.001
Nitrate (%)		11.6	
Exercise test variables			
Peak exercise oxygen uptake (ml/kg/min)	32.5 (7.5)	27.3 (7.6)	<0.001
Peak exercise oxygen uptake (l/min)	2.57 (5.89)	2.18 (6.23)	<0.001
Peak oxygen pulse (ml/beat)	16.4 (10.2)	15.6 (11.8)	0.08
Maximal heart rate (beats/min)	162 (21)	145 (27)	<0.001
Resting heart rate (beats/min)	62 (11)	62 (11)	0.926
Maximal systolic blood pressure (mmHg)	206.9 (25.9)	197.4 (30.1)	<0.001
Exercise-induced myocardial ischemia (%)[f]	6.7	10.5	0.001
Peak respiratory gas exchange ratio (VCO$_2$/VO$_2$)	1.12 (0.13)	1.06 (0.15)	<0.001
Percent predicted VO$_2$ (%)[g]	109.8	94.9	<0.001

[a] Pack-years denotes the lifelong exposure to smoking which was estimated as the product of years smoked and the number of tobacco products smoked daily at the time of examination.[10]

[b] Physical activity was assessed using a 12-month leisure-time history modified from the Minnesota Leisure Time Physical Activity Questionnaire to represent the 16 most common conditioning leisure-time physical activities of middle-aged Finnish men.[9]

[c] LDL denotes low-density lipoprotein and HDL denotes high-density lipoprotein.

[d] Most common arrhythmias were extrasystolic, regular or paroxysmal atrial fibrillation and supraventricular tachycardia.

[e] Men with a history of any pulmonary disease including bronchial asthma, chronic obstructive pulmonary disease or pulmonary tuberculosis.

[f] The criteria for myocardial ischaemia in electrocardiogram were horizontal or downsloping ST depression 1.0 mm at 80 ms after J point or any ST depression of more than 1.0 mm at 80 ms after J point.[8]

[g] Percent predicted VO$_2$ indicates the ratio of measured VO$_{2peak}$ and predicted VO$_{2peak}$.

Table 2 Clinical and exercise predictors of main outcomes in healthy and unhealthy men with pulmonary disease, cardiovascular disease or cancer at baseline

Risk factor	Overall death 174 events		Cardiovascular death 59 events		Coronary heart disease death 42 events	
	Relative risk[a] (95% CI)	p value	Relative risk[a] (95% CI)	p value	Relative risk[a] (95% CI)	p value
Healthy subjects (n=1294)						
Clinical variables						
Age (per 10 year increment)	1.60 (1.12–2.29)	0.009	2.46 (1.33–4.56)	0.004	2.43 (1.16–5.08)	0.018
Smoking (per 10 pack-years increment)	1.28 (1.20–1.35)	<0.001	1.34 (1.21–1.47)	<0.001	1.33 (1.18–1.49)	<0.001
Waist-to-hip ratio (per 0.06 increment)[b]	1.10 (0.91–1.33)	0.336	1.21 (0.87–1.70)	0.258	1.18 (0.79–1.77)	0.414
Hypertension[c]	1.47 (1.06–2.02)	0.019	2.79 (1.52–5.13)	0.001	2.30 (1.15–4.61)	0.018
Poor serum lipid profile[d]	1.04 (0.76–1.43)	0.791	1.23 (0.72–2.10)	0.443	1.30 (0.69–2.44)	0.415
Diabetes[e]	1.51 (0.88–2.60)	0.135	2.89 (1.33–6.30)	0.007	3.96 (1.73–9.03)	0.001
Family history of coronary disease	0.90 (0.66–1.23)	0.522	1.15 (0.68–1.94)	0.601	1.06 (0.57–1.98)	0.853
Regular use of aspirin, anti-hypertensive or lipid drugs	1.15 (0.76–1.73)	0.505	1.28 (0.65–2.49)	0.476	1.05 (0.47–2.36)	0.906
Exercise test variables						
Exercise capacity (per 3.5 ml/kg min increment)	0.80 (0.73–0.89)	<0.001	0.85 (0.72–1.00)	0.051	0.82 (0.66–0.99)	0.043
Exercise-induced ST-depression[f]	2.20 (1.32–3.68)	0.003	4.22 (2.05–8.71)	<0.001	6.17 (2.69–14.2)	<0.001
Low heart rate response[g]	0.98 (0.65–1.49)	0.941	0.78 (0.37–1.68)	0.533	1.25 (0.54–2.92)	0.603
Unhealthy subjects with CVD, pulmonary disease or cancer (n=1057)						
	251 events		145 events		111 events	
Clinical variables						
Age (per 10 year increment)	1.39 (0.96–2.00)	0.077	1.03 (0.65–1.63)	0.892	1.06 (0.63–1.77)	0.839
Smoking (per 10 pack-years increment)	1.20 (1.14–1.27)	<0.001	1.20 (1.11–1.30)	<0.001	1.24 (1.13–1.35)	<0.001
Waist-to-hip ratio (per 0.06 increment)[b]	0.97 (0.84–1.11)	0.641	0.84 (0.69–1.03)	0.098	0.85 (0.68–1.06)	0.163
Hypertension[c]	1.10 (0.84–1.42)	0.485	1.28 (0.90–1.82)	0.165	1.21 (0.81–1.80)	0.351
Poor serum lipid profile[d]	1.19 (0.91–1.55)	0.201	1.74 (1.21–2.51)	0.003	1.94 (1.27–2.97)	0.002
Diabetes[e]	1.33 (0.89–1.98)	0.156	1.58 (0.99–2.52)	0.053	1.72 (1.02–2.90)	0.043
Family history of coronary disease	1.31 (1.01–1.69)	0.041	1.39 (0.99–1.96)	0.056	1.73 (1.16–2.59)	0.008
Regular use of aspirin, anti-hypertensive or lipid drugs	0.99 (0.74–1.34)	0.998	1.23 (0.83–1.82)	0.300	1.34 (0.85–2.11)	0.208
Exercise test variables						
Exercise capacity (per 3.5 ml/kg min increment)	0.76 (0.70–0.82)	<0.001	0.71 (0.64–0.80)	<0.001	0.72 (0.63–0.82)	<0.001
Exercise-induced ST-depression[f]	1.31 (0.89–1.91)	0.167	1.62 (1.04–2.52)	0.003	1.59 (0.96–2.64)	0.073
Low heart rate response[g]	0.92 (0.67–1.27)	0.624	0.93 (0.60–1.44)	0.754	0.97 (0.59–1.60)	0.916

[a] Relative risks are derived from multivariate model adjusted for all other factors shown in Table.

[b] Relative risk is expressed as one standard deviation increment in the value, and waist-to-hip ratio is calculated as the ratio of the circumference of the waist to the hip.

[c] Hypertension was defined as systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg at rest.

[d] Poor serum lipid profile was defined as a ratio of serum total cholesterol to serum HDL cholesterol ⩾ 5.

[e] Diabetes was defined as fasting blood glucose ⩾ 6.1 mmol/l or a clinical diagnosis of diabetes with either dietary, oral or insulin treatment.

[f] The criteria for exercise-induced ST depression in electrocardiogram were horizontal or downsloping ST depression 1.0 mm at 80 ms after J point or any ST depression of more than 1.0 mm at 80 ms after J point.[8]

[g] Low heart rate response is defined as incapability to achieve 85% of the age-predicted target heart rate during exercise test.

case   (www.ktl.fi/publications/monica/manual/index.htm).[13] Acute coronary events that did not lead to death during the following 24-h were considered as a non-fatal event.

Statistical analysis

Differences in baseline characteristics were examined using the independent samples t test and the χ^2 test. Descriptive data are presented as mean and standard deviations for continuous data and percentages for categorical data. In Cox proportional hazards models, VO_{2peak} was entered into forced SPSS Cox proportional hazards' models by using VO_{2peak} as a continuous variable as well as categorised in quartiles. The continuous variables are presented first, followed by categorised data. The least 25% of men were defined as unfit, 25–75% of men were moderate fit and the remaining 25% as most fit. The cut-off values for VO_{2peak} among both healthy and unhealthy groups were based on the quartiles of VO_{2peak}. In these models, the reference group was the highest quartile (most fit group). Cox models were adjusted for age and examination year (1985–1989), and other risk factors, which were selected on the basis of their previously established role as a well-defined predictive factor on the basis of overall evidence and available data.[5]

The analyses were performed among men with high (unhealthy) and low (healthy) pre-test probability for the cardiovascular events. Analyses were repeated for participants stratified according to clinically relevant sub-groups. The fit of the proportional-hazards' models was examined by plotting the hazard functions in different categories of risk factors over time. Tests for statistical significance were two-sided. Statistical analyses were performed using the SPSS 11.5 for Windows (SPSS Inc., Chicago, Illinois). A p value less than 0.05 was considered statistically significant.

Results

Cardiorespiratory fitness and other characteristics

The mean of VO_{2peak} was 32.7 ml/kg/min (range 16.0–65.4 ml/kg/min) in healthy men, and 27.8 ml/kg/min (range 7.4–51.9 ml/kg/min) in unhealthy men. The measured VO_{2peak} was 109.8% and 94.9% of their predicted VO_{2peak} values in healthy and unhealthy men, respectively. The distributions of common baseline characteristics among healthy and unhealthy men are shown in Table 1.

In the study population, the correlation between VO_{2peak} and the mean intensity of conditioning physical activity was ($r = 0.32$, $p < 0.001$), whereas the relation between VO_{2peak} and the energy expenditure of conditioning physical activity was weaker ($r = 0.14$, $p < 0.001$). These correlations were slightly stronger in healthy men.

Follow-up events

A total of 425 deaths occurred during the median follow-up of 13.7 years (range 0.7–16.8 years) while half of these deaths ($n = 204$) were due to cardiovascular causes. Among 1294 healthy men at baseline, there were 174

deaths of which CVD ($n = 59$) was the leading cause. Among 1057 unhealthy men, there were 251 deaths of which 145 were due to CVD. A total of 323 non-fatal coronary events occurred during the follow-up. The numbers of fatal events as a first event was the highest among unfit.

Strongest risk predictors for non-fatal coronary events

The strongest risk predictors for non-fatal coronary events from the multivariable model were cardiorespiratory fitness ($p = 0.006$), the use of medications for CVDs ($p = 0.006$), poor lipid profile (ratio of serum total cholesterol to HDL cholesterol > 5) ($p = 0.01$), family history of CHD ($p = 0.02$), obesity ($p = 0.05$) and smoking ($p = 0.05$) in men with CVD whereas the independent predictors were smoking ($p = 0.0001$), diabetes ($p = 0.002$), poor lipid profile ($p = 0.009$), age ($p = 0.02$), hypertension ($p = 0.04$) and cardiorespiratory fitness ($p = 0.04$) in men without diagnosed CVD.

Cardiorespiratory fitness and outcomes

The multivariable-adjusted risk predictors for deaths among healthy and unhealthy men are presented in Table 2. Smoking and VO_{2peak} as a continuous variable represented the two strongest independent and consistent risk predictors for mortality. In addition to VO_{2peak}, ischaemic ST depression in ECG was a strong independent exercise test predictor for cardiac events.

In men with coronary heart disease, a VO_{2peak} increase of 3.5 ml/kg/min (1 METs) was related to 18% (RR = 0.82, 95% CI 0.75–0.89, $p < 0.0001$) and 32% (RR = 0.68, 95% CI 0.60–0.78, $p < 0.0001$) reduced age-adjusted risk for non-fatal and fatal cardiac events, respectively. After adjustment for other risk factors shown in Table 2, the respective risks were 0.87 (95% CI 0.78–0.96, $p = 0.017$) and 0.69 (95% CI 0.59–0.80, $p < 0.0001$). In men with other CVDs, pulmonary disease, diabetes, the use of medications for CVD, abnormal resting or exercise ECG changes or low HR response during exercise, 1 MET increase in VO_{2max} amounted to quite similar risk reductions as among men with coronary heart disease (data not shown).

There was no interaction of VO_{2peak} with respect to age, smoking, hypertension, hypercholesterolaemia, body weight, and the use of medication for high blood pressure or cholesterol. The increase in VO_{2peak} was related to decrease in CVD mortality in men without and those on medication such as the use of β-blockers, diuretics, calcium-channel antagonist or ACE-inhibitors. The relations were not markedly modulated by conventional risk factors as one MET increment in VO_{2peak} amounted to a decrease of an average of 17–29% in non-fatal and 28–51% in fatal cardiac events (Table 3). These associations remained significant after adjustment for other risk factors.

Cardiorespiratory fitness in various risk groups

The age-adjusted risks of main outcomes according to quartiles of VO_{2max} in healthy and unhealthy groups are presented in Fig. 1(a)–(c). Multivariable adjusted risks were similar in manner and magnitude for main outcomes showing a threshold between the least and the lowest and the next lowest group and CVD mortality in unhealthy men. Healthy men with a low VO_{2peak} (lowest quartile) had an increased risk of fatal (RR = 3.29, 95% CI 0.86–12.90, p = 0.060, p = 0.019 for linear trend across the quartiles) and non-fatal (RR = 2.16, 95% CI 1.12–4.18, p = 0.021, p = 0.010 for linear trend across the quartiles) coronary events after adjustment for many risk factors (age, alcohol consumption, smoking, diabetes, waist-to-hip ratio, fasting serum insulin, plasma fibrinogen, serum HDL and LDL cholesterol and triglycerides, systolic and diastolic blood pressure, the use of anti-hypertensive medication, aspirin or lipid lowering drugs and exercise-induced myocardial ischaemia). The respective risks among unhealthy men in the lowest quartile of VO_{2peak} were 5.84 (95% CI 2.51–13.62, p < 0.001, p < 0.001 for linear trend across the quartiles) and 1.85 (95% CI 1.09–3.05, p = 0.022, p = 0.028 for linear trend across the quartiles).

Unfit healthy subjects (<27.6 ml/kg/min) with ⩾ 2 risk factors had the highest risk of death as compared with most fit subjects (⩾ 37.1 ml/kg/min) but 1 ⩽ risk factors (Fig. 2(a)). The risk reduction seems to be linear between VO_{2peak} and total mortality among men with various combinations of these risk factors. The interaction between the number of risk factors and VO_{2peak} was statistically significant among healthy men. Unhealthy men with a low VO_{2peak} of <21.2 ml/kg/min in the presence of risk factors were at the highest risk (Fig. 2(b)).

Discussion

In a representative population of men, our study shows a dose-response relationship between directly measured cardiorespiratory fitness and CVD death among healthy men at baseline. This study demonstrates that a given 1 MET increment in the VO_{2peak} reduces the risk of non-fatal coronary events and coronary death by a constant proportion, regardless of coronary heart disease. However, a threshold was observed between very low and moderate levels of VO_{2peak} and non-fatal and fatal coronary events among those men with underlying cardiovascular or pulmonary disease or cancer.

In some previous studies, the overall risk reduction per 1 MET change in physical fitness has been about 10–20% in overall mortality.[6,14–16] Previous studies have shown that physical activity[1,2] and good cardiorespiratory fitness[3,4,6] reduces the risk of premature death among individuals with unfavourable risk profiles. In our study, the important finding is that VO_{2peak} provides incremental prognostic information on the risk related to

Table 3 Age adjusted risk reduction of cardiovascular events per 1 MET increment in VO_{2max} according to traditional risk predictors

Factor	Cohort	Coronary heart disease death (153 events)			Non-fatal acute coronary event (323 events)		
	N	Events	Relative risk (95% CI)	p value	Events	Relative risk (95% CI)	p value
Non-smokers	1608	75	0.66 (0.58–0.74)	<0.0001	200	0.77 (0.72–0.82)	<0.0001
Smokers[a]	753	78	0.68 (0.60–0.76)	<0.0001	132	0.82 (0.75–0.89)	<0.0001
Normal-weight (BMI <25 kg/m²)	738	36	0.67 (0.57–0.79)	<0.0001	75	0.83 (0.75–0.93)	0.001
Overweight (BMI 25–30 kg/m²)	1218	73	0.68 (0.60–0.76)	<0.0001	179	0.78 (0.72–0.88)	<0.0001
Obesity (BMI ⩾ 30 kg/m²)	405	44	0.58 (0.47–0.71)	<0.0001	78	0.71 (0.61–0.82)	<0.0001
Hypertension (no)	994	35	0.72 (0.61–0.85)	0.001	95	0.81 (0.73–0.89)	<0.0001
Hypertension (yes)[b]	1367	118	0.64 (0.58–0.71)	<0.0001	237	0.78 (0.72–0.83)	<0.0001
Serum LDL cholesterol <3.5 mmol/l	749	33	0.49 (0.40–0.60)	<0.0001	63	0.77 (0.68–0.88)	<0.0001
Serum LDL cholesterol ⩾ 3.5 mmol/l	1612	120	0.69 (0.63–0.76)	<0.0001	269	0.78 (0.74–0.83)	<0.0001

[a] A subject was defined as a smoker if he had ever regularly smoked cigarettes, cigars, or pipe.
[b] Hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg at rest.
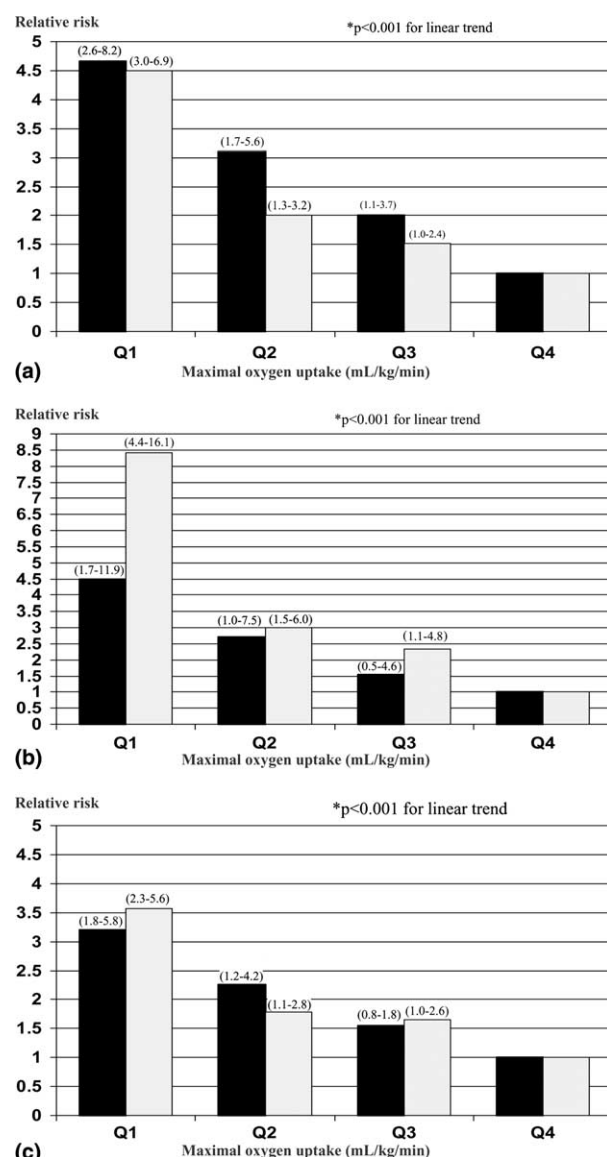
Fig. 1 The age-adjusted risk of overall mortality (a), fatal (b) and non-fatal (c) cardiac events according to the level of VO$_{2peak}$ in quartiles (*Q*). The black bars represent healthy men without underlying disease and the open bars represents those unhealthy men with diagnosed disease at baseline. Reference group was *Q*4 for both groups. The cut-offs were in healthy groups: *Q*1 < 27.6, *Q*2 = 27.6−32.2, *Q*3 = 32.3−37.1, *Q*3 > 37.1 ml/kg/min, and in unhealthy groups: *Q*1 < 21.2, *Q*2 = 21.2−27.2, *Q*3 = 27.3−32.4, *Q*4 > 32.4 ml/kg/min. **p* value for linear trend across the quartiles refers to both healthy and unhealthy men.

Fig. 2 (a) The multivariable-adjusted relative risks of overall death up to 15.8 years of follow-up in 1294 healthy men classified according to VO$_{2peak}$ and the combination of risk factors. Men were combined in two groups according to the number of the conventional risk factors (smoking, hypertension and overweight). Reference group included most fit (>37.1 ml/kg/min) subjects with ≤ 1 risk factor. The risk ratios were adjusted for age, alcohol consumption, diabetes, waist-to-hip ratio, fasting serum insulin, plasma fibrinogen, serum HDL and LDL cholesterol and triglycerides, the use of anti-hypertensive medication (β-blockers, diuretics, calcium-channel antagonist, ACE-inhibitors), lipid lowering drugs or aspirin and exercise-induced myocardial ischaemia. **p*, the statistical significance for the interaction between the number of risk factors and VO$_{2peak}$. (b) The multivariable-adjusted relative risks of overall death up to 15.8 years of follow-up in 1057 unhealthy men classified according to VO$_{2peak}$ and the combination of risk factors. Men were combined in two risk factor groups according to the number of the conventional risk factors (smoking, hypertension and being overweight). Reference group included most fit (>32.4 ml/kg/min) subjects with ≤ 1 risk factor. The risk ratios were adjusted for age, alcohol consumption, diabetes, waist-to-hip ratio, fasting serum insulin, plasma fibrinogen, serum HDL and LDL cholesterol and triglycerides, the use of anti-hypertensive medication (β-blockers, diuretics, calcium-channel antagonist, ACE-inhibitors), lipid lowering drugs or aspirin and exercise-induced myocardial ischaemia. **p*, the statistical significance for the interaction between the number of risk factors and VO$_{2peak}$.

traditional CVD risk predictors such as smoking, hypertension, being overweight, and lipid profile. In previous studies, it is proposed that being fit reduces the risks of obesity.[4,17] It is possible that men may benefit from higher physical fitness independent of changes in other major risk factors.

It has been reported that the use of medications for CVDs did not substantially attenuate the prognostic power of exercise capacity in clinical population.[6] In our study, good cardiorespiratory fitness improves the prognosis in a population-based sample of men with or without the regular use of medications for CVD. Secondly,
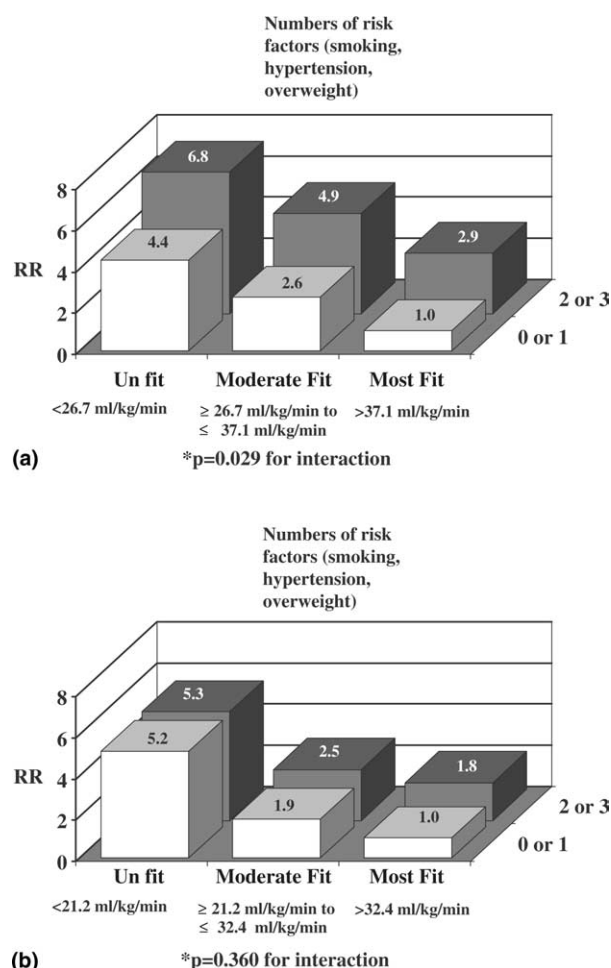
VO$_{2peak}$ was a strong predictor of CVD events in a number of common clinical subgroups including normal or abnormal ECG findings. Thus, low cardiorespiratory fitness was associated with an increased risk of non-fatal CVD outcomes and death not only in the presence of common

CVD risk factors and any CVD medications but also without risk factors.

Recent studies have shown that common CVD risk factors including overweight[18,19] hypertension,[20,21] lipids[21,22] and smoking[20,21,23] cause endothelial dysfunction in conditions related to pre-clinical atherosclerosis. On the other hand, physical exercise may increase the capacity of endothelial cells to evoke vasodilation in early stages of atherosclerosis.[24] The protective effect of cardiovascular fitness may be partly explained through physical exercise that has a favourable effect on lipid profile and fat metabolism,[25,26] blood pressure,[25,27] incidence of non-insulin-dependent diabetes,[28] insulin sensitivity[29,30] and blood coagulation[31,32] and inflammation.[29] Physical exercise may improve cardiorespiratory capacity by increasing left ventricle (LF) function and oxygen utilisation, cardiac output, the formation of collateral vessels, the extraction of oxygen from blood and the threshold for ventricular arrhythmias.[6,33] These protective mechanisms is supported by a study showing the effect of physical activity on LV function and the regression of LV mass.[34]

Genetic contributions to fitness are important but probably account for less of the variation observed in fitness than is due to environmental factors, principally physical activity. Current estimates place that genetic contribution to aerobic power at approximately 25—40%.[7] Furthermore, it is well established that exercise training can make substantial improvements in aerobic power, typically 15—20% in adult men and women. Changes in exercise capacity induced by endurance training and adjusted for pre-training values were also characterised by a significant familial resemblance.

The strengths of our study include a sample of men with or without underlying diseases in a randomly selected population. This study represents a sample of middle-aged male population from eastern Finland, an area known for its high prevalence and incidence of atherosclerotic vascular diseases.[35,36] Secondly, the participation rate was high and there were no losses during follow-up. Thirdly, we have reliable data on various causes of diseases because disease-specific major outcomes and non-fatal cardiac events were prospectively ascertained by Finnish National Discharge and Death Registry using PID codes, supplemented with reliable data on health status, exercise test variables and risk factors. We could show the role of VO_{2peak} on all major CVD outcomes and were able to minimise greatly the confounding of other risk factors. An additional strength of this study is the direct measurement of VO_{2peak} improving the accuracy of determination of exercise capacity. Furthermore, it should be taken into account that an exercise capacity is higher in subjects from population-based samples than in subjects from clinical populations or cardiac rehabilitation programs showing a clear difference in exercise capacity.[5,6,8,37—44] Finally, one measurement for VO_{2peak} cannot rule out some variation with time in VO_{2peak} during the follow-up, however if anything, this can underestimate the observed associations. Our results are based on an ethnically and genetically homogeneous population, and the same gender that may limit generalisation of our results. Our study emphasises the importance of

the role of VO_{2peak} in white middle-aged men who can undergo standardised cycle exercise test, but whether the same association exists in very old men, women and other races is not known. However, indirectly defined physical fitness has been shown to be predictive of mortality in the elderly[15] and females.[35,36] There is no evidence that the predictive value of physical fitness would be less important among female subjects.

Smoking and VO_{2peak} were the two strongest independent predictors for total mortality, even stronger than many other traditional clinical or exercise risk predictors. Although smoking was a strong risk factor for death, high VO_{2peak} remained protective for CVDs among smokers. It is reported that VO_{2peak}, smoking and the use of medication were three strongest predictors of cardiac death among rehabilitation patients.[40,43] In our current study, 1 MET increment in VO_{2peak} was associated with a greater risk reduction in fatal than in non-fatal coronary events, and physical fitness was inversely related to mortality among men with various combinations of risk factors. It is possible that high VO_{2peak} may be a protective factor against fatal events by causing minor myocardial damage due to increased oxygen supply. However, there is no data on the corresponding risk reduction for non-fatal and fatal coronary events in the same cohort with various clinically relevant subgroups.

There was a threshold at the level of 21.2 ml/kg/min in VO_{2peak} among unhealthy men at baseline and an increment in VO_{2peak} amounted to a strong risk reduction for CVD. This indicates that men with both very low exercise capacity and suspected cardiovascular disease in the presence of any risk factors are the target population for further evaluation of the severity of the cardiac disease by using more invasive methods such as coronary angiography. In a previous study, subjects with decreased VO_{2peak} (<7 METs) with other risk factors seemed to benefit most from the exercise program.[40] However, the evaluation of the stage of the disease is of vital importance as advanced three vessel coronary disease or left main disease may increase the risk of sudden cardiac death during exercise.[7] In addition, low exercise capacity may provide a useful diagnostic and prognostic tool for clinicians when exercise ECG testing has been considered lacking both in sensitivity and specificity in certain populations.[44] It would be important to reduce modifiable risk factor levels (smoking cessation, reduction in blood pressure, serum LDL cholesterol and body weight and avoid sedentary life-style and type II diabetes) and maintain at least moderate fitness for reducing the risk of coronary artery events. This prospective population study provides evidence that a low VO_{2peak} is associated with an increased risk of cardiovascular events, although only a randomised controlled trial of thousands of subjects could prove a causality. There are no controlled randomised trials showing that exercise training decreases the risk of death in general population.

Exercise testing with the definition of VO_{2peak} should be used more widely not only as a powerful tool for detecting those with decreased exercise capacity but also as a well-defined prognostic measure. It is apparent that VO_{2peak} declines with age, but with a physically active life-

style, one can maintain the VO_{2peak} level of an younger adult up through the years so that the risk of premature CVD remains unchanged with increasing age. In addition to cardiorespiratory fitness, however, the underlying health and risk factor status should be taken into account when prescribing individualised health prescriptions to avoid sedentary life style, and finding high risk patients with the greatest need for preventive measures.

Acknowledgement

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