Original scientific paper

European Journal of Preventive Cardiology

European Journal of Preventive Cardiology
0(00) 1–8

DOI: 10.1177/2047487316655466
ejpc.sagepub.com

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Low aerobic capacity in middle-aged men associated with increased mortality rates during 45 years of follow-up

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Abstract

Background: Low aerobic capacity has been associated with increased mortality in short-term studies. The aim of this study was to evaluate the predictive power of aerobic capacity for mortality in middle-aged men during 45-years of follow-up.

Design: The study design was a population-based prospective cohort study.

Methods: A representative sample from Gothenburg of men born in 1913 was followed from 50–99 years of age, with periodic medical examinations and data from the National Hospital Discharge and Cause of Death registers. At 54 years of age, 792 men performed an ergometer exercise test, with 656 (83%) performing the maximum exercise test.

Results: In Cox regression analysis, low predicted peak oxygen uptake ($VO_{2_{max}}$), smoking, high serum cholesterol and high mean arterial blood pressure at rest were significantly associated with mortality. In multivariable analysis, an association was found between predicted $VO_{2_{max}}$ tertiles and mortality, independent of established risk factors. Hazard ratios were 0.79 (95% confidence interval (CI) 0.71–0.89; $p < 0.0001$) for predicted $VO_{2_{max}}$, 1.01 (1.002–1.02; $p < 0.01$) for mean arterial blood pressure, 1.13 (1.04–1.22; $p < 0.005$) for cholesterol, and 1.58 (1.34–1.85; $p < 0.0001$) for smoking. The variable impact (Wald's χ^2) of predicted $VO_{2_{max}}$ tertiles (15.3) on mortality was secondary only to smoking (31.4). The risk associated with low predicted $VO_{2_{max}}$ was evident throughout four decades of follow-up.

Conclusion: In this representative population sample of middle-aged men, low aerobic capacity was associated with increased mortality rates, independent of traditional risk factors, including smoking, blood pressure and serum cholesterol, during more than 40 years of follow-up.

Keywords

Exercise testing, epidemiology, mortality, aerobic capacity, exercise capacity

Received 9 March 2016; accepted 30 May 2016

Introduction

Ischaemic heart disease is the most common cause of death worldwide.[1] Exercise testing has been available since the middle of the 20th century,[2–4] and in clinical practice it has mainly been used in the diagnosis of ischaemic heart disease. In addition, previous studies suggested that exercise data other than the electrocardiogram (ECG) could also be useful for prognostic purposes.[5–11] Of these data, aerobic capacity is of particular interest as it has been shown to be of prognostic importance for a wide range of conditions.[12–14]

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In a nine-year follow-up of the present study population, cardiovascular risk factors, including smoking, hypercholesterolaemia and high systolic blood pressure, were shown to increase the risk of myocardial infarction and death.[15] Adding information from exercise tests improved risk prediction compared with risk prediction scores (i.e. Systematic COronary Risk Evaluation (SCORE)[5,16] and Framingham),[17,18] which are based on classical risk factors. Previous studies have focused on maximum exercise testing and the risk of death within 10–15 years,[7] but only one study on maximum exercise testing had a prolonged follow-up of 26 years.[5] The predictive ability of aerobic capacity at maximum exercise stress test during more than 40 years of follow-up has not yet been studied.

The Study of Men Born in 1913 is a study of a population sample from Gothenburg followed for up to 50 years. The objective of the present study was to investigate the predictive capacity of a maximum exercise ergometer test in addition to established risk factors of cardiovascular disease for all-cause mortality over 45 years of follow-up.

Methods

Study population

The study sample has been described previously.[19] In brief, at the end of 1962, all men born in 1913 on dates evenly divisible by three (i.e. day 3, 6, 9, etc. of each month) and living in the city of Gothenburg, Sweden were invited to participate in the study. Of the sample of 973 men, 855 (88%) agreed to participate and were examined in 1963.[20] In 1967, at 54 years of age, 803 of the original sample were re-examined. Of the 52 non-respondents, 25 declined examination, 18 had died, and nine could not be traced. A further 11 men were excluded from the exercise testing: eight because of locomotor disturbances (neurological and orthopaedic causes), two because of previous myocardial infarction, and one for technical reasons. Finally, 792 men were available for an exercise ergometer test. Informed consent was obtained from all participants and the study was performed according to the Declaration of Helsinki. Follow-up for the present study was approved by the Regional Ethics Review Board, Uppsala (no. 2011/304).

Clinical examination and exercise testing

A thorough clinical examination, including medical history and physical examination, was performed before the exercise test (see Supplementary Material, Methods). Predetermined rules were followed to exclude participants from the test and to decide whether or not a maximum workload could be applied after a submaximal load.[19] In brief, ECG signs of acute cardiac conditions excluded men from exercise testing. For safety reasons, men with significant known heart disease were subject only to submaximal testing. In addition, chest pain, significant ECG changes, arrhythmia and systolic blood pressure >300 mm Hg, or severe airway obstruction during submaximal testing, excluded participants from a maximum exercise test.

The maximal exercise test followed the general principles described by Åstrand (1956)[2] and Åstrand and Rodahl[21] with one or several maximal workloads well above the lowest load estimated for reaching maximal values and with a total working time of 4–6 min. The maximal exercise test was interrupted due to general fatigue (including dyspnoea) in 618 subjects; to pain in muscles or joints in 35 cases; to chest pain in four cases and to ECG changes during exercise in five cases (some persons may have had more than one reason to stop). The exercise study protocol allowed us to use heart rate at a 'steady state' at a submaximal workload and recorded individual maximal heart rate for calculating maximal oxygen uptake. We used an internally validated formula from a subsample of the present material, where maximal oxygen uptake was determined during ergospirometry.[22] See Supplementary Material, Methods for details on exercise testing, function for estimating predicted peak oxygen uptake ($VO_{2_{max}}$),[22] definitions and assessment of leisure time physical activity.

Follow-up of clinical endpoints

Mortality data were obtained from baseline until 31 December 2012 from the National Cause of Death Registry, and included dates and cause of deaths. The latter was coded according to the International Classification of Diseases (ICD), versions 8–10. The primary outcome in this study was all-cause mortality, and the secondary endpoint of interest was cardiovascular mortality.

Statistical analyses

Statistical analyses were performed using SAS software (version 9.3; SAS Institute, Cary, North Carolina, USA). For the variables used in the primary analysis of this study 0.09% of data were missing, all related to smoking ($n = 3$). Leisure time physical activity data was missing in 33 participants. Predicted $VO_{2_{max}}$ was analysed according to tertiles to simplify interpretation. Simple differences between groups were tested with analysis of variance for continuous variables, and the chi-square test for discrete variables. The effect of

predicted VO_{2max} on survival was analysed using proportional hazards regression, to determine hazard ratios (HRs) and 95% confidence intervals (CIs) for exposure variables and outcome. In addition, the analysis provided Wald's χ^2, which may be used as a measure of the impact of the exposure variable on outcome.

Proportional hazards were investigated with the SAS life test procedure, which produced hazard rates for the three tertile groups. As shown in the Supplementary Material, Figure 1, group hazard rates were approximately proportional. In the proportional hazards regression analysis, the effect of predicted VO_{2max} was adjusted for the risk factors smoking habits, mean arterial blood pressure, serum cholesterol, as well as for body height, which was found to be a significant variance reducer (i.e. making the study population more homogenous). In addition, leisure time physical activity was added to the model above in an explanatory analysis.

All tests were two-tailed. Because of multiple testing (35 tests), a modified Bonferroni adjustment of the significant p-level was performed ($0.05/\sqrt{35}$), resulting in $p < 0.005$. However, p-values of <0.05 are presented in Tables 1–3 and all p-values are presented in Table 4.

Results

Characteristics of the study population

Of the 792 men eligible for exercise testing, 766 (97%) achieved 49 W (300 kpm/min), 753 (95%) achieved 98 W (600 kpm/min), and a maximal work was performed by 656 subjects (83%). As shown in Table 1, there were no significant differences between the predicted VO_{2max} tertiles in the 656 men who performed a maximum exercise test regarding blood pressure, serum cholesterol, and smoking habits. However, weight and body mass index increased by tertile. As evident in Table 1, only a few subjects were taking any kind of cardiovascular medication and none was taking beta-receptor blockers or digitalis. The vast majority of the study population had died by the end of follow-up. Baseline characteristics of patients performing submaximum exercise test compared with maximum exercise test are available in the Supplementary Material, Table 1.

Table 1. Characteristics of the 54-year-old men performing a maximal exercise test ($n = 656$).

	Predicted VO_{2max}			
	Tertile 1 ($n = 216$) Mean (SD) or %	Tertile 2 ($n = 223$) Mean (SD) or %	Tertile 3 ($n = 217$) Mean (SD) or %	p for trend
Blood pressure, mm Hg				
Systolic	141.7 (19.9)	142.4 (18.4)	141.6 (18.5)	n.s.
Diastolic	88.9 (12.3)	89.6 (10.8)	89.8 (10.6)	n.s.
Mean arterial	106.5 (13.3)	107.2 (11.8)	107.0 (11.7)	n.s.
Serum cholesterol, mmol/l	6.4 (1.10)	6.4 (1.00)	6.3 (1.01)	n.s.
Current smokers, %	59.5	55.2	49.3	<0.05
Height, centimetres	173.0 (5.9)	174.8 (5.3)	177.7 (5.5)	<0.0001
Weight, kilograms	70.0 (9.2)	76.4 (8.3)	83.7 (10.2)	<0.0001
Body mass index, kg/m^2	23.4 (2.87)	25.0 (2.66)	26.5 (2.98)	<0.0001
Medication				
Digitalis preparations, %	0	0	0	n.s
Other heart active drugs, %	0.9	0.5	0.5	n.s.
Antihypertensive drugs, %	1.9	0.9	0.9	n.s.
Mean follow-up, years	25.0 (9.6)	25.6 (9.7)	27.5 (10.0)	<0.01
All-cause mortality, %	96.3	98.7	95.9	n.s.
Leisure time physical activity level, %				<0.05
Sedentary	18.0	16.7	13.5	
Some light physical activity	58.5	54.9	55.3	
Regular, moderate physical activity	23.5	28.4	30.8	
Regular, hard training	0	0	0.5	

SD: standard deviation; VO_{2max}: peak oxygen uptake; n.s.: not significant.

Table 2. Exercise test data of 54-year-old men performing a maximal exercise test ($n = 656$).

	Predicted VO_{2max}			
	Tertile 1 Mean (SD) or %	Tertile 2 Mean (SD) or %	Tertile 3 Mean (SD) or %	p for trend
Predicted VO_{2max}, l/min	2.00 (0.12)	2.26 (0.06)	2.56 (0.17)	<0.01
Maximum workload, watt	328 (22)	376 (17)	432 (36)	<0.0001
Heart rate, beats/min				–
At rest	69.3 (13.1)	65.9 (10.5)	63.5 (10.5)	<0.0001
At maximum workload	170.9 (13.3)	171.2 (12.7)	172.8 (12.2)	n.s
At 4 min of rest after work	102.6 (13.2)	100.1 (11.7)	97.5 (11.5)	<0.0001
Heart rate reserve (rest to max)	101.6 (16.7)	105.2 (14.2)	109.4 (14.3)	<0.0001
Heart rate recovery (max to 4 min rest after work)	68.4 (11.6)	71.1 (10.4)	75.3 (11.1)	<0.0001
Respiratory rate/min at max workload	34.0 (7.9)	34.9 (7.7)	35.4 (7.7)	n.s.
Systolic blood pressure, mm Hg				
At rest	144.1 (17.9)	141.1 (18.0)	141.0 (15.7)	n.s.
At maximum work load	207.6 (25.3)	211.1 (23.7)	217.5 (23.7)	<0.0001
At 5 min of rest after work	142.5 (17.3)	143.2 (19.0)	143.2 (17.9)	n.s.
Diastolic blood pressure, mm Hg				
At rest	92.5 (10.7)	92.4 (10.5)	91.4 (8.6)	n.s.
At maximum work load	99.6 (11.6)	97.2 (12.4)	97.5 (11.7)	n.s.
At 5 min of rest after work	87.3 (9.7)	84.2 (10.3)	84.4 (8.9)	<0.005
Perceived exertion at maximum workload, Borg scale	17.7 (1.5)	17.7 (1.5)	17.8 (1.5)	n.s.

SD: standard deviation; VO_{2max}: peak oxygen uptake; n.s.: not significant.

Table 3. Proportional hazards regression analysis of tertiles of predicted peak oxygen uptake (VO_{2max}) on death from all causes ($n = 653$) and other potential risk variables.

	Estimate (SD)	Wald's χ^2	HR	95% CI	p
Predicted VO_{2max} tertile	0.23 (0.06)	15.3	0.79	0.71–0.89	<0.0001
Body height, cm	0.01 (0.005)	7.9	1.01	1.004–1.02	0.005
Mean arterial blood pressure, mm Hg	0.01 (0.004)	6.8	1.01	1.002–1.02	<0.01
Smoking habits, score	0.45 (0.08)	31.4	1.58	1.34–1.85	<0.0001
Serum cholesterol, mmol/l	0.12 (0.04)	9.3	1.13	1.04–1.22	<0.005

CI: confidence interval; HR: hazard ratio; SD: standard deviation.

Exercise test variables

Maximum workload, heart rate recovery, heart rate reserve and systolic blood pressure at maximum workload increased by predicted VO_{2max} tertiles, whereas the heart rate at maximal work load did not change (Table 2). In contrast, heart rate at rest and 4 min after work, and diastolic blood pressure 5 min after work decreased by predicted VO_{2max} tertiles. Predicted VO_{2max} was also significant when analysed as a continuous variable (Supplementary Material, Table 2).

Hazard rates

Supplementary Material, Figure 1 shows the hazard rates for death from all causes in the three predicted VO_{2max} tertile groups, as crude data (symbols) and splined data. The fit between crude data and splined data was excellent ($r^2 = 0.77$). As shown by the splined data, the HR between the three groups was approximately proportional (HR 0.87, $p < 0.005$), thereby allowing proportional hazards regression analysis. It is also obvious that the association of predicted VO_{2max} with death showed a lifelong effect.

Table 4. Proportional hazards regression of predicted peak oxygen uptake (VO_{2max}) tertiles and hazard ratios for death from cardiovascular and non-cardiovascular diseases ($n = 635$).

	n	Hazard ratio (95% CI)	*p*
Death from			
Cardiovascular diseases	313	0.88 (0.76–1.00)	0.06
Myocardial infarction	185	0.92 (0.77–1.10)	0.36
Stroke	72	0.77 (0.58–1.04)	0.08
Other cardiovascular diseases	56	0.92 (0.66–1.28)	0.63
Non-cardiovascular diseases	322	0.87 (0.76–0.99)	0.03
Infections	11	0.96 (0.45–2.04)	0.91
Malignant diseases	149	0.90 (0.74–1.10)	0.29
Benign tumours	7	0.68 (0.28–1.69)	0.41
Endocrine disorders	10	0.80 (0.36–1.77)	0.57
Psychiatric disease	22	0.74 (0.44–1.25)	0.26
Neurologic disease	14	0.52 (0.26–1.03)	0.06
Respiratory disease	41	0.64 (0.44–0.94)	0.02
Gastrointestinal disease	9	2.11 (0.86–5.22)	0.10
Urinary tract disease	8	0.72 (0.30–1.70)	0.45
Dermatologic disease	1	–	1.00
Musculoskeletal disease	3	0.90 (0.23–3.62)	0.89
Trauma	30	0.94 (0.60–1.46)	0.77
Other diseases	17	1.00 (0.55–1.82)	0.99

CI: confidence interval.

Proportional hazards regression

The result of proportional hazards regression is shown in Table 3. Apart from predicted VO_{2max}, the model included body height (confounder), mean arterial blood pressure, smoking habit, and total serum cholesterol. The effect of predicted VO_{2max} tertiles on mortality was highly significant (HR 0.79, 95% CI 0.71–0.89; $p < 0.0001$). The variable impact (15.3) was secondary only to that of smoking (30.4). Leisure time physical activity was not significant, when included in the model above ($p = 0.64$). The relation between VO_{2max} tertiles and leisure time physical activity is shown in Supplementary Material, Table 3.

Cumulative mortality

The cumulative mortality from all causes is shown in Figure 1. Tertile 1 had the highest cumulative mortality rate, followed by tertile 2 and tertile 3 ($p < 0.0001$). Mortality rates from cardiovascular as well as non-cardiovascular causes are shown in Table 4. According to expectations, mortality from cardiovascular causes would be associated with predicted VO_{2max} tertiles. However, mortality from cardiovascular causes in this sample was not significantly associated with predicted VO_{2max} tertiles. In addition, mortality was not significantly associated with any other causes according to ICD chapter, even though most of these causes had HR < 1.00. The results indicate that all chapter level causes of death were negatively associated with predicted VO_{2max}, except gastrointestinal disorders, with HR > 1.00.

Discussion

During 45 years of follow-up, low aerobic capacity expressed as predicted VO_{2max}, was associated with higher all-cause mortality in this cohort of middle-aged men, independent of established cardiovascular risk factors. To date, no other population-based sample with such a long follow-up time has been reported. The association between exercise capacity and all-cause mortality was graded, with the strongest risk in the tertile with the lowest maximum aerobic capacity. This graded risk has also been observed in other studies, including the Finnish population-based study by Laukkanen et al.,[16] a sample of Norwegian middle-aged employees with a follow-up of 16 years by Sandvik et al.,[23] and the 26-year follow-up of civil servants by Eriksen et al.[5] These and other studies of submaximal stress tests with shorter follow-up time, reported in the meta-analysis by Kodama et al.,[7] showed results consistent with our findings.

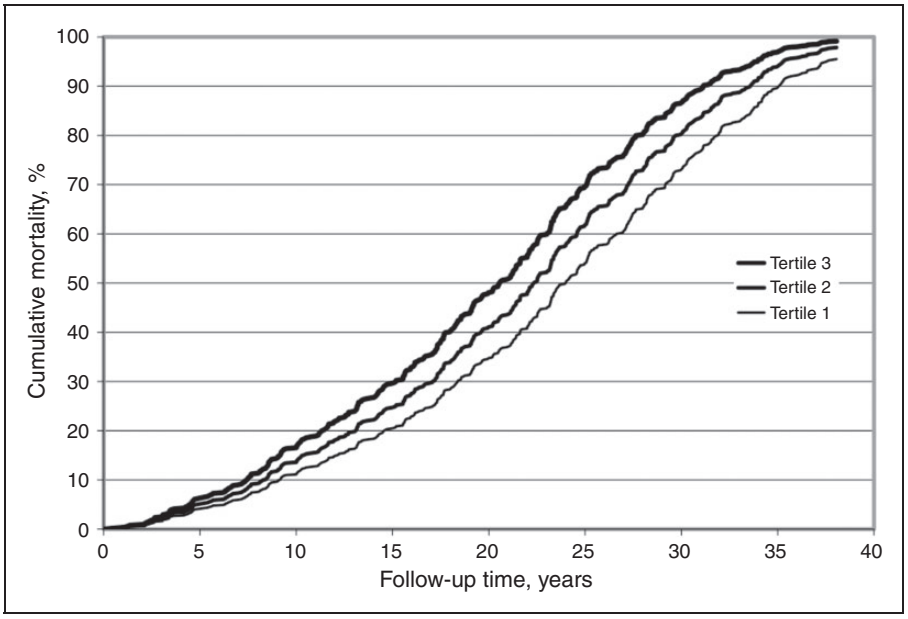

Figure 1. Cumulative mortality from all causes in relation to the three predicted peak oxygen uptake ($VO_{2_{max}}$) tertile groups.

In the present study, men were tested at 54 years and followed to 99 years. In a large hospital-based dataset, Berry et al. studied the predictive power of physical fitness of men and women at 45, 55, and 65 years of age.[24] In all age groups, a higher degree of fitness was associated with lower mortality. Furthermore, like the current study, adding fitness to conventional risk factors increased the precision of risk prediction of mortality. Findings from the current study and the study of Berry et al., suggest that exercise testing may enhance mortality risk prediction in middle-aged subjects aged 45–65 years.

Cardiovascular fitness has been described as an objective marker of physical activity, even though the relationship is usually rather weak.[25,26] Aerobic capacity is dependent both on central limitations, i.e. pulmonary diffusion, cardiac output, blood volume and blood flow, and on peripheral limitations (tissue extraction of oxygen).[27] The central limitations are the most important, and cardiac output may explain most of the cardiorespiratory fitness measured as $VO_{2_{max}}$.[27,28] Although the absolute aerobic capacity achieved may differ between different protocols,[29,30] the categorization of the individual's relative fitness compared with other men in our sample should be appropriate. The model of the current exercise test is still widely used in exercise physiology and sports medicine and as the basis for prediction of maximal $VO_{2_{max}}$.[31]

There are several pathways that could contribute to a positive effect of physical activity and better cardiovascular fitness on mortality. Physical activity has been shown to have positive effects on several cardiovascular risk factors including blood pressure,[32] insulin resistance,[33] lipid levels[34] and haemostasis,[35] coagulation and fibrinolysis.[36] There is of course an interaction between these risk factors, but the fact that aerobic capacity adds risk information of about 40% above that of single risk factors is consistent with exercise reducing risk through multiple pathways.[37]

We did not find any significant association between cardiovascular mortality and aerobic capacity; HR 0.88 (95% CI 0.76–1.00), as might have been expected. This might be an effect of power. Aerobic capacity affects mortality for several conditions including kidney disease,[14] liver disease[13] and lung cancer.[38] This, and the fact that most causes of death in our study had a HR below one (Table 4), suggests that cardiovascular fitness might be an advantage in most illnesses that can lead to death, and thus a benefit for general health and not only for cardiovascular health.

The current study has several strengths. First, the study had a prospective design. Second, the study consisted of a systematic sample of a normal population. Third, the prediction of $VO_{2_{max}}$ was based on a subsample of the same population and the maximal heart rate was determined in each individual. Furthermore, only Caucasian men of one age group were investigated, with reduced heterogeneity within the sample which made statistical correction for age and sex redundant. Finally, the study had an extremely long follow-up of 45 years. This follow-up length is unique. It is inevitable that risk factors such as hypertension and smoking and/or medication will change over this long time period, but the purpose of the present study was to assess long-term risk in middle-aged men on the basis

on the exercise test and clinical data available at that point in time. A limitation in the present study is the sample size, and therefore analyses on cause-specific mortality must be interpreted with caution.

In conclusion, a low exercise capacity during a maximum exercise ergometer test in middle-aged men predicted increased mortality risk over more than four decades, adjusted for traditional risk factors. The effect of exercise capacity on mortality was a strong predictor in our population, second only to smoking.

Author contribution

PL, CUP, LW, GG, KS, P-OH contributed to the conception or design of the work. GG and LW acquisitioned the data in 1967 and KS and P-OH acquisitioned follow-up data. PL drafted the manuscript. All authors contributed to analyses, interpretation of data, critically revised the manuscript, gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Acknowledgments

Part of this work was presented at the European Society of Cardiology (ESC) Congress 2015. Mattias Aurell, the late Jan Bjure and Barbro Ekström-Jodal performed the exercise tests together with coauthors GG and LW. The authors wish to thank participating men born in 1913.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: PL is an employee of AstraZeneca. The other authors have no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the insurance company Förenade Liv.

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