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SHORT REPORTS

Cardiorespiratory fitness and risk of dementia: a prospective population-based cohort study

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Abstract

Dementia is considered to be one of the major public health problems in light of the ageing population. Little is known about directly measured cardiorespiratory fitness as measured by maximal oxygen uptake and the risk of dementia. Our aim was to examine the relationship of cardiorespiratory fitness, as indicated by maximal oxygen uptake, with subsequent incidence of dementia. This was a population-based cohort study with an average follow-up of 22 (range 0.22–29.8) years from eastern Finland. About 2,031 men with a mean age of 52.8 years of age and no history of dementia or pulmonary disease at baseline participated in the study. Among these men, 208 cases of dementia occurred. Maximal oxygen uptake (ml/kg/min) was measured during exercise testing at baseline. One standard deviation increase in VO_{2max} was associated with a 20% decrease in dementia. Cardiorespiratory fitness was inversely related to the risk of dementia. Men with low cardiorespiratory fitness (VO_{2max} < 23.7 ml/kg/min, lowest quintile) had a 1.92-fold (1.24–2.967, $P = 0.003$), risk of dementia as compared with men who had high cardiorespiratory fitness (VO_{2max} >36.5 ml/kg/min, highest quintile) after adjusting for age and examination years. In a multivariate model, low cardiorespiratory fitness was associated with a 1.95-fold (1.24–3.05, $P = 0.003$) risk of dementia. Our findings show that low cardiorespiratory fitness was associated with an increased risk of dementia.

Keywords: *demenita, exercise test, older people, risk factor*

Introduction

Physical activity and indirectly measured good cardiorespiratory fitness have been shown to have protective effects on dementia and Alzheimer's disease [1–3]. A consensus statement on dementia prevention concluded that there was insufficient evidence to promote any lifestyle change as an effective preventive measure, including increasing self-reported physical activity [4] or improving measured cardiorespiratory fitness levels. It is difficult to measure the total amount, duration, frequency or intensity of habitual physical activity according to self-reported questionnaires. On the other hand, cardiorespiratory fitness measured directly by maximal oxygen uptake (VO_{2max}) during exercise testing provides a quantitative and objective measure of physical activity and fitness.

However, there are no cohort studies investigating the association between directly measured cardiorespiratory fitness and the risk of dementia. In this study, we investigated the association of VO_{2max}, as a measure of cardiorespiratory fitness, with the risk of dementia.

Methods

Subjects

Subjects were participants in the Kuopio Ischaemic Heart Disease Risk Factor Study, designed to investigate risk factors

for cardiovascular diseases, carotid atherosclerosis and related outcomes in a population-based, randomly-selected sample of men in eastern Finland [5]. The men were 42–61 years of age during baseline examinations performed between 20 March 1984 and 5 December 1989. Of 3,235 potentially randomly-selected eligible men, 2,682 (83%) volunteered to participate in this study, 186 did not respond to the invitation and 367 declined to give informed consent. The present analysis is based on 2,031 men with no missing data on exercise test variables, co-variates, stroke and pulmonary disease. This was a population-based cohort study with an average follow-up of 22 (range 0.22–29.8) years from eastern Finland. The study was approved by the Research Ethics Committee of the University of Kuopio, and each participant gave written informed consent.

Assessment of cardiorespiratory fitness

Cardiorespiratory fitness was assessed at baseline between March 1984 and December 1989 with a maximal symptom-limited exercise-tolerance test on an electrically braked bicycle ergometer. About 614 men were examined with the protocol comprising a 3-min warm-up at 50 W followed by a step-by-step increase in the workload by 20 W/min. The remaining 1,698 men were tested with a linear increase in workload by 20 W/min. VO_{2max} was used as measure of cardiorespiratory fitness. A detailed description of the measurement of VO_{2max} has been given elsewhere [5, 6]. VO_{2max} was defined as the highest value for, or the plateau on, oxygen uptake.

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. Blood pressure was measured between 8:00 and 10:00 a.m. by one nurse with a random-zero sphygmomanometer. The use of medications, years of education and the diagnosis of diseases were collected at baseline examination by an internist [5]. Alcohol consumption, collection of blood specimens, measurement of serum lipids, insulin, glucose and plasma fibrinogen, have been described elsewhere [5].

Outcomes

Information on dementia was obtained by computerised linkage to the national hospital discharge registry and death certificate registers. Dementia diagnoses were also obtained from the National Hospital Discharge Register. Subjects suspected of having dementia were examined by neurologists, underwent neuropsychological testing and magnetic resonance imaging of the brain at the time of diagnosis. Each dementia case was classified according to (International Classification of Diseases, 9th revision [ICD-9] codes); 290, 291.2 A, 292.8 C, 294.1 A, 331.0 A, 331.1 A and 437.8 A and ICD-10 codes F00, F01, F02, F03, G30 and G31.

Statistical analysis

The associations of VO_{2max} with the risk factors for dementia were examined by using co-variate analyses and with the risk of dementia by Cox proportional hazards' modelling. The levels of VO_{2max} were entered as dummy variables into forced Cox models. In these analyses, VO_{2max} was divided according to quintiles. Co-variates were entered uncategorised, when possible, into the Cox models. Two different sets of co-variates were used: (1) age and examination year and (2) model 1, smoking, alcohol, systolic blood pressure (SBP), prevalent coronary heart disease and type 2 diabetes.

Relative hazards, adjusted for risk factors, were estimated as antilogarithms of co-efficients from multivariate models. All tests for statistical significance were two-sided. Statistical analyses were performed using the SPSS 21.0 Windows software.

Results

Baseline characteristics

The mean age of the subjects was 52.8 years (range 42.0–61.2 years). The mean of VO_{2max} was 30.2 ml/kg/min (range 6.36–65.4 ml/kg/min). In our study, men with low VO_{2max} were older, they consumed more alcohol, smoked and had higher serum low-density lipoprotein (LDL) cholesterol and SBP as compared with who had high VO_{2max} (Table 1).

Risk factors for dementia

As continuous variables, the strongest and statistically significant risk factors for dementia were age ($P < 0.001$), maximal oxygen uptake ($P = 0.013$) and alcohol ($P < 0.001$), after adjustment for age and examination years. One standard deviation increase in VO_{2max} (3.5 ml/kg/min) decreased the risk of dementia by 20% (95% confidence intervals [CI] 30–47%).

Cardiorespiratory fitness and risk of dementia

Cardiorespiratory fitness was inversely related to the risk of dementia. Men with low cardiorespiratory fitness (VO_{2max} < 23.7 ml/kg/min, lowest quintile) had a 1.92-fold (1.24–2.967, $P = 0.003$), risk of dementia as compared with men who had high cardiorespiratory fitness (VO_{2max} >36.5 ml/kg/min, highest quintile) after adjusting for age and examination years. In a multivariate model, low cardiorespiratory fitness was associated with a 1.95-fold (1.24–3.05, $P = 0.003$) risk of dementia. Further adjustment for years of education, did not change the results 1.93-fold (1.23–3.02). Results remained the same after adjustment for socioeconomic status, and job status (blue collar jobs, farmers and others).

Comments

Cardiorespiratory fitness, as measured by VO_{2max} during exercise was related to the risk of dementia. To the best of our

Table 1. Characteristics of men at baseline in the quintiles of maximal oxygen uptake

	Mean (SD) (n = 2,031)	Q1[a] Mean (SD) (n = 410)	Q2[a] Mean (SD) (n = 405)	Q3[a] Mean (SD) (n = 406)	Q4[a] Mean (SD) (n = 404)	Q5[a] Mean (SD) (n = 406)	P-value
Age (years)	52.8 (5.0)	55.4 (3.7)	54.0 (4.5)	52.7 (4.8)	52.1 (5.0)	50.1 (5.4)	$P < 0.001$
Cigarette smoking (pack-years)[b]	8.4 (16.6)	7.2 (11.4)	6.1 (10.6)	6.1 (10.2)	5.1 (9.8)	3.1 (7.7)	$P < 0.001$
Serum HDL cholesterol (mmol/l)	1.29 (0.30)	1.20 (0.28)	1.26 (0.30)	1.27 (0.28)	1.32 (0.30)	1.41 (0.32)	$P < 0.001$
Serum LDL cholesterol (mmol/l)	4.01 (1.00)	4.15 (1.07)	4.04 (1.00)	4.13 (1.00)	4.04 (1.00)	3.85 (0.95)	$P < 0.001$
Serum triglycerides (mmol/l)	1.29 (0.82)	1.59 (1.05)	1.37 (0.82)	1.25 (0.65)	1.22 (0.82)	1.00 (0.51)	$P < 0.001$
Systolic blood pressure (mmHg)	134.0 (16.8)	137.1 (19.3)	135.7 (17.4)	135.3 (16.7)	132.1 (14.9)	129.9 (14.0)	$P < 0.001$
Diastolic blood pressure (mmHg)	88.8 (10.4)	89.9 (11.4)	89.8 (10.7)	90.0 (10.2)	88.2 (10.2)	86.4 (9.1)	$P < 0.001$
Type 2 diabetes (%)	5.5	13.0	5.0	5.0	3.0	1.9	$P < 0.001$
Body mass index (kg/m^2)	26.8 (3.5)	28.5 (4.1)	27.8 (3.5)	26.7 (3.1)	26.2 (2.8)	25.0 (2.4)	$P < 0.001$
Serum C-reactive protein (mg/l)	2.3 (3.4)	3.6 (4.8)	2.6 (3.7)	2.1 (2.8)	1.6 (2.1)	1.5 (2.6)	$P < 0001$
Alcohol consumption (g/week)	74.2 (121.0)	83.7 (160.4)	81.5 (121.8)	83.1 (130.1)	60.5 (84.5)	62.0 (92.1)	$P = 0.001$

Quintiles of cardiorespiratory fitness and the risk of dementia among 2,031 men.

	Dementia (234 men) Age-adjusted		Number (n) %	Dementia (234 men) Multivariable adjusted	
	Relative risk[a] (95% CI)	P-value		Relative risk[c] (95% CI)	P-value
Cardiorespiratory fitness (%)					
Q1 (<23.69 ml/mmHg, 0–20%)	1.92 (1.24–2.97)	0.003	(50) 23.5	1.95 (1.24–3.05)	0.003
Q2 (23.70–28.14 ml/mmHg, >20–40%)	1.43 (0.93–1.21)	0.102	(51) 24.5	1.38 (0.89–2.14)	0.147
Q3 (28.15–31.96 ml/mmHg >40–59%)	0.98 (0.62–1.57)	0.964	(37) 18.0	0.92 (0.58–1.47)	0.729
Q4 (31.97–36.45 ml/mmHg 60–80%)	1.17 (0.76–1.83)	0.471	(40) 19.0	1.15 (0.74–1.79)	0.527
Q5 (>36.45 ml/mmHg >80%)	1.00 (reference)		(31) 15.0	1.00 (reference)	

[a]Q1 ≤ 23.69 ml/mmHg, Q2 = 23.70–28.14 ml/mmHg, Q3 = 28.15–31.96 ml/mmHg, Q4 = 31.97–36.45 ml/mmHg, Q5 > 36.45 (Quintiles).
[b]Pack-years denotes the lifelong exposure to smoking which was estimated as a product of years smoked and the number of tobacco products smoked daily at the time of examination, HDL denotes high-density lipoprotein and LDL denotes low-density lipoprotein.
[c]Age, examination year, cigarette smoking, alcohol consumption, systolic blood pressure, prevalent coronary heart disease and type 2 diabetes.

knowledge, this is the first population-based follow-up study showing an association between cardiorespiratory fitness, as indicated by directly measured VO_{2max}, and the risk of dementia with a long follow-up of 23 years. Our study shows that an increased risk of dementia was observed among men with lowest level of VO_{2max}. A difference in VO_{2max} of 3.5 ml/kg/min at baseline corresponds to 20% decrease in the risk for dementia among these men.

Previous studies have found an association between physical activity and subsequent risk of dementia and Alzheimer's disease [1–3]. High levels of cardiorespiratory fitness may help in delaying the progression of dementia. Good cardiorespiratory fitness and physical activity may reduce the risk of dementia by affecting modifiable risk factors including dyslipidemia, diabetes and hypertension [7–10]. Fitness may also have an effect on neuroplasticity and production of growth factors including brain-derived neurotrophic factor [11] that lowers the risk of dementia. However, in our study, adjustment for known risk factors did not markedly change the association and there was an independent relationship between cardiorespiratory fitness and risk for dementia.

VO_{2max}, which is the product of cardiac output and the maximal arteriovenous oxygen difference, is determined by age, gender, the duration, frequency, intensity and type of physical activity, genetic factors and clinical and subclinical diseases. For most individuals, increases in physical exercise produces an increase in VO_{2max}, although the amount of adaption in VO_{2max} to standard exercise dose varies widely and is under genetic control. The optimal level of physical activity required to improve cardiorespiratory fitness may depend on the initial health and fitness status as well as familial factors. VO_{2max} usually decreases by 5–15% per decade between the ages of 20–80 and the rate at which oxygen uptake declines is directly related to the maintenance of physical activity level, emphasising the importance of physical activity.

VO_{2max} is a gold standard for measuring cardiorespiratory fitness and thus, is a recommendable measure for cardiorespiratory fitness. The self-reported format for physical activity assessment in population studies may result in inaccuracy, whereas the use of VO_{2max} helps to reduce such measurement errors. The strength of our study is that we have a representative population-based sample of middle-aged men with a high participation rate and no losses during follow-up, as each subject is identified on the basis of their National social security number. Furthermore, we have reliable data on baseline health status and risk factors which allowed for the adjustment of potential confounders. In terms of limitations, it is important to state that one measurement of VO_{2peak} cannot rule out some variation with time in terms of VO_{2max} during the

follow-up period. However, if anything, this may underestimate the observed observations. Furthermore, our study focussed on all dementia types; associations were not risk stratified by type, as reliable data for specific subtypes were not available. Additionally, our results are based on an ethnically and genetically homogenous population of the same gender which limits the generalisation of results. However, there is no evidence that the predictive value of physical fitness would be less important among female subjects. Another significant limitation of the study is that only those subjects who visited a hospital for diagnosis were detected. It is therefore possible that the diagnosis of dementia was missed in other subjects. Our findings show that low cardiorespiratory fitness was associated with an increased risk of dementia. It is apparent that VO_{2max} declines with age, but with a physically active lifestyle, one can maintain a good VO_{2max} level despite ageing so that the risk of dementia may be reduced.

Key points

- VO_{2max} is a gold standard for measuring cardiorespiratory fitness.
- Cardiorespiratory fitness was inversely related to the risk of dementia.
- A standard deviation increase in VO_{2max} was associated with a 20% decrease in dementia.

Conflict of interest

None.

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