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Original Scientific Paper

Low cardiorespiratory fitness is a strong predictor for clustering of cardiovascular disease risk factors in children independent of country, age and sex

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Background and design **Few studies have investigated the association between maximal cardiorespiratory capacity (fitness) and the clustered cardiovascular disease (CVD) risk in children and youth from culturally diverse countries. This cross-sectional study examined the association between fitness and clustered CVD risk in children and adolescents from three European countries.**

Methods **Participants were 2845 randomly selected school children aged 9 or 15 years from Portugal ($n = 944$), Denmark ($n = 849$) and Estonia ($n = 1052$). Cardiorespiratory fitness was determined during a maximal test on a cycle ergometer. CVD risk factors selected to assess the degree of clustering were the total cholesterol/high-density lipoprotein cholesterol ratio, plasma triglycerides, insulin resistance (homeostasis model assessment), sum of four skinfolds, and systolic blood pressure.**

Results **There was a strong association between cardiorespiratory fitness and the clustering of CVD risk factors. The odds ratios for clustering in each quartile of fitness, using the quartile with the highest fitness as reference, were 13.0 [95% confidence interval (CI) 8.8–19.1]; 4.8 (95% CI 3.2–7.1) and 2.5 (95% CI 1.6–3.8), respectively, after adjusting for country, age, sex, socio-economic status, pubertal stage, family history of CVD and diabetes. In stratified analyses by age group, sex and country, similar strong patterns were observed.**

Conclusion **Low cardiorespiratory fitness is strongly associated with the clustering of CVD risk factors in children independent of country, age and sex. *Eur J Cardiovasc Prev Rehabil* 14:526–531 © 2007 The European Society of Cardiology**

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Introduction

Insulin resistance, obesity, an abnormal lipid and lipoprotein profile, and elevated blood pressure are all independent risk factors for cardiovascular disease (CVD) in adults [1]. Several of these factors may often be present in the same individual (clustering) and have been associated with an increased risk of atherosclerosis and CVD outcomes [2]. The clustering of elevated levels of these risk factors have also been observed in children and youth [3,4], and there is evidence that clustering persists from childhood into adulthood [5]. Even though CVD mainly manifests in older age, these observations are important because the atherosclerotic process begins in childhood [6,7], and data from autopsy studies in children and youth indicate that as the numbers of CVD risk factors increases, so too does the severity of coronary and aortic atherosclerosis [8].

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There are multiple underlying causes of risk factor elevation among children and youth. In adults, low cardiorespiratory fitness and low physical activity levels are associated with adverse risk factor profiles and the development of CVD, and increasing activity or fitness levels results in improved CVD risk profile and premature mortality risk [9,10]. Similar data regarding the determinants of risk factor elevation are sparse in children and youth, but it is likely that both levels of physical activity and cardiorespiratory fitness play a pivotal role in risk factor elevation.

Previous studies have shown associations between cardiorespiratory fitness and single CVD risk factors in childhood [11]. Similarly, cardiorespiratory fitness has been associated with features of the metabolic syndrome [12–14], although evidence is inconsistent [15]. Few studies have investigated the association between objectively determined cardiorespiratory fitness and clustered CVD risk in children and youth, and we are unaware of any previous study investigating whether this association differs between countries. As levels of both fitness and biological risk factors change throughout adolescence as a consequence of maturation and lifestyle behaviours [16,17] differences or consistencies between different geographical regions, age groups, and sexes may provide insight with respect to cardiorespiratory fitness as a predictor of clustered risk. The aims of this study were to examine the association between cardiorespiratory fitness and clustered CVD risk in three European countries, and whether this differs by age or sex.

Methods

Study population

Recruitment, data gathering and laboratory procedures have been described in detail elsewhere [18]. In short, this was a cross-sectional survey including children and youth from Portugal (Madeira), Denmark (Odense) and Estonia (Tartu). All procedures and methods in this study conformed to the ethical guidelines laid down in the World Medical Association's Declaration of Helsinki. The study was approved by the local ethical committees and all children gave verbal informed consent. Written informed consent was obtained from the child's parent or legal guardian. A common test protocol was followed by all participating centres, and quality control visits were conducted to ensure similarity with respect to data gathering throughout the duration of the study.

Participants were boys and girls aged 9 or 15 years. Within each country, schools were stratified according to location (urban, suburban, rural) and the socio-economic character of its uptake area. From each stratum, a proportional, two-stage cluster sample of children was selected. The primary units were the schools. The secondary units were the children within the schools. The overall participation rates were 73% in Portugal ($n = 944$), 75% in Denmark ($n = 849$) and 76% in Estonia ($n = 1052$). A complete CVD risk factor profile including blood lipids, fasting insulin and glucose, blood pressure, fatness and cardiorespiratory fitness was assessed in 1454 girls and 1391 boys.

Measures

Venous blood samples were obtained in the morning after an overnight fast and were stored at $-80°C$ until analysis. Body height (nearest millimetre) and body weight (nearest 100 g) were measured in light clothing. The sum of the thickness of four skinfolds (biceps, triceps, subscapular and suprailiac) was measured using a Harpenden calliper, with the mean of three measurements used at each site. After at least 5 min seated rest, blood pressure was measured five times at 2 min intervals (Dinamap adult/paediatric and neonatal vital signs monitor, model XL; Critikron, Inc., Tampa, Florida, USA). The mean of the last three measurements was used in the analyses. Pubertal stage was assessed according to Tanner [19], and the judgement was performed by a physician or an exercise physiologist. Cardiorespiratory fitness was assessed during a cycle test with a progressively increasing work rate until exhaustion using an electronically braked cycle ergometer (Ergomedic 839; Monark, Varberg, Sweden). Initial and incremental work rates were 20 W for children weighing less than 30 kg and 25 W for children weighing 30 kg or more. For 15-year-old girls and boys the initial and incremental work rates were 40 and 50 W, respectively. Work rate was increased every third minute until exhaustion. Heart rate (HR) was recorded every 5 s throughout the test using an HR monitor (Polar Vantage, Finland). Criteria for a maximal effort were HR of 185 beats per minute or greater, and a subjective judgement by the observer that the individual could no longer continue, even after encouragement. The cycle ergometer was electronically calibrated every test day and mechanically calibrated after being moved. Fitness was expressed as maximal power output per kilogram. This measure has a low test–retest coefficient of variation (2.5–4.8%). It has been validated against the direct measurement of oxygen consumption ($V\text{O}_2$) in 222 girls and 255 boys 9 years of age; and 279 girls and 312 boys 15 years of age, in whom it was highly correlated with $V_{\text{O}_{2\text{max}}}$ ($r > 0.90$, $P < 0.001$), producing the following relationships (girls 0, boys 1):

$$\text{9 year olds}: V_{\text{O}_{2\text{max}}}(\text{ml}) = (9.323 * \text{watts}) + (55 * \text{sex}) + 613$$

$$\text{15 year olds}: V_{\text{O}_{2\text{max}}}(\text{ml}) = (10.390 * \text{watts}) + (223 * \text{sex}) + 555$$

Both parents reported their educational attainment and personal income. In each country we classified parental education into four categories (basic/primary; secondary/

trade apprentice; higher vocational qualifications; university). We classified income into eight categories representing the ways in which income was most commonly reported in each country and used country-specific categories. Scores from both income and education were summed and averaged into a socio-economic status score. The family history of CVD reported angina, myocardial infarction, hypertension, and hypercholesterolemia, with response options of 'no' and 'yes'.

Blood analyses

Total cholesterol and high-density lipoprotein (HDL) cholesterol, triglycerides and glucose were analysed by colorimetry on an Olympus AU600 autoanalyser (Olympus Diagnostica, Hamburg, Germany). Serum insulin was analysed using an enzyme immunoassay (microtitre plate format; Dako Diagnostics, Ely, UK). Homeostasis model assessment (HOMA) of insulin resistance was calculated as (fasting glucose × fasting insulin)/22.5 as described by Radziuk [20].

Definition of clustered risk

Five biological CVD risk factors (the ratio of total cholesterol : HDL-cholesterol, plasma triglycerides, HOMA, sum of four skin folds, and systolic blood pressure) were selected to assess the degree of clustering. First, each risk factor was converted into a *z*-score by country, age group, and sex. The *z*-score is the number of standard deviations a specific value differs from the mean [*z*-score = (observed-mean)/SD). The sum of four skinfolds, triglycerides and the HOMA score were normalized by the natural logarithm before constructing *z*-scores. The five *z*-scores were then summed to compute an overall, continuous measure of metabolic risk. In order to calculate odds ratios, metabolic risk was dichotomized at the cutoff value plus 1 SD, identifying children with clustered risk. The cutpoint of 1 SD was chosen to match the prevalence of risk factor clustering roughly, independent of chance and was thus assumed to be a biological phenomenon. Clustering was defined on the basis of the observed versus the expected number of children with zero to five risk factors (defined as the least favourable quartile). The expected number can be calculated with the binomial formula, which assumes risk factors are independent.

Statistical analyses

Subjects were ranked into quartiles of fitness by country, sex, and age group. Odds ratios of clustered risk were calculated between quartiles of fitness using logistic regression. Models were adjusted for potential confounding factors (pubertal stage, socio-economic status, family history of CVD, diabetes). With the exception of pubertal stage, none of these potential confounders changed the estimates substantially. Analyses are therefore presented adjusted for pubertal stage only. In the total model (using the pooled data from the three countries), however, all potential confounders are adjusted for. To examine whether the association between clustered risk and fitness differed between countries we tested for interaction between country and cardiorespiratory fitness. As only analyses on complete data are presented, we analysed whether those with complete data differed from those without. There were no differences in mean age, sex distribution, body mass index or bodyweight between those with and those without data for fitness and CVD risk factors. All analyses were conducted using SPSS statistical software (version 13.0; SPSS Inc., Chicago, Illinois, USA).

Results

The characteristics of the study population are shown in Table 1. Systolic and diastolic blood pressure, insulin, and HOMA scores were greater in the older age groups

Table 1 Characteristics of the study population (mean ± SD)

Variable	Children		Youths	
	Girls, *N* = 729	Boys, *N* = 716	Girls, *N* = 725	Boys, *N* = 675
Age (years)	9.6 (0.4)	9.7 (0.4)	15.5 (0.6)	15.5 (0.5)
Height (cm)	137.6 (6.5)	137.8 (6.4)	163.2 (6.7)	172 (7.6)
Weight (kg)	32.7 (7.0)	33.2 (7.0)	55.7 (8.5)	61.5 (10.3)
BMI (kg/m^2)	17.2 (2.7)	17.4 (2.7)	20.9 (2.9)	20.7 (2.8)
Sum of four skinfolds (mm)	37.7 (17.9)	32.2 (18.2)	49.2 (17.0)	33.2 (16.1)
SBP (mmHg)	100.7 (9.1)[a]	101.2 (9.8)[a]	106.2 (9.2)	113.5 (12.2)
DBP (mmHg)	59.5 (6.9)[a]	58.8 (7.6)[a]	62.8 (6.6)	61.5 (7.0)
Fasting glucose (mmol/l)	5.03 (0.38)	5.16 (.35)	5.09 (0.41)	5.30 (0.47)
Fasting insulin (μU/ml)	7.80 (4.28)[a]	6.52 (3.96)[a]	12.41 (5.58)	10.91 (6.63)
HOMA score	1.77 (1.03)[a]	1.51 (0.93)[a]	2.83 (1.36)	2.61 (1.77)
Total cholesterol (mmol/l)	4.47 (0.79)	4.31 (0.74)[b]	4.25 (0.77)	3.84 (0.72)
HDL-cholesterol (mmol/l)	1.47 (0.29)	1.52 (0.30)[b]	1.42 (0.28)	1.30 (0.26)
Total cholesterol/HDL-cholesterol	3.13 (3.08–3.17)	2.92 (2.88–2.96)	3.09 (3.05–3.14)	3.13 (3.08–3.19)
Triglycerides (mmol/l)	0.79 (0.33)	0.70 (0.32)	0.86 (0.39)	0.79 (0.49)
Fitness, $W_{max} \cdot kg^{-1}$	2.55 (0.61)	2.97 (0.64)[b]	2.56 (0.53)	3.50 (0.59)

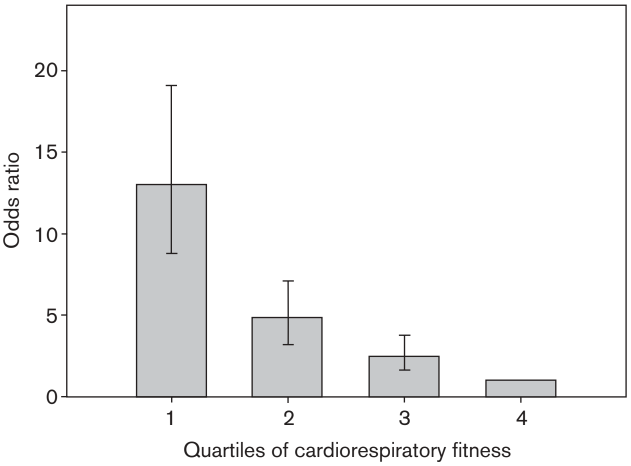
BMI, Body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA, homeostasis model assessment (insulin resistance); SBP, systolic blood pressure. The total cholesterol : HDL-cholesterol ratio is given with 95% confidence interval. [a] Significant difference from the 15 year olds, $P < 0.01$. [b] Significant difference from the 15-year-old boys, $P < 0.01$.

($P < 0.01$). Both HDL-cholesterol and total cholesterol were lower in older boys compared with younger boys. Cardiorespiratory fitness was equal in both age groups among girls, but was significantly higher in 15-year-old boys compared with the 9 year olds. The children were predominantly prepubertal (80%), with the remainder in early puberty. Among the adolescents, 60% were post-pubertal, with only 1% prepubertal or in early puberty. These proportions did not differ by country.

Figure 1 shows odds ratio for the clustering of CVD risk factors in quartiles of cardiorespiratory fitness. This analysis includes all participants and is adjusted for potential confounding factors. The odds ratio for having clustered risk was 13.0 [95% confidence interval (CI) 8.8–19.1] in the least fit quartile (quartile 1) compared with the referent quartile (quartile 4). The test for trend was highly significant ($P < 0.001$). For each 1 SD decrease in the z-score of fitness the risk of having clustered risk increased three times (exp B = 0.35). One SD in fitness equals approximately 7 ml/min per kilogram in oxygen uptake.

Table 2 displays odds ratios for the clustering of CVD risk factors between quartiles of cardiorespiratory fitness by country. The analyses were performed with adjustment for sexual maturation only. Within each country the overall association is similar: there was a strong association between the different levels of cardiorespiratory fitness and the clustering of CVD risk factors. No significant interaction between country and fitness was detected. Similarly, results were materially unaltered when data were standardized only by age and sex or when analysed in their continuous form.

Fig. 1



Odds ratios (±95% confidence intervals) for clustering of cardiovascular risk factors in different quartiles of cardiorespiratory fitness including all participants ($n = 2845$). Individuals in quartile 4 are the most fit (used as referent). The analysis is adjusted for country, age, sex, puberty, socio-economic status, parent's history of cardiovascular disease and diabetes type 2.

Table 2 **Odds ratios (OR) and 95% confidence intervals (CI) for the relationship between fitness and the clustering of cardiovascular disease risk factors by country**

	Portugal OR (95% CI)	Denmark OR (95% CI)	Estonia OR (95% CI)
Lowest quartile of fitness	17.3 (8.7–34.4)	14.0 (6.8–28.9)	9.5 (5.1–17.5)
2nd quartile of fitness	7.6 (3.8–15.3)	3.4 (1.5–7.3)	3.9 (2.1–7.4)
3rd quartile of fitness	2.5 (1.2–5.4)	2.0 (0.9–4.5)	2.8 (1.4–5.4)
Highest quartile of fitness	1	1	1

The model is adjusted for sexual maturation only.

Table 3 **Odds ratios (OR) and 95% confidence intervals (CI) for the relationship between fitness and the clustering of cardiovascular disease risk factors by age group or sex**

Stratified by age group	Children (9 years) OR (95% CI)	Youth (15 years) OR (95% CI)
Lowest quartile of fitness	13.2 (7.7–22.5)	12.0 (6.8–21.0)
2nd quartile of fitness	4.50 (2.6–7.9)	4.9 (2.7–8.8)
3rd quartile of fitness	2.2 (1.2–4.0)	2.8 (1.5–5.1)
Highest quartile of fitness	1	1
Stratified by sex	Girls, OR (95% CI)	Boys, OR (95% CI)
Lowest quartile of fitness	10.4 (6.1–17.8)	15.8 (9.0–27.6)
2nd quartile of fitness	4.3 (2.4–7.5)	5.3 (3.0–9.5)
3rd quartile of fitness	2.1 (1.2–3.8)	2.9 (1.6–5.3)
Highest quartile of fitness	1	1

The model is adjusted for sexual maturation.

Table 3 displays quartiles of cardiorespiratory fitness and the clustering of CVD risk factors by age and sex. Within each age group a strong association was observed between the different quartiles of cardiorespiratory fitness and the clustering of CVD risk factors. The pattern is similar in the two age groups, and there is no statistically significant difference between them. In parallel, within each sex strata, strong and similar associations between the different quartiles of cardiorespiratory fitness and the clustering of CVD risk factors were observed with no statistically significant difference between boys and girls.

Discussion

This study demonstrates that cardiorespiratory fitness is strongly associated with the clustering of CVD risk factors in children and youth, and that the association is independent of country, age and sex. The participants in this study represent southern (Portugal), northern (Denmark) and eastern (Estonia) Europe, with very different physical, socio-economic and cultural environments. These findings thus aid in understanding the importance of cardiorespiratory fitness as a strong correlate of the clustering of CVD risk factors in a population of (clinically) healthy children.

Previous studies have reported correlations between single individual CVD risk variables and cardiorespiratory fitness or physical activity in children and youth [*21,22*], and weak associations have been found. Analysis of clustered CVD risk factors may give a more precise picture, because a child with clustered risk has a poorer health status than if just one risk factor was elevated. Furthermore, part of the error variation each risk factor includes, which contributes to obscure true relationships, is diminished in the construction of clustered risk. Moreover, risk is probably a continuum in healthy children, which makes it arbitrary as to where a cutpoint for risk should be defined. However, our results indicate that this may not be the case. In an earlier study, we defined the upper quartile in each risk factor as being ‘at risk’, and calculated the number of risk factors for each child [4]. If risk factors were randomly distributed then the number of children with a certain number of risk factors would follow a binominal distribution. We found an eightfold higher number of children with the highest number of risk factors than would be expected just by chance. The number of children with clustered risk in that study was 15% of the population, and we believe there is rationale for defining those children as having an elevated risk. The percentage of children in the present study with the highest risk is defined by a cutoff point of greater than 1 SD in the summed z-score variable. When risk factors cluster, it is likely that they share common underlying factors that affect all or some of these simultaneously. Such underlying factors might include poor diet, physical inactivity, low cardiorespiratory fitness and genetics, or more likely a combination of these and other factors.

The cause of risk factor clustering has yet to be fully understood. Increased physical activity simultaneously improves components of the ‘metabolic syndrome’ such as triglycerides, low-density lipoprotein cholesterol particle size, apolipoprotein A, adiposity, and insulin resistance [23–25], and CVD risk factors may therefore cluster because of a sedentary lifestyle. However, many of the biological mechanisms responsible for changes caused by physical inactivity are shared with the effects of obesity. Obesity has been shown to be strongly associated with insulin resistance [16] and other important CVD risk factors, raising the possibility that CVD risk clustering is mediated by fatness [26]. This was partly true in our study, in which skinfold thickness was responsible for some of the association between fitness and clustered risk. However, the exclusion of HOMA from the clustered risk variable also decreased odds ratios for quartiles of fitness substantially, and the clustering of blood lipids and blood pressure was independently associated with fitness, with an odds ratio for the least fit quartile of 3.4. As increased body weight may be associated with a lifestyle with low levels of physical activity, both inactivity and fatness may be independent risk factors, as well as reinforcing each other in the agglomeration of CVD risk factors. The assumption that obesity is the main cause of clustered risk may derive from the fact that physical inactivity or low fitness has been less studied or indeed poorly measured.

The prevalence of risk factors in a population may vary over time. For example, total cholesterol has declined over the past few decades in many western countries [27], whereas the average body mass index has increased in all age groups. Accordingly, the population attributable risks of different risk factors for CVD also vary over time. Our data stem from three countries that differ culturally, socially and economically. For example, Estonia and Portugal are two of the poorest countries in Europe in contrast to Denmark, which is one of the richest, and Estonia differs from the others in terms of recent social, cultural and economic change. The consistent finding that cardiorespiratory fitness is strongly associated with the clustering of risk factors, independent of age, sex and country, underscores the importance of fitness as an important correlate of CVD clustering in young people. The implication of this may be that with the westernization of eastern European countries such as Estonia, and declining levels of physical activity as a consequence of economic improvements, fitness may well decline among the young in the years to come, which would increase the population attributable risk of low fitness for the clustering of CVD risk factors.

To evaluate whether the observed relationship between cardiorespiratory fitness and CVD risk clustering could be of a causal nature, some limitations of the present study should be highlighted. First, any observational study may be subject to measurement bias and confounding, but the phenotypes we examine here are characterized by a high degree of measurement precision, because they are relatively stable over time (say < 1 year) and were obtained under standardized controlled conditions. Second, the cross-sectional nature of this study makes it impossible to determine the direction of the association. However, our observations were strong and robust to adjustments for age, sex, country, and socio-economic factors, thus eliminating a confounding effect from these factors. Genetic factors may still confound, or more likely, modify the association between cardiorespiratory fitness and CVD clustering [28]. Potentially, the main source of bias is the fact that the sum of skinfolds is part of the outcome and skinfold thickness is correlated with body weight, which is used in the computation of the primary exposure, cardiorespiratory fitness. However, cardiorespiratory fitness was still strongly related to clustered CVD risk when we excluded skinfolds from the clustered risk variable. Moreover, some of the effect of cardiorespiratory fitness on CVD risk factors may be mediated through the effect on fatness.

Conclusion

We found negative associations between cardiorespiratory fitness and the clustering of CVD risk factors, independent of country, sex and age groups. Associations are biologically plausible, and we conclude that cardiorespiratory fitness is an important predictor for the clustering of CVD risk. As risk factors are known to track, these data suggest that the prevention of CVD should start early in life, especially targeting those who are least fit.

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