Supporting Information

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SI Methods

Study Population. A cohort of 18-year-old Swedish male subjects who enlisted for military service between 1968 and 1994 (i.e., born between 1950 and 1976; $N = 1{,}221{,}727$) was compiled from the Swedish Military Service Conscription Register. Swedish law requires all 18-y-old Swedish men to undergo extensive and highly standardized intelligence and physical examinations before conscription assignment in the Swedish Armed Forces. Until recently, exemptions were granted only for incarcerated male subjects and those with severe chronic medical conditions or handicaps documented by a medical certificate (in approximately 2%–3% of the male population per year). Links to the Multi-Generation Register (http://www.scb.se/Pages/List___257501.aspx) and Swedish Twin Register (1) enabled the identification of full brothers and twins. Education and occupation information was obtained from the longitudinal LISA database (see Fig. 1). The Ethics Committee of Sahlgrenska Academy, University of Gothenburg, and the Secrecy Clearance at Statistics Sweden approved the study.

Swedish Military Service Conscription Register Data. ***Cardiovascular fitness test.*** Cardiovascular fitness was assessed using the previously described cycle ergonometry test, and included elements of validity and reliability (2). After a normal resting ECG, 5 min of submaximal exercise was performed at work rates of 75 to 175 W, depending on body mass. The work rate was continuously increased by 25 W/min until volitional exhaustion. The subject was instructed to maintain pedal cadence between 60 and 70 rpm. Heart rate was continuously measured. The final work rate (W_{max}) was recorded and divided by body mass. W_{max}/kg was used because of better correlation with measured maximum oxygen consumption (V_{O2max}; correlation coefficient, ≈0.9) (29, 30) than predicted V_{O2max} (correlation coefficient, ≈0.6–0.7) (3, 4). The resulting value (W_{max}/kg) was transformed into stanine scores, with 1 as the lowest and 9 as the maximal performance, and served as a measure of cardiovascular fitness.

Muscular strength test. Isometric muscle strength was measured by knee extension (weighted ×1.3), elbow flexion (weighted ×0.8), and hand grip (tested with a tensiometer; weighted ×1.7) (2, 5). The values were integrated, using different weighted values, into one estimate in kilopond (before 1979) or Newton (after 1979), and divided into 9 stanines.

Cognitive performance tests. The cognitive performance tests are described in detail elsewhere (6), and results have been used in other studies (7–9). Four cognitive tests were used during the years of assessment covered by these analyses: logical performance test, verbal test of synonym and opposites, test of visuospatial/geometric perception, and technical/mechanical skills including mathematical/physics problems. Performance on all 4 tests were combined to obtain a global intelligence score, which was regarded as a measure of general cognitive ability (6). In particular, between 1984 and 1996, raw data were not electronically recorded and could not be accessed for statistical analysis. However, stanine scores were available. Test results were standardized against data from previous years to give scores from 1 (low) to 9 (high) for each of the 5 scores: global intelligence and logical, verbal, visuospatial, and technical/physics scores. Conversion to a 9-point stanine scale provided long-term stability of data sets.

Longitudinal integration database for health insurance and labor market studies (Swedish acronym LISA). The LISA database (http://www.scb.se/Pages/List___257743.aspx) includes all individuals 16 y of age and older registered in Sweden in 1990 or later. The database, which is annually updated, integrates data from the labor market, as well as educational and social sectors. Information on parental and subsequent education, date of occupation, and professional achievements (professions ranked with high vs. low socioeconomic index) were obtained from LISA.

Pupil register. From the Swedish Pupil Register at The Swedish National Agency for Education, physical education grades were compiled from the final year of compulsory school. Grades were awarded points on a scale of 1 to 5. Physical education grades from the final year of compulsory school were available only from 1988 and onward.

Statistical Analyses. All statistical calculations were performed with SAS software (version 8.1; SAS Institute).

Cross-Sectional Analyses. ***Linear regression models.*** Initially, linear regression models were analyzed with PROC GLM, using global intelligence, logical, verbal, visuospatial, and technical scores as dependent variables, and cardiovascular fitness and muscle strength scores as independent variables. To determine if intelligence score means were significantly separated from each other, the Student-Newman-Keuls post-hoc test was used. Effect sizes were presented as regression coefficients (b) with 95% CIs in all models, i.e., change in a specific dimension if intelligence was associated with one unit of change in cardiovascular fitness.

Adjusted models. Next, we tested the associations between cardiovascular fitness and intelligence scores in multiple regression models while adjusting for multiple confounders. Because differences over time as well as among the 6 test centers could introduce bias, conscription year and conscription test centers were considered as possible confounders. In addition, parental educational level was included as a confounder, because more highly educated parents might encourage their children to exercise more and participate in activities that may improve cognitive performance. This is a classic example of a potential gene-environment correlation (10). The proportion of the variation explained by the adjusted model is given by the adjusted coefficient of determination (R^2).

We also performed the adjusted models using the identical number of observations and the identical set of explanatory variables. In this analysis, the coefficients of regression and degrees of determinations are fully comparable among the models. Therefore, the coefficients of determination indicate which response has the highest degree of variation explained by the factors included in the models, whereas the coefficients of regression or subgroup means show the magnitude of importance for each intelligence score.

Brother and twin analyses. Associations between cardiovascular fitness and intelligence scores were evaluated in models within brother pairs to assess familial factors, adjusting for conscription year and test center, as well as brothers' cardiovascular and cognitive performance. One brother was randomly selected to provide dependent variable values and the other brother's values formed the independent variables. In the case of several brothers, the median served as the proxy for familial or heritable effects. The same analyses were repeated within DZ and MZ twin pairs, equivalent to a co-twin control analysis (11), although without adjustment for conscription year.

Using Pearson correlation coefficients (r) within brother pairs, as well as DZ and MZ twin pairs, we assessed the univariate heritability of cardiovascular fitness, global intelligence, and logical, verbal, visuospatial, and technical scores (heritability = 2*[rMZ-rDZ]; shared environment = [rMZ − heritability]; and non-shared = [1 − rMZ]) (12).

Similarly, to calculate the familial component of associations between cardiovascular fitness and cognitive performance, a cross-twin cross-trait analysis (13) was performed to yield bivariate heritabilities. By comparing the cross-correlation coefficients between DZ and MZ twin pairs, the influence of genetic, shared environmental, and non-shared environmental factors on the associations was calculated (14).

Longitudinal Analyses. ***Prediction of cognitive performance from changes in cardiovascular fitness.*** Consistent with a previous study (15) of the relationship between school grades and cognitive tests, clear correlations between school grades at age 15 y and cognitive performance at age 18 y were observed ($r = 0.7$, $P < 0.0001$ for the correlation between mean grades and global intelligence). We hypothesized, similarly, that a middling physical education grade (i.e., 3 on a scale of 1–5) at age 15 y should predict average cardiovascular fitness at age 18 y (i.e., 5 on a range of stanine scores of 1–9). Regression modeling was performed with physical education grades at age 15 y as the independent variable and the cardiovascular fitness score at age 18 y as the dependent variable. The rationale is shown in Fig. 3*A*. Individuals' deviations from the regression line were identified as residuals in this model, and 3 groups were defined according to cardiovascular fitness at age 18 y. The high group comprised the 90th percentile (i.e., 10% highest cardiovascular fitness vs. predicted) and the low group the 10th percentile (i.e., 10% lowest fitness vs. predicted). Finally, the middle group represented 10th through 90th percentile (i.e., the remaining 80%). The 3 groups were labeled as having increased, decreased, and unchanged cardiovascular fitness, respectively. Cognitive performance at age 18 y (measured as global/logical/verbal/visuospatial/technical intelligence scores) was compared among the 3 groups, adjusting for conscription year. These analyses were based on the 232,612 individuals with complete records of final-year grades, cardiovascular fitness score, intelligence scores, and conscription year.

Prediction of education and occupation. The relationships between cardiovascular fitness at age 18 y and subsequent academic and educational achievements were determined using Cox proportional-hazards regression models. In 2 separate models using PROC PHREG, adjusted for conscription test center and parental education, the relationships between cardiovascular fitness at age 18 y and subsequent time-dependent events was determined; events included university degree (compared with pre-high school or high school) or high socioeconomic indexed occupation (compared with an occupation with low socioeconomic index). The follow-up period spanned from conscription until the event or December 31, 2004 (minimum 10-year and maximum 36-year follow-up). Cardiovascular fitness was treated as a continuous variable with 9 levels (i.e., stanine scores) or was categorized as high cardiovascular fitness (i.e., stanine score of 6–9) versus low cardiovascular fitness (i.e., stanine score of 1–4).

As a result of the large number of observations, the majority of P values and SEMs were very small. Therefore, P values <0.0001 and SEMs in tables and figures were not reported unless otherwise stated. As a measure of variation, SDs are included in the legends.

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