Cardiorespiratory Fitness and Cognitive Function in Midlife: Neuroprotection or Neuroselection?

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Objective: A study was undertaken to determine whether better cognitive functioning at midlife among more physically fit individuals reflects neuroprotection, by which fitness protects against age-related cognitive decline, or neuroselection, by which children with higher cognitive functioning select more active lifestyles.

Methods: Children in the Dunedin Longitudinal Study (N = 1,037) completed the Wechsler Intelligence Scales and the Trail Making, Rey Delayed Recall, and Grooved Pegboard tasks as children and again at midlife (age = 38 years). Adult cardiorespiratory fitness was assessed using a submaximal exercise test to estimate maximum oxygen consumption adjusted for body weight in milliliters/minute/kilogram. We tested whether more fit individuals had better cognitive functioning than their less fit counterparts (which could be consistent with neuroprotection), and whether better childhood cognitive functioning predisposed to better adult cardiorespiratory fitness (neuroselection). Finally, we examined possible mechanisms of neuroselection.

Results: Participants with better cardiorespiratory fitness had higher cognitive test scores at midlife. However, fitness-associated advantages in cognitive functioning were already present in childhood. After accounting for childhood baseline performance on the same cognitive tests, there was no association between cardiorespiratory fitness and midlife cognitive functioning. Socioeconomic and health advantages in childhood and healthier lifestyles during young adulthood explained most of the association between childhood cognitive functioning and adult cardiorespiratory fitness.

Interpretation: We found no evidence for a neuroprotective effect of cardiorespiratory fitness as of midlife. Instead, children with better cognitive functioning are selecting healthier lives. Fitness interventions may enhance cognitive functioning. However, observational and experimental studies testing neuroprotective effects of physical fitness should consider confounding by neuroselection.

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Higher levels of physical fitness are associated with fewer medical comorbidities, reduced risk for cardiovascular disease, and greater functional capacity.[1–4] In addition, there is growing evidence that physical fitness is also associated with better cognitive functioning and lower risk of dementia.[5–9] New evidence from a longitudinal study has emerged showing a prospective association between physical fitness in young adulthood and later cognitive function in midlife.[10] This finding suggested the possibility that young adult physical activity can have neuroprotective effects that are manifest already by the middle of the life course. The implication is that an active lifestyle during young adulthood could be a prevention strategy to delay or postpone age-related cognitive decline.[11]

Parallel to research showing that physical fitness predicts better cognitive functioning, longitudinal studies

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that follow children into adulthood find that better cognitive functioning in childhood predicts better physical and brain health outcomes in older adults.[12–16] These findings suggest the possibility that better cognitive functioning in childhood could contribute to higher levels of physical fitness in adulthood. If such neuroselection contributes to the correlation between fitness and midlife cognitive function, there is a need to identify mechanisms through which childhood differences in cognitive functioning give rise to fitness disparities later in life.

To advance the science on how physical fitness is related to midlife cognitive functioning, studies are needed that can test neuroprotection and neuroselection hypotheses within a single sample. Data must include measurements of cognitive functioning in midlife, but also in childhood, before adult fitness levels are achieved. Childhood baseline measurements are necessary to distinguish cognitive benefits of fitness from differences in cognitive functioning that may precede adult fitness attainments.

We examined the relationship between fitness and cognitive functioning in a 4-decade longitudinal study of a single birth cohort. Cohort members completed the same cognitive test battery as children and again when they reached midlife, and also completed cycle ergometry testing to estimate their cardiorespiratory fitness. We tested whether more fit individuals performed better on a battery of midlife cognitive tests as compared to their less fit peers (previously interpreted as *neuroprotection*), and also whether children with better cognitive functioning were predisposed to better adult fitness (which we call *neuroselection* to reflect the nonrandom patterning of fitness across the cognitive ability distribution). Finally, we examined potential mechanisms that might account for any association between childhood cognition and cardiorespiratory fitness at midlife. We considered 2 possibilities. The first is that socioeconomic and health advantages might help children develop better cognitive abilities and subsequently better cardiorespiratory fitness. The second is that children with better cognitive abilities go on to live healthier lives, and that such lifestyle differences mediate the relationship between childhood intelligence and adult fitness.

Subjects and Methods

Sample

Participants are members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal investigation of health and behavior in a complete birth cohort. Study members (N = 1,037; 91% of eligible births; 52% male) were all individuals born between April 1972 and March 1973 in Dunedin, New Zealand, who were eligible for the longitudinal study based on residence in the province at age 3 years and who participated in the first follow-up assessment at age 3 years. A review of hospital records indicated that the 102 eligible children who did not participate did not differ significantly from the 1,037 participating children in their maternal prenatal complications, their birth weights, their neonatal complications, or the socioeconomic status of their families. The cohort represents the full range of socioeconomic status in the general population of New Zealand's South Island and is primarily white.[17] On adult health, the cohort matches the New Zealand National Health and Nutrition Survey (eg, body mass index, smoking, general practitioner visits).[18] Assessments were carried out at birth and at age 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and, most recently, 38 years, when 95% of the 1,007 study members still alive took part. At each assessment wave, study members are brought to the Dunedin Research Unit for a full day of interviews and examinations. The Otago Ethics Committee approved each phase of the study, and informed consent was obtained from all study members.

Measures

CARDIORESPIRATORY FITNESS. We estimated maximum oxygen consumption adjusted for body weight ([VO_2max]; in ml/min/kg) from measured heart rate in response to a submaximal exercise test on a friction-braked cycle ergometer according standard protocols.[19] Details on fitness testing are provided in Table 1.

COGNITIVE TESTING. The Dunedin Study conducted cognitive testing in childhood (when study members were age 7, 9, 11, and 13 years, averaged to produce childhood cognitive test performance measures) and at the midlife follow-up at age 38 years. We focused our analysis on the intelligence quotient (IQ), a highly reliable measure of general intellectual functioning that captures overall ability across a variety of cognitive functions.[20,21] We also examined performance on IQ subscales and performance on measures testing memory, executive functioning, and motor functioning.[22,23] The study conducted a parallel battery of cognitive testing in childhood and adulthood (see Table 1).

ADDITIONAL MEASURES. Measurements of childhood socioeconomic status, childhood health (a composite including repeated measures of adiposity, blood pressure, lung function, motor function, and diseases and injuries taken when study members were age 3–11 years), adult physical activity, obesity, smoking, and educational attainment are described in Table 1.[24–33]

Analysis

Analyses included n = 944 cohort members with cardiorespiratory fitness data. As compared to participants at age 38 years, study members who did not participate (including 30 who were deceased) had scored 6.6 IQ points lower on childhood IQ ($p < 0.001$).

To test for a cross-sectional association that could be consistent with a neuroprotective effect of cardiorespiratory fitness, we used linear regression to test whether individuals with good

TABLE 1. Description of Study Measures

Measure	Description
Cardiorespiratory fitness	Cardiorespiratory fitness was assessed by measuring heart rate in response to a submaximal exercise test on a friction-braked cycle ergometer. Dependent on the extent to which heart rate increased during a 2-minute 50W warmup, the workload was adjusted to elicit a steady heart rate in the range 130–170 beats per minute. After a further 6-minute constant power output stage, the maximum heart rate was recorded and used to calculate predicted maximum oxygen uptake adjusted for body weight in milliliters per minute per kilogram (VO_2max) according to standard protocols.[19] The mean (standard deviation [SD]) VO_2max was 23.72 (4.94) for women and 34.69 (6.23) for men. Sex-specific quartiles were formed based on performance at age 38 years. Quartile 1 is least fit; quartile 4 is most fit. The upper bounds of quartiles 1–3 were, respectively, 20.17, 23.64, and 26.64 for women and 30.46, 34.68, and 38.63 for men. n = 107 study members were either absent from the age- 38 assessment or did not complete fitness testing (34 declined fitness testing or were unable to complete testing due to illness, injury, disability, pregnancy, or other consideration; 27 completed assessments outside of the unit and fitness testing was not conducted). Of this group, 44 had completed cardiorespiratory fitness testing at the age- 32 assessment. Based on the high rank order stability of VO_2max across assessments (Pearson $r = 0.84$), we imputed age- 38 VO_2max for these study members by predicting it from their age- 32 measurements. The resulting analysis sample consisted of n = 944 study members. Effect sizes for VO_2max are reported in terms of sex-specific SD units.
Cognitive functioning	We measured IQ from the individually administered Wechsler Intelligence Scale for Children-Revised (WISC-R; averaged across ages 7, 9, 11, and 13 years)[20] and the Wechsler Adult Intelligence Scale-IV (WAIS-IV),[21] both with mean = 100 and SD = 15. In addition to the WISC-R and WAIS-IV, the Rey Auditory Verbal Learning Test,[22] the Trail Making Test,[23] and the Grooved Pegboard Test were administered at ages 13 and 38 years to assess, respectively, memory, executive, and motor functioning.[22] Scores for cognitive tests were scaled to have mean = 100 and SD = 15 to match the distribution of IQ scores. Scores for the Grooved Pegboard Test and the Trail Making Test were reversed so that higher values corresponded to better cognitive performance.
Childhood socioeconomic status	The socioeconomic statuses of cohort members' families were measured using a 6-point scale that assessed parents' occupational statuses, defined based on average income and educational levels derived from the New Zealand Census. The highest occupational status of either parent was averaged across the childhood assessments.[24]
Childhood health	We measured cohort members' childhood health from a panel of biomarkers and clinical ratings taken at assessments spanning birth to age 11 years. Motor development was assessed at ages 3, 5, 7, and 9 years using the Bailey Motor Scales (age 3 years),[28] McCarthy Motor Scales[29] (age 5 years), and Basic Motor Ability Test[30] (ages 7 and 9 years).[31] Children's overall health at ages 3, 5, 7, 9, and 11 years was rated by 2 Dunedin Research Unit staff members based on review of birth records and assessment dossiers including clinical assessments and reports of infections, diseases, injuries, hospitalizations, and other health problems collected from children's mothers during standardized interviews. Ratings were made on a 5-point scale (inter-rater agreement = 0.85). Body mass index (BMI) was calculated from height and weight measurements taken at ages 5, 7, 9, and 11 years. In addition, tricep and subscapular skinfold thicknesses were measured at ages 7 and 9 years by trained anthropometrists.[25] (For calculation of the overall measure, tricep and subscapular skinfold thicknesses were averaged to create a single score.) Systolic and diastolic blood pressure were measured at ages 7, 9, and 11 years using a London School of Hygiene and Tropical Medicine blind mercury sphygmomanometer (Cinetronics, Mildenhall, UK).[26] Fixed expiratory volume in 1 second (FEV_1) and the ratio of FEV_1 to forced vital capacity (FVC) were measured at ages 9 and 11 years using a Godart water spirometer.[27] To calculate the childhood health measure, assessments were standardized to have mean = 0 SD = 1 within age- and sex-specific groups. Cross-age scores for each measure were then computed by averaging standardized scores across measurement ages. Reliabilities for measurements for girls/boys are: motor ability = 0.79/0.73, clinician health rating = 0.66/0.68, BMI = 0.92/0.93, triceps skinfold thickness = 0.85/0.75, subscapular skinfold thickness = 0.90/0.85, systolic blood pressure = 0.81/0.84, diastolic blood pressure = 0.57/0.69, FEV_1 = 0.92/0.96, FEV_1/FVC = 0.84/0.85. The final childhood health score was calculated by taking the natural log of the average score across all measures, resulting in a normally distributed childhood health index.

TABLE 1: Continued

Measure	Description
Adult leisure-time physical activity	We measured study members' adulthood leisure-time physical activity level from data collected during structured interviews with Study members when they were aged 32 and 38 years. Trained interviewers guided study members through reporting the different types of physically demanding activities they engaged in during an average week and an average weekend. Study members then indicated number of minutes spent doing each activity at a moderate or more strenuous level of difficulty. Time spent on each activity was converted to metabolic equivalent (MET) units.[52] Moderate intensity activity was given a weight of 4; hard activity was given a weight of 6; and very hard activity was given a weight of 10. We summed weekday and weekend METs from moderate or more strenuous leisure activities to calculate physical activity levels at ages 32 and 38 years. METs per week were averaged across the 2 assessments to calculate adulthood physical activity. Physical activity was distributed as follows: 13% of the cohort (n = 123) were sedentary (ie, they engaged in 0 hours of moderate or more strenuous leisure activity per week at the age- 32 and -38 assessments); 27% (n = 266) were nonsedentary, but did not achieve the 500 METs/wk minimum recommended dosage of physical activity[53]; 26% (n = 256) achieved 500–1,000 METs/wk; and 34% (n = 335) exceeded 1,000 METs/wk. Because METs/wk exhibited a strong right skew, values were log transformed for analyses.
Obesity	We measured obesity from anthropometric data at ages 15, 18, 21, 26, 32, and 38 years. Obesity was defined at age 15 years as BMI >90th percentile of the sex-specific US Centers for Disease Control and Prevention reference distribution and thereafter as BMI of ≥30.[25] Between ages 15 and 38 years, 27% of the cohort met criteria for obesity at ≥1 assessments (n = 276). This prevalence is in line with the general New Zealand population (in the most recent Ministry of Health report, obesity prevalence was 28% for New Zealanders ≥15 years of age).[54] We calculated the cumulative number of assessments at which a cohort member had been obese during the 25-year interval between IQ assessments, hereafter "life-course cumulative obesity."
Educational attainment as of age 38 years	Education level was measured on a 5-point scale relevant to the New Zealand educational system: 1 = no secondary school qualifications (14.7%), 2 = school certificate (14.9%), 3 = high school graduate or equivalent (14.2%), 4 = postsecondary diploma or certificate (27.3%), 5 = bachelor's degree or higher (28.8%).[33]
Cigarette smoking	We measured smoking history as pack-years, the number of cigarettes smoked per day divided by 20 and multiplied by the number of years smoked at that rate through 38 years of age.[32]

cardiorespiratory fitness performed better on midlife cognitive testing as compared to peers with poor cardiorespiratory fitness.

To test neuroselection of children with better cognitive function into healthier lives, we used linear regression to test whether children with better cognitive functioning grew up to have better cardiorespiratory fitness as compared to peers with poorer cognitive functioning.

To test neuroprotection effects after accounting for any neuroselection into better fitness, we regressed the adult cognitive test score on adult cardiorespiratory fitness with adjustment for the childhood score on the same cognitive test. If the effect of fitness on adult cognitive test performance was reduced and no longer statistically significant after adjusting for childhood cognitive test performance, it would suggest that fitness-associated differences in cognitive function were already present from childhood.

To test whether neuroselection effects could be explained by differences in children's lives leading up to childhood cognitive testing, we re-estimated regression models testing neuroselection, this time adding childhood socioeconomic status and childhood health measures as antecedent covariates. If covariate adjustment attenuated the neuroselection effect, it would suggest that neuroselection effects were attributable to these childhood factors.

To test whether neuroselection effects came about through differences in the lives study members lived during the 25-year interval between childhood cognitive testing and adult fitness assessment, we conducted mediation analyses. For each potential mediator (physical activity, obesity, smoking, educational attainment), we tested associations between childhood IQ and the mediator; we tested associations between the mediator and adult fitness; and we tested the association between childhood IQ and adult fitness, including the mediator as a covariate. We used the system of equations described by Baron and Kenny[34] and the methods described by Preacher et al[35,36] to estimate total, direct, and indirect effects, and the proportion of the neuroselection effect accounted for by each of the mediators.

We analyzed cardiorespiratory fitness in population-defined quartiles to facilitate comparison with the analysis conducted by Zhu and colleagues.[10] We also analyzed cardiorespiratory fitness as a continuous z score (transformed to have

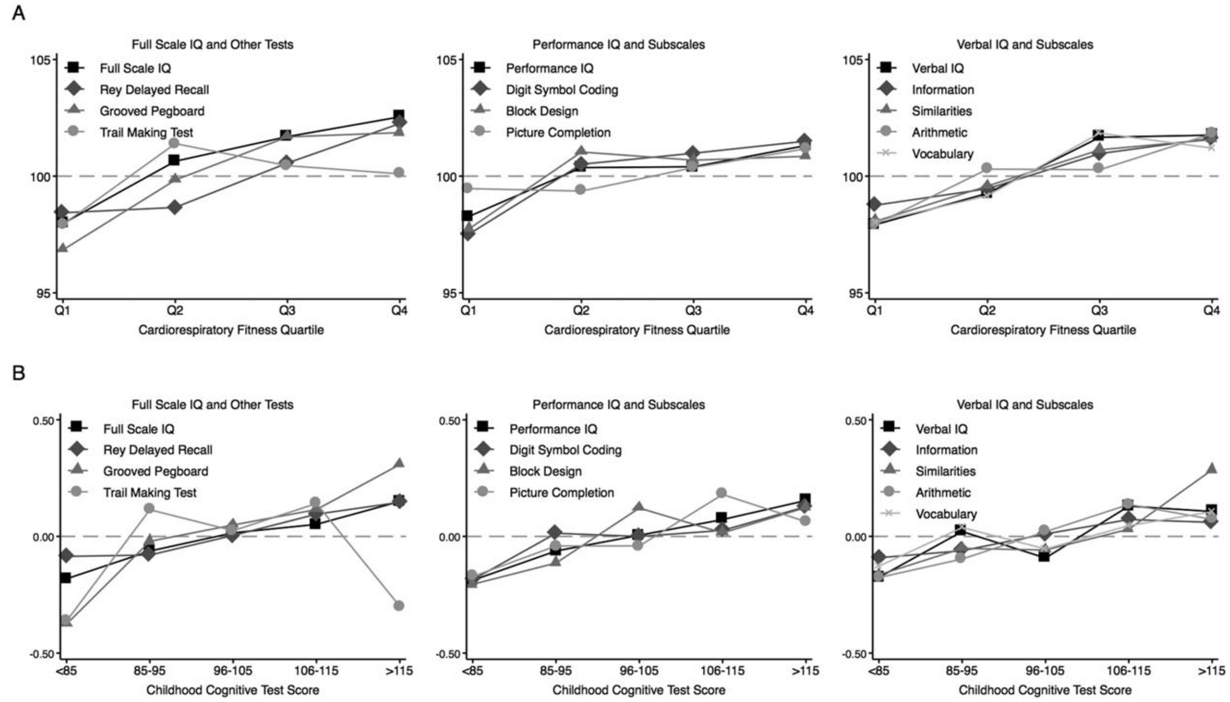

FIGURE 1: Association of cardiorespiratory fitness with midlife cognitive functioning (A) and association of childhood cognitive functioning with midlife cardiorespiratory fitness (B). Data are plotted for cardiorespiratory fitness quartiles and for categories of childhood cognitive functioning for illustrative purposes. Linear associations with continuous variables are reported in Tables 2 and 3. IQ = intelligence quotient.

mean = 0, standard deviation [SD] = 1). Fitness quartiles and *z* scores were calculated separately for men and women. We used linear regression models to analyze continuous dependent variables (eg, cognitive test performance). We used Poisson regression models to estimate relative risks (RRs) for dichotomous dependent variables (eg, being in the top fitness quartile). We used negative binomial regression models to estimate incidence rate ratios (IRRs) for count dependent variables (lifetime cumulative obesity).

Effect sizes for cardiorespiratory fitness are reported in terms of SD units. Effect sizes for cognitive tests are reported in IQ points (mean = 100, SD = 15). In analyses where childhood IQ is the predictor, effect sizes are reported for a 15-point (1 SD) change in childhood IQ. For analyses of other study variables, effect sizes are reported in terms of RRs or standardized coefficients (equivalent to Pearson *r*). Because the sample is a representative birth cohort, it forms its own norms for the purpose of estimating effect sizes. Regression models were adjusted for sex to account for differences in cardiorespiratory fitness. Analyses were conducted using Stata 13.0 (StataCorp, College Station, TX).

Results

Cross-Sectional Association of Cardiorespiratory Fitness with Cognitive Functioning in Adulthood

Dunedin Study members with better cardiorespiratory fitness scored higher on cognitive tests at age 38 years. Study members in the highest fitness quartile had full-scale IQ scores 4.57 points higher as compared to study members in the lowest fitness quartile (95% confidence interval [CI] = 1.88–7.27, $p = 0.001$). Across the cardiorespiratory fitness distribution, each SD increase in fitness predicted a 1.31-point increase in full-scale IQ score (standard error [SE] = 0.50, $p = 0.009$). Differences of similar magnitude were observed for performance and verbal intelligence subscales and for the Rey Delayed Recall task and the Grooved Pegboard task (Fig 1A, Table 2).

Prospective Association of Cognitive Functioning in Childhood with Adult Cardiorespiratory Fitness

Consistent with the neuroselection hypothesis that individuals with better cognitive functioning develop and maintain better cardiorespiratory fitness, Dunedin Study members who scored higher on cognitive tests in childhood had better cardiorespiratory fitness 25 years later (see Fig 1B, Table 3). Each SD increase in full-scale IQ score measured in childhood predicted a 0.12 SD increase in cardiorespiratory fitness at follow-up (SE = 0.04, $p = 0.002$) and a 20% increase in a study member's likelihood of being in the top cardiorespiratory fitness quartile (RR = 1.20, 95% CI = 1.07–1.35, $p = 0.003$). Effect sizes were similar for performance and verbal intelligence subscales and for the Rey Delayed Recall task and Grooved Pegboard task.

TABLE 2. Association of Physical Fitness with Midlife Cognitive Function

	Linear Association			Comparison of Top and Bottom Fitness Quartiles		
Cognitive Test	**b**	**SE**	***p***	**b**	**SE**	***p***
Full-scale IQ	1.31	(0.50)	0.009	4.57	(1.37)	0.001
Performance IQ	0.86	(0.51)	0.092	3.05	(1.42)	0.032
Digit symbol Coding	1.11	(0.48)	0.020	3.94	(1.32)	0.003
Block design	0.97	(0.52)	0.061	3.13	(1.40)	0.026
Picture completion	0.59	(0.51)	0.251	1.73	(1.38)	0.212
Verbal IQ	1.12	(0.48)	0.019	3.85	(1.33)	0.004
Information	0.71	(0.48)	0.143	2.91	(1.33)	0.028
Similarities	1.07	(0.51)	0.034	3.51	(1.41)	0.013
Arithmetic	1.12	(0.49)	0.023	3.90	(1.35)	0.004
Vocabulary	1.02	(0.47)	0.031	3.16	(1.31)	0.016
Rey Delayed Recall	1.29	(0.48)	0.007	3.79	(1.34)	0.005
Grooved Pegboard	1.81	(0.58)	0.002	5.02	(1.43)	0.000
Trail Making Test	0.36	(0.51)	0.475	2.14	(1.45)	0.138

Predictor is physical fitness; outcome is midlife cognitive function.
IQ = intelligence quotient; SE = standard error.

Mechanisms Mediating the Prospective Association of Cognitive Functioning in Childhood with Adult Cardiorespiratory Fitness

When associations between adult cognitive test performance and cardiorespiratory fitness were adjusted for study members' performance on the same cognitive tests when they were children, effect sizes were reduced by as much as 90% and were no longer statistically significant (Fig 2, Table 4). This result indicates that whatever fitness differences developed during the interval between baseline cognitive testing in childhood and follow-up cognitive testing at age 38 years did not contribute to better cognitive functioning at age 38 years. Any cognitive advantage associated with better adult cardiorespiratory fitness had been present since childhood. This evidence supports neuroselection, but not neuroprotection.

What might account for this neuroselection? One hypothesis is that children's early socioeconomic status and health influence their cognitive development and, later, their cardiorespiratory fitness. In the Dunedin Cohort, children born into higher socioeconomic status households scored higher on cognitive tests in childhood and had better cardiorespiratory fitness in adulthood as compared to children born into lower socioeconomic status households (for childhood IQ, $r = 0.38$, $p < 0.001$; for adult cardiorespiratory fitness, $r = 0.10$, $p = 0.001$). Similarly, children in better physical health scored higher on cognitive tests in childhood and had better cardiorespiratory fitness 25 years later as compared to less healthy children (for childhood IQ, $r = 0.20$, $p < 0.001$; for cardiorespiratory fitness, $r = 0.21$, $p < 0.001$). Adjusting for these characteristics attenuated the association between childhood cognitive ability and adult cardiorespiratory fitness, but the association remained statistically significant (with adjustment for socioeconomic disadvantage, b = 0.11, SE = 0.04, $p = 0.011$; with adjustment for childhood health, b = 0.09, SE = 0.04, $p = 0.014$). With adjustment for childhood socioeconomic position and health together, the *p*-value no longer met the alpha = 0.05 threshold for statistical significance (b = 0.08, SE = 0.04, $p = 0.054$).

A second explanation for why children with higher IQs go on to have better cardiorespiratory fitness as adults is that they select healthier lives. A proximate cause of cardiorespiratory fitness is physical activity. Children with higher IQ scores were less likely to be sedentary adults (sedentary RR = 0.74, 95% CI = 0.63–0.86, $p < 0.001$). Among those who were nonsedentary, higher childhood IQ predicted increased adult leisure activity ($r = 0.09$, $p = 0.006$). In turn, as expected, a more active lifestyle was associated with better cardiorespiratory fitness ($r = 0.16$, $p < 0.001$). But mediation analysis indicated that adult

TABLE 3. Association of Childhood Cognitive Function with Adult Physical Fitness

	Linear Association			Probability of Membership in Top Fitness Quartile		
Cognitive Test	**b**	**SE**	***p***	**RR**	**95% CI**	***p***
Full-scale IQ	0.12	(0.04)	0.002	1.20	1.07–1.35	0.003
Performance IQ	0.10	(0.04)	0.007	1.16	1.03–1.29	0.013
Digit symbol coding	0.08	(0.04)	0.034	1.13	1.01–1.27	0.029
Block design	0.09	(0.04)	0.011	1.12	1.00–1.26	0.042
Picture completion	0.07	(0.04)	0.047	1.12	1.00–1.26	0.043
Verbal IQ	0.11	(0.04)	0.003	1.20	1.07–1.34	0.002
Information	0.06	(0.03)	0.076	1.15	1.03–1.28	0.016
Similarities	0.14	(0.03)	0.000	1.24	1.11–1.40	0.000
Arithmetic	0.10	(0.04)	0.008	1.16	1.04–1.30	0.009
Vocabulary	0.06	(0.03)	0.065	1.13	1.02–1.25	0.024
Rey Delayed Recall	0.11	(0.04)	0.004	1.19	1.04–1.35	0.009
Grooved Pegboard	0.19	(0.04)	0.000	1.34	1.16–1.54	0.000
Trail Making Test	0.09	(0.04)	0.042	1.08	0.95–1.22	0.230

Coefficients (b) reflect standardized effect-sizes equivalent to Pearson's r.
Predictor is childhood cognitive function; outcome is physical fitness.
CI = confidence interval; IQ = intelligence quotient; RR = relative risk; SE = standard error.

physical activity accounted for only 16% of the association between childhood IQ and adult cardiorespiratory fitness (*p*-value for indirect effect = 0.005). After accounting for differences in physical activity, the childhood-IQ–adult cardiorespiratory fitness association was only modestly attenuated (b = 0.11, SE = 0.04, $p = 0.006$).

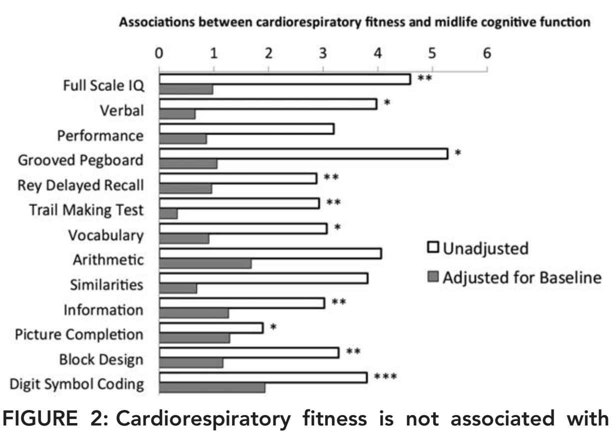

FIGURE 2: Cardiorespiratory fitness is not associated with midlife cognitive test performance after adjustment for childhood baseline performance on the same cognitive test. Differences in midlife cognitive test performance between individuals in the top and bottom quartiles of cardiorespiratory fitness are shown. Unadjusted effect sizes are shown for associations between cardiorespiratory fitness and midlife cognitive functioning *(white bars)* and effect sizes after adjusting for childhood baseline performance on the same cognitive test *(gray bars)*. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. IQ = intelligence quotient.

Physical activity during a single decade of adult life may provide an insufficient summary of healthy lifestyle processes that support the development and maintenance of cardiorespiratory fitness. We therefore considered lifetime obesity as a surrogate marker for healthy lifestyle. We analyzed a cumulative obesity measure that captured the onset and persistence of obesity across the 25-year interval between the completion of childhood IQ testing at age 13 years and the assessment of cardiorespiratory fitness at age 38 years. Children with higher IQ scores were less likely to become obese during follow-up (RR = 0.83, 95% CI = 0.75–0.91, $p < 0.001$), and they were obese at fewer assessments (IRR = 0.76, 95% CI = 0.66–0.86, $p < 0.001$). In turn, as expected, study members with less lifetime obesity had better cardiorespiratory fitness; each additional assessment at which a study member remained lean was associated with a 0.43-SD (SE = 0.02) increase in their cardiorespiratory fitness ($p < 0.001$). Mediation analysis indicated that 47% of the association between childhood IQ and adult cardiorespiratory fitness was accounted for by lifetime obesity (*p*-value for indirect effect = 0.005). After accounting for differences in obesity histories, the childhood-IQ–adult fitness association was reduced by nearly half and was no longer statistically significant (b = 0.05, SE = 0.03, $p = 0.142$). Together, physical activity and obesity accounted for a total of 61% of the childhood-IQ–adult fitness association.

TABLE 4. Association of Cardiorespiratory Fitness with Midlife Cognitive Test Performance, before and after Adjustment for Childhood Baseline Performance on the Same Cognitive Test

	Linear Associations						Comparison of Top and Bottom Fitness Quartiles					
	Unadjusted Effect Size			Effect Size Adjusted for Childhood Baseline			Unadjusted Effect Size			Effect Size Adjusted for Childhood Baseline		
Cognitive Test	**b**	**SE**	***p***	**b**	**SE**	***p***	**b**	**SE**	***p***	**b**	**SE**	***p***
Full-scale IQ	1.31	0.50	0.009	0.11	0.29	0.717	4.57	1.37	0.001	0.98	0.84	0.246
Performance IQ	0.86	0.51	0.092	0.07	0.39	0.852	3.05	1.42	0.032	0.87	1.09	0.426
Digit symbol coding	1.11	0.48	0.020	0.48	0.38	0.204	3.94	1.32	0.003	1.94	1.06	0.069
Block design	0.97	0.52	0.061	0.24	0.38	0.521	3.13	1.40	0.026	1.17	1.04	0.263
Picture completion	0.59	0.51	0.251	0.35	0.49	0.471	1.73	1.38	0.212	1.29	1.32	0.330
Verbal IQ	1.12	0.48	0.019	0.08	0.29	0.781	3.85	1.33	0.004	0.66	0.87	0.449
Information	0.71	0.48	0.143	0.16	0.34	0.639	2.91	1.33	0.028	1.27	0.96	0.187
Similarities	1.07	0.51	0.034	0.11	0.42	0.801	3.51	1.41	0.013	0.69	1.21	0.569
Arithmetic	1.12	0.49	0.023	0.37	0.36	0.314	3.90	1.35	0.004	1.68	1.06	0.112
Vocabulary	1.02	0.47	0.031	0.42	0.34	0.220	3.16	1.31	0.016	0.91	0.98	0.356
Rey Delayed Recall	1.29	0.48	0.007	0.21	0.48	0.669	3.79	1.34	0.005	0.96	1.38	0.486
Grooved Pegboard	1.81	0.58	0.002	0.26	0.57	0.654	5.02	1.43	0.000	1.06	1.53	0.490
Trail Making Test	0.36	0.51	0.475	−0.51	0.51	0.316	2.14	1.45	0.138	0.33	1.54	0.830

The table presents linear associations between continuously distributed fitness and cognitive function (left side) and also, for illustrative purposes, comparisons of cognitive function in the top and bottom fitness quartiles (right side).
IQ = intelligence quotient; SE = standard error.

A history of cigarette smoking and truncated education may also influence physical health. When we added measures of smoking history and educational attainment to the mediation model, the full set of mediators accounted for 74% of the childhood-IQ–adult fitness association (Supplementary Table).

Discussion

We analyzed data from a 4-decade longitudinal study of a birth cohort to test neuroprotective effects of fitness. More physically fit adults exhibited better cognitive performance at midlife. However, this advantage was almost completely explained by differences in cognitive function already present in childhood. We then examined how children with better cognitive function came to have better fitness 25 years later. Dunedin Study children with better cognitive function grew up in higher socioeconomic status households and enjoyed better health before childhood baseline cognitive testing. These early life differences accounted for a portion of the neuroselection effect. It is possible that other unmeasured characteristics of the children would further account for the better fitness we observed among children with higher IQ scores. In addition, we found that neuroselection into better adult fitness appeared to reflect differences in the lives children led between baseline IQ testing and follow-up 25 years later, particularly regarding their lifetime histories of obesity.

We acknowledge limitations. First, the Dunedin cohort comes from a single nation and is predominantly white. The cohort represents the full spectrum of socioeconomic status and health, and has a track record of replication in American, British, and international cohorts. Nonetheless, replication in diverse cohorts is needed. Second, cardiorespiratory fitness was not assessed in childhood. As a result, we could not account for the possibility that poor cardiorespiratory fitness in childhood was a cause of low childhood IQ. However, to address this limitation, our analysis did take into account differences in children's blood pressure, lung function, adiposity, and experience of childhood illnesses. Third, cognitive testing data were right censored; the most recent follow-up was completed at age 38 years. It remains possible that cardiorespiratory fitness will have neuroprotective properties later in the life course. Fourth, we assessed cardiorespiratory fitness as heart rate response to a submaximal exercise test rather than with direct measurement of VO_2max.[37] We note that epidemiologic studies, including the original investigation reporting possible neuroprotective effects of young adult fitness, use indirect methods to evaluate cardiorespiratory fitness.[10,38,39] We do not anticipate that use of directly measured VO_2max would substantively alter results, because correlations between indirect and direct measures of VO_2max are approximately $r = 0.9$ in studies comparing the two.[19,40,41]

The findings have implications for research, policy, and intervention. There is now evidence from randomized trials that increasing physical activity in late life may improve cognitive function.[4,6,42] This evidence has spurred observational research and intervention studies to examine the possibility that active lifestyle promotion for young adults could serve as an early prevention strategy to promote healthy cognitive aging population-wide.[43–45] Physical fitness at any age has important physical health benefits. But our data suggest that, at least where young adult fitness is concerned, protecting cognitive function through midlife is not among them. This does not rule out the possibility that fitness interventions could improve cognitive functioning. But our data indicate that future studies examining cognitive benefits of fitness at any stage in life must take account of the neuroselection phenomenon, in which children with the best cognitive function select lives that promote the development and maintenance of cardiorespiratory fitness. Neuroselection is an important consideration even in randomized trials, where cognitive ability may influence who enrolls, who adheres to the physical activity program, and who drops out.

At the level of policy, neuroselection findings lend additional support to efforts to promote early childhood cognitive health as a means of improving outcomes in adulthood.[46] Reducing toxic exposures and increasing nourishing ones (both chemical and psychological) are proven means of enhancing cognitive development.[47–51] As our data show, the dividends of healthy cognitive development may extend to adult fitness through the fourth decade of life—a strong indicator of reduced age-related morbidity to follow.

Neuroselection findings also have implications for interventions to promote physical fitness. Obesity prevention is already a public health priority. Some progress is being made. What our study adds is insight into how current population-level prevention strategies promoting active lifestyle and healthy diet may benefit some population segments more than others. We found that children with higher IQ scores grew up to be adults who were less sedentary and less obese, and in turn, had better cardiorespiratory fitness. It is possible that individuals with strong cognitive resources are responding to public health messages, whereas their peers with fewer cognitive resources may be struggling to take up behavior change recommendations. Recommendations to eat healthily and exercise are easy to understand, but require cognitive effort to implement. Moreover, eating healthy food and getting more leisure activity are not always cheap or easy. Given that unhealthy calories and sedentary lifestyle are cheap and easy, public health messaging and incentive programs to promote healthy diet and exercise should be paired with resources and services to help at-risk individuals accomplish these objectives.

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Potential Conflicts of Interest

Nothing to report.

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