Association of cardiorespiratory fitness with dementia risk across different levels of genetic predisposition: a large community-based longitudinal study

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ABSTRACT

Objective We aimed to investigate the association of cardiorespiratory fitness (CRF) with cognitive function and dementia risk, taking genetic predisposition for dementia into account.

Methods Within the UK Biobank, 61 214 dementia-free participants aged 39–70 years were followed for up to 12 years. CRF score was estimated using a 6 min submaximal exercise test on a stationary bike and divided into tertiles (ie, low, moderate, and high; standardised by age and sex). Global cognitive function was evaluated at baseline. Dementia was identified based on medical history and medical records. Genetic predisposition for dementia was estimated using the polygenic risk score for Alzheimer's disease (PRS_{AD}), tertiled as low, moderate, or high. Data were analysed using linear regression, Poisson regression, and Laplace regression.

Results Compared with low CRF, high CRF was related to better global cognitive function (β=0.05, 95% CI 0.04 to 0.07). Over the follow-up period, 553 individuals developed dementia. Compared with low CRF, the incidence rate ratio (IRR) of all dementia was 0.60 (95% CI 0.48 to 0.76) for high CRF, and the onset of all dementia was delayed by 1.48 (95% CI 0.58 to 2.39) years among people with high versus low CRF. Among people with a moderate/high polygenic risk score, high CRF attenuated all dementia risk by 35% (IRR 0.65, 95% CI 0.52 to 0.83).

Conclusion High CRF is associated with better cognitive performance at baseline, and lower dementia risk long-term. High CRF could mitigate the impact of genetic predisposition on the development of dementia by 35%.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardiorespiratory fitness (CRF), estimated using maximal exercise testing, has been associated with cognitive function and dementia risk, with some inconsistent results.

WHAT THIS STUDY ADDS

⇒ High CRF is associated with better global and domain-specific cognitive functions and lower risk of dementia in both middle-aged and older adults.

⇒ Higher CRF may partially mitigate the polygenic risk for Alzheimer's disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ CRF may be used as a predictor of cognitive health.

⇒ Enhancing CRF could be a strategy for the prevention of dementia, even among people with a high genetic predisposition for Alzheimer's disease.

INTRODUCTION

Cardiorespiratory fitness (CRF) refers to the capacity of the circulatory and respiratory systems to supply oxygen to skeletal muscle mitochondria in order to meet the energy demands of physical activity.[1] CRF declines over the life course, and the rate of decline accelerates with advancing age, from −3% to −6% per decade in the 20s and 30s to over −20% per decade in the 70s and beyond.[2] This is mainly driven by declines in skeletal muscle metabolism and function in older age.[2] Low CRF has been recognised as a strong and independent predictor of cardiovascular events and all-cause mortality.[3] Maximal exercise testing is considered to be the most accurate measurement of CRF.[3] However, it requires participants to exercise to exhaustion and therefore can only be performed in relatively healthy populations, with obvious selection biases and lack of generalisability.[4] The submaximal test, which estimates CRF from the relationship between the incremental heart rate response and work rate, is safer, relatively less expensive, and simpler to perform than maximal exercise testing, and therefore is more appropriate for estimating CRF in large epidemiological studies.[3 4] In addition, the submaximal exercise test is much more accurate than the non-exercise prediction equation (using variables such as age, sex, resting heart rate, body mass index (BMI), physical activity, etc) for estimating CRF.[3 5]

To date, most studies investigating the CRF–cognition association have been characterised by relatively small sample sizes, limited populations, and inconsistent findings. Several studies have associated high CRF with better performance on cognitive domains such as attention, executive function, and visual memory among older adults.[6–10] However, one study reported no association between CRF and global or domain-specific cognitive functions in older adults,[11] and another study found that high CRF was related to better performance on visual memory and problem-solving ability in adults aged 55–65 years, but not in those aged 40–54 years.[12] So far, three community-dwelling cohort studies have explored the relationship between CRF (using

the maximal exercise test) and all dementia in adults aged <65 years, showing that higher CRF is associated with a lower all dementia risk.[13–15] However, due to the limited sample size and age range of older participants, the relationship between CRF and dementia risk among older adults warrants further investigation. Additionally, no studies have explored the relationship between CRF measured by submaximal exercise testing and dementia. To date, the association of CRF with cognitive function and risk of dementia remains unclear among middle-aged and older adults.

Genetic predisposition plays an important role in the development of dementia.[16] Polygenic risk scores derived from genome-wide association studies (GWAS) are widely used to assess the genetic risk for Alzheimer's disease (AD) and all dementia.[17–19] Growing evidence suggests that the genetic risk of dementia can be modified by the protective effects of some modifiable influencing factors.[20] To our knowledge, no study to date has explored the combined effect of CRF and genetic risk on dementia. Open questions remain regarding whether and to what extent favourable CRF may reduce dementia risk, even in those with a high genetic predisposition for dementia.

In this study, using data from the UK Biobank, we aimed to: (1) investigate the association between CRF and cognitive function in different domains; (2) explore the association between CRF and dementia risk, including all dementia, AD, and vascular dementia (VaD); and (3) investigate whether high CRF can attenuate the risk of all dementia among people with a high genetic predisposition.

METHODS

Study design and population

The study population was derived from the UK Biobank, a community-based longitudinal study designed to provide a detailed investigation of the genetic and non-genetic determinants of disease in middle and old age.[21] Between 2006 and 2010, 502 412 UK residents aged 37–73 years who were registered with the National Health Service attended a baseline examination at one of 22 assessment centres across the country.[22]

Among the 61 887 individuals with available data on CRF, we excluded 131 with chronic obstructive pulmonary disease, 269 with asthma, 169 with heart failure, 26 with prevalent dementia that occurred before baseline, and 87 with outlier values of CRF (ie, ≥3 standard deviations from the mean). This left an analytical sample of 61 214 individuals for the current analysis (online supplementary figure 1).

Equity, diversity and inclusion

Our research and author team included five women and two men, who were at early-, mid-, and senior-stage in their careers with different races (including Asian and white). The study population included a spectrum of ages, genders, demographics (most of white descent), and comorbidities. In discussing the generalisability of our results and limitations of the findings, we acknowledge that the participants of the UK Biobank were derived from less socioeconomically deprived areas; therefore this study may include individuals with better health conditions than the general population.[22]

Data collection

At baseline, participants provided information on sociodemographic characteristics (age, sex, race, socioeconomic status, and education), lifestyle factors (smoking, alcohol consumption, physical activity, and social activity), and medical history (self-reported disease history and medication history) through a computerised touchscreen questionnaire, provided a blood sample, and underwent a verbal interview and comprehensive physical examination (including measurement of blood pressure, height, weight, and resting heart rate). Information on disease was ascertained based on information of self-reported, primary care, inpatient registry, and the death registry records. All diagnoses in medical records were recorded according to the 9th and 10th versions of the International Classification of Diseases (ICD-9 and ICD-10). Due to space constraints, more details are presented in the supplementary materials (see online supplemental method 1 and table 1). The cognitive tests and submaximal exercise test for CRF were conducted at the assessment centres on the same day.

Assessment of CRF

At baseline, a subset of UK Biobank participants was invited to complete a 6 min submaximal exercise test on a stationary bike (eBike Comfort Ergometer, General Electric, firmware version 1.7) while wearing a four-lead electrocardiographic monitor. Each participant was assigned an individualised protocol based on their risk category (assessed through interviews) and maximum workload (calculated according to age, height, weight, resting heart rate, and sex) (online supplemental method 3). All participants who underwent the test were asked to cycle at 60 revolutions per min during all cycling phases. More details can be found at https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=100229.

CRF was calculated based on standard protocols from a previous study.[23] A flowchart for the calculation of CRF is shown in Supplementary Figure 2. Linear regression was used to fit the linear relationship between workload and heart rate, which was then extrapolated to age-predicted maximum heart rate (208–0.7×age) to estimate an individual's maximal work rate (Watts (W)). Maximum oxygen consumption (in mL kg^{-1} min^{-1}) was calculated using the equation: 7 + (10.8×maximal work rate (W))/body weight (kg), which was then expressed in terms of maximal metabolic equivalents (METs) (where 1 MET=3.5 mL kg^{-1} min^{-1}). To make CRF more appropriate for clinical settings, the value of CRF was further standardised by age (10 years a group) and sex. Finally, CRF was tertiled as low (−2.74 to −0.43), moderate (−0.59 to 0.36), and high (0.28 to 6.61) within age and sex groups.

Assessment of global and domain-specific cognitive function

Cognitive function was assessed at baseline with neuropsychological tests and administered through a touchscreen interface. These cognitive tests were intentionally brief and constructed to evaluate cognitive domains that are sensitive to ageing and/or pathological processes.[24] In the present study, four cognitive tests were used to reflect different cognitive domains: prospective memory (prospective memory test; scored as the ability to successfully carry out an instruction after a filled delay); visual memory (pairs matching test; scored as the number of errors when recalling positions of matching pairs); verbal/numeric memory (fluid intelligence test; scored as the number of correct answers given to the 13 fluid intelligence questions); and processing speed (reaction time test; scored as the mean time to first press of snap-button summed over rounds in which both cards matched). Detailed descriptions of each test have been described previously.[24 25] The average scores of each test were calculated to obtain a measure of global cognitive function. Higher value on each measure indicates a better cognitive function.

More details about each cognitive test and the calculation of cognitive scores can be found in online supplemental method 3.

Assessment of dementia

All types of dementia (including AD, VaD, Lewy body dementia, frontotemporal dementia, and mixed dementia), AD, and VaD were algorithmically-defined based on information from self-reports (participants indicated to have been diagnosed with dementia at baseline), medical records (clinical diagnoses from primary care or hospital admissions), and death records (provided by physicians).[26 27] The date of dementia occurrence was set as the earliest date of the record, regardless of the source used. ICD-9 and ICD-10 codes for dementia diagnosis and classification are shown in online supplemental table 2.

Assessment of polygenic risk score for AD

A standard polygenic risk score was developed to capture an individual's load of common genetic variants associated with AD and dementia risk using a Bayesian approach.[28] More details can be found in online supplemental method 4. Participants' number of AD-related alleles were summed after weighing for the strength of each allele's association with AD which was ascertained based on a comprehensive meta-analysis of numerous GWAS, and then Z-standardised to derive a polygenic risk score for AD (PRS_{AD}). This score was further tertiled to yield three categories: low, moderate, and high.

Statistical analysis

Baseline characteristics of the study population by CRF level were compared using χ^2 tests for categorical variables, one-way analysis of variance (ANOVA) for normally distributed and variance homogeneity continuous variables, and Kruskal-Wallis H test for skewed distributed or variance heterogeneity continuous variables. The magnitude of effect size was assessed by Cramer's V for categorical variables and eta squared (η^2) for continuous variables. The sample size of this study was adequate to assure a 90% power at a two-sided $\alpha=0.05$ (exposure time 11.5 years vs 11.6 years; alt rate ratio 0.54).

Linear regression models were used to estimate standardised β-coefficients and 95% confidence intervals (95% CIs) for the cross-sectional association of CRF with global and domain-specific cognitive function. All models meet the assumptions for linear regression, including linearity, independence of observations, and normality. Robust regression was used to account for heteroscedasticity of residuals. Considering the low incidence of dementia in this study population (0.90%), Poisson regression offset by the natural logarithm of the exposure time was used to evaluate incidence rate ratios (IRRs) with 95% CIs for the relationship of CRF and the risks of all dementia/AD/VaD. We found no evidence of overdispersion in the Poisson regression models and the models met the assumption of linearity. Follow-up time was calculated as the time interval from study entry to dementia diagnosis, death, or the latest available follow-up (20 January 2022), whichever occurred first. The censoring proportion of this study was 99.10%, including 3.82% who died. Laplace regression models were used to estimate the percentile differences (PDs) in time (years, with 95% CIs) of all dementia/AD/VaD onset according to different levels of CRF. According to the cumulative incidence of dementia in this study population and the applicability of Laplace regression, the fifth PDs of all dementia/AD/VaD onset were estimated. No multicollinearity was detected in the models above (variance inflation factors <10). Furthermore, stratified analyses were performed according to age (middle-aged (<60) vs old age (≥60)) and PRS_{AD} (low vs moderate vs high).

Multiplicative interactions were tested by including an indicator variable with the cross-product of CRF and the variable of interest (CRF×age or CRF×PRS_{AD}) in linear regression or Poisson regression models. The joint effect of CRF and PRS_{AD} on all dementia was assessed by creating indicator variables based on joint exposures to both factors. The additive interaction was assessed by calculating the relative excess risk due to interaction (RERI), attributable proportion, and synergy index.

All analyses were adjusted for age (categorised), education, race, socioeconomic status, smoking status, alcohol consumption, BMI, physical activity, social activities, diabetes, hypertension, cardiovascular disease, dyslipidaemia, global cognitive function, and PRS_{AD} (if applicable). The factors that are potentially related to both the exposure and outcome were considered as potential confounders as shown in other relevant studies. Missing values for socioeconomic status (0.12%), education (1.07%), BMI (0.05%), smoking status (0.53%), alcohol consumption (0.29%), physical activity (6.29%), social activity (0.77%), and dyslipidaemia (7.58%) were imputed using multiple imputations of chained equations with 10 imputed datasets generated. Age, sex, race, diabetes, hypertension, cardiovascular disease, global cognitive function, PRS_{AD}, and CRF were used as independent variables. Missing values for race were not imputed because it is an inherent characteristic and independent of other variables. Similarly, imputation of PRS_{AD} should be based on GWAS data,[29] thus was not imputed as well.

In sensitivity analysis, we repeated the analyses after: (1) creating the CRF groups based on unstandardised CRF values and adjusting models for age and sex (to provide unstandardised regression coefficients to facilitate comparison with other studies)[30]; (2) further adjusting for survival status at the end of follow-up (only CRF-dementia association; consider the competing risk of death); (3) excluding participants who were diagnosed with dementia within the first 3 years of follow-up (to exclude potential prodromal dementia or undiagnosed dementia at baseline given the progressive nature of the disease); (4) further adjusting for statins, β-blockers, and calcium channel blockers (reported to be associated with both cardiac function and dementia[31–34]); and (5) using data without multiple imputations for missing values of covariates. All p values were two-tailed, and those <0.05 were considered statistically significant. Multiple comparisons were corrected using the false discovery rate (FDR). Analyses were performed using Stata SE 15.0 (StataCorp, College Station, TX, USA).

RESULTS

Baseline characteristics of the study population

At baseline, the mean (SD) age of the 61 214 participants was 56.33 (8.15) years (range 39–70 years), and 51.96% were female. The mean (SD) values of age- and sex-specific CRF (unit: MET) were −1.02 (0.40) for the low CRF group, −0.10 (0.23) for the moderate group, and 1.12 (0.71) for the high group. Compared with those with moderate or high CRF, participants with low CRF were more likely to be older, non-white, have a lower socioeconomic status and education level, have a higher BMI, abstain from smoking and alcohol drinking, have lower levels of physical activity and social activity, have a higher prevalence of diabetes, hypertension, cardiovascular disease, and dyslipidaemia, and have worse cognitive function and a lower PRS_{AD} (table 1). A table of original CRF values (not standardised) by age and sex has been provided as online supplemental table

Table 1 Characteristics of the study population by cardiorespiratory fitness (N=61 214)

Characteristics	CRF			χ^2/F	Effect size	P value
	Low (N=20 408)	Moderate (N=20 405)	High (N=20 401)			
CRF, MET	−1.02±0.40	−0.10±0.23	1.12±0.71	5.44E4	0.888	<0.001
Age at baseline, years	56.62±8.28	56.35±8.14	56.02±8.01	71.37	0.001	<0.001
Sex (female)	10 604 (51.96)	10 603 (51,96)	10 600 (51.96)	1.00E-3	–	1.000
Race (white)	17 624 (86.96)	17 835 (87.98)	17 946 (88.47)	22.47	0.019	<0.001
Socioeconomic status	−1.66 (−3.35 to 1.07)	−1.90 (−3.50 to 0.53)	−1.99 (−3.56 to 0.53)	151.05	0.002	<0.001
Education (university)	6270 (31.16)	7381 (36.57)	9018 (44.52)	779.44	0.113	<0.001
BMI, kg/m^2	28.86±5.12	26.95±3.96	25.58±3.52	5.03E3	0.082	<0.001
<20	319 (1.57)	381 (1.87)	700 (3.43)	5.00E3	0.201	<0.001
20–25	4373 (21.45)	6323 (31.00)	8868 (43.47)			
25–30	8237 (40.41)	9686 (47.48)	8608 (42.20)			
≥30	7454 (36.57)	4010 (19.66)	2222 (10.89)			
Smoking status				20.54	0.013	<0.001
Never	11 504 (56.71)	11 316 (55.76)	11 068 (54.50)			
Previous	6949 (34.26)	7126 (35.11)	7333 (36.11)			
Current	1831 (9.03)	1853 (9.13)	1909 (9.40)			
Alcohol consumption				201.58	0.041	<0.001
Never	1027 (5.05)	803 (3.95)	536 (2.63)			
Previous	711 (3.50)	627 (3.08)	506 (2.49)			
Current	18 594 (91.45)	18 918 (92.97)	19 316 (94.88)			
Physical activity				1.10E3	0.139	<0.001
Insufficient	5884 (31.57)	4794 (25.03)	3323 (16.97)			
Sufficient	12 753 (68.43)	14 356 (74.97)	16 225 (83.03)			
Social activity				6.10	0.010	0.047
Low	4794 (23.73)	4601 (22.72)	4668 (23.01)			
High	15 412 (76.27)	15 651 (77.28)	15 619 (76.99)			
Diabetes	1366 (6.69)	832 (4.08)	617 (3.02)	332.01	0.074	<0.001
Hypertension	12 727 (62.36)	10 117 (49.58)	8536 (41.84)	1.80E3	0.169	<0.001
Cardiovascular disease	1461 (7.16)	1187 (5.82)	1308 (6.41)	30.52	0.022	<0.001
Dyslipidaemia	3561 (18.89)	3014 (15.95)	2363 (12.55)	285.12	0.071	<0.001
Global cognitive function	−0.05±0.66	0.00±0.63	0.05±0.60	225.18	0.004	<0.001
PRS_{AD}	0.02±0.99	0.05±0.99	0.05±0.99	7.35	2.5E−4	<0.001
Low	6670 (34.15)	6441 (32.88)	6478 (32.97)	11.35	0.010	0.023
Moderate	6502 (33.29)	6516 (33.27)	6571 (33.45)			
High	6361 (32.57)	6631 (33.85)	6597 (33.58)			

Data are presented as mean±SD, n (%), or median (IQR). 'E' means the results were expressed in exponential notation.
Effect sizes were estimated by eta squared (η^2) for continuous variables or Cramer's V for categorical variables. The level of association was defined as negligible (η^2<0.01; Cramer's V <0.10), weak (η^2: 0.01–0.06; Cramer's V: 0.10 to 0.29), moderate (η^2: 0.06–0.14; Cramer's V: 0.30 to 0.49), or strong (η^2 ≥0.14; Cramer's V ≥0.50).
Missing data: 390 for race, 74 for socioeconomic status, 654 for education, 33 for BMI, 325 for smoking status, 176 for alcohol consumption, 3849 for physical activity, 469 for social connection, 4642 for dyslipidaemia, 119 for cognitive function, 2447 for PRS_{AD}.
AD, Alzheimer's disease; BMI, body mass index; CRF, cardiorespiratory fitness; MET, metabolic equivalents; PRS_{AD}, polygenic risk score for Alzheimer's disease.

3. A table comparing the characteristics of participants with or without CRF value has been provided as online supplemental table 4.

Association between CRF and global and domain-specific cognitive function

In multi-adjusted linear regression models, higher CRF (as a continuous variable; per 1-SD increment) was dose-dependently associated with better global cognitive function (β=0.03, 95% CI 0.02 to 0.03), prospective memory (β=0.03, 95% CI 0.02 to 0.04), verbal/numeric memory (β=0.05, 95% CI 0.05 to 0.06), and processing speed (β=0.03, 95% CI 0.02 to 0.04). The β for the CRF–cognitive function association indicates that 1-unit change in CRF corresponds to each score change in cognitive function. When CRF was considered as a categorical variable, compared with low CRF, moderate/high CRF was associated with better global cognitive function (β=0.03, 95% CI 0.02 to 0.04/β=0.05, 95% CI 0.04 to 0.07), prospective memory (β=0.04, 95% CI 0.01 to 0.06/β=0.06, 95% CI 0.04 to 0.08), verbal/numeric memory (β=0.05, 95% CI 0.03 to 0.07/β=0.11, 95% CI 0.09 to 0.13), and processing speed (β=0.04, 95% CI 0.02 to 0.06/β=0.06, 95% CI 0.04 to 0.08) (figure 1). The magnitude and direction of the association between CRF and domain-specific cognitive functions remained similar in terms of different age groups and levels of PRS_{AD}. No multiplicative interactions were detected between CRF and age/PRS_{AD} on cognitive function (FDR-adjusted q-interactions >0.05) (online supplemental tables 5 and 6).

Association of CRF with incident dementia

During the follow-up (median (IQR) 11.72 (11.62–11.87) years), a total of 553 (0.90%) participants developed all dementia,

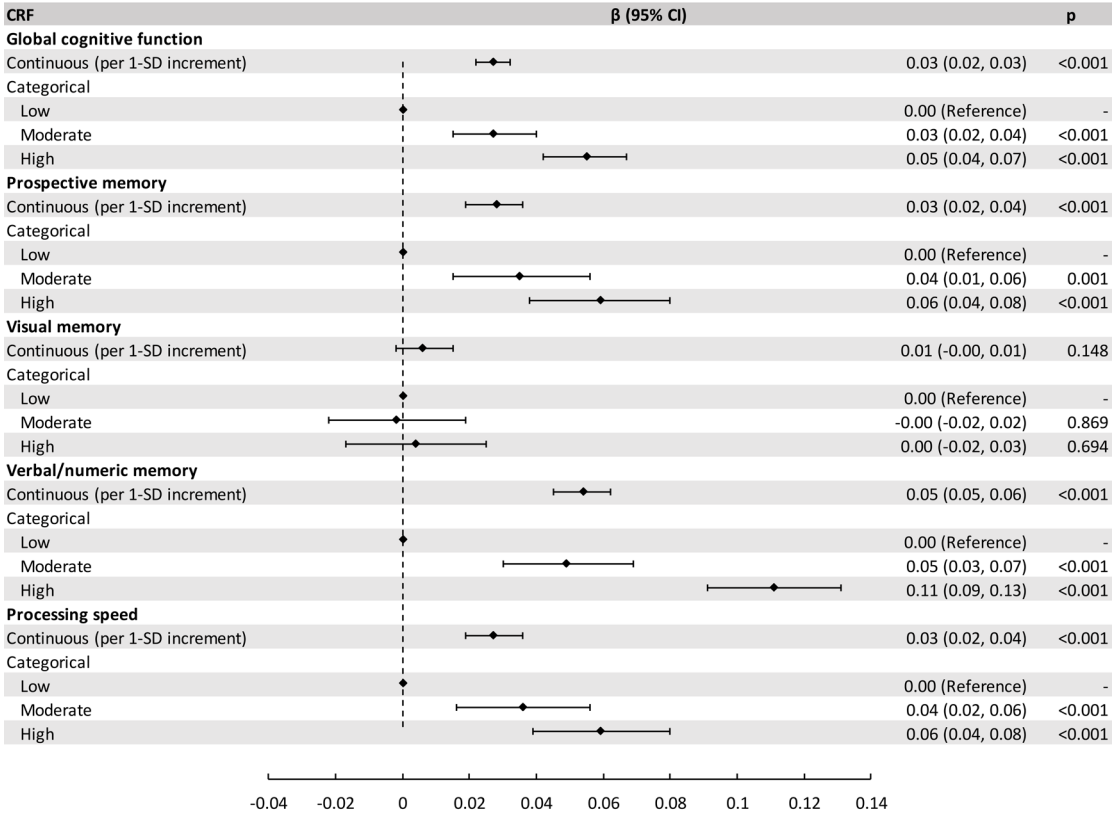

Figure 1 Standardised β (95% CI) for the association of cardiorespiratory fitness (CRF; reference: low CRF) with cognitive function (N=61 214). Models were adjusted for age, race, socioeconomic status, education, body mass index, smoking status, alcohol consumption, physical activity, social connection, diabetes, hypertension, cardiovascular disease, dyslipidaemia, and polygenic risk score for Alzheimer's disease.

including 223 with AD (0.36%) and 103 with VaD (0.17%). In multi-adjusted Poisson regression, higher CRF (as a continuous variable; per 1-SD increment) was dose-dependently associated with reduced risks of all dementia (IRR 0.81, 95% CI 0.73 to 0.89) and AD (IRR 0.83, 95% CI 0.72 to 0.97). Compared with low CRF, the risk of all dementia was reduced by 40% (IRR 0.60, 95% CI 0.48 to 0.76) and the risk of AD was reduced by 38% (IRR 0.62, 95% CI 0.43 to 0.89) for high CRF. No significant associations were found between CRF and VaD (high CRF vs low CRF: IRR 0.77, 95% CI 0.47 to 1.28, p=0.313) (figure 2).

In multi-adjusted Laplace regression, higher CRF (as a continuous variable; per 1-SD increment) was dose-dependently associated with a delayed onset of all dementia (5th PD 0.65, 95% CI 0.26 to 1.03 years) and AD (5th PD 0.66, 95% CI 0.11 to 1.22 years). The onset of all dementia was delayed by 1.48 years (95% CI 0.58 to 2.39) and the onset of AD was delayed by 1.77 years (95% CI 0.54 to 3.01) among participants with high CRF compared with low CRF, respectively. No significant differences in the onset of VaD were detected across different levels of CRF (high CRF vs low CRF: 0.27 years, 95% CI −1.49 to 2.02, p=0.765) (figure 2).

In stratified analysis by age, the CRF–dementia association remained significant and the IRRs for dementia were lower among those aged <60 years compared with those aged ≥60 (online supplemental table 7). The CRF-dementia association was similar after stratified by PRS_{AD} (online supplemental table 8). There were no significant multiplicative interactions between CRF and age/PRS_{AD} on all dementia (FDR-adjusted q-interactions >0.05) (online supplemental tables 7 and 8).

Joint effect of CRF and genetic risk on dementia risk

Both high CRF and moderate/high PRS_{AD} were associated with the increased risk of dementia (figure 2 and online supplemental table 9), so we combined them into a single group (low/moderate vs high CRF and low vs moderate/high PRS_{AD}) for joint effect analysis. The risk of all dementia decreased monotonically with increasing CRF and decreasing PRS_{AD}. Among those with moderate/high PRS_{AD}, the risk of all dementia reduced by 35% for high CRF (IRR 0.65, 95% CI 0.52 to 0.83), compared with low CRF (figure 3). However, the additive interaction between low/moderate CRF and moderate/high PRS_{AD} on all dementia risk was not significant (RERI 0.50, 95% CI −0.13 to 1.12, p=0.118; attributable proportion 0.17, 95% CI −0.07 to 0.41, p=0.155; synergy index 1.36, 95% CI 0.80 to 2.30, p=0.258) (online supplemental table 10).

Sensitivity analysis

The association between CRF and cognition/dementia remained significant when unstandardised CRF was used to create the CRF groupings. Compared with low CRF, high CRF was associated with better global cognitive function (β=0.06, 95% CI 0.04 to 0.07), prospective memory (β=0.06, 95% CI 0.04 to 0.08), verbal/numeric memory (β=0.12, 95% CI 0.10 to 0.14), and processing speed (β=0.05, 95% CI 0.03 to 0.07). The risk of dementia was reduced by 46% (IRR 0.54, 95% CI 0.42 to 0.70, p<0.001) and the risk of AD was reduced by 45% (IRR 0.55, 95% CI 0.37 to 0.84, p=0.005) for high CRF (online supplemental tables 11 and 12).

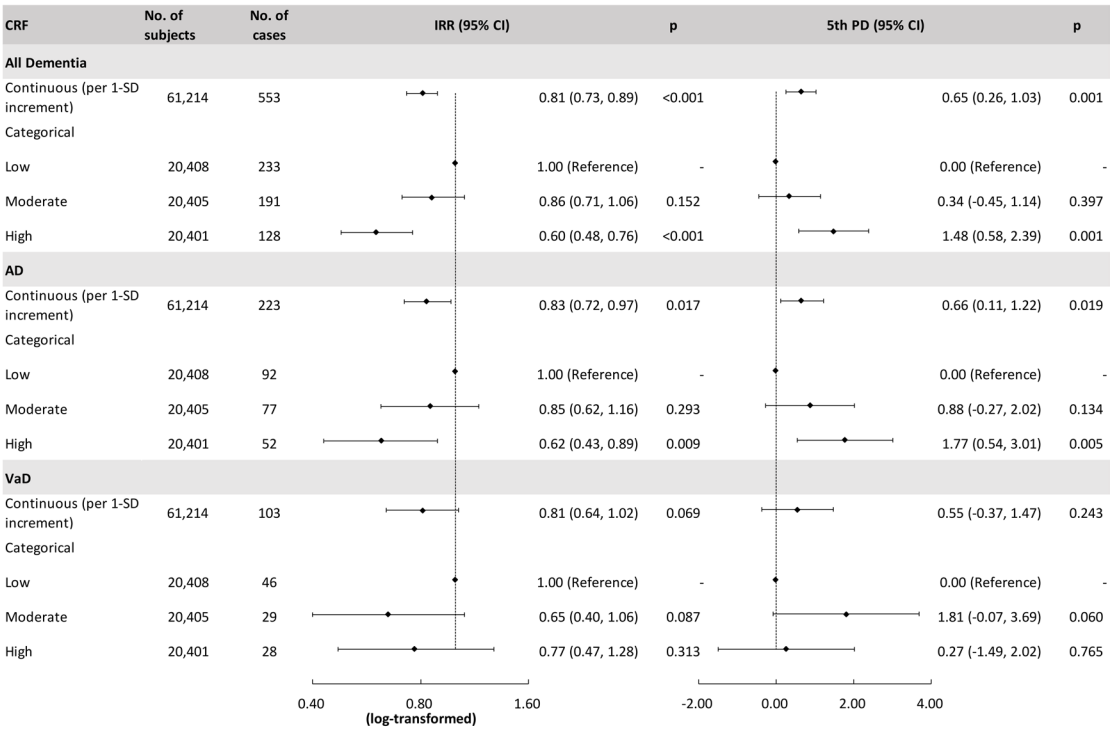

Figure 2 Incidence rate ratios (IRR) from Poisson regression, the fifth percentile differences (PD) in years from Laplace regression, and 95% CI for the association between cardiorespiratory fitness (CRF) and subsequent dementia. Models were adjusted for age, race, socioeconomic status, education, body mass index, smoking status, alcohol consumption, physical activity, social connection, diabetes, hypertension, cardiovascular disease, dyslipidaemia, global cognitive function, and polygenic risk score for Alzheimer's disease (AD). VaD, vascular dementia.

The associations of CRF with cognitive function and dementia were not much altered when we repeated the analyses after (1) further adjusting for survival status at the end of follow-up (online supplemental table 13); (2) excluding participants who were diagnosed with dementia within the first 3 years of follow-up (online supplemental tables 14 and 15); (3) further adjusting for statins, β-blockers, and calcium channel blockers (online supplemental tables 16 and 17); and (4) using non-imputed data (online supplemental tables 18 and 19).

DISCUSSION

Main study findings

In this large community-based longitudinal study from the UK Biobank, we found that higher CRF was associated with: (1) better baseline global cognitive function and performance in multiple cognitive domains; (2) lower risk of dementia and a delay in the onset of dementia across middle and older age; and (3) 35% reduction in the risk effect of genetic predisposition on all dementia risk.

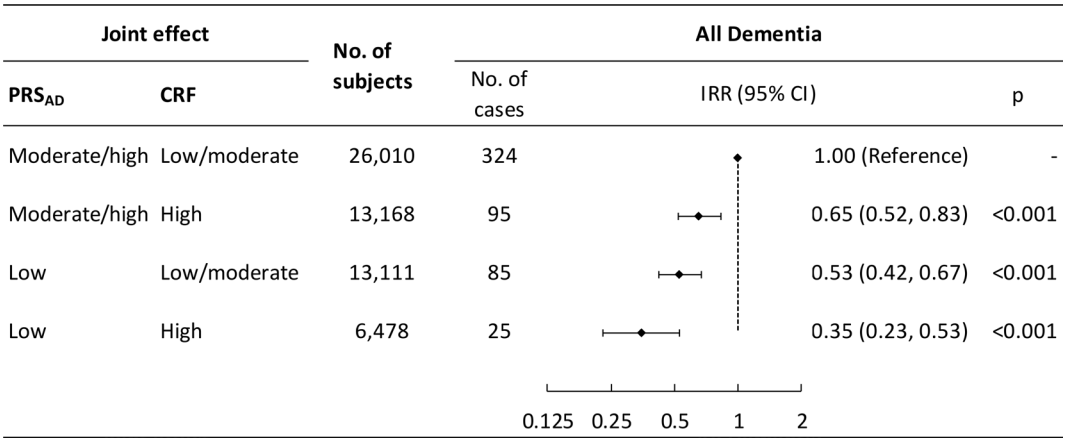

Figure 3 Incidence rate ratios (IRR) and 95% CI of incident dementia in relation to joint exposure of cardiorespiratory fitness (CRF) and polygenic risk score for Alzheimer's disease (PRS_{AD}). The x-scale was logarithmic scaled. Models were adjusted for age, race, socioeconomic status, education, body mass index, smoking status, alcohol consumption, physical activity, social connection, diabetes, hypertension, cardiovascular disease, dyslipidaemia, and global cognitive function.

Consistency of evidence from the present study with other studies

Several cross-sectional studies have suggested a positive correlation between CRF and cognitive function among older adults, including global cognitive function[35] and cognitive domains like attention,[6 7] executive function,[8 9] and visual memory[9 10]; while another cross-sectional study including 64 dementia-free participants failed to find any association between CRF and global or domain-specific cognitive functions.[11] Currently, only two cross-sectional studies have explored the CRF–cognition association among middle-aged adults.[12 36] One included 315 adults aged 40–65 and reported that high CRF was related to better visual memory, verbal memory, and executive function.[36] Another reported that high CRF was only significantly related to better visual memory and problem-solving ability in adults aged 55–65 years, but not in those aged 40–54 years nor in the whole population.[12] The discrepancies between these studies could be due to differences in the measurement of CRF (eg, graded maximal exercise testing and non-exercise estimation), sample sizes (n=33 to 501), assessments of dementia and cognitive function, types of cognitive measures assessed, and the heterogeneity of covariates included in the analysis (eg, some studies did not consider physical activity and chronic diseases). In this study, high CRF was associated with better global, prospective memory, verbal/numeric memory, and processing speed in all participants. The association between CRF and cognitive function was consistent in the different age and PRS_{AD} strata.

So far, several studies have examined the association between CRF and all dementia risk.[13–15 37 38] A community-dwelling cohort study followed 19 458 adults aged under 65 for a median of 25 years and showed that higher CRF was associated with a lower risk of all dementia without previous stroke.[13] A study identified 649 605 US veterans aged 30 to 95 years and reported an independent, inverse, and graded association between CRF and all dementia.[37] Similarly, another cohort study that enrolled 6104 US veterans (mean age 59 years) reported a nearly 8% reduction in the risk of all dementia for every 1-MET increase in CRF.[38] Two additional studies including only male (age 42–61 years)[14] or female (age 38–60 years)[15] participants found that high CRF was associated with lower all dementia risk. Despite the consistent conclusions drawn from the above studies, there are still limitations in generalising the results due to the highly selected study populations (mostly middle-aged or from specific occupations). Moreover, all these studies used the maximal exercise test to estimate CRF, using either the maximal treadmill test or the maximal ergometer cycling test. Submaximal exercise, the approach used to measure CRF in the present study, requires less physical exertion and therefore it can be more feasible to implement in older adults from the community. In the present study, we found that high CRF was related to lower risks of all dementia and AD and may delay their onset. Higher CRF tended to be associated with VaD as well, but the results were not statistically significant. This could be due to the limited number of VaD cases. In stratified analysis by age, the negative association between CRF and dementia risk remained significant in both middle-aged (<60) and older adults (≥60). Although CRF–dementia association tended to be stronger in middle-aged compared with older adults, this difference was not statistically significant. Moreover, having high CRF could mitigate 35% of the impact of genetic predisposition on all dementia risk. To the best of our knowledge, no studies have so far examined the joint effect of CRF and PRS_{AD}. Due to the lack of effective treatment for dementing disorders, our findings highlight the importance of enhancing CRF for the control and prevention of dementia among older adults.

Biological mechanisms

Several mechanisms may underlie the association of CRF with cognitive function and dementia. First, CRF represents the function of the cardiovascular system, respiratory system, and skeletal muscle metabolism, and is an objective reflection of the overall health status.[1] Previous studies have related cardiovascular disease,[39] low pulmonary function,[40] and sarcopenia to dementia risk.[41] Therefore, CRF could serve as an indicator of dementia risk.[3] Second, low CRF has been reported to be related to reduced cerebral blood flow[42] and increased cerebral vessel pulsatility[43] and further contributes to chronic brain hypoperfusion. Disruption of cerebral microcirculation may further lead to neurodegeneration, blood-brain barrier impairment, amyloid β protein deposition, and neuroinflammation.[44] It has been reported that CRF is associated with lower β-amyloid and τ protein burden in cerebrospinal fluid, even in those with high genetic risk for AD pathology.[45] This is in line with our finding that high CRF is associated with lower dementia risk even among people with a moderate/high genetic predisposition. More investigations are warranted to determine the mechanisms underlying the CRF–cognition/dementia association.

Strengths and limitations

The main strength of this study lies in the comprehensive measurement of CRF in a large population. Additionally, the availability of data on PRS_{AD} derived by GWAS provides the opportunity to examine CRF-dementia associations in different genetic backgrounds. Nonetheless, some limitations should be pointed out. First, the participants of the UK Biobank are generally healthier and more socioeconomically advantaged than the general population in the UK.[22] In addition, to guarantee the safety of the participants, individuals with certain health conditions (such as chest pain at rest, high weight, high blood pressure, pacemaker, etc) were excluded from the submaximal exercise, making this study population 'healthier' than the rest of the UK Biobank participants. This might have resulted in a lower incidence of dementia in this study leading to an underestimation of the observed association. Second, incident dementia cases during follow-up were determined using register-based information of dementia diagnosis, which might have led to an underestimation of the observed associations if some dementia diagnoses were missed or delayed. A study has evaluated the accuracy of using the medical register to identify dementia and concluded that it is reliable to be used in epidemiological studies.[46] Third, the subtypes of dementia (such as AD and VaD) based on clinical diagnosis might be questionable,[46] because mixed pathologies are very common in the brains of patients with dementia; even neuroimaging could not distinguish the subtypes very well, especially in older participants.[47] Fourth, because of lack of data on repeated CRF measurements among most participants, the association of CRF change and dementia risk could not be examined. Fifth, although we have controlled for all potential confounders, residual bias due to unmeasured covariates and measurement errors of confounders (such as smoking status and alcohol consumption) could not be completely ruled out. Also, the selection of confounders was based on previous studies, and the more rigorous causal directed acyclic graph selection of confounders was not applied in this study. Finally, compared with a maximal test, a submaximal exercise test could be less accurate.[3] This could contribute to non-misclassification of the CRF groupings

and lead to an underestimation of the CRF–dementia association. However, the submaximal exercise test on bike ergometer deployed in the UK Biobank study has been proven to be strongly related to the gold standard measurement.[5 48]

Research implications

The principal modifiable factor of CRF is physical activity. Several studies have indicated that aerobic training, resistance training, and combined training all have beneficial effects on CRF in older adults,[49] with high-intensity interval training showing the most significant effects.[50] Long-term moderate-intensity lifestyle physical activity is also as effective as a structured exercise programme among previously sedentary healthy adults.[51] In our data, we also found a significant association between frequent physical activity and higher CRF (data not shown).

Future research on the relationship between CRF and brain health, especially in older adults, is warranted, and the mechanisms by which CRF modifies the relationship between genetic risk and dementia deserve further investigation. As the measurement of CRF in clinical settings becomes both important and feasible, CRF may be used as a routine health monitoring tool or an indicator of health conditions.

CONCLUSION

Our study shows that higher CRF is associated with better cognitive function and decreased dementia risk. Moreover, high CRF may buffer the impact of genetic risk of all dementia by 35%. Our findings suggest that maintaining favourable CRF could be a strategy for the prevention of dementia, even among people with a high genetic predisposition.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by North West Multi-Centre Research Ethics Committee (21/NW/0157). Participants gave informed consent to participate in the study before taking part.

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