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Associations of Fitness, Physical Activity, Strength, and Genetic Risk With Cardiovascular Disease

Longitudinal Analyses in the UK Biobank Study

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BACKGROUND: Observational studies have shown inverse associations among fitness, physical activity, and cardiovascular disease. However, little is known about these associations in individuals with elevated genetic susceptibility for these diseases.

METHODS: We estimated associations of grip strength, objective and subjective physical activity, and cardiorespiratory fitness with cardiovascular events and all-cause death in a large cohort of 502 635 individuals from the UK Biobank (median follow-up, 6.1 years; interquartile range, 5.4–6.8 years). Then we further examined these associations in individuals with different genetic burden by stratifying individuals based on their genetic risk scores for coronary heart disease and atrial fibrillation. We compared disease risk among individuals in different tertiles of fitness, physical activity, and genetic risk using lowest tertiles as reference.

RESULTS: Grip strength, physical activity, and cardiorespiratory fitness showed inverse associations with incident cardiovascular events (coronary heart disease: hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.77–0.81; HR, 0.95; 95% CI, 0.93–0.97; and HR, 0.68; 95% CI, 0.63–0.74, per SD change, respectively; atrial fibrillation: HR, 0.75; 95% CI, 0.73–0.76; HR, 0.93; 95% CI, 0.91–0.95; and HR, 0.60; 95% CI, 0.56–0.65, per SD change, respectively). Higher grip strength and cardiorespiratory fitness were associated with lower risk of incident coronary heart disease and atrial fibrillation in each genetic risk score group (P_{trend} <0.001 in each genetic risk category). In particular, high levels of cardiorespiratory fitness were associated with 49% lower risk for coronary heart disease (HR, 0.51; 95% CI, 0.38–0.69) and 60% lower risk for atrial fibrillation (HR, 0.40; 95%, CI 0.30–0.55) among individuals at high genetic risk for these diseases.

CONCLUSIONS: Fitness and physical activity demonstrated inverse associations with incident cardiovascular disease in the general population, as well as in individuals with elevated genetic risk for these diseases.

Key Words: cardiovascular disease ■ epidemiology ■ fitness ■ genetics ■ physical activity

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Clinical Perspective

What Is New?

- In this study of ≈500 000 individuals from the UK Biobank, we report and compare the associations of objective and subjective measures of fitness and physical activity with prospective cardiovascular disease events and all-cause death.
- We found consistent and robust inverse associations, particularly between objective measures of fitness and physical activity, and 6 cardiovascular outcomes and total mortality.
- Using genetic risk scores for coronary heart disease and atrial fibrillation, we show that these inverse associations were present in each genetic risk category, suggesting that elevated genetic risk for these diseases can be compensated for by exercise.

What Are the Clinical Implications?

- Little is known about the risk-modifying effects of exercise in individuals with increased genetic risk of cardiovascular disease.
- Our results demonstrating the risk-decreasing associations of exercise across genetic risk strata have important public health impact; the knowledge that lifestyle choices have substantial effects on disease risk could encourage individuals to initiate a healthier lifestyle to reduce their overall risk.
- In the longer term, identifying subgroups based on genetic risk that benefit most from lifestyle interventions could help personalize prevention strategies of chronic diseases.
- Furthermore, personalized prevention and treatment strategies could help motivate individuals more efficiently compared with general guidelines.

Cardiovascular disease (CVD) is a major public health issue and societal burden worldwide. Exercise has been highlighted as a cost-effective strategy for CVD prevention; it improves cardiorespiratory fitness (CRF) and muscular strength, which are both shown to be inversely associated with future CVD events in population-based studies.[1,2] However, fitness and physical activity are hard to measure accurately and consistently on a large scale; thus, observational analyses prospectively relating fitness and physical activity with new-onset CVD among healthy individuals have typically been limited to smaller study samples and self-reported measures. Moreover, the extent to which the genetic risk for CVD can be compensated with exercise is not known.

In this article, we analyzed objective and subjective measures of fitness and physical activity together with information of CVD risk factors and genomics in relation to prospective CVD disease events and all-cause death in 502 635 individuals from the UK Biobank. We had 2 aims: (1) evaluate associations of fitness and physical activity with incident cardiovascular disease and all-cause death, and (2) assess whether these associations are modified by genetic risk.

METHODS

Study Sample

From 2006 to 2010, >500 000 individuals 40 to 69 years of age were enrolled in the UK Biobank, a longitudinal cohort study based in the United Kingdom. Participants have undergone a range of physical measurements, detailed assessments about health-related factors, and sampling of blood, urine, and saliva. The participants have also agreed to have their future health, including disease events, monitored. In our study, we utilized the data collected at the UK Biobank assessment centers at baseline, combined with information on incident disease events from the hospital and death registry. After excluding individuals who had withdrawn consent at the time of the study and prevalent CVD events (N=19 933), 482 702 individuals remained in our study sample for observational analyses of CVD. In addition, 2524 individuals reported too high or low reported values for physical activity variables according to data cleaning rules of International Physical Activity Questionnaire (IPAQ),[3] and these were removed in analyses involving physical activity data. For analyses of CRF, we utilized a subset of 66 438 individuals free from CVD at the baseline who underwent a submaximal exercise test on a treadmill. In addition, we also analyzed a subset of 103 702 individuals with objectively measured physical activity with a wrist-worn accelerometer. To evaluate the gene–environment interaction effects of fitness and physical activity on disease incidence, we used 468 095 individuals with genome-wide genetic data available (19 311 prevalent CVD cases removed). The UK Biobank study was approved by the North West Multi-Center Research Ethics Committee, and all participants provided written informed consent to participate in the UK Biobank study. The study protocol is available online.[4] The data reported in this article are available via application to the UK Biobank to other researchers for purposes of reproducing the results or replicating the procedure.

Baseline Data

In this study, the exposures of interest were different measures of fitness and physical activity (grip strength, total physical activity, and CRF). Grip strength was measured in a sitting position using a Jamar J00105 hydraulic hand dynamometer. The participants were asked to squeeze the device as hard as they could for 3 seconds, and the maximum value reached during that time was recorded. Both hands were measured in turn (UK Biobank field ID 46 for left hand and 47 for right hand). In line with prior studies,[5,6] to adjust for confounding of strength by body mass, we calculated relative grip strength as an average of measurements of right and left hand divided by weight (ID 21002). Physical activity was assessed with a short form IPAQ questionnaire,[3] which includes 6 questions of frequency (IDs 864, 884, and 904) and duration (IDs 874, 894, and 914) of walking, moderate-intensity exercise, and vigorous exercise. The answer "Unable to walk" in 864 was

recoded to 0, and "Prefer not to answer" and "Do not know" in all 6 variables were set missing. Objective assessment of physical activity was measured for a 7-day period using an Axivity AX3 wrist-worn triaxial accelerometer. The nonwear time was detected and imputed by the expert working group, and total physical activity was calculated by averaging all worn and imputed values.[7] CRF was assessed with net oxygen consumption, calculated from individuals' body weight and maximum workload (ID 6032) during the cycle ergometry on a stationary bike (eBike, Firmware v1.7) using the equation net oxygen consumption=7+10.8(workload)/weight.[8]

In addition, we used information of potential confounders, specifically age (field ID 21022), sex (ID 31), region of the UK biobank assessment center (ID 54; recoded to three groups: United Kingdom, Scotland, and Wales), ethnicity (ID 21000; recoded to 4 groups: white, black, Asian, and mixed), Townsend index reflecting socioeconomic status (ID 189), smoking status (ID 20116; current, former, and never), body mass index (ID 21001), diabetes mellitus (ID 2443), lipid medication (ID 20003; including simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, ezetimibe, nicotinic acid product, or fenofibrate), systolic blood pressure (ID 4080, but if missing ID 93), and height (ID 50) as covariates in our models. The details of these measurements can be found in the study protocol.[4]

Outcomes and Follow-Up

The disease outcomes were defined as primary or secondary events using inpatient hospital and death registry data linked to the UK Biobank. Coronary heart disease (CHD) was defined as International Classification of Diseases (ICD) 9th edition (ICD-9) codes 410 to 411, edition 10 codes I20.0, I21, and I22, and surgical codes for percutaneous transluminal coronary angioplasty and coronary artery bypass graft (codes K40-K46, K49-K50, and K75). Stroke was defined as ischemic (ICD-9: 433–434; ICD-10: I63) or hemorrhagic stroke (ICD-9: 430–432; ICD-10: I60–I62). Heart failure was defined as ICD-9 code 428 and ICD-10 code I50. Atrial fibrillation (AF) was defined as ICD-9 code 427.3, ICD-10 code I48, and surgical codes K50.1 and K62.2–K62.4. The hospital registry-based follow-up ended on March 31, 2015, in England; August 31, 2014, in Scotland; and February 28, 2015, in Wales. Individuals were censored on these dates, the time of event in question, or the time of death, whichever occurred first. Death because of CVD was defined using the same ICD-10 codes for different end points from the death registry. Death registry included all deaths that occurred before January 31, 2016, in England and Wales and before November 30, 2015, in Scotland.

Statistical Analysis

Missing values of the baseline data were imputed with multivariate imputation by chained equation by using predictive mean matching.[9] By using all variables of the final analysis model (frequency and duration of exercise, grip strength, body mass index, smoking, lipid medication, systolic blood pressure, diabetes mellitus, height, and Townsend index), the Nelson–Aalen estimate of cumulative hazard, and the event indicator as the input, we selected predictors for each variable with missing values by using quickpred function from mice package in R. This function computes predictor matrix for each variable based on (1) correlations between observed values of the variable of interest and other variables, and (2) correlations between an indicator of missingness of the variable of interest and other variables. We performed 5 repetitions of imputations. The imputed values were compared with the observed values to evaluate the performance of the imputation. We then performed data quality control for frequency and duration variables and calculated total physical activity (IPAQ-PA) as MET hours per week according to the IPAQ scoring protocol.[3] We did not perform imputation for the CRF and acceleration variables.

Associations among measures of fitness, physical activity, and CVD events were analyzed using Cox proportional hazards models. The distributions of subjective (IPAQ) and objective (accelerometer) measures of physical activity were skewed, whereas the distributions of grip strength and CRF were approximately normal (Figure I in the online-only Data Supplement). Thus, to facilitate comparison between effect sizes of different measures, physical activity measures were first rank transformed, and then all measures were scaled to standard normal distribution. Analyses were conducted separately for CHD, AF, ischemic and hemorrhagic stroke, and heart failure, as well as for composite CVD events. In secondary analyses, we also analyzed associations with all-cause death. Accelerometer data were used for all-cause death analysis only because of short follow-up (data were collected from May 2013 to December 2015). For each end point, we ran 3 sets of multivariable-adjusted models: (1) adjusting for age, sex, and region of the UK Biobank assessment center; (2) additional adjustment for possible confounders,[2] including ethnicity, body mass index, smoking, lipid medication, systolic blood pressure, diabetes mellitus, height, and Townsend index; and (3) adjusting for IPAQ-PA or grip strength in addition to those in (2). Proportional hazards assumption was assessed using Schoenfeld's test, and when not fulfilled ($P \leq 0.001$), we added interaction terms with time for those covariates for which proportional hazards assumption was not met. In addition, we stratified all models by region to allow different baseline hazard function for each stratum. All analyses were conducted separately for 5 imputed datasets, and results were pooled with Rubin's rule.[9]

Next, we evaluated the risk-modifying associations of fitness and physical activity in individuals with different genetic risk load for CHD and AF. First, we calculated a genetic risk score (GRS) for CHD and AF representing joint effects of individual and independent genetic markers. The genetic markers were selected from the largest (external from the UK Biobank) published genome-wide association study for CHD[10] and AF,[11] and the GRS was calculated as the weighted sum of the risk alleles by using effect sizes from the reference genome-wide association study[10,11] as weights (Tables I and II in the online-only Data Supplement). The GRS was then divided into tertiles to stratify individuals into high, intermediate, and low genetic risk categories. Similarly, we stratified grip strength, IPAQ-PA, and CRF into tertiles to compare hazard ratios for subjects in different groups. Individuals at the lowest GRS and grip strength, IPAQ-PA, and CRF tertile were used as the reference group in each model. In addition, we conducted a subgroup analysis by estimating the hazard ratios

(HRs) in each genetic risk group separately. Furthermore, to evaluate whether there was an interaction between exercise traits and genetic risk of CHD, we added interaction terms among the measures of fitness, physical activity, and GRS. The models were adjusted for age, sex, ethnicity, genotype array, and 10 principal components and stratified by region of the UK Biobank assessment center.

RESULTS

The study characteristics are shown in Table 1. Mean age at baseline was 56.5 years (SD, 8.1 years), and 54% of subjects were females. During follow-up (median 6.1 years; interquartile range, 5.4–6.8 years; 2 899 342 person-years at risk), 20 914 incident CVD cases occurred in participants free from the disease at baseline (8518 CHD, 9836 AF, 2222 ischemic stroke, 1116 hemorrhagic stroke, and 3298 heart failure events).

Observational Analyses

The results from observational analyses are shown in Tables 2 and 3. We found inverse associations between grip strength and all outcomes (HR between 0.59 for heart failure and 0.90 for hemorrhagic stroke) in our age-, sex-, and region-adjusted models. The associations were slightly attenuated when adjusting for confounding factors but still highly significant. Grip strength was also associated with these end points after adjusting for IPAQ-PA.

Higher levels of IPAQ-PA were associated with lower risk of CVD events and all-cause death, but the associations were more modest than for grip strength (Tables 2-4). Associations with the composite CVD outcome, heart failure, and all-cause death remained significant after adjusting for confounding factors and grip strength. Physical activity assessed with a wrist-worn accelerometer had the strongest inverse association with all-cause death when compared with all other measures (HR, 0.52; 95% confidence interval [CI], 0.46–0.58; Table 4). The HR for the subjective measure of physical activity, IPAQ-PA, was notably more modest than that of the objective measurement (HR, 0.83; 95% CI, 0.82–0.84; Table 4) than the association of physical activity objectively measured by accelerometer. The correlation of these 2 measures was modest (R=0.20), indicating substantial measurement inaccuracy in self-reported physical activity.

In a subgroup analysis including 66 438 individuals who underwent a submaximal fitness test, CRF was inversely associated with all CVD events, except hemorrhagic stroke (no. of events=91). The strongest associations were observed for heart failure (HR, 0.56; 95% CI, 0.49–0.65) and AF (HR, 0.60; 95% CI, 0.56–0.65).

There were some evidence of nonlinear associations of fitness and physical activity on CVD events (Figures II through IV in the online-only Data Supplement) and all-cause death (Figure V in the online-only Data Supplement). In particular, the association of IPAQ-PA was U-shaped for CHD, AF, and CVD ($P_{nonlinearity}$ <0.0001). However, objectively measured physical activity by accelerometry did not show a similar U-shaped association with mortality (Figure V in the online-only Data Supplement).

Table 1. Baseline Characteristics of the UK Biobank (N=502 635)

Variable	Value
Sex	
Female	273 465 (54)
Male	229 173 (46)
Baseline age, y	56.5 (8.1)
Ethnicity*	
White	475 378 (94.6)
Black	8152 (1.6)
Asian	11 534 (2.3)
Mixed	7574 (1.5)
Smoking status*	
Never	275 221 (54.8)
Previous	174 129 (34.6)
Current	53 288 (10.6)
Body mass index*, kg/m^2	27.4 (4.8)
Blood pressure*, mm Hg	
Systolic	139.8 (19.7)
Diastolic	82.3 (10.7)
Diabetes mellitus*	26 587 (5.3)
Lipid medication	82 369 (16.4)
Cardiovascular disease at baseline	19 933 (4.0)
Grip strength*, kg	0.40 (0.13)
Physical activity*, MET hours/week	43.8 (43.7)
Cardiorespiratory fitness, 7+10.8 watts/kg	18.5 (3.3)

Data are mean (SD) or n (%).
*Missing values of the variable were imputed with predictive mean matching.

Interactions Among Fitness, Physical Activity, Strength, and Genetic Determinants of CVD

Overall, individuals in the highest tertiles of the CHD and AF GRSs showed increased risk for incident CHD and AF when compared with those in the lowest tertile (HR, 1.77; 95% CI, 1.67–1.87; HR, 1.95; 95% CI, 1.86–2.06, respectively). Further adjustment for traditional CVD risk factors (body mass index, smoking, lipid medication, systolic blood pressure, and diabetes mellitus), grip strength, and physical activity did not change the results notably (Table 5). To compare the HRs for those at extreme ends of the GRS distributions, we divided the CHD and AF GRSs into 20

Table 2. Incidence and Hazard Ratios for Coronary Heart Disease, Atrial Fibrillation and Combined Cardiovascular Disease, by Measures of Fitness and Physical Activity

Variable	Model	Coronary Heart Disease			Atrial Fibrillation			Cardiovascular Disease		
		No. of Events	HR (95% CI)	*P* Value	No. of Events	HR (95% CI)	*P* Value	No. of Events	HR (95% CI)	*P* Value
Grip strength	1	8518	0.79 (0.77–0.81)	<0.001	9836	0.75 (0.73–0.76)	<0.001	20914	0.76 (0.75–0.77)	<0.001
	2	8518	0.88 (0.85– 0.90)	<0.001	9836	0.88 (0.85–0.90)	<0.001	20914	0.87 (0.85–0.89)	<0.001
	3	8475	0.88 (0.85–0.91)	<0.001	9780	0.88 (0.85–0.90)	<0.001	20799	0.87 (0.85–0.89)	<0.001
IPAQ-PA	1	8475	0.95 (0.93–0.97)	<0.001	9780	0.93 (0.91–0.95)	<0.001	20799	0.93 (0.92–0.94)	<0.001
	2	8475	0.98 (0.96–1.00)	0.045	9780	0.99 (0.97–1.01)	0.196	20799	0.97 (0.95–0.98)	<0.001
	3	8475	0.99 (0.97–1.01)	0.197	9780	0.99 (0.97–1.01)	0.554	20799	0.98 (0.96–0.99)	<0.001
Cardiorespiratory fitness	1	749	0.68 (0.63–0.74)	<0.001	904	0.60 (0.56–0.65)	<0.001	1855	0.65 (0.62–0.69)	<0.001
	2	749	0.75 (0.67–0.83)	<0.001	904	0.61 (0.55–0.67)	<0.001	1855	0.68 (0.63–0.72)	<0.001
	3	746	0.75 (0.68–0.84)	<0.001	902	0.61 (0.55–0.67)	<0.001	1850	0.68 (0.64–0.73)	<0.001

CI indicates confidence interval; HR, hazard ratio; and IPAQ-PA, physical activity assessed by the International Physical Activity Questionnaire. Associations are reported per SD units of fitness and physical activity traits. Model adjustments: 1. Age, sex, and region; 2. Age, sex, region, diabetes mellitus, smoking, systolic blood pressure, body mass index, lipid medication, height, ethnicity, and Townsend index; 3. Age, sex, region, diabetes mellitus, smoking, systolic blood pressure, body mass index, lipid medication, height, ethnicity, Townsend index, IPAQ-PA (grip strength analyses), or grip strength (IPAQ-PA analyses). Analyses of cardiorespiratory fitness were adjusted for both IPAQ-PA and grip strength.

groups. Those at the highest 5% of the GRS distributions had 2.7- and 3.4-fold increased risk for CHD and AF, respectively, when compared with those at the lowest 5% (95% CI, 2.38–3.17 and 2.97–3.93, respectively; Table 5).

Grip strength and CRF demonstrated inverse associations with incident CHD and AF in each GRS group (P_{trend} <0.001 in each GRS group; Figures 1 and 2). High CRF was associated with 49% lower risk for CHD (HR, 0.51; 95% CI, 0.38–0.69) and 60% lower risk for AF (HR, 0.40; 95% CI, 0.30–0.55, compared with those at low CRF group) among individuals at the highest tertiles of CHD and AF GRSs (Tables III and IV in the online-only Data Supplement). Similarly, high grip strength was associated with lower risk for CHD (HR, 0.69; 95% CI, 0.62–0.75) and AF (HR, 0.61; 95% CI, 0.56–0.67), compared with those at low grip strength (Tables III and IV in the online-only Data Supplement).

IPAQ-PA showed inverse associations with CHD in the lowest and highest GRS group (P_{trend} =0.007 and P_{trend} =0.003, respectively) and with AF in the intermediate and highest GRS group (P_{trend} <0.001 and P_{trend} =0.004, respectively), but the inverse patterns of associations were more modest than for grip strength and CRF. The hazard ratio in the high CHD GRS group was 0.89 (95% CI, 0.82–0.96) and in the high AF GRS group 0.90 (95% CI, 0.83–0.97), compared with those at low IPAQ-PA (Tables III and IV in the online-only Data Supplement).

Table 3. Incidence and Hazard Ratios for Ischemic Stroke, Hemorrhagic Stroke and Heart Failure, by Measures of Fitness and Physical Activity

Variable	Model	Ischemic Stroke			Hemorrhagic Stroke			Heart Failure		
		No. of Events	HR (95% CI)	*P* Value	No. of Events	HR (95% CI)	*P* Value	No. of Events	HR (95% CI)	*P* Value
Grip strength	1	2222	0.78 (0.74–0.82)	<0.001	1116	0.90 (0.83–0.96)	0.003	3298	0.59 (0.56–0.61)	<0.001
	2	2222	0.83 (0.78–0.88)	<0.001	1116	0.85 (0.78–0.93)	<0.001	3298	0.74 (0.70–0.78)	<0.001
	3	2204	0.83 (0.78–0.88)	<0.001	1112	0.86 (0.79–0.94)	<0.001	3285	0.75 (0.71–0.79)	<0.001
IPAQ-PA	1	2204	0.95 (0.91–0.99)	0.009	1112	0.93 (0.88–0.99)	0.020	3285	0.80 (0.77–0.83)	<0.001
	2	2204	0.97 (0.93–1.01)	0.151	1112	0.93 (0.87–0.98)	0.011	3285	0.87 (0.84–0.90)	<0.001
	3	2204	0.98 (0.94–1.02)	0.374	1112	0.98 (0.94–1.02)	0.374	3285	0.89 (0.86–0.92)	<0.001
Cardiorespiratory fitness	1	172	0.68 (0.56–0.81)	<0.001	91	0.99 (0.76–1.29)	0.946	254	0.56 (0.49–0.65)	<0.001
	2	172	0.69 (0.56–0.87)	0.001	91	0.93 (0.66–1.32)	0.697	254	0.56 (0.47–0.66)	<0.001
	3	171	0.71 (0.57–0.89)	0.003	91	0.96 (0.68–1.37)	0.829	254	0.58 (0.49–0.68)	<0.001

CI indicates confidence interval; HR, hazard ratio; and IPAQ-PA, physical activity assessed by the International Physical Activity Questionnaire. Associations are reported per SD units of fitness and physical activity traits. Model adjustments: 1. Age, sex, and region; 2. Age, sex, region, diabetes mellitus, smoking, systolic blood pressure, body mass index, lipid medication, height, ethnicity, and Townsend index; 3. Age, sex, region, diabetes mellitus, smoking, systolic blood pressure, body mass index, lipid medication, height, ethnicity, Townsend index, IPAQ-PA (grip strength analyses), or grip strength (IPAQ-PA analyses). Analyses of cardiorespiratory fitness were adjusted for both IPAQ-PA and grip strength.

Table 4. Incidence and Hazard Ratios for All-Cause Mortality, by Measures of Fitness and Physical Activity

Variable	Model	No. of Events	HR (95% CI)	*P* Value
Grip strength	1	14419	0.75 (0.73–0.76)	<0.001
	2	14419	0.76 (0.74–0.78)	<0.001
	3	14350	0.78 (0.76–0.79)	<0.001
IPAQ-PA	1	14350	0.83 (0.82–0.84)	<0.001
	2	14350	0.86 (0.84–0.87)	<0.001
	3	14350	0.87 (0.86–0.89)	<0.001
Cardiorespiratory fitness	1	1162	0.78 (0.72–0.83)	<0.001
	2	1162	0.75 (0.69–0.81)	<0.001
	3	1157	0.76 (0.70–0.83)	<0.001
PA	1	348	0.52 (0.46–0.58)	<0.001
	2	348	0.56 (0.50–0.63)	<0.001
	3	347	0.56 (0.50–0.63)	<0.001

CI indicates confidence interval; HR, hazard ratio; IPAQ-PA, physical activity assessed by the International Physical Activity Questionnaire; and PA, physical activity assessed by wrist-worn accelerometer. Associations are reported per SD units of fitness and physical activity traits. Model adjustments: 1. Age, sex, and region; 2. Age, sex, region, diabetes mellitus, smoking, systolic blood pressure, body mass index, lipid medication, height, ethnicity, and Townsend index; 3. Age, sex, region, diabetes mellitus, smoking, systolic blood pressure, body mass index, lipid medication, height, ethnicity, Townsend index, IPAQ-PA (grip strength analyses), or grip strength (IPAQ-PA analyses). Analyses of cardiorespiratory fitness and PA were adjusted for both IPAQ-PA and grip strength.

The overall inverse linear association of grip strength was strongest in the lowest GRS group ($P_{interaction}$ =0.0002 for CHD, $P_{interaction}$ =0.01 for AF). For CRF, the pattern was similar for CHD ($P_{interaction}$ =0.03), whereas for AF, there was no statistically significant interaction ($P_{interaction}$ =0.22). For IPAQ-PA, we observed no significant differences by GRS groups ($P_{interaction}$ =0.52 for CHD, $P_{interaction}$ =0.37 for AF).

Table 5. Associations Between Genetic Risk Scores and Cardiovascular Events

Model	Outcome	No. of Events	HR (95% CI) for Top Versus Bottom Categories of Genetic Risk Scores	
			Top 33% Versus Bottom 33%	Top 5% Versus Bottom 5%
1	Coronary heart disease	8227	1.77 (1.67–1.87)	2.74 (2.38–3.17)
2	Coronary heart disease	8185	1.73 (1.64–1.83)	2.67 (2.31–3.08)
1	Atrial fibrillation	9498	1.95 (1.86–2.06)	3.42 (2.97–3.93)
2	Atrial fibrillation	9444	1.95 (1.86–2.06)	3.42 (2.97–3.94)

CI indicates confidence interval; and HR, hazard ratio. Associations are for highest versus lowest 33% and 5% of the genetic risk score distribution. Model adjustments: 1. Age, sex, ethnicity, genotype array, and principal components; 2. Age, sex, ethnicity, genotype array, principal components, diabetes mellitus, smoking, systolic blood pressure, body mass index, lipid medication, physical activity assessed by international physical activity questionnaire, and grip strength.

DISCUSSION

Principal Findings

In this study of 502 635 individuals from the UK Biobank, we analyzed the associations of objective and subjective measures of fitness and physical activity with 6 cardiovascular outcomes and total mortality, and we explored these associations in individuals with different genetic burden for CVD. Our main findings were 2-fold. First, in an observational study of unprecedented size, we established that fitness and physical activity demonstrated inverse associations with different types of incident CVD events. In addition, among all measures of fitness and physical activity, accelerometry-based physical activity showed the strongest inverse association for the risk of premature death. It is interesting to note that the associations for questionnaire-based physical activity were weaker than those for objectively measured physical activity, and the correlation between these measures was low (*R*=0.20). Second, the inverse associations of grip strength and CRF with CHD and AF were seen in each category of genetic risk, indicating that maintaining good fitness can compensate for genetic risk of these diseases.

Comparison With Prior Literature

Exercise has been highlighted as a cost-effective prevention strategy for CVD. Both human and animal studies have demonstrated multifactorial effects of exercise,[12] including skeletal muscle growth, vascular remodeling, and beneficial effects on metabolism. Exercise also induces structural changes in cardiac muscle, which helps to protect against ischemic damage.[12] Intervention studies have reported that both aerobic and strength training have favorable effects on cardiovascular risk factors in individuals at high risk for CVD (eg, those with dyslipidemia or type 2 diabetes mellitus).[13–15]

Because of the challenges of measuring fitness and physical activity, studies relating these traits with prospective CVD in the general population have previously been limited by small sample size or lack of measurement accuracy. Attempts to combine data in meta-analyses have had to use broad categories of fitness and physical activity to harmonize the data across many small studies.[16,17] Compared with these studies, the UK Biobank has a clear advantage because the traits were measured in the same way in >500 000 individuals. Nevertheless, our results are consistent with previous meta-analyses reporting weaker associations for questionnaire-based physical activity assessment when compared with objective measures.[16] This finding suggests that associations of physical activity with outcome are most likely underestimated in studies using questionnaire data. Moreover, our results demonstrated a modest correlation between self-reported and objective physical activity, as well as a

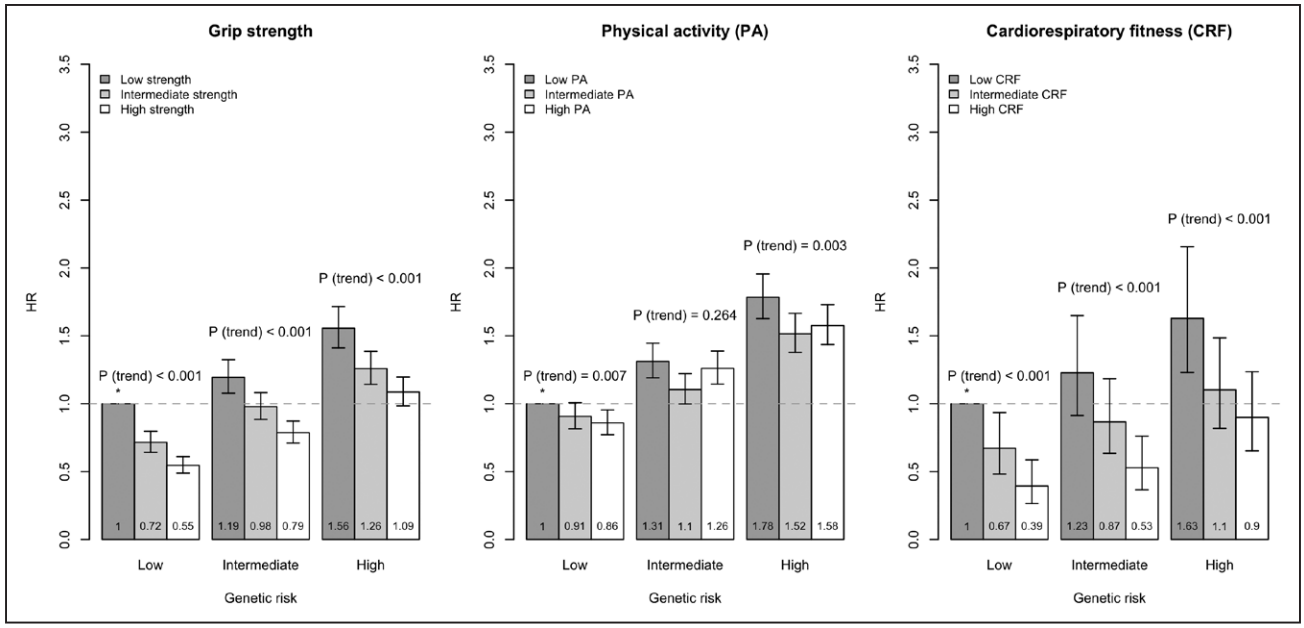

Figure 1. Associations of grip strength, physical activity, and cardiorespiratory fitness with coronary heart disease by genetic risk.

Hazard ratios with 95% confidence intervals for coronary heart disease (CHD) according to tertiles of genetic risk and grip strength (**left**), physical activity (**middle**), and cardiorespiratory fitness (**right**). *Denotes the reference group.

U-shaped association between self-reported but not objective physical activity and all-cause death, suggesting that some additional factors might explain an increased risk in those individuals reporting high values of self-reported physical activity.

Observational studies have reported contradictory results on the relationship among physical activity, fitness and AF. Although moderate-intensity exercise has been shown to decrease the risk of AF, especially long-term strenuous endurance exercise has been associated with an increased risk.[18] For example, in contrast to our results, a large study conducted in Swedish young men at military service reported a positive association between CRF and AF.[2] The contradictory results in the field might

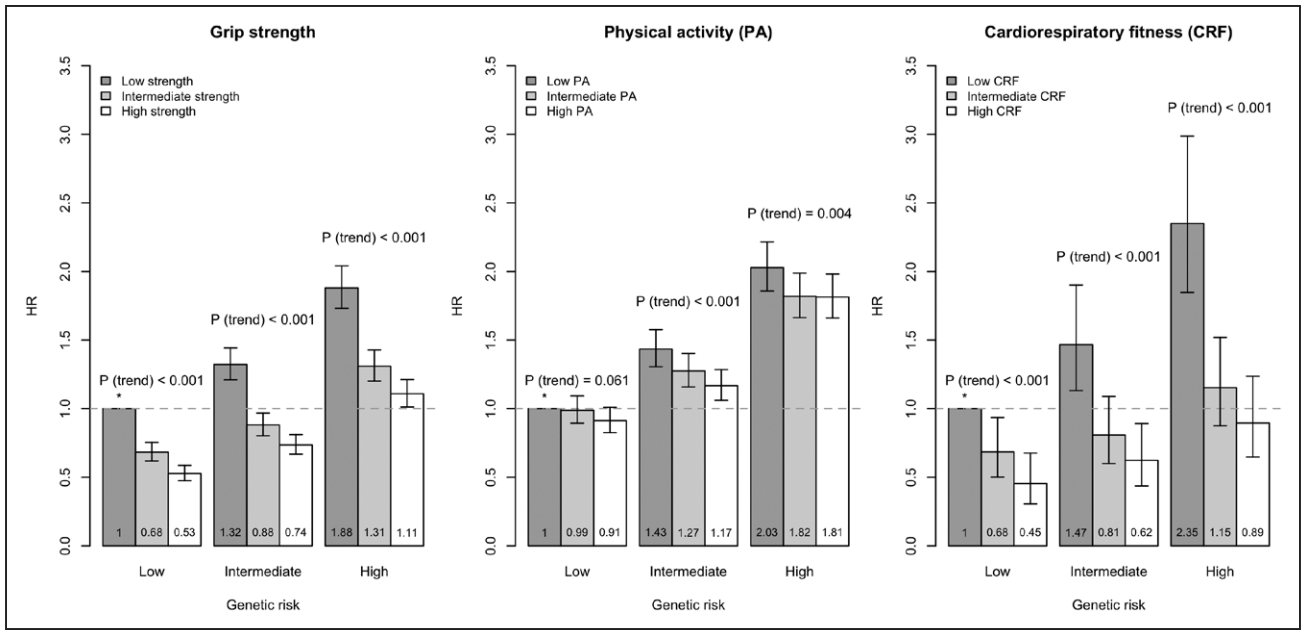

Figure 2. Associations of grip strength, physical activity, and cardiorespiratory fitness with atrial fibrillation by genetic risk.

Hazard ratios with 95% confidence intervals for atrial fibrillation (AF) according to tertiles of genetic risk and grip strength (**left**), physical activity (**middle**), and cardiorespiratory fitness (**right**). *Denotes the reference group.

be explained by several methodological factors, such as the confounders included, as well as different age distributions and sex. The majority of studies, including the study by Andersen and colleagues,[2] have been conducted only in men. Indeed, it has been suggested that the exercise-associated AF mostly affects male endurance athletes, and the etiology might be different from that of general AF,[18] presumably examined in the present study. In the present study, we were able to adjust for a large set of potential confounders, and this strengthened the inverse association between CRF and AF.

Clinical Implications

Little is known about the risk-modifying effects of exercise among individuals with increased genetic risk for cardiovascular diseases. Our results showing inverse associations of grip strength and CRF with CVD outcomes across different categories of cardiovascular genetic risk are in line with a recent study[19] reporting similar associations of healthy lifestyle (defined by 4 lifestyle factors: smoking, obesity, physical activity, and diet) in each of the genetic risk score strata for CHD. Although the direct comparison is not feasible because of differences in variable definitions, together these studies highlight the importance of lifestyle factors in the prevention of CVD, as well as in genetically predisposed individuals, demonstrating the nondeterministic nature of genetic risk. They also stress the potential advantages of genetic risk profiling for better detection of individuals at increased risk for CVD. Although more information is needed to evaluate how people understand the genetic risks, the knowledge that lifestyle choices have substantial effects on the disease risks could encourage individuals to initiate a healthier lifestyle to reduce their overall risk.

Strengths and Limitations

The strengths of this study include a large study sample with objective and subjective measures of fitness and physical activity and a prospective ascertainment of different types of CVD events. Our study also has limitations. First, the tradeoff for the large sample collection is weaker measurement accuracy. For example, grip strength is a simple proxy for general muscular strength level, and it captures mainly upper body strength, especially when measured in a sitting position. However, it is highly correlated with knee extension muscle strength (r=0.77–0.81),[20] which makes it a decent indicator of general strength level in large samples, where more detailed assessments of muscular strength are not feasible. Moreover, CRF was measured with a submaximal fitness test, which is less accurate but more applicable and safer in large samples than a laborious maximal fitness test. Furthermore, some unmeasured or inadequately measured confounders could have had an effect on the results obtained in our analyses.

Second, as in any population-based cohort study, the disease prevalence and incidence rates derived in the UK Biobank are not broadly generalizable because of healthy volunteer bias among study participants. That is, when compared with the general population, the UK Biobank participants had fewer self-reported illnesses and were less likely to be obese, smoke, and drink alcohol.[21] However, valid assessment of associations between exposures and outcomes does not require participants to be representative of the population at large. Thus, associations among fitness, physical activity, and disease events are still likely be generalizable to other populations.[21]

Last, although our analyses were conducted in a cohort with different ethnicities, the majority of participants were of European ancestry. Hence, the generalizability of the results to other ethnicities is not fully understood.

Conclusions

In conclusion, different measures of fitness and physical activity demonstrated inverse associations with future CVD events and all-cause death in a large population-based sample. Among those at high, intermediate, or low genetic predisposition for CHD and AF, there was a graded inverse association with these parameters among each strata of genetic risk. Future studies evaluating the effects of strength versus aerobic training on subclinical or clinical cardiovascular outcomes could help to tailor exercise programs for individuals with elevated genetic risk for these diseases.

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Disclosures

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REFERENCES

1. Timpka S, Petersson IF, Zhou C, Englund M. Muscle strength in adolescent men and risk of cardiovascular disease events and mortality in middle age: a prospective cohort study. *BMC Med*. 2014;12:62. doi: 10.1186/1741-7015-12-62.
2. Andersen K, Rasmussen F, Held C, Neovius M, Tynelius P, Sundström J. Exercise capacity and muscle strength and risk of vascular disease and arrhythmia in 1.1 million young Swedish men: cohort study. *BMJ*. 2015;351:h4543.
3. International Physical Activity Questionnaire. https://sites.google.com/site/theipaq/home. Accessed January 10, 2017.
4. UK Biobank. https://http://www.ukbiobank.ac.uk/. Accessed January 10, 2017.
5. Choquette S, Bouchard DR, Doyon CY, Sénéchal M, Brochu M, Dionne I. Relative strength as a determinant of mobility in elders 67–84 years of age: a nuage study: nutrition as a determinant of successful aging. *J Nutr Health Aging*. 2009:1–6. doi: 10.1007/s12603-009-0132-8.
6. Lawman HG, Troiano RP, Perna FM, Wang CY, Fryar CD, Ogden CL. Associations of relative handgrip strength and cardiovascular disease biomarkers in U.S. Adults, 2011–2012. *Am J Prev Med*. 2016;50:677–683. doi: 10.1016/j.amepre.2015.10.022.
7. Doherty A, Jackson D, Hammerla N, Plötz T, Olivier P, Granat MH, White T, van Hees VT, Trenell MI, Owen CG, Preece SJ, Gillions R, Sheard S, Peakman T, Brage S, Wareham NJ. Large scale population assessment of physical activity using wrist worn accelerometers: the UK Biobank study. *PLoS One*. 2017;12:e0169649. doi: 10.1371/journal.pone.0169649.
8. Swain DP. Energy cost calculations for exercise prescription: an update. *Sports Med*. 2000;30:17–22.
9. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. *BMC Med Res Methodol*. 2009;9:57. doi: 10.1186/1471-2288-9-57.
10. Nikpay M, Goel A, Won HH, Hall LM, Willenborg C, Kanoni S, Saleheen D, Kyriakou T, Nelson CP, Hopewell JC, Webb TR, Zeng L, Dehghan A, Alver M, Armasu SM, Auro K, Bjonnes A, Chasman DI, Chen S, Ford I, Franceschini N, Gieger C, Grace C, Gustafsson S, Huang J, Hwang SJ, Kim YK, Kleber ME, Lau KW, Lu X, Lu Y, Lyytikäinen LP, Mihailov E, Morrison AC, Pervjakova N, Qu L, Rose LM, Salfati E, Saxena R, Scholz M, Smith AV, Tikkanen E, Uitterlinden A, Yang X, Zhang W, Zhao W, de Andrade M, de Vries PS, van Zuydam NR, Anand SS, Bertram L, Beutner F, Dedoussis G, Frossard P, Gauguier D, Goodall AH, Gottesman O, Haber M, Han BG, Huang J, Jalilzadeh S, Kessler T, König IR, Lannfelt L, Lieb W, Lind L, Lindgren CM, Lokki ML, Magnusson PK, Mallick NH, Mehra N, Meitinger T, Memon FU, Morris AP, Nieminen MS, Pedersen NL, Peters A, Rallidis LS, Rasheed A, Samuel M, Shah SH, Sinisalo J, Stirrups KE, Trompet S, Wang L, Zaman KS, Ardissino D, Boerwinkle E, Borecki IB, Bottinger EP, Buring JE, Chambers JC, Collins R, Cupples LA, Danesh J, Demuth I, Elosua R, Epstein SE, Esko T, Feitosa MF, Franco OH, Franzosi MG, Granger CB, Gu D, Gudnason V, Hall AS, Hamsten A, Harris TB, Hazen SL, Hengstenberg C, Hofman A, Ingelsson E, Iribarren C, Jukema JW, Karhunen PJ, Kim BJ, Kooner JS, Kullo IJ, Lehtimäki T, Loos RJF, Melander O, Metspalu A, März W, Palmer CN, Perola M, Quertermous T, Rader DJ, Ridker PM, Ripatti S, Roberts R, Salomaa V, Sanghera DK, Schwartz SM, Seedorf U, Stewart AF, Stott DJ, Thiery J, Zalloua PA, O'Donnell CJ, Reilly MP, Assimes TL, Thompson JR, Erdmann J, Clarke R, Watkins H, Kathiresan S, McPherson R, Deloukas P, Schunkert H, Samani NJ, Farrall M. A comprehensive 1,000 genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet*. 2015;47:1121–1130. doi: 10.1038/ng.3396.
11. AFGen Consortium, Metastroke Consortium of the ISGC, Neurology Working Group of the Charge Consortium. Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation. *Nat Genet*. 2017; 49:946–952. doi: 10.1038/ng.3843.
12. Mann N, Rosenzweig A. Can exercise teach us how to treat heart disease? *Circulation*. 2012;126:2625–2635. doi: 10.1161/CIRCULATIONAHA.111.060376.
13. Martins RA, Neves AP, Coelho-Silva MJ, Veríssimo MT, Teixeira AM. The effect of aerobic versus strength-based training on high-sensitivity C-reactive protein in older adults. *Eur J Appl Physiol*. 2010;110:161–169. doi: 10.1007/s00421-010-1488-5.
14. Cauza E, Hanusch-Enserer U, Strasser B, Ludvik B, Metz-Schimmerl S, Pacini G, Wagner O, Georg P, Prager R, Kostner K, Dunky A, Haber P. The relative benefits of endurance and strength training on the metabolic factors and muscle function of people with type 2 diabetes mellitus. *Arch Phys Med Rehabil*. 2005;86:1527–1533. doi: 10.1016/j.apmr.2005.01.007.
15. Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, Bales CW, Henes S, Samsa GP, Otvos JD, Kulkarni KR, Slentz CA. Effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med*. 2002;347:1483–1492. doi: 10.1056/NEJMoa020194.
16. Nocon M, Hiemann T, Müller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Eur J Cardiovasc Prev Rehabil*. 2008;15:239–246. doi: 10.1097/HJR.0b013e3282f55e09.
17. Sofi F, Capalbo A, Cesari F, Abbate R, Gensini GF. Physical activity during leisure time and primary prevention of coronary heart disease: an updated meta-analysis of cohort studies. *Eur J Cardiovasc Prev Rehabil*. 2008;15:247–257. doi: 10.1097/HJR.0b013e3282f232ac.
18. Sanchis-Gomar F, Perez-Quilis C, Lippi G, Cervellin G, Leischik R, Löllgen H, Serrano-Ostáriz E, Lucia A. Atrial fibrillation in highly trained endurance athletes - Description of a syndrome. *Int J Cardiol*. 2017;226:11–20. doi: 10.1016/j.ijcard.2016.10.047.
19. Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, Chasman DI, Baber U, Mehran R, Rader DJ, Fuster V, Boerwinkle E, Melander O, Orho-Melander M, Ridker PM, Kathiresan S. Genetic risk, adherence to a healthy lifestyle, and coronary disease. *N Engl J Med*. 2016;375:2349–2358. doi: 10.1056/NEJMoa1605086.
20. Bohannon RW, Magasi SR, Bubela DJ, Wang YC, Gershon RC. Grip and knee extension muscle strength reflect a common construct among adults. *Muscle Nerve*. 2012;46:555–558. doi: 10.1002/mus.23350.
21. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, Collins R, Allen NE. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol*. 2017;186:1026–1034. doi: 10.1093/aje/kwx246.