Dose-response associations of cardiorespiratory fitness with all-cause mortality, and also cancer, cardiovascular and respiratory disease mortality and incidence: the UK Biobank cohort study

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Abbreviations: Body mass index (BMI); Confidence intervals (CIs); Hazard ratio (HR); Cardiovascular disease (CVD); Chronic Obstructive Pulmonary Disease (COPD); Interquartile range (IQR); Metabolic equivalent (MET); Electrocardiogram (ECG); National Health Service (NHS); Health episode statistics (HES); Scottish Morbidity Records (SMR01).

Abstract

Objective – To investigate the association of cardiorespiratory fitness with all-cause mortality, and cardiovascular, respiratory, COPD and cancer mortality and incidence.

Design - Prospective population based study.

Setting - UK Biobank.

Participants – Of the 502,628 (5.5% response rate) participants recruited by UK Biobank, we included 73,259 (14.6%) participants with available data in this analysis. Of these, 1,374 participants died and 4,210 developed circulatory diseases, 1,293 respiratory diseases and 4,281 cancer, over a median of 5.0 years [IQR 4.3–5.7] follow-up.

Main outcome measures - All-cause mortality and circulatory disease, respiratory disease, chronic obstructive e pulmonary disease (COPD) and cancer (any-type, colorectal, lung, breast and prostate) mortality/incidence. Fitness was estimated with a submaximal cycle ergometer test.

Results – The hazard ratio for all-cause mortality for each MET higher fitness was 0.96 ([95% CI 0.93–0.98]). Similar results were observed for incident circulatory (HR 0.96 [0.95–0.97]), respiratory disease (HR 0.96 [0.94–0.98]), COPD (HR 0.90 [0.86–0.95]), and colorectal cancer (HR 0.96 [0.92–1.00]). Nonlinear analysis revealed that a high level of fitness (>10 METs) was associated with a greater incidence of atrial fibrillation (HR 1.24 [1.07–1.44]) and prostate cancer (HR 1.16 [1.02–1.32]) compared with average fitness. All results were adjusted for sociodemographic, lifestyle, and dietary factors, body composition, and morbidity at baseline and excluded events in the first 2 years of follow up.

Conclusions – Higher cardiorespiratory fitness was associated with lower risk of premature mortality and incidence of cardiovascular, respiratory disease and colorectal cancer.

INTRODUCTION

There is a large amount of evidence demonstrating that low cardiorespiratory fitness (hereafter "fitness") is a risk factor for all-cause mortality and CVD,[1 2] however, evidence regarding its association with other health outcomes such as respiratory disease, chronic obstructive pulmonary disease (COPD) and cause-specific cancers is scarce.[2] The incidence of these health outcomes is growing worldwide, and the World Health Organisation lists them within the top ten leading-causes of mortality globally. To our knowledge, the associations between fitness and these outcomes has not been assessed in a large population-based cohort using standardised methods and with systematic adjustment for major confounding factors that could obscure the true association between fitness and health outcomes.

A recent meta-analysis conducted by Schmid and colleagues, including six prospective studies (71,654 individuals and 2002 cases) reported an inverse association between fitness levels and all-cancer mortality.[3] However, due to a lack of available data (data was mainly from the Aerobics Center Longitudinal Study [4-6]), Schmid and colleagues were unable to produce pooled estimates for specific cancers. Given the different aetiologies underlying individual cancers, a homogeneous association with fitness is unlikely. Therefore, they concluded that more evidence is needed to elucidate the true association between fitness and cause-specific cancers.[3] Similarly, there is limited evidence regarding the association of fitness with respiratory diseases, including COPD - one of the major diseases with a projected increase in prevalence worldwide.[7] The aim of this study, therefore, was to investigate the associations of fitness with cause-specific incidence and mortality and all-cause mortality in a large, prospective, population based cohort.

METHODS

Study Design

UK Biobank recruited 502,628 participants (5.5% response rate), aged 40-69 years, from the UK general population between April 2007 and December 2010.[8] Baseline assessments took place as described in detail elsewhere.[9] Outcomes for this study were all-cause mortality and incidence and mortality for circulatory disease, all respiratory disease, COPD, all cancers, breast cancer, prostate cancer, colorectal cancer and lung cancer. The exposure variable was cardiorespiratory fitness (presented as MET: 3.5ml/kg/min VO_2). The covariates were sociodemographic factors (age, sex, ethnicity, deprivation, professional qualifications, gross income, employment status and month of recruitment), smoking status, dietary intake factors, systolic blood pressure, medication for cholesterol or blood pressure, self-rated health status, BMI, body fat % and TV-viewing. We performed a landmark analysis, to reduce the potential for reverse causality, with follow-up commencing two years after recruitment and only including participants who were event-free at this time.

Procedures

Death certificates held within the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland) were used to obtain date of death. Record linkage to Health Episode Statistics (HES) (England and Wales) and to the Scottish Morbidity Records (SMR01) (Scotland) was used to identify date and cause of hospital admissions. Detailed information regarding the linkage procedure can be found at http://www.ic.nhs.uk/services/medical-research-information-service. Mortality data were available up to 31st January 2016 at the time of analysis and so our analysis of all-cause mortality was censored at this date or date of death if this occurred earlier. Hospital admission data were available until 31st March 2015, therefore analyses of disease specific outcomes were

censored at this date, or the date of first relevant hospitalisation or death if these occurred earlier. ICD10 codes were used to define incident and cause-specific mortality outcomes. ICD10 codes I05-I89.9 were used to define circulatory disease (chronic rheumatic heart diseases, hypertensive diseases, ischaemic heart disease, pulmonary heart diseases, pulmonary circulation disease, cerebrovascular diseases, diseases of arteries, arterioles, and capillaries, and diseases of veins, lymphatic vessels, and lymph nodes), ICD10 code J09-J98 or I26-I27 was used to define respiratory disease and an ICD10 code J44 used to define COPD. An ICD code of C0.0-C9.9, recorded on a cancer registration, death certificate or hospital admission was used to define cancer events. The following ICD10 codes were used to define cause specific cancers: breast cancer (C50), prostate cancer (C61), lung cancer (C34), colorectal cancer (C18, C19 or C20) recorded on a cancer registration, death certificate or hospital admission.

Physical measurements were taken by trained nurses during participants' initial assessment centre visits, using standardised procedures. Fitness testing was introduced in UK Biobank from August 2009, so these data are only available in a sub-group of 74,836 participants. Fitness was measured using a previously validated 6-minute incremental ramp cycle ergometer test by extrapolating pre-exercise heart rate (work rate at zero Watts), heart rate during exercise, and heart rate at the end of the test, to age predicted maximal heart rate (208 – (0.7 x age))[10], assuming a linear relationship[11] as described in detail elsewhere.[12 13]

Body mass index (BMI) was calculated as weight (kg) divided by height (metres) squared, and then categorised according to the WHO criteria[14]: underweight <18.5, normal weight 18.5-24.9, overweight 25-29.9, and obese ≥30.0 $kg.m^{-2}$. Body composition (body fat and fat free mass), body fat percentage and weight were measured by bio-impedance using a Tanita BC 418MA body composition analyser. Smoking status was categorised into 'current', 'previous'

or 'never'. Area-based socioeconomic status was derived using the Townsend deprivation index.[15] Professional qualifications, employment status and gross house income were self-reported at baseline. Baseline questionnaires collected information regarding disease history, however all self-reported disease was diagnosed by a physician.[13] Self-rated health rating was collected through questionnaire.

Physical activity levels were estimated using the self-report IPAQ short-form[16], with total PA being calculated as the sum of walking, moderate and vigorous activity undertaken in a week, expressed as metabolic equivalents (MET-hours.week^{-1}), as described elsewhere.[13] Time spent TV-viewing (hours.day^{-1}) was collected through a questionnaire, as described elsewhere.[17] Handgrip strength was assessed using a Jamar J00105 hydraulic hand dynamometer and the mean of three measurements for each hand was used, grip strength was expressed as kg.[18]

Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Statistical Analyses

Non-linear associations between fitness and health outcomes were explored using penalised cubic splines fitted in Cox proportional hazard models. Penalised spline is a variation of basis spline which achieved better estimation accuracy in nonlinear data than the commonly used restricted cubic spline.[19] The estimated hazard ratio curves were zeroed at the median fitness of the sample. Likelihood ratio tests were used to examine the overall statistical of the exposures and whether the nonlinear specification achieved better goodness-of-fit. To reduce the potential influence of reverse causality, we performed a landmark analysis, with follow-up commencing two years after recruitment and excluded participants who had any focal events prior to this time. Moreover, we excluded from all analyses individuals who reported a relevant

conditions for each outcome, e.g. excluding prior circulatory events for circulatory disease outcomes and prior cancer events for cancer outcomes. Cox proportional hazard models were repeated assuming linear associations between 1-MET increase in fitness and health outcomes. All results are reported as hazard ratios (HRs) together with 95% confidence intervals.

To investigate potential interaction effects with socio-demographic factors such as age, sex and deprivation, we fitted an interaction term between fitness and each of these factors in our models. There was no evidence of interaction with any of the health outcomes (all $p>0.05$).

Main analyses were adjusted for age, sex, ethnicity, deprivation index, education attainment, employment, BMI categories, percent body fat, medication for CVD, TV-viewing, self-perceived health, smoking status, intake of alcohol, fruit and vegetables, red meat, oily fish, processed meat, and prevalent morbidity at recruitment including hypertension and diabetes. The selection of these covariates was based on the causal assumption as depicted in Figure S1. Sensitivity analyses were conducted to exclude all participants (n=8,358) with prevalent major morbidities at baseline (depression, COPD, chronic asthma, chronic liver diseases, alcohol problems, substance abuse, eating disorders, schizophrenia, cognitive impartment, Parkinson, dementia, chronic pain syndrome, heart diseases and cancer). A sensitivity analysis for competing risk was also conducted using the subdistribution method proposed by Fine and Gray, with the competing event being the death from all causes other than the focal event.[20] The proportional hazard assumption was verified by tests based on Schoenfeld residuals. Statistical significance was set at $\alpha <.05$, and all analyses were performed using R Statistical Software version 3.5.1 with the package *survival*.

Ethical Approval

The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee and all participants provided written informed consent to participate in the UK Biobank study.

Patient involvement

There was no patient involvement in this study and there are no plans to disseminate the results of the research to study participants.

RESULTS

Of the 502,628 participants recruited to UK Biobank, fitness was measured in 74,836 (14.9%) people. However, after excluding participants with existing diseases at baseline and conducting 2-year landmark analyses 73,259 were included in the final analyses. The median follow-up period was 5.0 years [IQR 4.3–5.7] for deaths, and 4.1 years [IQR 3.5–4.7] for hospital admissions. Over the follow-up period, 1,374 participants died and 4,210 developed circulatory diseases, 1,293 respiratory diseases and 4,281 cancer.

The characteristics of participants stratified by fitness tertiles, are displayed in Table 1. In summary, 45.9% of the study population were female, 91.7% white, 66.4% overweight or obese, and 9.3% were current smokers. Mean age was 56.8 years (SD: 8.1), and mean fitness was 8.7 METs (SD: 3.4). At baseline, 73.7% reported having and excellent or good health and 5.3% and 7.0% reported being on medication for cholesterol or blood pressure, respectively. The cohort characteristics of participants with and without fitness data are presented in Supplementary Table S1. In summary, those with fitness data available had similar age, BMI, percent body fat, grip strength compared to those without fitness data available. There was a similar proportion of men and women, obese individuals, but a slightly lower proportion of

individuals in the most deprived tertile, slightly higher representation of black and south Asians, and better self-rated than individuals without fitness data.

Higher fitness was associated with a lower risk of developing circulatory, respiratory disease and lung cancer, and a lower risk of all-cause mortality. After adjusting for potential confounders, each MET higher fitness was associated with lower risk for the following outcomes: all-cause mortality (HR 0.96 [0.95–0.98], p<0.0001), circulatory disease mortality (HR 0.93 [0.90–0.96], p<0.0001), respiratory disease mortality (HR 0.94 [0.90–0.98], p=0.004) (Figure 1). We found similar results for disease incidence: each MET higher fitness was associated with a lower risk for circulatory disease (HR 0.96 [0.95–0.97], p<0.0001), coronary heart disease (HR 0.96 [0.94–0.97], p<0.0001), respiratory diseases (HR 0.96 [0.94–0.98], p<0.0001), and colorectal cancer (HR 0.96 [0.92–1.00], p=0.03) (Figure 2).

The nonlinear associations between fitness and mortality outcomes are shown in Figure 3. Fitness in the range 2 to 6 METs was generally not associated with all-cause and cancer mortality. However, in the 6 to 14 METs range there were linear inverse associations for all-cause circulatory, respiratory disease, and all cancer mortality (i.e. higher fitness, lower mortality). The associations of fitness with circulatory and respiratory disease mortality were similar to an inverse sigmoid function, where the curves were relatively flat at both the lower (2–4 METs) and upper (10–14 METs) ends and linearly inverse in the middle (4–10 METs).

The nonlinear associations of fitness with incidence outcomes are shown in Figure 4. In the range 2 to 8 METS fitness was associated with lower incidence of circulatory disease, coronary heart disease, stroke, atrial fibrillation, heart failure, respiratory disease, COPD, and digestive and colorectal cancer. The associations flattened at the upper end of fitness (>8 METs) for circulatory disease, coronary heart disease, and heart failure, but remained generally linear for

stroke, respiratory disease, COPD and digestive and colorectal cancer. High fitness (>10 METs) was associated with higher incidence of atrial fibrillation and prostate cancer. Sensitivity analysis excluding participants with morbidities at recruitment showed similar results to the main analysis (Figures S2–S5).

The competing risk analysis was consistent with the main analysis on circulatory and respiratory outcomes (Table S2). Fitness was also significantly associated with lower digestive (Subdistributional HR [SHR] 0.96 [0.93–1.00], p=0.03) and breast (SHR 0.97 [0.94–1.00], p=0.03) cancer incidence, but with a higher hazard for all cancer incidence (SHR 1.01 [1.00–1.02], p=0.02), in particular prostate cancer (SHR 1.06 [1.04–1.10], p<0.001).

DISCUSSION

The current study provides evidence that fitness is associated with a wide range of health outcomes that includes respiratory disease, digestive and colorectal cancer, as well as circulatory disease and all-cause mortality. Furthermore, these associations are independent of potential measured confounding factors including socio-demographics, diet, adiposity, TV-viewing and self-rated health.

Our study provides novel evidence regarding the association of fitness with respiratory disease; COPD specifically. Previous prospective studies have reported a negative association between physical activity and COPD[21-23] but this is, to our knowledge, the first study to report an association with fitness. This is an important novel finding since COPD represents an increasing public health burden globally, and is in the top five leading cause of mortality worldwide.[24] The mechanisms underlying this association remain to be established and are

likely multifactorial in nature. One potential mechanism could be due to a higher fitness being associated with lower levels of inflammation, which is plays a pivotal role in the pathophysiology of COPD.[25]

Our results corroborate previous reports of the protective effect of fitness against all-cause mortality and circulatory disease events.[2 26-28] A previous meta-analysis (102,980 participants and 6,910 cases of all-cause mortality; 84,323 participants and 4,485 CVD events) reported those with low fitness to be at 56% increased risk of all-cause mortality and 47% increased risk of CVD incidence, compared to those with intermediate fitness. The magnitude of the association was greater in comparison with high fitness individuals. Our associations were of smaller magnitude; however, the current study included adjustment for a wide range of potentially confounding lifestyle factors which were not included as covariates in any of the studies included in the meta-analysis. Another more recent study of 3,141 participants, which adjusted for a similar number of covariates as the current study, reported those in the intermediate and high fitness groups to be at 20% and 24% reduced hazard of all-cause mortality, respectively, after long term (median 28 years) follow up.[26] This compares to the 12.8% reduced risk of all-cause mortality for each SD (3.37 METs) increase in fitness in this current study, suggesting fitness is a useful clinical indicator for both short and long term mortality risk. What is also evident from these studies is that there is not a strong dose response relationship evident between fitness and every health outcome, although some are evident (Figures 3–4). The current observational study is not able to uncover the underlying mechanisms but it may be that for certain conditions, such as circulatory disease, there is a threshold effect (e.g. >10 METs) after which no further benefits of higher fitness are measurable.

The majority of previous studies demonstrate that higher levels of fitness may confer protective effects against all-cancer mortality,[2 3 29 30] with limited evidence demonstrating an association between fitness and specific cancers. A recent meta-analysis[3] conducted by Schmid and colleagues, including six prospective studies (71,654 individuals and 2,002 cases; median follow up of 16.4 years) reported an inverse association between fitness level and all-cancer mortality: high fitness HR: 0.55 [95% CI 0.47-0.65]. Our study found a reverse J-shaped relationship, in the nonlinear analysis, for cancer mortality but a non-significant association for all cancer incidence, regardless of linearity assumption. It should be noted that the current study has a relatively short follow-up compared to previous evidence (meta-analysis median follow up 16.4 years)[3].

Previous publications from the Aerobics and Cooper Center Longitudinal Studies reported that, when compared to unfit men, fit men had lower colorectal cancer incidence (HR 0.67 [0.46-0.98]) and mortality (HR 0.58 [0.37- 0.92]). Similar results have been reported by Thompson and colleagues, in pre-diabetic and diabetic men. Our finding of an association between fitness and colorectal cancer incidence is consistent with these studies.

Contrary to the potential health benefits, this study found a high level of fitness (>10 METs) to be associated with higher risk of incident atrial fibrillation and prostate cancer. Our findings on prostate cancer was consistent with some of the previous studies.[4 31] While the positive associations are not broadly replicated [32] and can be subject to health consciousness bias, we should note there is mechanistic plausibility for such an association. For example, dehydroepiandrosterone sulphate (DHEA-S), an adrenal androgen associated with physical fitness [33], has been suggested to promote prostate cancer.[32] Furthermore, it has also been reported that elite athletes have a significantly higher atrial fibrillation prevalence than the

general population[34], which is consistent our observed association of fitness with incident atrial fibrillation.

We should be cautious in interpreting the findings of the competing risk analysis. In scenarios where the exposure is associated with the competing event, the SHR for the focal event may be exaggerated and (incorrectly) statistically significant.[35] This may be a partial reason for the positive association between fitness and all cancer incidence, given that fitness is strongly associated with lower circulatory and respiratory mortality in both the main and competing risk analyses.

Strengths and Limitations

While the UK Biobank enabled our research question to be tested in a large prospective cohort, these analyses are not without limitations. The UK Biobank cohort is relatively representative of the UK general population in respect of age, sex, ethnicity and deprivation within the recruited age range, however there was only a 5.5% response rate for recruitment, and the cohort is not representative of the population in other respects with evidence of a "selection" or "healthy volunteer" bias such as lower disease rates, alcohol consumption and smoking levels.[361] This would limit the generalisation of our findings but it could also influence our estimates of associations, through collider bias.[37] Prospective data collection of incident events reduces, but does not eliminate, the risk of reverse causation. Residual confounding is possible in any observational study, but we have tried to minimise this risk by adjusting for all measured potential confounding factors, excluding individuals with medically diagnosed comorbidities at baseline and performing our analyses using a 2-years landmark analysis. The UK Biobank did not employ the gold standard direct maximal measurement of cardiorespiratory fitness, as such tests were not feasible on this scale, previous data has shown that submaximal predictions using linear extrapolation are reliable and valid,[38] although a degree of error will be introduced.

Furthermore, we have relied on self-reporting for several of our covariates which opens up the possibility of residual confounding, although this is likely to be small. On top of this, several outcomes have relatively low number of events (e.g. COPD mortality have less than 100 events) and thus cannot be used in the analysis. Further work is, therefore, needed to confirm our findings for these outcomes.

Conclusions

The current study extends previous evidence that higher fitness is associated with lower CVD disease and all-cause mortality by demonstrating that fitness is also associated with wider health outcomes including respiratory disease and colorectal cancer. Although fitness has an important genetic component, regularly performing moderate to vigorous intensity, endurance-based activities (e.g. brisk walking, running, cycling) can increase fitness. Such exercise training (ranging from 4–36 weeks) can increase fitness by ≥1 MET (~10%) in a range of adult populations (e.g. healthy, obese, heart disease, hypertension and diabetes),[2 39] which highlights that the majority of adults in the population can acquire clinically important gains in fitness.

SUMMARY BOX

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Fitness is associated with cardiovascular disease and all-cause mortality.

WHAT THIS STUDY ADDS

- This study provides robust evidence in a large prospective population-based cohort that the association between fitness and health outcomes extends beyond CVD to respiratory disease, colorectal cancer and all-cause mortality.

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Contributors: SRG, JPP, NS, JMRG and CACM contributed to the conception and design of the study, advised on all statistical aspects and interpreted the data. LS, FKH, SRG and CACM performed the statistical analysis. LS, FKH, SG, and CACM drafted the manuscript. All authors reviewed the manuscript and approved the final version to be published. LS, FKH, SRG and had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (REC reference: 11/NW/03820). All participants gave written informed consent before enrolment in the study, which was conducted in accord with the principles of the Declaration of Helsinki.

Data sharing: Researchers can apply to use the UK Biobank resource and access the data used. No additional data are available.

Transparency: The manuscript's guarantors (CACM, SG, JPP, JMRG and NS) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

FIGURE/TABLE LEGENDS

Table 1. Cohort characteristics by cardiorespiratory fitness tertiles

Figure 1. Associations between cardiorespiratory fitness and mortality outcomes
Hazard ratio associated with 1-MET increase in cardiorespiratory fitness adjusted for age, sex, ethnicity, deprivation index, education attainment, employment, BMI categories, percent body fat, medication for CVD, TV-viewing, self-perceived health, smoking status, intake of alcohol, fruit and vegetables, red meat, oily fish, processed meat, prevalent morbidity at recruitment including hypertension and diabetes. Participants with prior relevant conditions and events in the first two years of follow-up were excluded.

Figure 2. Associations between cardiorespiratory fitness and incidence outcomes
Hazard ratio associated with 1-MET increase in cardiorespiratory fitness adjusted for age, sex, ethnicity, deprivation index, education attainment, employment, BMI categories, percent body fat, medication for CVD, TV-viewing, self-perceived health, smoking status, intake of alcohol, fruit and vegetables, red meat, oily fish, processed meat, prevalent morbidity at recruitment including hypertension and diabetes. Participants with prior relevant conditions and events in the first two years of follow-up were excluded.

Figure 3. Nonlinear associations between cardiorespiratory fitness and mortality outcomes
Hazard ratio associated different levels of cardiorespiratory fitness adjusted for age, sex, ethnicity, deprivation index, education attainment, employment, BMI categories, percent body fat, medication for CVD, TV-viewing, self-perceived health, smoking status, intake of alcohol, fruit and vegetables, red meat, oily fish, processed meat, prevalent morbidity at recruitment including hypertension and diabetes. Participants with prior relevant conditions and events in the first two years of follow-up were excluded.

Figure 4. Nonlinear associations between cardiorespiratory fitness and incidence outcomes
Hazard ratio associated with different levels of cardiorespiratory fitness adjusted for age, sex, ethnicity, deprivation index, education attainment, employment, BMI categories, percent body fat, medication for CVD, TV-viewing, self-perceived health, smoking status, intake of alcohol, fruit and vegetables, red meat, oily fish, processed meat, prevalent morbidity at recruitment including hypertension and diabetes. Participants with prior relevant conditions and events in the first two years of follow-up were excluded.

SUPPLEMENTARY MATERIALS

Table S1. Cohort characteristics of participants with and without fitness data

Table S2. Competing risk analysis

Figure S1. Directed acyclic graph illustrating the causal assumption of this study

Figure S2. Associations between CRF and mortality outcomes among healthy participants
Hazard ratio associated with 1-MET increase in cardiorespiratory fitness adjusted for age, sex, ethnicity, deprivation index, education attainment, employment, BMI categories, percent body fat, medication for CVD, TV-viewing, self-perceived health, smoking status, intake of alcohol, fruit and vegetables, red meat, oily fish, processed meat, prevalent morbidity at recruitment including hypertension and diabetes. Participants with prevalent morbidities at recruitment and events in the first two years of follow-up were excluded.

Figure S3. Associations between CRF and mortality outcomes among healthy participants
Hazard ratio associated with 1-MET increase in cardiorespiratory fitness adjusted for age, sex, ethnicity, deprivation index, education attainment, employment, BMI categories, percent body fat, medication for CVD, TV-viewing, self-perceived health, smoking status, intake of alcohol, fruit and vegetables, red meat, oily fish, processed meat, prevalent morbidity at recruitment including hypertension and diabetes. Participants with prevalent morbidities at recruitment and events in the first two years of follow-up were excluded.

Figure S4. Nonlinear associations between CRF and mortality outcomes among healthy participants
Hazard ratio associated with different levels of cardiorespiratory fitness adjusted for age, sex, ethnicity, deprivation index, education attainment, employment, BMI categories, percent body fat, medication for CVD, TV-viewing, self-perceived health, smoking status, intake of alcohol, fruit and vegetables, red meat, oily fish, processed meat, prevalent morbidity at recruitment including hypertension and diabetes. Participants with prevalent morbidities at recruitment and events in the first two years of follow-up were excluded.

Figure S5. Nonlinear associations between CRF and mortality outcomes among healthy participants
Hazard ratio associated with different levels of cardiorespiratory fitness adjusted for age, sex, ethnicity, deprivation index, education attainment, employment, BMI categories, percent body fat, medication for CVD, TV-viewing, self-perceived health, smoking status, intake of alcohol, fruit and vegetables, red meat, oily fish, processed meat, prevalent morbidity at recruitment including hypertension and diabetes. Participants with prevalent morbidities at recruitment and events in the first two years of follow-up were excluded.

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Table 1. Cohort characteristics by cardiorespiratory fitness tertiles

	Overall (n=73259)	**Low fitness (n=14365)**	**Medium fitness (n=29342)**	**High fitness (n=29552)**
Mean (SD) age	56.80 (8.10)	57.29 (7.97)	56.96 (8.07)	56.41 (8.19)
Female	33637 (45.9)	6582 (45.8)	13479 (45.9)	13576 (45.9)
Ethnicity				
White	66912 (91.7)	12364 (86.4)	26469 (90.6)	28079 (95.4)
South Asians	2078 (2.8)	626 (4.4)	1031 (3.5)	421 (1.4)
Black	2068 (2.8)	874 (6.1)	905 (3.1)	289 (1.0)
Chinese	300 (0.4)	50 (0.3)	107 (0.4)	143 (0.5)
Mixed background	1612 (2.2)	399 (2.8)	699 (2.4)	514 (1.7)
Mean (SD) deprivation index	-1.13 (2.95)	-0.51 (3.21)	-1.18 (2.93)	-1.39 (2.80)
BMI categories				
Underweight	355 (0.5)	67 (0.5)	70 (0.2)	218 (0.7)
Normal	24192 (33.0)	2812 (19.6)	7545 (25.7)	13835 (46.8)
Overweight	31151 (42.5)	5384 (37.6)	13628 (46.5)	12139 (41.1)
Obese	17516 (23.9)	6070 (42.3)	8088 (27.6)	3358 (11.4)
Mean (SD) percent body fat	31.41 (8.52)	34.62 (8.86)	32.54 (8.18)	28.77 (7.89)
Medications				
Blood pressure medications	5160 (7.0)	1572 (10.9)	2049 (7.0)	1539 (5.2)
Cholesterol medications	3897 (5.3)	1152 (8.0)	1597 (5.4)	1148 (3.9)
None of above	64202 (87.6)	11641 (81.0)	25696 (87.6)	26865 (90.9)
Mean (SD) TV viewing	2.73 (1.62)	3.20 (1.88)	2.83 (1.57)	2.41 (1.47)
Mean (SD) self-perceived health	2.16 (0.71)	2.54 (0.79)	2.17 (0.66)	1.97 (0.65)
Alcohol drinking				
Never	5761 (7.9)	1813 (12.6)	2353 (8.0)	1595 (5.4)
Special occasions only	8823 (12.0)	2386 (16.6)	3862 (13.2)	2575 (8.7)
One to three times a month	8265 (11.3)	1814 (12.6)	3547 (12.1)	2904 (9.8)
Once or twice a week	18331 (25.0)	3427 (23.9)	7482 (25.5)	7422 (25.1)
Three or four times a week	16819 (23.0)	2464 (17.2)	6489 (22.1)	7866 (26.6)

Daily or almost daily	15260 (20.8)	2461 (17.1)	5609 (19.1)	7190 (24.3)
Smoking				
Never	40783 (55.7)	7944 (55.3)	16636 (56.7)	16203 (54.8)
Former	25655 (35.0)	4861 (33.8)	10210 (34.8)	10584 (35.8)
Current	6821 (9.3)	1560 (10.9)	2496 (8.5)	2765 (9.4)
Mean (SD) weekly dietary intake				
Portions of fruit and vegetable	4.15 (2.50)	3.98 (2.58)	4.06 (2.51)	4.32 (2.44)
Portions of red meat	1.92 (1.39)	2.02 (1.54)	1.95 (1.40)	1.84 (1.30)
Frequency of oily fish	1.66 (0.92)	1.61 (0.95)	1.63 (0.92)	1.71 (0.90)
Frequency of processed meat	1.85 (1.07)	1.94 (1.09)	1.89 (1.06)	1.77 (1.06)
Prevalent morbidities at recruitment				
Hypertension	16718 (22.8)	4746 (33.0)	6939 (23.6)	5033 (17.0)
Diabetes	3919 (5.3)	1410 (9.8)	1583 (5.4)	926 (3.1)
Others	15757 (21.5)	4255 (29.6)	5926 (20.2)	5576 (18.9)