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Association of fitness and grip-strength with heart failure: Findings from the UK Biobank population-based study

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Abstract

OBJECTIVES - To investigate the associations of objectively measured cardiorespiratory fitness (CRF) and grip strength (GS) with incident heart failure (HF), using UK Biobank data.

BACKGROUND – HF results in substantial social and economic burden. The association of CRF and GS with incident HF is not fully understood.

METHODS – Of the 502,628 participants recruited into the UK biobank between April 1st 2007 and December 31st 2010, 374,493 were included in our GS analysis and 57,053 were included in CRF analysis. Associations between CRF and GS, and incident HF were investigated using Cox proportional hazard models, with adjustment for known measured confounders.

RESULTS – Over a mean of 4.1 (range: 2.4 – 7.1) years, 631 HF events occurred in those with GS data, and 66 HF events occurred in those with CRF data. Higher CRF was associated with a 18% lower risk of HF (0.82 [95% CI: 0.76; 0.88]) per 1-MET increment increase and GS was associated with a 19% lower incidence of HF risk (0.81 [95% CI: 0.77; 0.86]) per 5-kg increment increase. When CRF and GS were standardised the HR for CRF was 0.50 per 1-SD increment [95% CI: 0.38; 0.65]) and for GS was 0.65 per 1-SD increment [95% CI: 0.58; 0.72].

CONCLUSION – Our data indicate that objective measurements of physical function (GS and CRF) are strongly and independently associated with lower HF incidence. Future studies targeting improving CRF and muscle strength should include HF as outcomes to assess if these results are causal.

Keywords – Heart failure, cardiorespiratory fitness, grip strength,

Abbreviations:

BMI = Body mass index

CHD = Coronary Heart Disease

CVD = Cardiovascular disease

CRF = Cardiorespiratory Fitness

GS = Grip Strength

HF = Heart Failure

HR = Hazard ratio

CI = confidence intervals

INTRODUCTION

Heart failure (HF) is a clinical syndrome caused by structural or functional impairment of the left ventricle of the heart, resulting in an inability to pump blood effectively around the body. Heart failure currently affects approximately 900,000 people in the UK and has a very poor prognosis, with up to 17% of patients dying within the first year of diagnosis [1]. Despite advances in treatment options for HF, the social and economic burden to both patients and the health service remains high, with HF estimated to account for 2% of total NHS expenditure [2]. One of the leading causes of HF is coronary heart disease (CHD), but the aetiology of HF is broad and includes dysrhythmias, hypertension, type 2 diabetes mellitus and obesity as well as lifestyle factors including smoking. Cardiovascular disease (CVD), including CHD, remains the leading cause of death worldwide [3], but whilst there has been a decline in CVD mortality over the last three decades, there has been a steady increase in the prevalence of HF over this same period [4; 5]. With an aging population, higher obesity and diabetes levels and lower mortality due to CHD, the prevalence of HF is likely to increase further [6], thus prevention at a population level is key to improving outcomes.

Traditional risk-factors for assessing HF risk, including CVD risk assessment, include blood pressure measurements and plasma lipid levels. In recent times however, CRF has been proposed as a potentially useful marker of future CVD health [6]. Previous work has shown a clear, inverse relationship between CRF and various chronic health conditions, including CVD [7; 8], T2DM and some cancers, as well as all-cause mortality [9]. Whilst these measurable physical characteristics have been consistently shown to be associated with lower CVD risk [9-15], studies which have looked specifically at HF as the outcome are limited. Previous work, including a recent study using the UK Biobank cohort [7], have demonstrated that higher levels of CRF are associated with a lower incidence of HF [16-18]. Although these latter studies had a large sample size (n= 19,485 to 66,329), these cohorts included a high percentage of individuals with illness, including CVD, who were therefore already at an increased risk of HF. Furthermore, each of these studies failed to conduct landmark analyses to minimise the effect of reverse causation and they did not account for the effect of diet and alcohol consumption, which have known associations with HF outcomes. These limitations could have confounded the true association between fitness and HF.

Grip strength (GS) is a further objective measurement that is increasingly recognised as a valuable indicator of overall health, as well as muscular fitness. Lower GS has been shown to be associated with a higher mortality risk across various cohorts [13; 19-25]. It is a quick and reproducible measurement that can be used to stratify people's risk of CVD. The PURE study demonstrated that GS may have potential as a risk-stratifying method for all-cause and cardiovascular mortality, as well as CVD [11]. It did not, however, measure HF as an outcome. We have recently shown GS to improve prediction of CVD in an office based risk score, and is thus useful in areas where laboratory measurements are not readily available [26], but again we did not look at HF specifically as an outcome. Therefore, the aims of the current study were to investigate the associations of objectively measured CRF and GS with heart failure incidence, using data from the UK Biobank, a large population-based cohort.

METHODS

Study design

Between April 1st 2007 and December 31st 2010, UK Biobank recruited 502,628 participants (5.5% response rate), aged between 40-69 years from the general population [27]. We included a total of 374,493 participants who had GS data and 57,053 with CRF data. Participants attended one of 22 assessment centres across England, Wales and Scotland [28; 29] where they completed a touch-screen questionnaire, and had physical measurements taken, as described in detail elsewhere [28; 29]. In this prospective, population-based study HF incidence (fatal and non-fatal events) was used as the outcome. CRF and GS were used as exposures. Analyses were adjusted for sex, age, deprivation index, ethnicity, month of recruitment, education qualifications, employment, gross income, medication for CVD, comorbidities (diabetes and hypertension), BMI categories, smoking and dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat). When GS was used as an exposure, height was additionally added as a covariate into the model. Participants who reported any of the following pre-existing physician-made diagnoses including heart diseases including atrial fibrillation (AF), chronic obstructive pulmonary disease (COPD), chronic asthma, chronic liver diseases, cancer, alcohol problems, substance abuse, eating disorders, sleep apnoea, schizophrenia, cognitive impartment, Parkinson's disease, dementia, chronic pain syndrome, rheumatoid arthritis, other inflammatory polyarthropathies and osteoporosis, were excluded from the analyses.

Procedures

Date of death was obtained from death certificates held by the National Health Service (NHS) Information Centre (England and Wales) and the NHS Central Register Scotland (Scotland). Date and reason for hospital admission were identified via record linkage to Health Episode Statistics (HES) (England and Wales) and to the Scottish Morbidity Records (SMR01) (Scotland). Detailed information regarding the linkage procedure can be found at http://www.ic.nhs.uk/services/medical-research-information-service. At the time of analysis, mortality data were available up to 31 January 2016. Mortality analysis was therefore censored at these dates or date of death if this occurred earlier. Hospital admission data were available until 31 March 2015, resulting in disease specific analyses being censored at this date, or the date of hospital admission or death if these occurred earlier. Incident heart failure was defined as a hospital admission or death with ICD10 code I50.0, I50.2, I50.9 [30].

GS was assessed using a Jamar J00105 hydraulic hand dynamometer and the mean of three measurements for each hand were used; GS was expressed as kg. Fitness testing was introduced in UK Biobank from August 2009, so these data are only available in a sub-group totalling 74,836 participants, of these 57,053 with full data available for all covariates were included in this study. In these individuals, CRF was assessed using a sub-maximal 6-minute incremental ramp cycle ergometer test with workload calculated according to age, height, weight, resting heart rate and sex, and heart rate monitored via 4-lead ECG, with the aim of achieving a final work rate of 50% of predicted maximal power [15]. Further details regarding CRF testing are included in the online supplemental material.

Dietary information was collected via a self-reported dietary questionnaire. Participants were asked how many portions of specified foods they generally ate. Subjective sleep duration was obtained by asking: "About how many hours sleep do you get in every 24 hours?" and then based on this question we derived a categorical sleep duration variable (short sleeper <7 $h.day^{-1}$, normal sleeper 7-9 $h.day^{-1}$ or long sleepers >9 $h.day^{-1}$). Area-based socioeconomic status was derived from postcode of residence, using the Townsend score which is derived from census data on housing, employment, social class and car availability [31]. Other socio-demographic information were self-reported at baseline, and outlined in our supplemental material. Age was calculated from dates of birth at baseline assessment. Ethnicity was self-reported and smoking status was categorised into never, former and current smoking. Medical history of comorbidities was collected from a self-completed, baseline assessment questionnaire. Height, body weight and waist circumference were measured by trained nurses during the baseline assessment. Body composition (percentage body fat and lean mass) was measured by trained nurses using standardised bio-impedance protocols. Body mass index (BMI) was calculated as ($weight/height^2$) and the WHO criteria (32) used to classify BMI into: underweight <18.5, normal weight 18.5-24.9, overweight 25.0-29.9 and obese ≥30.0 $kg.m^{-2}$. Central obesity was defined as waist circumference >88 cm for women and >102 cm for men. Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Statistical Analysis

Associations of CRF and GS with heart failure incidence (fatal and non-fatal events combined) were investigated using Cox-proportional hazard models with years of follow-up as the time-scale. The results were reported as hazard ratios together with 95% confidence intervals. To reduce the potential influence of reverse causality, we performed a landmark analysis, with follow-up commencing two years after recruitment and including participants who were event-free at this time. Moreover, we excluded from all analyses individuals who reported any of the following conditions, known to be linked to weight changes, diagnosed by a physician: heart diseases including atrial fibrillation, COPD, chronic asthma, chronic liver diseases, cancer, alcohol problems, substance abuse, eating disorders, sleep apnoea, schizophrenia, cognitive impairment, Parkinson's disease, dementia, chronic pain syndrome, rheumatoid arthritis, other inflammatory polyarthropathies, osteoporosis, and those who indicated they were unable to walk (n=2664).

To investigate the associations of CRF and GS with heart failure incidence, two approaches were used. Firstly, we fitted exposures into a fully base adjusted model as continuous variables, using both original and standardised (i.e. 1-SD increase in the exposure) units. We then fitted the exposure into the models using age- and sex-specific quartiles (See Supplemental Table 1). The lowest quartile for each exposure was used as the reference group in our analyses. Non-linear associations between exposures (GS and CRF) and HF were visually explored using multivariable cubic regression splines. As no evidence of deviation from linearity was found, Cox-proportional hazard models were performed.

For the analyses, we ran one fully base adjusted model (model 0) that included the following covariates: sex, age, deprivation index, ethnicity, month of recruitment, education qualifications, employment, gross income, medication for CVD, comorbidities (diabetes and hypertension), BMI categories, smoking and dietary intake

(alcohol, fruit and vegetable, oily fish, red meat and processed meat). When GS was used as an exposure, height was additionally added as a covariate into the model. Additionally, we performed a sensitivity analysis; model 1, was identical to model 0 but individuals who had had an MI episodes before having a heart failure event were removed from the analysis, on the basis that in these individual's HF would be a secondary, rather than primary, manifestation of CVD. The proportional hazard assumption was checked by tests based on Schoenfeld residuals.

To investigate the combined effect of CRF and GS we categorised all participants with both measurements into four groups as follow: (a) high CRF and GS, (b) Low CRF and High GS, (c) High CRF and low GS, and (d) low CRF and GS. Lower levels of GS and CRF were defined as those in the lowest quartile for GS and CRF (lowest 25th percentile), whereas the high levels of GS and CRF included all those in the highest three quartiles. The individuals categorised as high CRF and high GS were used as reference group. Cox proportional hazard models were performed and results were reported as hazard ratios together with 95% confidence intervals. The analyses were adjusted for model 1 as describe above.

Because Cox models with event-to-variable ratio < 10 may have unreliable estimates in some scenarios [33], we conducted a sensitivity analysis including all non-CVD patients (n=70,808; events=133) with a minimal set of adjustments variables: age, sex, deprivation index, ethnicity, current/former smoker, overweight/obesity, and comorbidities. This was conducted for CRF trend analysis (per 1-MET, 1-SD, and 1-quartile increment), age- and sex-specific quartile analysis, and combined CRF/GS effect analysis. The event-to-variable ratios for these analyses were 12.1:1, 10.2:1, and 10.2:1 respectively.

In order to compare the hazard estimates for lower levels of CRF and GS to conventional modifiable risk factors for HF (alcohol consumed daily or almost daily, current smokers, obesity BMI≥30.0 kg.m^{-2}, medically diagnosed hypertension, diabetes and hypercholesterolemia) Cox proportional hazard models were performed and results were reported as HR and its 95% CI. Three models were fitted to investigate this question, model 0 each of the modifiable risk factors was fitted into the model individually and no adjustment were made; model 1 was similar to model 0 but it was adjusted for age, sex, ethnicity, deprivation, gross income, professional qualifications; and model 2 which was mutually adjusted for all modifiable risk factors of interest and adjusted for age, sex, ethnicity, deprivation, gross income, professional qualifications.

All analyses were performed using STATA 14 statistical software (StataCorp LP).

Ethical Approval

The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee (Ref 11/NW/0382 on 17th June 2011) and all participants provided written informed consent to participate in the UK Biobank study. The study protocol is available online (http://www.ukbiobank.ac.uk/). This research has been conducted using the UK Biobank resource under application number 7155.

RESULTS

Of the 502,628 participants recruited to UK Biobank, 374,493 (74%) participants were included in the current study for GS, after excluding participants with comorbidities at baseline (n=112,776) and those who were not event-free during the 2 years of follow up. The numbers included in analyses of CRF were 57,053 (110%). The mean follow-up period, after exclusion of the first 2 years, was 4.1 years [ranging from 2.4 to 7.1].

The characteristics of participants by categories of CRF and GS are presented in Supplementary Tables S2 and S3. Compared to individuals with lower CRF (quartile 1), those in quartile 4 (the fittest) were less deprived with higher education qualifications and income levels, more likely to be currently working and more likely to be white Europeans. Similarly, those with the highest level of GS (quartile 4) were more likely to be less deprived, have higher academic qualifications and earn more than those with the lowest GS (Supplemental Table 3). Those in quartile 4 for CRF were more likely to be of a normal weight and had the lowest waist circumference of all groups, with a corresponding lower level of central obesity. Compared to the group with the lowest GS, the group with the highest GS were more overweight or obese and had waist circumference which was evenly distributed across all groups, with corresponding central obesity. In both cohorts defined by CRF or GS, those in the highest quartile had a lower incidence of diabetes and hypertension, compared with those in the lowest quartile (Supplemental Table 2 and 3).

The hazard ratios for the association of CRF and GS with HF are presented in Table 1. In our fully adjusted model (Model 0), for both CRF and GS, the risk for HF was 18% and 19% lower per 1-MET or 5-kg increment, respectively. When a non-linear association was investigated for the exposures of interest (CRF and GS) with HF, the trend of the association remained significant for both CRF (HR-trend: 0.51 [95% CI: 0.38; 0.68], *P*<.001) and GS (HR-trend: 0.78 [95% CI: 0.72; 0.84], *P*<.001) (Figure 1). For CRF and GS, HF incidence was lower in all quartiles compared to the lowest quartile for both exposures (the least fit and lowest grip strength) (Table 2). When sensitivity analyses were conducted by removing individuals who had an MI episode before having a heart failure event (Model 1) the association remained significant for CRF (HR-trend: 0.50 per 1-SD [95% CI: 0.37; 0.69], *P*<.001) and GS (HR-trend: 0.77 [95% CI: 0.72; 0.83], *P*<.001), with limited attenuation of HRs in each case (Table 1 and 2).

When analysed together, the combination of low GS and low CRF conferred an increased risk (HR 5.40 [95% CF: 2.58; 11.2], *P*<.001), compared to a reference group with high GS and high CRF. Extrapolation of this showed an increased risk in the low CRF and high GS compared to the reference group (HR 3.38 [95% CF: 1.77; 6.40], *P*<.001), but no difference in risk in the low GS and high CRF group (HR 1.05 [95% CF: 0.42; 2.61], *P*=.91) (Figure 2). Sensitivity analysis has shown that the above HRs and statistical significance remained stable with event-to-variable ratio > 10 (Supplemental Table 4).

When the hazard for low GS and CRF was compared to other modifiable risk factors for HF we found that each of the modifiable risk factors (alcohol consumed daily or almost daily, current smokers, obesity BMI ≥30.0 $kg.m^{-2}$,

medically diagnosed hypertension, diabetes and hypercholesterolemia) was associated to HF in a univariate model (Figure 3 and Supplemental Table 5). Although the hazard estimates when the analyses were adjusted for confounder factors, these remained associated to HF. However, when these modifiable risk factors were mutually adjusted for each other, only CRF (HR 3.91 [95% CI: 1.92; 7.96], *P*<.001), smoking (HR: 2.36 [95% CI: 1.02 5.48], *p*=.05) and diabetes (HR: 3.10 [95% CI: 1.41; 6.84], *p*=.005) were associated to HF (Supplemental Table 5).

DISCUSSION

Heart failure is a debilitating disease with a poor prognosis, and is complex to treat, with most pharmacological treatments having side effects. For these reasons, it is important to identify at risk groups within a population to enable early intervention, including optimisation of cardiovascular and lifestyle risk factors. In the current study, we found that objectively measured markers of physical function (CRF and GS) are strongly associated with HF incidence and may have a role in identifying patients who are at highest risk at a population level. GS is particularly easy to measure, is a low cost measurement and takes less than a few minutes to measure. As such, it has clear translational potential for wider use in clinical practice.

Higher levels of CRF, even within a low risk population, are associated with significantly better cardiovascular, and mortality outcomes [9; 10; 34]. CRF is not only a proxy of current physical activity levels but also of the physical activity and exercise patterns accumulated over a period of time, in addition to a well-recognised genetic component [35]. It is therefore a better estimate of an individual's physical behaviours than a single measurement of physical activity [9; 36]. We have shown that all levels of CRF above the reference level, i.e. the least fit cohort, are associated with a lower risk of incident HF. This finding, whilst in keeping with previous studies [7; 16; 17; 37], is one of the largest, and we employed very conservative statistical adjustment to minimise the potential effect of reverse causation in our findings. A recent study using UK Biobank reported an association between CRF and different CVD outcomes including HF. Although the estimates observed for the association between CRF and HF suggest that a higher CRF is associated with a lower HF incidence (HR: 0.58 [0.49; 0.68] per 1 SD increment in CRF) this analyses included individuals with co-morbidities. It also failed to conduct a landmark analysis, which may mean the results are affected by reverse causation. Moreover, the analyses lacked adjustment for some relevant confounding factors such as dietary risk behaviours and alcohol intake [7]. Another retrospective study of 66,329 adults found low CRF to be associated with increased HF incidence. Similar to our study, they showed that per 1-MET increase in CRF, HF incidence was 16% lower. Although a large, and bi-ethnic cohort (28% Black, 65.0% White), the patients in that study had all been referred for exercise stress testing by physicians, in the majority of cases due to chest pain or shortness of breath, with the suspicion of underlying CVD disease requiring assessment. The cohort studied in our current analysis is therefore more representative of a general population without evidence of disease at baseline.

Although a very useful, objective, predictor of HF, CRF is not easily measured in clinical practice and its utility in screening is therefore limited. Conversely, GS is easily measured, and is quick and reproducible, meaning it can be obtained in a variety of clinical settings [38]. It allows a measurement of overall muscle strength, as well as

function, and current European recommendations include GS as in the assessment for older people at risk of sarcopenia [38]. Our analysis has shown that a higher GS is associated with a lower risk of HF. The PURE study demonstrated that GS was inversely associated with all-cause mortality, non-cardiovascular and cardiovascular mortality (myocardial infarction and stroke) [11], but did not look at HF as an outcome. It is perhaps unsurprising that those who are at lower CVD risk, i.e. those with the highest GS, are also at a lower risk of HF, as commonly, though not always, CVD precedes the diagnosis of HF. That noted, risk levels remained virtually the same when we removed all those (~10%) with MI events prior to their incident HF. A study conducted by Tikkanen et al., using UK Biobank participants also reported a protective association between GS and CVD outcomes, including HF. Similar to the limitations mentioned for CRF previously, this study failed to perform conservative analyses, and didn't account for the effect of diet [7].

A novel result of the current study is the risk associated with low GS in combination with low CRF. This risk is attenuated if CRF is increased. This may be driven by potential underlying mechanisms that specifically link low CRF with HF. Although not fully understood, previous work has suggested that an increased risk of HF in patients with low CRF may be different to the increased risk of CVD with low CRF, therefore, potentially driven by different aetiologies [39; 40]. However, with respect to our current study, these findings could help risk stratify patients in a more time efficient way; if GS is found to be low, then patients could subsequently be referred for assessment of CRF, thus identifying those with the highest risk.

Our findings also suggest that the risk associated with having a low CRF compared to the risk of having a high genetic susceptibility for CHD or atrial fibrillation, is 2-times higher. Tikkanen et al[7], reported that those individuals in the highest tertile for a CHD genetic risk score (those more genetically susceptible) had a hazard ratio for CHD incidence equivalent to 1.77 (95% CI: 1.67; 1.87) and a hazard ratio equivalent to 1.95 (95%CI: 1.86; 2.06) for atrial fibrillation compared to those in the lower tertile for the genetic risk score. However, if we compare these results with the risk of HF incidence in those with low fitness (4.60 [95% CI: 2.74; 7.71]) or those who have low CRF plus low GS (HR=6.05 [95% CI: 2.92; 12.5]), it is clear that the risk is higher for these modifiable exposures than the genetic risk score for CHD or atrial fibrillation. The current study also highlights the importance of CRF and GS as modifiable risk factors compared with well-established lifestyle and non-modifiable factors contributing to HF risk. Interestingly, when GS and CRF are fitted individually into the models both are associated with HF. This may be explained by these factors being involved in causal pathways, or acting as mediators. For example, high alcohol intake, obesity and smoking are associated with an increased risk of hypertension, diabetes and hypercholesterolemia. Therefore a mutually adjusted model may take away a high proportion of the variance shared between these factors.

To enhance the utility of these results, further randomised studies are required to assess if the relationships we have described are causal. Our data implies that each increasing level of GS above the reference group is associated with a lower risk of HF, with a similar trend demonstrated for CRF. Intervention studies to investigate the benefits of aerobic exercise to increase CRF and resistance training to increased muscle strength, and the resultant effects on HF risk would be beneficial.

Strengths and limitations

The UK Biobank is not fully representative of the general British population [41], which means we are unable to fully generalize estimates of the magnitude of associations [42]. However, it still allows us to test our research question in a very large, prospective cohort. Additionally, CRF and GS were assessed using validated methods [15; 43-45], trained staff and standard operating procedures. A wide range of potential confounding variables were controlled for in our analyses, including removal of all participants with comorbidities at baseline, including but not limited to CVD, hypertension and diabetes, all of which are significant risk factors for developing HF. Moreover, our results were conducted using a 2-year landmark analysis. This, along with the exclusion of individuals with comorbidities, reduces the potential influence of reverse causality on our findings. However, we also recognised that the lower number of events observed for CRF could produce unreliable hazard estimates. However, our sensitivity analyses where the models were adjusted for comorbidities rather than exclude them, retained a high number of HF events, and showed similar risk estimates. This indicates that the hazards derived from the most conservative models are likely to be reliable.

CONCLUSIONS

In conclusion, the current data generated from the large UK biobank cohort has demonstrated that, independent of major confounding factors, higher CRF and GS are associated with lower risk of incident HF. Although this trend is stronger for CRF, with its ease of measurement, relative to the others, we suggest that GS should be further investigated for its clinical utility as a first line screening in identifying people at high risk of HF, who may then benefit from CRF assessment to ascertain if they fall into a higher risk group.

Clinical Perspective

The early identification of those at risk of HF could be mediated by focusing on modifiable risk factors, such as GS, which is easy to measure, and CRF. Our findings add to the increasing body of evidence that GS is a useful clinical measurement that can be used alongside traditional methods to risk stratify patients.

Translational Outlook

Future studies are needed to assess whether CRF and GS measurements could improve the predictive ability of current risk scores for HF. Our findings also suggest that interventions to improve GS could be investigated in the future against biomarkers of HF risk.

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Figures

Figure 1. Hazard ratio for Heart Failure by quartiles of fitness and grip strength

Data is presented as hazard ratio and its 95% CI. The reference group for each exposure were those individuals in the lowest quartile for fitness and strength. All analyses were conducted using a 2-years landmark analysis. Hazard ratio for trend indicate the increase in the hazard ratio for HF per one quartile higher in the exposure. Model 0 was fully adjusted and include age, height, deprivation index, ethnicity, month of recruitment, education qualifications, employment, income, comorbidities (diabetes and hypertension), medication for cholesterol, BMI categories, smoking and dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat intake) as covariates. A sensitivity analysis was conducted "Model 1", this model was identical to model 0 but individuals who had a MI episode before having a heart failure event were removed from the analysis. CRF: cardiorespiratory fitness; HR: hazard ratio, CI: confidence intervals.

Figure 2. Hazard ratio for the association of heart failure with high and low fitness and strength

Data is presented as hazard ratio and its 95% CI. Total number of individuals included in the analyses were n= 56, 822, of these n=59 developed a HF event during the follow-up time. Low levels of GS (handgrip strength) and CRF (cardiorespiratory fitness) include those participants in the lowest quintiles for these exposures. Therefore, higher levels include those participants in the highest four quintiles for these exposures. Models were adjusted for sex, age, deprivation index, ethnicity, month of recruitment, education qualifications, employment, gross income, medication for CVD, comorbidities (diabetes and hypertension), BMI categories, smoking and dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat). CRF: cardiorespiratory fitness; HR: hazard ratio, CI: confidence intervals.

Figure 3. Hazard ratio for heart failure associated with CRF, grip strength and conventional modifiable risk factors.

Data are presented as hazard ratio and its 95% CI. The analyses were adjusted for age, sex, ethnicity, deprivation, gross income and professional qualification but exposures were fitted individually into the models. Risk factors were defined as follow: high alcohol intake was defined as alcohol consumed daily or almost daily, medically diagnosed hypertension, diabetes and hypercholesterolemia were self-reported, current smokers was self-reported, obesity was defined as BMI>30.0 $kg.m^{-2}$, and low grip strength and low fitness was defined as the bottom 25^{th} percentile. CRF: cardiorespiratory fitness; HR: hazard ratio, CI: confidence intervals.

Table 1. Hazard ratio for the association of heart failure with cardiorespiratory fitness and grip strength

CRF	Total n / events	Per 1-MET	*P*	1-SD increment	*P*
Model 0	57,053 / 66	0.82 (0.76; 0.88)	<.001	0.50 (0.38; 0.65)	<.001
Model 1*	57,046 / 59	0.81 (0.76; 0.88)	<.001	0.49 (0.37; 0.65)	<.001
Grip strength		**Per 5-kg**		**1-SD increment**	
Model 0	374,494 / 631	0.81 (0.77; 0.86)	<.001	0.65 (0.58; 0.72)	<.001
Model 1*	374,442 / 579	0.81 (0.77; 0.85)	<.001	0.64 (0.57; 0.72)	<.001

Data are presented as hazard ratio and its 95% CI per 1-SD increase in the exposure 1-MET increase in fitness and 5-kg increase in grip strength. All analyses were conducted using a 2-years landmark analysis.
Model 0 was fully adjusted and include age, height, deprivation index, ethnicity, month of recruitment, education qualifications, employment, income, comorbidities (diabetes and hypertension), medication for cholesterol, diabetes or hypertension, BMI categories, smoking and dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat intake) as covariates. A sensitivity analysis was conducted "Model 1", this model was identical to model 0 but individuals who had a MI episode before having a heart failure event were removed from the analysis. CRF: cardiorespiratory fitness; HR: hazard ratio, CI: confidence intervals.

Table 2. Hazard ratio for the association of heart failure with age- and sex-specific quartiles of fitness and strength

	Model 0			Model 1*		
CRF	**Total n/events**	**HR (95% CI)**	***P***	**Total n/events (%)**	**HR (95% CI)**	***P***
Lowest (Unfit)	12,858 / 39	1.00	(Ref.)	12,855 / 36	1.00	(Ref.)
Lower-Middle	14,501 / 12	0.33 (0.16; 0.62)	.001	14,499 / 10	0.29 (0.15; 0.60)	<.001
Middle-Higher	14,819 / 12	0.36 (0.18; 0.70)	.003	14,817 / 10	0.33 (0.16; 0.69)	<.001
Highest (Fit)	14,875 / 3	0.11 (0.03; 0.35)	<.001	14,875 / 3	0.12 (0.04; 0.40)	<.001
Trend	57,053 / 66	0.51 (0.38; 0.68)	<.001	57,046 / 59	0.50 (0.37; 0.69)	<.001
Grip strength						
Lowest (Low Grip)	90,668 / 221	1.00	(Ref.)	90,651 / 204	1.00	(Ref.)
Lower-Middle	96,819 / 156	0.66 (0.54; 0.81)	<.001	96,805 / 142	0.64 (0.52; 0.80)	<.001
Middle-Higher	97,098 / 143	0.60 (0.48; 0.74)	<.001	97,087 / 132	0.59 (0.47; 0.74)	<.001
Highest (High Grip)	89,908 / 111	0.46 (0.36; 0.58)	<.001	89,898 / 101	0.45 (0.35; 0.57)	<.001
Trend	374,493 / 631	0.78 (0.72; 0.84)	<.001	374,441 / 579	0.77 (0.72; 0.83)	<.001

Data is presented as hazard ratio and its 95% CI. The reference group for each exposure were those individuals in the lowest quartile for fitness and strength. All analyses were conducted using a 2-years landmark analysis. Hazard ratio for trend indicate the increase in the hazard ratio for HF per one quartile higher in the exposure.
Model 0 was fully adjusted and include age, height, deprivation index, ethnicity, month of recruitment, education qualifications, employment, income, comorbidities (diabetes and hypertension), medication for cholesterol, diabetes or hypertension, BMI categories, smoking and dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat intake) as covariates. A sensitivity analysis was conducted "Model 1", this model was identical to model 0 but individuals who had a MI episode before having a heart failure event were removed from the analysis. CRF: cardiorespiratory fitness; HR: hazard ratio, CI: confidence intervals.

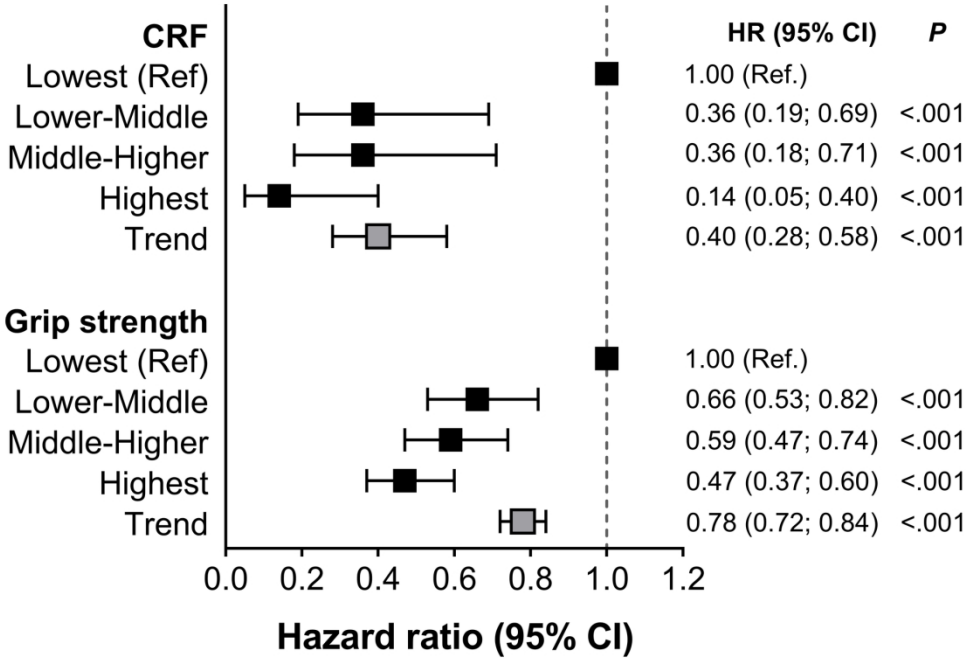

Figure 1. Hazard ratio for Heart Failure by quartiles of fitness and grip strength

Data is presented as hazard ratio and its 95% CI. The reference group for each exposure were those individuals in the lowest quartile for fitness and strength. All analyses were conducted using a 2-years landmark analysis. Hazard ratio for trend indicate the increase in the hazard ratio for HF per one quartile higher in the exposure.
Model 0 was fully adjusted and include age, height, deprivation index, ethnicity, month of recruitment, education qualifications, employment, income, comorbidities (diabetes and hypertension), medication for cholesterol, diabetes or hypertension, BMI categories, smoking and dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat intake) as covariates. In addition, grip strength was added as a covariate when CRF was used as main exposure variable. A sensitivity analysis was conducted "Model 1", this model was identical to model 0 but individuals who had a MI episode before having a heart failure event were removed from the analysis. CRF: cardiorespiratory fitness; HR: hazard ratio, CI: confidence intervals.

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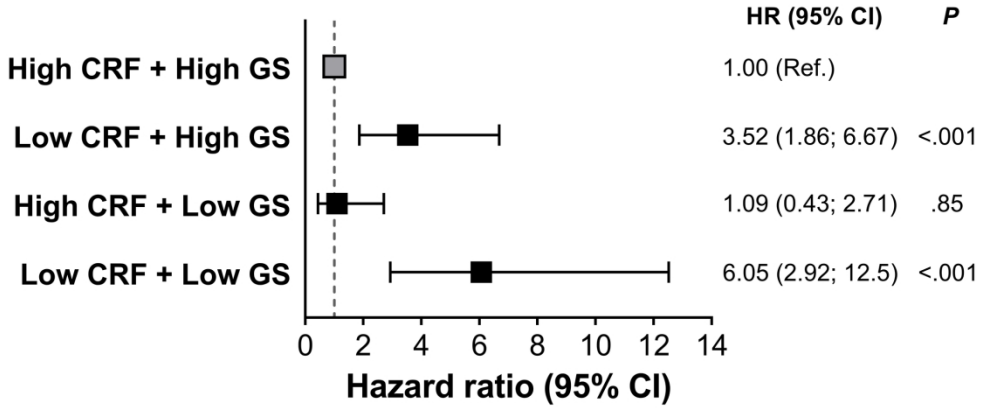

Figure 2. Hazard ratio for the association of heart failure with high and low fitness and strength

Data is presented as hazard ratio and its 95% CI. Total number of individuals included in the analyses were n= 56, 822, of these n=59 developed a HF event during the follow-up time. Low levels of GS (handgrip strength) and CRF (cardiorespiratory fitness) include those participants in the lowest quintiles for these exposures. Therefore, higher levels include those participants in the highest four quintiles for these exposures. Models were adjusted for sex, age, deprivation index, ethnicity, month of recruitment, education qualifications, employment, gross income, medication for CVD, comorbidities (diabetes and hypertension), BMI categories, smoking and dietary intake (alcohol, fruit and vegetable, oily fish, red meat and processed meat). CRF: cardiorespiratory fitness; HR: hazard ratio, CI: confidence intervals.

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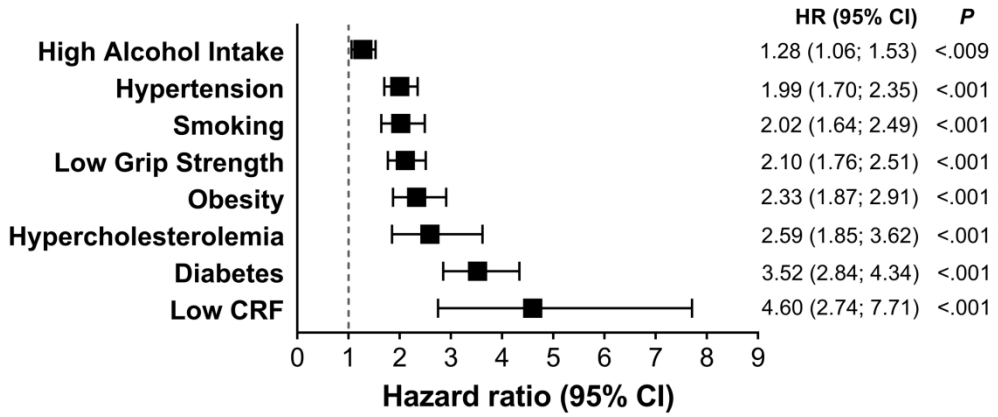

Figure 3. Hazard ratio for heart failure associated with CRF, grip strength and conventional modifiable risk factors.
Data are presented as hazard ratio and its 95% CI. The analyses were adjusted for age, sex, ethnicity, deprivation, gross income and professional qualification but exposures were fitted individually into the models. Risk factors were defined as follow: high alcohol intake was defined as alcohol consumed daily or almost daily, medically diagnosed hypertension, diabetes and hypercholesterolemia were self-reported, current smokers was self-reported, obesity was defined as BMI>30.0 kg.m-2, and low grip strength and low fitness was defined as the bottom 25th percentile. CRF: cardiorespiratory fitness; HR: hazard ratio, CI: confidence intervals.

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Online-Only Supplemental Material

Procedures:

Fitness Testing - Tests were terminated if heart rate exceeded 75% of age-predicted maximum. In individuals with systolic blood pressure between 160-179 mm Hg or diastolic blood pressure between 95-109 mm Hg or who answered 'yes' or 'unsure' to the question "Has a doctor ever said that you have a heart condition and should only do physical activity recommended by a doctor", the test protocol was modified to achieve a final work rate of 35% of predicted maximal power (n = 3,054). Fitness testing was not performed in individuals who were unable to walk or cycle unaided for 10 minutes; were pregnant or had high blood pressure (systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg. Work rate at maximal heart rate was estimated by extrapolating the pre-exercise heart rate (i.e. at work rate zero Watts) and the heart rate and work rate at the end of the test, to the age-predicted maximal heart rate (208 – 0.7 x age (1) assuming a linear relationship (2). The linear nature of the work rate vs heart rate relationship means that the estimated maximal work rate for an individual should be independent of the work rate achieved during the exercise test. Maximal oxygen uptake (i.e. at predicted maximal heart rate) was estimated from the regression equation for the relationship between work rate and oxygen uptake (oxygen uptake (in $ml.kg^{-1}.min^{-1}$) = 7 + (10.8 x work rate (in Watts))/body mass (in kg)) (3) and then expressed in terms of maximal metabolic equivalent of task (METs) (where 1 MET ≡ 3.5 $ml.kg^{-1}.min^{-1}$).

Sociodemographic information such as employment (paid employment, retired, unable to work, unemployed, student and other), education (college or university degree, A levels or equivalent, GCSE or equivalent, CSEs or equivalent levels, HND or equivalent and other professional qualifications) and income (<£18,000, £18,000-29,999, £30,000-51,999, £52,000-100,000 and >£100,000) were self-reported at baseline.

Supplemental Table 1. Cut-off point for age and sex-specific quartiles of fitness and grip strength.

		Lowest	Lower/Middle	Middle/higher	Highest
CRF (METs)	**Women**				
	<50 years	<7.5	7.5-9.1	9.2-10.7	>10.7
	50-60 years	<6.3	6.3-7.8	7.9-9.2	>9.2
	>60 years	<5.3	5.3-6.8	6.9-8.2	>8.2
	Men				
	<50 years	<9.4	9.4-11.2	11.3-13.1	>13.1
	50-60 years	<8.4	8.4-10.3	10.4-12.1	>12.1
	>60 years	<7.4	7.4-9.3	9.4-11.2	>11.2
Grip strength (kg)	**Women**				
	<50 years	<22.0	22.0-26.0	26.1-30.0	>30.0
	50-60 years	<19.5	19.5-23.4	23.5-27.0	>27.0
	>60 years	<17.5	17.5-21.4	21.5-25.0	>25
	Men				
	<50 years	<36.5	36.5-42.0	42.1-48.0	>48.0
	50-60 years	<34.0	34.0-39.5	39.6-45.0	>45.0
	>60 years	<31.5	31.5-37.0	37.1-42.0	>42.0

Supplemental Table 2. Cohort Characteristic by fitness in the UK Biobank

	Lowest	Lower-Middle	Middle-Higher	Highest	*P**
Socio-demographics					
Total n	12,858	14,501	14,819	14,875	
Women, n (%)	6,733 (53.2)	7,679 (53.2)	7,936 (53.4)	7,980 (53.4)	>.99
Age (years), mean (SD)	56.0 (8.1)	56.0 (8.1)	55.8 (8.2)	55.4 (8.2)	<.001
Deprivation index quintiles, n (%)					<.001
Lower	3,279 (25.2)	4,362 (29.6)	4,724 (31.3)	4,783 (31.6)	
Middle	4,195 (32.2)	5,036 (34.3)	5,212 (34.6)	5,157 (34.2)	
Higher	5,536 (42.6)	5,307 (36.1)	5,149 (34.1)	5,159 (34.2)	
Professional qualifications, n (%)					<.001
College or University degree	3,737 (35.1)	4,875 (38.7)	5,749 (43.2)	6,977 (50.4)	
A levels/AS levels or equivalent	1,489 (14.0)	1,717 (13.6)	1,867 (14.0)	1,901 (13.7)	
O levels/GCSEs or equivalent	2,905 (27.3)	3,286 (26.1)	3,253 (24.4)	2,795 (20.2)	
CSEs or equivalent	922 (8.6)	977 (7.8)	805 (6.1)	675 (4.9)	
NVQ or HND or HNC or equivalent	933 (8.8)	1,023 (8.1)	944 (7.1)	770 (5.6)	
Other professional qualifications	664 (6.2)	721 (5.7)	694 (5.2)	713 (5.2)	
Income categories, n (%)					<.001
Less than £18,000	2,879 (26.2)	2,381 (18.7)	2,122 (15.9)	1,716 (12.7)	
£18,000 to £29,999	2,972 (27.1)	3,316 (26.1)	3,073 (23.1)	2,908 (21.6)	
£30,000 to £51,999	2,808 (25.6)	3,429 (27.0)	3,697 (27.8)	3,616 (26.8)	
£52,000 to £100,000	1,887 (17.2)	2,827 (22.2)	3,291 (24.7)	3,709 (27.5)	
Greater than £100,000	431 (3.9)	760 (6.0)	1,138 (8.5)	1,541 (11.4)	
Employment status, n (%)					<.001
In paid employment or self-employed	7,431 (57.8)	8,980 (61.7)	9,661 (64.7)	9,750 (65.1)	
Retired	3,969 (30.9)	4,525 (31.1)	4,364 (29.2)	4,279 (28.6)	
Looking after home and/or family	393 (3.1)	442 (3.0)	437 (2.9)	495 (3.3)	
Unable to work because of sickness or disability	475 (3.7)	147 (1.0)	99 (0.7)	88 (0.6)	
Unemployed	453 (3.5)	356 (2.4)	273 (1.8)	244 (1.6)	
Doing unpaid or voluntary work	78 (0.6)	71 (0.5)	72 (0.5)	93 (0.6)	
Full or part-time student	52 (0.4)	46 (0.3)	38 (0.2)	39 (0.2)	
Ethnicity, n (%)					<.001
White	10,602 (84.2)	12,907 (89.4)	13,864 (93.3)	14,280 (95.6)	
South Asian	637 (5.1)	579 (4.0)	354 (2.4)	161 (1.1)	
Black	886 (7.0)	516 (3.6)	268 (1.8)	122 (0.8)	
Chinese	54 (0.4)	64 (0.4)	74 (0.5)	81 (0.5)	
Mixed background / others	408 (3.2)	366 (2.5)	305 (2.1)	304 (2.0)	
Smoking status, n (%)					<.001
Never	7,756 (59.8)	8,488 (57.9)	8,576 (56.9)	8,399 (55.7)	
Previous	3,988 (30.8)	4,942 (33.7)	5,062 (33.6)	5,224 (34.6)	
Current	1,217 (9.4)	1,243 (8.4)	1,423 (9.5)	1,460 (9.7)	
Obesity-related markers					
BMI, mean (SD)	29.6 (5.6)	27.9 (4.2)	26.5 (3.8)	25.0 (3.5)	<.001
BMI Categories, n (%)					<.001
Underweight (<18.5 $kg.m^{-2}$)	40 (0.3)	27 (0.2)	57 (0.3)	135 (0.8)	
Normal weight (18.5-24.9 $kg.m^{-2}$)	2,557 (19.7)	3,640 (24.7)	5,580 (37.0)	7,917 (52.4)	
Overweight (25.0 to 29.9 $kg.m^{-2}$)	5,076 (39.1)	7,028 (47.8)	7,021 (46.5)	5,797 (38.4)	
Obese (≥30.0 $kg.m^{-2}$)	5,326 (40.9)	4,021 (27.3)	2,442 (16.2)	1,267 (8.4)	
Waist Circumference (cm), mean (SD)	95.3 (14.5)	91.5 (12.4)	88.1 (11.9)	84.5 (11.7)	<.001
Central Obesity, n (%)	6,468 (49.7)	5,535 (37.6)	3,911 (25.9)	2,363 (15.6)	<.001
Physical activity and Sleep, mean (SD)					

Total physical activity (MET.h.week^{-1})	43.7 (62.9)	45.3 (58.6)	50.0 (60.1)	54.9 (60.8)	<.001
Fitness (MET)	4.9 (2.5)	8.3 (1.5)	9.9 (1.6)	12.6 (2.5)	<.001
Grip strength (kg)	29.5 (10.7)	30.4 (10.6)	30.7 (10.6)	31.2 (10.4)	<.001
TV-viewing (h.day^{-1})	3.0 (1.7)	2.8 (1.5)	2.6 (1.5)	2.3 (1.4)	<.001
PC-screen time (h.day^{-1})	1.4 (1.5)	1.4 (1.5)	1.4 (1.4)	1.4 (1.3)	0.49
Sleeping time (h.day^{-1})	7.1 (1.2)	7.1 (1.0)	7.1 (1.0)	7.1 (1.0)	0.07
Dietary intakes, mean (SD)					
Total energy (Kcal.day^{-1})	2,096 (715)	2,078 (646)	2,104 (630)	2,164 (655)	<.001
Protein intake (% of TE)	15.7 (4.1)	15.7 (3.8)	15.5 (3.6)	15.4 (3.5)	<.001
Carbohydrates intake (% of TE)	47.4 (8.6)	47.2 (8.4)	47.2 (8.2)	47.4 (8.1)	0.49
Total Fat intake (% of TE)	32.0 (7.1)	32.1 (6.9)	31.8 (6.7)	31.6 (6.7)	<.001
Saturated intake (% of TE)	12.3 (3.5)	12.3 (3.4)	12.2 (3.3)	12.0 (3.3)	<.001
Sugar intake (% of TE)	22.4 (7.6)	22.5 (7.3)	22.6 (7.0)	22.8 (6.8)	<.001
Alcohol intake (% of TE)	4.8 (6.9)	5.0 (6.7)	5.5 (6.6)	5.6 (6.4)	<.001
Red meat intake (portion.week^{-1})	2.0 (1.6)	1.9 (1.4)	1.9 (1.3)	1.8 (1.3)	<.001
Processed meat intake (portion.week^{-1})	2.0 (1.1)	1.9 (1.1)	1.9 (1.1)	1.7 (1.1)	<.001
Vegetable and Fruit intake (grams.day^{-1})	314.4 (204.5)	320.9 (200.0)	329.0 (200.7)	349.4 (194.1)	<.001
Oily fish (portion.week^{-1})	1.1 (1.1)	1.1 (1.0)	1.1 (1.0)	1.2 (1.0)	<.001
Health status					
Diabetes history, n (%)	1,066 (8.2)	726 (4.9)	514 (3.4)	360 (2.4)	<.001
High blood pressure history, n (%)	4,669 (35.9)	3,671 (25.0)	3,061 (20.3)	2,519 (16.7)	<.001
Systolic blood pressure (mmHg), mean (SD)	147.0 (22.3)	141.1 (18.3)	137.1 (17.6)	133.7 (17.4)	<.001
Diastolic blood pressure (mmHg), mean (SD)	86.6 (11.7)	83.3 (9.9)	80.8 (9.6)	78.5 (9.7)	<.001
Medication for cholesterol or blood pressure, n (%)					<.001
None of the above	11,083 (85.1)	13,103 (89.0)	13,786 (91.3)	14,013 (92.7)	
Cholesterol lowering medication	967 (7.4)	847 (5.8)	721 (4.8)	578 (3.8)	
Blood pressure medication	976 (7.5)	769 (5.2)	597 (3.9)	526 (3.5)	

BMI body mass index; PA physical activity; MET basal metabolic-equivalent; TE total energy intake. SD standard deviation; n number; central obesity was defined as waist circumference >88cm for females and >102cm for males. TE: total energy; METs: Metabolic equivalent; PA: physical activity.

*P-values were corrected for multiple testing using Holm's Bonferroni method.

Supplemental Table 3. Cohort Characteristic by grip strength in the UK Biobank

	Lowest	Lower-Middle	Middle-Higher	Highest	*P**
Socio-demographics					
Total n	90,668	96,819	97,098	89,908	
Women, n (%)	46,558 (54.3)	50,646 (54.0)	51,419 (54.2)	46,059 (52.3)	<.001
Age (years), mean (SD)	55.3 (8.0)	55.7 (8.1)	55.4 (8.1)	55.0 (8.2)	<.001
Deprivation index quintiles, n (%)					<.001
Lower	26,051 (29.2)	32,735 (33.9)	34,798 (35.9)	33,860 (37.7)	
Middle	28,737 (32.3)	32,819 (34.1)	33,269 (34.2)	30,736 (34.2)	
Higher	34,286 (38.5)	30,910 (32.0)	29,084 (29.9)	25,338 (28.1)	
Professional qualifications, n (%)					<.001
College or University degree	28,048 (39.0)	32,484 (40.4)	34,316 (41.5)	33,404 (42.7)	
A levels/AS levels or equivalent	9,862 (13.7)	10,802 (13.5)	11,391 (13.8)	10,771 (13.8)	
O levels/GCSEs or equivalent	18,680 (26.0)	20,814 (25.9)	20,739 (25.1)	18,782 (24.0)	
CSEs or equivalent	5,750 (8.0)	5,601 (7.0)	5,403 (6.5)	4,738 (6.0)	
NVQ or HND or HNC or equivalent	5,427 (7.6)	6,048 (7.5)	6,133 (7.4)	6,059 (7.7)	
Other professional qualifications	4,160 (5.7)	4,581 (5.7)	4,785 (5.7)	4,511 (5.8)	
Income categories, n (%)					<.001
Less than £18,000	18,130 (24.2)	16,312 (19.7)	14,602 (17.3)	12,009 (15.2)	
£18,000 to £29,999	19,087 (25.5)	20,998 (25.4)	20,361 (24.2)	18,325 (23.3)	
£30,000 to £51,999	19,302 (25.9)	22,429 (27.2)	23,837 (28.3)	22,857 (29.0)	
£52,000 to £100,000	14,586 (19.5)	18,126 (21.9)	19,956 (23.7)	19,948 (25.3)	
Greater than £100,000	3,678 (4.9)	4,808 (5.8)	5,461 (6.5)	5,662 (7.2)	
Employment status, n (%)					<.001
In paid employment or self-employed	54,879 (62.4)	60,430 (63.2)	62,786 (65.1)	59,667 (66.8)	
Retired	24,133 (27.4)	28,656 (30.0)	27,452 (28.5)	24,315 (27.2)	
Looking after home and/or family	2,745 (3.1)	2,733 (2.9)	2,869 (3.0)	2,670 (3.0)	
Unable to work because of sickness or disability	3,318 (3.8)	1,523 (1.6)	1,162 (1.2)	870 (1.0)	
Unemployed	2,204 (2.5)	1,634 (1.7)	1,484 (1.5)	1,148 (1.3)	
Doing unpaid or voluntary work	458 (0.5)	432 (0.4)	429 (0.4)	408 (0.4)	
Full or part-time student	301 (0.3)	276 (0.2)	291 (0.3)	265 (0.3)	
Ethnicity, n (%)					<.001
White	77,811 (90.7)	89,010 (94.8)	90,887 (95.8)	84,452 (96.1)	
South Asian	3,931 (4.6)	1,709 (1.8)	1,019 (1.1)	484 (0.6)	
Black	1,620 (1.9)	1,428 (1.5)	1,398 (1.5)	1,756 (2.0)	
Chinese	500 (0.6)	365 (0.4)	282 (0.3)	137 (0.2)	
Mixed background / others	1,948 (2.3)	1,367 (1.5)	1,276 (1.4)	1,085 (1.2)	
Smoking status, n (%)					<.001
Never	52,625 (59.3)	55,372 (57.5)	54,806 (56.5)	49,785 (55.5)	
Previous	26,774 (30.1)	31,257 (32.5)	32,360 (33.4)	31,005 (34.5)	
Current	9,442 (10.6)	9,648 (10.0)	9,808 (10.1)	8,984 (10.0)	
Obesity-related markers					
BMI, mean (SD)	27.3 (4.9)	27.0 (4.6)	27.0 (4.5)	27.4 (4.5)	<.001
BMI Categories, n (%)					<.001
Underweight (<18.5 $kg.m^{-2}$)	625 (0.7)	510 (0.5)	404 (0.4)	231 (0.2)	
Normal weight (18.5-24.9 $kg.m^{-2}$)	30,700 (34.5)	34,711 (36.0)	33,991 (35.0)	28,242 (31.4)	
Overweight (25.0 to 29.9 $kg.m^{-2}$)	36,638 (41.3)	40,854 (42.4)	42,283 (43.5)	40,333 (44.9)	
Obese (≥30.0 $kg.m^{-2}$)	20,912 (23.5)	20,367 (21.1)	20,498 (21.1)	21,125 (23.5)	
Waist Circumference (cm), mean (SD)	90.0 (13.5)	89.1 (13.0)	89.1 (12.9)	90.1 (13.0)	<.001
Central Obesity, n (%)	29,390 (33.0)	28,644 (29.7)	28,693 (29.5)	28,511 (31.7)	<.001

Physical activity and Sleep, mean (SD)					
Total physical activity (MET.h.week^{-1})	45.6 (63.2)	48.7 (63.8)	49.9 (64.6)	52.6 (66.2)	<.001
Fitness (MET)	8.7 (3.4)	9.1 (3.4)	9.3 (3.4)	9.4 (3.4)	<.001
Grip strength (kg)	22.6 (7.5)	29.2 (7.9)	33.7 (8.7)	40.6 (10.6)	<.001
TV-viewing (h.day^{-1})	2.8 (1.7)	2.7 (1.6)	2.6 (1.5)	2.6 (1.5)	<.001
PC-screen time (h.day^{-1})	1.2 (1.4)	1.2 (1.4)	1.2 (1.3)	1.2 (1.3)	<.001
Sleeping time (h.day^{-1})	7.1 (1.1)	7.1 (1.0)	7.2 (1.0)	7.2 (1.0)	<.001
Dietary intakes, mean (SD)					
Total energy (Kcal.day^{-1})	2,096 (668)	2,108 (643)	2,125 (636)	2,159 (657)	<.001
Protein intake (% of TE)	15.5 (3.7)	15.5 (3.6)	15.5 (3.6)	15.6 (3.5)	0.06
Carbohydrates intake (% of TE)	47.6 (8.4)	47.3 (8.2)	47.1 (8.1)	46.8 (8.0)	<.001
Total Fat intake (% of TE)	32.0 (6.9)	32.0 (6.8)	32.1 (6.6)	32.2 (6.7)	<.001
Saturated intake (% of TE)	12.3 (3.4)	12.3 (3.3)	12.3 (3.3)	12.4 (3.3)	<.001
Sugar intake (% of TE)	22.5 (7.3)	22.4 (7.0)	22.4 (6.9)	22.4 (6.8)	<.001
Alcohol intake (% of TE)	4.9 (6.6)	5.2 (6.6)	5.4 (6.5)	5.4 (6.5)	<.001
Red meat intake (portion.week^{-1})	1.9 (1.5)	1.9 (1.4)	1.9 (1.4)	2.0 (1.4)	<.001
Processed meat intake (portion.week^{-1})	1.9 (1.1)	1.9 (1.1)	1.9 (1.1)	1.9 (1.1)	0.004
Vegetable and Fruit intake (grams.day^{-1})	319.7 (202.4)	324.6 (191.8)	329.7 (190.3)	332.7 (188.7)	<.001
Oily fish (portion.week^{-1})	1.0 (1.0)	1.1 (1.0)	1.1 (1.0)	1.1 (1.0)	<.001
Health status					
Diabetes history, n (%)	5,484 (6.2)	4,075 (4.2)	3,423 (3.5)	2,791 (3.1)	<.001
High blood pressure history, n (%)	22,676 (25.5)	23,007 (23.9)	22,498 (23.2)	20,868 (23.2)	<.001
Systolic blood pressure (mmHg), mean (SD)	137.5 (19.6)	139.0 (19.6)	139.7 (19.6)	140.8 (19.4)	<.001
Diastolic blood pressure (mmHg), mean (SD)	81.6 (10.8)	82.1 (10.7)	82.6 (10.6)	83.4 (10.6)	<.001
Medication for cholesterol or blood pressure, n (%) None of the above Cholesterol lowering medication Blood pressure medication	79,394 (89.0) 5,069 (5.7) 4,748 (5.3)	86,821 (89.9) 4,859 (5.0) 4,906 (5.1)	87,951 (90.4) 4,532 (4.7) 4,792 (4.9)	82,064 (91.2) 3,776 (4.2) 4,180 (4.6)	<.001

BMI body mass index; PA physical activity; MET basal metabolic-equivalent; TE total energy intake. SD standard deviation; n number; central obesity was defined as waist circumference >88cm for females and >102cm for males. TE: total energy; METs: Metabolic equivalent; PA: physical activity.

*P-values were corrected for multiple testing using Holm's Bonferroni method.

Supplemental Table 4. Sensitivity analysis with higher event-to-variable ratios

	n / events	HR (95% CI)	*P*
CRF trend			
1-MET increment	70,808 / 133	0.84 (0.80-0.89)	<.001
1-SD increment	70,808 / 133	0.57 (0.48-0.67)	<.001
1-quartile increment	70,808 / 133	0.51 (0.42-0.62)	<.001
CRF age- and sex-specific quartiles			
Lowest (Unfit)	17,021 / 81	1.00	(Ref.)
Lower-Middle	17,872 / 25	0.37 (0.23-0.58)	<.001
Middle-Higher	18,018 / 20	0.30 (0.18-0.51)	<.001
Highest (Fit)	17,798 / 7	0.13 (0.06-0.28)	<.001
Combination of CRF and GS			
High CRF + High GS	39,111 / 41	1.00	(Ref.)
Low CRF + High GS	10,726 / 44	2.94 (1.90-4.56)	<.001
High CRF + Low GS	14,624 / 11	0.76 (0.39-1.49)	.43
Low CRF + Low GS	6,214 / 37	4.16 (2.58-6.69)	<.001

Data is presented as hazard ratio and its 95% CI. The reference group for each exposure were those individuals in the lowest quartile for fitness. Hazard ratio for trend indicate the increase in the hazard ratio for HF per one quartile higher in the exposure. No landmark analyses or exclusion of participants with comorbidities were applied except for those participants with prevalent CVD (including HF) at baseline, who were excluded. Analyses were adjusted for age (1 degree of freedom), sex (1), deprivation index (1), ethnicity (4), current/former smoker (1), overweight/obesity (1), and comorbidities (1). Event-to-variable ratios for trend and categorical analyses were 12.1:1, and 10.2:1, respectively.
CRF: cardiorespiratory fitness; GS: grip strength; HR: hazard ratio, CI: confidence intervals.

Supplemental Table 5. Hazard ratio for heart failure associated with CRF, grip strength and conventional modifiable risk factors.

Risk Factor	Univariate Unadjusted model		Adjusted model*		Mutually adjusted model**	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Low Grip Strength	2.32 (1.95; 2.74)	<.001	2.10 (1.76; 2.51)	<.001	1.02 (0.48; 2.14)	.97
Low CRF	5.42 (3.27; 8.97)	<.001	4.60 (2.74; 7.71)	<.001	3.91 (1.92; 7.96)	<.001
Obesity	2.94 (1.61; 2.40)	<.001	2.33 (1.87; 2.91)	<.001	1.39 (0.61; 3.14)	.43
Smokers	1.97 (1.61; 2.40)	<.001	2.02 (1.64; 2.49)	<.001	2.36 (1.02 5.48)	.05
High Alcohol Intake	1.50 (1.25; 1.79)	<.001	1.28 (1.06; 1.53)	.009	0.66 (0.32; 1.34)	.25
Hypertension	3.05 (2.61; 3.56)	<.001	1.99 (1.70; 2.35)	<.001	1.09 (0.51; 2.32)	.82
Diabetes	6.10 (5.00; 7.44)	<.001	3.52 (2.84; 4.34)	<.001	3.10 (1.41; 6.84)	.005
Hypercholesterolemia	1.99 (1.51; 2.62)	<.001	2.59 (1.85; 3.62)	<.001	2.34 (0.64; 8.58)	.20

Data are presented as hazard ratio and its 95% CI. For univariate unadjusted model the exposures were fitted into the model individually and no adjustment were made. *For the adjusted model exposures were fitted individually into the models but these analyses were adjusted for age, sex, ethnicity, deprivation, gross income and professional qualification. **For the mutually adjusted model, all exposures were fitted simultaneously into the model in addition to the covariates (age, sex, ethnicity, deprivation, gross income and professional qualification).

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