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The association between physical activity and risk of mortality is modulated by grip strength and cardiorespiratory fitness: evidence from 498,135 UK-Biobank participants

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ABSTRACT (250 words)

Aims: It is unclear whether the potential benefits of physical activity differ according to level of cardiorespiratory fitness (CRF) or strength. The aim of this study was to determine whether the association between physical activity and mortality is moderated by CRF and grip strength sufficiently to inform health promotion strategies.

Methods and Results: 498,135 participants (54.7% women) participants from the UK Biobank were included (CRF data available in 67,702 participants). Exposure variables were grip strength, CRF and physical activity. All-cause mortality and cardiovascular disease (CVD) events were the outcomes. 8,591 died over median 4.9 years [IQR 4.3-5.5] follow-up. There was a significant interaction between total physical activity and grip strength ($p<0.0001$) whereby the higher hazard of mortality associated with lower physical activity was greatest among participants in the lowest tertile for grip strength (HR:1.11 [95% CI 1.09-1.14]) and lowest amongst those in the highest grip strength tertile (HR:1.04 [1.01-1.08]). The interaction with CRF did not reach statistical significance but the pattern was similar. The association between physical activity and mortality was larger among those in the lowest tertile of CRF (HR:1.13 [1.02-1.26) than those in the highest (HR:1.03 [0.91-1.16]). The pattern for CVD events was similar.

Conclusions: These data provide novel evidence that strength, and possibly CRF, moderates the association between physical activity and mortality. The association between physical activity and mortality is strongest in those with the lowest strength (which is easily measured), and lowest CRF, suggesting that these sub-groups could benefit most from interventions to increase physical activity.

Keywords: mortality; cardiovascular disease; physical activity; fitness, strength; UK biobank

INTRODUCTION

The independent, protective associations of physical activity, cardiorespiratory fitness (CRF) and strength with mortality are well established, with studies generally reporting stronger associations with mortality for CRF and strength than physical activity.[1-3] Increasing physical activity is a major mechanisms by which CRF and strength can be increased;[4-6] thus the association between physical activity and mortality is partially mediated by its effect on CRF and strength and is partially independent of them.[7] However, around half of the variation in CRF and strength is inherited[8, 9] and it is unclear whether the association between physical activity and mortality is moderated by a person's underlying level of CRF and strength. There are limited data suggesting that low levels of physical activity are associated with increased hazard of mortality in men and women with low CRF but that the association between physical activity and mortality may be weaker in those with high CRF;[1] and data are completely lacking on whether the association between physical activity and mortality varies by strength.

Understanding the interactions between physical activity, CRF and strength has implications for health promotion strategies. Currently, physical activity interventions are generally targeted at everyone in the least active sub-group of the population.[10] This is based on the overall curvilinear relationship between level of physical activity and all-cause mortality which suggests that the incremental benefit is greatest among those with the lowest baseline level of physical activity.[4,11] However this approach assumes that the association between physical activity and mortality is consistent, irrespective of CRF and strength or other characteristics. If the relationship between physical activity and mortality does differ according to strength and CRF, information on grip strength – which is easily measured – and CRF could help to define better the sub-group of the population who could benefit most from physical activity interventions. The purpose of this study was therefore to determine whether the associations of physical activity with mortality and cardiovascular disease (CVD) events were influenced by CRF and grip strength among adults enrolled in UK Biobank, a very large, prospective, population-based cohort study.

METHODS

Study design

Between April 2007 and December 2010, UK Biobank recruited 502,682 participants (5.5% response rate), aged 40-69 years from the general population.[12] Participants attended one of 22 assessment centres across England,

Wales and Scotland[13] where they completed a touch-screen questionnaire, had physical measurements taken and provided biological samples, as described in detail elsewhere.[13,14] In this prospective, population-based study, all-cause mortality and incidence of CVD were the outcomes; CRF, grip strength and total physical activity were the exposure variables; and socio-demographic factors (age, sex, ethnicity, area socioeconomic deprivation index) smoking status, body mass index, diagnosis of diabetes, cancer, heart disease (stroke, high blood pressure angina and heart attack) and long standing illness were covariates. Our sample was restricted to the 498,135 participants who had valid data on mortality status at follow-up, and baseline data for least one of the following: grip strength, physical activity and CRF. Physical activity and grip strength data were available 498,135 and 495,786 participants respectively. 77,961 participants, recruited from August 2009, underwent a CRF test and valid CRF data were obtained in 67,702 participants.

Procedures

Date of death was obtained from death certificates held by the National Health Service (NHS) Information Centre for participants from England and Wales and the NHS Central Register Scotland for participants from Scotland. Hospital admissions were identified via record linkage to Health Episode Statistics records for England and Wales and to the Scottish Morbidity Records for Scotland. Incident cardiovascular vascular disease was defined as an ICD 10 code of I21, I21.4 and I21.9, recorded on a death certificate or hospital admission (see Supplementary Material for details). Grip strength was assessed using a Jamar J00105 hydraulic hand dynamometer and the mean of the right hand and left hand values, expressed as kg, was used in the analysis. CRF was assessed using a 6-minute incremental ramp cycle ergometer test with workload calculated according to age, height, weight, resting heart rate and sex. Heart rate was monitored pre-exercise, throughout activity and during recovery via a 4-lead ECG. The 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 ($208 - 0.7 \times age$[15] assuming a linear relationship.[16] Maximal oxygen uptake (i.e. at 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))[17] and then expressed in terms of maximal METs (where 1 MET ≡ 3.5 $ml.kg^{-1}.min^{-1}$). Physical activity was based on self-report, using the IPAQ short form,[18] and total physical activity was computed as the sum of walking, moderate and vigorous activity, measured as metabolic equivalents (MET-hours/week). Total time spent in sedentary behaviours were derived from the sum of self-reported time spent driving, using computer and watching television (TV). Area-based socioeconomic status was derived from postcode of residence, using the

Townsend score.[19] Age was calculated from dates of birth and baseline assessment. Smoking status was categorised into never, former and current smoking. Medical history (physician diagnosis of depression, stroke, angina, heart attack, hypertension, cancer, diabetes, or long-standing illness) was collected from the self-completed, baseline assessment questionnaire. Alcohol intake frequency was collected using a self-reported lifestyle questionnaire. Height and body weight were measured by trained nurses during the initial assessment centre visit. Body mass index (BMI) was calculated as (weight/height^2) and the WHO criteria 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}. Body composition (body fat and fat free mass) were measured using bio-impedance by trained nurses. Further details of these measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk) and our supplementary material.

Statistical analyses

The relationship between grip strength, CRF and physical activity were explored using Pearson correlation coefficients. The associations of grip strength, CRF and total physical activity with all-cause mortality and CVD events were investigated using Cox-proportional hazard models. Two approaches were used. Firstly, separate associations of grip strength, CRF and physical activity with mortality/CVD events were calculated. Grip strength, CRF and physical activity were treated as continuous variables and hazard ratios (HR) were calculated per 1-SD difference in fitness, grip strength and total PA, using age- and sex-specific z-scores. To enable comparability with other reports in the literature, HRs were also calculated for a 5 kg difference in grip strength, 1-MET difference in CRF and 5-MET.h^{-1}.week^{-1} difference in total physical activity. Secondly, joint associations between physical activity, CRF and mortality/CVD events and physical activity, grip strength and mortality/CVD events were calculated. Age- and sex-specific quintiles for physical activity and age- and sex-specific tertile for grip strength and CRF were derived and HRs were calculated, with the referent category comprising individuals who were in both the highest quintile of physical activity and strongest/fittest tertile. To investigate whether CRF and/or grip strength moderated the association between physical activity and mortality/CVD events, we also tested the statistical significance of interaction terms and conducted sub-group analyses where appropriate.

For each of the approaches described above, we ran four incremental models that included an increasing number of covariates: “model 0” included age, sex; “model 1” included age, sex, ethnicity (white, black, South Asian, Chinese and other), smoking status (current, former, never), BMI category (underweight, normal weight, overweight and obese),deprivation index and alcohol intake as covariates; “model 2” also adjusted for depression, stroke, angina, heart attack, hypertension, cancer, diabetes, or long-standing illness; and “model 3” also adjusted for total sedentary time per day, as well as total physical activity per day and grip strength as appropriate. Finally, “model 4” was equivalent to “model 2” but participants with a history of cancer, stroke, angina or myocardial infarction at baseline were excluded from the analysis. CRF was not included as a covariate in the models for physical activity or grip strength because data on CRF were only available for ~14% (n=67,702) of the UK Biobank cohort. The proportional hazard assumption was checked by tests based on Schoenfeld residuals. 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 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/).

RESULTS

8,591 (1.7%) participants died over a median follow-up period of 4.9 years [IQR 4.3-5.5] and 2.1 years for CVD [IQR 1.4 to 2.8]. Over the follow-up period, 8,591 participants died and there were 3,433 CVD events, of which 2,787 were fatal.

The main characteristics of the participants by quintiles of total physical activity, tertile of CRF and grip strength are summarised in Tables S1, S2 and S3, respectively. The correlation between grip strength and CRF was moderate ($r=0.415$, $p<0.0001$), but total physical activity only correlated weakly with both CRF ($r=0.111$, $p<0.0001$) and grip strength ($r=0.088$, $p<0.0001$). Excluding people with diabetes, cancer, long standing illness and heart-related disease in a sensitivity analysis did not alter these correlations (Table S4).

Table 1 shows the HRs for all-cause mortality for physical activity, grip strength and CRF. Higher levels of activity, strength and CRF were associated with lower mortality, with stronger associations observed for grip

strength and CRF than for physical activity. These associations were slightly attenuated, but remained statistically significant, after adjustment for potential confounders. Similar findings were observed when CVD events was the outcome (Table S5).

Table 2 shows the association between physical activity and mortality, stratified by grip strength and CRF tertile, with those with the highest activity as the reference group within in strength/CRF tertile. Figure 1 displays these data with the most active and most fit/strong individuals as reference group. There was a statistically significant interaction between physical activity and grip strength with mortality with the HR per quintile change in physical activity being almost three times as great in those low compared with high grip strength. A similar pattern was observed for CRF, but the interaction was not statistically significant. Figure 2 and Supplementary Table S6 show the same data for CVD events. Here a significant increase in CVD events with decreasing physical activity was only observed in those in the lowest tertile for grip strength or CRF. There was a statistically significant interaction between physical activity and grip strength with CVD events.

When the sensitivity analyses were performed following exclusion of all participants with a history of cancer, stroke, angina or heart attack from the analysis, the findings were not substantially altered (Table 1 and Table S5, model 4). Similarly, when first year follow-up events were removed from the analysis the results were not altered.

DISCUSSION

The main finding of this study is that the association of physical activity with mortality and CVD events is moderated by grip strength and possibly CRF. Grip strength and CRF were moderately correlated with each other, but both had weak correlations with self-reported physical activity: all three factors were associated with mortality, independent of each other and potential confounders. The associations between grip strength (HR of 1.35 per SD difference) and CRF (HR 1.29) with mortality were of similar magnitude and were both stronger than the association physical activity (HR 1.15) and mortality in the group overall. However, although physical activity was inversely associated with all-cause mortality in all levels of grip strength and those with low and middle CRF, the association was strongest in those with the lowest strength, and possibly lowest CRF, suggesting that these sub-groups would potentially benefit most from interventions aimed at increasing physical

activity. For CVD events, significant increases in risk with decreasing physical activity were only evident in those with the lowest strength or lowest CRF. The evidence is stronger in relation to grip strength which could be easily measured in clinical practice and, therefore, may be a useful method of identifying a high risk group and targeting interventions accordingly.

Our finding of inverse associations between of CRF,[2] grip strength[20] and total physical activity[3] and all-cause mortality is in agreement with previous studies. A meta-analysis conducted on 102,980 study participants reported that 1-MET lower CRF was associated with a 13% increased hazard of all-cause mortality.[2] These results are similar to our findings, where we show that 1-MET lower CRF is associated with a HR of 1.11 for all-cause mortality. In our study, adjusting for a history of disease and excluding participants with pre-existing CVD-related diseases or prior cancer, attenuated the HR for a 1-MET reduction in CRF by about a third to 1.08. A similar association was observed for grip strength, where a 5-kg lower grip strength was associated with a HR of 1.22 for all-cause mortality. A comparable result was reported in a recent study conducted on the 139,691 participants in the PURE study,[20] where a 5 kg lower grip strength was associated with a HR of 1.16 for all-cause mortality. As was observed for CRF, our HR for all-cause mortality per 5-kg reduction in grip strength was attenuated by about a third to 1.12 HR after adjusting the model for disease history or by excluding participants with pre-existing CVD-related diseases or cancer. Thus, low CRF and grip strength were both significantly associated with higher mortality hazard, independent of pre-existing disease, and our results appear to have good external validity.

Blair et al.[1] reported an inverse additive association of physical activity and CRF in relation to all-cause mortality among 35,519 participants from the Aerobic Centre Longitudinal Study. Mortality was highest among the unfit, inactive group and lowest among the fit, highly active group. However, when these analyses were adjusted for confounders, the association disappeared,[1] possibly due to insufficient statistical power. Our study has substantially greater statistical power due to its much larger size. The trends demonstrated in Figure 1 clearly illustrate that for those who have low CRF or grip strength, there is a strong, dose-related relationship between physical activity and all-cause mortality whereas among those with high CRF or grip strength, the association is much weaker. These findings are relevant for public health policies which currently encourage increased physical activity among all those who are physically inactive, however based on our results, tailoring

physical activity interventions at individuals who have low grip strength or low CRF it may have a greater impact on reducing disease or mortality outcomes for these individuals who have a 'low fitness profile' (i.e. physically inactive plus low strength or low CRF). There is evidence from longitudinal observational studies showing that inactive individuals who increased their PA levels or fitness show a greater reduction on all-cause, and cardiovascular mortality.[21] However, is unknown whether individuals, who have a 'low fitness profile', could actually benefit even more by increasing their PA, therefore this need to be further investigated using appropriate intervention trials. Regarding the applicability of CRF or grip strength on clinical settings, we know that CRF is not easy to measure in routine clinical practice, however, grip strength requires little training, is simple and cheap to administer, and has high reproducibility.[22] Therefore, it could easily be administered as a screening tool in routine clinical practice to identify individuals for whom increasing physical activity would be particularly beneficial.[22]

Hand-grip strength is highly correlated with leg strength, and thus provides a valid index of overall limb muscle strength throughout the age range.[23] There is some evidence to suggest that resistance training interventions – which improve strength – have been shown to increase in glycolytic capacity and up-regulate insulin action and capacity for glucose utilization in muscle.[24] Randomized trials have also shown that resistance exercise training can improve glucose regulation, lipid levels, and reduce adiposity and type 2 diabetes risk,[25] all well-known risk factors for mortality. Thus, the association between grip strength and mortality is mechanistically plausible. Similarly, animal model studies have demonstrated that selective breeding low cardiorespiratory fitness leads to an adverse cardio-metabolic risk profile[26] and reduced life-expectancy[27] in rats, implying a causal relationship between CRF and mortality.

Strengths and limitations

The UK Biobank provided an opportunity to test our research question in a very large, prospective cohort and the main outcome used in this study was collected using NHS deaths records. Additionally, strength and CRP were objectively assessed using validated methods, trained staff and standard operating procedures. Hand-grip strength is highly correlated with leg strength, and provides a valid index of overall limb muscle strength throughout the age range.[23] Although the response rate to UK Biobank was only 5.5%, the UK Biobank cohort is representative of the general population with respect to age, sex, ethnicity and deprivation within the age

range recruited, although it is not representative in other regards.[12] Whilst this limits the ability to generalize prevalence rates, estimates of the magnitude of associations regarding disease or mortality risk in the current study will not be affected by this and will therefore be generalizable.[12,28] Reverse causality is possible in any observational study; however, when all participants with existing disease were removed from the analysis the effect and direction of the association remained significant. Although existing disease and comorbidities before the UK Biobank measurement day were self-reported, these self-reported records were based on disease that had been medical diagnosed. Data for atrial fibrillation and heart failure were not explicitly reported as separate conditions in the dataset at baseline, but these conditions are likely to have been captured in the 'long-standing illness' variable that we adjusted for in our models. Thus, any potential confounding effects of these conditions would have been largely captured in our statistical adjustments. Endpoint determination for CVD events was based only on ICD-10 codes and was not subject to further scientific adjudication. Physical activity was measured by self-report using a validated questionnaire. Thus misreporting of activity levels may have attenuated the association between physical activity and mortality compared to objective physical activity measurement.[29] However this is unlikely to have substantially confounded the differential influence of physical activity on mortality risk across the grip strength and CRF groups, unless the extent misreporting of physical activity was systematically higher in the high CRF and high grip strength groups, where the effects of physical activity on mortality were least strong. CRF data were only available in ~14% of participants, although this sub-group was representative of the wider cohort (see Tables S1 and S2). However, the absence of a significant interaction between CRF and physical activity with mortality – despite similar trends to those for the grip strength and physical activity with mortality – may reflect a lack of statistical power to detect effect in this smaller sample. As dietary intake data were only available for around half of the cohort (n=211,066) we did not include this as covariate in our models. Alcohol intake was available for the entire cohort and we did adjust for this; however, we cannot exclude the possibility that other that dietary factors could have influence our findings.

In conclusion, insufficient physical activity is a preventable contributor to the global burden of morbidity and mortality. However to maximise potential public health gains population level interventions to encourage physical activity in the whole population could be complemented by specific interventions targeted at the sub-group of the population who are at highest risk. CRF and strength are both predictors of all-cause mortality and CVD events independent of physical activity. Our results suggest that the ability of physical activity to reduce hazard of death or CVD events may be greatest among those with low baseline strength and fitness. Current

guidelines advocate targeting physical activity interventions merely on the basis of current levels of physical activity. Our findings suggest that targeting on the basis of strength, and possibly fitness, could greatly improve our ability to identify those individuals who could benefit most, thereby increasing the clinical and cost effectiveness of physical activity interventions. These conclusions require testing in the context of a future randomised controlled trial.

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REFERENCES

1. Blair SN, Cheng Y, Holder JS. Is physical activity or physical fitness more important in defining health benefits? Medicine and Science in Sports and Exercise 2001;**33**(6):S379-S399.

2. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone H. Cardiorespiratory Fitness as a Quantitative Predictor of All-Cause Mortality and Cardiovascular Events in Healthy Men and Women A Meta-analysis. Jama-Journal of the American Medical Association 2009;**301**(19):2024-2035.

3. Cooper R, Kuh D, Hardy R, Team FAS, Team HAS. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. British Medical Journal 2010;**341**.

4. Lee D-c, Artero EG, Sui X, Blair SN. Mortality trends in the general population: the importance of cardiorespiratory fitness. Journal of Psychopharmacology 2010;**24**(11):27-35.

5. Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure - A randomized controlled trial. Jama-Journal of the American Medical Association 2007;**297**(19):2081-2091.

6. Duscha BD, Slentz CA, Johnson JL, Houmard JA, Bensimhon DR, Knetzger KJ, Kraus WE. Effects of exercise training amount and intensity on peak oxygen consumption in middle-age men and women at risk for cardiovascular disease. Chest 2005;**128**(4):2788-2793.

7. Williams PT. Usefulness of Cardiorespiratory Fitness to Predict Coronary Heart Disease Risk Independent of Physical Activity. American Journal of Cardiology 2010;**106**(2):210-215.

8. Frederiksen H, Gaist D, Petersen HC, Hjelmborg J, McGue M, Vaupel JW, Christensen K. Hand grip strength: A phenotype suitable for identifying genetic variants affecting mid- and late-life physical functional. Genetic Epidemiology 2002;**23**(2):110-122.

9. Bouchard C. Genomic predictors of trainability. Experimental Physiology 2012;**97**(3):347-352.

10. WHO. Global recommendations on physical activity for health. In: World Health Organization; 2010.

11. Blair SN, Kohl HW, Barlow CE, Paffenbarger RS, Gibbons LW, Macera CA. Changes in physical-fitness and all-cause mortality - a prospective-study of healthy and unhealthy men. Jama-Journal of the American Medical Association 1995;**273**(14):1093-1098.

12. Collins R. What makes UK Biobank special? Lancet 2012;**379**(9822):1173-1174.

13. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, Liu B, Matthews P, Ong G, Pell J, Silman A, Young A, Sprosen T, Peakman T, Collins R. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. Plos Medicine 2015;**12**(3).

14. Palmer LJ. UK Biobank: bank on it. Lancet 2007;**369**(9578):1980-1982.

15. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. Journal of the American College of Cardiology 2001;**37**(1):153-156.

16. Medicine ACoS. *Guidelines for Exercise Testing and Prescription*. 9th Edition ed. Baltimore: Wolters Kluwer Health/Lippinoctt, Williams & Wilkins; 2014.

17. Swain DP. Energy cost calculations for exercise prescription - An update. Sports Medicine 2000;**30**(1):17-22.

18. Guo W, Bradbury KE, Reeves GK, Key TJ. Physical activity in relation to body size and composition in women in UK Biobank. Annals of Epidemiology 2015;**25**(6):406-413.

19. Townsend P, Phillimore M, Beattie A. *Health and Deprivation: Inequality and the North*. London: Croom Helm Ltd; 1988.

20. Leong DP, Teo KK, Rangarajan S. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. The Lancet 2015:8.

21. Li G, Zhang P, Wang J, An Y, Gong Q, Gregg EW, Yang W, Zhang B, Shuai Y, Hong J, Engelgau MM, Li H, Roglic G, Hu Y, Bennett PH. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes & Endocrinology 2014;**2**(6):474-480.

22. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, Sayer AA. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. Age and Ageing 2011;**40**(4):423-429.

23. Bohannon RW, Magasi SR, Bubela DJ, Wang Y-C, Gershon RC. Grip and knee extension muscle strength reflect a common construct among adults. Muscle & Nerve 2012;**46**(4):555-558.

24. Holten MK, Zacho M, Gaster M, Juel C, Wojtaszewski JFP, Dela F. Strength training increases insulin-mediated glucose uptake, GLUT4 content, and insulin signaling in skeletal muscle in patients with type 2 diabetes. Diabetes 2004;**53**(2):294-305.

25. Cornelissen VA, Fagard RH, Coeckelberghs E, Vanhees L. Impact of Resistance Training on Blood Pressure and Other Cardiovascular Risk Factors A Meta-Analysis of Randomized, Controlled Trials. Hypertension 2011;**58**(5):950-U564.

26. Wisloff U, Najjar SM, Ellingsen O, Haram PM, Swoap S, Al-Share Q, Fernstrom M, Rezaei K, Lee SJ, Koch LG, Britton SL. Cardiovascular risk factors emerge after artificial selection for low aerobic capacity. Science 2005;**307**(5708):418-420.

27. Koch LG, Kemi OJ, Qi N, Leng SX, Bijma P, Gilligan LJ, Wilkinson JE, Wisloff H, Hoydal MA, Rolim N, Abadir PM, van Grevenhof EM, Smith GL, Burant CF, Ellingsen O, Britton SL, Wisloff U. Intrinsic Aerobic Capacity Sets a Divide for Aging and Longevity. Circulation Research 2011;**109**(10):1162-U151.

28. Manolio TA, Collins R. Enhancing the Feasibility of Large Cohort Studies. Jama-Journal of the American Medical Association 2010;**304**(20):2290-2291.

29. Celis-Morales CA, Perez-Bravo F, Ibanez L, Salas C, Bailey ME, Gill JM. Objective vs. self-reported physical activity and sedentary time: effects of measurement method on relationships with risk biomarkers. PloS one 2012;**7**(5):e36345.

Figure Legends.

Figure 1. Association between all-cause mortality and physical activity within cardiorespiratory fitness (panel A) and grip strength (panel B) strata.

Data presented as Hazard Ratio (95%CI), adjusted for age, sex, ethnicity, deprivation index, BMI, smoking status, total sedentary time, alcohol intake, depression, diabetes, hypertension, cancer diagnosis, stroke, angina, heart attack and long standing illness. Q5 represents highly active individuals and Q1 highly inactive individuals. Individuals in the highest quintile of physical activity (Q5) and the highest tertile for cardiorespiratory fitness or grip strength were used as the reference group (*). P-interaction describes the interaction between physical activity and cardiorespiratory fitness or grip strength with all-cause mortality; P-trend describes the association between physical activity with all-cause mortality within tertiles for cardiorespiratory fitness or grip strength.

Figure 2. Association between cardiovascular disease (CVD) events and physical activity within cardiorespiratory fitness (panel A) and grip strength (panel B) strata.

Data presented as Hazard Ratio (95%CI), adjusted for age, sex, ethnicity, deprivation index, BMI, smoking status, total sedentary time, alcohol intake, depression, diabetes, hypertension, cancer diagnosis, stroke, angina, heart attack and long standing illness. Q5 represents highly active individuals and Q1 highly inactive individuals. Individuals in the highest quintile of physical activity (Q5) and the highest tertile for cardiorespiratory fitness or grip strength were used as the reference group (*). P-interaction describes the interaction between physical activity and cardiorespiratory fitness or grip strength with CVD events; P-trend describes the association between physical activity with CVD events within tertiles for cardiorespiratory fitness or grip strength.

Table 1. Cox proportional hazard model of the association between physical activity, grip strength and cardiorespiratory fitness and all-cause mortality

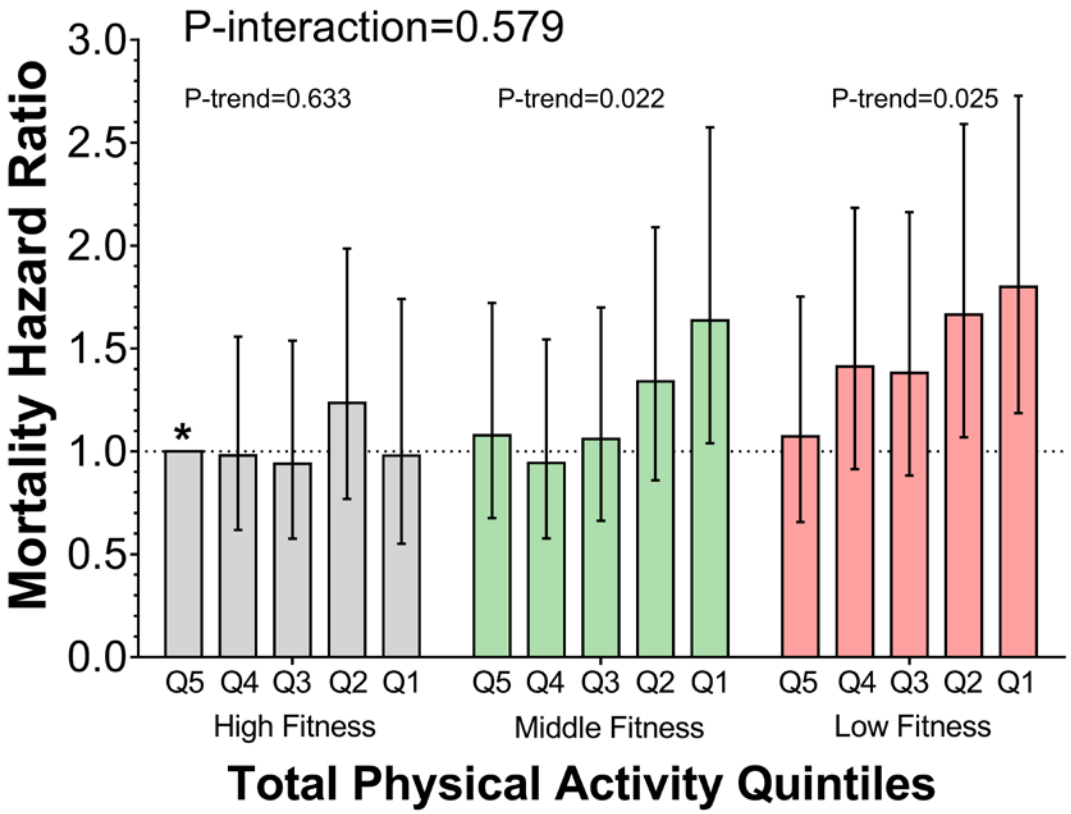
	n	n deaths		P		P
Physical activity			**HR per 1 SD decrease**		**HR per 5 MET.hr^{-1}.week^{-1} decrease**	
Model 0	498,135	8,588	1.15(1.12;1.18)	<0.0001	1.04(1.03;1.05)	<0.0001
Model 1	479,495	8,207	1.13(1.10;1.15)	<0.0001	1.03(1.03;1.04)	<0.0001
Model 2	462,422	7,809	1.09(1.06;1.12)	<0.0001	1.03(1.02;1.03)	<0.0001
Model 3	461,919	7,784	1.07(1.05;1.10)	<0.0001	1.02(1.01;1.03)	<0.0001
Model 4	384,794	4,208	1.05(1.02;1.09)	<0.0001	1.01(1.00;1.02)	<0.0001
Grip strength			**HR per 1 SD decrease**		**HR per 5 kg decrease**	
Model 0	495,786	8,491	1.35(1.32;1.38)	<0.0001	1.21(1.20;1.23)	<0.0001
Model 1	478,968	8,181	1.29(1.26;1.31)	<0.0001	1.18(1.16;1.20)	<0.0001
Model 2	461,919	7,784	1.19(1.16;1.22)	<0.0001	1.12(1.11;1.14)	<0.0001
Model 3	461,919	7,784	1.19(1.16;1.21)	<0.0001	1.12(1.10;1.14)	<0.0001
Model 4	384,794	4,208	1.18(1.14;1.21)	<0.0001	1.12(1.09;1.14)	<0.0001
Cardiorespiratory fitness			**HR per 1 SD decrease**		**HR per 1-MET decrease**	
Model 0	67,702	597	1.29(1.18;1.41)	<0.0001	1.11(1.07;1.15)	<0.0001
Model 1	64,637	577	1.29(1.17;1.42)	<0.0001	1.11(1.07;1.15)	<0.0001
Model 2	62,507	549	1.23(1.11;1.35)	<0.0001	1.09(1.04;1.13)	<0.0001
Model 3	61,859	543	1.19(1.08;1.32)	<0.0001	1.07(1.03; 1.12)	<0.0001
Model 4	52,266	319	1.22(1.07;1.39)	<0.0001	1.08(1.03; 1.14)	<0.0001

Data presented as Hazard Ratio (95%CI). A 1 SD change in fitness, grip strength and total physical activity is equivalent to 2.3 METs, 6.2 kg and 2845 MET.hr^{-1}.week^{-1} for women and 2.7 METs, 8.9 kg and 3379 MET.hr.week^{-1} for men, respectively.
Model 0 was adjusted for age and sex.
Model 1 was adjusted for sex, age, ethnicity, smoking status, deprivation index, BMI and alcohol intake.
Model 2 was adjusted for model 0 plus depression, stroke, angina, heart attack, hypertension, cancer, diabetes, or long-standing illness.
Model 3 for grip strength was adjusted for model 1 plus total sedentary time and total physical activity.
Model 3 for fitness was adjusted for model 1 plus total sedentary time, total physical activity and grip strength.
Model 3 for total physical activity was adjusted for model 1 plus total sedentary time and grip strength.
Model 4 was adjusted as model 2 but individuals with cancer, stroke, angina and heart attack were excluded.
SD standard deviation; HR hazard ratio; MET basal metabolic equivalent.

Table 2. Cox proportional hazard models of the association between physical activity and all-cause mortality by tertile of cardiorespiratory fitness and grip strength.

			Quintiles of Physical Activity							
All	**Total number**	**Number of deaths**	**Q5 (Highest)**	**Q4**	**Q3**	**Q2**	**Q1 (Lowest)**	**Hazard Ratio per one quintile change in physical activity[ł]**	**P-trend**	**P-interaction**
Cardiorespiratory fitness*										
Lowest	20,227	224	1.00(reference)	1.26(0.78;2.03)	1.31(0.83;2.08)	1.54(0.96;2.47)	1.63(1.04;2.54)	1.13(1.02;1.26)	0.025	
Middle	20,733	176	1.00(reference)	0.97(0.60;1.57)	0.86(0.52;1.43)	1.25(0.79;1.96)	1.55(0.98;2.47)	1.11(1.01;1.22)	0.022	**0.579**
Highest	21,059	147	1.00(reference)	1.01(0.56;1.80)	0.95(0.58;1.55)	0.98(0.61; 1.56)	1.22(0.75;1.97)	1.03(0.91;1.16)	0.633	
Grip strength*										
Lowest	161,007	3,473	1.00(reference)	1.06(0.94;1.21)	1.11(0.98;1.26)	1.30(1.15;1.45)	1.51(1.35;1.68)	1.11(1.09;1.14)	<0.0001	
Middle	157,296	2,438	1.00(reference)	0.95(0.83;1.08)	0.97(0.85;1.10)	1.05(0.93;1.20)	1.27(1.12;1.44)	1.06(1.03;1.09)	<0.0001	**<0.0001**
Highest	143,616	1,873	1.00(reference)	0.88(0.76;1.02)	0.98(0.85;1.13)	0.97(0.84;1.12)	1.19(1.04;1.37)	1.04(1.01;1.08)	0.007	

Data presented as adjusted Hazard Ratio (95%CI). [ł] HR are presented per quintile decrease in PA by fitness and grip strength strata.
*Analyses were adjusted for age, sex, ethnicity, deprivation index, BMI, smoking status, total sedentary time, alcohol intake, depression, stroke, angina, heart attack, hypertension, cancer, diabetes, or long-standing illness.


P-interaction=0.579
P-trend=0.633
P-trend=0.022
P-trend=0.025
Mortality Hazard Ratio
3.0
2.5
2.0
1.5
1.0
0.5
0.0
*
Q5 Q4 Q3 Q2 Q1
High Fitness
Q5 Q4 Q3 Q2 Q1
Middle Fitness
Q5 Q4 Q3 Q2 Q1
Low Fitness
Total Physical Activity Quintiles

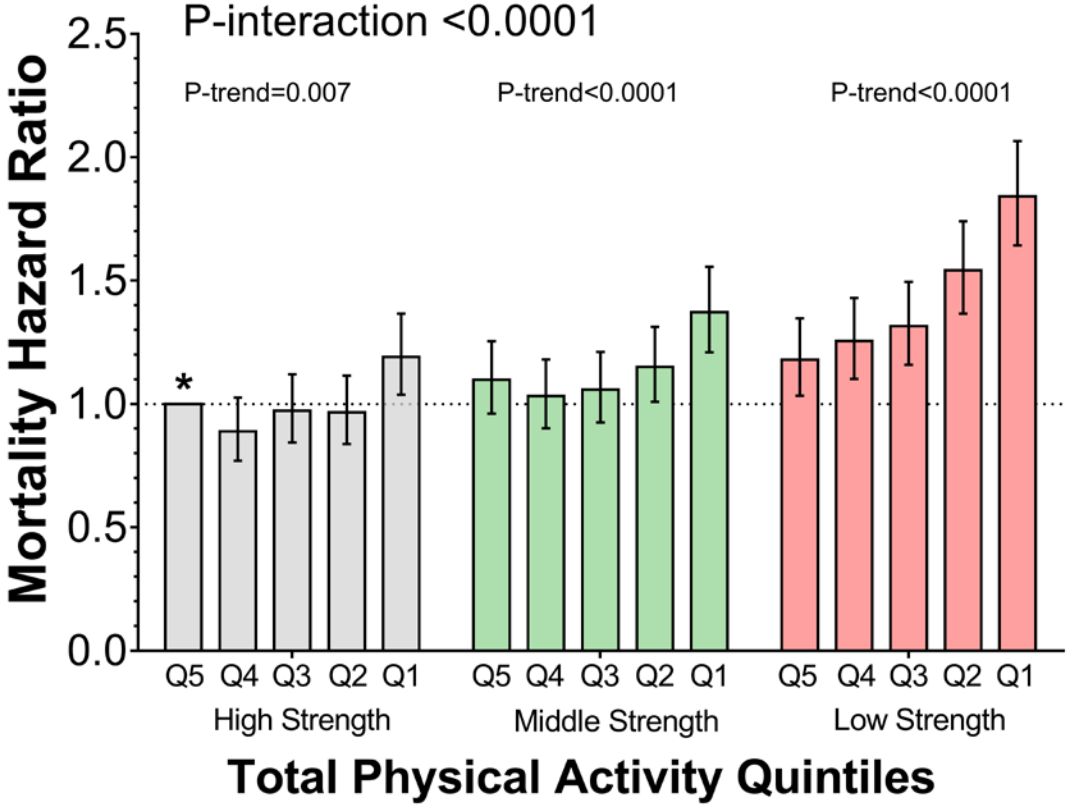

P-interaction <0.0001
P-trend=0.007
P-trend<0.0001
P-trend<0.0001
Mortality Hazard Ratio
2.5
2.0
1.5
1.0
0.5
0.0
*
Q5 Q4 Q3 Q2 Q1
High Strength
Q5 Q4 Q3 Q2 Q1
Middle Strength
Q5 Q4 Q3 Q2 Q1
Low Strength
Total Physical Activity Quintiles

Figure 1

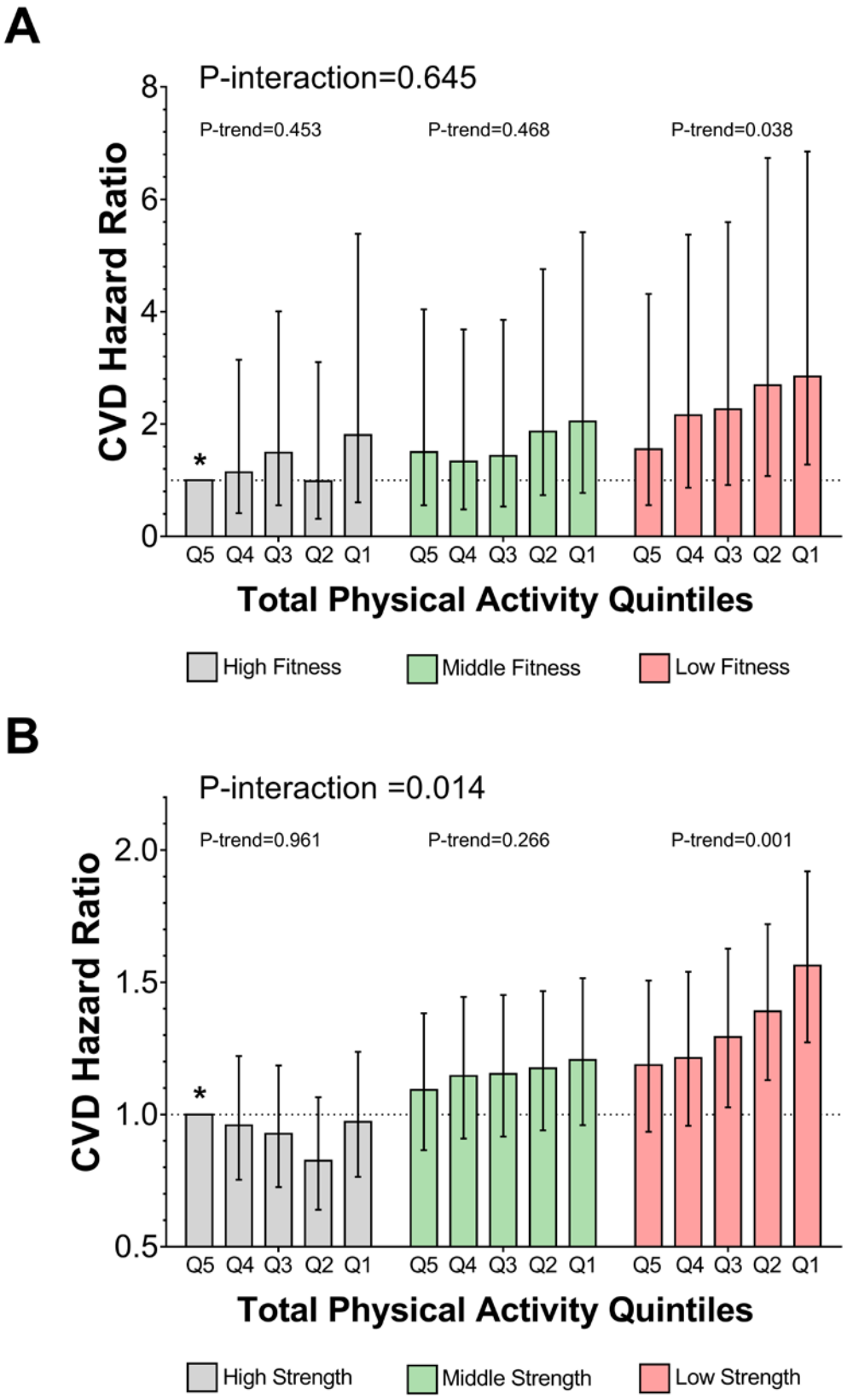

A
P-interaction=0.645
P-trend=0.453
P-trend=0.468
P-trend=0.038
CVD Hazard Ratio
0
2
4
6
8
*
Q5 Q4 Q3 Q2 Q1 Q5 Q4 Q3 Q2 Q1 Q5 Q4 Q3 Q2 Q1
Total Physical Activity Quintiles
High Fitness
Middle Fitness
Low Fitness
B
P-interaction =0.014
P-trend=0.961
P-trend=0.266
P-trend=0.001
CVD Hazard Ratio
0.5
1.0
1.5
2.0
*
Q5 Q4 Q3 Q2 Q1 Q5 Q4 Q3 Q2 Q1 Q5 Q4 Q3 Q2 Q1
Total Physical Activity Quintiles
High Strength
Middle Strength
Low Strength

Figure 2

SUPPLEMENTARY MATERIAL

Supplementary methods

Death records

Date of death was obtained from death certificates held by the National Health Service (NHS) Information Centre for participants from England and Wales and the NHS Central Register Scotland for participants from Scotland. Detailed information about the record linkage procedure is available online.[1, 2] At the time of analysis, mortality data were available up to 17 February 2014 for England and Wales and 31 December 2012 for Scotland. Therefore, the follow-up period for participants was from the date of their UK Biobank baseline assessment to either 17 February 2014 (England and Wales) or 31 December 2012 (Scotland) or date of death if this occurred earlier.

Cardiovascular events

Date and cause of death were obtained from death certificates held by the National Health Service (NHS) Information Centre for participants from England and Wales and the NHS Central Register Scotland for participants from Scotland. Date and cause of hospital admissions were identified via record linkage to Health Episode Statistics (HES) records for England and Wales and to the Scottish Morbidity Records (SMR1) for Scotland. Detailed information about the record linkage procedure is available online.[1,2] At the time of analysis, mortality data were available up to 17 February 2014 for England and Wales and 31 December 2012 for Scotland. Therefore, for the analyses of mortality, follow-up was censored at these dates, or at the date of death if this occurred earlier. Hospital admission data were available for the Scottish and English/Welsh participants until the 30th June 2012 and 1st March 2011 respectively. Therefore, for CVD fatal and nonfatal events, end of follow up was classified as these dates unless preceded by the date of death or the date of first cardiovascular. Incident cardiovascular disease was defined as an ICD 10 code of I21, I21.4 or I21.9 recorded on a death certificate or hospital admission.

Physical activity

Physical activity was based on self-report, using the IPAQ short form, with participants reporting frequency and duration of walking, moderate and vigorous activity undertaken in a typical week.[8] Data were analysed in accordance with the International Physical Activity Questionnaire (IPAQ) scoring protocol (http://www.ipaq.ki.se/scoring.pdf), and total physical activity was computed as the sum of walking, moderate and vigorous activity, measured as metabolic equivalents (MET-hours/week). Total time spent in sedentary behaviours were derived from the sum of self-reported time spent driving, using computer and watching television (TV). Physical activity was used in analyses as a continuous variable, and as a categorical variable with participants stratified into age- and sex-specific quintiles as described in Table S7.

Grip strength

Grip strength was assessed using a Jamar J00105 hydraulic hand dynamometer and the mean of the right hand and left hand values, expressed as kg, was used in the analysis. Isometric grip force was assessed from a single 3-second maximal grip effort of the right and left arms with the participant seated upright with their elbow by their side and flexed at 90º so that their forearm was facing forwards and resting on an armrest. The mean of the right and left values, expressed as kg, was used in the analysis. Measurements of grip strength taken with the Jamar dynamometer have evidence for good to excellent ($r > 0.80$) test–retest reproducibility[3] and excellent ($r = 0.98$) inter-rater reliability.[4] A total of 1,612 participants did not complete the grip strength test due to health issues (n=1,254), equipment failure (n=296) or declined performing the test (n=62). Grip strength was used in analyses as a continuous variable, and as a categorical variable with participants stratified into age- and sex-specific tertiles as described in Table S8.

Cardiorespiratory fitness (CRF)

77,961 participants underwent a 6-minute incremental ramp cycle ergometer test with workload calculated according to age, height, weight, resting heart rate and sex. Heart rate was monitored pre-exercise, throughout activity and during recovery via a 4-lead ECG. The 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 ($208 – 0.7 \times age$[5] assuming a linear relationship[6] Maximal oxygen uptake (i.e. at 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))[7] and then expressed in terms of maximal METs (where 1 MET ≡ 3.5 $ml.kg^{-1}.min^{-1}$). 10,252 participants were further excluded from the analysis due to abnormal heart rate records during the exercise test (maximal recorded heart rate <40 $beats.min^{-1}$ or >220 $beats.min^{-1}$) or missing data for factors used in the equation to estimate CRF, leaving a final sample of 67,702 available for data analysis. CRF was used in analyses as a continuous variable, and as a categorical variable with participants stratified into age- and sex-specific tertiles as described in Table S9.

Socio-demographic and other covariates

Area-based socioeconomic status was derived from postcode of residence, using the Townsend deprivation index which is derived from census data on housing, employment, social class and car availability.[9] Age was calculated from dates of birth and baseline assessment. Smoking status was categorised into never, former and current smoking. Medical history (physician diagnosis of long-standing illness, stroke, angina, myocardial infarction, hypertension, cancer, diabetes and other cardiovascular diseases (CVDs)) was collected from the self-completed, baseline assessment questionnaire.

Anthropometrics and body composition

Height and body weight were measured by trained nurses during the initial assessment centre visit. Body mass index (BMI) was calculated as ($weight/height^2$) and the WHO criteria[10] to classify BMI into: underweight <18.5,

normal weight 18.5-24.9, overweight 25.0-29.9 and obese ≥30.0 $kg.m^{-2}$. Body composition (body fat and fat free mass) were measured using bio-impedance by trained nurses. Weight and percentage body fat (by bio-impedance) were measured, without shoes or outdoor clothing, using the Tanita BC 418MA body composition analyser. Height was measured, without shoes, using the wall-mounted SECA 240 height measure.

Supplementary results

Table S1. Baseline characteristics by quintiles of physical activity

		Quintiles of Total Physical Activity				
	All	**Q5 (Highest)**	**Q4**	**Q3**	**Q2**	**Q1 (Lowest)**
Socio-demographic						
n	498,135	99,515	100,850	99,612	98,325	99,833
Women, n (%)	272,217 (54.6)	54,383 (54.6)	55,026 (54.6)	54,418 (54.6)	53,804 (54.7)	54,586 (54.7)
Age (years), mean (SD)	56.55 (8.1)	56.57 (8.2)	56.48 (8.2)	56.50 (8.1)	56.56 (.8.0)	56.61 (7.9)
Deprivation Townsend score, mean (SD)	-1.30 (3.1)	-1.28 (3.1)	-1.45 (3.0)	-1.42 (3.0)	-1.35 (3.1)	-0.99 (3.25)
Ethnicity						
Whites	468,604 (94.6)	94,683 (95.9)	95,776 (95.2)	94,170 (94.8)	92,232 (94.1)	91,743 (93.3)
South Asians	9,818 (2.0)	1,429 (1.4)	1,648 (1.6)	1,806 (1.8)	2,279 (2.3)	2,656 (2.7)
Blacks	7,966 (1.6)	1,417 (1.4)	1,490 (1.5)	1,518 (1.5)	1,601 (1.6)	1,940 (2.0)
Chinese	1,555 (0.3)	271 (0.3)	256 (0.2)	325 (0.3)	351 (0.4)	352 (0.3)
Mixed background	2,924 (0.6)	613 (0.6)	594 (0.6)	593 (0.6)	561 (0.6)	563 (0.6)
Others	4,514 (0.9)	771 (0.8)	784 (0.8)	870 (0.9)	979 (1.0)	1,110 (1.1)
Smoking status, n (%)						
Never	271,531 (54.8)	53,479 (53.9)	55,922 (55.6)	55,755 (56.1)	54,531 (55.7)	51,844 (52.8)
Previous	171,564 (34.6)	34,930 (35.2)	35,622 (35.4)	34,553 (34.8)	33,368 (34.1)	33,091 (33.7)
Current	52,101 (10.5)	10,782 (10.9)	9,015 (9.0)	9,008 (9.1)	10,074 (10.3)	13,222 (13.5)
Anthropometric						
BMI, mean (SD)	27.43 (4.8)	26.76 (4.3)	26.90 (4.4)	27.17 (4.5)	27.66 (4.8)	28.67 (5.5)
BMI Categories, n (%)						
Underweight (<18.5)	2,609 (0.5)	591 (0.6)	523 (0.5)	485 (0.5)	500 (0.5)	510 (0.5)
Normal weight (18.5-24.9)	161,270 (32.6)	36,621 (36.9)	36,209 (36.0)	33,519 (33.8)	30,027 (30.7)	24,894 (25.3)
Overweight (25.0 to 29.9)	210,229 (42.4)	42,511 (42.9)	43,074 (42.8)	43,149 (43.5)	41,795 (42.7)	39,700 (40.4)
Obese (≥30.0)	121,120 (24.5)	19,456 (19.6)	20,710 (20.6)	22,116 (22.3)	25,576 (26.1)	33,262 (33.8)
% Body fat, mean (SD)	31.48 (8.5)	30.18 (8.3)	30.65 (8.4)	31.26 (8.4)	32.08 (8.5)	33.29 (8.8)
Fat free mass (kg), mean (SD)	53.17 (11.5)	52.88 (11.3)	53.05 (11.4)	53.11 (11.4)	53.25 (11.5)	53.55 (11.7)
Fitness, strength and physical activity						
Fitness (METs), mean (SD)	9.53 (2.7)	9.92 (2.8)	9.68 (2.8)	9.58 (2.7)	9.42 (2.6)	8.85 (2.5)
Tertile of fitness						

Low, n (%)	22,385 (33.3)	3,888 (27.2)	5,101 (33.0)	4,447 (31.7)	3,891 (31.5)	5,058 (45.8)
Medium, n (%)	22,377 (33.3)	4,614 (32.3)	4,711 (30.5)	4,839 (34.5)	4,644 (37.6)	3,569 (32.3)
High, n (%)	22,410 (33.4)	5,794 (40.5)	5,640 (36.5)	4,759 (33.9)	3,810 (30.9)	2,407 (21.8)
Grip strength (kg), mean (SD)	30.56 (11.0)	31.35 (11.0)	31.11 (10.9)	31.78 (10.9)	30.28 (10.9)	29.23 (11.2)
Tertile of grip strength						
Low, n (%)	176,361 (35.6)	31,179 (31.4)	32,804 (32.6)	34,125 (34.4)	36,260 (37.0)	41,993 (42.5)
Medium, n (%)	167,698 (33.8)	34,148 (34.4)	34,809 (34.6)	34,235 (34.5)	33,114 (33.8)	31,392 (31.8)
High, n (%)	151,727 (30.6)	33,858 (34.1)	32,933 (32.7)	30,917 (31.1)	28,567 (29.2)	25,452 (25.7)
Total PA ($MET.h^{-1}.week^{-1}$), mean (SD)	41.07 (51.7)	121.99 (63.7)	43.63 (11.5)	24.43 (4.6)	13.06 (7.4)	2.00 (2.3)
Sedentary behaviour ($h.day^{-1}$)	5.01 (2.3)	4.76 (2.0)	4.91 (2.2)	4.07 (2.2)	5.12 (2.3)	5.32 (2.7)
Medical history, n (%)						
Diabetes	26,142 (5.3)	3,864 (3.9)	4,382 (4.3)	4,627 (4.7)	5,633 (5.7)	7,636 (7.8)
Cancer	38,362 (7.7)	7,517 (7.6)	7,552 (7.5)	7,553 (7.6)	7,666 (7.8)	8,074 (8.2)
Myocardial infarction	11,481 (2.3)	1,941 (1.9)	2,070 (2.1)	2,107 (2.1)	2,310 (2.4)	3,053 (3.1)
Angina	11,240 (2.3)	1,933 (1.9)	1,936 (1.9)	2,110 (2.1)	2,287 (2.3)	2,974 (3.0)
Stroke	6,179 (1.2)	1,062 (1.1)	1,037 (1.0)	1,109 (1.1)	1,208 (1.2)	1,763 (1.8)
Hypertension	119,167 (24.0)	21,766 (21.9)	22,558 (22.4)	23,429 (23.6)	24,504 (25.0)	26,910 (27.4)
Long-standing illness	158,418 (32.7)	28,445 (29.2)	28,546 (28.9)	29,453 (30.2)	31,871 (33.2)	40,103 (42.1)

BMI body mass index; PA physical activity; MET basal metabolic-equivalent; Q5 highest quintile for physical activity (highly active); Q1 lowest quintile for physical activity (highly inactive). SD standard deviation; n number

Table S2. Participants' characteristics by tertile of cardiorespiratory fitness

	Overall	Lower	Middle	Higher
Socio-demographic				
n	67,702	22,568	22,566	22,568
Women, n (%)	36,297 (53.6)	12,099 (53.6)	12,099 (53.6)	12,099 (53.6)
Age (years), mean (SD)	56.57 (8.1)	57.13 (7.9)	56.56 (8.1)	56.02 (8.4)
Deprivation Townsend score, mean (SD)	-1.15 (2.9)	-0.83 (3.1)	-1.26 (2.9)	-1.34 (2.8)
Ethnicity				
Whites	61,337 (91.2)	19,283 (86.1)	20,674 (92.3)	21,380 (95.3)
South Asians	2,073 (3.1)	1,109 (4.9)	657 (2.9)	307 (1.4)
Blacks	1,987 (2.9)	1,264 (5.6)	506 (2.3)	217 (1.0)
Chinese	295 (0.4)	74 (0.3)	98 (0.4)	123 (0.5)
Mixed background	581 (0.9)	211 (0.9)	183 (0.8)	187 (0.8)
Others	969 (1.4)	453 (2.0)	286 (1.3)	230 (1.0)
Smoking status, n (%)				
Never	37,782 (56.1)	12,990 (57.9)	12,524 (55.8)	12,268 (54.6)
Previous	23,381 (34.7)	7,582 (33.8)	7,793 (34.7)	8,006 (35.6)
Current	6,146 (9.1)	1,843 (8.2)	2,111 (9.4)	2,192 (9.8)
Adiposity				
BMI, mean (SD)	27.15 (4.5)	29.19 (5.0)	26.95 (3.9)	25.30 (3.6)
BMI Categories, n (%)				
Underweight (<18.5)	325 (0.5)	56 (0.2)	76 (0.3)	193 (0.9)
Normal weight (18.5-24.9)	22,950 (33.9)	4,405 (19.5)	7,348 (32.6)	11,197 (49.6)
Overweight (25.0 to 29.9)	29,126 (43.0)	9,515 (42.2)	10,678 (47.3)	8,933 (39.6)
Obese (≥30.0)	15,296 (22.6)	8,589 (38.1)	4,464 (19.8)	2,243 (9.9)
% Body fat, mean (SD)	31.15 (8.4)	34.07 (8.4)	31.13 (7.9)	28.25 (7.8)
Fat free mass (kg), mean (SD)	53.30 (11.5)	53.91 (11.7)	53.11 (11.4)	52.88 (11.2)
Fitness and Physical activity				
Fitness (METs), mean (SD)	9.53 (2.7)	7.12 (1.5)	9.35 (1.5)	12.12 (2.4)
Grip strength (kg), mean (SD)	30.04 (10.6)	29.26 (10.6)	30.11 (10.7)	30.76 (10.5)
Tertile of grip strength				
Low, n (%)	26,581 (39.4)	9,962 (44.3)	8,784 (39.0)	7,835 (34.8)
Middle, n (%)	23,322 (34.5)	7,403 (32.9)	7,799 (34.7)	8,120 (36.0)
High, n (%)	17,623 (26.1)	5,142 (22.9)	5,912 (26.3)	6,569 (29.2)
Total PA ($MET.h^{-1}.week^{-1}$), mean (SD)	43.17 (51.8)	37.08 (49.6)	42.63 (50.8)	49.78 (54.0)
Sedentary behaviour ($h.day^{-1}$)	5.07 (2.3)	5.36 (2.5)	5.11 (2.3)	4.75 (2.1)
Medical history, n (%)				
Diabetes	3,345 (5.0)	1,726 (7.7)	948 (4.2)	671 (3.0)
Cancer	5,284 (7.8)	1,827 (8.2)	1,764 (7.9)	1,693 (7.5)
Myocardial infarction	1,084 (1.6)	397 (1.8)	298 (1.3)	389 (1.7)
Angina	1,044 (1.5)	445 (2.0)	288 (1.3)	311 (1.4)
Stroke	702 (1.0)	289 (1.3)	223 (1.0)	190 (0.8)
Hypertension	15,318 (22.7)	6,775 (30.2)	4,695 (20.9)	3,848 (17.1)
Long-standing illness	19,213 (29.1)	7,646 (35.0)	6115 (27.8)	5,452 (24.6)

BMI body mass index; PA physical activity; MET basal metabolic-equivalent; SD standard deviation; n number

Table S3. Participants' characteristics by tertile of grip strength

	Overall	Lower	Middle	Higher
Socio-demographic				
n	495,786	176,361	167,698	151,727
Women, n (%)	271,002 (54.7)	98,893 (56.1)	89,933 (53.6)	82,176 (54.2)
Age (years), mean (SD)	56.55 (8.1)	56.97 (7.8)	56.73 (8.1)	55.85 (8.3)
Deprivation Townsend score, mean (SD)	-1.31 (3.1)	-0.91 (3.2)	-1.4 (3.0)	-1.63 (2.9)
Ethnicity				
Whites	467,022 (94.6)	161,720 (92.3)	159,859 (95.7)	145,443 (96.2)
South Asians	9,681 (1.9)	6,520 (3.7)	2,245 (1.3)	916 (0.61)
Blacks	7,842 (1.6)	2,848 (1.6)	2,292 (1.4)	2,702 (1.8))
Chinese	1,537 (0.31)	768 (0.44)	494 (0.30)	275 (0.18)
Mixed background	2,905 (0.59)	2,307 (1.3)	894 (0.54)	954 (0.63)
Others	4,440 (0.90)	1,057 (0.60)	1,251 (0.75)	882 (0.58)
Smoking status, n (%)				
Never	270,505 (54.8)	97,302 (55.6)	91,400 (54.7)	81,803 (54.1)
Previous	170,968 (34.7)	58,355 (33.3)	58,427 (35.0)	54,186 (35.8)
Current	51,763 (10.5)	19,439 (11.1)	17,151 (10.3)	15,173 (10.0)
Obesity-related markers				
BMI, mean (SD)	27,43 (4.8)	27.57 (5.1)	27.23 (4.6)	27.48 (4.6)
BMI Categories, n (%)				
Underweight (<18.5)	2,597 (0.5)	1,296 (0.7)	816 (0.5)	485 (0.3)
Normal weight (18.5-24.9)	161,099 (32.6)	57,050 (32.5)	56,662 (33.8)	47,387 (31.3)
Overweight (25.0 to 29.9)	210,017 (42.4)	71,574 (40.7)	71,678 (42.8)	66,765 (44.1)
Obese (≥30.0)	120,974 (24.4)	45,759 (26.1)	38,317 (22.9)	36,898 (24.3)
% Body fat, mean (SD)	31.48 (8.5)	32.25 (8.7)	31.18 (8.5)	30.92 (8.4)
Fat free mass (kg), mean (SD)	53.17 (11.5)	51.36 (10.9)	53.12 (11.3)	55.31 (11.9)
Fitness and Physical activity				
Fitness (METs), mean (SD)	9.53 (2.7)	9.28 (2.7)	9.61 (2.8)	9.79 (2.8)
Tertile of fitness				
Low, n (%)	22,324 (33.3)	9,878 (37.4)	7,341 (31.7)	5,105 (29.2)
Middle, n (%)	22,307 (33.3)	8,719 (33.1)	7,731 (33.4)	5,857 (33.5)
High, n (%)	22,366 (33.4)	7,779 (29.5)	8,072 (34.9)	6,515 (37.3)
Grip strength (kg), mean (SD)	30.56 (11.0)	22.90 (8.0)	31.23 (8.5)	38.71 (10.3)
Total PA ($MET.h^{-1}.week^{-1}$), mean (SD)	41.12 (51.8)	37.38 (50.2)	41.90 (51.8)	44.62 (53.2)
Sedentary behaviour ($h.day^{-1}$)	5.02 (2.3)	5.03 (2.4)	5.02 (2.2)	5.00 (2.2)
Health status, n (%)				
Diabetes history	25,969 (5.3)	12,656 (7.2)	7,670 (4.6)	5,643 (3.7)
Cancer history	38,236 (7.7)	14,740 (8.4)	12,776 (7.6)	10,720 (7.1)
Heart attack history	11,411 (2.3)	5,015 (2.9)	3,662 (2.2)	2,734 (1.8)
Angina history	11,183 (2.3)	5,214 (3.0)	3,496 (2.1)	2,473 (1.6)
Stroke history	6,135 (1.2)	3,133 (1.8)	1,703 (1.0)	1,299 (0.9)
High blood pressure history	118,644 (24.0)	44,261 (25.2)	39,438 (23.6)	34,945 (23.1)
Long-standing illness	157,556 (32.6)	68,883 (40.3)	49,176 (30.1)	39,497 (26.6)

BMI body mass index; PA physical activity; MET basal metabolic-equivalent; SD standard deviation; n number

Table S4. Univariate correlations between fitness, grip strength, and physical activity

Correlation	Fitness	Grip strength	Total PA
Fitness (METs)	1.00	r: 0.415* r: 0.419*ǂ	r: 0.111* r: 0.111*ǂ
Grip strength (kg)		1.00	r: 0.088* r: 0.085*ǂ
Total PA (MET.h.week^{-1})			1.00

The association between variables were determined with linear regression analysis.
*p<0.0001
ǂ Cases with diagnoses of diabetes, cancer and heart disease excluded from the analysis.

Table S5. Cox proportional hazard model of the association between physical activity, grip strength and cardiorespiratory fitness and CVD events

Physical activity	**n**	**Number of events**	**HR per 1 SD decrease**	P	**HR per 5 MET.hr^{-1}.week^{-1} decrease**	P
Model 0	465,290	2,456	1.06(1.01;1.11)	0.009	1.03(1.02;1.04)	<0.0001
Model 1	450,382	2,373	1.05(1.01;1.09)	0.033	1.02(1.01;1.03)	0.003
Model 2	435,549	2,288	1.04(1.01;1.09)	0.041	1.01(1.00;1.02)	0.033
Model 3	435,549	2,288	1.03(0.98;1.06)	0.305	1.01(1.00;1.02)	0.071
Model 4	402,916	2,029	1.02(0.97;1.06)	0.460	1.01(0.99;1.01)	0.183
Grip strength			**HR per 1 SD decrease**		**HR per 5 kg decrease**	
Model 0	465,290	2,456	1.30(1.25;1.35)	<0.0001	1.18(1.15;1.21)	<0.0001
Model 1	450,382	2,373	1.24(1.19;1.30)	<0.0001	1.15(1.11;1.18)	<0.0001
Model 2	435,549	2,288	1.18(1.13;1.24)	<0.0001	1.12(1.08;1.15)	<0.0001
Model 3	435,549	2,288	1.18(1.13;1.23)	<0.0001	1.12(1.08;1.15)	<0.0001
Model 4	402,916	2,029	1.18(1.13;1.24)	<0.0001	1.12(1.09;1.16)	<0.0001
Cardiorespiratory fitness			**HR per 1 SD decrease**		**HR per 1-MET decrease**	
Model 0	63,894	154	1.41(1.17;1.68)	<0.0001	1.13(1.06;1.22)	<0.0001
Model 1	61,173	152	1.36(1.12;1.64)	0.002	1.12(1.04;1.20)	0.003
Model 2	59,306	149	1.33(1.10;1.62)	0.004	1.11(1.03;1.19)	0.004
Model 3	59,306	149	1.32(1.09;1.61)	0.005	1.11(1.03;1.20)	0.005
Model 4	54,720	126	1.37(1.11;1.70)	0.003	1.12(1.04;1.22)	0.005

Data presented as Hazard Ratio (95%CI). A 1 SD change in fitness, grip strength and total physical activity is equivalent to 2.3 METs, 6.2 kg and 2845 MET.h.week^{-1} for women and 2.7 METs, 8.9 kg and 3379 MET.h.week^{-1} for men, respectively.
Model 0 was adjusted for age and sex.
Model 1 was adjusted for sex, age, ethnicity, smoking status, deprivation index, BMI and alcohol intake.
Model 2 was adjusted for model 0 plus depression, cancer, diabetes, or long-standing illness.
Model 3 for grip strength was adjusted for model 1 plus total sedentary time and total physical activity.
Model 3 for fitness was adjusted for model 1 plus total sedentary time, total physical activity and grip strength.
Model 3 for total physical activity was adjusted for model 1 plus total sedentary time and grip strength.
Model 4 was adjusted as model 2 but individuals with cancer were excluded.
SD standard deviation; HR hazard ratio; MET basal metabolic equivalent.

Table S6. Cox proportional hazard models of the association between physical activity and CVD events by tertile of fitness and grip strength3

			Quintiles of Physical Activity							
All	**Total number**	**Number of events**	**Q5 (Highest)**	**Q4**	**Q3**	**Q2**	**Q1 (Lowest)**	**Hazard Ratio per one quintile change in physical activity[ł]**	**P-trend**	**P-interaction**
Cardiorespiratory fitness*										
Lowest	19,226	69	1.00(reference)	1.39(0.58;3.29)	1.45(0.61;3.41)	1.74(0.73;4.16)	1.85(0.81;4.26)	1.10(0.85;1.41)	0.038	
Middle	20,001	48	1.00(reference)	0.86(0.33;2.24)	0.95(0.37;2.39)	1.22(0.51;2.90)	1.76(0.58;5.30)	1.08(0.87;1.33)	0.468	0.645
Highest	20,233	35	1.00(reference)	1.16(0.42;3.22)	1.46(0.54;3.95)	0.98(0.31;3.11)	1.41(0.57;3.49)	1.07(0.91;1.27)	0.453	
Grip strength*										
Lowest	148,917	891	1.00(reference)	1.04(0.82;1.32)	1.10(0.87;1.39)	1.22(0.98;1.50)	1.37(1.11;1.69)	1.08(1.03;1.13)	0.001	
Middle	149,092	781	1.00(reference)	0.90(0.71;1.12)	0.95(0.75;1.18)	0.94(0.75;1.17)	0.98(0.78;1.22)	1.00(0.95;1.05)	0.961	0.014
Highest	137,540	616	1.00(reference)	0.93(0.73;1.19)	0.92(0.71;1.17)	0.81(0.62;1.04)	0.92(0.71;1.17)	0.97(0.92;1.02)	0.266	

Data presented as adjusted Hazard Ratio (95%CI). [ł] HR are presented per quintile decrease in PA by fitness and grip strength strata.
*Analyses were adjusted for age, sex, ethnicity, deprivation index, BMI, smoking status, total sedentary time, alcohol intake, depression, cancer, diabetes, or long-standing illness.

Table S7. Cut-off point for age and sex-specific physical activity quintiles.

Sex	Age group	Q1 (Lowest)	Q2	Q3	Q4	Q5 (Highest)
Women	<56 years	<370	371 – 977	978 – 1806	1807 – 3360	>3360
	56 to 65 years	<346	347 – 973	974 – 1862	1864 – 3555	>3555
	>65 years	<344	345 – 993	994 – 1953	1954 – 3816	>3816
Men	<56 years	<418	419 – 1113	1114 – 2076	2077 – 3972	>3972
	56 to 65 years	<412	413 – 1092	1093 – 2066	2067 – 3999	>3999
	>65 years	<480	480 - 1199	1200 - 2238	2239 - 4266	>4266

Data presented as MET.h.week^{-1}.

Table S8. Cut-off point for age and sex-specific grip strength tertiles.

Sex	Age group	Q1 (Lower)	Q2	Q3 (Higher)
Women	<56 years	<23	23 – 28	>28
	56 to 65 years	<20	20 – 25	>25
	>65 years	<18	18 – 23	>23
Men	<56 years	<38	38 – 46	>46
	56 to 65 years	<35	35 – 42	>42
	>65 years	<33	33 – 39	>39

Data presented as kg.

Table S9. Cut-off point for age and sex-specific fitness tertiles.

Sex	Age group	Q1 (Lower)	Q2	Q3 (Higher)
Women	<56 years	<8.2	8.2 – 10.1	>10.1
	56 to 65 years	<7.0	7.0 – 8.6	>8.6
	>65 years	<6.3	6.3 – 7.8	>7.8
Men	<56 years	<10.3	10.3 – 12.5	>12.5
	56 to 65 years	<9.3	9.3 – 11.4	>11.4
	>65 years	<8.5	8.5 – 10.5	>10.5

Data presented as METs.

REFERENCES

1. Palmer LJ. UK Biobank: bank on it. Lancet 2007;**369**(9578):1980-1982.
2. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, Liu B, Matthews P, Ong G, Pell J, Silman A, Young A, Sprosen T, Peakman T, Collins R. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. Plos Medicine 2015;**12**(3).
3. Mathiowetz V, Weber K, Volland G, Kashman N. Reliability and validity of grip and pinch strength evaluations. Journal of Hand Surgery-American Volume 1984;**9A**(2):222-226.
4. Peolsson A, Hedlund R, Oberg B. Intra- and inter-tester reliability and reference values for hand strength. Journal of Rehabilitation Medicine 2001;**33**(1):36-41.
5. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. Journal of the American College of Cardiology 2001;**37**(1):153-156.
6. Medicine ACoS. *Guidelines for Exercise Testing and Prescription*. 9th Edition ed. Baltimore: Wolters Kluwer Health/Lippinoctt, Williams & Wilkins; 2014.
7. Swain DP. Energy cost calculations for exercise prescription - An update. Sports Medicine 2000;**30**(1):17-22.
8. Guo W, Bradbury KE, Reeves GK, Key TJ. Physical activity in relation to body size and composition in women in UK Biobank. Annals of Epidemiology 2015;**25**(6):406-413.
9. Townsend P, Phillimore M, Beattie A. *Health and Deprivation: Inequality and the North*. London: Croom Helm Ltd; 1988.
10. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organization technical report series 2000;**894**:i-xii, 1-253.