Handgrip strength is inversely associated with fatal cardiovascular and all-cause mortality events

Running Title: Handgrip strength and fatal outcomes

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ABSTRACT

Purpose: We aimed to assess the associations of handgrip strength (HS) with cardiovascular and all-cause mortality and whether adding data on HS to cardiovascular disease (CVD) risk factors is associated with improvement in CVD mortality prediction.

Design: Handgrip strength was assessed in a population-based sample of 861 participants aged 61-74 years at baseline. Relative HS was obtained by dividing the absolute value by body weight.

Results: During a median (interquartile range) follow-up of 17.3 (12.6-18.4) years, 116 fatal coronary heart diseases (CHDs), 195 fatal CVDs, and 412 all-cause mortality events occurred. On adjustment for several risk factors, the hazard ratios (95% CIs) for fatal CHD, fatal CVD, and all-cause mortality were 0.59 (0.37-0.95), 0.59 (0.41-0.86), and 0.66 (0.51-0.84) respectively comparing extreme tertiles of relative HS. Adding relative HS to a CVD mortality risk prediction model containing established risk factors did not improve discrimination or reclassification using Harrel's C-index (C-index change: 0.0034; p=0.65), integrated-discrimination-improvement (0.0059; p=0.20), and net-reclassification-improvement (-1.31%; p=0.74); however, there was a significant difference in in -2 log likelihood (p<0.001).

Conclusion: Relative HS is inversely associated with CHD, CVD and all-cause mortality events. Adding relative HS to conventional risk factors improves CVD risk assessment using sensitive measures of discrimination.

Keywords handgrip strength; cardiovascular disease; mortality; risk prediction

KEY MESSAGES

- Handgrip strength assessment is simple, inexpensive and it takes only a few minutes to measure in clinical practice; however, its prognostic role for fatal cardiovascular outcomes on top of traditional risk factors in apparently healthy populations is uncertain.
- In a population-based prospective cohort study, good handgrip strength adjusted for body weight was associated with lower risk of fatal cardiovascular outcomes and the associations remained consistent across several clinically relevant subgroups.
- Handgrip strength may be a useful prognostic tool for fatal CHD and CVD events, in the general population.

Introduction

Cardiovascular diseases (CVDs) account for over 17 million deaths per year, hence remaining the leading cause of mortality globally.(1) Though great strides have been made in the treatment and prevention of CVDs over the last few decades, deaths due to CVDs are increasing because of increased life expectancy of the population.(2) Physical activity is well established to prevent vascular disease as well as mortality.(3) Physical fitness, a strong predictor of future health status,(4) has cardiorespiratory fitness (CRF) and muscular fitness as its main components.(5) Cardiorespiratory and muscular fitness are becoming well recognized in the prevention of chronic disease including vascular disease and all-cause mortality.(4, 6-9) Muscular fitness comprises of muscular strength, muscular endurance and muscular power.(5) Among these components, it appears muscular strength is the most widely studied in terms of its relationship to health. Muscular strength is defined as the ability of a specific muscle or muscle group to generate force or torque.(5) Handgrip strength, commonly used as a typical measure of muscular strength, has been shown in several prospective studies to be inversely associated with CVD, cause-specific mortality and all-cause mortality outcomes.(10-19) However, majority of these studies were based in selected populations, included only male or female participants, or had short-term follow-up durations, which could potentially introduce biases such as reverse causation. The assessment of handgrip strength is particularly easy to measure, is a low-cost measurement tool, and takes only a few minutes to measure. Whether handgrip strength could be a useful prognostic tool for adverse clinical outcomes when added on the top of common risk factors in apparently healthy and aging populations is not well known. Given the uncertainty in the evidence, our primary aim was to assess the nature and magnitude of the associations of relative handgrip strength with the risk of fatal CHD and CVD events, and all-cause mortality using a population-based prospective cohort study. A secondary aim was to evaluate whether

addition of relative handgrip strength measurements to conventional cardiovascular risk factors could improve the prediction of CVD mortality.

Materials and methods

Study design and population

This report was performed in accordance to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting observational studies in epidemiology (**Supplementary Table S1**).(20) The study cohort employed for this analysis was part of the Kuopio Ischemic Heart Disease (KIHD) risk factor Study, a prospective population-based cohort study designed to investigate potential risk factors for atherosclerotic CVD and other related chronic disease outcomes.(21) The initial study participants comprised a representative sample of men recruited from the city of Kuopio and its surrounding rural communities in eastern Finland. These participants underwent re-examinations at 4 years, 11 years and 20 years after baseline. During the 11-year follow-up examination, women were invited to join the study. This cohort was employed for the current analysis and initially comprised 2358 invited participants (1007 men and 1351 women) who were aged 53 to 74 years at baseline.(22) Of the 2072 participants found to be potentially eligible, 193 did not agree to participate, 66 did not respond to the invitation and 39 declined to provide informed consent, which left 1774 participants.(22) Baseline examinations were conducted from March 1998 to December 2001.(22) The current analysis included 861 men and women who had complete information on handgrip strength, relevant covariates, and specified outcomes (**Supplementary Table S2**). The study protocol was approved by Research Ethics Committee of the University of Eastern Finland, Kuopio, Finland.

Assessment of handgrip strength and relevant risk markers

Handgrip strength was measured by a hand dynamometer (Martin-Balloon-Vigorimeter; Gebrüder Martin, Tuttlingen, Germany). Measurements were taken with the subjects standing in upright position and their arms parallel to their body. Two measurements were taken for the dominant hand and the mean of both values was used for analysis. One-minute resting gap was given between both handgrip measurements. To minimize the effect of body weight on the magnitude of handgrip strength, values of handgrip strength were then divided by weight in kilograms to yield relative handgrip strength (in kg). The dynamometers were calibrated at the beginning of each testing. Blood sample collection procedures, assessment of lifestyle characteristics and physical measures, and measurement of blood-based markers have been described in detail in previous reports.(23) Before blood collection, participants fasted overnight and abstained from drinking alcohol for at least 3 days and from smoking for at least 12 hours. Blood lipids including total cholesterol and high-density lipoprotein cholesterol (HDL-C) were measured enzymatically (Boehringer Mannheim, Mannheim, Germany) from fresh serum samples after combined ultracentrifugation and precipitation.(24) Fasting plasma glucose was estimated by the glucose dehydrogenase method (Merck, Darmstadt, Germany) after protein precipitation by trichloroacetic acid.(24) Serum high sensitivity C-reactive protein (hsCRP) measurements were made with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA, USA). Resting blood pressure was measured between 8 and 10 a.m. using a random-zero sphygmomanometer (Hawskley, UK) after 5 and 10 minutes of rest in a seated position.(25) Self-administered questionnaires were used to assess baseline socio-demographic and lifestyle characteristics, prevalent medical conditions and use of medications.(26) The energy expenditure of physical activity was assessed from a validated 12-month leisure-time physical activity questionnaire.(27) This detailed quantitative questionnaire deals with the most common leisure-time physical activities (LTPAs) of

middle-aged Finnish men. For the type of physical activity performed, participants were asked to document the frequency (number of sessions per month), average duration (hours and minutes per session) and intensity.(28) Energy expenditure was measured for each physical activity by multiplying the metabolic index of activity (in metabolic equivalent*hour/week) by body weight in kilograms. Body mass index (BMI) was calculated by dividing weight measured in kilograms by the square of height in meters.

Ascertainment of outcomes

Outcomes evaluated included fatal CHD and CVD outcomes as well as all-cause mortality. We included all deaths that occurred from study enrollment through to 31st December 2017. Participants are under continuous annual surveillance for the occurrence of new CVD events, which include incident cases and deaths. There were no losses to follow-up. Information on outcomes was ascertained by computerized data linkage to the Finnish national hospital discharge registry and death certificate registers. Other sources of information were based on review of all available hospital records, questionnaires administered to health workers, wards of healthcare centres or hospitals, interviews with informants and medico-legal reports. Coronary heart disease and CVD deaths were coded using the *International Statistical Classification of Diseases, 10th Revision (ICD-10),* codes. All-cause mortality outcomes comprised of any deaths including CVD and CHD deaths. All documents were checked in detail by two physicians. The Independent Events Committee of the KIHD study, blinded to clinical data, performed classification of all outcomes.

Statistical analysis

Baseline characteristics were presented as means (standard deviation, SD) or medians (interquartile range, IQR) for continuous variables and percentages for categorical variables using descriptive analyses. Age-

and sex-adjusted partial correlation coefficients were estimated to assess the cross-sectional associations of relative handgrip strength with several risk markers. Hazard ratios (HRs) with 95% confidence intervals (CIs) for fatal CHD and CVD and all-cause mortality were calculated using Cox proportional hazard models after confirmation of no major departure from the proportionality of hazards assumptions using Schoenfeld residuals. The shape of the relationship between relative handgrip strength and each outcome was assessed by calculating HRs within quartiles of baseline relative handgrip strength, which were then plotted against mean values of relative handgrip strength within each quartile. Floating variances were used to calculate 95% CIs for the log hazard ratio in each group (including the reference group), which allowed for comparisons across the groups irrespective of the arbitrarily chosen reference category (bottom quartile).(29) We modeled relative handgrip strength as both continuous [per standard deviation (SD) increase] and categorical (tertiles) exposures; given the relatively low sample size, tertile cutoffs were employed for the assessment of associations to ensure adequate power in each exposure category. Hazard ratios were adjusted for in two models: (i) age and sex and (ii) plus systolic blood pressure, total cholesterol, HDL-C, smoking status, prevalent CHD history of diabetes mellitus, resting heart rate, and energy expenditure of total LTPA. Subgroup analyses were performed using tests of interaction to assess statistical evidence of any differences in hazard ratios across levels/categories of pre-specified individual level characteristics. To minimize biases due to reverse causation, sensitivity analysis excluded the first two years of follow-up.

To evaluate whether adding information on relative handgrip strength to conventional cardiovascular risk factors would be associated with an improvement in CVD mortality risk prediction and if relative handgrip strength helps to correctly classify participants into predicted CVD risk categories, we calculated measures of discrimination for censored time-to-event data (Harrell's C-index (30)) and reclassification.(31, 32) To investigate the change in C-index on the addition of relative handgrip

strength, two CVD mortality risk prediction models were fitted: one model based on traditional risk factors (i.e., age, SBP, history of diabetes, total cholesterol, HDL-C, and smoking) included in well-known CVD risk algorithms (such as the Framingham Risk Score (FRS)(33) and the Pooled Cohort equations(34)) and the second model containing the traditional risk factors plus relative handgrip strength. Reclassification was assessed using the net-reclassification-improvement (NRI)(31, 32) and integrated-discrimination-improvement (IDI)(31) by comparing the model containing conventional risk factors to the predicted risk from the model containing conventional risk factors plus relative handgrip strength. Reclassification analysis was based on predicted 10-year CVD mortality risk categories of low (< 1%), intermediate (1 to < 5%), and high (≥ 5%) risk as previously reported.(35) Finally, we calculated the integrated discrimination improvement (IDI), which integrates the NRI over all possible cutoffs of predicted risk and mathematically corresponds to the difference in discrimination slopes of the 2 models in comparison.(31) Given that Harrell's C-index is based on ranks rather than on continuous data, it can be insensitive in detecting differences.(36, 37) To avoid discarding potential biomarkers that can be used in risk prediction, sensitive risk discrimination methods such as the -2 log likelihood test (likelihood ratio test) have been recommended.(36, 37) Therefore, in addition to Harrel's C-index, we tested for differences in the -2 log likelihood of prediction models with and without inclusion of calprotectin. All statistical analyses were conducted using Stata version MP 16 (Stata Corp, College Station, Texas).

Results

Baseline characteristics and correlates of handgrip strength

The mean (SD) age of study participants at baseline was 69 (3) years and 47.3% comprised of males. The mean (SD) value of relative handgrip strength at baseline was 1.03 (0.34) kpa/kg (**Table 1**). Weak to moderate inverse correlations were observed between relative handgrip strength and age, BMI, fasting

plasma glucose and hsCRP. Relative handgrip strength was weakly and positively correlated with HDL-C. During a median (IQR) follow-up of 17.3 (12.6-18.4) years (13,055 person-years at risk), a total of 116 fatal CHDs, 195 fatal CVDs, and 412 all-cause mortality events were recorded.

Relative handgrip strength and risk of outcome events

In analyses adjusted for several established and emerging risk factors (age, sex, systolic blood pressure, total cholesterol, HDL-C, smoking status, prevalent CHD history of diabetes mellitus, resting heart rate, and energy expenditure of total LTPA), relative handgrip strength was continually and inversely associated with fatal CHD, fatal CVD, and all-cause mortality, and these were potentially consistent with curvilinear shapes (**Figure 1**). **Table 2** shows the associations of relative handgrip strength with each outcome. The age- and sex-adjusted HRs (95% CIs) per 1 SD increase in relative handgrip strength for fatal CHD, fatal CVD, and all-cause mortality were 0.61 (0.46-0.79), 0.67 (0.54-0.82), and 0.79 (0.69-0.91) respectively. These were only minimally attenuated to 0.65 (0.49-0.85), 0.69 (0.56-0.86), and 0.81 (0.70-0.93) respectively after adjustment for established and emerging risk factors. In analyses that compared the top versus bottom thirds of relative handgrip strength values, the age-and sex-adjusted HRs (95% CIs) for fatal CHD, fatal CVD, and all-cause mortality were 0.51 (0.32-0.83), 0.55 (0.38-0.79), and 0.64 (0.50-0.82) respectively. On multivariable adjustment, the corresponding HRs (95% CIs) were 0.59 (0.37-0.95), 0.59 (0.41-0.86), and 0.66 (0.51-0.84) respectively. The associations did not vary significantly by levels or categories of several clinically relevant characteristics (**Figures 2-4**). The associations of relative handgrip strength with outcomes remained consistent in analyses that excluded the first two years of follow-up (**Supplementary Table S3**).

Handgrip strength and CVD mortality risk prediction

A CVD mortality risk prediction model containing conventional risk factors (age, SBP, history of diabetes, total cholesterol, HDL-C, and smoking) yielded a C-index of 0.7202 (95% CI: 0.6838 to 0.7566; $p<0.001$). On addition of information on relative handgrip strength to this prognostic model, there was a non-significant increase in the C-index by 0.0034 (95% CI: -0.01128 to 0.0181; $p=0.65$). When investigating differences in the -2 log likelihood of the risk score with and without inclusion of handgrip strength, the -2 log likelihood was significantly improved on addition of information on handgrip strength to the model (p for comparison<0.001). There was no significant improvement in the classification of participants into predicted 10-year CVD mortality risk categories (NRI: -1.31%, -8.90 to 6.27%; $p=0.74$). The IDI was 0.0058 (-0.0031 to 0.0148; $p = 0.20$).

Discussion

Based on a general population sample of Finnish men and women, the current findings show that relative handgrip strength is continuously and inversely associated with the risk of fatal CHD and CVD, and all-cause mortality in analyses adjusted for several established and emerging cardiovascular risk factors. There were mostly weak to modest inverse correlations of relative handgrip strength with several cardiovascular risk markers. The associations of relative handgrip strength with outcomes remained generally similar across several clinically relevant subgroups. With regard to assessment of the clinical value of handgrip strength, the addition of information on relative handgrip strength to a risk model containing traditional risk factors did not improve discrimination of CVD mortality risk using Harrell's C-index; however, there was a significant improvement on using the -2 log likelihood method, a more sensitive measure when evaluating the added predictive value of a new measurement

The inverse associations demonstrated between handgrip strength (an easily available objective and reproducible measure in clinical practice) and vascular mortality outcomes are consistent with previous findings on this topic.(10-14) Hand grip strength may enhance risk prediction for all-cause mortality on top of the risk prediction seen with age or sex.(38, 39) A recent study also showed that handgrip strength improved the prediction ability of all-cause mortality and cardiovascular mortality, using an office based risk score comprising of common risk factors such as age, sex, diabetes, body mass index, systolic blood pressure, and smoking.(40) However, none of these studies have shown whether the addition of handgrip strength to an established CVD risk score, including age, SBP, history of diabetes, total cholesterol, HDL-C, and smoking, improves risk prediction accuracy of fatal cardiovascular outcomes. A recent UK Biobank study proposed in population-based screening settings where demanding physical fitness assessment tools may not be feasible, the measurement of handgrip strength may add clinical utility over existing risk prediction scores.(40) Earlier findings from the Prospective Urban Rural Epidemiology (PURE) study showed that grip strength has a stronger association with cardiovascular mortality than with incident CVD, with an effect-size that was twice as large for cardiovascular death as for CVD.(16) This finding implies that low hand grip strength is associated with increased susceptibility to cardiovascular mortality especially in people who may develop chronic CVDs. However, a population-based study among participants from Lausanne (CoLaus) suggested that low hand grip strength was not related to incident cardiovascular events and overall morality after multivariate adjustment.(41)

Cardiorespiratory fitness largely reflects functional status,(42-44) whereas handgrip strength is a measure of upper body (arms) muscle strength. Though handgrip strength may be a proxy for overall muscle strength, it has been recently shown that it cannot accurately measure all other muscle groups strength.(45) However, handgrip strength is correlated with leg strength, and thus provides a valid index of overall limb muscle strength. There is some evidence to suggest that resistance muscle training

interventions can increase in glycolytic capacity and up-regulate insulin action and capacity for glucose utilization in muscles.(46) Structured resistance training promotes muscle function and alleviate the levels of cardiometabolic risk factors.(46) There is growing evidence that objective measures of physical performance such as handgrip strength, sitting-rising and standing balance tests not only characterize physical capability but also act as markers of general health status.(47) Handgrip strength decrease is also an indicator of frailty and age-associated loss of muscle mass(17) which appears to be inevitable and is likely to be the most significant contributing factor to the decline in muscle strength. Frailty is usually quantified by the degree of impairment in functional reserve across multiple organ systems and is often associated with fatigue, reduced muscle strength, and high susceptibility to chronic disease. In addition, associations between these measures of frailty and functional capacity (muscle strength) and cause specific mortality outcomes, may help to clarify the pathways underlying the associations between muscle fitness and CVDs. The muscle is a paracrine and exocrine organ. Myokines may act in autocrine, paracrine, and endocrine manner and regulate several processes associated with physical frailty.(48, 49) The release of myokines from skeletal muscle preserves or augments cardiovascular function. Increased muscle strength may provide capabilities for more active life-styles that are related to a lower CVD risk. Elucidating the proposed biological mechanistic pathways between poorer functional capacity such muscle strength and fatal CVD events may help in the development of more effective muscle training interventions. The assessment of grip strength can be recommended as a stand-alone measurement or as a component of measurements for identifying older adults at risk of poor health status.(17)

Clinical implications

Findings from our risk prediction analysis using the more sensitive -2 log likelihood method shows that handgrip strength urine augments CVD mortality risk prediction beyond that of traditional risk factors, and the observation of a graded association suggests that handgrip strength is potentially suitable for population-level risk assessment. Handgrip strength may be a potential risk assessment tool in general or specialized clinical setting to identify patients at high risk for worse outcomes, but more evaluation is needed. Handgrip strength, as a predictive biomarker of specific outcomes, can be improved through regular resistance training to improve and maintain muscular fitness.

Strengths and limitations

Although previous prospective cohort studies have investigated the associations of handgrip strength with fatal vascular outcomes, this is the first prospective evaluation of the associations between relative handgrip strength and the risk of cardiovascular and all-cause mortality outcomes as the investigation of the potential utility of relative handgrip strength for CVD mortality risk prediction assessment. The cohort had a long follow-up period and no losses to follow-up were recorded, given that study participants undergo annual monitoring and outcomes are checked using well-linked established databases.(7, 50) The sample was a nationally representative population-based cohort of middle-aged to elderly Caucasian men and women, which makes it possible to generalize the results in Northern European populations. Because body size is a key factor that explains muscle strength results, we used body weight adjusted values as a main handgrip strength exposure. We employed comprehensive analyses which included adjustment for several lifestyle and biological markers with underlying disease status, testing for effect modification by several relevant clinical subgroups, and accounting for reverse causation bias. Our risk prediction analyses used sensitive measures such as the -2 log likelihood. Despite the several strengths of this study and analyses, there are limitations which merit mention. The findings were based on older men and

women, hence cannot be generalised to other age groups. The addition of information on relative handgrip strength to the risk model did not improve CVD mortality risk discrimination using Harrell's C-index and this could be attributed to the fact that changes in C-index are largely dependent on the risk model, follow-up time and outcome events that have been used. Furthermore, Harrell's C-index can be insensitive in detecting differences because it is based on ranks.(36, 37) Our assessment of handgrip strength did not employ testing procedures recommended by the American Society of Hand Therapists (ASHT)(51) or the Southampton protocol,(52) which could have introduced biases in our findings. Handgrip strength assessment was conducted in accordance with the KIHD study protocol and utilised the Martin-Balloon-Vigorimeter, which was considered to be appropriate for the study population. Evidence suggests the Martin Vigorimeter is a reliable and practical tool for assessing handgrip strength in the elderly population.(53) The substantial heterogeneity between the handgrip strength test protocols used in studies on hand grip strength and outcome studies, has created difficulties in drawing comparative and consistent conclusions.(54) Though several potential confounders were taken into account, there is a potential for residual confounding, which is quite likely for observational study designs. Though we took into account the level of physical activity in our analyses, data on objectively assessed CRF was not available for all participants and hence could not be used. The observed associations could be underestimates because of the inability to correct for regression dilution bias, as the associations were based on baseline assessments of relative handgrip strength. Due to aging, disease, and changes in health habits, physical fitness among individuals could have changed.

Conclusions

This population-based prospective study shows inverse and continuous associations of relative handgrip strength with cardiovascular and all-cause mortality outcomes. Adding relative handgrip strength to

conventional risk factors improves CVD mortality risk assessment using more sensitive measures of discrimination. The use of handgrip strength as a predictor of cardiovascular health status and outcomes requires further investigation. It would also be relevant to ascertain if physical exercise and specific muscle strength training with other life-style interventions would decrease frailty and the risk of CVD events.

Acknowledgments

We thank the staff of the Kuopio Research Institute of Exercise Medicine and the Research Institute of Public Health and University of Eastern Finland, Kuopio, Finland for the data collection in the study.

Disclosure of interest

The authors report no conflicts of interest

Funding

This work has been supported in part by grants from the Finnish Foundation for Cardiovascular Research, Helsinki, Finland. Dr. Setor K. Kunutsor acknowledges support from the NIHR Biomedical Research Centre at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The views expressed in this publication are those of the author and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

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Figure Legends

Figure 1. Hazard ratios for fatal coronary heart disease, fatal cardiovascular disease, and all-cause mortality by quartiles of relative handgrip strength

Hazard ratios were adjusted for age, gender, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status, prevalent coronary heart disease, history of diabetes mellitus, resting heart rate, and physical activity; CHD, coronary heart disease; CVD, cardiovascular disease

Figure 2. Hazard ratios for fatal coronary heart disease by several participant level characteristics

Hazard ratios compared top versus bottom thirds of relative handgrip strength and were adjusted for age, gender, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status, prevalent coronary heart disease, history of diabetes mellitus, resting heart rate, and physical activity; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; LTPA, leisure-time physical activity; *, *p*-value for interaction; cut-offs for age, body mass index, systolic blood pressure, total cholesterol, HDL cholesterol, and total LTPA are based on median values.

Figure 3. Hazard ratios for fatal cardiovascular disease by several participant level characteristics

Hazard ratios compared top versus bottom thirds of relative handgrip strength and were adjusted for age, gender, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status, prevalent coronary heart disease, history of diabetes mellitus, resting heart rate, and physical activity; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio;

LTPA, leisure-time physical activity; *, *p*-value for interaction; cut-offs for age, body mass index, systolic blood pressure, total cholesterol, HDL cholesterol, and total LTPA are based on median values.

Figure 4. Hazard ratios for all-cause mortality by several participant level characteristics

Hazard ratios compared top versus bottom thirds of relative handgrip strength and were adjusted for age, gender, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status, prevalent coronary heart disease, history of diabetes mellitus, resting heart rate, and physical activity; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; LTPA, leisure-time physical activity; *, *p*-value for interaction; cut-offs for age, body mass index, systolic blood pressure, total cholesterol, HDL cholesterol, and total LTPA are based on median values.