**Rising from the grip of death: The combined association of skeletal muscle strength and physical activity on mortality in older women: the HUNT2 Study**

Trine Karlsen, PhD1,2, Javaid Nauman, PhD1,2, Håvard Dalen, MD PhD1,2,3, Arnulf Langhammer, MD PhD4, Ulrik Wisløff, PhD1,5

1. K.G. Jebsen Center of Exercise in Medicine at Department of Circulation and Medical Imaging, The Faculty of Medicine, NTNU, Norwegian University of Science and Technology, Trondheim, Norway
2. Department of Cardiology St. Olav’s Hospital, Trondheim University Hospital, Trondheim, Norway
3. Department of Medicine, Levanger Hospital, Nord-Trøndelag Hospital Trust, Levanger, Norway
4. HUNT Research Center, Department of Public Health and General Practice, The Faculty of Medicine, NTNU, Norwegian University of Science and Technology, Levanger, Norway
5. School of Human Movement & Nutrition Sciences, University of Queensland, Australia

Financial support: The authors are supported by grants from the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology (TK, JN), the K.G. Jebsen Foundation (UW, JN) and the Norwegian Research Council (UW).

Conflict of interest disclosure: None

Corresponding author: Trine Karlsen, PhD

NTNU, Det medisinske fakultet, Institutt for Sirkulasjon og Bildediagnostikk

Postboks 8905, Medisinsk teknisk forskningssenter, 7491 Trondheim, Norway

Email: trine.karlsen@ntnu.no, Phone: +47 92644422

Word count text only: 2673, Abstract: 253

References: 22, Tables: 3

**Abstract**

**Objective:** To assess the isolated and combined associations of leg- and arm strength with adherence to current physical activity guidelines with all-cause and cause specific mortality in healthy elderly women.

**Patients and Methods:** Prospective cohort study of 2529 elderly women (72.6±4.8 years) from the Norwegian HUNT2 survey between August 1995 and June 1997 with a median of 15.6 (IQR, 10.4-16.3) years follow up. Chair-rise-test and handgrip strength performances were assessed, and divided into tertiles. The hazard ratio (HR) of all-case and cause specific mortality by tertiles of handgrip strength and chair rise test performance, and combined associations with physical activity were estimated by using Cox proportional hazard regression models.

**Results:** We observed independent associations of physical activity and the chair-rise test performance with all-cause and cardiovascular mortality, and between hand-grip strength and all-cause mortality. Despite following physical activity guidelines, women with low muscle strength had increased risk of all-cause mortality (HR chair test: 1.37 (95% confidence interval [CI], 1.07-1.76); grip-strength 1.39 (95% CI, 1.05-1.85)), and cardiovascular disease (CVD) mortality (HR, chair test: 1.57 (95% CI, 1.01-2.42). Slow chair test performance was associated with all-cause (HR 1.32 (95% CI, 1.16-1.51)), cardiovascular disease (HR 1.41 (95% CI, 1.14-1.76)). The association between handgrip strength and all-cause mortality was dose dependent (*P* value for trend <.01).

**Conclusion:** Handgrip strength and chair rise test performance predicted the risk of all-cause and CVD mortality independent of physical activity. Clinical feasible tests of skeletal muscle strength could increase the precision of prognosis, even in elderly women following current physical activity guidelines.

Key words: hand-grip strength, chair rise test, cardiovascular disease, mortality, health, prevention

**Abbreviations**

BMI = Body mass index

CI = confidence interval

cm = centimeter

CVD = cardiovascular disease

HR = hazard ratio

HUNT2 = Healthy survey of Northern Trøndelag (second wave)

ICD = International Classification of Diseases

IHD = ischemic heart disease

Kg = kilogram

Kpa = Kilo Pascal

m = meters

mmHg = millimeter mercury

n = number

PA = Physical Activity

SD = standard deviation

sec = seconds

**Introduction**

Skeletal muscle strength is an important health predictor[1](#_ENREF_1), [2](#_ENREF_2) found to be negatively associated with all-cause,[3](#_ENREF_3), [4](#_ENREF_4) cardiovascular,[3-6](#_ENREF_3) and cancer mortality,[7](#_ENREF_7) as well as with myocardial infarction and stroke.[3](#_ENREF_3) Multiple tests of skeletal muscle strength exist. Two simple, clinically feasible and inexpensive tests are handgrip strength and chair-rise ability.[3](#_ENREF_3), [8](#_ENREF_8), [9](#_ENREF_9) Handgrip strength has been found to be a robust predictor of all-cause mortality in both men and women in many cohort studies,[3](#_ENREF_3), [5](#_ENREF_5), [6](#_ENREF_6), [10](#_ENREF_10) and has shown to predict all-cause mortality in both healthy and disabled women over a large age range (35-74 years)[10](#_ENREF_10), [11](#_ENREF_11) [6](#_ENREF_6). Muscle strength declines with increasing age,[9](#_ENREF_9), [12](#_ENREF_12) and leg strength decreases to a lesser degree with aging than handgrip strength.[12](#_ENREF_12) The chair rising test, a surrogate of functional leg strength, is integrated with several other tests into the clinical short *physical performance battery score*.[13](#_ENREF_13), [14](#_ENREF_14) As both muscle strength[3](#_ENREF_3) and physical activity predict health outcomes,[15](#_ENREF_15) it is of interest to understand the combined association between muscle strength, adherence to guidelines for physical activity and health outcomes.[16](#_ENREF_16), [17](#_ENREF_17) The combined associations of physical activity with handgrip and leg strength in prediction of all-cause and cause-specific mortality has never been studied. Therefore, the aim of this study was to determine the isolated and combined association between leg- and arm strength and adherence to current physical activity guidelines with all-cause and cause-specific mortality in healthy elderly women.

**Methods**

*Study population*

Between August 1995 and June 1997, adults 20 years and older, living in the county of Nord-Trøndelag in Norway, were invited to participate in the second wave of the HUNT study (HUNT2). In total 65,237 individuals participated (69.5 % of invited). In an osteoporosis sub-study, women aged >65 years were invited to forearm bone densitometry test, and among these 3016 randomly selected women between 65 to 88 years of age performed a handgrip strength- and a chair-rise test. The full survey details are described elsewhere.[18](#_ENREF_18), [19](#_ENREF_19) For this study, we excluded the women with self-reported history of myocardial infarction (n=131), angina pectoris (n=259), and stroke (n=79). Eighteen women had missing data on the chair rise test, therefore, a total of 2529 women were included in this study. The HUNT2 survey and the current study were approved by the regional committee for medical research ethics (REK# 152/95/AH/JGE and REK# 2012/669).

*Chair test performance*

The test started from the seated position, and participants were instructed to stand up and sit down as fast as possible for five consecutive times. Arms were crossed at the chest to avoid use of arm force while rising and sitting. The test administrator timed the individuals, and test time was recorded in whole seconds with a stopwatch. The test was performed once.

*Handgrip strength*

Handgrip strength was measured in the non-dominant arm with a Martin Vigorimeter (Gebrüder Martin, W. Germany).[9](#_ENREF_9) Participants seated in a chair with the arm held freely and comfortably without any support. They squeezed the Vigorimeter rubber ball with all their strength three consecutive times to evaluate grip strength. The size of the rubber balls was adjusted according to hand size (three different sizes), and 1 minutes of rest were given in-between attempts. The test administrator registered the mean of the two highest tests as maximal effort.

*Clinical information*

A medical examination by trained nurses included blood pressure, resting heart rate and anthropometric measurements. Height was measured to the nearest 1 cm, and weight to the nearest 0.5 kg. Hypertension was defined as having systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mmHg. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters square, and categorized into following categories: <18.5, 18.5-24.9, 25.0-29.9, and ≥30.0 kg·m-2.

Participants filled in questionnaires on smoking, alcohol consumption, education **and occupation,** and current and previous medical history. Smoking status was classified into never, current or former smoker. Alcohol consumption was categorized as, abstainer, 0-7, 8-14, and >14 drinks over a period of two weeks. Self-reported use of blood pressure medication, diabetes and first-degree family history of cardiovascular disease were classified as either yes or no.

*Physical activity*

Physical activity was self-reported through the HUNT2 questionnaire.[20](#_ENREF_20) Participants reported average hours of light and vigorous leisure time physical activity for a normal, representative week the past year. Light activity was explained as not sweating/being out of breath, while vigorous activity was explained as sweating/being out of breath. Four response options were available for each intensity; none, <1 hour, 1-2 hours, or ≥3 hours. As the questions about vigorous and light physical activity were not mutually exclusive, we constructed a physical activity variable that roughly corresponded to the current recommendation of physical activity (WHO ref). In the constructed variable, duration of physical activity was divided into light physical activity (less than one hour and at least three hours of light activity) and hard physical activity (less than one hour and at least one hour of activity). Further, light and hard physical activity were combined into four activity categories. No physical activity (no activity of both light and vigorous physical activity), low (less than three hours of light- and no vigorous physical activity), moderate (less than three hours of light- and less than one hour of vigorous physical activity or at least three hours of light, and no hard physical activity) or high physical activity (at least three hours of light physical activity and less than hour of vigorous physical activity, at least three hours of light physical activity and at least one hour of vigorous physical activity, or less than three hours of light physical activity and at least one hour of vigorous physical activity),[21](#_ENREF_21) and further into below or above current physical activity recommendations of 150 minutes of light and 75 minutes of vigorous physical activity weekly.[16](#_ENREF_16) Low physical activity indicated below current recommendations, moderate physical activity corresponded fairly well with the recommendations, and high physical activity indicated higher levels than the minimum recommendations. The physical activity index has been shown to be associated with mortality in a general population and among people with the metabolic syndrome.[21](#_ENREF_21) The physical activity questionnaire has previously been validated in males in the cohort.[20](#_ENREF_20)

*Endpoints*

Our study had a virtually complete follow-up due to the unique 11- digit Norwegian person identification number that allows accurate matching to the National Cause of Death Register. The primary endpoint was death from any cause until the end of follow-up on December 31, 2012. In addition, we assessed deaths from cardiovascular causes (International Classification of Diseases (ICD), 9th revision: 390-459; ICD, 10th revision: I00-99), deaths from ischaemic heart disease (ICD, 9th revision: 410-414; ICD, 10th revision: I20-25), deaths from stroke (ICD, 9th revision: 430-438; ICD, 10th revision: I60-69), and deaths from cancer (ICD, 10th revision: C00-97).

*Statistical analyses*

Data were categorized into tertiles based on handgrip strength and chair-rise performance. Continuous data are presented as mean (SD), and baseline characteristics of participants were compared using linear regression analyses for continuous variables, and chi-square tests for categorical variables. By use of Cox proportional hazards regression analysis, hazard ratios with 95% confidence intervals were estimated for the association between tertiles of handgrip strength, chair-rise performance and cause specific mortality. The proportional hazard assumption was evaluated by plots of Schoenfeld residuals, and we found no evidence of departure.

The basic models included explanatory variables adjusted for age by entering attained age as the time scale, while the multi-adjusted models further included BMI, smoking, alcohol consumption, hypertension, blood pressure medication, diabetes, family history of cardiovascular disease, (Model 1 is adjusted for age by entering attained age as the time scale, Model 2 is further adjusted for BMI, smoking, alcohol consumption, hypertension, blood pressure medication, diabetes, family history of myocardial infarction, physical activity, Model 3 is adjusted for Model 2 and chair test performance for handgrip strength, and handgrip strength for chair test performance, respectively*.* In analysis of cancer mortality, hypertension, blood pressure medication and family history of MI were not included as confounders). In total, 1153 women had missing information about physical activity (n = 1088), or any of the confounders (n = 65). As participants with complete data might have a different health status compared with those with missing data, we performed both a complete case analysis, and analyses including multiple imputation of missing values to reduce the biases that can occur in complete case analysis along with a substantial loss of power and precision.[22](#_ENREF_22) We used ICE procedure in Stata[23](#_ENREF_23" \o "Royston, 2009 #355) to obtain 20 imputed datasets, and used Rubin’s rules to combine effect estimates and estimate standard errors to allow for the uncertainty caused by missing data.

We further assessed the combined associations of handgrip strength and chair-rise performance respectively, with physical activity for cause-specific mortality. The formal tests were performed by an interaction term between tertiles of handgrip strength, or chair-rise performance with physical activity above and below current recommendations. Participants in tertiles with fast chair performance and high grip strength, respectively, and following the current recommendations of physical activity were used as the referent. All statistical tests were 2 sided. A *P*-value of <.05 was considered significant. All analyses were conducted using Stata (version 13.1 StataCorp).

**Results**

The median follow-up time in the study was 15.6 (interquartile range, 10.4-16.3) years. A total of 1300 (51%) women died during follow-up, of which 40% (n=515) due to CVD and 22.7% (n=295) because of cancer. Mean age in the cohort was 72.6 ± 4.8 years and BMI was 27.5 ± 4.4 kg·m2 (Table 1).

The mean chair test time was 14.8±11.8 seconds, and average hand grip strength was 72.0±18.5 Kpa. Both high handgrip strength and fast chair test were associated with younger age, lack of diabetics, lack of blood pressure medication, fewer alcohol abstainers, and higher physically activity level (*P*<.001). The women in the fastest chair test tertile had lower BMI and body weight compared to the middle and slow tertiles, and those with highest handgrip strength had higher BMI and body weight (*P*<.01) (Table 1).

Chair rise test performance was associated with all-cause, CVD and stroke mortality (Table 2), but not IHD and cancer mortality. Women in the slowest chair test tertile had 32% (HR, 1.32; 95% CI, 1.16-1.51), 41% (HR, 1.41; 95% CI, 1.14-1.76), and 80% (HR, 1.80; 95% CI, 1.23-2.64) higher risk of all-cause, CVD and stroke mortality, respectively, compared with the fastest tertile (Model 3) (Table 2).

Hand-grip strength was associated with all cause and CVD mortality, but not with stroke, IHD and cancer mortality. Women in the weak tertile had 41% (HR, 1.41; 95% CI, 1.20-1.66) higher risk of all-cause mortality compared with the strongest tertile. The weakest tertile had 32% (HR, 1.32; 95% CI, 1.02-1.71) higher risk of CVD mortality compared to the strongest tertile (Model 1) (Table 2). Further confounder adjustment, maintained the significant association for all-cause mortality, while the association between grip strength and CVD mortality was no longer statistical significant (Model 2 and 3) (Table 2). The results of complete case analyses were not materially different than the imputation analyses (Supplementary Table 1).

Table 3 shows the hazard ratios of mortality according to chair test and hand grip strength respectively, in combination with physical activity above and below current recommendations. There was an independent association between physical activity and the chair-rise test performance in predicting all-cause and CVD mortality. Women with a slow chair rise test, and below current recommendations of physical activity had higher risk of all-cause and CVD mortality (*P* for interaction; 0.36 for all-cause, 0.23 for CVD) compared with the reference group (fast chair test and following current recommendations of physical activity). Women with a slow chair rise test and following current recommendations had comparable risk of all-cause mortality (HR, 1.37; 95% CI, 1.07-1.76) with women with a fast chair rise test and below current recommendations of physical activity (HR, 1.38; 95% CI ,1.07-1.77) (Model 3). The handgrip test results were independent of physical activity in predicting all-cause mortality (*P* for interaction; 0.28 for all-cause). Women with weak handgrip strength had higher risk of all-cause mortality compared to the reference (strong handgrip strength and recommended physical activity), independent of whether they followed the physical activity recommendations (HR, 1.39; 95% CI, 1.05-1.85) or not (HR, 1.70; 95% CI, 1.28-2.26) (Model 3).

The combined analyses of grip strength and chair rise performance showed that each measure of muscle strength was independently associated with all cause and CVD mortality (*P* for interaction; 0.52 for all-cause, 0.13 for CVD), with worse performance on either handgrip or chair performance being associated with higher risk (Supplementary Table 2). Compared with the reference group of fast chair test and high grip strength, the hazard ratios were 1.59 (95% CI, 1.27-2.00) for all-cause mortality, and 1.49 (95% CI, 1.04-2.13) for CVD mortality in those with slow chair performance and low handgrip (Model 3).

**Discussion**

This prospective study of apparently healthy older women at baseline demonstrates that two affordable, quick and clinically feasible tests of skeletal muscle strength in the arms (handgrip strength) and the legs (chair rise test) predicts future all-cause, CVD and stroke (the latter associated with chair rise test only) mortality. The novel finding is that these tests predict mortality independent of whether the today’s recommendations of physical activity were followed or not. This implies that elderly women following the current recommendations for physical activity still have a higher risk of mortality if skeletal muscle strength is reduced. It has been speculated that physical activity may improve factors as autonomic imbalance, arterial stiffness and endothelial dysfunction, and that this might mediate the association between muscle strength and cardiovascular events.[3](#_ENREF_3) As muscle strength was independent of physical activity in the association with both all-cause, CVD and stroke mortality in our study, muscle strength seems to be an independent predictor of mortality.[17](#_ENREF_17)

We observed a dose response relationship between handgrip strength and all-cause and CVD mortality, confirming the results from other studies with shorter follow up time in old and disabled women,[6](#_ENREF_6), [11](#_ENREF_11) in both high and low income countries.[3](#_ENREF_3) Prior studies have suggested that reduced muscle strength is a risk factor for incident CVD, and that loss of muscular strength might be part of a CVD event casual cascade.[3](#_ENREF_3) As we found low muscle strength to be associated with CVD mortality, our data supports this notion. We observed no association between muscle strength and cancer-[12](#_ENREF_12) or ischemic heart disease mortality.[6](#_ENREF_6) This is somewhat in contradiction to the PURE study,[3](#_ENREF_3) where low handgrip strength was associated with low cancer risk in participants from high-income countries; unknown for what reason. Future studies might reveal why this association is more pronounced for cardiovascular diseases than for cancer mortality. The low number of women dying of ischemic heart disease may have influenced our analysis. Women in our study had a strong grip strength compared to normative data from Canadian women above 60 years of age reporting to be in excellent health, and highly physically active.[9](#_ENREF_9) This could be due to the woman in our study being taller and heavier, as body height in particular has been found to predict grip strength as the Martin Vigorimeter was used to measure grip strength in both studies.[9](#_ENREF_9)

The strengths of this study are that we have a long term prospective design follow-up in home dwelling older women that were healthy at baseline, high quality national disease specific mortality registers, and the ability to control for physical activity and several well-known confounding factors for cardiovascular disease, cancer and mortality.

Study limitations include, that 1088 women did not respond to the questions about physical activity. As shown in Table 1 in the supplementary material, the complete case analyses did not reveal a materially different result for the associations, confirming that the imputation analysis made is valid. Physical activity was self-reported, not objectively measured.[24](#_ENREF_24) Another limitation is the lack of diet behaviour, muscle mass and inflammatory measurements. It has been shown that older adult women with the poorest grip strength, also have the worse nutrition status,[6](#_ENREF_6) however few women in our study were underweighted according to BMI. Also, only women above 65 years of age were studied, limiting generalizability to male gender and other age groups.

*Clinical importance*

As this was an observational study, the causal relationship between grip strength and chair rise test may indicate underlying disease and a lifestyle effecting future adverse outcomes. Both the chair rise- and handgrip test could be used independently of physical activity to identify women at higher risk of dying; thereby muscle strength may be viewed as a biomarker for underlying disease or lifestyle.[3](#_ENREF_3) As both tests require very little equipment, and can be performed everywhere in a short amount of time and with little instruction, the practical implications might be that tests of skeletal muscle strength should be used more extensively when current and future health prognosis is to be evaluated, also in women fulfilling the current recommendations for endurance based physical activity. The study may indicate a need for a stronger focus on adhering to strength training recommendations, particularly in older women.[25](#_ENREF_25) Clinicians diagnosing patients with low skeletal muscle strength should prescribe systematic strength training and investigate if patients suffer from malnutrition or cachexia[17](#_ENREF_17).

**Conclusion**

Handgrip strength and chair rise test performance is strongly associated with all-cause and CVD mortality in elderly women, independent of whether they follow todays recommendations for physical activity or not.

*Conflicts of interest*

The authors have no conflicts of interest to report

*Acknowledgements*

The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology NTNU), Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Health. We are grateful to the participants, and the management in the HUNT Study for the use of data. Data on cause of death, were obtained from the Norwegian Cause of Death Registry, data of myocardial infarct status, were obtained from the Regional Infarct register for Mid Norway.The study has used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

**References**

**1.** Newman AB, Kupelian V, Visser M, et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2006;61(1):72-77.

**2.** Metter EJ, Talbot LA, Schrager M, Conwit R. Skeletal muscle strength as a predictor of all-cause mortality in healthy men. *The journals of gerontology. Series A, Biological sciences and medical sciences.* 2002;57(10):B359-365.

**3.** Leong DP, Teo KK, Rangarajan S, et al. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. *Lancet.* 2015;386(9990):266-273.

**4.** Ortega FB, Silventoinen K, Tynelius P, Rasmussen F. Muscular strength in male adolescents and premature death: cohort study of one million participants. *Bmj.* 2012;345(e7279.

**5.** Lopez-Jaramillo P, Cohen DD, Gomez-Arbelaez D, et al. Association of handgrip strength to cardiovascular mortality in pre-diabetic and diabetic patients: a subanalysis of the ORIGIN trial. *International journal of cardiology.* 2014;174(2):458-461.

**6.** Rantanen T, Volpato S, Ferrucci L, Heikkinen E, Fried LP, Guralnik JM. Handgrip strength and cause-specific and total mortality in older disabled women: exploring the mechanism. *J Am Geriatr Soc.* 2003;51(5):636-641.

**7.** Ruiz JR, Sui X, Lobelo F, et al. Association between muscular strength and mortality in men: prospective cohort study. *Bmj.* 2008;337(a439.

**8.** Hardy R, Cooper R, Shah I, Harridge S, Guralnik J, Kuh D. Is chair rise performance a useful measure of leg power? *Aging clinical and experimental research.* 2010;22(5-6):412-418.

**9.** Desrosiers J, Bravo G, Hebert R, Dutil E. Normative data for grip strength of elderly men and women. *The American journal of occupational therapy : official publication of the American Occupational Therapy Association.* 1995;49(7):637-644.

**10.** Sasaki H, Kasagi F, Yamada M, Fujita S. Grip strength predicts cause-specific mortality in middle-aged and elderly persons. *The American journal of medicine.* 2007;120(4):337-342.

**11.** Al Snih S, Markides KS, Ray L, Ostir GV, Goodwin JS. Handgrip strength and mortality in older Mexican Americans. *Journal of the American Geriatrics Society.* 2002;50(7):1250-1256.

**12.** Xue QL, Beamer BA, Chaves PH, Guralnik JM, Fried LP. Heterogeneity in rate of decline in grip, hip, and knee strength and the risk of all-cause mortality: the Women's Health and Aging Study II. *J Am Geriatr Soc.* 2010;58(11):2076-2084.

**13.** Cesari M, Kritchevsky SB, Newman AB, et al. Added value of physical performance measures in predicting adverse health-related events: results from the Health, Aging And Body Composition Study. *Journal of the American Geriatrics Society.* 2009;57(2):251-259.

**14.** Prommer N, Sottas PE, Schoch C, Schumacher YO, Schmidt W. Total hemoglobin mass--a new parameter to detect blood doping? *Medicine and science in sports and exercise.* 2008;40(12):2112-2118.

**15.** Wisloff U, Nilsen TI, Droyvold WB, Morkved S, Slordahl SA, Vatten LJ. A single weekly bout of exercise may reduce cardiovascular mortality: how little pain for cardiac gain? 'The HUNT study, Norway'. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology.* 2006;13(5):798-804.

**16.** Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Medicine and science in sports and exercise.* 2011;43(7):1334-1359.

**17.** Celis-Morales CA, Lyall DM, Anderson J, et al. The association between physical activity and risk of mortality is modulated by grip strength and cardiorespiratory fitness: evidence from 498 135 UK-Biobank participants. *European heart journal.* 2016.

**18.** Krokstad S, Langhammer A, Hveem K, et al. Cohort Profile: the HUNT Study, Norway. *International journal of epidemiology.* 2013;42(4):968-977.

**19.** Holmen J, Midthjell K, Krüger Ø, et al. The Nord-Trøndelag HEalth Study 1995-97 (HUNT 2): Objectives, contents, methods and participation *Norsk Epidemiologi.* 2003;13(1):19-32.

**20.** Kurtze N, Rangul V, Hustvedt BE, Flanders WD. Reliability and validity of self-reported physical activity in the Nord-Trondelag Health Study (HUNT 2). *European journal of epidemiology.* 2007;22(6):379-387.

**21.** Stensvold D, Nauman J, Nilsen TI, Wisloff U, Slordahl SA, Vatten L. Even low level of physical activity is associated with reduced mortality among people with metabolic syndrome, a population based study (the HUNT 2 study, Norway). *BMC medicine.* 2011;9(109.

**22.** Clark TG, Altman DG. Developing a prognostic model in the presence of missing data: an ovarian cancer case study. *Journal of clinical epidemiology.* 2003;56(1):28-37.

**23.** Royston P, Carlin JB, White IR. Multiple imputation of missing values: New feathers for mim. *The Stata Journal* 2009;9(2):252-264.

**24.** Strath SJ, Kaminsky LA, Ainsworth BE, et al. Guide to the assessment of physical activity: Clinical and research applications: a scientific statement from the American Heart Association. *Circulation.* 2013;128(20):2259-2279.

**25.** . *Global Recommendations on Physical Activity for Health*. Geneva2010.

**Table 1. Descriptive of participants according to tertiles of hand-grip strength and chair test performance.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Chair test**  | **Total** (n=2529) | **Slow**(n=730) | **Middle** (n=698) | **Fast** (n=1101) |
| Chair test performance (seconds)  | 14.8 ± 11.8 | 22.4 ± 19.9 | 13.9 ± 0.8 | 10.4 ± 1.4 |
| Age (years) | 72.6 ±4.8 | 74.1 ±5.11 | 72.5 ± 4.7 | 71.6 ± 4.5 |
| Body mass index (kg · m2) | 27.5 ± 4.4 | 28.0 ± 4.6 | 27.8 ± 4.4 | 27.0 ± 4.1 |
| Height (cm) | 159.6 ± 5.6 | 159.2 ± 5.9 | 159.9 ± 5.6 | 159.8 ± 5.5 |
| Body weight (kg) | 70.1 ± 11.7 | 70.9 ± 12.4 | 71.0 ± 11.9 | 69.0 ± 11.0 |
| Systolic blood pressure (mmHg) | 158 ± 234 | 159 ± 24 | 158 ± 24 | 157 ± 23 |
| Diastolic blood pressure (mmHg) | 86 ± 14 | 87 ± 14 | 87 ± 14 | 86 ± 14 |
| Hypertension, n (%) | 1960 (78) | 583 (80) | 545 (78) | 832 (76) |
| Free from blood pressure medication, n (%) | 1777 (70) | 480 (66) | 480 (69) | 817 (74) |
| Diabetic, n (%) | 147 (6) | 53 (7) | 37 (5) | 57 (5) |
| Alcohol abstainer, n (%) | 807 (32) | 280 (38) | 206 (30) | 321 (29) |
| Physical active, n  | 1441  | 363  | 374  | 704  |
| Inactive, n (%) | 180 (12) | 77 (21) | 46 (12) | 57 (8) |
| Low active, n (%)  | 613 (43) | 172 (47) | 164 (44) | 277 (39) |
| Moderate active, n (%)  | 512 (36) | 94(26) | 130 (35) | 288 (41) |
| Highly active, n (%)  | 136 (9) | 20 (6) | 34 (9) | 82 (12) |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
| **Handgrip Strength**  | **Total**(n=2529) | **Low**(n=818) | **Middle** (n=1087) | **High** (n=624) |
| Handgrip strength (Kpa) | 72.0 ± 18.5 | 51.9 ± 11.5 | 73.7 ± 5.4 | 94.4 ± 9.2 |
| Age (years) | 72.6 ±4.8 | 74.3 ± 5.1 | 72.4 ± 4.6 | 70.6 ±4.0 |
| Body mass index (kg · m2) | 27.5 ± 4.4 | 27.0 ± 4.4 | 27.5 ± 4.4 | 28.1 ± 4.1 |
| Height (cm) | 159.6 ± 5.6 | 158.3 ± 5.8 | 159.6 ± 5.5 | 161.5 ± 5.2 |
| Body weight (kg) | 70.1 ± 11.7 | 67.8 ± 11.4 | 70.0 ± 11.8 | 73.4 ± 11.3 |
| Systolic blood pressure (mmHg) | 158 ± 23 | 158 ± 25 | 158 ± 23 | 157 ± 22 |
| Diastolic blood pressure (mmHg) | 86 ± 14 | 86 ± 15 | 87 ± 14 | 8 ± 13 |
| Hypertension, n (%) | 1960 (78) | 621 (76) | 846 (78) | 493 (79) |
| Free from blood pressure medication, n (%) | 1777 (70) | 561 (69) | 754 (69) | 462 (74) |
| Diabetic, n (%) | 147 (6) | 52 (6) | 68 (6) | 27 (4) |
| Alcohol abstainer, n (%) | 807 (32) | 288 (35) | 336 (31) | 183 (29) |
| Physical active, n  | 1441  | 432  | 620  | 389  |
| Inactive, n (%) | 180 (12) | 72 (16) | 78 (13) | 30 (8) |
| Low active, n (%) | 613 (43) | 198 (46) | 253 (41) | 162 (42) |
| Moderate active, n (%)  | 512 (36) | 129 (30) | 230 (37) | 153 (39) |
| Highly active, n (%)  | 136 (9) | 33 (8) | 59 (9) | 44 (11) |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

 Data are mean±SD, otherwise indicated.

Chair test performance (seconds): slow, 16-300; middle, 13-15; fast, 5-12.

Handgrip strength (Kpa): low, 5-60; middle, 61-80; high, 81-140.

**Table 2. Hazard ratio (95% confidence interval) for all-cause, cardiovascular disease, stroke, ischemic heart disease or cancer mortality.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Chair test**  | **Deaths (n)** | **Model 1** | **Model 2** | **Model 3** |
| All-cause mortality |  |  |  |  |
| Fast (5-12 sec) | 482 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| Middle (13-15 sec) | 340 | 1.06 (0.93-1.22) | 1.04 (0.90-1.20) | 1.03 (0.90-1.19) |
| Slow (16-300 sec) | 478 | 1.43 (1.26-1.82) | 1.37 (1.20-1.57) | 1.32 (1.16-1.51) |
| *P*-trend |  | <.001 | <.001 | <.001 |
| CVD mortality  |  |  |  |  |
| Fast (5-12 sec) | 174 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| Middle (13-15 sec) | 139 | 1.18 (0.95-1.48) | 1.12 (0.90-1.41) | 1.12 (0.89-1.40) |
| Slow (16-300sec) | 202 | 1.60 (1.29-1.96) | 1.45 (1.17-1.79) | 1.41 (1.14-1.76) |
| *P*-trend |  | <.001 | <.01 | <.01 |
| Stroke mortality  |  |  |  |  |
| Fast (5-12 sec) | 50 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| Middle (13-15 sec) | 47 | 1.38 (0.93-2.06) | 1.33 (0.89-1.99) | 1.33 (0.88-1.90) |
| Slow (16-300 sec) | 72 | 1.95 (1.35-2.82) | 1.84 (1.26-2.68) | 1.80 (1.23-2.64) |
| *P*-trend |  | <.001 | <.01 | <.01 |
| IHD mortality  |  |  |  |  |
| Fast (5-12 sec) | 58 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| Middle (13-15 sec) | 49 | 1.26 (0.86-1.85) | 1.24 (0.85-1.83) | 1.24 (0.84-1.83) |
| Slow (16-300 sec) | 48 | 1.15 (0.78-1.70) | 1.05 (0.71-1.57) | 1.06 (0.70-1.59) |
| *P*-trend |  | .44 | .73 | .72 |
| Cancer mortality**†**  |  |  |  |  |
| Fast (5-12 sec) | 128 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| Middle (13-15 sec) | 79 | 0.98 (0.74-1.29) | 0.98 (0.74-1.31) | 0.97 (0.73-1.29) |
| Slow (16-300 sec) | 88 | 1.15 (0.87-1.52) | 1.16 (0.87-1.54) | 1.11 (0.83-1.48) |
| *P*-trend |  | .37 | .35 | .52 |
| **Handgrip strength** |  |  |  |  |
| All-cause mortality  |  |  |  |  |
| High (81-140 Kpa) | 234 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| Middle (61-80 Kpa) | 549 | 1.23 (1.05-1.43) | 1.21 (1.03-1.41) | 1.18 (1.01-1.38) |
| Low (5-60 Kpa) | 517 | 1.41 (1.20-1.66) | 1.37 (1.16-1.61) | 1.29 (1.09-1.53) |
| *P*-trend |  | <.001 | <.001 | <.01 |
| CVD mortality  |  |  |  |  |
| High (81-140 Kpa) | 91 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| Middle (61-80 Kpa) | 215 | 1.18 (0.92-1.51) | 1.15 (0.89-1.47) | 1.11 (0.86-1.43) |
| Low (5-60 Kpa) | 209 | 1.32 (1.02-1.71) | 1.28 (0.98-1.67) | 1.19 (0.91-1.56) |
| *P*-trend |  | .03 | .06 | .18 |
| Stroke mortality  |  |  |  |  |
| High (81-140 Kpa) | 28 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| Middle (61-80 Kpa) | 72 | 1.28 (0.82-1.98) | 1.24 (0.79-1.93) | 1.19 (0.76-1.86) |
| Low (5-60 Kpa) | 69 | 1.41 (0.89-2.23) | 1.34 (0.84-2.13) | 1.21 (0.75-1.94) |
| *P*-trend |  | .16 | .24 | .48 |
| IHD mortality  |  |  |  |  |
| High (81-140 Kpa) | 32 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| Middle (61-80 Kpa) | 68 | 1.06 (0.70-1.63) | 1.06 (0.69-1.63) | 1.05 (0.68-1.62) |
| Low (5-60 Kpa) | 55 | 1.00 (0.63-1.58) | 1.00 (0.63-1.59) | 1.00 (0.63-1.59) |
| *P*-trend |  | .94 | .98 | .96 |
| Cancer mortality**†** |  |  |  |  |
| High (81-140 Kpa) | 63 | 1.00 (ref) | 1.00 (ref) | 1.00 (ref) |
| Middle (61-80 Kpa) | 128 | 1.20 (0.89-1.63) | 1.19 (0.87-1.62) | 1.18 (0.87-1.60) |
| Low (5-60 Kpa) | 104 | 1.37 (0.99-1.89) | 1.34 (0.97-1.87) | 1.32 (0.94-1.84) |
| *P*-trend |  | .06 | .08 | .11 |

CVD, Cardiovascular disease; IHD, Ischemic heart disease

Model 1 is adjusted for age by entering attained age as the time scale, Model 2 is further adjusted for BMI, smoking, alcohol consumption, hypertension, blood pressure medication, diabetes, family history of myocardial infarction, physical activity, Model 3 is adjusted for Model 2 and chair test performance for handgrip strength, and handgrip strength for chair test performance, respectively*.* **†**In analysis of cancer mortality, hypertension, blood pressure medication and family history of MI were not included as confounders.

**Table 3. Hazard ratios (95% confidence interval) for all-cause and CVD mortality in a combined association between chair test performance and handgrip strength, respectively, with physical activity levels.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Chair test**  | **Model 1** | **Model 2** | **Model 3** |
|  | Following PA recommendations  | Below PA recommendations  | Following PA recommendations  | Below PA recommendations  | Following PA recommendations  | Below PA recommendations  |
| All cause death |  |  |  |  |  |  |
| Fast (5-12 sec) | 1.00 (ref) | 1.44 (1.13-1.83) | 1.00 (ref) | 1.38 (1.08-1.78) | 1.00 (ref) | 1.38 (1.07-1.77) |
| Middle (13-15 sec) | 1.17 (0.93-1.47) | 1.36 (1.07-1.75) | 1.16 (0.92-1.46) | 1.34 (1.04-1.74) | 1.15 (0.91-1.44) | 1.32 (1.02-1.71) |
| Slow (16-300 sec) | 1.44 (1.13-1.85) | 1.95 (1.56-2.45) | 1.43 (1.11-1.83) | 1.86 (1.47-2.35) | 1.37 (1.07-1.76) | 1.78 (1.40-2.27) |
| CVD death  |  |  |  |  |  |  |
| Fast (5-12 sec) | 1.00 (ref) | 1.63 (1.02-2.61) | 1.00 (ref) | 1.50 (0.93-2.42) | 1.00 (ref) | 1.49 (0.92-2.41) |
| Middle (13-15 sec) | 1.40 (0.92-2.14) | 1.63 (1.06-2.51) | 1.34 (0.87-2.07) | 1.50 (0.96-2.33) | 1.33 (0.87-2.05) | 1.48 (0.95-2.31) |
| Slow (16-300 sec) | 1.70 (1.11-2.59) | 2.33 (1.55-3.50) | 1.61 (1.04-2.48) | 2.04 (1.34-3.11) | 1.57 (1.01-2.42) | 1.99 (1.30-3.03) |
| **Handgrip strength**  |  |  |  |
| All cause death |  |  |  |  |  |  |
| High (81-140 Kpa) | 1.00 (ref) | 1.44 (1.03-2.02) | 1.00 (ref) | 1.41 (1.00-1.99) | 1.00 (ref) | 1.39 (0.99-1.96) |
| Middle (61-80 Kpa) | 1.27 (0.99-1.63) | 1.72 (1.29-2.28) | 1.26 (0.98-1.62) | 1.65 (1.23-2.20) | 1.22 (0.95-1.57) | 1.59 (1.19-2.13) |
| Low (5-60 Kpa) | 1.48 (1.12-1.95) | 1.93 (1.46-2.55) | 1.48 (1.12-1.96) | 1.83 (1.38-2.44) | 1.39 (1.05-1.85) | 1.70 (1.28-2.26) |
| CVD death  |  |  |  |  |  |  |
| High (81-140 Kpa) | 1.00 (ref) | 1.53 (0.89-2.64) | 1.00 (ref) | 1.46 (0.83-2.54) | 1.00 (ref) | 1.43 (0.82-2.49) |
| Middle (61-80 Kpa) | 1.22 (0.81-1.85) | 1.75 (1.07-2.84) | 1.23 (0.81-1.86) | 1.60 (0.97-2.63) | 1.18 (0.78-1.79) | 1.52 (0.92-2.51) |
| Low (5-60 Kpa) | 1.39 (0.88-2.19) | 1.92 (1.20-3.06) | 1.39 (0.88-2.20) | 1.76 (1.10-2.82) | 1.29 (0.82-2.05) | 1.61 (1.00-2.58) |

CVD, Cardiovascular disease; IHD, Ischemic heart disease; PA, Physical Activity. n = 1376 (complete case data). The strongest tertile of muscle strength and following the physical activity recommendations served as the reference value.

Model 1 is adjusted for age by entering attained age as the time scale, Model 2 is further adjusted for BMI, smoking, alcohol consumption, hypertension, blood pressure medication, diabetes and family history of myocardial infarction. Model 3 is adjusted for Model 2 and chair test performance for handgrip strength, and handgrip strength for chair test performance, respectively.