Associations of grip strength and walking pace with mortality in stroke survivors: a prospective study from UK Biobank

Maryam Soltanisarvestani[1], Nathan Lynskey[1], Stuart Gray[1], Jason MR Gill[1], Jill P Pell[2], Naveed Sattar[1], Paul Welsh[1], Frederick K Ho[2], Carlos Celis-Morales[1,3]†, Fanny Peterman-Rocha[1,4]†

[1]British Heart Foundation Glasgow Cardiovascular Research Centre, School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK.

[2]School of Health and Wellbeing, University of Glasgow, Glasgow, UK.

[3]Laboratorio de Rendimiento Humano, Grupo de Estudio en Educación, Actividad Física y Salud (GEEAFyS), Universidad Católica del Maule, Talca, Chile

[4]Centro de Investigación Biomédica, Facultad de Medicia, Universidad Diego Portales, Santiago, Chile

† CC-M and FP-R contributed equally to this work and are joint senior authors

Corresponding author

Dr Fanny Petermann-Rocha

College of Medical, Veterinary and Life Sciences

University of Glasgow

Glasgow, UK

Mail: fanny.petermann@glasgow.ac.uk

Acknowledgement

We are appreciative of the participants in the UK Biobank. This study was carried out with the help of the UK Biobank Resource under Application Number 7155.

Contributors

M.S, C.C-M and F.P-R contributed to the conception and design of the study, advised on all statistical aspects, and interpreted the data. M.S and F.P-R performed the literature search. M.S performed the analyses with the support of F.P-R. All authors critically reviewed the manuscript. All authors approved the final version for submission. C.C-M and F.P-R are the guarantors.

Sources of Funding

UK Biobank was established by the Wellcome Trust medical charity, Medical Research Council, Department of Health, Scottish Government and the Northwest Regional Development Agency. It has also had funding from the Welsh Assembly Government and the British Heart Foundation. All authors had final responsibility for submission for publication.

Competing interest declaration

UK Biobank was established by the Wellcome Trust medical charity, Medical Research Council, Department of Health, Scottish government, and Northwest Regional Development Agency; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

UK Biobank was approved by the North West Multi-Centre Research Ethics Committee (Ref: 11/NW/0382). All participants provided written informed consent to participate in the UK Biobank study. The study protocol is available online (http://www.ukbiobank.ac.uk/).

Transparency

The manuscript's guarantor (CC-M and FP-R) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing: No additional data are available.

Patient and public involvement

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

Word count: 3070

Abstract:

Introduction – Although stroke is an emerging cause of disability and mortality globally, associations between physical capability markers and mortality in stroke survivors are less well known. This study investigated the individual and combined associations of walking pace and grip strength with all-cause and stroke mortality in stroke survivors.

Methods – Individual and combined associations of walking pace and grip strength with stroke deaths and all-cause mortality were investigated using Cox proportional-hazard models adjusted for sociodemographic, lifestyle and health-related variables.

Results – 7,486 stroke survivors from the UK Biobank study (aged 40 to 70 years; 42.4% women) were included in this prospective study. Over a median follow-up of 12.6 (IQR: 11.9-13.3) years, 1,490 (19.9%) participants died, of whom 222 (3.0%) died from stroke. After adjusting for confounding factors, and compared to individuals in the average/brisk walking pace category, those who reported a slow walking pace had 2.00 (95% CI: 1.50 to 2.68) and 1.99 (95% CI: 1.78 to 2.23) times higher risk of stroke mortality and all-cause mortality, respectively. Similar associations were identified for participants with low grip strength than those with normal levels. For combined associations, those with both slow walking pace and low grip strength showed the highest risk of stroke mortality (hazard ratio: 2.86 [95% CI: 1.93; 4.22]). Similar results were found for all-cause mortality.

Conclusions- Low grip strength and slow walking pace were associated with a higher risk of stroke and all-cause mortality in stroke survivors. If these associations are causal, improving physical capability among stroke survivors might potentially prolong survival.

Keywords: stroke, grip strength, walking speed, survival, mortality.

Abbreviations: Hazard Ratio (HR), Body Mass Index (BMI), Standard Deviation (SD), Metabolic Equivalent (MET).

Introduction

Stroke, also known as cerebrovascular accidents, is a group of medical conditions defined by neurologic abnormalities induced by a disruption in cerebral blood flow.[1] Stroke is the second main cause of mortality and the third main cause of disability globally.[2] In the UK, nearly 130,000 people have a stroke or transient ischaemic attacks each year, over 300,000 people are disabled due to a stroke,[3] and about 1 million stroke survivors live in the country.[4] These figures will probably rise since people are living longer.[4] Stroke also has considerable economic and societal effects in the UK, with an annual societal cost of £26 billion[5] – a large number taking into account that in 2005 the costs were estimated at £9 billion.[5] Therefore, implementing preventative strategies would benefit both governments and individuals by reducing health and social care costs.

Among the known risk factors associated with stroke, studies have identified both non-modifiable (age, sex, ethnicity, and genetic) and modifiable factors (obesity, poor dietary habits, smoking, alcohol consumption, prevalent chronic diseases and low physical activity levels).[6-9] Physical capability – represented by walking pace and muscle strength – is also a significant predictor of stroke mortality.[10-12] However, even if the literature has been extensive regarding the association between these markers and stroke incidence in the general population,[10-12] long-term evidence in stroke survivors comes from clinical trials in a few survivors participants (usually <50)[13-17] rather than large prospective studies.[18] Moreover, people who have had a stroke have a higher risk of recurrent stroke and a higher mortality rate due to stroke or any causes.[19,20] According to a five-year prospective study, individuals who survived a stroke, have a nine-times higher risk of recurrent stroke than those with no history of stroke.[21]

In this context, while the association of low grip strength and/or slow walking pace with cardiovascular and all-cause mortality in the general population is well established,[22,23] data on the association between these factors and health outcomes in stroke survivors is less well known. Therefore, this study aimed to investigate the individual and combined association of grip strength and walking pace with stroke and all-cause mortality in stroke survivors from the UK Biobank prospective cohort study.

Method

This is a prospective cohort study using data from UK Biobank. UK Biobank is an open-access and large-scale general population cohort study containing in-depth health information. Between 2006 and 2010, over 500,000 individuals (5.5% response rate) aged 37 to 72 years were examined in 22 test sites across the UK, including England, Wales, and Scotland, from diverse socioeconomic and ethnic backgrounds.[24,25] All participants completed a touchscreen questionnaire, had physical measurements taken, and provided blood, urine, and saliva samples at baseline. Data from UK Biobank can be accessed by submitting an application to UK Biobank directly (http://www.ukbiobank.ac.uk/). More information about UK Biobank is available elsewhere.[24,25] For this study, only participants who self-reported at baseline assessment having a stroke were included (Figure 1).

Ethical considerations

All participants provided written informed consent to UK Biobank investigators. UK Biobank was approved by The National Health Service (NHS) (Ref: 11/NW/0382). This study was carried out under application number 7155.

Outcome

The outcomes in this study were mortality due to stroke and all-cause of death. Using the International Classification of Disease 10[th] version (ICD, 10[th]), mortality due to stroke was defined as codes I60, I61, I63, and I64, while all-cause mortality was identified as the mortality for any cause. Death certificates from the NHS, Information Centre (England and Wales), and the NHS Central Register Scotland were used to determine the date of death. Details of the linkage can be found at http://content.digital.nhs.uk/services. Data on mortality was accessible until October 2021. As a result, mortality follow-up was censored on this date or the date recorded for death.

Exposures

Walking pace and grip strength were included as the main exposures. A touchscreen questionnaire was used to record self-reported walking pace at the baseline visit as a proxy of gait speed. Self-reported walking pace has been previously identified as a good marker of walking speed and a strong predictor of health outcomes.[26,27] Participants were asked, 'How do you define your regular walking pace?' They selected three options: slow (<3 mph), average (3 to 4 mph), or brisk (>4 mph). The latter two categories were collapsed to provide a dichotomous variable average/brisk or slow walking pace, with the former treated as the reference group.

A Jamar J00105 hydraulic hand dynamometer was used to determine grip strength in kilogrammes. The dynamometer measures grip force isometrically and can be adjusted for hand size in five half-inch increments. Isometric grip force was assessed from a single 3-second maximal grip effort, in 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. For this study, the average of both hands was derived; therefore, participants who skipped measuring left or right hand were excluded from the analyses (e.g., people who were unable [amputee hand /weakness/paralysis] or just declined). More information about the protocol used can be found here https://biobank.ndph.ox.ac.uk/ukb/refer.cgi?id=100232.

Values >16 kg in women and >26 kg in men were defined as normal grip, whereas values ≤16 kg in women and ≤26 kg in men were defined as low grip using the Foundation for the National Institute of Health cut-off points.[28] The normal grip was treated as the reference group.

Finally, the walking pace and grip strength categories were combined to investigate their combined associations using the following categories: i) normal grip strength and average/brisk pace (reference); ii) normal grip strength and slow walking pace; iii) low grip strength and average/brisk pace; and iv) low grip strength and slow walking pace.

Covariates

Demographic and lifestyle information was self-reported using the baseline questionnaires. Age was derived from dates of birth and baseline assessment. The ethnic groups included were white, black, south Asian, Chinese, and others. Townsend score was used as a measure of area-based deprivation index, based on the postcode of residence,[29] and individual-level deprivation was measured using the highest academic qualification. The frequency of alcohol consumption was self-reported as daily/almost daily, 3-4 times a week, once/twice a week, 1-3 times a month, special occasions only and never. Self-reported smoking status was categorised as never, former or current smoker. Fruit and vegetable, red meat, and processed meat were also self-reported using a touch screen questionnaire. The average time spent driving, using a computer, and watching television, was used to derive the total time spent on sedentary behaviours. Trained nurses measured blood pressure, height and body weight during the baseline assessment. Body mass index (BMI) was derived from weight/height^2, and then was classified using the WHO guidelines into: underweight <18.5 kg/ m^2, normal weight 18.5–24.9 kg/m^2, overweight 25.0–29.9 kg/m^2, and obese ≥30.0 kg/m^2. Physician diagnosed prevalent conditions were self-reported during baseline nurse-led interviews. Morbidity counts were derived from a list of 43 long-term conditions described elsewhere[30,31] and classified as 0 or ≥1. More information about UK Biobank can be found on the online protocol (http://www.ukbiobank.ac.uk).

Statistical analyses

The characteristics of the population by grip strength, walking pace, and combined grip strength and walking pace categories are reported by frequencies and proportions for categorical data and means and standard deviations (SD) for continuous variables.

Associations of the exposures with stroke and all-cause mortality were first investigated by the separate exposures of grip strength and walking pace using Cox proportional hazard models. Then, the models were re-run using the composite measure derived from the two exposures. Findings are presented as hazard ratios (HR) with their respective confidence intervals (CIs). The time of follow-up was used as the time-dependent variable. The proportional hazard assumption was checked using Schoenfeld residuals.

Analyses were adjusted for confounding factors previously reported in the literature using four models, each with increasing covariates. Model 1, included sociodemographic covariates (sex, age, deprivation status, professional qualification, and ethnic group). Model 2 was, as per model 1, but also included lifestyle factors (fruit and vegetable, red and processed meat, alcohol consumption, smoking status, duration of sedentary behaviour, and sleep time). Model 3 was, as per model 2, but also included health-related variables (systolic blood pressure and morbidity count). Model 4 was, as per model 3, but additionally included BMI. These covariates were included considering previous literature on risk factors associated with stroke and the available data in UK Biobank.[6-9] Moreover, a directed acyclic graph explaining the association between the exposures, the outcome, and covariates is available in Supplementary Figure 1. In addition, we ran a sensitivity analysis using a 2-year landmark period where we excluded participants who died from a stroke or any cause within the first two years of follow-up. The latter was performed to exclude people who died from possible severe stroke cases from the analyses. However, considering some potential confounder variables were not available in UK Biobank, e-value were calculated to estimate the minimum strength of the association that an unmeasured confounder would be required to explain both the exposure and the outcome as a sensitivity analysis (more details provided in Supplementary material). E-value is an approach to evaluate the confounding effect in observational studies as it is described elsewhere.[32,33]

Participants were excluded if they did not have a history of stroke at baseline (n= 493,561) or had missing data for any of the exposures (n=278) or covariates (n=1,087) (Figure 1). All analyses were conducted using Stata version 17 statistical software (StataCorp LP). Statistical significance was defined as $p<0.05$.

Results

After excluding individuals who had no history of stroke at baseline and those with missing exposure or covariate data, 7,486 individuals were included in this prospective study (Figure 1). The median follow-up period was 12.6 years (interquartile range: 11.9 to 13.3 years; 93,710.2 person-days of follow-up) for stroke mortality and 12.3 years (interquartile range: 11.5 to 13.1 years; 87,345.2 person-days of follow-up) for all-cause mortality. Over this time, 1,490 (19.9%) people died, of whom 222 (3%) died from stroke.

The general characteristic of stroke survivors, broken down by walking pace and grip strength categories, are shown in Table 1. Overall, the mean age was 61.0 (6.6) years, and the majority of the study participants were men, white and from higher deprived areas. Compared to those in the low grip category, individuals in the normal category were more likely to have been educated at the college or university level. Also, compared with those in the slow walking pace category, individuals with an average/brisk walking pace were less likely to be current smokers or consume alcohol daily. Baseline cohort characteristics broken down by the combined walking pace and strength categories are contained in Supplementary Table 1.

The associations of walking pace and grip strength with stroke and all-cause mortality are shown in Figure 2. Compared to individuals with an average/brisk walking pace, those with a slow walking pace had over 2-fold (HR: 2.12 [95% CI: 1.61 to 2.79]) higher stroke mortality risk (Model 1, Figure 2a). This association was attenuated after including the covariates in models 2 and 3 but remained statistically significant. When the association was further adjusted for BMI (Model 4), individuals with low walking pace had 2.00-times (95% CI: 1.50 to 2.68) higher stroke mortality risk. On the other hand, compared to individuals with normal grip strength, those with low grip strength had a 1.96-times (95% CI: 1.46 to 2.63) higher stroke mortality risk (Model 1, Figure 2a). When this association was adjusted for lifestyle factors (Model 2), the association attenuated, and individuals with low grip strength had 1.87-times (95% CI: 1.39 to 2.51) higher risk of stroke mortality. The associations remained significant when the analyses were adjusted for health-related covariates (Model 3) and BMI (Model 4) (Figure 2a).

After adjusting walking pace for sociodemographic factors (Model 1, Figure 2b), the highest risk of all-cause mortality was found in individuals with a slow walking pace (HR: 2.29 [95% CI: 2.06 to 2.54)]); when this association was adjusted for lifestyle factors and health-related variables (model 2 and 3), this association attenuated to 1.97-times (95% CI: 1.77 to 2.20) and 1.92-times (95% CI: 1.72 to 2.14) higher risk, respectively. With adjusting this association for all covariates, the mortality risk rose to 2-times (HR: 1.99 [95% CI:1.78 to 2.23) higher risk. Following this, individuals with lower grip strength experienced 1.57-times

(95% CI: 1.39 to 1.77) higher risk than their counterparts (Model 1, Figure 2b), and after adjusting this association for health-related and adiposity covariates, the risk was reduced to 46% (HR: 1.46 [95% CI: 1.29 to 1.65]) but remained statistically significant (Model 4, Figure 2b). A similar magnitude of associations was identified for these categories and the two outcomes when a 2-year landmark was applied to the analyses (Supplementary Table 2).

Compared to individuals with both normal grip and average/brisk walking pace, individuals with both low grip and slow walking pace had the highest risk of stroke mortality (HR: 2.86 [95% CI: 1.93 to 4.22]), followed by those with a normal grip and slow walking pace (HR: 1.96 [95% CI: 1.38 to 2.78)] and those with low grip but normal walking pace (HR: 1.89 [95% CI: 1.22 to 2.94]) (Model 4, Table 2). Participants with a low grip and slow walking pace also had the highest all-cause mortality risk (HR: 2.31 [95% CI: 1.97 to 2.70)] than the reference group (model 4, Table 2). When the 2-year landmark analysis was carried out, the associations were attenuated, but remained significant (Supplementary Table 3).

Finally, e-values measuring unmeasured confounders for the individual and combined associations are available in Supplementary Tables 4 and 5. The e-values ranged from 1.82 to 5.17. Hence, it is unlikely that unmeasured confounders would be very strong to attenuate the result since this confounder needs to have, for instance, a HR of 5.17 with the exposure and the outcome to attenuate the association.

Discussion

The main findings of this study highlighted that stroke survivors with a slow walking pace and low grip strength had a higher risk of all-cause and stroke mortality compared to individuals in the highest category of each exposure. The strongest association was seen in individuals with a slow walking pace and, when the two exposures were pooled together, in those with low grip strength and slow walking pace. These associations were kept when we ran a 2-year landmark analysis excluding people who died from possible severe stroke cases from the analyses. Considering gait impairment and low grip strength are among the main issues among stroke survivors, exploring the associations of these markers with mortality in this population provides meaningful information regarding the potential role of these markers during the survival follow-up.

Although associations between grip strength and walking pace and both all-cause and stroke mortality have been previously reported both in middle-aged and older populations, as well as in men and women,[23,31,34-40] studies on stroke survivors are usually clinical trials[13-17] rather than large prospective studies as it is the case of our work. One observational study stated that impairments in lower contralesional hand-grip strength resulting from stroke had not shown any improvement in 2 years of follow-up compared to the control group; however, in that study, the target population was not large enough, with only 10 participants remaining at the end of the investigation.[18] Regarding experimental studies, Alexander et al.[41] reported that rehabilitation interventions could improve grip strength in stroke survivors. However, the literature regarding the role of physical activity in this population has been inconclusive.[13-17] For instance, Saunders et al. highlighted that even if cardiorespiratory fitness training (especially walking) can improve fitness, balance and waking pace after stroke, the evidence came from moderate to low-quality studies.[17] Consequently, further well-designed control trials are still needed to determine the range of benefits of physical activity and, therefore, physical capability markers.[17]

The American Stroke Association advised stroke survivors to engage in muscle-strengthening and aerobic activities (low to moderate).[42] However, stroke survivors may suffer from residual disabilities caused by the stroke.[42] In chronic stroke patients, for example, severe impairments in movement coordination and precision of arm and joint kinematics have been reported,[43] and when compared to age-matched control subjects using the same arm, the ipsilesional arm performed significantly worse.[44] Also, a stroke might affect the symmetry, regularity, and stability of hemiparetic movement.[45] According to Fayaz et al., balance problems are observed in about half of the stroke patients.[46] Moreover, it has been argued that slow gait velocity can be due to a reduction in aerobic endurance and leg strength in chronic stroke patients. Rehabilitation programmes have been one of the key solutions.[47] However, fewer than 30% of stroke survivors will undertake the physical activity recommendations.[48] A study reported that among the main barriers to not achieving this recommendation are the self-perception of being 'too tired' or the belief that their health status is 'too poor'; therefore, physical activity might damage their health.[48] In this regard, their health status and belief remain among the challenges to improving stroke survivors' quality of life.

Limitations

There are some limitations to this research that should be considered. Firstly, although many confounding factors were included in our models, unmeasured or residual confounders could still partially influence our findings. However, our e-value analyses provided evidence that it is unlikely that these would be very strong enough to nullify the results (HR: 1.82 to 5.17; Supplementary Tables 4 and 5). Moreover, information regarding stroke severity was unavailable; therefore, we could not look at survival rates by stroke severity. We tried to avoid such potential limitations using a 2-year landmark analysis excluding people who died during this period. Secondly, there is a risk of bias in self-reported data for walking pace. Previous studies have shown that although this variable was self-reported, it has a robust mortality prediction compared to other traditional risk factors.[26] Thirdly, even though the grip strength and walking pace categories showed a statistically significant association with the outcomes, wider CIs in the stroke mortality analyses may be attributable to the low number of events available in these categories. Fourthly, the majority of included participants had a white background; therefore, we did not conduct specific analyses by ethnicity due to the small number of participants in the non-white category (315, representing only 4.2% of the total included population). In this context, generalising the summary statistics finding has some limitations, as the prevalence of morbidities, lifestyle factors, and sociodemographic factors are not representative of the UK population. However, the effect size is generalisable.[49] Future studies should investigate stroke severity and the effect on the variables assessed in the present study. Finally, the observational nature of our study does not allow us to infer causality from the results.

Conclusion

In conclusion, stroke survivors with a slow walking pace and low grip strength had a higher risk of dying due to stroke or for any cause. Among these exposures, the highest risk was identified in individuals with both low grip strength and a slow walking pace. Considering these exposures have been recognised among the main issues in stroke survivors, further public health policies should be put in place to improve muscle strength and physical performance across the stroke population.

Perspective

While the association of low grip strength and/or slow walking pace with cardiovascular and all-cause mortality in the general population is well established, data on the association between these factors and health outcomes in stroke survivors has been less established. Our results highlighted that low grip strength and slow walking pace were associated with a higher risk of stroke and all-cause mortality in stroke survivors. Exploring these markers' associations with mortality in this population provides meaningful information regarding the potential role of these markers during the survival follow-up.

References

1. Zhang Y, Chapman AM, Plested M, Jackson D, Purroy F. The Incidence, Prevalence, and Mortality of Stroke in France, Germany, Italy, Spain, the UK, and the US: A Literature Review. *Stroke Res Treat.* 2012;2012:436125.
2. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet.* 2014;383(9913):245-254.
3. Rowe FJ, Wright D, Brand D, et al. A prospective profile of visual field loss following stroke: prevalence, type, rehabilitation, and outcome. *Biomed Res Int.* 2013;2013:719096.
4. King D, Wittenberg R, Patel A, Quayyum Z, Berdunov V, Knapp M. The future incidence, prevalence and costs of stroke in the UK. *Age Ageing.* 2020;49(2):277-282.
5. Patel A, Berdunov V, Quayyum Z, King D, Knapp M, Wittenberg R. Estimated societal costs of stroke in the UK based on a discrete event simulation. *Age Ageing.* 2020;49(2):270-276.
6. Goldstein LB, Adams R, Becker K, et al. Primary prevention of ischemic stroke: A statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke.* 2001;32(1):280-299.
7. Tuomilehto J, Rastenyte D, Jousilahti P, Sarti C, Vartiainen E. Diabetes mellitus as a risk factor for death from stroke. Prospective study of the middle-aged Finnish population. *Stroke.* 1996;27(2):210-215.
8. Synhaeve NE, van Alebeek ME, Arntz RM, et al. Kidney Dysfunction Increases Mortality and Incident Events after Young Stroke: The FUTURE Study. *Cerebrovasc Dis.* 2016;42(3-4):224-231.
9. Boehme AK, Esenwa C, Elkind MS. Stroke risk factors, genetics, and prevention. *Circulation research.* 2017;120(3):472-495.
10. Kubota Y, Iso H, Yamagishi K, Sawada N, Tsugane S, Group JS. Daily Total Physical Activity and Incident Stroke: The Japan Public Health Center-Based Prospective Study. *Stroke.* 2017;48(7):1730-1736.
11. Elbaz A, Sabia S, Brunner E, et al. Association of walking speed in late midlife with mortality: results from the Whitehall II cohort study. *Age (Dordr).* 2013;35(3):943-952.
12. Cooper R, Kuh D, Hardy R, Mortality Review G, Falcon, Teams HAS. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. *BMJ.* 2010;341:c4467.
13. Zimbelman J, Daly JJ, Roenigk KL, Butler K, Burdsall R, Holcomb JP. Capability of 2 gait measures for detecting response to gait training in stroke survivors: Gait Assessment and Intervention Tool and the Tinetti Gait Scale. *Arch Phys Med Rehabil.* 2012;93(1):129-136.
14. Saltychev M, Sjögren T, Bärlund E, Laimi K, Paltamaa J. Do aerobic exercises really improve aerobic capacity of stroke survivors? A systematic review and meta-analysis. *Eur J Phys Rehabil Med.* 2016;52(2):233-243.
15. Durand MJ, Boerger TF, Nguyen JN, et al. Two weeks of ischemic conditioning improves walking speed and reduces neuromuscular fatigability in chronic stroke survivors. *J Appl Physiol (1985).* 2019;126(3):755-763.
16. Langhammer B, Lindmark B, Stanghelle JK. Physiotherapy and physical functioning post-stroke: exercise habits and functioning 4 years later? Long-term follow-up after a 1-year long-term intervention period: a randomised controlled trial. *Brain Inj.* 2014;28(11):1396-1405.
17. Saunders D, Sanderson M, Hayes S, et al. Physical fitness training for stroke patients. *Cochrane Database of Systematic Reviews.* 2020;3.
18. Schimmel M, Leemann B, Schnider A, Herrmann FR, Kiliaridis S, Muller F. Changes in oro-facial function and hand-grip strength during a 2-year observation period after stroke. *Clin Oral Investig.* 2013;17(3):867-876.

19. Dhamoon MS, Sciacca RR, Rundek T, Sacco RL, Elkind MS. Recurrent stroke and cardiac risks after first ischemic stroke: the Northern Manhattan Study. *Neurology.* 2006;66(5):641-646.
20. Feng W, Hendry RM, Adams RJ. Risk of recurrent stroke, myocardial infarction, or death in hospitalised stroke patients. *Neurology.* 2010;74(7):588-593.
21. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. *Stroke.* 1994;25(2):333-337.
22. Nofuji Y, Shinkai S, Taniguchi Y, et al. Associations of Walking Speed, Grip Strength, and Standing Balance With Total and Cause-Specific Mortality in a General Population of Japanese Elders. *J Am Med Dir Assoc.* 2016;17(2):184 e181-187.
23. Sasaki H, Kasagi F, Yamada M, Fujita S. Grip strength predicts cause-specific mortality in middle-aged and elderly persons. *Am J Med.* 2007;120(4):337-342.
24. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* 2015;12(3):e1001779.
25. Collins R. What makes UK Biobank special? *Lancet.* 2012;379(9822):1173-1174.
26. Ganna A, Ingelsson E. 5 year mortality predictors in 498 103 UK Biobank participants: a prospective population-based study. *The Lancet.* 2015;386(9993):533-540.
27. Syddall HE, Westbury LD, Cooper C, Sayer AA. Self-reported walking speed: a useful marker of physical performance among community-dwelling older people? *J Am Med Dir Assoc.* 2015;16(4):323-328.
28. Alley DE, Shardell MD, Peters KW, et al. Grip strength cutpoints for the identification of clinically relevant weakness. *J Gerontol A Biol Sci Med Sci.* 2014;69(5):559-566.
29. Phillimore P, Beattie A, Townsend P. Widening inequality of health in northern England, 1981-91. *BMJ.* 1994;308(6937):1125-1128.
30. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet.* 2012;380(9836):37-43.
31. Steell L, Ho FK, Sillars A, et al. Dose-response associations of cardiorespiratory fitness with all-cause mortality and incidence and mortality of cancer and cardiovascular and respiratory diseases: the UK Biobank cohort study. *Br J Sports Med.* 2019;53(21):1371-1378.
32. Blum MR, Tan YJ, Ioannidis JPA. Use of E-values for addressing confounding in observational studies—an empirical assessment of the literature. *International Journal of Epidemiology.* 2020;49(5):1482-1494.
33. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-Value to Assess the Potential Effect of Unmeasured Confounding in Observational Studies. *JAMA.* 2019;321(6):602-603.
34. Shimizu M, Misumi M, Yamada M, Ohishi W, Yamamoto H, Kihara Y. Choice reaction time and grip strength as predictors of cardiovascular mortality in middle-aged and elderly Japanese: from the Radiation Effects Research Foundation Adult Health study. *Intern Med J.* 2018;48(11):1331-1336.
35. Chua KY, Lim WS, Lin X, Yuan JM, Koh WP. Hand-grip Strength and Timed Up-and-Go (TUG) Test are Predictors of Short-Term Mortality among Elderly in a Population-Based Cohort in Singapore. *J Nutr Health Aging.* 2020;24(4):371-378.
36. Bohannon RW. Grip Strength: An Indispensable Biomarker For Older Adults. *Clin Interv Aging.* 2019;14:1681-1691.
37. Abizanda P, Navarro JL, Garcia-Tomas MI, Lopez-Jimenez E, Martinez-Sanchez E, Paterna G. Validity and usefulness of hand-held dynamometry for measuring muscle strength in community-dwelling older persons. *Arch Gerontol Geriatr.* 2012;54(1):21-27.
38. Cai Y, Liu L, Wang J, Gao Y, Guo Z, Ping Z. Linear association between grip strength and all-cause mortality among the elderly: results from the SHARE study. *Aging Clin Exp Res.* 2021;33(4):933-941.

39. Celis-Morales CA, Gray S, Petermann F, et al. Walking Pace Is Associated with Lower Risk of All-Cause and Cause-Specific Mortality. *Med Sci Sports Exerc.* 2019;51(3):472-480.
40. Argyridou S, Zaccardi F, Davies MJ, Khunti K, Yates T. Walking pace improves all-cause and cardiovascular mortality risk prediction: A UK Biobank prognostic study. *Eur J Prev Cardiol.* 2020;27(10):1036-1044.
41. Remsik AB, Gjini K, Williams L, Jr., et al. Ipsilesional Mu Rhythm Desynchronization Correlates With Improvements in Affected Hand Grip Strength and Functional Connectivity in Sensorimotor Cortices Following BCI-FES Intervention for Upper Extremity in Stroke Survivors. *Front Hum Neurosci.* 2021;15:725645.
42. Billinger SA, Arena R, Bernhardt J, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2014;45(8):2532-2553.
43. Woytowicz EJ, Rietschel JC, Goodman RN, et al. Determining Levels of Upper Extremity Movement Impairment by Applying a Cluster Analysis to the Fugl-Meyer Assessment of the Upper Extremity in Chronic Stroke. *Arch Phys Med Rehabil.* 2017;98(3):456-462.
44. Maenza C, Good DC, Winstein CJ, Wagstaff DA, Sainburg RL. Functional Deficits in the Less-Impaired Arm of Stroke Survivors Depend on Hemisphere of Damage and Extent of Paretic Arm Impairment. *Neurorehabil Neural Repair.* 2020;34(1):39-50.
45. Li M, Tian S, Sun L, Chen X. Gait Analysis for Post-Stroke Hemiparetic Patient by Multi-Features Fusion Method. *Sensors (Basel).* 2019;19(7).
46. Khan F, Chevidikunnan MF. Prevalence of Balance Impairment and Factors Associated with Balance among Patients with Stroke. A Cross Sectional Retrospective Case Control Study. *Healthcare (Basel).* 2021;9(3).
47. Taylor-Piliae RE, Latt LD, Hepworth JT, Coull BM. Predictors of gait velocity among community-dwelling stroke survivors. *Gait Posture.* 2012;35(3):395-399.
48. Nicholson SL, Greig CA, Sniehotta F, et al. Quantitative data analysis of perceived barriers and motivators to physical activity in stroke survivors. *J R Coll Physicians Edinb.* 2017;47(3):231-236.
49. Batty GD, Gale CR, Kivimäki M, Deary IJ, Bell S. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. *BMJ.* 2020;368:m131.

Table 1 – cohort characteristics by physical activity, grip strength and walking pace.

	Total stroke survivors	Grip strength		Walking pace	
		Normal	Low	Average/brisk	Slow
Total number	7,486	5,678	1,275	5,166	1,787
Age (years), mean (SD)	61.0 (6.6)	61.7 (6.2)	60.8 (6.7)	60.9 (6.8)	61.3 (6.3)
Sex (female), n (%)	3,172 (42.4)	2,419 (39.7)	753 (54.0)	2,339 (42.5)	833 (41.9)
Ethnicity, n (%)					
White	7,171 (95.8)	5,876 (96.4)	1,295 (92.9)	5,294 (96.2)	1,877 (94.5)
South Asian	132 (1.8)	75 (1.2)	57 (4.1)	91 (1.6)	41 (2.1)
Black	104 (1.4)	84 (1.4)	20 (1.4)	64 (1.7)	40 (2.0)
Chinese	8 (0.1)	8 (0.1)	0.00 (0.00)	7 (0.1)	1 (0.0)
Other	71 (0.9)	49 (0.8)	22 (1.6)	44 (0.8)	27 (1.4)
Smoke, n (%)					
Never	3,170 (42.3)	2,594 (42.6)	576 (41.3)	2,536 (46.1)	634 (31.9)
Previous	3,227 (43.1)	2,643 (43.4)	584 (41.9)	2,341 (42.6)	886 (44.6)
Current	1,089 (14.6)	855 (14.0)	234 (16.8)	623 (11.3)	466 (23.5)
Deprivation, n (%)					
Lower	2,085 (27.8)	1,798 (29.5)	287 (20.6)	1,726 (31.4)	359 (18.1)
Middle	2,341 (31.3)	1,956 (32.1)	385 (27.6)	1,830 (33.3)	511 (25.7)
Higher	3,060 (40.9)	2,338 (38.4)	722 (51.8)	1,944 (35.3)	1,116 (56.2)
Sleep time, n (%)					
Normal 7-9 h/day	4,989 (66.4)	4,174 (68.5)	815 (58.5)	3,884 (70.6)	1,105 (55.6)
Short sleep <7 h/day	2,124 (28.4)	1,665 (27.3)	459 (32.9)	1,453 (26.4)	671 (33.8)
Long sleep >9 h/day	373 (5.0)	253 (4.1)	120 (8.6)	163 (3.0)	210 (10.6)
Morbidity count, n (%)					
0	1,087 (14.5)	967 (15.9)	120 (8.6)	975 (17.7)	112 (5.6)
≥ 1	6,399 (85.5)	5,125 (84.1)	1,274 (91.4)	4,525 (82.3)	1,874 (94.4)
Alcohol intake frequency, n (%)					
Daily or almost daily	2,074 (27.7)	1,513 (24.8)	561 (40.2)	1,284 (23.3)	790 (39.8)
3–4 times a week	2,557 (34.2)	2,090 (34.3)	467 (33.5)	1,923 (35.0)	634 (31.9)
Once or twice a week	2,855 (38.1)	2,489 (40.9)	366 (26.7)	2,293 (41.7)	562 (28.3)
BMI (kg/m^2), mean (SD)	28.8 (5.0)	28.7 (4.9)	29.2 (5.5)	28.1 (4.5)	30.7 (5.9)
BMI categories, n (%)					
Underweight (<18.5 kg/ m 2)	28 (0.4)	19 (0.3)	9 (0.6)	16 (0.3)	12 (0.6)
Normal weight (18.5–24.9 kg/m 2)	1,650 (22.0)	1,363 (22.8)	287 (20.6)	1,362 (24.8)	288 (14.5)
Overweight (25.0–29.9 kg/m2)	3,186 (42.6)	2,626 (43.1)	560 (40.2)	2,487 (45.2)	699 (35.2)
Obese (≥30.0 kg/m2)	2,622 (35.0)	2,084 (34.2)	538 (38.6)	1,635 (29.7)	987 (49.7)
Systolic BP (mm Hg), mean (SD)	139.8 (18.8)	138.0 (18.4)	140.2 (18.8)	140.1 (18.5)	139.1 (19.7)
Red meat, (times/week), mean (SD)	2.2 (1.5)	2.3 (1.7)	2.2 (1.5)	2.2 (1.5)	2.3 (1.7)
Processed meat, (times/week),	2.0 (1.1)	1.9 (1.1)	2.0 (1.1)	1.9 (1.1)	2.1 (1.1)

mean (SD)					
Fruit and vegetable, (grams/day) mean (SD)	330.7 (216.5)	329.8 (211.3)	330.9 (217.7)	337.8 (212.8)	310.8 (225.3)
Sedentary behaviour (h/day), mean (SD)	5.4 (2.5)	5.4 (2.7)	5.4 (2.4)	5.3 (2.3)	5.9 (3.0)
Education status, (%)					
None of the options	3,312 (44.2)	2,545 (41.8)	767 (55.0)	2,182 (39.7)	1,130 (56.9)
CSEs	322 (4.3)	264 (4.3)	58 (4.7)	251 (4.6)	71 (3.6)
0-levels	1,547 (20.7)	1,284 (21.1)	263 (18.9)	1,184 (21.5)	363 (18.3)
A-levels	677 (9.0)	565 (9.3)	112 (8.0)	524 (9.5)	153 (7.7)
College/ University degree	1,628 (21.8)	1,434 (23.5)	194 (13.9)	1,359 (24.7)	269 (13.5)

Continuous variables are presented as mean (SD); categorical variables are presented as n (%). SD indicates standard deviation; n, total number; h/day, hours per day; BMI, body mass index; CSE, Certificate of Secondary Education; BP, blood pressure. Low grip strength was defined as ≤16 kg in women and ≤26 kg in men using the National Institute of Health cut-off points. Slow walking pace was self-reported using a questionnaire about the regular walking pace.

Table 2. Associations between grip strength and walking pace categories and mortality due to stroke and all-cause

Models	**Normal grip and average/brisk walking pace**		**Normal grip and slow walking pace**			**Low grip and average/brisk walking pace**			**Low grip and slow walking pace**		
Stroke mortality	**Events/Total participants**	**HR (95% CI)**	**Events/Total participants**	**HR (95% CI)**	**p-value**	**Events/Total participants**	**HR (95% CI)**	**p-value**	**Events/Total participants**	**HR (95% CI)**	**p-value**
Model 1	98/4,813	1.00 (Ref.)	56/1,279	2.07 (1.48; 2.89)	<0.001	26/687	1.92 (1.24; 2.98)	0.003	42/707	2.99 (2.06; 4.34)	<0.001
Model 2	98/4,813	1.00 (Ref.)	56/1,279	1.84 (1.31; 2.60)	<0.001	26/687	1.88 (1.21; 2.92)	0.005	42/707	2.70 (1.83; 3.97)	<0.001
Model 3	98/4,813	1.00 (Ref.)	56/1,279	1.83 (1.30; 2.59)	0.001	26/687	1.90 (1.22; 2.95)	0.004	42/707	2.74 (1.85; 4.05)	<0.001
Model 4	98/4,813	1.00 (Ref.)	56/1,279	1.96 (1.38; 2.78)	<0.001	26/687	1.89 (1.22; 2.94)	0.005	42/707	2.86 (1.93; 4.22)	<0.001
All-cause mortality											
Model 1	694/4,813	1.00 (Ref.)	420/1,279	2.31 (2.04; 2.61)	<0.001	133/687	1.43 (1.19; 1.73)	<0.001	243/707	2.64 (2.27; 3.07)	<0.001
Model 2	694/4,813	1.00 (Ref.)	420/1,279	1.98 (1.74; 2.25)	<0.001	133/687	1.40 (1.16; 1.69)	<0.001	243/707	2.28 (1.95; 2.66)	<0.001
Model 3	694/4,813	1.00 (Ref.)	420/1,279	1.92 (1.69; 2.18)	<0.001	133/687	1.40 (1.16; 1.68)	0.001	243/707	2.24 (1.91; 2.61)	<0.001
Model 4	694/4,813	1.00 (Ref.)	420/1,279	2.00 (1.75; 2.27)	<0.001	133/687	1.39 (1.15; 1.68)	0.001	243/707	2.31 (1.97; 2.70)	<0.001

Data presented as hazard rations and their 95% CI. Normal grip and average-brisk pace categories were defined as the reference group. Models 1 was adjusted for Model 1 featured sociodemographic covariates (sex, age, deprivation status, professional qualification, and ethnicity). Model 2, as per model 1, but also included lifestyle factors (fruit and vegetable, red meat, and processed meat, alcohol consumption, smoking status, sedentary behaviour, and sleep-time). Model 3, as per model 2, but also included health-related variables (systolic blood pressure, and history of morbidities). Model 4, as per model 3, but additionally included BMI. Low grip strength was defined as ≤16 kg in women and ≤26 kg in men using the National Institute of Health cut-off points. Slow walking pace was self-reported using a questionnaire about the regular walking pace.

Figure 1. Diagram of sample selection

Figure 2. Associations of walking pace and grip strength with mortality due to stroke and all-cause mortality. Data presented as adjusted HR and their 95% confidence interval. Average/brisk pace and normal grip were treated as the reference categories. Analysis were adjusted for sociodemographic covariates (model 1), lifestyle factors (model 2), health-related variables (model 3) and BMI (model 4). Low grip strength was defined as ≤16 kg in women and ≤26 kg in men using the National Institute of Health cut-off points. Slow walking pace was self-reported using a questionnaire about the regular walking pace.