Joint association of genetic risk and accelerometer-based step count with cardiovascular disease: a UK-Biobank cohort study

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Abstract

Aims

This population-based prospective cohort study investigated whether accelerometer-measured step count is associated with incident cardiovascular disease (CVD), independently from genetic risk.

Methods

The study included UK Biobank participants with valid accelerometer and genetic data and without prevalent CVD at baseline. Genetic risk for CVD was categorised as low (1st fifth), moderate (2nd-4th fifths), and high (5th fifth). Median daily step count was categorised as low (<6,500), moderate (6,500-12,499), and high (≥12,500). The association of genetic risk and step count with incident CVD, defined as a composite of coronary artery disease and ischaemic stroke, was examined using adjusted Cox proportional hazards models.

Results

Of 84,286 participants, 4,847 developed CVD during follow-up (median 7.9 years). High genetic risk and low step count were independently associated with higher risk of CVD, with no evidence of a multiplicative interaction (*P* for interaction = 0.46). Compared with the reference group (low genetic risk and high step count; absolute risk: 62 per 1,000), the highest risk of CVD was observed in participants with high genetic risk and low step count (hazard ratio: 2.81, 95% confidence interval: 2.27-3.46, $p < 0.0001$; absolute risk: 174 per 1,000). There was an inverse dose-response association between the hazard of CVD and step counts up to 10,000 steps/day, which then plateaued in moderate and high genetic risk groups.

Conclusions

High daily step count was associated with lower CVD risk in individuals with moderate and high genetic risk, indicating that walking should be encouraged for all, especially those predisposed to CVD.

Lay summary

This study found that walking more each day is linked to a lower risk of developing heart disease and stroke, especially for people with a higher inherited risk of these conditions.

- People with moderate or high inherited risk who took fewer than 6,500 steps per day were much more likely to develop heart disease or stroke than those who took 12,500 or more steps daily.
- The benefits of walking increased with more steps participants took up to about 10,000 steps per day, after which the risk levelled off in those at moderate or high inherited risk.

Keywords: cardiovascular disease, physical activity, accelerometry, genetic predisposition, polygenic risk score

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality globally, with an increasing prevalence due to the aging population, increasing prevalence of obesity and diabetes and changing dietary patterns.[1] Various modifiable and non-modifiable risk factors have been associated with higher risk of CVD. Multiple genetic variants conferring predisposition to CVD have been found and summarised into polygenic risk scores (PRS), which can be used to identify individuals at higher risk of CVD for primary prevention purposes.[2,3] Among modifiable risk factors, the role of physical activity has also been well established through large cohort studies, which indicate an inverse dose-response association between physical activity and CVD incidence.[4,5] Due to the complex gene-environment interactions and their impact on disease development, it is important to consider both genetic predisposition and physical activity on CVD risk.[6]

However, studies investigating the joint association of genetic and lifestyle factors with incident CVD are limited. Most studies rely on self-reported physical activity,[7–13] which is prone to recall and social desirability bias.[14,15] Recent studies using wearable devices, which

measure physical activity levels more accurately than self-report, have investigated activity intensity levels, such as light, moderate or vigorous, which are often difficult to interpret or use to develop guidance for the public.[16,17]

A more intuitive measure of physical activity is the number of steps a person takes daily, which is readily available on mobile phones and commercial wearable devices. There is accumulating evidence for a non-linear inverse dose-response association between step counts and cardiovascular outcomes, which could be translated into actionable public health policies recommending a minimum number of steps per day for optimal health.[18,19] However, no studies have explored whether objectively measured step count can modify the association between genetic risk and cardiovascular incidence. We therefore aimed to investigate whether accelerometer-measured step count was associated with the incidence of CVD independently from genetic risk.

Methods

Study population

The UK Biobank (UKB) is a prospective cohort of over 500,000 individuals aged 40-69 years living in England, Scotland, and Wales at the time of recruitment, from 2006 to 2010.[20] The UKB received ethical approval from the North West Multi-centre Research Ethics Committee (16/NW/0274), and all participants provided written informed consent before taking part. Upon enrolment in the study, participants completed a touchscreen questionnaire, underwent verbal interviews, had physical measurements, and provided blood samples for biochemical and genetic analysis. From 1st June 2013 to 31st December 2015, participants with an email address were invited to participate in an accelerometer study, during which they were required to wear an Axivity AX3 triaxial accelerometer on their dominant wrist for seven days.[21]

Genetic risk

The standard CVD PRS in the UKB was used as a marker of genetic susceptibility to CVD, and its development is described in detail elsewhere.[22] In summary, UKB participants were genotyped using a custom Axiom array of 825,927 genetic variants, followed by genome-wide imputation to approximately 96 million variants using the Haplotype Reference Consortium and the UK10k/1000 Genomes reference panels. The standard PRS for CVD was then constructed by performing fixed-effect inverse variance meta-analysis of external summary statistics from the three largest genome-wide association studies of CVD.[22] We used a raw PRS value that was calculated for each UKB participant as the genome-wide sum of the per-variant posterior effect size multiplied by allele dosage, and then a corrected PRS

value was generated by centering and variance-standardising the PRS to achieve a standard normal distribution with zero mean and unit variance, while accounting for an individual's inferred genetic ancestry group.[22] In the UKB, this PRS demonstrated modest discrimination for incident CVD, with the area under the receiver operating characteristic curve (AUC) ranging from 0.534 to 0.591 across ancestry groups, with the highest discrimination observed in participants with European ancestry.[22] The PRS distribution was divided into fifths, categorising participants into low (1st fifth), moderate (2nd-4th fifths), or high (5th fifth) genetic risk groups, similar to other studies.[7,23]

Median daily step count

To measure step count from raw accelerometer data, a hybrid self-supervised machine learning and peak detection algorithm (github.com/OxWearables/stepcount, version 3.7.0) was used, where an activity classification model first detected periods of walking and non-walking, followed by step counting only on predicted walking data periods.[24] This was validated against reference video measurements.

Participants were excluded if they did not have sufficient wear time, defined as ≥3 days of data with coverage in every one-hour period of the 24-hour cycle. Non-wear time was defined as unbroken periods of ≥90 minutes during which the standard deviation (SD) of acceleration on each axis was <13 mg. To address potential diurnal bias in wear time, recording interruptions and non-wear periods were imputed using the average value for the corresponding minute of the day across the remaining valid days.[25] Overall daily step count was reported as median number of steps taken across the seven-day measurement window and was used as marker of physical activity. After excluding participants with insufficient wear time, further exclusions were made if the device could not be calibrated, more than 1% of readings exceeded the device's dynamic range (±2 *g*; 'clipped' readings) before or after calibration, average acceleration was implausibly high (>100 mg), or step count could not be estimated or was implausibly low (<50 steps/day), in line with previous studies.[24,26]

To ensure adequate group sizes and improve the interpretability of our results, median daily step count was first divided into quintiles and subsequently collapsed into three categories. Cut-points were rounded to the nearest 500 steps, resulting in low (quintile 1; <6,500 steps/day), moderate (quintiles 2-4; 6,500-12,500 steps/day), and high (quintile 5; >12,500 steps/day) step count groups (Supplementary Figure 1). This approach was adopted because there are currently no universally accepted cut-points for device-measured step count, as existing public health guidelines are predominantly based on self-reported data.[18] The median daily step count was also explored as a continuous variable using restricted cubic spline models with knots placed at the 10th, 50th, and 90th percentiles of the step count distribution, as the association with CVD was not linear.

Covariates

Potential confounders and mediators were selected a priori using a causal diagram based on the current literature (Supplementary Figure 2). The following demographic, socioeconomic, and lifestyle factors were treated as confounders and derived from self-report or accelerometry (Supplementary Table 1): age at time of accelerometer wear, sex, ethnicity, educational attainment, employment status, Townsend Deprivation Index (TDI), country of residence, smoking status, alcohol consumption, red or processed meat consumption, fish consumption, fruit and vegetable consumption, salt intake, sleep duration, family history of CVD, and season of accelerometer wear. The following adiposity and cardiometabolic factors were considered potential mediators and derived from physical measurements, blood samples, or self-report (Supplementary Table 1): body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), hypercholesterolaemia, diabetes, and hypertension.

Outcomes

The primary outcome was the incidence of non-fatal and fatal CVD, defined as a composite of coronary artery disease (CAD) and ischaemic stroke (IS), ascertained through linkage with electronic hospital inpatient records and mortality registers using a combination of diagnosis and procedure codes. The International Classification of Diseases (ICD-9 and ICD-10) was used for coding of hospital diagnoses and causes of death, while the UK Office of Population Censuses and Surveys Classification of Interventions and Procedures (OPCS-4) was used for surgical operations (Supplementary Table 2). The follow-up period started at the end of each individual's 7-day accelerometer wear period and ended on 31st October 2022 for participants in England, on 31st August 2022 for those in Scotland, and on 31st May 2022 for those in Wales. Participants were censored at the time of first CVD event, non-CVD death, loss to follow-up, or at the end of the follow-up period, whichever occurred first.

Statistical analysis

Summary statistics were presented as frequencies and proportions for categorical variables, mean and SD for continuous normally distributed variables, and median and interquartile range (IQR) for continuous not normally distributed variables. Baseline characteristics were compared between excluded and included participants using the chi-square test of association for categorical and the F-test from a linear regression model for continuous variables.

Multivariable cause-specific Cox proportional hazards models were employed to examine the independent associations of step count and PRS with incident CVD, using age as the timescale consistent with previous studies.[27] The proportional hazards assumption was assessed using Schoenfeld residuals and log(-log) survival plots. Minor departures were

observed for sex and family history of CVD (Supplementary Figure 3), while all other covariates satisfied the assumption.

Sequential adjustments for potential confounders were performed in the following order: 1) age + sex + ethnicity; 2) + socioeconomic factors (educational attainment, employment status, TDI, and country of residence); 3) + lifestyle factors (smoking status, alcohol consumption, red or processed meat consumption, fish consumption, fruit and vegetable consumption, salt intake, and sleep duration); 4) + family history of CVD; 5) + season of accelerometer wear; 6) + PRS or step count (depending on the exposure). Maximally adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were reported in the main text. In addition to the maximally adjusted model, we also ran models with each potential mediator added sequentially to examine their impact on the HRs: BMI, SBP, DBP, hypercholesterolaemia, diabetes, and hypertension. These results are descriptive and should not be interpreted as formal evidence of mediation.

Participants were stratified into nine mutually exclusive groups based on their PRS and median daily step count to explore their combined effects on incident CVD. Those with low genetic risk and high step count (ideal scenario) served as the reference, in keeping with other studies.[7,28] To formally test for an interaction, we performed a likelihood ratio (LR) test comparing the maximally adjusted model with and without an interaction term between genetic risk and step count.

In addition to HRs, we estimated individual-level absolute 8-year risk of CVD from the maximally adjusted Cox model. Absolute risk was summarised per 1,000 participants for each PRS x step count combination, as well as for PRS and step count groups separately.

Three sensitivity analyses were conducted. The first excluded individuals with less than two and less than four years of follow-up to assess potential reverse causality, as these individuals could have subclinical CVD at the time of the accelerometer study that affected their step counts. A second sensitivity analysis was performed in which participants were sequentially excluded for pre-existing chronic conditions that could have limited their ability to walk during accelerometer wear. Exclusions were applied in the following order: hospital-recorded cancer, CVD (except CAD and IS), chronic lower respiratory disease, chronic neurological disease, musculoskeletal or connective tissue disorder, abnormal gait or mobility, and self-reported long-standing illness or disability (Supplementary Tables 1 and 2). A third sensitivity analysis explored the associations of genetic risk and step count with the two components of CVD, CAD and IS, separately.

Participants with missing values on exposures or covariates, as well as those with prevalent CVD at the time of accelerometer wear, were excluded. All analyses were conducted as

complete-case analyses. All statistical tests were two-sided and a p-value of <0.05 was considered statistically significant. Datasets were processed in R version 4.3.1 and statistical analyses were performed in STATA 18.0. The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[29]

Results

Baseline characteristics

Of the 103,664 participants with accelerometer data, 7,667 (7.4%) were excluded due to poor accelerometer data quality, 2,326 (2.2%) due to lack of genetic data, 6,789 (6.5%) due to prevalent CVD and 2,596 (2.5%) due to missing data in covariates, leaving 84,286 individuals in the analysis (Figure 1). Participants excluded from the final analytic sample were older and more likely to be male, non-white, and unemployed or retired, with lower levels of education and wealth. They were also more likely to be previous or current smokers, abstain from alcohol, and have a poorer diet. Finally, excluded participants were more likely to have a family history of CVD, as well as prevalent diabetes and hypertension, and had higher BMI and SBP (Supplementary Table 3).

Median age at the time of accelerometer wear was 63 years (IQR 56-68), 58.1% (n=48,994) of participants were women and 97.1% (n=81,826) were of white ethnicity. Participants had high socioeconomic status, with high proportion of university educated (44.6%, n=37,563) and employed individuals (63.5%, n=53,562) and low levels of deprivation (least deprived 50.9%, n=42,929). There were significant differences across step count groups for all baseline characteristics (Table 1). Participants in the low step count group were older, less well educated, consumed more red meat and salt and less fish, fruit, and vegetables, and there was higher proportion of smokers, people with diabetes, hypercholesterolaemia, and hypertension, compared to the high step count group. The median daily step count was 9,134 steps (IQR 6,910-11,749), with no significant differences between genetic risk groups (p=0.099) (Supplementary Table 4).

During a median follow-up of 7.9 years (IQR 7.3-8.4) (total = 644,621 person-years), 4,847 participants (5.8%) experienced a cardiovascular event, 3,746 (77.3%) of which were CAD events and 1,101 (22.7%) IS events (Table 2).

Independent association between step count and incident CVD

Median daily step count was independently associated with CVD incidence. In the maximally adjusted model, participants in the low step count group had a 40% higher risk (HR: 1.40, 95% CI: 1.27-1.53, $p < 0.0001$), and those in the moderate group had a 15% higher

risk (HR: 1.15, 95% CI: 1.06-1.24, $p = 0.001$), compared with the high step count reference group (Table 2 and Supplementary Figure 4). Corresponding 8-year absolute risks were 131, 99, and 82 per 1,000 participants, respectively. BMI modestly attenuated the associations between step count and incident CVD (low: HR 1.25, 95% CI 1.14-1.37, $p < 0.0001$; moderate: HR 1.11, 95% CI 1.02-1.20, $p = 0.013$), whereas SBP, DBP, hypercholesterolaemia, diabetes, and hypertension had minimal impact (Supplementary Figure 5).

Excluding events that happened in the first two (n=1,052) and four (n=2,278) years of follow-up progressively attenuated the associations between step count and incident CVD. After excluding the first four years, the low step count group had a 19% higher risk than the high step count reference group (HR: 1.19, 95% CI: 1.06-1.35, $p = 0.005$), while the association for the moderate group was no longer suggestive of statistical significance (HR: 1.04, 95% CI: 0.93-1.16, $p = 0.471$; Supplementary Figure 6). Excluding participants with pre-existing chronic conditions that could have limited their ability to walk during accelerometer wear also progressively attenuated the association. After all exclusions, the low step count group had a 17% higher risk than the high step count group (HR: 1.17, 95% CI: 1.00-1.37, $p = 0.048$), while the association for the moderate group was no longer suggestive of statistical significance (HR: 1.08, 95% CI: 0.96-1.23, $p = 0.211$; Supplementary Figure 7).

Fewer daily steps were associated with a higher risk of CAD, with similar effect sizes to overall CVD. In the maximally adjusted model, participants in the low step count group had a 42% higher risk of CAD (HR: 1.42, 95% CI: 1.28-1.57, $p < 0.0001$), and those in the moderate group had a 16% higher risk (HR: 1.16, 95% CI: 1.06-1.27, $p = 0.001$), compared with the high step count reference group (Table 2). Fewer daily steps were also associated with a higher risk of IS, but this association was weaker than for both CAD and overall CVD. In the maximally adjusted model, participants in the low step count group had a 29% higher risk of IS than the high step count group (HR: 1.29, 95% CI: 1.06-1.56, $p = 0.009$), while the association for the moderate group was not suggestive of statistical significance (HR: 1.10, 95% CI: 0.93-1.30, $p = 0.283$, Table 2).

Independent association between genetic risk and incident CVD

Genetic risk had a stronger independent association with incident CVD than step count. In the maximally adjusted model, participants in the high genetic risk group had a 116% higher risk (HR: 2.16, 95% CI: 1.96-2.38, $p < 0.0001$), and those in the moderate group had a 57% higher risk (HR: 1.57, 95% CI: 1.44-1.71, $p < 0.0001$), compared with the low genetic risk reference group (Table 2 and Supplementary Figure 4). Corresponding 8-year absolute risks were 132, 104, and 69 per 1,000 participants, respectively. Adjusting for potential mediators (BMI, SBP, DBP, hypercholesterolaemia, diabetes, and hypertension) did not significantly

alter the strong associations between genetic risk and incident CVD (Supplementary Figure 5).

Excluding events that happened in the first two (n=1,052) and four (n=2,278) years of follow-up progressively attenuated the associations between genetic risk and incident CVD. After excluding the first four years, participants in the high genetic risk group had a 94% higher risk (HR: 1.94, 95% CI: 1.71-2.20, $p < 0.0001$), and those in the moderate group had a 46% higher risk (HR: 1.46, 95% CI: 1.30-1.63, $p < 0.0001$), compared with the low genetic risk reference group (Supplementary Figure 6). In contrast, excluding participants with pre-existing chronic conditions that could have limited their ability to walk during accelerometer wear slightly strengthened the association. After all exclusions, participants in the high genetic risk group had a 145% higher risk (HR: 2.45, 95% CI: 2.07-2.90, $p < 0.0001$), and those in the moderate group had a 75% higher risk (HR: 1.75, 95% CI: 1.51-2.04, $p < 0.0001$), compared with the low genetic risk group (Supplementary Figure 7).

Higher genetic risk was associated with a higher risk of CAD, with a slightly stronger association than for overall CVD. In the maximally adjusted model, participants in the high genetic risk group had a 135% higher risk of CAD (HR: 2.35, 95% CI: 2.10-2.62, $p < 0.0001$), and those in the moderate group had a 62% higher risk (HR: 1.62, 95% CI: 1.47-1.80, $p < 0.0001$), compared with the low genetic risk reference group (Table 2). Higher genetic risk was also associated with a higher risk of IS, but this association was weaker than for both CAD and overall CVD. In the maximally adjusted model, participants in the high genetic risk group had a 55% higher risk of IS (HR: 1.55, 95% CI: 1.27-1.89, $p < 0.0001$), and those in the moderate group had a 39% higher risk (HR: 1.39, 95% CI: 1.18-1.65, $p < 0.0001$), compared with the low genetic risk group (Table 2).

Joint association of step count and genetic risk with incident CVD

Overall, there was no evidence of a multiplicative interaction between step count and genetic risk with incident CVD (*P* for interaction = 0.46). Compared with the reference group – low genetic risk and high step count (absolute risk: 62 per 1,000) – neither of the other low genetic risk groups had a higher risk of CVD, whereas all moderate and high genetic risk groups did (Figure 2 and Table 2). The highest risk was among those with both high genetic risk and low step count (HR: 2.81, 95% CI: 2.27-3.46, $p < 0.0001$; absolute risk: 174 per 1,000). Including all potential mediators (BMI, SBP, DBP, hypercholesterolaemia, diabetes, and hypertension) did not substantially alter the interaction or joint risk estimates (*P* for interaction = 0.49; Supplementary Table 5).

Excluding events that happened in the first four years (n=2,278) slightly attenuated the joint risk estimates, whereas excluding participants with pre-existing chronic conditions that

could have limited their ability to walk during accelerometer wear did not (Supplementary Table 5). There was no evidence of an interaction between step count and genetic risk with incident CVD in either of these sensitivity analyses (*P* for interaction = 0.44 and 0.94, respectively).

Overall, there was no evidence of an interaction between step count and genetic risk with either incident CAD (*P* for interaction = 0.51) or incident IS (*P* for interaction = 0.77). The joint risk estimates for CAD were slightly stronger than for overall CVD (Table 2). Compared with the reference group – low genetic risk and high step count – neither of the other low genetic risk groups had a higher risk of CAD, whereas all moderate and high genetic risk groups did. Similar to overall CVD, the highest risk of CAD was among those with both high genetic risk and low step count (HR: 2.98, 95% CI: 2.34-3.78, $p < 0.0001$). For IS, the joint risk estimates were weaker than for both CAD and overall CVD (Table 2). Only combinations of moderate or high genetic risk with moderate or low step count were associated with a higher risk of IS. Again, the highest risk of IS was among those with both high genetic risk and low step count (HR: 2.11, 95% CI: 1.36-3.28, $p = 0.001$).

Association between continuous step count and incident CVD

Examining step count as a continuous variable using restricted cubic splines revealed more granular information on the association of step count with incidence CVD (Figure 3 and Supplementary Table 6). There was an inverse dose-response association between the hazard of CVD and step counts up to approximately 10,000 daily steps observed in moderate and high genetic risk groups, which then plateaued. No such association was found in the low genetic risk group.

Discussion

This large prospective cohort study of 84,286 UKB participants found that low step count was associated with higher incidence of CVD, especially in individuals at moderate or high genetic risk of CVD, after adjustment for various sociodemographic and lifestyle factors. This association was more notable below 10,000 steps/day, while there was no marked change in CVD hazard above 10,000 steps/day. These findings indicate that maintaining approximately 10,000 steps/day may help offset a substantial portion of genetically determined CVD risk, highlighting the potential importance of step count for high-risk individuals.

A novel finding of this study is the difference in associations of step count with CVD between genetic risk groups, which indicates that walking may be more important for primary prevention of CVD among individuals at high genetic risk compared to low. A similar

difference in the magnitude of association of physical activity with CVD was found in a study of self-reported walking pace,[11] but not in other studies of self-reported physical activity, which demonstrated similar associations across all genetic groups.[10,30] The significant association between physical activity and incident CVD found in those with high genetic risk indicates that exercise has a notable impact on CVD risk in high-risk individuals. It is also possible that longer follow-up could reveal similar associations in the low genetic risk group, as the effects of genetic predisposition might become outweighed by non-genetic factors. These findings underscore the importance of lifestyle choices to mitigate the genetic risk of CVD. Additionally, as in other studies, no multiplicative interaction between PRS and physical activity was found apart from their additive effects.[7,16,17,28] Further comparisons with the literature are difficult, as no previous studies have examined the association between step count and genetic risk on CVD.

While in agreement with existing literature,[18,31,32] our study found a weaker association between step count and CVD, with 24% higher risk of CVD in low vs. high step count groups in fully adjusted models, compared to 138% higher risk reported in a meta-analysis of 4 studies.[18] A possible reason for this is that we accounted for genetic risk of CVD in our models, which may have played an important role given the strong association between genetic risk and incident CVD. Additionally, we used a stricter definition of incident CVD, focusing on CAD and IS, compared to other studies.[31] Finally, we accounted for an extensive range of lifestyle factors, such as diet and sleep, which could have attenuated the observed association of step count with CVD. The incidence of CVD per 1,000 participants was 131, 99, and 82 for those taking <6,500, 6,500-12,499, and ≥12,500 steps/day, respectively. These absolute differences, while modest, are meaningful at the population level and highlight the public health relevance of increasing step count.

The association of walking with low cardiovascular risk may be due to its impact on cardiopulmonary, circulatory, and immune functions, and its indirect effects on obesity, blood pressure, sleep quality and mental well-being.[33] However, as in many physiological processes, after a certain threshold an individual may be in an optimal health state beyond which no further improvements can be made, resulting in the plateau we observed. The stronger association between step count and CAD compared to IS may reflect differences in underlying pathophysiology. CAD is predominantly driven by progressive atherosclerosis of the coronary arteries, whereas IS has a more heterogeneous pathophysiology, including atherosclerosis and cardioembolic events, such as those related to atrial fibrillation, which may be less directly influenced by habitual step count.

Strengths and limitations

This study has various strengths, such as its prospective design, the large cohort size, and the moderately long follow-up of eight years. Additionally, step count was derived from raw acceleration data using an open-source machine learning algorithm, which has shown greater reliability and validity than self-reported measures.[24]

However, it also has some limitations. It is not possible to infer causal associations due to the observational study design. Similarly, individuals taking fewer steps may have done so due to preclinical CVD limiting their mobility, therefore reverse causality cannot be excluded but the risk is low based on the conducted sensitivity analyses. The accelerometer measurement period was limited to a maximum of seven days per participant, which may not fully capture habitual physical activity and could introduce regression dilution bias, underestimating true associations.[34] Most covariates were measured at study entry, a few years prior to the accelerometer study, potentially introducing measurement error. However, previous UKB analyses suggest that key covariates are generally stable over time.[35] Even though the analyses were adjusted for key demographic, socioeconomic, lifestyle, genetic, and clinical factors, there is still the possibility of residual confounding from factors not captured in the UKB.

The PRS for CVD in the UKB was primarily derived from studies including individuals of European ancestry and its absolute performance was lower in non-European ancestries.[22] In addition, 97% of participants in the analytic sample identified as White. Consequently, the findings of our study may not necessarily apply to individuals of different ethnic origins and additional genetic and accelerometry studies in non-European populations would add to the existing evidence. UKB participants have also been shown to be more physically active, wealthier, and healthier than the general population, raising the potential for healthy volunteer bias.[36] In addition, the baseline characteristics of participants excluded from the final analytic sample differed from those included, potentially further affecting the generalisability of our findings. Despite these sources of bias, associations between risk factors and outcomes in the UKB in general and on this topic specifically were largely comparable to existing literature[37].

Conclusions

Overall, higher median daily step count was significantly associated with lower risk of CVD in moderate and high genetic risk individuals. Given the global prevalence of physical inactivity of approximately 31%[38] and the increasing incidence of CVD in the ageing population, walking should be promoted as part of a wider set of prevention strategies, as it is a low-cost, does not require equipment or facilities, and has been associated with improved cardiovascular outcomes.

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Conflict of interest

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Author contributions

This study was originally conceived by AD and LP. AD, LP, TJL, and PB contributed to the study design. PB and LB performed the analysis and wrote the first draft and the revised draft of the manuscript. All authors interpreted the results, critically revised the manuscript and approved the final version of the manuscript. AD obtained funding for the study. All authors had full access to all the data in the study and accept responsibility to submit the manuscript for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data availability statement

Researchers can access individual participant data by registering to the UK Biobank through https://www.ukbiobank.ac.uk/. Data fields used in the study are provided in the Supplementary Materials.

References

1 Roth GA, Mensah GA, Johnson CO, *et al*. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. *J Am Coll Cardiol* 2020; **76**: 2982–3021.

2 Khera AV, Chaffin M, Aragam KG, *et al*. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet* 2018; **50**: 1219–24.

3 Schunkert H, Di Angelantonio E, Inouye M, *et al*. Clinical utility and implementation of polygenic risk scores for predicting cardiovascular disease. *Eur Heart J.* 2025; ehae649. doi: 10.1093/eurheartj/ehae649. Epub ahead of print.

4 Kazemi A, Soltani S, Aune D, *et al*. Leisure-time and occupational physical activity and risk of cardiovascular disease incidence: a systematic-review and dose-response meta-analysis of prospective cohort studies. *Int J Behav Nutr Phys Act* 2024; **21**: 45. doi: 10.1186/s12966-024-01593-8.

5 Ramakrishnan R, Doherty A, Smith-Byrne K, *et al*. Accelerometer measured physical activity and the incidence of cardiovascular disease: Evidence from the UK Biobank cohort study. *PLoS Med* 2021; **18**: e1003487. doi: 10.1371/journal.pmed.1003487.

6 Virolainen SJ, VonHandorf A, Viel KCMF, Weirauch MT, Kottyan LC. Gene–environment interactions and their impact on human health. *Genes Immun* 2023; **24**: 1–11.

7 Said MA, Verweij N, van der Harst P. Associations of Combined Genetic and Lifestyle Risks With Incident Cardiovascular Disease and Diabetes in the UK Biobank Study. *JAMA Cardiol* 2018; **3**: 693–702.

8 Rutten-Jacobs LC, Larsson SC, Malik R, *et al.* Genetic risk, incident stroke, and the benefits of adhering to a healthy lifestyle: cohort study of 306 473 UK Biobank participants. *BMJ* 2018; **363**: k4168. doi: 10.1136/bmj.k4168.

9 Ye Y, Chen X, Han J, Jiang W, Natarajan P, Zhao H. Interactions Between Enhanced Polygenic Risk Scores and Lifestyle for Cardiovascular Disease, Diabetes, and Lipid Levels. *Circ Genomic Precis Med* 2021; **14**: e003128. doi: 10.1161/CIRCGEN.120.003128

10 Wang M, Brage S, Sharp SJ, Luo S, Au Yeung SL, Kim Y. Associations of genetic susceptibility and healthy lifestyle with incidence of coronary heart disease and stroke in individuals with hypertension. *Eur J Prev Cardiol* 2022; **29**: 2101–10.

11 Zaccardi F, Timmins IR, Goldney J, *et al.* Self-reported walking pace, polygenic risk scores and risk of coronary artery disease in UK biobank. *Nutr Metab Cardiovasc Dis* 2022; **32**: 2630–7.

12 Song Z, Wan L, Wang W, *et al.* Daily stair climbing, disease susceptibility, and risk of atherosclerotic cardiovascular disease: A prospective cohort study. *Atherosclerosis* 2023; **386**: 117300. doi: 10.1016/j.atherosclerosis.2023.117300

13 Joensuu L, Waller K, Kankaanpaa A, Palviainen T, Kaprio J, Sillanpaa E. Genetic Liability to Cardiovascular Disease, Physical Activity, and Mortality: Findings from the Finnish Twin Cohort. *Med Sci Sports Exerc* 2024;**56**: 1954–63

14 Adams SA, Matthews CE, Ebbeling CB, *et al*. The effect of social desirability and social approval on self-reports of physical activity. *Am J Epidemiol* 2005; **161**: 389–98.

15 Skender S, Ose J, Chang-Claude J, *et al*. Accelerometry and physical activity questionnaires - a systematic review. *BMC Public Health* 2016; 16: **515**. doi: 10.1186/s12889-016-3172-0.

16 Kim Y, Jang H, Wang M, *et al*. Replacing device-measured sedentary time with physical activity is associated with lower risk of coronary heart disease regardless of genetic risk. *J Intern Med* 2024; **295**: 38–50.

17 Schell RC, Dow WH, Fernald LCH, Bradshaw PT, Rehkopf DH. Joint association of genetic risk and accelerometer-measured physical activity with incident coronary artery disease in the UK biobank cohort. *PloS One* 2024; **19**: e0304653. doi: 10.1371/journal.pone.0304653.

18 Stens NA, Bakker EA, Mañas A, *et al*. Relationship of Daily Step Counts to All-Cause Mortality and Cardiovascular Events. *J Am Coll Cardiol* 2023; **82**: 1483–94.

19 Banach M, Lewek J, Surma S, *et al*. The association between daily step count and all-cause and cardiovascular mortality: a meta-analysis. *Eur J Prev Cardiol* 2023; **30**: 1975–85.

20 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**. doi: 10.1371/journal.pmed.1001779.

21 Doherty A, Jackson D, Hammerla N, *et al.* Large Scale Population Assessment of Physical Activity Using Wrist Worn Accelerometers: The UK Biobank Study. *PloS One* 2017; **12**: e0169649. doi: 10.1371/journal.pone.0169649.

22 [preprint] Thompson DJ, Wells D, Selzam S, *et al.* UK Biobank release and systematic evaluation of optimised polygenic risk scores for 53 diseases and quantitative traits. 2022. doi: 10.1101/2022.06.16.22276246.

23 Khera AV, Emdin CA, Drake I, *et al.* Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease. *N Engl J Med* 2016; **375**: 2349–58.

24 Small SR, Chan S, Walmsley R, *et al.* Self-Supervised Machine Learning to Characterise Step Counts from Wrist-Worn Accelerometers in the UK Biobank. *Med Sci Sports Exerc* 2024;**56**: 1945–53.

25 van Hees VT, Fang Z, Langford J, et al. Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents. *Journal of Applied Physiology* 2014; **117**(7): 738–44

26 Yun J, Brocklebank L, Harper C, Doherty A. Joint associations of device-measured step count and sleep duration with incident major adverse cardiovascular events: prospective analysis of the UK Biobank. *eClinicalMedicine* 2026; **92**: 103769.

27 Thiébaut ACM, Bénichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat Med* 2004; **23**: 3803–20.

28 Yiannakouris N, Katsoulis M, Trichopoulou A, Ordovas JM, Trichopoulos D. Additive influence of genetic predisposition and conventional risk factors in the incidence of coronary heart disease: a population-based study in Greece. *BMJ Open* 2014; **4**: e004387. doi: 10.1136/bmjopen-2013-004387.

29 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**: 1453–7.

30 Tikkanen E, Gustafsson S, Ingelsson E. Associations of Fitness, Physical Activity, Strength, and Genetic Risk With Cardiovascular Disease: Longitudinal Analyses in the UK Biobank Study. *Circulation* 2018; **137**: 2583–91.

31 Del Pozo Cruz B, Ahmadi MN, Lee I-M, Stamatakis E. Prospective Associations of Daily Step Counts and Intensity With Cancer and Cardiovascular Disease Incidence and Mortality and All-Cause Mortality. *JAMA Intern Med* 2022; **182**: 1139–48.

32 Paluch AE, Bajpai S, Bassett DR, *et al*. Daily steps and all-cause mortality: a meta-analysis of 15 international cohorts. *Lancet Public Health* 2022; **7**: e219–28.

33 Ungvari Z, Fazekas-Pongor V, Csiszar A, Kunutsor SK. The multifaceted benefits of walking for healthy aging: from Blue Zones to molecular mechanisms. *GeroScience* 2023; **45**: 3211–39.

34 Saint-Maurice PF, Troiano RP, Bassett DR, et al. Association of Daily Step Count and Step Intensity With Mortality Among US Adults. JAMA 2020; **323**(12): 1151–60

35 Rutter CE, Millard LAC, Borges MC, Lawlor DA. Exploring regression dilution bias using repeat measurements of 2858 variables in ≤49 000 UK Biobank participants. *Int J Epidemiol* 2023; **52**(5): 1545–1556.

36 Fry A, Littlejohns TJ, Sudlow C, *et al*. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. *Am J Epidemiol* 2017; **186**: 1026–34.

37 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. doi: 10.1136/bmj.m131.

38 Strain T, Flaxman S, Guthold R, *et al*. National, regional, and global trends in insufficient physical activity among adults from 2000 to 2022: a pooled analysis of 507 population-based surveys with 5.7 million participants. *Lancet Glob Health* 2024; **12**: e1232–43.

Figure legends

Figure 1. Study participant flow diagram

CVD, cardiovascular disease; TDI, Townsend Deprivation Index; BMI, body mass index.

Figure 2. Joint association of step count and genetic risk with incident CVD in the maximally adjusted Cox model

Squares represent HRs and vertical lines represent 95% CIs.

Median daily step count categories: low (<6,500 steps/day), moderate (6,500-12,499 steps/day), high (≥12,500 steps/day). Genetic risk categories: low (1st fifth), moderate (2nd – 4th fifths), high (5th fifth). High step count and low genetic risk was the reference group.

The maximally adjusted model adjusted for the following confounders: age at time of accelerometer wear, sex, ethnicity, socioeconomic factors (educational attainment,

employment status, TDI, and country of residence), lifestyle factors (smoking status, alcohol consumption, red or processed meat consumption, fish consumption, fruit and vegetable consumption, salt intake, and sleep duration), family history of CVD, season of accelerometer wear, and PRS or step count (depending on the exposure).

CVD, cardiovascular disease; HR, hazard ratio; 95% CI, 95% confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure. TDI, Townsend Deprivation Index; PRS, polygenic risk score.

Figure 3. Association between median daily step count as a continuous variable and incident CVD in the maximally adjusted Cox model by genetic risk group

Median daily step count was modelled using restricted cubic splines with knots placed at the 10th, 50th, and 90th percentiles of the step count distribution.

The HR (solid line) and 95% CI (shaded area) are from the maximally adjusted Cox model. The dashed red line at 10,000 steps/day highlights the approximate plateau in the association.

The maximally adjusted model adjusted for the following confounders: age at time of accelerometer wear, sex, ethnicity, socioeconomic factors (educational attainment, employment status, TDI, and country of residence), lifestyle factors (smoking status, alcohol consumption, red or processed meat consumption, fish consumption, fruit and vegetable consumption, salt intake, and sleep duration), family history of CVD, season of accelerometer wear, and PRS.

CVD, cardiovascular disease; HR, hazard ratio; 95% CI, 95% confidence interval; TDI, Townsend Deprivation Index; PRS, polygenic risk score.

Table 1. Baseline characteristics of study participants by step count group

	Median daily step count			
	Low (N=17,667)	**Moderate** (N=49,948)	**High** (N=16,671)	**Total** (N=84,286)
Median daily steps	5,233 (4,254-5,918)	9,189 (7,888-10,619)	14,543 (13,378-16,439)	9,134 (6,910-11,749)
Genetic risk				
Low	3,401 (19.3)	10,074 (20.2)	3,383 (20.3)	16,858 (20.0)
Moderate	10,646 (60.3)	29,885 (59.8)	10,040 (60.2)	50,571 (60.0)
High	3,620 (20.5)	9,989 (20.0)	3,248 (19.5)	16,857 (20.0)
Age (years)	64.0 (56.5-69.2)	63.0 (55.8-68.2)	61.9 (55.1-67.2)	62.9 (55.8-68.2)

Sex				
Female	10,483 (59.3)	29,332 (58.7)	9,179 (55.1)	48,994 (58.1)
Male	7,184 (40.7)	20,616 (41.3)	7,492 (44.9)	35,292 (41.9)
Ethnicity				
White	17,079 (96.7)	48,526 (97.2)	16,221 (97.3)	81,826 (97.1)
Nonwhite	588 (3.3)	1,422 (2.8)	450 (2.7)	2,460 (2.9)
Educational attainment				
Basic education	4,600 (26.0)	10,929 (21.9)	3,213 (19.3)	18,742 (22.2)
Further education	6,345 (35.9)	16,279 (32.6)	5,357 (32.1)	27,981 (33.2)
University	6,722 (38.0)	22,740 (45.5)	8,101 (48.6)	37,563 (44.6)
Employment status				
Employed	10,368 (58.7)	32,083 (64.2)	11,111 (66.6)	53,562 (63.5)
Not employed	1,348 (7.6)	3,011 (6.0)	1,295 (7.8)	5,654 (6.7)
Retired	5,951 (33.7)	14,854 (29.7)	4,265 (25.6)	25,070 (29.7)
TDI				
Least deprived	8,673 (49.1)	25,988 (52.0)	8,268 (49.6)	42,929 (50.9)
2nd Quintile	4,064 (23.0)	11,244 (22.5)	3,714 (22.3)	19,022 (22.6)
3rd Quintile	2,453 (13.9)	6,781 (13.6)	2,456 (14.7)	11,690 (13.9)
4th Quintile	1,798 (10.2)	4,457 (8.9)	1,681 (10.1)	7,936 (9.4)
Most deprived	679 (3.8)	1,478 (3.0)	552 (3.3)	2,709 (3.2)
Country				
England	15,854 (89.7)	44,878 (89.8)	14,886 (89.3)	75,618 (89.7)
Scotland	1,068 (6.0)	3,175 (6.4)	1,228 (7.4)	5,471 (6.5)
Wales	745 (4.2)	1,895 (3.8)	557 (3.3)	3,197 (3.8)
Smoking status				
Never	9,698 (54.9)	29,542 (59.1)	9,820 (58.9)	49,060 (58.2)
Previous	6,448 (36.5)	17,223 (34.5)	5,887 (35.3)	29,558 (35.1)
Current	1,521 (8.6)	3,183 (6.4)	964 (5.8)	5,668 (6.7)
Alcohol consumption				
Daily	3,459 (19.6)	11,657 (23.3)	4,256 (25.5)	19,372 (23.0)
1-4 /week	8,418 (47.6)	26,218 (52.5)	8,796 (52.8)	43,432 (51.5)
< 1/week	4,516 (25.6)	9,623 (19.3)	2,823 (16.9)	16,962 (20.1)
Never	1,274 (7.2)	2,450 (4.9)	796 (4.8)	4,520 (5.4)
Red/processed meat				
<1 time/week	1,198 (6.8)	3,918 (7.8)	1,656 (9.9)	6,772 (8.0)
1-3 times/week	6,646 (37.6)	19,531 (39.1)	6,393 (38.3)	32,570 (38.6)
3-4 times/week	5,311 (30.1)	14,672 (29.4)	4,706 (28.2)	24,689 (29.3)
5+ times/week	4,512 (25.5)	11,827 (23.7)	3,916 (23.5)	20,255 (24.0)
Fish consumption				

0-1 times/week	8,843 (50.1)	24,128 (48.3)	8,117 (48.7)	41,088 (48.7)
2+ times/week	8,824 (49.9)	25,820 (51.7)	8,554 (51.3)	43,198 (51.3)
Fruit/veg consumption				
<5 servings/day	4,328 (24.5)	9,891 (19.8)	3,016 (18.1)	17,235 (20.4)
5-7.9 servings/day	7,198 (40.7)	21,492 (43.0)	7,000 (42.0)	35,690 (42.3)
8+ servings/day	6,141 (34.8)	18,565 (37.2)	6,655 (39.9)	31,361 (37.2)
Salt consumption				
Never/rarely	10,304 (58.3)	30,209 (60.5)	10,196(61.2)	50,709 (60.2)
Sometimes	4,697 (26.6)	13,255 (26.5)	4,371 (26.2)	22,323 (26.5)
Usually/Always	2,666 (15.1)	6,484 (13.0)	2,104 (12.6)	11,254 (13.4)
Sleep duration				
6h or fewer	5,848 (33.1)	16,492 (33.0)	6,323 (37.9)	28,663 (34.0)
7-8h	11,107 (62.9)	32,348 (64.8)	10,148 (60.9)	53,603 (63.6)
9h or more	712 (4.0)	1,108 (2.2)	200 (1.2)	2,020 (2.4)
Family history of CVD	10,161 (57.5)	28,027 (56.1)	9,122 (54.7)	47,310 (56.1)
Diabetes	1,520 (8.6)	2,441 (4.9)	665 (4.0)	4,626 (5.5)
Hypercholesterolaemia	14,273 (80.8)	39,655 (79.4)	12,983 (77.9)	66,911 (79.4)
Hypertension	9,923 (56.2)	23,797 (47.6)	7,372 (44.2)	41,092 (48.8)
Body Mass Index (kg/m^2)	27 (24-31)	26 (23-29)	25 (23-28)	26 (24-29)
SBP (mmHg)	138.0 ± 18.3	135.9 ± 18.0	135.1 ± 17.9	136.2 ± 18.1
DBP (mmHg)	82.8 ± 10.0	81.5 ± 9.9	81.0 ± 9.9	81.7 ± 10.0
Season of wear				
Autumn	5,338 (30.2)	14,796 (29.6)	4,742 (28.4)	24,876 (29.5)
Winter	4,529 (25.6)	10,409 (20.8)	2,769 (16.6)	17,707 (21.0)
Spring	3,863 (21.9)	11,479 (23.0)	4,058 (24.3)	19,400 (23.0)
Summer	3,937 (22.3)	13,264 (26.6)	5,102 (30.6)	22,303 (26.5)

Summary statistics are presented as n (%) for categorical variables, mean ± SD for continuous normally distributed, and median (IQR) for not normally distributed variables.

TDI, Townsend Deprivation Index; CVD, cardiovascular disease; SBP, systolic blood pressure; SBP, diastolic blood pressure; SD, standard deviation; IQR, interquartile range.

Table 2. Associations of step count and genetic risk with incident CVD, CAD, and IS in maximally adjusted Cox models

	N	CVD		CAD		IS	
		Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)
Overall	84,286	4,847		3,746		1,101	
Median daily step count							
High (reference)	16,671	778	1.00	601	1.00	177	1.00
Moderate	49,948	2,767	**1.15 (1.06-1.24)**	2,136	**1.16 (1.06-1.27)**	631	1.10 (0.93-1.30)
Low	17,667	1,302	**1.40 (1.27-1.53)**	1,009	**1.42 (1.28-1.57)**	293	**1.29 (1.06-1.56)**
Genetic risk							
Low (reference)	16,858	634	1.00	466	1.00	168	1.00
Moderate	50,571	2,930	**1.57 (1.44-1.71)**	2,242	**1.62 (1.47-1.80)**	688	**1.39 (1.18-1.65)**
High	16,857	1,283	**2.16 (1.96-2.38)**	1,038	**2.35 (2.10-2.62)**	245	**1.55 (1.27-1.89)**
Combined variable							
Low genetic risk							
High step count (reference)	3,383	116	1.00	88	1.00	28	1.00
Moderate step count	10,074	365	1.02 (0.83-1.26)	262	0.97 (0.76-1.24)	103	1.15 (0.76-1.74)
Low step count	3,401	153	1.16 (0.91-1.47)	116	1.17 (0.89-1.55)	37	1.10 (0.67-1.80)
Moderate genetic risk							
High step count	10,040	471	**1.39 (1.13-1.70)**	361	**1.39 (1.10-1.76)**	110	1.36 (0.90-2.06)
Moderate step count	29,885	1677	**1.61 (1.34-1.95)**	1,284	**1.64 (1.32-2.03)**	393	**1.51 (1.03-2.22)**
Low step count	10,646	782	**1.94 (1.60-2.36)**	597	**1.97 (1.57-2.47)**	185	**1.79 (1.20-2.67)**
High genetic risk							
High step count	3,248	191	**1.84 (1.46-2.32)**	152	**1.90 (1.46-2.48)**	39	1.59 (0.98-2.58)
Moderate step count	9,989	725	**2.19 (1.80-2.66)**	590	**2.35 (1.88-2.94)**	135	**1.61 (1.07-2.43)**
Low step count	3,620	367	**2.81 (2.27-3.46)**	296	**2.98 (2.34-3.78)**	71	**2.11 (1.36-3.28)**

Median daily step count categories: low (<6,500 steps/day), moderate (6,500-12,499 steps/day), high (≥12,500 steps/day). Genetic risk categories: low (1st fifth), moderate (2nd – 4th fifths), high (5th fifth)

The maximally adjusted model adjusted for the following confounders: age at time of accelerometer wear, sex, ethnicity, socioeconomic factors (educational attainment, employment status, TDI, and country of residence), lifestyle factors (smoking status, alcohol consumption, red or processed meat consumption, fish consumption, fruit and vegetable consumption, salt intake, and sleep duration), family history of CVD, season of accelerometer wear, and PRS or step count (depending on the exposure).

CVD, cardiovascular disease; CAD, coronary artery disease; IS, ischaemic stroke; HR, hazard ratio; 95% CI, 95% confidence interval; TDI, Townsend Deprivation Index; PRS, polygenic risk score.

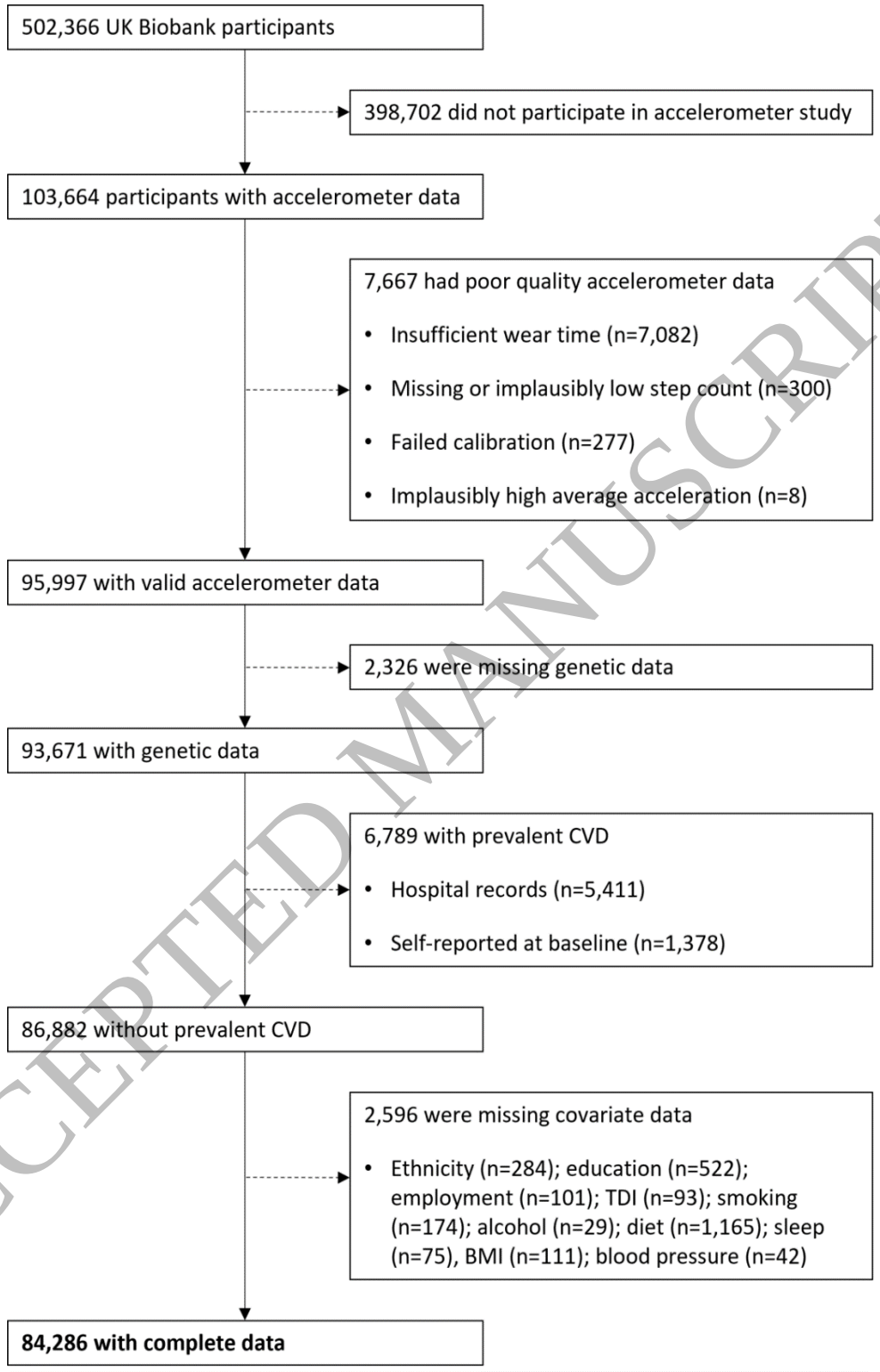

Figure 1

150x229 mm (x DPI)

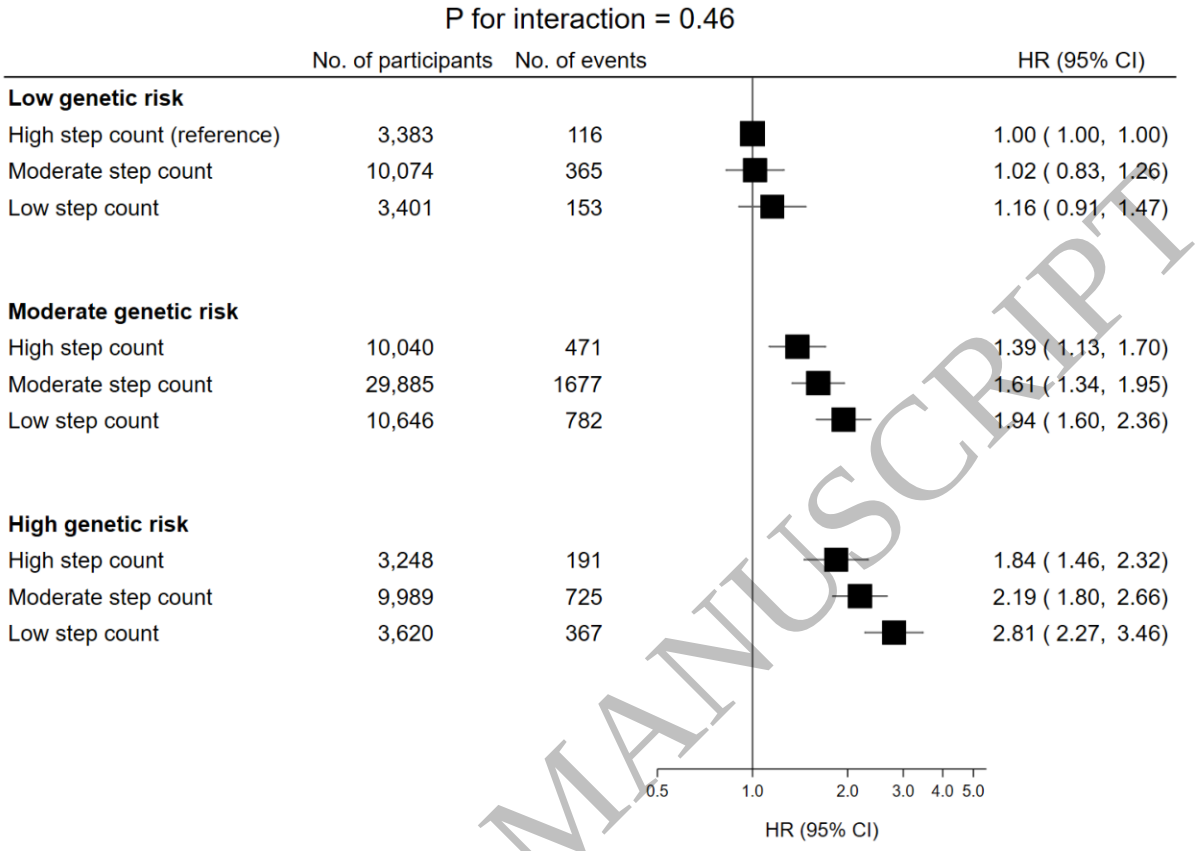

Figure 2

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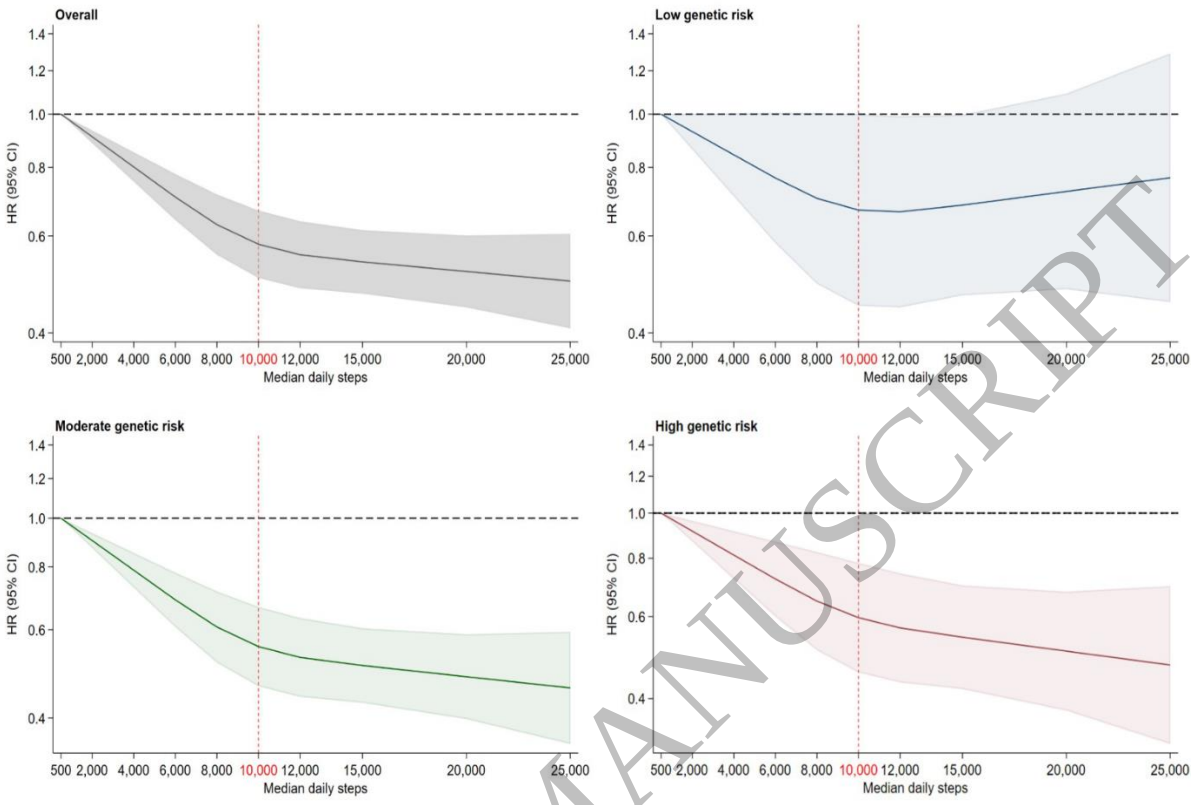
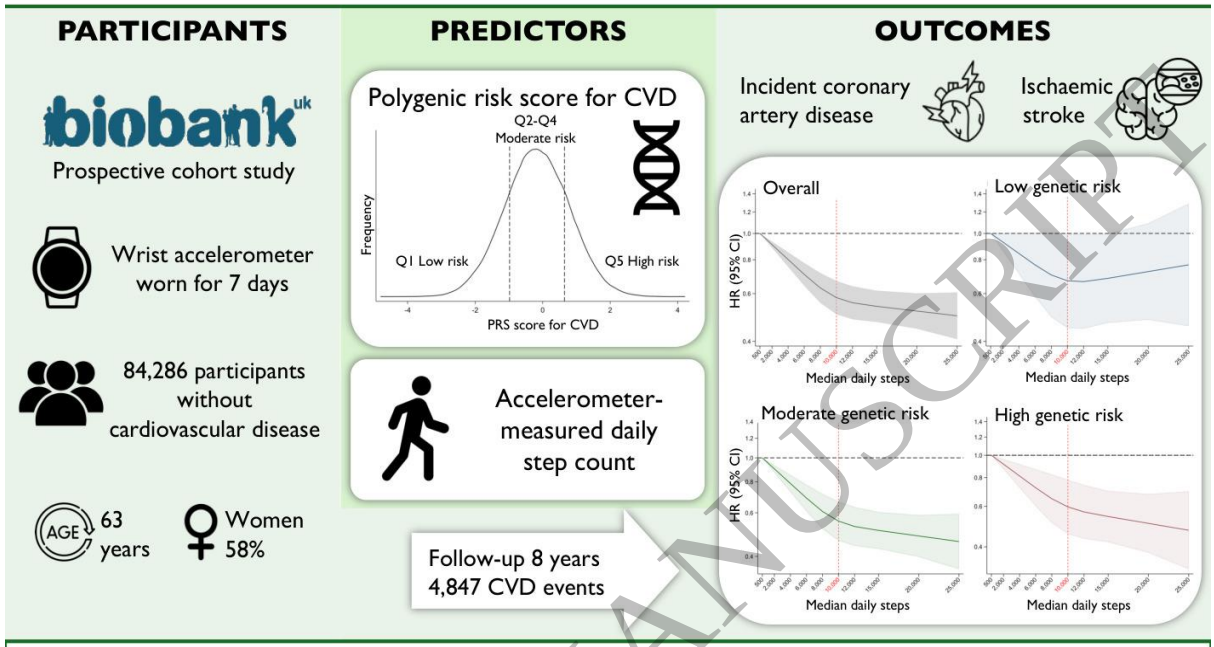


Figure 3

229x137 mm (x DPI)

Joint association of genetic risk and accelerometer-based step count with cardiovascular disease: a UK-Biobank cohort study



CONCLUSION: High daily step count was associated with lower risk of cardiovascular events in individuals with moderate and high genetic risk of cardiovascular disease.

Graphical Abstract

182x126 mm (x DPI)