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Physical activity, genetic predisposition, and incident cardiovascular disease: Prospective analyses of the UK Biobank

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Highlights

- Among 303,950 UK Biobank participants (mean follow-up 11.6 years), higher MVPA was linked with lower CHD risk across genetic strata; in the high-risk group, low to medium vigorous intensity activity levels lowered CHD risk by 22% to 34% (HR: 0.78–0.66).
- Stroke risk was inversely associated with moderate intensity activity, with high-risk individuals having a 23% to 36% (HR: 0.77–0.64) lower risk for low to medium moderate intensity activity levels, while associations for AF were inconsistent
- These findings suggest that vigorous activity may offset genetic CHD risk and moderate activity lower stroke risk, supporting precision lifestyle interventions.

Abstract

Background: It is unclear whether physical activity can benefit participants with high genetic predisposition to cardiovascular disease. We examined the joint associations of intensity-specific physical activity and genetic predisposition (based on polygenetic risk score) with incident coronary heart disease (CHD), stroke, and atrial fibrillation (AF).

Methods: This prospective cohort study included 303,950 adults (age = 56.4 ± 8.0 years, mean ± SD; 52.5% females) from the UK Biobank with physical activity and disease-related genotypes. Moderate-to-vigorous physical activity (MVPA) and intensity-specific activity was classified according to volume (e.g., MVPA was classified as none, low, medium, and high). Genetic predisposition for CHD, stroke, and AF were classified as low (Quintile 1), intermediate (Quintiles 2–4), and high (Quintile 5).

Results: During 11.6 ± 2.1 years of follow-up: 19,865 CHD; 7907 stroke; and 16,688 AF events occurred. Compared to the no MVPA and high genetic risk group, we observed lower CHD risk for increasing levels of MVPA over and above genetic risk groupings. These associations were primarily driven by vigorous-intensity activity. For example, in the high genetic risk group, those with low vigorous-intensity activity levels (compared to none) had a hazard ratio (HR) of 0.78 (95% confidence interval (95%CI):0.72–0.86) compared to an HR of 0.90 (95%CI: 0.83–0.98) for low moderate-intensity activity levels. For stroke incidence, we observed a protective association for MVPA across genetic risk groups that was mostly driven by moderate-intensity activity volume. Among the high genetic risk group, low moderate-intensity had an HR of 0.77 (95%CI:0.66–0.90), whereas low vigorous-intensity had no association (HR = 0.95, 95%CI:0.82–1.09). We did not observe a consistent joint association of MVPA and AF genetic predisposition.

Conclusions: We observed lower CHD and stroke risk for low to high MVPA among participants with high genetic predisposition. The associations of moderate- and vigorous-intensity activity volume differed considerably across cardiovascular disease sub-types. Overall, our findings suggest vigorous intensity activity may mitigate genetic predisposition for CHD while moderate intensity activity may be associated with similar effects for stroke. Joint associations were less consistent across AF genetic predisposition groups. Our results inform precision medicine approaches and future lifestyle modification interventions by quantifying the potential benefits of physical activity among at-risk individuals.

Keywords: Physical activity, genetic risk, cardiovascular disease, coronary heart disease, stroke

1. Introduction

Cardiovascular disease (CVD) is the dominant cause of death worldwide, accounting for approximately 18 million deaths per year (31% of total mortality).[1] Of these deaths, 7.5 million are attributable to coronary heart disease (CHD) and 7 million are due to strokes.[2] Substantial observational and clinical evidence suggests engaging in moderate-to-vigorous physical activity (MVPA) can lower the risk of CVD. A meta-analysis of 33 studies and an individual participant data analysis of 6 studies similarly reported 25%–50% lower CVD mortality rates with increasing MVPA volumes.[3,4] More recently, an investigation of the Nurses' Health Study and population cohorts estimated an additional 7- to 8-year gain in CVD-free years and 40%–50% lower CVD incidence and mortality rate among the most physically active participants.[5–9] However, there have been mixed findings on the relationship between MVPA and atrial fibrillation (AF).[10–13] AF is the most common sustained arrhythmia (lifetime risk of 37% at age 55 and older), with increasing global prevalence, and it is linked with adverse cardiovascular events.[14–16]

CVD is a complex cluster of conditions that is partly determined by genetic factors. Recent reports by the European Society of Cardiology Task Force[17] and American Heart Association[18] have identified the potential clinical utility of genetic risk scoring to improve personalized primary prevention of CVD with modifiable risk factors. Traditionally, CVD genetic risk factors have been difficult to accurately assess in large prospective studies; however, recent advances in technology have expanded our knowledge of human genetic variation. Genome-wide association studies have identified variants associated with CVD phenotypes such as CHD,[19] stroke,[20] and AF.[21]

It is unclear how the association between physical activity and CVD is affected by genetic predisposition. A previous study examining the joint associations of physical activity and genetic risk found that more time spent in MVPA did not attenuate the risk of incident CHD among participants with intermediate to high genetic risk.[22] In contrast, a pooled analysis of 3 prospective cohorts reported that 1 weekly session of

MVPA attenuated the risk of incident CHD by 12% across increasing genetic risk groups compared to no physical activity.[23] Similar discrepancies have been reported for stroke and AF.[22,24–26] Existing studies are limited to examining combined MVPA volume; however, moderate-intensity activity and vigorous-intensity activity elicit differing cardiovascular adaptations,[27–29] and recent studies have shown variations in morbidity and mortality risk based on specific intensity levels.[30–32] It is unknown how the protective associations of moderate- and vigorous-intensity activity are affected by underlying genetic predisposition. To understand the interplay between genetic risk and intensity-specific physical activity, we examined the association of MVPA and its constituent components (moderate and vigorous intensity) with CHD, stroke, and AF in more than 300,000 UK Biobank participants with genetic data. We hypothesized higher volumes of intensity-specific physical activity would be associated with lower risk across strata of CVD genetic predisposition.

2. Methods

2.1. Study participants

Participants were included from the UK Biobank Study, a prospective cohort of 502,629 participants between 40–69 years. All participants were enrolled between 2006–2010 and provided informed written consent. Ethical approval was provided by the UK's National Health Service, National Research Ethics Service (Ref 11/NW/0382). Participants completed physical examinations by trained staff and touchscreen questionnaires at 1 of 22 assessment centers in the UK between 2006 and 2010.[33] During the examination, blood samples were collected for genotyping. We excluded participants who did not have genetic data available or who were from a non-white British ancestry. We further excluded participants who had a history of each CVD-specific outcome ascertained through self-report and hospital admission records,

participants with missing covariate data, those who were unable to walk, and those who had an event within the first 12 months of follow up (**Supplementary Fig. 1)**.

2.2. Physical activity assessment

Physical activity was measured using the International Physical Activity Questionnaire (IPAQ) short form, which was previously validated among European middle aged and older adults[34,35] and included items on frequency and duration of moderate-intensity activity and vigorous-intensity activity (**Supplementary Table 1**). Physical activity was expressed as metabolic equivalent of task (MET) min/week and based on the IPAQ scoring procedure (i.e., moderate intensity = 4.0 MET; vigorous intensity = 8.0 MET). Participants were categorized into tertile groups based on MVPA (<440 MET-mins/week, 440–1680 MET-mins/week, and >1680 MET-mins/week), and moderate- and vigorous- intensity (<300 MET-mins/week, 300–900 MET-mins/week, and >900 MET-mins/week). Moderate- and vigorous-intensity groups used the same cut-offs to allow for a volume-standardized comparison across groupings.

2.3. Genotyping

The UK Biobank genotyping, quality control, and imputation processes have been extensively described previously.[36] Briefly, genome-wide genotyping in UK Biobank was performed using the UK Biobank Axiom Array. This array covers 805,426 markers and includes coding variants across a range of minor allele frequencies (MAF), including rare markers (<1% MAF) and markers that provide good genome-wide coverage for imputation in European populations in the common (>5%) and low frequency (1%–5%) MAF ranges. Imputation was performed using computationally efficient methods and resulted in the generation of approximately 96 million genetic variants.

2.4. Polygenic risk scores

To generate the polygenic risk scores (PRS), UK Biobank participants were genotyped using Plink Version 1.9 (https://www.cog-genomics.org/plink/). For significant single-nucleotide polymorphisms (SNPs) identified for each of the 3 phenotypes (CHD,[19] stroke,[20] and AF[21]). Briefly, the variant alleles for each individual were tallied (0, 1, and 2, respectively) and multiplied by the associated effect sizes (reported for each allele in these studies) before being summed together as the PRS for each individual for each phenotype. Filtering was then performed to remove individuals of non-white British ancestry. The SNPs and their effect sizes used for CHD (208 SNPs), stroke (11 SNPs), and AF (30 SNPs) are shown in **Supplementary Table 2**. PRS was used to determine whether participants were at high (Quintile 5), intermediate (Quintiles 2–4), or low (Quintile 1) genetic risk for each outcome, as previously described.[37]

2.5. CHD, stroke, and AF ascertainment

Participants were followed up to March 31, 2021, with deaths obtained through linkage with the National Health Service (NHS) Digital of England and Wales or the NHS Central Register and National Records of Scotland. Inpatient hospitalization data were provided by either the Hospital Episode Statistics for England, the Patient Episode Database for Wales, or the Scottish Morbidity Record for Scotland. Methods for the assessment of CVD mortality and hospitalization are provided in **Supplementary Table 3**. Briefly, CHD was defined as International Classification of Diseases (ICD) 10th edition codes I21, I22, I23, I24, I25, Z951, and Z955. Stroke was defined as G951, H341, H342, I60, I61, I62, I63, I64, I678, I690, I693, and S066. AF was defined as I48. Due to the nature of rolling updates for the data linkage, censoring dates varied between resources (between February 2021 and March 2021).

2.6. Covariates

Our *a priori* selection of covariates was informed by previous literature[26,38,39] and included information about participant lifestyle and health status. These included: age; sex; smoking status; alcohol consumption; sleep duration; fruit and vegetable consumption; discretionary screen-time defined as time spent watching TV or using the computer outside of work; highest attained education level; non-outcome prevalent CVD; and prescriptions of medication for cholesterol, blood pressure, and diabetes. Physical activity intensity-specific models were mutually adjusted for moderate and vigorous intensity where appropriate (e.g., moderate intensity as the exposure was adjusted for vigorous intensity and *vice versa*). In sensitivity analyses, we included clinical factors that may be potential mediators of the association between physical activity and CVD: body mass index, glycated hemoglobin A1C, high-density and low-density lipoprotein cholesterol, and triglycerides. Complete covariate definitions are provided in **Supplementary Table 4.**

2.7. Analysis

We plotted the 10-year cumulative risk of an event by joint genetic risk–physical activity categories and calculated the crude risk and age- and sex-adjusted incidence rate ratios. We examined the joint associations of genetic risk and MVPA, moderate-intensity activity, and vigorous-intensity activity with incident CVD outcomes using cause-specific Cox proportional hazards regression and treating mortality events from non-outcome causes as competing risks. The joint reference group was high genetic risk and no MVPA (or no moderate/vigorous physical activity in the intensity-specific models). All analyses were adjusted for the covariates listed above. Proportional hazards assumptions were assessed using Schoenfeld residuals, and stratification of covariates were added if assumptions were not met. For MVPA, we performed interaction tests to assess whether physical activity and genetic predisposition jointly influence CVD risk or whether their effects are independent. In the separate associations analysis, physical activity dose–response was assessed using cubic splines (knots at the 10th, 50th, and 90th percentiles) and 0

moderate- or vigorous-intensity min as the referent; departure from linearity was assessed by a Wald test examining the null hypothesis that the coefficient of the second spline was equal to 0. Independent associations for genetic risk were assessed using PRS categories with high PRS as the referent group.

We calculated E-values to assess the potential impact of unmeasured confounding.[40] The E-values quantify the minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome to reduce the observed conditional associations to null. We also used a negative control outcome of accident-related hospitalizations (excluding cycling, self-harm, and falls incidence), an outcome that does not have an explicit mechanistic link to CVD genetic risk and physical activity, to assess residual confounding. Negative controls can improve causal inference by illustrating pervasive bias and confounding.[41] If the negative control has a similar association pattern as the primary outcomes, then it is more plausible that associations are due to bias and confounding than causal mechanisms. In sensitivity analyses, we adjusted for potential mediators that included body mass index, lipid profile, and blood glucose levels.

We performed all analysis using R statistical software with the rms and survival packages.[42,43] We reported this study as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (**Supplementary STROBE Statement**).

3. Results

Our analytic sample for incident CHD included 303,950 participants (age = 56.4 ± 8.0 years, mean ± SD; 52.5% females) followed up for an average of 11.6 ± 2.1 years (3,528,676 person-years) with 19,865 events (**Supplementary Table 5**). Participants were more likely to have a college or university degree (*n* = 101,729) and have no history of smoking (*n* = 167,169). Median moderate- and vigorous-intensity activity volume was 480 (interquartile range (IQR): 120–1200) MET min/week (equivalent to 120 (IQR: 30–300) MET-min/week), and 240 (IQR: 0–960)

MET min/week (equivalent to 30 (IQR: 0–120) min/week), respectively. In total, 41,910 participants reported no moderate-intensity activity and 113,507 reported no vigorous-intensity activity. Participant characteristics by CHD genetic predisposition and MVPA intensity groupings with incidence rates are provided in **Table 1**. Our incident stroke sample included 313,618 participants with 7907 events (**Supplementary Table 5**). Our incident AF sample included 310,792 participants with 16,688 events (**Supplementary Table 5**). **Supplementary Tables 6 and 7** provide participant characteristics by stroke and AF genetic predisposition and MVPA intensity groupings.

Unadjusted incident rate ratio (IRR) was approximately one-third to one-fifth lower in the high genetic risk–low moderate activity group compared to the high genetic risk–no moderate activity group (e.g., CHD IRR = 0.64 (95%CI: 0.59–0.70); stroke IRR = 0.66 (95%CI: 0.56–0.77); AF IRR = 0.83 (95%CI: 0.76–0.92)) (**Supplementary Table 8**). The rate was approximately half in the moderate genetic risk–low vigorous activity group for CHD (IRR = 0.57 (95%CI: 0.53–0.60)) and AF (IRR = 0.58 (95%CI: 0.54–0.62)) incidence (**Supplementary Table 9**). The 10-year risk for CHD, stroke, and AF incidence by joint genetic risk–physical activity intensity categories are shown in **Supplementary Figs. 2–7.**

3.1. CHD

In the joint association analysis, we observed an inverse multivariable-adjusted association between MVPA volume and CHD risk, with the medium and high MVPA groups having similar associations within each genetic risk level (**Fig. 1A**; interaction test $p = 0.007$). For example, in the high genetic risk group, low MVPA had a hazard ratio (HR) of 0.88 (95%CI: 0.80–0.97) while medium and high MVPA had HRs of 0.78 (95%CI: 0.71–0.85) and 0.80 (95%CI: 0.74–0.88), respectively. These associations were more influenced by vigorous-intensity activity volume than moderate-intensity activity volume. For moderate intensity, there were minimal differences in HR values within genetic risk groups. For

example, among the high genetic risk group, HR values were 0.92 (95%CI: 0.86–0.99), 0.90 (95%CI: 0.83–0.98), and 0.95 (95%CI: 0.89–1.01) for low, medium, and high moderate-intensity groups, respectively (**Fig. 1B**). In comparison, among the high genetic risk group, we consistently observed stronger protective dose–response gradients for low, medium, and high vigorous intensity, with HR values of 0.78 (95%CI: 0.72–0.86), 0.66 (95%CI: 0.60–0.73), and 0.67 (95%CI: 0.61–0.73), respectively (**Fig. 1C**). For intermediate genetic risk, engaging in medium or high vigorous-intensity activity was associated with a lower HR than no vigorous-intensity activity. We observed the same pattern for medium or high vigorous-intensity activity in the low genetic risk group. When we modeled the continuous physical activity data, we observed a U-shaped, independent dose–response association for both moderate- and vigorous-intensity physical activity as shown in **Supplementary Figs. 8 and 9**. For an equivalent HR, we observed a 7:1 time ratio between moderate-intensity activity and vigorous-intensity activity in the dose–response curves up to 120 min/week. Independent genetic risk associations are shown in **Supplementary Fig. 10**.

—Insert Figure 1 near here—

3.2. Stroke

In the joint association, low and medium MVPA was associated with incrementally lower stroke risk within each genetic risk group (interaction test $p = 0.01$). For example, among the high genetic risk group, compared to the referent no MVPA, those with low MVPA volumes had an HR of 0.81 (95%CI: 0.69–0.96) and those with medium MVPA volumes had an HR of 0.71 (95%CI: 0.60–0.84) whereas no further attenuation was observed for high MVPA (HR = 0.77 (95%CI: 0.66–0.91)) (**Fig. 2A**). These associations were more influenced by moderate-intensity activity volume than vigorous-intensity activity volume. For moderate intensity, as volume increased, we observed an incrementally lower risk up to high moderate intensity, across all genetic risk groups. In the intermediate genetic risk group, a medium volume of moderate-intensity activity was

associated with an HR (e.g., 0.43 (95%CI: 0.33–0.55)) comparable to the low genetic risk group with low volume of moderate-intensity activity (HR = 0.40 (95%CI: 0.28–0.55)) (**Fig. 2B**). For vigorous-intensity activity, the joint association was primarily dictated by genetic risk. We did not observe lower risk among the high genetic risk group for any volume of vigorous-intensity activity (**Fig. 2C**). In the independent dose–response analysis, moderate-intensity activity had a U-shaped association for lower risk whereas vigorous-intensity activity was not associated with stroke risk (**Supplementary Figs. 11 and 12**). Independent genetic risk associations are shown in **Supplementary Figs. 13**.

--Insert Figure 2 near here—

3.3. AF

Independent dose–response associations for moderate-intensity activity and vigorous-intensity activity both showed a protective association (**Supplementary Figs. 14 and 15**). The independent genetic risk levels showed a graded association (**Supplementary Fig. 16**). The joint association pattern was driven primarily by genetic risk level. We observed a weak gradient in the joint association between MVPA groups, with no protective association for MVPA among the high genetic risk groups (**Fig. 3A**). Interaction tests were statistically significant for each MVPA × PRS group ($p < 0.001$) except for the high PRS group, where interaction tests were not significant. This pattern was consistent in the intensity-band-specific analyses. The largest association differences occurred between none and low activity for both moderate- and vigorous-intensity activity (**Fig. 3B and 3C**).

--Insert Figure 3 near here—

3.4. Additional and sensitivity analyses

Our sensitivity analyses that included adjusting for biomarkers produced a similar pattern of findings, with the associations marginally attenuated (**Supplementary Figs. 17–22**). For example, the association for incident CHD in the high genetic risk group had HR values of 0.99 (95%CI: 0.91–1.07) in the low moderate-intensity activity group and 0.80 (95%CI: 0.73–0.88) in the low vigorous-intensity activity volume group. Analyses for negative control outcomes and E-values indicated residual and unmeasured confounding had minimal impact on the findings. With respect to negative control outcomes specifically, the HR point estimate pattern was inconsistent with wide 95%CIs and there were no significant associations (**Supplementary Figs. 23 and 24**). The E-values suggest a substantial degree of unmeasured confounding would be required to reduce our observed associations for CHD (high genetic risk–low vigorous-intensity activity group = 1.88 (lower 95%CI= 1.60)) and stroke (high genetic risk–low moderate-intensity activity group = 1.92 (lower 95%CI = 1.46)) to null (**Supplementary Table 10**).

4. Discussion

In one of the largest prospective CVD genetic predisposition studies of more than 300,000 individuals, we assessed the joint association of physical activity intensity-specific volume and genetic risk with incidence of major CVDs including CHD, stroke, and AF. Our key findings suggest that relatively low physical activity levels lower risk even in participants with high genetic predisposition for CVD. We found a joint association for CHD genetic risk and MVPA that was primarily driven by vigorous-intensity activity volume, whereas the joint association for stroke risk was a consequence of moderate-intensity activity volume. For AF, we did not observe a joint association gradient, although independent analyses showed a protective association for both moderate- and vigorous-intensity activity. Few studies have examined the associations of intensity-specific physical activity, and there is an absence of studies examining the role of genetic predisposition on intensity-specific associations with CVD risk. The novelty of our findings may help inform precision medicine approaches for physical activity prescription among at-risk individuals as well as future interventions involving lifestyle modifications.

Regular MVPA has been found to have a positive effect on several risk factors for developing CHD, including obesity, diabetes, dyslipidaemia, and hypertension.[44–46] Consequently, the association between increasing MVPA volume and a lower risk of incident CHD is well-established in the literature.[47–50] Our findings align with previous studies suggesting that maintaining a healthy lifestyle, in which physical activity is a primary component, is associated with lower incident CHD, including among those with a higher genetic predisposition.[22,26,39] Our findings extend these studies and provide nuanced insight by focusing on the differences in the relative contributions of intensity-specific activity volumes across genetic predisposition levels. We found vigorous-intensity activity volume, to a higher degree than moderate-intensity activity volume, can lower CHD risk among those with intermediate or high genetic predisposition. This was particularly evident among the highest genetic risk group, where there was a weak to null association between moderate-intensity activity volume and lower CHD risk. Importantly, higher vigorous-intensity activity volume was associated with lower incident CHD with HRs comparable to the next lowest genetic predisposition group. It is possible our findings are attributable, in part, to the greater cardiac adaptations elicited through vigorous-intensity activity as opposed to moderate-intensity activity.[51–53] Together, these results highlight the potentially key role of vigorous-intensity activity for CHD prevention, regardless of genetic predisposition.

We observed a U-shaped association between MVPA and stroke risk, with moderate-intensity activity volume as the primary contributor for lower stroke risk across genetic predisposition groups. The association for vigorous-intensity activity volume was weaker, and we observed the joint association was driven by genetic predisposition level. Notably, among those with high genetic predisposition, only moderate-intensity activity volume was consistently associated with lower risk. Our analysis of the intensity-specific contributions of moderate- and vigorous-intensity activity provides nuanced insight extending prior research which reported conflicting association patterns for physical activity and stroke.[54–56] It is possible vigorous-intensity activity elicits higher hemodynamic stress than moderate-intensity activity, which may affect vascular shear stress;

also, more intense changes in the autonomic nervous system may contribute to increased platelet aggregation.[57–59] In addition, vigorous-intensity activity in the form of heavy lifting may lead to higher intrathoracic pressure, which can result in transient increases in blood pressure.[60] Increases in blood pressure as a result of vigorous-intensity activity, particularly among those who do not habitually exercise, have been found to increase the risk of hemorrhage stroke by 3-fold.[61] If confirmed to be causal in future randomized controlled trials, our intensity-specific findings may augment future personalized clinical intervention strategies for stroke prevention through physical activity intensity prescription conducive to patients with varying comorbidities and underlying genetic predispositions.

The joint association with AF risk was driven by the level of genetic predisposition. We found neither moderate- nor vigorous-intensity activity attenuated risk of AF among the high genetic predisposition group. This contradicts previous findings as well as health messaging that indicates engaging in sufficient levels of MVPA (i.e., meeting physical activity recommendations) may lower the risk of AF.[10,62] It is probable the relationship between MVPA and AF is attributable to cardiorespiratory fitness rather than overall activity volume,[22,63,64] and the importance of cardiorespiratory fitness to this relationship increases with age.[65] Similar to prior studies, we found a protective association in the independent intensity-specific analyses.[62,66,67] However, the joint analyses indicated genetic predisposition outweighed the associations of physical activity alone. Importantly, we did not detect any harmful associations from low to high volumes of either moderate- or vigorous-intensity activity in any of the genetic predisposition groups among our sample of middle-aged to older adults in the general population. This contrasts with prior findings, specifically in endurance athletes, indicating an increased risk of AF from high physical activity volume, due in part to atrial dilation and fibrosis and parasympathetic tone at rest.[68–70] Our findings reinforce the potential safety of engaging in moderate- or vigorous-intensity activity for adults in the general population, even among those with high predisposition for AF.

Our study suggests a non-bounding role of genetic risk whereby physical activity may attenuate the higher genetic predisposition for incident CHD and stroke. This finding maybe particularly important for personalized medicine initiatives, clinicians treating at-risk patients, and public health messaging to motivate the general population to do more physical activity, irrespective of their genetic risk for CVD. Our findings highlight the potentially different roles of moderate and vigorous physical activity for prevention of CHD and stroke in relation to genetic predisposition. This information could be used to provide more personalized prevention approaches in the context of these 2 major CVDs. In addition to engaging in adequate volumes of physical activity, additional lifestyle behaviors should be encouraged in combination to induce an additive effect for preventive interventions targeting reductions in AF risk. Collectively, our results across CHD, stroke, and AF represent future avenues to enhance intervention strategies such as physical activity prescription to lower disease risk and improve longevity in middle-aged and older adults.

5. Strengths and limitations

This is, to date, one of the largest prospective studies with available genetic data. This unique study aspect allowed us to estimate the risk of incident CVD stratified by genetic predisposition, thereby reducing the bias found in traditional analyses. Our estimates were robust to adjustment for multiple confounders and sensitivity analyses. The negative control analysis and E-values further indicated the robustness of our estimates and strengthened our moderate- and vigorous-intensity-specific findings. Due to the observational design of our study, we cannot rule out the possibility of reverse causation due to prodromal illness. In addition, the analysis was performed only in individuals of white British descent, which may reduce the generalizability of our findings to other ethnicities. The SNPs used in the polygenic risk scores may have pleiotropic effects on lifestyle factors. Further, epigenetic modifications resulting from environmental factors may affect gene expression. Physical activity, although assessed with a validated instrument, was self-reported and some degree of differential misclassification is expected. The UK Biobank had a low response rate, and exclusion of participants with missing exposure or covariate data may further contribute to selection bias.

Although the UK Biobank cohort is not representative of the general UK population, prior epidemiological evidence has shown that there is little indication of bias due to non-participation and physical activity–disease findings are widely generalizable.[71,72]

6. Conclusion

Moderate- and vigorous-intensity activity both attenuated risks associated with genetic predisposition to CHD and stroke. We found moderate-intensity activity was associated with lower incidence of stroke, with risk levels comparable in magnitude to the next lower genetic predisposition level. We observed a similar association pattern for vigorous-intensity activity and CHD. Results for AF were less clear. Our results provide nuanced insights that may help inform precision medicine approaches and lifestyle modification interventions through physical activity prescriptions among at-risk individuals.

Authors' contributions

MNA, ESi, and HDM contributed to the conceptualization, methodology, software development, formal analysis, validation, visualization, and writing of the original draft. GTS, MH, ESt, JMB, and BdPC contributed to the methodology and provided critical revisions during the review and editing process. All authors read and approved the final manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

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Table 1: Participant characteristics by polygenic risk score and moderate-to-vigorous-intensity activity volume groups.

MVPA volume	High				Intermediate				Low				Overall
	None	Low	Med	High	None	Low	Med	High	None	Low	Med	High	
n	7344	12,246	21,445	19,664	21,745	37,511	64,073	59,039	7327	12,514	21,369	19,673	303,950

Follow-up (year)	11.3 ± 2.5	11.5 ± 2.3	11.6 ± 2.1	11.5 ± 2.2	11.5 ± 2.3	11.6 ± 2.1	11.7 ± 2.0	11.6 ± 2.0	11.6 ± 2.2	11.7 ± 1.9	11.7 ± 1.9	11.7 ± 1.9	11.6 ± 2.1
Age (year)	56.0 ± 7.8	55.9 ± 7.8	56.1 ± 8.1	56.6 ± 8.2	56.1 ± 7.8	56.0 ± 7.8	56.3 ± 8.1	56.8 ± 8.2	56.1 ± 7.8	56.2 ± 7.8	56.4 ± 8.0	56.9 ± 8.2	56.4 ± 8.0
Male (%)	3374 (45.9)	5590 (45.6)	9463 (44.1)	10,076 (51.2)	10,034 (46.1)	17,611 (46.9)	28,918 (45.1)	30,125 (51.0)	3396 (46.3)	5884 (47.0)	9717 (45.5)	10,107 (51.4)	144,295 (47.5)
Vigorous activity (MET min/week)	0.0 (0.0; 0.0)	0.0 (0.0; 80.0)	320.0 (80.0; 640.0)	1440.0 (480.0; 2160.0)	0.0 (0.0; 0.0)	0.0 (0.0; 80.0)	320.0 (80.0; 640.0)	1440.0 (480.0; 2160.0)	0.0 (0.0; 0.0)	0.0 (0.0; 80.0)	320.0 (80.0; 640.0)	1440.0 (480.0; 2160.0)	240.0 (0.0; 960.0)
Moderate activity (MET min/week)	0.0 (0.0; 0.0)	160.0 (80.0; 240.0)	480.0 (320.0; 800.0)	1680.0 (1080.0; 3360.0)	0.0 (0.0; 0.0)	160.0 (80.0; 240.0)	480.0 (320.0; 800.0)	1800.0 (1120.0; 3360.0)	0.0 (0.0; 0.0)	160.0 (80.0; 240.0)	480.0 (320.0; 800.0)	1680.0 (1120.0; 3360.0)	480.0 (120.0; 1200.0)
Television time (h/day)	3.2 ± 1.8	2.9 ± 1.6	2.7 ± 1.5	2.7 ± 1.4	3.2 ± 1.8	2.8 ± 1.6	2.7 ± 1.5	2.7 ± 1.5	3.2 ± 1.8	2.8 ± 1.6	2.7 ± 1.5	2.7 ± 1.5	2.8 ± 1.5
Sleep duration (h/day)	7.1 ± 1.2	7.2 ± 1.1	7.2 ± 1.0	7.2 ± 1.1	7.2 ± 1.2	7.2 ± 1.1	7.2 ± 1.0	7.2 ± 1.0	7.2 ± 1.2	7.2 ± 1.0	7.2 ± 1.0	7.2 ± 1.0	7.2 ± 1.1
Education (%)													
College or university degree	2064 (28.1)	4567 (37.3)	7891 (36.8)	5841 (29.7)	6142 (28.2)	14,133 (37.7)	23,536 (36.7)	17,057 (28.9)	2030 (27.7)	4666 (37.3)	7995 (37.4)	5807 (29.5)	101,729 (33.5)
A/AS level	893 (12.2)	1615 (13.2)	2694 (12.6)	2104 (10.7)	2719 (12.5)	5022 (13.4)	7910 (12.3)	6553 (11.1)	890 (12.1)	1680 (13.4)	2584 (12.1)	2149 (10.9)	36,813 (12.1)

CSE	444 (6.0)	574 (4.7)	1022 (4.8)	1351 (6.9)	1239 (5.7)	1824 (4.9)	3079 (4.8)	3825 (6.5)	433 (5.9)	590 (4.7)	1003 (4.7)	1202 (6.1)	16,586 (5.5)
NVQ/HND/HNC	452 (6.2)	709 (5.8)	1336 (6.2)	1599 (8.1)	1323 (6.1)	2209 (5.9)	3985 (6.2)	4629 (7.8)	456 (6.2)	772 (6.2)	1328 (6.2)	1601 (8.1)	20,399 (6.7)
O level/GCSE	1833 (25.0)	2786 (22.8)	4721 (22.0)	4504 (22.9)	5395 (24.8)	8310 (22.2)	14,218 (22.2)	13,720 (23.2)	1865 (25.5)	2872 (23.0)	4743 (22.2)	4508 (22.9)	69,475 (22.9)
Other	1658 (22.6)	1995 (16.3)	3781 (17.6)	4265 (21.7)	4927 (22.7)	6013 (16.0)	11,345 (17.7)	13,255 (22.5)	1653 (22.6)	1934 (15.5)	3716 (17.4)	4406 (22.4)	58,948 (19.4)
Alcohol consumption (%)													
Previous	368 (5.0)	332 (2.7)	640 (3.0)	632 (3.2)	977 (4.5)	1062 (2.8)	1777 (2.8)	1781 (3.0)	328 (4.5)	365 (2.9)	555 (2.6)	614 (3.1)	9431 (3.1)
Daily or almost daily	1542 (21.0)	2746 (22.4)	4703 (21.9)	4353 (22.1)	4633 (21.3)	8479 (22.6)	14,231 (22.2)	13,049 (22.1)	1550 (21.2)	2802 (22.4)	4777 (22.4)	4350 (22.1)	67,215 (22.1)
3 or 4 times a week	1543 (21.0)	2958 (24.2)	5636 (26.3)	4984 (25.3)	4580 (21.1)	9189 (24.5)	16,972 (26.5)	14,677 (24.9)	1513 (20.6)	3053 (24.4)	5679 (26.6)	4820 (24.5)	75,604 (24.9)
Once or twice a week	1871 (25.5)	3177 (25.9)	5711 (26.6)	5256 (26.7)	5464 (25.1)	9815 (26.2)	17,017 (26.6)	15,913 (27.0)	1860 (25.4)	3248 (26.0)	5628 (26.3)	5453 (27.7)	80,413 (26.5)
1 to 3 times a month	856 (11.7)	1413 (11.5)	2338 (10.9)	2035 (10.3)	2682 (12.3)	4262 (11.4)	6792 (10.6)	6298 (10.7)	894 (12.2)	1436 (11.5)	2242 (10.5)	2048 (10.4)	33,296 (11.

													0)
Special occasions only	922 (12.6)	1265 (10.3)	1904 (8.9)	1831 (9.3)	2611 (12.0)	3710 (9.9)	5644 (8.8)	5657 (9.6)	908 (12.4)	1239 (9.9)	1937 (9.1)	1835 (9.3)	29,463 (9.7)
Never	237 (3.2)	354 (2.9)	505 (2.4)	567 (2.9)	784 (3.6)	982 (2.6)	1619 (2.5)	1637 (2.8)	268 (3.7)	368 (2.9)	545 (2.6)	548 (2.8)	8414 (2.8)
Smoking history (%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
Current	997 (13.6)	1247 (10.2)	1889 (8.8)	1880 (9.6)	2853 (13.1)	3780 (10.1)	5545 (8.7)	5569 (9.4)	959 (13.1)	1264 (10.1)	1898 (8.9)	1872 (9.5)	29,753 (9.8)
Previous	2535 (34.5)	4137 (33.8)	7402 (34.5)	7096 (36.1)	7589 (34.9)	12,724 (33.9)	22,329 (34.8)	21,233 (36.0)	2521 (34.4)	4308 (34.4)	7466 (34.9)	7045 (35.8)	106,385 (35.0)
Never	3791 (51.6)	6834 (55.8)	12,113 (56.5)	10,641 (54.1)	11,227 (51.6)	20,940 (55.8)	36,086 (56.3)	32,102 (54.4)	3831 (52.3)	6921 (55.3)	11,971 (56.0)	10,712 (54.5)	167,169 (55.0)
Diet	2.6 (4.9)	3.0 (4.5)	3.7 (4.3)	4.2 (4.4)	2.6 (5.0)	3.0 (4.7)	3.7 (4.4)	4.2 (4.4)	2.4 (5.2)	3.0 (4.6)	3.6 (4.3)	4.2 (4.4)	3.6 (4.5)
Medication (%)													
Blood pressure	1788 (24.3)	2439 (19.9)	3919 (18.3)	3440 (17.5)	4961 (22.8)	7148 (19.1)	11,246 (17.6)	9796 (16.6)	1569 (21.4)	2235 (17.9)	3560 (16.7)	3127 (15.9)	55,228 (18.2)

Cholesterol	1443 (19.6)	2124 (17.3)	3304 (15.4)	2997 (15.2)	3959 (18.2)	5634 (15.0)	8855 (13.8)	7837 (13.3)	1189 (16.2)	1650 (13.2)	2667 (12.5)	2277 (11.6)	43,936 (14.5)
Diabetes	96 (1.3)	108 (0.9)	163 (0.8)	153 (0.8)	324 (1.5)	368 (1.0)	469 (0.7)	410 (0.7)	109 (1.5)	99 (0.8)	164 (0.8)	127 (0.6)	2590 (0.9)
History of non-CHD CVD	244 (3.3)	338 (2.8)	537 (2.5)	516 (2.6)	739 (3.4)	879 (2.3)	1383 (2.2)	1321 (2.2)	210 (2.9)	311 (2.5)	410 (1.9)	417 (2.1)	7305 (2.4)
History of cancer	637 (8.7)	924 (7.5)	1744 (8.1)	1566 (8.0)	1804 (8.3)	3085 (8.2)	5241 (8.2)	4703 (8.0)	671 (9.2)	1038 (8.3)	1843 (8.6)	1636 (8.3)	24,892 (8.2)
Incidence rate (per 1000 person-years)													
CHD	9.6	7.4	6.6	7.4	6.9	5.5	5.1	5.6	5.2	4.0	4.0	4.1	5.6
Stroke	2.8	2.0	2.0	2.2	2.7	2.0	2.0	2.2	2.3	2.0	1.9	2.1	2.1
AF	7.2	6.2	6.2	6.5	5.1	4.3	4.2	4.5	3.5	3.1	3.1	3.3	4.6

Note: Data are represented as Mean ± SD, median (IQR, meaning the 25th percentile to the 75th percentile) or *n* (%).

Abbreviations: A/AS level = advanced/advanced subsidiary level; AF = atrial fibrillation; CHD = coronary heart disease; CSE = certificate of secondary education; CVD = cardiovascular disease; IQR = interquartile range; MET = metabolic equivalent of task; MVPA = moderate-to-vigorous physical activity; NVQ/HND/HNC = national vocational qualification/higher national diploma/higher national certificate; O level/GCSE = ordinary level/ general certificate of secondary education; PRS = polygenic risk score.

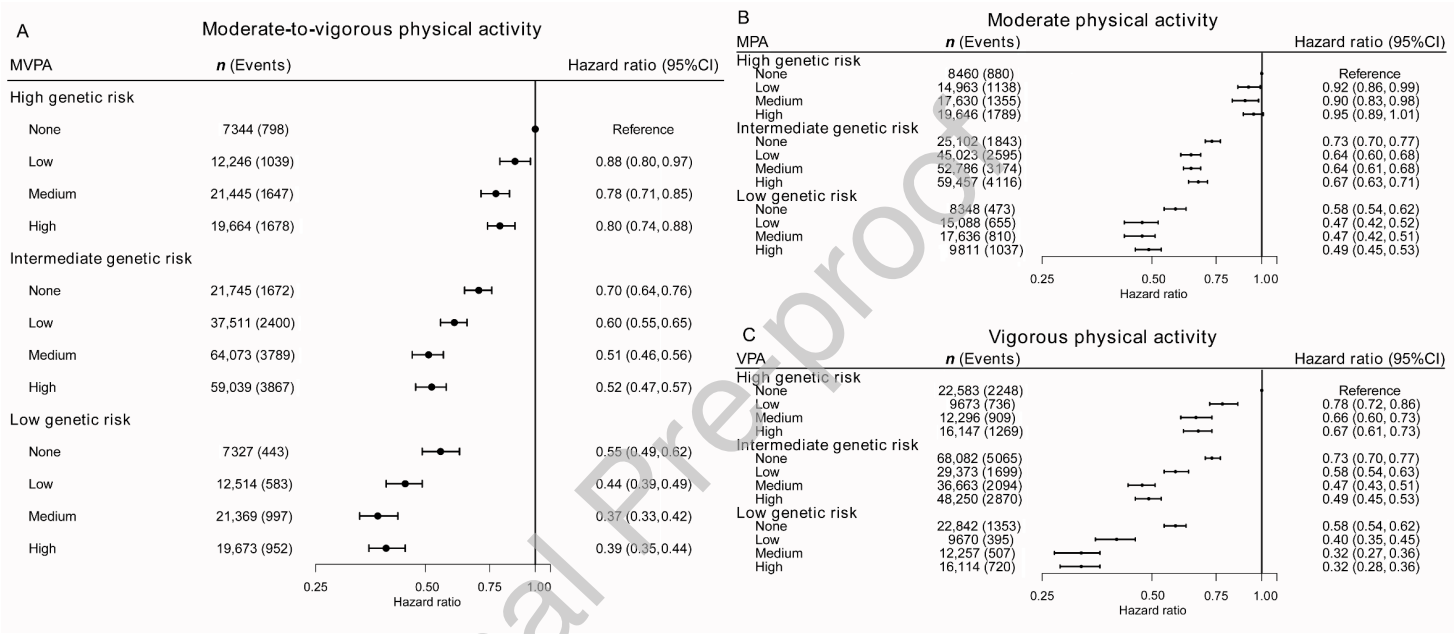

Fig. 1: Joint association of genetic risk and physical activity intensity with coronary heart disease incidence (*n* = 303,950; events = 19,865). Adjusted for age, sex, smoking status, alcohol consumption, moderate or vigorous intensity (intensity-specific models), sleep duration, diet, discretionary screen-time, education, non-outcome prevalent CVD, and medication use (cholesterol, blood pressure, and diabetes). 95%CI = 95% confidence interval; CVD = cardiovascular disease; MPA = moderate physical activity; MVPA = moderate-to-vigorous physical activity; VPA = vigorous physical activity.

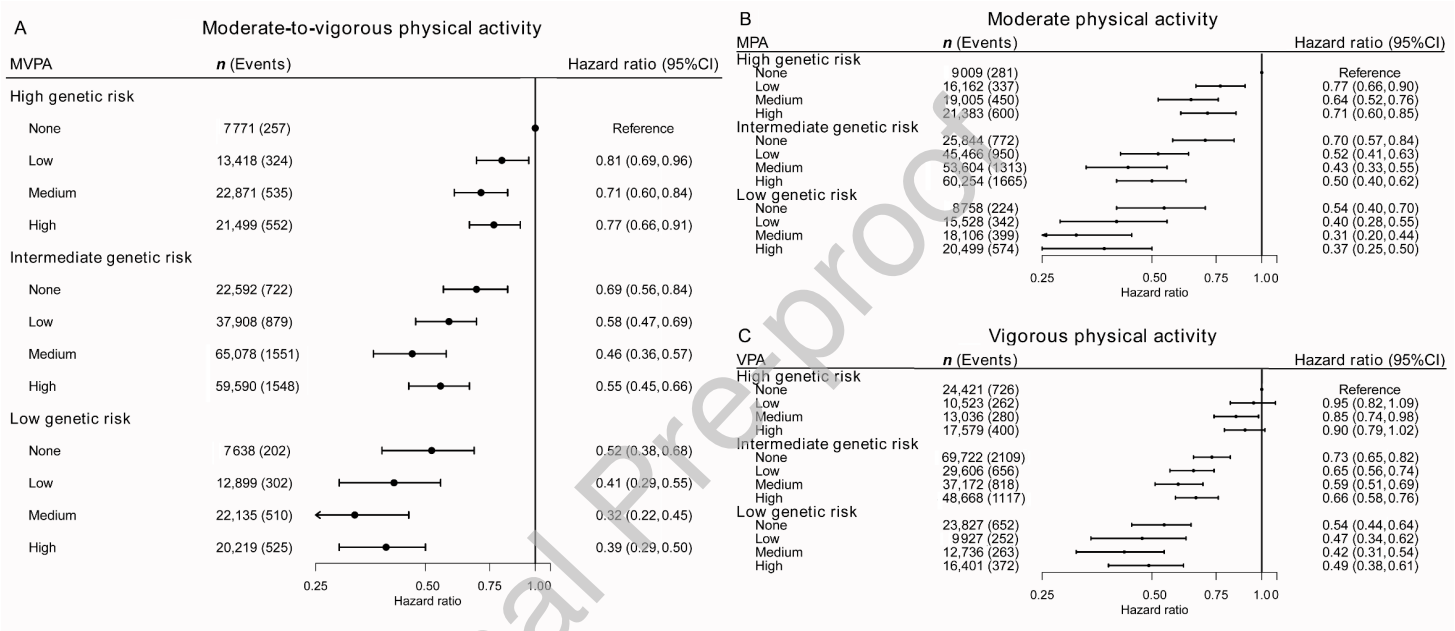

Fig. 2. Joint association of genetic risk and physical activity intensity with stroke (*n* = 313,618; events = 7907). Adjusted for age, sex, smoking status, alcohol consumption, moderate or vigorous intensity (intensity-specific models), sleep duration, diet, discretionary screen-time, education, non-outcome prevalent CVD, and medication use (cholesterol, blood pressure, and diabetes). 95%CI = 95% confidence interval; CVD = cardiovascular disease; MPA = moderate physical activity; MVPA = moderate-to-vigorous physical activity; VPA = vigorous physical activity.

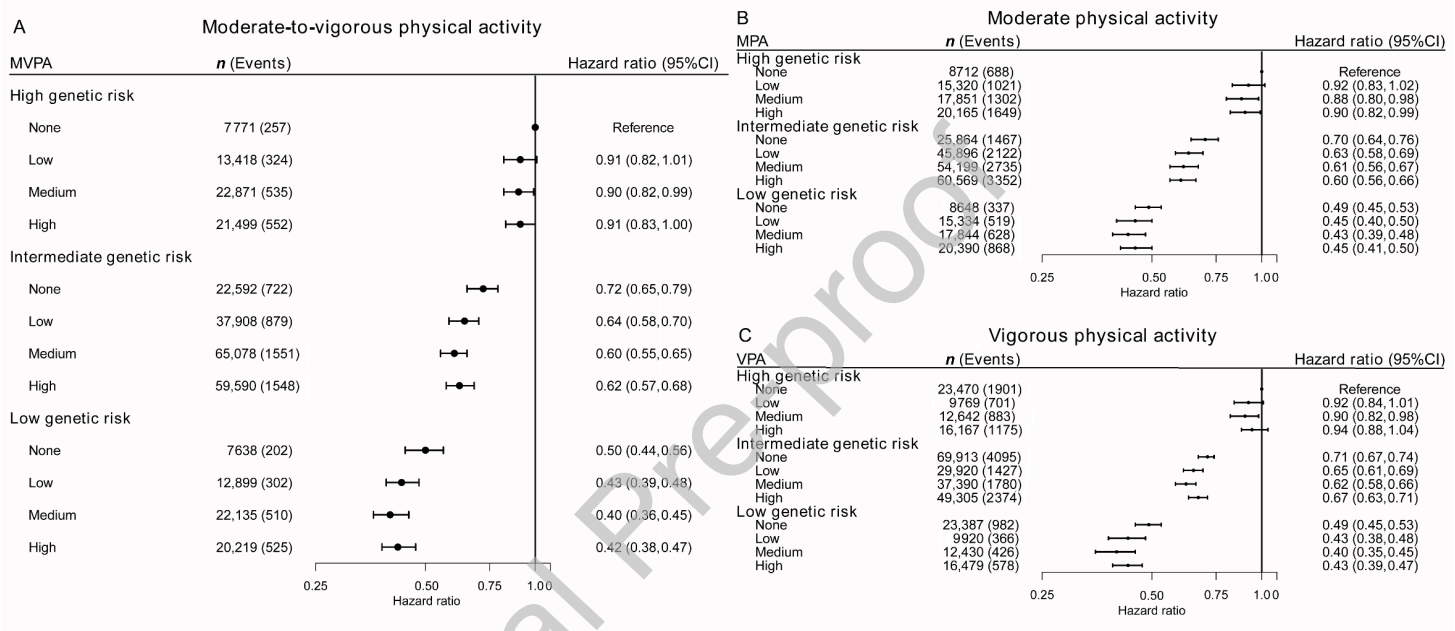

Fig. 3. Joint association of genetic risk and physical activity intensity with atrial fibrillation (*n* = 310,792; events = 16,688). Adjusted for age, sex, smoking status, alcohol consumption, moderate or vigorous intensity (intensity-specific models), sleep duration, diet, discretionary screen-time, education, non-outcome prevalent CVD, and medication use (cholesterol, blood pressure, and diabetes). 95%CI = 95% confidence interval; CVD = cardiovascular disease; MPA = moderate physical activity; MVPA = moderate-to-vigorous physical activity; VPA = vigorous physical activity..