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Interaction of accelerometer-measured physical activity and genetic risk on cardiovascular diseases: a prospective cohort study from UK Biobank

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ABSTRACT

Objectives This study aimed to evaluate the interactions of physical activity and polygenic risk score (PRS) on risks of atrial fibrillation, coronary heart disease (CHD), hypertension, and ischaemic stroke.

Methods This study included 91 629 participants from UK Biobank in this study, all of whom had worn a wrist-worn accelerometer for 7 consecutive days. We computed total volume of physical activity (TPA) and time spent in moderate to vigorous intensity physical activity (MVPA) and light intensity physical activity (LPA). Cox proportional hazard models were used to evaluate associations of physical activity with the four cardiovascular outcomes. Interactions between physical activity and PRS were investigated on multiplicative and additive scales.

Results During a median follow-up of 7.9 years, 3811 atrial fibrillation, 3994 CHD, 7345 hypertension and 1001 ischaemic stroke cases were recorded. TPA, MVPA and LPA were all negatively associated with risks of the four cardiovascular outcomes, generally independent of genetic risk. Association between LPA and atrial fibrillation was U-shaped among low-PRS stratum (p=0.01), and association between TPA and hypertension was attenuated with genetic risk increasing (p=0.02). Attributable risk (AR) of inactivity was higher in the high-PRS population. For example, increasing MVPA resulted in a twofold greater reduction in CHD cases among individuals with high PRS (AR=2.17%) than among those with low PRS (AR=1.09%).

Conclusions Increasing physical activity, including LPA, was associated with a reduced risk of cardiovascular diseases. The extent of this benefit may differ among individuals with different genetic risks.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Physical activity is a protective factor against cardiovascular diseases.

WHAT THIS STUDY ADDS

⇒ The benefit of increasing physical activity may vary based on genetic risk, the intensity of physical activity and specific disease categories.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ While population-wide physical activity promotion remains crucial, a greater reduction in cardiovascular disease burden can be achieved by focusing on high-risk individuals identified through polygenic risk scores.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of global mortality and a major contributor to disability.[1–3] To reduce the incidence of CVDs, the WHO recommends all adults engage in at least 150 min of moderate-intensity, or 75 min of vigorous-intensity physical activity per week, or any equivalent combination of the two.[4] However, more than a quarter of adults fail to meet the recommendation globally, and the situation is worsening in high-income countries.[5] Inactivity contributes significantly to the global health and economic burden[6] and has been a major concern of public health.[7 8] Worldwide, 7.6% of CVD deaths and 5.0% of coronary heart diseases (CHD) and strokes are attributable to physical inactivity.[9]

However, most of the evidence for associations between physical activity and health outcomes is based on self-report,[10] which is prone to reporting bias and measurement error.[11 12] Moreover, the impact of light intensity physical activity (LPA) on health remains unclear, as self-reporting cannot capture these ubiquitous behaviours accurately.[13] Given that LPA, such as stroll and light intensity housework, is a feasible way to keep active for some elderly and activity-limited people, it is important to clarify its impact on health outcomes. In recent years, wearable devices such as accelerometers have been used in many population-based cohorts to objectively quantify physical activity. A few studies investigated associations between accelerometer-measured

physical activity and specific disease risk but paid less attention to LPA.[14–16]

As massive single-nucleotide polymorphisms (SNPs) were identified through extensive genome-wide association studies, the polygenic risk score (PRS), constructed by multiple risk-associated SNPs, proves to be a valuable tool for quantifying individual genetic susceptibility to complex diseases. Taking PRS into clinical and public health decision-making considerations could help to identify high-risk populations and implement personalised intervention. Although gene–environment interactions are gaining attention in CVD prevention, few studies examined these interactions due to limited sample size, difficulty in precise estimation of exposure and the weak effects of genetic and environmental factors.[17]

In this prospective cohort study, we evaluated the associations between accelerometer-measured total and intensity-specific physical activity and the risk of four common CVD outcomes, including hypertension, atrial fibrillation (AF), CHD and ischaemic stroke (IS). Then, we investigated the interactions between physical activity and PRS on CVD risks on both multiplicative and additive scales.

METHODS

Study design and participants

UK Biobank is a prospective population-based cohort, in which approximately 500 000 residents in the UK aged 40–69 were recruited between 2006 and 2010. The baseline data were collected in 22 assessment centres throughout the UK, including sociodemographic characteristics, lifestyles, biological samples and physical measurements.[18] Field IDs of data from UK Biobank are listed in online supplemental table 1. Between 2013 and 2015, approximately 100 000 participants of the UK Biobank accepted the invitation to physical activity measurement. They were asked to wear a wrist-worn triaxial accelerometer (Axivity, Newcastle, UK) on their dominant wrist for 7 consecutive 24 hour days and carry on with their normal activities. Detailed procedures of this assessment and raw data processing were reported elsewhere.[19] The main analysis excluded participants (1) without available data derived from the accelerometer; (2) with insufficient wear time or with an implausibly high acceleration average (>100 mg); (3) without qualified genetic data to compute standard PRS; (4) lost to follow-up or developing AF, CHD, hypertension or IS before completing the physical activity measurement or (5) with missing covariates data.

Accelerometer-measured physical activity

The Euclidean norm of acceleration minus one gravitational unit averaged over 7 days (the unit is milli-gravity units, mg) was used to quantify the total volume of physical activity (TPA) of each participant. Previous studies have demonstrated the validity of acceleration intensity at the dominant wrist as an estimate of energy expenditure.[20 21] The average time spent in moderate to vigorous intensity physical activity (MVPA) and LPA per day (minutes) was estimated using machine learning models.[22] The MVPA and LPA were defined as physical activities in ≥3 metabolic equivalent of tasks (METs) and 1.5–3 METs, respectively. In this study, TPA, MVPA and LPA were all stratified into three groups: TPA was based on tertiles (T1, T2 and T3), while MVPA (<150, 150–350 and >350 min per week) and LPA (<1800, 1800–2400 and >2400 min per week) were according to cut-off values of time accumulated weekly.

Genetic susceptibility

Genetic susceptibilities to AF, CHD, hypertension and IS were estimated by standard PRS constructed by Thompson *et al*.[23] The PRS was generated using a Bayesian approach applied to meta-analysed summary statistics obtained entirely from external GWAS data. PRS values were calculated as the genome-wide sum posterior effect size of each variant, multiplied by allele dosage, with subsequent centring and standardisation according to the genetic ancestry, as described in their paper. In this study, participants were classified into three genetic risk categories based on the tertiles of PRS: low, medium and high PRS.

Outcomes

Outcomes were determined by the algorithmically defined outcomes (IS) or the first occurrences of outcomes (AF, CHD and hypertension) which combined data from linkage to electronic health records and self-reported medical conditions at baseline of UK Biobank. The incident cases were defined as their first diagnosis of the specific disease after completing the accelerometer assessment, while the prevalent cases were those who developed the outcome disease before it. The follow-up time for each participant was calculated from the last day of wearing the accelerometer until the date of onset, death, dropout or the censoring date of UK Biobank at the time of analysis (31 October 2022), whichever came first.

Covariates

Participants completed a touchscreen questionnaire, providing the following information: sex (male or female), race (white or others), education level (with or without college or university degree), smoking status (never, previous or current), alcohol consumption (never or special occasions only, one to three times a month, once or twice a week, three or four times a week, daily or on most days) and diet (healthy, intermediate or unhealthy). A healthy, intermediate or unhealthy diet was respectively defined as meeting 4–5, 2–3 or 0–1 of the following five items: vegetable intake ≥four tablespoons/day; fruit intake ≥three pieces/day; fish intake ≥twice/week; unprocessed red meat intake ≤twice/week and processed meat intake ≤twice/week. Townsend Deprivation Index (TDI) is a composite score of deprivation, with a greater score indicating a greater degree of deprivation.

TDI at recruitment was based on the preceding national census and assigned to each participant according to postcode, divided into four levels based on quartile.

Statistical analysis

Analyses were performed using SAS V.9.4 and R V.4.2.2. We employed two-sided tests for all statistical analyses and considered a p<0.05 as statistically significant. Descriptive statistics were presented as count (proportions) for categorical variables or median (IQR) for continuous variables. Associations between specific exposure variables and the risk of specific diseases were assessed using Cox proportional hazards models with age as the time scale. The proportional hazards assumption was checked using the Schoenfeld residuals. As sex violated the proportional hazards assumption (p<0.001), we stratified the Cox regression models on sex. Although no intersection was found in the Kaplan-Meier curve (online supplemental figure 1), the Schoenfeld residuals testing suggested that MVPA violated the proportional hazards assumption in the analysis of hypertension. Thus, we interpreted the HR as an average effect measure of the time-varying HRs over the entire follow-up period.[24] Sex, race, education, TDI, smoking status, alcohol consumption and diet quality were adjusted in the main analyses. LPA was also adjusted in the MVPA analyses and vice versa. We repeated our main analyses by excluding participants diagnosed with CVD within the first year of follow-up to avoid reverse causation. The shape of the relation was explored by using restricted cubic spline (RCS, knots=3), with data trimmed to reduce the influence of outliers. Departure from linearity was examined using the Wald test.

We examined the joint associations of physical activity and PRS with CVDs by categorising participants into 3×3 groups. To predict the survival curves using the Cox models, baseline hazard functions were estimated by using the Breslow estimator.[25] Survival functions of the nine groups were derived by fixing covariates to certain values: female, white, without a college or university degree, in the second quartile group of TDI, never smoking, drinking once or twice a week, with intermediate diet quality and with 1800–2400 min LPA (for MVPA) or 150–300 min MVPA (for LPA) per week. The cumulative incident rates at 70 years old were obtained to compare the absolute risks between the groups. Interaction on a multiplicative scale was evaluated by adding a product term of physical activity and genetic risk into the multivariable Cox proportional hazards models and comparing models with and without the product term using the likelihood ratio test. Interaction on an additive scale was evaluated using the relative excess risk due to interaction (RERI) and the 95% CI of RERI was calculated using the delta method.

RESULTS

Characteristics of participants

After excluding participants with incomplete or low-quality data, 91 629 participants were retained. By further excluding pre-existing cases before accelerometer assessment, 88 998, 86 362, 66 923 and 90 651 participants were left for the main analyses for AF, CHD, hypertension and IS, respectively (online supplemental figure 2). As shown in table 1, of all 91 629 participants, the median age at baseline was 63. Of which, 56% were female, 92% were white, and 44% had a college or university degree. Baseline characteristics of participants included in analyses of each outcome are presented in online supplemental table 2.

Table 1 Baseline characteristics of participants

Characteristic	No. (%)
Total	91 629
Age (years)*	63 (56, 69)
Female	51 638 (56.4)
White	84 319 (92.0)
Higher education	40 082 (43.7)
Townsend Deprivation Index*	–2.470 (–3.830, –0.220)
Smoking status	
Never	52 411 (57.2)
Previous	32 946 (36.0)
Current	6272 (6.8)
Alcohol consumption	
Daily or on most days	21 080 (23.0)
Three or four times a week	23 982 (26.2)
Once or twice a week	22 956 (25.1)
One to three times a month	9945 (10.9)
Never or special occasions only	13 666 (14.9)
Diet quality†	
Healthy	42 664 (46.6)
Intermediate	41 775 (45.6)
Unhealthy	7190 (7.8)
MVPA (min/week)*	232 (113, 403)
LPA (min/week)*	2069 (1637, 2552)

*Continuous variables are presented as median (IQR).
†Diet quality was determined by the number of dietary recommendations met by each participant, as detailed in the 'Methods section'.
LPA, light intensity physical activity; MVPA, moderate to vigorous intensity physical activity.

Associations of physical activity with CVDs

During a median follow-up of 7.9 years, 3811 (4.28%) participants developed AF, 3994 (4.62%) developed CHD, 7345 (10.98%) developed hypertension and 1001 (1.10%) developed IS. After adjusting all covariates, increased TPA, MVPA and LPA were all associated with lower risks of the four CVDs, whereas associations of LPA with CVDs were relatively weak (table 2). The findings did not change substantially after excluding cases diagnosed within the first 1 year of the follow-up (online supplemental table 3).

Table 2 Associations between physical activity and specific cardiovascular diseases

	Atrial fibrillation	Coronary heart disease	Hypertension	Ischaemic stroke
Total volume of physical activity				
T1	Reference	Reference	Reference	Reference
T2	0.79 (0.73 to 0.85)	0.78 (0.68 to 0.91)	0.81 (0.77 to 0.86)	0.74 (0.59 to 0.93)
T3	0.75 (0.69 to 0.82)	0.71 (0.60 to 0.84)	0.67 (0.63 to 0.71)	0.68 (0.52 to 0.89)
Moderate to vigorous intensity physical activity (MVPA) (minutes per week)				
<150	Reference	Reference	Reference	Reference
150–350	0.78 (0.72 to 0.84)	0.77 (0.72 to 0.83)	0.75 (0.71 to 0.79)	0.85 (0.73 to 0.98)
>350	0.75 (0.69 to 0.82)	0.67 (0.62 to 0.73)	0.64 (0.61 to 0.68)	0.72 (0.61 to 0.84)
Light intensity physical activity (LPA) (minutes per week)				
<1800	Reference	Reference	Reference	Reference
1800–2400	0.94 (0.88 to 1.02)	0.96 (0.89 to 1.03)	0.92 (0.87 to 0.98)	0.86 (0.74 to 1.00)
>2400	0.88 (0.81 to 0.96)	0.89 (0.82 to 0.97)	0.88 (0.83 to 0.93)	0.84 (0.71 to 0.98)

The HRs and 95% CIs were estimated from Cox regression models adjusting for age (as timescale), sex, race, education, Townsend Deprivation Index, smoking status, alcohol consumption, diet quality, LPA (for MVPA analyses) and MVPA (for LPA analyses).

Dose–response associations between physical activity and CVDs were evaluated by RCS (figure 1). Negative linear relations were found for TPA and LPA. However, the association between MVPA and incident AF was J-shaped, with the lowest HR at approximately 300–400 min and then slightly increasing (figure 1e). Besides, for MVPA, its associations with CHD and hypertension were L-shaped. After MVPA reached 400 min per week, further increasing might not lead to a further decrease in the risk of CHD and hypertension (figure 1f,g).

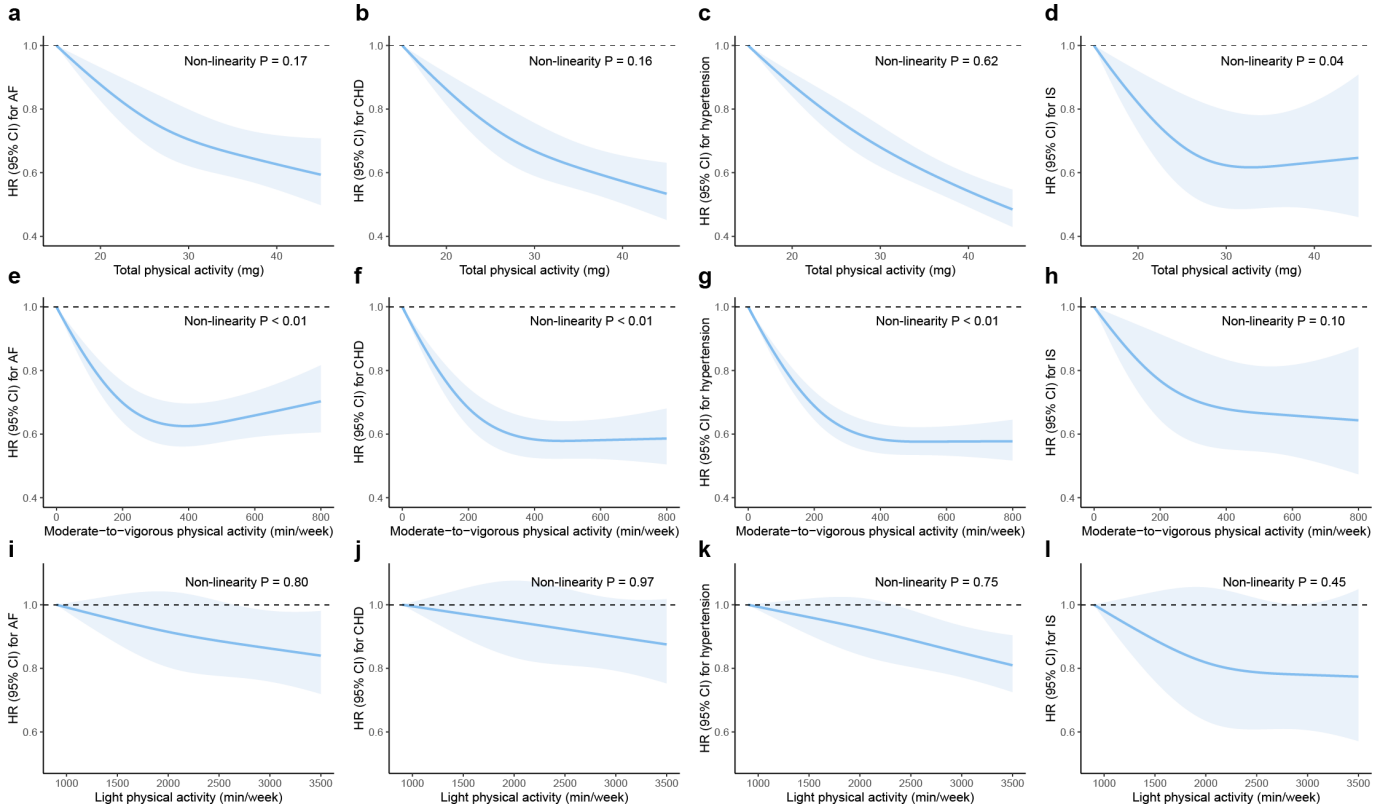

Figure 1 Dose–response relations between physical activity and specific cardiovascular diseases. The solid line denotes HRs and the shaded area denotes 95% CIs. Sex, race, education, TDI, smoking status, alcohol consumption, diet quality, LPA (for MVPA analyses) and MVPA (for LPA analyses) were adjusted. AF, atrial fibrillation; CHD, coronary heart disease; IS, ischaemic stroke; LPA, light physical activity; MVPA, moderate to vigorous physical activity; TDI, Townsend Deprivation Index.

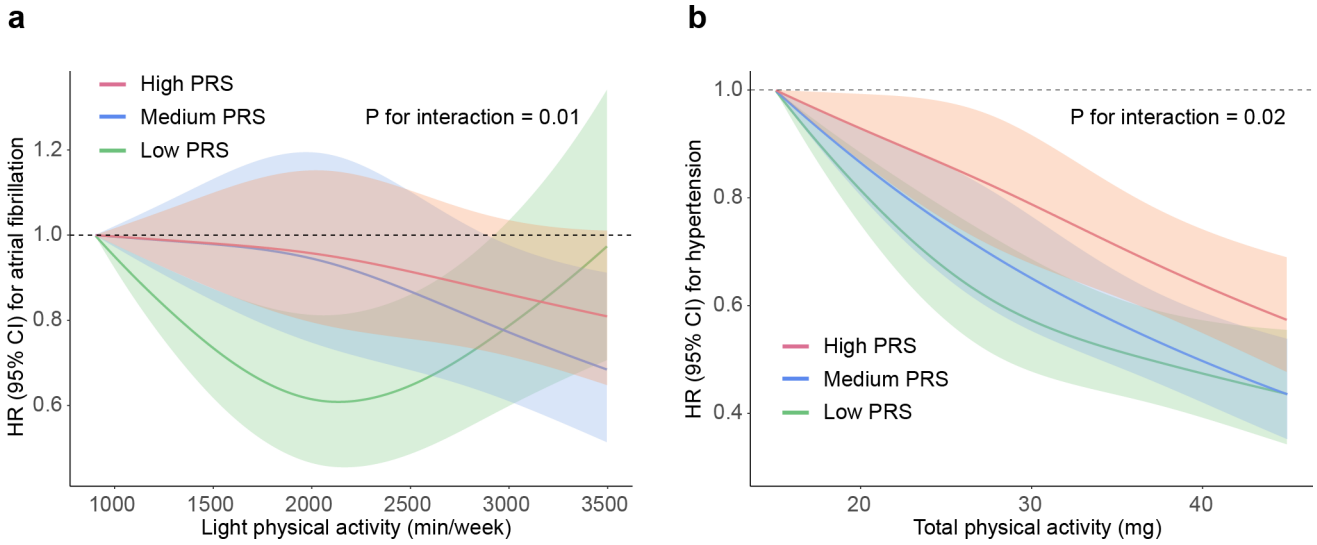

Figure 2 Polygenic risk score (PRS)-stratified dose–response relations. (a) PRS-stratified dose–response relations between light intensity physical activity and atrial fibrillation. (b) PRS-stratified dose–response relations between total volume of physical activity and hypertension. The solid line denotes HRs and the shaded area denotes 95% CIs. Sex, race, education, TDI, smoking status, alcohol consumption and diet quality were adjusted. TDI, Townsend Deprivation Index.

Multiplicative interactions

The distributions of PRS among CVD cases and controls are shown in online supplemental figure 3. Compared with the low PRS group, the HRs (95% CIs) of individuals with high PRS (top tertile) were 2.58 (2.38 to 2.81), 2.00 (1.85 to 2.17), 1.79 (1.6 to 1.90) and 1.66 (1.42 to 1.93) for AF, CHD, hypertension and IS, respectively (online supplemental table 4). In most cases, the effect of physical activity did not significantly vary among three genetic risk strata (online supplemental tables 5–8). Remarkably, although negative linear relations were found between LPA and AF risks in the high and medium PRS strata, in the low PRS stratum, the association was U-shaped, with the lowest risk at weekly 2100 min LPA (figure 2a, online supplemental table 5). In addition, the association between TPA and hypertension was stronger in individuals with low PRS than those with high PRS, as shown in figure 2b and online supplemental table 7.

Additive interactions

Attributable risks of physical activity stratified by genetic risk are shown in figure 3. The highest risk groups were found in participants with high PRS and low physical activity across all outcomes. For example, the incidence of AF for participants in the high TPA and low PRS joint group was 1.52%, while the incidence of AF for participants in the low TPA and high PRS joint group can be as high as 5.27% (figure 3a). By calculating the RERI and its 95% CI, four statistically significant additive interactions between PRS and physical activity were identified (online supplemental tables 9–11). For example, the attributable risk of LPA for IS in participants with high PRS was 0.28 while the attributable risk in participants with low PRS was −0.02 (RERI=0.44 95% CI 0.01 to 0.88) (figure 3i, online supplemental table 12).

DISCUSSION

In this study, we systematically evaluated the association of accelerometer-measured physical activity with four CVD outcomes. We found that increased TPA, MVPA or LPA was all significantly associated with lower risk of CVDs. MVPA demonstrated a strong effect with no minimum threshold, but a ceiling effect was observed. By further incorporating genetic susceptibility, we identified two significant multiplicative interactions and four significant additive interactions between physical activity and PRS, indicating the modification effect of genetic risk on the association of physical activity with CVDs.

Among the four outcomes in our study, which shared common risk factors and pathophysiology, hypertension had the strongest association with physical activity. The relation between physical activity and cardiovascular events may be mediated by blood pressure,[26] as well as other subclinical cardiovascular-related factors like arterial stiffness and lipid profile.[27 28] A J-shaped relation was found between MVPA and AF risk in our study, which was slightly different from what Shaan *et al* found. According to their results, 150–300 min of MVPA per week was associated with a lower risk of AF (HR 0.78, 95% CI 0.70 to 0.87), while more than 300 min of MVPA per week was not (HR 0.89, 95% CI 0.78 to 1.01).[14] The discrepancy may be explained by the fact that they used a cut-point method to identify MVPA (defined as the sum of 5 s epochs where mean acceleration was ≥100 mg), whereas we used the machine learning model which has a higher accuracy of intensity classification.[22] Remarkably, we found that individuals may benefit from more than 10% CVD hazard rate reduction by increasing enough LPA, potentially attributable to the shorter duration in sedentary behaviour. Previous studies indicated no statistically significant correlation between LPA and the risk of CVDs,

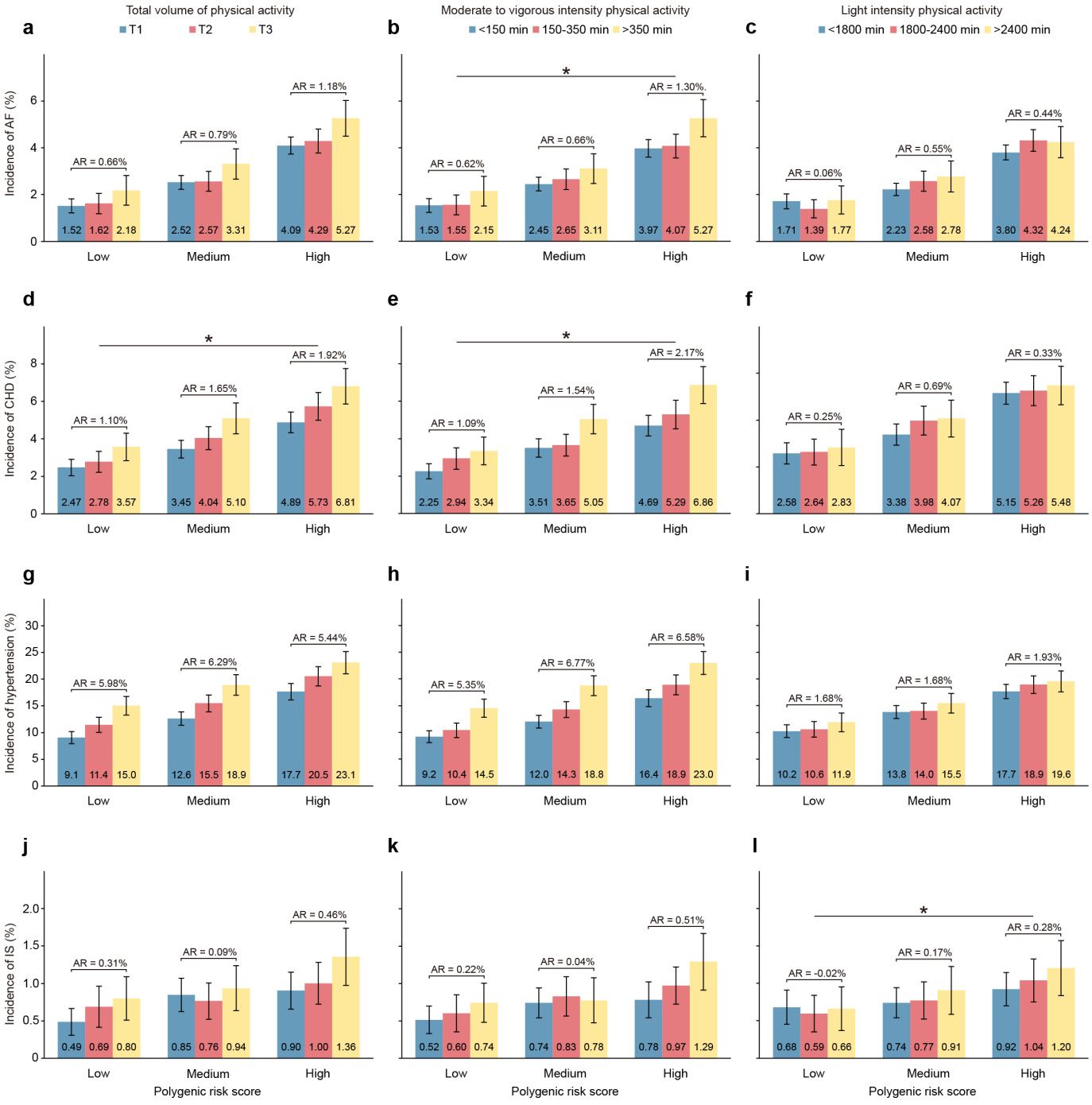

Figure 3 Attributable risks of physical activity for specific cardiovascular diseases stratified by polygenic risk score. Cumulative incidence at 70 years old was estimated by Cox regression model, fixing covariates as female, white, without a college or university degree, in the second quartile group of Townsend Deprivation Index, never smoking, drinking once or twice a week, with intermediate diet quality, and with 1800–2400 min LPA (for MVPA analyses) or 150–300 min MVPA (for LPA analyses) per week. The * denotes a statistically significant additive interaction. The error bars represent the 95% CIs. AF, atrial fibrillation; AR, attributable risk; CHD, coronary heart disease; IS, ischaemic stroke; LPA, light physical activity; MVPA, moderate to vigorous physical activity.

which may be due to the low power of statistical testing and varied methodologies of LPA identification.[29] For those with poor mobility, increasing LPA is easy to achieve and may have better compliance. Additionally, a recent study showed that lower CVD and all-cause mortality were observed among older adults engaging in light-moderate exercise, rather than more intense exercise.[30]

For our most results, physical activity was associated with the risks of CVD-related outcomes independently of genetic risk, which is consistent with previous studies.[31–33] Particularly, there were statistically significant multiplicative interactions between PRS and LPA on incident AF, and between PRS and TPA on incident hypertension. In both cases, weakened effects were observed in the stratum

of higher PRS. An explanation is that CVDs occurring in individuals with low genetic susceptibility are primarily linked to modifiable factors, but cases with high PRS are largely driven by genetic variants and the pathogenic pathways might be independent of physical activity. These new findings require further validation in other populations. In the additive interaction analyses, we found four positive additive interactions between physical activity and PRS. All of these results demonstrated that an increment in physical activity could result in more reduction of CVDs in the population with high PRS. Similar results were found in another study that focused on CHD.[32]

Public health implications

Physical activity contributes to the prevention of CVDs for people with different genetic susceptibility. MVPA demonstrates effectiveness with no minimum threshold. Meanwhile, people should also be encouraged to engage in LPA and reduce sedentary behaviour. A more significant reduction in CVD burden can be achieved by increasing physical activity among individuals with high PRS. Moreover, the subgroup might exhibit better adherence to a healthy lifestyle due to intensified risk perception.[34] Therefore, the importance of physical activity should be further emphasised among this population.

Strengths and limitations

This was among the first studies investigating the interactions between objectively measured physical activity and genetic risk on incident AF, CHD, hypertension and IS. Major strengths are as follows. First, we included nearly 100 000 participants with integrated data on physical activity measurement, genetics and health outcomes in this large population-based prospective study. Second, the physical activity data of participants were derived from accelerometers worn for 7 days, rather than questionnaires which are subjective and unable to give precise information about the intensity and volume of activities. Third, to identify intensity-specific physical activities, we used a validated machine learning model that has better performance compared with the cut-point method. Meanwhile, several limitations should be noted. First, most participants in this study are white British, which may impair the generalisability of our conclusions. Second, the accelerometer assessment within 7 days may not represent the long-term pattern of physical activity. Third, causal relationships between physical activity and CVDs may not be directly inferred from this study, although we tried to reduce the influences of confounding and reverse causation by adjusting covariates and a sensitivity analysis of excluding cases diagnosed within the first year of follow-up.

CONCLUSIONS

TPA, MVPA and LPA all demonstrated inverse associations with incident CVDs. Interactions between physical activity and genetic risk were observed on both multiplicative and additive scales. Further investigation is needed to validate these findings.

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Contributors LZ, TL and HC contributed to the conception and study design. QZ, SX and YX collected, assembled the data. CX and QZ carried out statistical analyses. SX, YX, WG, YZ and HC advised on statistical analysis and interpreted the data. CX drafted the first manuscript, and QZ, LZ, TL and HC substantively revised it. All authors reviewed the manuscript and approved the final version. HC is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by North West - Haydock Research Ethics Committee (IRAS project ID: 299116). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The data from UK Biobank cannot be shared directly due to the material transfer agreement but can be accessed by researchers on the application (https://www.ukbiobank.ac.uk/). This research was conducted using the application number 78559.

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