# Association between questionnaire-based and accelerometer-based physical activity and the incidence of chronic kidney disease using data from UK Biobank: a prospective cohort study

Xingyuan Zhang,[a,b,c,i] Ye-Mao Liu,[a,b,d,i] Fang Lei,[e] Xuewei Huang,[f] Weifang Liu,[g] Tao Sun,[g] Lijin Lin,[g] Peng Zhang,[c] Jingjing Cai,[f] Xiao-Jing Zhang,[a,b,c,*] Zhouyi Wang,[h,**] and Hongliang Li[a,b,g,***]

[a]State Key Laboratory of New Drug Discovery and Development for Major Diseases, Gannan Medical University, Ganzhou, China
[b]Gannan Innovation and Translational Medicine Research Institute, Gannan Medical University, Ganzhou, China
[c]School of Basic Medical Sciences, Wuhan University, Wuhan, China
[d]Department of Cardiology, Huanggang Central Hospital, Huanggang, China
[e]Medical Science Research Center, Zhongnan Hospital of Wuhan University, Wuhan, China
[f]Department of Cardiology, The Third Xiangya Hospital of Central South University, Changsha, China
[g]Department of Cardiology, Renmin Hospital of Wuhan University, Wuhan, China
[h]Department of Rehabilitation Medicine, Huanggang Central Hospital of Yangtze University, Huanggang, China

eClinicalMedicine
2023;66: 102323

Published Online xxx
https://doi.org/10.1016/j.eclinm.2023.102323

## Summary

**Background** Prior studies on the relationship between chronic kidney disease (CKD) and physical activity (PA) mainly relied on subjective PA data and rarely considered the genetic risk. This study aims to thoroughly investigate this relationship by utilizing both accelerometer-measured and questionnaire-measured PA data.

**Methods** This prospective cohort study encompasses two cohorts from the UK Biobank. The questionnaire-based cohort involves 448,444 CKD-free participants who completed an International Physical Activity Questionnaire between 2006 and 2010 and had genetic data. PA was categorized into distinct activities: leisure, housework, job-related, and transportation. The accelerometer-based cohort involves 89,296 CKD-free participants who provided a full week of accelerometer-based physical activity data between 2013 and 2015 and had genetic data. PA was classified as light-intensity, moderate-intensity, vigorous-intensity, moderate to vigorous-intensity PA (LPA, MPA, VPA, MVPA), and total PA. Incident CKD was ascertained from linked hospital inpatient and death records. Genetic risk was assessed using polygenic risk scores. Cox proportional hazard models with restricted cubic splines were used for the analysis.

**Findings** In the questionnaire-based cohort, 18,184 (4.05%) participants developed CKD during 13.6 years of follow-up. Engaging in strenuous sports, other exercises, walking for pleasure, stair climbing, and heavy DIY were associated with a reduced risk of CKD. In the accelerometer-based cohort, 2297 (2.57%) participants developed CKD during 7.9 years of follow-up. Higher levels [highest quartile vs lowest quartile] of MPA (HR 0.639, 95% CI 0.554–0.737), VPA (HR 0.639, 95% CI 0.549–0.745), MVPA (HR 0.630, 95% CI 0.545–0.729), and total PA (HR 0.649, 95% CI 0.563–0.750) were associated with a lower CKD risk. There were significant interactions between MPA and genetic risk on the risk of CKD incidence (P for interaction = 0.025). A linear dose–response relationship was observed between MPA, total PA, and the risk of CKD incidence with no minimal or maximal threshold. These associations are robust in different subgroups and a series of sensitivity analyses.

**Interpretation** Engaging in multiple types of PA and higher levels of total PA, MPA, VPA, and MVPA may be associated with a lower risk of developing CKD, regardless of genetic risk. This finding holds substantial implications for clinical approaches to CKD prevention and provides evidence to inform future PA guideline development.

*Corresponding author. School of Basic Medical Sciences of Wuhan University, 115 Donghu Road, Wuhan, 430060, China.
**Corresponding author. Department of Rehabilitation Medicine, Huanggang Central Hospital of Yangtze University, 11 Kaopeng Street, Huanggang, 438000, China.
***Corresponding author. Department of Cardiology, Renmin Hospital of Wuhan University, 99 Zhangzhidong Rd, Wuhan, 430060, China.
*E-mail addresses:* zhangxjing@whu.edu.cn (X.-J. Zhang), wangzhouyi0730@163.com (Z. Wang), lihl@whu.edu.cn (H. Li).
[i]These authors have contributed equally to this work.

Funding Medical Science Advancement Program of Wuhan University, and the National Science Foundation of China.



Keywords: Physical activity; Questionnaire; Accelerometer; Chronic kidney disease

## Research in context

### Evidence before this study

We conducted a comprehensive search on PubMed for studies published until July 01, 2023, using search terms including accelerometer, device, physical activity, PA, exercise, sports, kidney, chronic kidney disease, CKD, renal function, and renal disease, with these terms present in abstracts, titles, or MESH headings. We also searched references listed in the identified papers. Some previous studies suggest a protective role for physical activity (PA) in chronic kidney disease (CKD). However, previous studies mainly relied on subjective questionnaire data, and subjective PA data may have limitations in accurately capturing the intensity and duration of full-day PA, and there is potential recall bias and measurement error during data collection. In contrast, data collected from wrist-worn accelerometers provide a comprehensive assessment of PA by capturing its intensity and duration. It is crucial to investigate the relationship between PA and CKD using PA data measured by wrist-worn accelerometers.

### Added value of this study

Our study thoroughly investigated the relationship between PA and the risk of CKD incidence by utilizing both accelerometer-measured and questionnaire-measured PA data. We found that engaging in multiple types of PA and higher levels of total PA, MPA, VPA, and MVPA were associated with a lower risk of developing CKD, regardless of genetic risk. A linear dose–response relationship was observed between accelerometer-measured MPA, total PA, and the risk of CKD incidence. Individuals can still benefit from engaging in higher levels of PA even after meeting the recommended levels by the WHO. Besides, there were significant interactions between MPA and genetic risk on the risk of CKD incidence.

### Implications of all the available evidence

Our study and prior research provide evidence for considering PA as a potential intervention measure for both preventing and treating CKD. The current PA guidelines mainly rely on subjective PA data. Our study, along with other accelerometer-based studies, provides evidence to inform clinical treatment strategies and future revision of PA guidelines. By incorporating objective PA data, these guidelines can provide more accurate recommendations for individuals to reduce the burden of NCDs.

## Introduction

Chronic kidney disease (CKD), typically characterized by a low glomerular filtration rate (GFR) or elevated albuminuria,[1] has emerged as a significant global public health concern.[2] CKD has contributed to a considerable number of deaths and disabilities globally,[3] placing a heavy burden on the global healthcare system. According to the Global Burden of Disease 2019 study, CKD ranked as the 11th leading cause of death, resulting in 1.4 million deaths in 2019.[3] Furthermore, CKD has experienced a significant rise in its burden on disability-adjusted life years (DALYs), moving from 29th rank in 1990 to 18th in 2019.[3] Additionally, CKD-related complications such as cardiovascular disease, end-stage renal disease, kidney transplant, and mortality significantly burden the global healthcare system.[1,4] By 2040, CKD is projected to become the 5th most common cause of years of life lost worldwide.[5,6] Since CKD is largely preventable and treatable, finding a reliable approach to mitigate the global burden of CKD is of utmost importance.

Physical activity (PA), as a modifiable lifestyle factor, has been shown to effectively reduce the risk of cardiovascular disease (CVD), cancer, and all-cause mortality.[7,8] However, the correlations between PA and the risk of CKD incidence are inconsistent based on the evidence from previous studies.[9–13] Besides, limited research investigating the relationship between different types of PA and the risk of CKD incidence. A recent meta-analysis of 12 cohort studies involving 1.2 million participants reported that individuals who are most physically active have a lowered risk (RR: 0.91 [95%CI: 0.85, 0.97]) of CKD incidence compared to those who are not or least physically active.[14] It is worth noticing all the PA data from the 12 cohort studies were collected through questionnaires. This method of data collection has limitations in accurately capturing the intensity and duration of full-day PA, as well as energy expenditure. There is also a potential recall bias and measurement error during data collection. In contrast, data collected from wrist-worn accelerometers provide a comprehensive assessment of PA by capturing its intensity and

duration,[15] and the energy expenditure could be accurately estimated through the accelerometer-based PA data.[16–18] A cross-sectional study found PA measured by accelerometer may be associated with a lower risk of CKD in community-based older adults.[19] However, the strength of the evidence is limited due to its moderate sample size (n = 1268) and the inherent limitations of cross-sectional studies. Besides, it remains unknown whether genetic risk may modify the effect of PA on the risk of CKD incidence. In sum, the evidence regarding the relationship between PA and CKD from previous studies may have certain limitations.

To overcome these limitations, we conducted analyses in two cohorts: a questionnaire-based and an accelerometer-based cohort. In the questionnaire-based cohort, we initially examined the association between various types of PA and the risk of CKD incidence using questionnaire-based PA data collected at recruitment from the UK Biobank. In the accelerometer-based cohort, we examined the association between PA, energy expenditure, and the risk of CKD incidence using objective accelerometer-based PA data obtained from a subsample of the UK Biobank. The analysis also fully explored the potential interaction between PA categories and different genetic risks of developing CKD. By incorporating both questionnaire-based and accelerometer-based analyses, this study aims to strengthen the evidence regarding the association between PA and CKD, providing a more accurate depiction of the magnitude and nature of this relationship.

## Methods

### Data source and study design

The UK Biobank is a population-based prospective study with approximately 500,000 participants aged 40–69 years recruited in 2006–2010 from across the UK.[20] Participants received examinations in one of the 22 assessment centres at enrollment. Their baseline information on social demography, lifestyle, health, and physical assessments was collected through touchscreen questionnaires and physical measurements.[21] In addition, participants who had provided valid email addresses were randomly invited to wear an accelerometer for 7 consecutive days between February 2013 and December 2015, and 103,712 raw accelerometer datasets were received at the end.[22] Participants who agreed to participate in accelerometer measurements had similar baseline demographic and health-related characteristics as those who declined the measurements.[23] The UK Biobank received ethical approval from the North West Multicentre Research Ethical Committee and all participants signed written consent. This study was performed under UK Biobank application number 77195.

In this study, we investigated the associations between PA and the risk of CKD incidence in two cohorts: a questionnaire-based and an accelerometer-based cohort. To analyse the association between questionnaire-measured PA and the risk of CKD incidence, among 498,423 individuals who had questionnaire-measured PA data, we excluded participants with prevalent CKD before baseline (n = 8035), and participants who failed genetic data quality control (Lost genetic data, n = 13,326; Inconsistent sex, n = 348; Biologically relatedness >0.125, n = 28,270), leaving 448,444 participants in the questionnaire-based cohort. To analyse the association between accelerometer-measured PA and the risk of CKD incidence, among 103,662 individuals who had raw accelerometer-measured PA records, we excluded participants who failed accelerometer data quality control (Failed calibration, n = 3056; Insufficient data, n = 4382; Insufficient wear time, n = 1884), participants who with prevalent CKD before accelerometer wearing (n = 1422), and participants who failed genetic data quality control (Lost genetic data, n = 2121; Inconsistent sex, n = 50; Biologically relatedness >0.125, n = 1451), leaving 89,296 participants in the accelerometer-based cohort.

### Assessment of physical activity (Questionnaire-based and Accelerometer-based)

In the questionnaire-based cohort, the data collected from a well-validated short self-reported International Physical Activity Questionnaire at recruitment were used to assess physical activity for each individual.[24] This questionnaire includes five different types of physical activities, namely physical activity in leisure time (strenuous sports, other exercises, walking for pleasure, and climbing a flight of stairs), housework-related activity (heavy DIY and light DIY), job-related activity (job involved standing or walking and the job involved heavy manual or physical activity), transportation for work (by walk, cycle, car, and public transport), and transportation for others (by walk, cycle, car, and public transport). Participants reported their attendance (yes or no), frequency (days per week), and duration (minutes per day) for specific physical activity within the first 2 categories. Additional information is available in Supplemental Table S1.

In the accelerometer-based cohort, the data collected from Axivity AX3 wrist-worn triaxial accelerometers were used to assess objective physical activity for each individual. More details about data collection and processing can be found elsewhere.[22] We selected 5 indicators, including light-intensity PA (LPA), moderate-intensity PA (MPA), vigorous-intensity PA (VPA), moderate to vigorous-intensity PA (MVPA), and total volume of PA to observe the relationship between PA and the risk of CKD incidence. According to the PA guidelines from WHO, on an absolute scale, LPA represents an activity that is performed between 1.5 and 3 metabolic equivalent of tasks (METs), such as slow walking, bathing, or other incidental activities. MPA represents an activity that is performed between 3 and 6

METs, such as fast walking, riding a bike, slow swimming, or other aerobic activities. VPA represents an activity that is performed over 6.0 METs, such as fast running, fast swimming, tennis ball, or other aerobic activities. MVPA represents an activity that is performed over 3 METs.[7] One MET is the energy equivalent expended by an individual while seated at rest, usually expressed as ml $O_2$/kg/min.[7] In our study, minutes of LPA, MPA, and VPA per week were determined as the percentage of time spent in 30 mg–125 mg, 125 mg–400 mg, and above 400 mg, respectively.[16,18] To simultaneously consider intensity and duration, total PA and MVPA were transformed into physical activity energy expenditure (PAEE) from total PA and MVPA,[17,18] which had been validated by previous study.[16] PAEE from total PA and MVPA were expressed as the total METs minutes per week.[25]

### Ascertainment of CKD

CKD in the UK Biobank was ascertained through hospital inpatient and death records. The dates and causes of hospital admissions were identified by record linkage to Hospital Episode Statistics (England and Wales) and the Scottish Morbidity Record (Scotland). The data on dates and causes of death were obtained from the death registries of the National Health Service Information Centre (England and Wales) and the National Health Service Central Register (Scotland). Further detailed information on linkage procedures is available at http://content.digital.nhs.uk/services. CKD was identified through medical assessments during subsequent visits, following KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease.[26] The International Classification of Diseases (ICD) is applied for CKD coding in the medical record. In our study, CKD was defined using the ICD–10 codes (I12.0, I13.1, I13.2, N18, N18.0, N18.1, N18.2, N18.3, N18.4, N18.5, N18.8, N18.9) and ICD-9 codes (585, 5859).[27] A detailed description of these codes is given in Supplementary Table S2. A baseline estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 $m^2$ is utilized as a supplementary diagnostic criterion for baseline CKD prevalence.[26] Incident CKD was defined as the first diagnosis of CKD. At the time of analysis, hospital admission data were available for participants until 31 October 2022. Due to variations in follow-up frequency and medical visit intervals among participants, we considered the first occurrence of CKD in the follow-up visits as the end point for those who developed CKD. Therefore, participants were censored at the date associated with the incidence of CKD, date of death, or last known follow-up (31 October 2022), whichever occurred first.

### Calculation of polygenic risk score for CKD

To construct the polygenic risk score (PRS) for CKD, we obtained the imputed genotype data from the UK Biobank and selected 251 single nucleotide polymorphisms (SNPs) associated with renal function.[28] Detailed information about quality control and genotyping in UK Biobank was reported previously.[29] The information on the selected 251 SNPs is listed in Supplementary Table S3. Using a weighted method,[30] PRS = β1*SNP1 + β2*SNP2 + ... + β251*SNP251, with each SNP recoded as 0, 1, or 2, according to the number of risk alleles. The β of each SNP was taken from the reported meta-analysis.[28] As the participant's PRS increases, their eGFR tends to be higher, leading to a reduced risk of CKD occurrence. Therefore, participants were classified into "low genetic risk," "intermediate genetic risk," and "high genetic risk" based on the tertiles of the PRS, arranged from high to low.

### Covariate measurement

We evaluated potential confounders using various sources of data, including touch-screen questionnaires, anthropometric measurements, biochemical indexes, accelerometer-measured variables, and medical history. The variables considered as potential confounders include age, sex (female/male), UK Biobank assessment centre, Townsend deprivation index (categorized into quarters), education level (degree or above/any other qualification/no qualification), body-mass index (BMI) categories [normal/underweight (<25 kg/$m^2$)/overweight (25≤ to <30 kg/$m^2$)/obese (≥30 kg/$m^2$)], smoking status (never/previous/current), frequency of alcohol intake (not current/less than three times a week/three or more times a week), diet (ideal/poor), baseline eGFR (using 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine-based equation),[31] genetic ethnic group (White/Non-White), PRS, and the first 10 principal components of ancestry, baseline hypertension, baseline diabetes, and baseline CVD. In the questionnaire-based cohort, age was calculated from dates of birth and enrollment; Baseline hypertension, diabetes, and CVD were diagnosed before enrollment. In the accelerometer-based cohort, age was calculated from dates of birth and the finish of accelerometer wear; Baseline hypertension, diabetes, and CVD were diagnosed before the accelerometer wear; Besides, the season of accelerometer wear (Spring/Summer/Autumn/Winter) was also included as confounders. For defining an ideal or poor diet, we selected 7 dietary components. For each dietary component, participants were assigned 1 point if they met the intake goal, and 0 points if they did not. The sum of scores for all 7 dietary components ranges from 0 to 7 points. A total diet score of 4 or higher is considered an ideal diet. The variables and codes used for disease diagnosis and 7 dietary components are shown in Supplement Tables S4 and S5.

### Statistical analyses

First, to investigate the association between different types of PA and the risk of CKD incidence, we

conducted analyses in the questionnaire-based cohort. In the questionnaire-based cohort, baseline characteristics by incident CKD or not were reported as mean ± SD for continuous variables and frequencies with percentages for categorical variables. We investigated the associations of 21 questionnaire-based PA terms with the risk of CKD incidence using Cox proportional hazard regression models, with time at recruitment as the start of follow-up. The Cox models were adjusted for age, sex, recruitment centre, Townsend deprivation index, education level, diet ideal or poor, cigarette smoking, alcohol consumption, BMI category, history of diabetes, history of hypertension, history of CVD, PRS of CKD, genetic ethnic group, and first 10 principal components of ancestry.

Second, to accurately elucidate the association between PA and the risk of CKD incidence and further enhance the strength of evidence regarding PA, we conducted analyses in the accelerometer-based cohort. In the accelerometer-based cohort, baseline characteristics by quartile of total PA in MET were reported as mean ± SD for continuous variables and frequencies with percentages for categorical variables. Using Cox proportional hazard regression models, with the time accelerometer wearing finished as the start of follow-up, we investigated the associations of genetic risk categories, PA categories (LPA, MPA, VPA, total PA, and MVPA), and their combination with the risk of CKD incidence. Cox models were adjusted as in questionnaire-based analysis and additionally for the season of accelerometer wear. Moreover, we included an interaction term involving PA categories and genetic risk categories in the Cox models. Subsequently, a likelihood ratio test was performed to assess the statistical significance of this interaction. In addition, we assessed the shape of the relationship between PA categories and the risk of CKD incidence using a restricted cubic spline model. To minimize the influence of outliers on the model, we trimmed observations below the 5th percentile and above the 95th percentile based on the distribution of the PA data (total PA, MVPA, LPA, MPA, and VPA) from the lowest to the highest. Additionally, we specified the knots at the 25th, 50th, and 75th centiles, which were utilized for categorizing the LPA, MPA, VPA, total PA, and MVPA. Furthermore, we also performed several subgroup analyses to assess the robustness of our findings and explore potential variations. These analyses were stratified by PRS (Low, Intermediate, High), age (<65/≥ 65 years), sex (Female/Male), BMI (<30/≥ 30 kg/m$^2$), diabetes (Yes/No), hypertension (Yes/No), and CVD (Yes/No). To enhance the comprehensibility of our results while avoiding redundancy, we placed the results of the LPA in the Supplemental Materials.

Additionally, we performed several sensitivity analyses to ensure the reliability and robustness of our findings. First, we calculated the Pearson correlation coefficients for all types of PAs, and we put LPA, MPA, and VPA into one model to mutually adjust for each other. Second, we conducted the main analyses exclusively among participants with complete covariate data to minimize potential biases due to missing information. Third, we excluded events that occurred within two years after accelerometer wearing to address any concerns regarding reverse causality. Fourth, we carried out the main analyses among participants without diabetes, hypertension, and cardiovascular disease (CVD) to avoid the potential impact of these comorbidities on the association between PA and CKD risk. Fifth, considering death as a competing risk for CKD incidence, we employed the Fine–Gray subdistribution hazards using the competing risk model to examine any potential bias from competing risks.

To address any missing covariate values in the questionnaire-based and accelerometer-based analysis, we employed multiple imputations utilizing the "mice" R package,[32] ensuring the statistical power and minimizing inferential bias. Supplementary Tables S6 and S7 provide detailed information on missing covariates of participants in the questionnaire-based and accelerometer-based analysis.

Throughout both of these analyses, we assessed the proportionality of hazards assumption using the Schoenfeld residuals technique and no violations were observed.[33] Moreover, we performed a correlation matrix analysis to evaluate collinearity between all included covariates, and no multicollinearity was detected. We calculated hazard ratios (HRs) and their corresponding 95% confidence intervals (95% CIs) to quantify the associations. To account for multiple tests, we corrected P values using the False Discovery Rate (FDR) via the Benjamin-Hochberg method.[34]

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies. All statistical analyses were performed using R software version 4.0.5. We employed two-sided tests for all statistical analyses, considering a P value of less than 0.05 as statistically significant.

### Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

### Population characteristics

The flowchart of participant selection of the two cohorts is shown in Fig. 1. Baseline characteristics of the 448,444 participants involved in the questionnaire-based cohort are shown in Supplemental Table S8, by incident CKD or not. The mean age was 56.9 (SD, 8.1) years, the

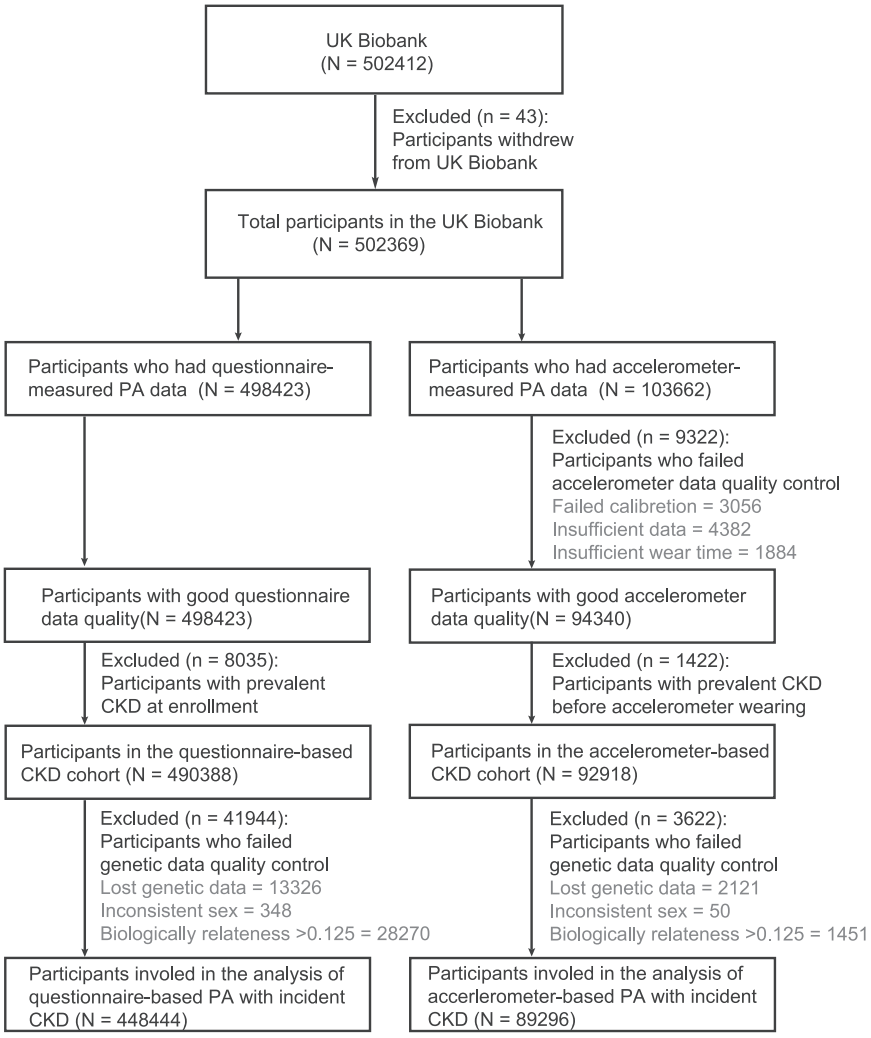


***Fig. 1:*** **The flow chart of participants through the study.**

mean BMI was 27.4 (SD, 4.8) kg/m$^2$, the mean eGFR was 94.9 (SD, 11.8) ml/min/1.73 m$^2$ and 54.0% were female. During a median follow-up of more than 13.6 years, there were 18,184 individuals were diagnosed with CKD. Compared to the participants without CKD, those with incident CKD were more likely to be older, male, smokers, obese, less educated, lower baseline eGFR, higher levels of materially deprived, less PA (frequency and duration), and were more likely to have CVD, diabetes, and hypertension.

Baseline characteristics of the 89,296 participants involved in the accelerometer-based cohort are shown in Table 1, by quarters of total PA. The mean age of them was 62.2 (SD, 7.8) years, the mean BMI was 26.7 (SD, 4.5) kg/m$^2$, the mean eGFR was 95.1 (SD, 11.5) ml/min/1.73 m$^2$ and 56.1% were female. Participants in the highest category of total PA engaged in more accelerometry-measured MPA and VPA. Compared with participants in the highest category of total PA, participants in the lowest category were more likely to be older, male, smokers, obese, less educated, lower baseline eGFR, higher levels of materially deprived, and were more likely to have CVD, diabetes, and hypertension. During a median follow-up of 7.9 years, 2297 participants were diagnosed with CKD. Besides, the characteristics of the excluded participants were similar to those of the included (Supplemental Table S9). Baseline characteristics of the 89,296 participants are also shown in Supplemental Table S10 by incident CKD or not.

### Associations of genetic risk with the risk of CKD incidence

As shown in Table 2, the risk of CKD exhibited a consistent upward trend across genetic risk categories. Individuals with a high genetic risk showed a 1.266-fold higher risk of CKD incidence compared to those with a

| Characteristics | Accelerometer-measured total PA, MET-min/week | | | | |
|---|---|---|---|---|---|
| | Overall | Q1 (≤3693) | Q2 (3693–4487) | Q3 (4487–5395) | Q4 (≥5395) |
| Participants, n | 89,296 | 22,347 | 22,317 | 22,316 | 22,316 |
| PA-related factors (min/week, mean (SD)) | | | | | |
| Light intensity | 2056.4 (442.6) | 1646.7 (323.8) | 2008.0 (313.1) | 2199.4 (353.2) | 2372.2 (406.8) |
| Moderate intensity | 483.1 (234.7) | 240.6 (91.1) | 393.3 (87.3) | 529.7 (103.8) | 769.0 (207.2) |
| Vigorous intensity | 31.8 (42.4) | 8.2 (10.0) | 17.5 (14.9) | 29.8 (23.0) | 71.6 (63.1) |
| Age at accelerometer measurement—(mean (SD)) | 62.2 (7.8) | 64.9 (7.3) | 63.0 (7.6) | 61.5 (7.7) | 59.5 (7.6) |
| Genetic ethnic group, n (%) | | | | | |
| White | 76,823 (86.0) | 19,543 (87.5) | 19,246 (86.2) | 19,153 (85.8) | 18,881 (84.6) |
| Non-White | 12,473 (14.0) | 2804 (12.5) | 3071 (13.8) | 3163 (14.2) | 3435 (15.4) |
| Sex, n (%) | | | | | |
| Male | 39,168 (43.9) | 11,217 (50.2) | 9671 (43.3) | 9172 (41.1) | 9108 (40.8) |
| Female | 50,128 (56.1) | 11,130 (49.8) | 12,646 (56.7) | 13,144 (58.9) | 13,208 (59.2) |
| Cigarette smoking, n (%) | | | | | |
| Never | 50,910 (57.2) | 11,838 (53.1) | 12,702 (57.1) | 13,027 (58.5) | 13,343 (59.9) |
| Previous | 31,994 (35.9) | 8467 (38.0) | 8047 (36.2) | 7841 (35.2) | 7639 (34.3) |
| Current | 6157 (6.9) | 1977 (8.9) | 1509 (6.8) | 1386 (6.2) | 1285 (5.8) |
| Alcohol consumption, n (%) | | | | | |
| Not current | 5004 (5.6) | 1533 (6.9) | 1194 (5.4) | 1136 (5.1) | 1141 (5.1) |
| Two or less times a week | 40,456 (45.3) | 10,614 (47.5) | 10,099 (45.3) | 9929 (44.5) | 9814 (44.0) |
| Three or more times a week | 43,772 (49.1) | 10,184 (45.6) | 11,007 (49.4) | 11,239 (50.4) | 11,342 (50.9) |
| Education level, n (%) | | | | | |
| No qualification | 7326 (8.3) | 2472 (11.2) | 1806 (8.1) | 1603 (7.2) | 1445 (6.5) |
| Any other qualification | 42,757 (48.2) | 10,757 (48.5) | 10,574 (47.7) | 10,722 (48.3) | 10,704 (48.3) |
| Degree or above | 38,619 (43.5) | 8934 (40.3) | 9796 (44.2) | 9855 (44.4) | 10,034 (45.2) |
| Townsend deprivation index, (mean (SD)) | −1.7 (2.8) | −1.6 (2.9) | −1.8 (2.8) | −1.8 (2.8) | −1.7 (2.8) |
| Healthy diet, n (%) | | | | | |
| Poor | 52,647 (64.2) | 13,718 (66.9) | 13,160 (64.3) | 13,044 (63.6) | 12,725 (61.8) |
| Ideal | 29,389 (35.8) | 6774 (33.1) | 7294 (35.7) | 7467 (36.4) | 7854 (38.2) |
| Season of accelerometer wear, n (%) | | | | | |
| Spring | 20,309 (22.7) | 4759 (21.3) | 4850 (21.7) | 5232 (23.4) | 5468 (24.5) |
| Summer | 23,291 (26.1) | 5306 (23.7) | 5686 (25.5) | 5990 (26.8) | 6309 (28.3) |
| Autumn | 26,570 (29.8) | 6770 (30.3) | 6789 (30.4) | 6525 (29.2) | 6486 (29.1) |
| Winter | 19,126 (21.4) | 5512 (24.7) | 4992 (22.4) | 4569 (20.5) | 4053 (18.2) |
| eGFR, (ml/min/1.73 $m^2$, mean (SD)) | 95.1 (11.5) | 92.7 (11.6) | 94.6 (11.4) | 95.6 (11.3) | 97.4 (11.1) |
| BMI (kg/$m^2$, mean (SD)) | 26.7 (4.5) | 28.4 (5.1) | 26.9 (4.4) | 26.2 (4.1) | 25.2 (3.7) |
| BMI category (kg/$m^2$), n (%) | | | | | |
| <25 | 35,236 (39.5) | 5715 (25.7) | 8090 (36.3) | 9466 (42.5) | 11,965 (53.7) |
| 25–30 | 36,760 (41.2) | 9614 (43.2) | 9646 (43.3) | 9363 (42.0) | 8137 (36.5) |
| ≥30 | 17,130 (19.2) | 6937 (31.2) | 4549 (20.4) | 3453 (15.5) | 2191 (9.8) |
| Diabetes history, n (%) | 2297 (2.6) | 1057 (4.7) | 567 (2.5) | 402 (1.8) | 271 (1.2) |
| Hypertension history, n (%) | 3441 (3.9) | 1690 (7.6) | 819 (3.7) | 586 (2.6) | 346 (1.6) |
| CVD history, n (%) | 20,627 (23.1) | 7420 (33.2) | 5463 (24.5) | 4362 (19.5) | 3382 (15.2) |

Townsend deprivation index = a composite area-level measure of deprivation based on unemployment, non-car ownership, non-home ownership, and household overcrowding; a higher score indicates higher deprivation. BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate using 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine-based equation; MET, metabolic equivalent of tasks; PA, physical activity; SD, standard deviation.

***Table 1:*** **Baseline characteristics of participants involved in accelerometer-measured PA analysis by quarters of the total volume of PA.**

low genetic risk (HR: 1.266, 95% CI: 1.141–1.405). It is worth noting that these results remain robust even after accounting for the accelerometer-based total PA (HR: 1.266, 95% CI: 1.141–1.405). This suggests that the genetic risk for CKD is statistically independent of an individual's level of PA.

### Associations of questionnaire-based PA with the risk of CKD incidence

Fig. 2 and Supplementary Table S11 present the hazard ratios (HRs) for incident CKD in different questionnaire-based PA terms. In terms of PA in leisure time, all four terms (strenuous sports, other exercise,

| Genetic risk | Total no. of participants | Events/person-years | Model 1 | Model 2 | Model 3 | Model 4 |
|---|---|---|---|---|---|---|
| | | | HR (95% CI); P | HR (95% CI); P | HR (95% CI); P | HR (95% CI); P |
| Low genetic risk | 29,765 | 586/232,382 | 1 [Ref] | 1 [Ref] | 1 [Ref] | 1 [Ref] |
| Intermediate genetic risk | 29,765 | 732/231,632 | 1.263 (1.133, 1.408); <0.001 | 1.264 (1.134, 1.409); <0.001 | 1.098 (0.985, 1.225); 0.092 | 1.100 (0.986, 1.226); 0.088 |
| High genetic risk | 29,766 | 979/230,718 | 1.713 (1.546, 1.899); <0.001 | 1.725 (1.557, 1.912); <0.001 | 1.266 (1.14, 1.405); <0.001 | 1.266 (1.14, 1.405); <0.001 |
| P value for trend | | | <0.001 | <0.001 | <0.001 | <0.001 |

Analyses were conducted using Cox proportional hazard models. Model 1 adjusted for sex, age at accelerometer measurement, genetic ethnic group, and first 10 principal components of ancestry. Model 2 was adjusted as in Model 1 and for cigarette smoking, alcohol consumption, Townsend Deprivation Index, education level, diet ideal or poor, and recruitment centre. Model 3 was adjusted as in Model 2 and for BMI categories, history of diabetes, history of hypertension, history of CVD, and baseline eGFR. Model 4 additionally adjusted for an average accelerometer-measured total volume of PA, and season of accelerometer wear. Ref, reference; CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate using 2021 CKD-EPI creatinine equation.

***Table 2:*** **Risk of incident CKD according to genetic risk.**

walking for pleasure, stair climbing) demonstrate a protective effect against CKD, irrespective of frequency and duration. Regarding housework-related activity, heavy DIY shows a protective effect against CKD regardless of the frequency and duration, while light DIY shows a protective effect only when the frequency

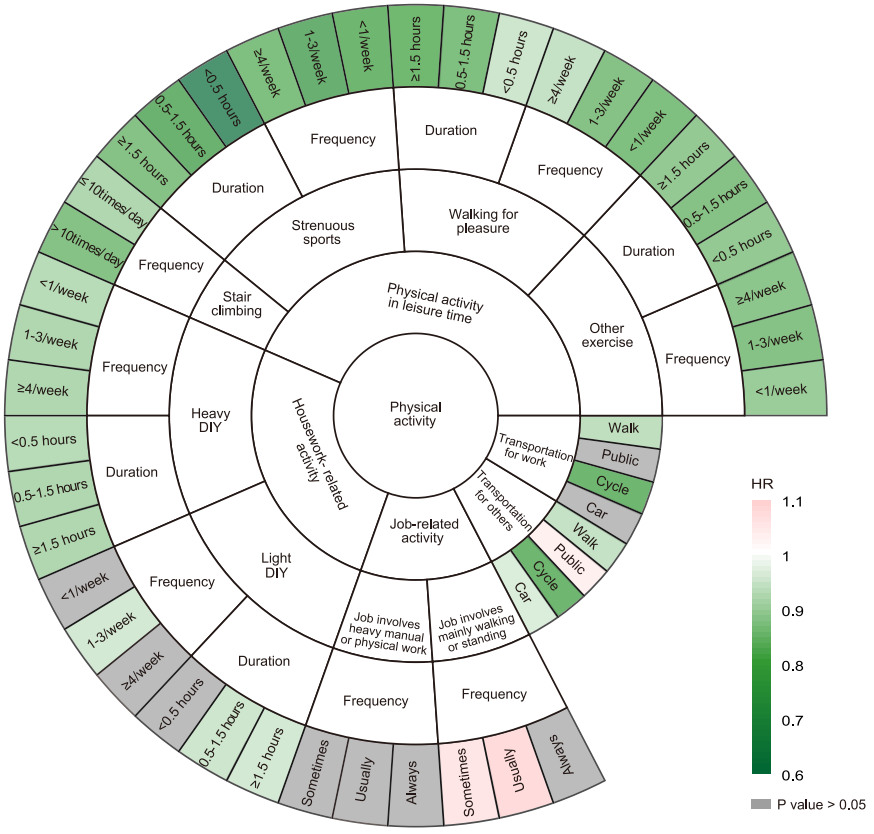


***Fig. 2:*** **HRs for the associations between all questionnaire-based physical activity items and CKD incidence**. All adjusted for sex, age at enrollment, genetic ethic group, recruitment centre, cigarette smoking, alcohol consumption, Townsend deprivation index, education level, diet ideal or poor, BMI categories, history of diabetes, history of hypertension, history of CVD, baseline eGFR, genetic risk, genetic ethnic group, and first 10 principal components of ancestry. All P values were corrected using the FDR via the Benjamin-Hochberg method, and a P value of less than 0.05 was regarded as statistically significant. HR, hazard ratio; CI, confidence interval; CKD, chronic kidney disease; Ref, reference; FDR, False Discovery Rate.

ranges 1–3 times per week or the duration is 0.5–1.5 h. However, no factors related to job-related activity exhibit a protective effect against CKD. In terms of transportation for work, only cycling and walking demonstrate a protective effect against CKD. Additionally, when it comes to transportation for others, walking, cycling, and car shows a protective effect against CKD. To further adjust for other PA terms, we put all the PA terms as binary variables (yes or no) into an additional model, the results indicated participating in strenuous sports, other exercises, walking for pleasure, and heavy DIY, are still exhibited a significant protective effect on the risk of CKD incidence (Supplemental Table S12).

### Associations of accelerometer-based PA with the risk of CKD incidence

As shown in Fig. 3 and Supplementary Table S13, we observed a significant inverse association between total PA, MPA, VPA, and MVPA and the risk of CKD incidence. Comparing the lowest quarter of MPA, the HRs and 95% CIs for increasing quarters were 0.751 (0.676, 0.834), 0.735 (0.651, 0.83), and 0.639 (0.554, 0.737). Similarly, for VPA, the corresponding values were 0.809 (0.719, 0.909), 0.712 (0.624, 0.813), and 0.639 (0.549, 0.745). Similar trends were observed for total PA and MVPA in their association with the risk of CKD incidence. Besides, comparing the lowest quarter of LPA, the HRs and 95% CIs for increasing quarters were 0.895 (0.803, 0.998), 0.893 (0.797, 1.000), and 0.776 (0.685, 0.879) (Supplemental Figure S1A). Notably, only the highest quartile demonstrated a statistically significant association with the risk of CKD incidence. These associations remained consistent even after correcting for the FDR. These results with additional adjustment for PRS indicated that the association between PA and the risk of CKD incidence is independent of genetic risk. In addition, Supplemental Table S14 showed the Pearson correlation coefficient between all types of PA.

Further analyses stratified by genetic risk category suggested that higher levels of MPA, VPA, total PA, and MVPA were still associated with a lower CKD risk across genetic groups, especially high genetic risk groups (Supplementary Table S15). In addition, subgroup analyses stratified by age, sex, BMI, CVD, hypertension, and diabetes revealed similar results with our main analysis, indicating that the findings were consistent across different subgroups (Supplementary Figures S2–S7, Supplementary Tables S16–S21). It's worth mentioning that we found significant interactions between MPA (P = 0.004, likelihood ratio test), VPA (P = 0.038), MVPA (P = 0.011), and the age categories.

Furthermore, we observed a linear dose–response relationship between MPA (P for non-linear: 0.106), total PA (P for non-linear: 0.374), and the risk of CKD

| Types of physical activity | Total No. of Participants | Events/Person-years | HR (95%CI) | FDR P |
|---|---|---|---|---|
| **MPA (min/week)** | | | | |
| ≤ 312.48 | 22583 | 1083/171014 | 1 (Ref) | |
| 312.48 - 453.6 | 23218 | 556/181079 | 0.751(0.676,0.834) | <0.001 |
| 453.6 - 614.88 | 21525 | 390/168946 | 0.735(0.651,0.830) | <0.001 |
| > 614.88 | 21970 | 268/173692 | 0.639(0.554,0.737) | <0.001 |
| *P value for trend* | | | *<0.001* | |
| **VPA (min/week)** | | | | |
| ≤ 10.08 | 38494 | 1438/294981 | 1 (Ref) | |
| 10.08 - 20.16 | 16107 | 367/125805 | 0.809(0.719,0.909) | <0.001 |
| 20.16 - 40.32 | 16321 | 281/128329 | 0.712(0.624,0.813) | <0.001 |
| > 40.32 | 18374 | 211/145616 | 0.639(0.549,0.745) | <0.001 |
| *P value for trend* | | | *<0.001* | |
| **Total PA (MET/min - week)** | | | | |
| ≤ 3693.05 | 22347 | 1057/169304 | 1 (Ref) | |
| 3693.05 - 4487.3 | 22317 | 567/173929 | 0.784(0.707,0.871) | <0.001 |
| 4487.3 - 5395.29 | 22316 | 402/175020 | 0.699(0.620,0.788) | <0.001 |
| > 5395.29 | 22316 | 271/176478 | 0.649(0.563,0.750) | <0.001 |
| *P value for trend* | | | *<0.001* | |
| **MVPA (MET/min - week)** | | | | |
| ≤ 855.01 | 22324 | 1082/168881 | 1 (Ref) | |
| 855.01 - 1284.22 | 22324 | 572/173784 | 0.779(0.702,0.865) | <0.001 |
| 1284.22 - 1845.13 | 22324 | 381/175345 | 0.668(0.591,0.755) | <0.001 |
| > 1845.13 | 22324 | 262/176722 | 0.630(0.545,0.729) | <0.001 |
| *P value for trend* | | | *<0.001* | |

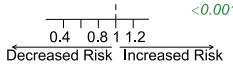


***Fig. 3:*** **Risk of incident CKD by quarters of accelerometer-measured average total volume, moderate-intensity, vigorous-intensity, and moderate-to vigorous-intensity physical activities in 89,296 UK Biobank participants**. All adjusted for sex, age at accelerometer measurement, recruitment centre, season of accelerometer wear, cigarette smoking, alcohol consumption, Townsend deprivation index, education level, diet ideal or poor, BMI categories, history of diabetes, history of hypertension, history of CVD, baseline eGFR, genetic ethnic group, genetic risk, and first 10 principal components of ancestry. All P values were corrected via the FDR by using the Benjamin-Hochberg method. HR: hazard ratio; CI, confidence interval; CKD, chronic kidney disease; MET, metabolic equivalent of task; MPA, moderate-intensity physical activity; MVPA, moderate-to vigorous-intensity physical activity; PA, physical activity; VPA, vigorous-intensity physical activity; Ref, reference; FDR, False Discovery Rate.

incidence with no minimal or maximal threshold (Fig. 4). We also observed a non-linear relationship between VPA (P for non-linear: 0.009), MVPA (P for non-linear: 0.032), and the risk of CKD incidence with no minimal or maximal threshold (Fig. 4). Besides, we also observed a decreasing trend in the risk of CKD incidence with increasing levels of LPA (P for non-linear: 0.678) (Supplemental Figure S1B).

### Joint association interaction of genetic risk and accelerometer-based PA on the risk of CKD incidence

Fig. 5 and Supplemental Figure S1C illustrate the risk of incident CKD based on the combined categories of genetic risk and accelerometer-based PA. In terms of MPA, the strongest protective effect was observed among participants with low genetic risk and the third quarter of MPA (HR: 0.488, 95% CI: 0.383, 0.622) compared to those with high genetic risk and the lowest quarter of MPA. Similarly, for VPA, the strongest protective effect was observed among participants with low genetic risk and the highest quarter of VPA (HR: 0.435, 95% CI: 0.325, 0.583). For total PA, individuals with low genetic risk and the third quarter of PA demonstrated the strongest protective effect against incident CKD (HR: 0.471, 95% CI: 0.371, 0.597). For MVPA, the strongest protective effect of incident CKD was observed among participants with low genetic risk and the third quarter of MVPA (HR: 0.499, 95% CI: 0.396, 0.630). For LPA, the strongest protective effect of incident CKD was observed among participants with low genetic risk and the highest quarter of LPA (HR: 0.608, 95% CI: 0.483, 0.765). These associations remained statistically significant after the FDR correction.

We found significant interactions between MPA (P = 0.025, likelihood ratio test), and the PRS on the risk of CKD incidence. However, there was no significant interaction between LPA (P = 0.391), VPA (P = 0.080), total PA (P = 0.057), MVPA (P = 0.171), and the PRS (Supplementary Table S15).

All findings remained robust and consistent across a range of sensitivity analyses. These analyses included incorporating LPA, MPA, and VPA into the same model to mutually adjust for each other, using competing risk regression, restricting the analysis to participants with complete covariate data, excluding

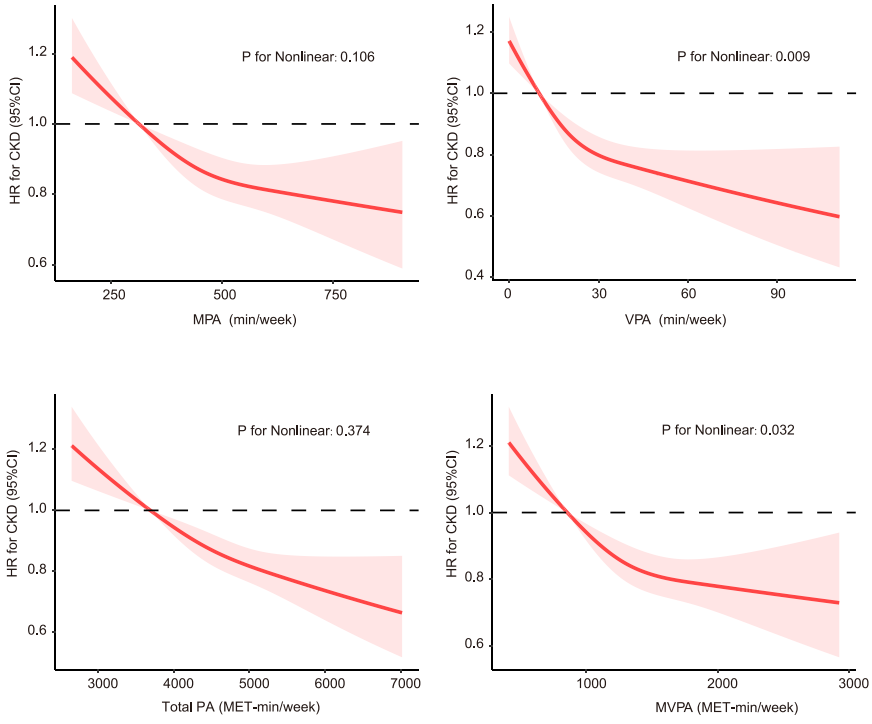


***Fig. 4:*** **Restricted cubic spline for the association between accelerometer-measured average total volume, moderate-intensity, vigorous-intensity, and moderate-to vigorous-intensity physical activities and the risk of CKD incidence**. All adjusted for sex, age at accelerometer measurement, recruitment centre, season of accelerometer wear, cigarette smoking, alcohol consumption, Townsend deprivation index, education level, diet ideal or poor, BMI categories, history of diabetes, history of hypertension, history of CVD, baseline eGFR, genetic risk, genetic ethnic group, and first 10 principal components of ancestry. The solid line is the estimate (HR) and the shaded area is the 95% CI. HR indicates hazard ratio; CI, confidence interval; CKD, chronic kidney disease; MET, metabolic equivalent of task; MPA, moderate-intensity physical activity; VPA, vigorous-intensity physical activity; PA, physical activity; MVPA, moderate-to vigorous-intensity physical activity.

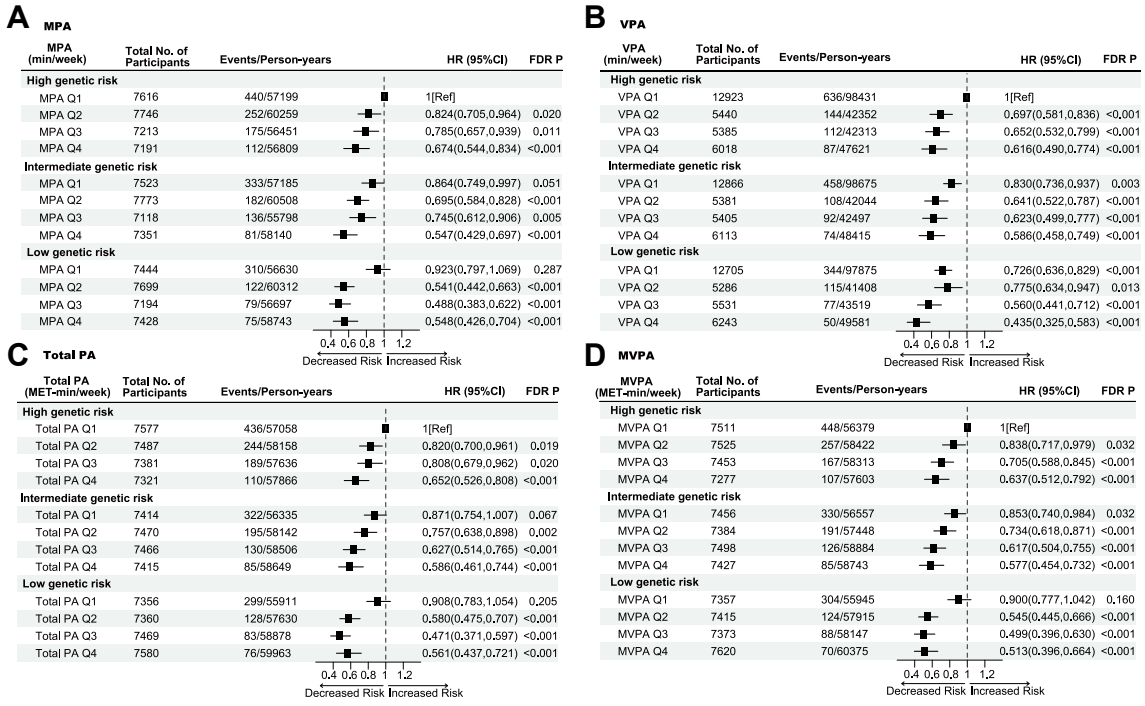


***Fig. 5:*** **Risk of incident CKD according to genetic and accelerometer-measured average total volume, moderate-intensity, vigorous-intensity, and moderate-to vigorous-intensity physical activities in 89,296 UK Biobank participants**. All adjusted for sex, age at accelerometer measurement, recruitment centre, season of accelerometer wear, cigarette smoking, alcohol consumption, Townsend deprivation index, education level, diet ideal or poor, BMI categories, history of diabetes, history of hypertension, history of CVD, baseline eGFR, genetic ethnic group, and first 10 principal components of ancestry. P values were corrected via the FDR by using the Benjamin-Hochberg method. HR, hazard ratio; CI, confidence interval; Q, quartile; CKD, chronic kidney disease; MET, metabolic equivalent of task; MPA, moderate-intensity physical activity; MVPA, moderate-to vigorous-intensity physical activity; PA, physical activity; and VPA, vigorous-intensity physical activity; Ref, reference; FDR, false discovery rate.

events within the first two years of follow-up, and excluding participants with CVD, diabetes, and hypertension at baseline (Supplementary Tables S22–S26).

## Discussion

In this study, in the questionnaire-based cohort, we observed that engaging in strenuous sports, other exercises, walking for pleasure, stair climbing, and heavy DIY, are associated with a lower risk of CKD incidence. In the accelerometer-based cohort, we found that higher levels of MPA, VPA, MVPA, and total PA were associated with a lower risk of CKD incidence across their full range, and this association was even more pronounced in the high genetic risk subgroup. Furthermore, there is a linear dose–response protection between MPA, VPA, total PA, and the risk of CKD incidence. However, the association between LPA and the risk of CKD incidence is not statistically significant. When examining the joint associations of PA and genetic risk with CKD, individuals with a low genetic risk in combination with a high level of PA were associated with a nearly 50% reduction in the risk of CKD incidence compared to those with a high genetic risk and low level of PA. Besides, there were significant interactions between MPA and genetic risk on the risk of CKD incidence. Additionally, our findings remained robust and consistent across a range of subgroup analyses and sensitivity analyses. To the best of our knowledge, this is the first population-based prospective cohort study that comprehensively investigates the association between accelerometer-measured PA and the risk of CKD incidence, considering genetic risk. These findings provide valuable insights for future PA guidelines and robust evidence of the association between PA and CKD.

The evidence on the prospective association between PA and CKD is controversial. Some studies have reported evidence of associations between physical activity and a reduced risk of CKD, which was consistent with our findings.[9–11] However, two cohort studies and one cross-sectional study reported no evidence of associations between PA and the risk of CKD.[12,13,35] Besides, a previous study investigated the association between various types of PA and the risk of CKD in a working population. They suggest that occupational PA is associated with a lower risk of CKD, while leisure-time and

commuting PA do not show a significant association with CKD risk.[36] On the contrary, our questionnaire-based analysis showed job-related PA (Job involves heavy manual or physical work, Job involves mainly walking or standing) was not associated with a lower CKD risk, while leisure-time PA (strenuous sports, other exercises, walking for pleasure, and stair climbing), and some housework-related activity (heavy DIY) is associated with a lower risk of CKD. The inconsistent findings between their study and ours may be attributed to different sample sizes, the presence of recall bias and misclassification due to questionnaire data, and the distinctive characteristics of the study populations. In 2020, a meta-analysis of 8 cross-section studies and 6 cohort studies involving 353,975 participants reported that PA was inversely associated with CKD risk (odds ratio [OR]: 0.94 [95%CI: 0.91, 0.98]), and the risk of CKD was reduced by 2% (OR: 0.98 [95% CI: 00.96, 1.00]) with each 10 MET h/week increment of PA.[37] However, this meta-analysis was limited by its inclusion of a limited number of observational cohort studies and its search end date of March 2020. Recently, a novel meta-analysis of 12 cohort studies involving 1.2 million participants reported that individuals who engage in higher levels of PA have a reduced risk (RR: 0.91 [95% CI: 0.85, 0.97]) of CKD compared to those with lower or no PA.[14] This meta-analysis encompassed all available cohort studies examining the association between PA and the risk of CKD to date, including studies that reported both positive and null associations, providing a comprehensive overview of the current evidence on this topic and further supporting the association between PA and CKD. Our study, based on accelerometer-measured PA data, found higher levels of MPA, VPA, MVPA, and total PA were associated with a lower risk of CKD incidence, which further proved the association between PA and the risk of CKD.

The benefits of PA on the kidney's health may be the result of various contributing factors. The reduction in chronic systemic inflammation, involving decreased inflammatory characteristics of immune cells and cytokine release, is recognized as a key mechanism contributing to the numerous beneficial effects of PA in CKD.[38] Besides, regular exercise can reduce angiotensin II accumulation in the heart, which might improve cardiovascular health.[39] In addition, early evidence suggests that a six-month exercise intervention may yield positive impacts on insulin resistance among individuals with CKD.[40] Moreover, PA may also protect against the development of CKD by enhancing endothelial function, reducing sympathetic overactivity, and optimizing lipid metabolism, etc.[38,41–43] It is worth noticing that there is a gap between our findings and conventional physiological knowledge. Conventional physiological knowledge suggests that intense PA may potentially increase the burden on the kidneys, which is inconsistent with our findings. This highlights the need for further research into the underlying mechanisms of PA's benefits on kidney health. An enhanced comprehension of these mechanisms could pave the way for future CKD prevention and treatment strategies.

The significance of PA in promoting overall health is well-established and is recommended by the WHO as a key strategy for reducing the burden of non-communicable diseases (NCDs).[44] However, the current PA guidelines do not explicitly state that PA can reduce the risk of CKD incidence in adults. Our findings serve as a valuable supplement to the current PA guidelines by demonstrating that higher levels of PA are inversely associated with the risk of CKD, and individuals can still benefit from engaging in higher levels of PA even after meeting the recommended levels by the WHO. Besides, the current WHO PA guidelines are largely based on data obtained through questionnaires. However, the mean MPA value observed in our accelerometer-based analysis was 482.2 (SD: 234.8) min/week, which was significantly higher than those reported in other questionnaire-based studies. This indicates that the PA data obtained through questionnaires may be subjective and may not accurately capture the objective levels of PA. In general, our study, along with other accelerometer-based studies, lays a robust foundation for the future refinement of PA guidelines.[45–48] In addition, we found a significant interaction between MPA and the genetic risk of CKD. Our speculation regarding this is that MPA constitute the main components of human PA, and their long duration may facilitate potential interactions with genetic risk. Further exploration is warranted.

Our study also has important implications for public health in preventing CKD. Firstly, we identified a dose–response relationship between MPA, VPA, MVPA, total PA, and the risk of incident CKD with no minimal or maximal threshold. This finding indicates that individuals should be encouraged to be as physically active as possible to maximize the benefits. Second, our study found higher levels of MPA, VPA, MVPA, and total volume of PA were associated with a lower risk of CKD incidence regardless of genetic CKD risk, and our findings remained robust and consistent across a range of subgroup analyses and sensitivity analyses. This indicates individuals at high risk of CKD should be encouraged to engage in regular PA to prevent the onset of CKD. In general, our research, along with prior studies, provides powerful evidence for considering PA as a potential intervention measure for both preventing and treating CKD.

This study has several important strengths. As we know, the accelerometer is capable of measuring the intensity and duration of PA throughout the wearing time, although may not precisely identify different types of PAs. The questionnaire gathers information regarding their engagement in specific types of PA, including the frequency and duration by asking

respondents to recall. Still, it may overlook certain potential patterns of PA that haven't been mentioned. Both of these approaches provide unique insights into the relationship between PA and the risk of CKD incidence. Consequently, we believe that both analyses complement each other, enhancing the overall understanding of this relationship. Besides, we additionally adjusted for the genetic risk of CKD, which was not accounted for in previous studies. We also investigated the modification effect of genetic risk on the association between PA and the risk of CKD. The exclusion of genetic influence strengthens the validity of our findings. Furthermore, the strengths of this study also include the large sample size, the prospective and population-based study design, and the conclusions that were validated by multiple sensitivity analyses and subgroup analyses.

However, this study still has several limitations. First, in the questionnaire-based analysis, the analysis was limited by potential recall bias and measurement error when collecting data, and certain types of PA were not fully investigated in terms of frequency and duration. Second, in the accelerometer-based analysis, the baseline for accelerometer data was set after wearing the device, and the covariates used for adjustment were measured at recruitment, which may not accurately reflect the true baseline characteristics of the participants. Third, although we accounted for the season of accelerometer wear in our analysis, using single time-point PA data limits our ability to infer within-person changes or variability in physical activity over time. Fourth, some types of activities such as resistance exercise or cycling may not be appropriately characterized using wrist accelerometry. Fifth, the mean age of participants in the accelerometer-based analysis was 62.6 (SD:7.8) years old, and there is evidence suggesting the presence of healthy volunteer selection bias in the UK biobank. Therefore, our study's conclusions may not apply to the other population. Sixth, wrist accelerometers might not distinctly differentiate between sedentary behaviors and LPA. Seventh, we did not consider the role of timing of daily PA. Recent studies suggest that PA at different times of day may have varying effects on health.[49,50] Such impacts on health warrant further investigation. Eighth, as with any observational study, our study cannot establish causal relationships.

In conclusion, in the CKD-free participants from the UK biobank, higher levels of accelerometer-measured MPA, VPA, MVPA, and total PA are associated with a lower risk of CKD incidence. Engaging in multiple types of questionnaire-measured PA is also associated with a decreased risk of CKD. These findings provide robust evidence supporting the relationship between PA and the risk of CKD incidence, which can inform clinical treatment strategies for CKD and serve as a reliable reference for the future development of PA guidelines.

#### Contributors

**ZXY**, **LYM**: Data curation, Formal analysis, Methodology, Writing an original draft. **LF**, **HXW**, **LWF**, **LLJ**, and **ST**: Software, Supervision, Visualization. **ZP**, and **CJJ**: Validation, Writing - review & editing. **WZY**, **ZXJ**, and **LHL**: Funding acquisition, Project administration.

#### Data sharing statement

Researchers interested in accessing the data used in this study can apply for access to the UK Biobank by visiting their website (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access) and submitting an application that includes a research protocol summary and requested data fields. Upon approval by the UK Biobank management team and payment of applicable fees, researchers will be granted access to the database.

#### Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Acknowledgements

We gratefully acknowledge the commitment and dedication of the participants of the UK Biobank.

This work was supported by grants from the Medical Science Advancement Program of Wuhan University [TFJH2018006] and the National Science Foundation of China (81970070, 82170595).

#### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102323.

#### References

1 Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375(9731):2073–2081.
2 Levey AS, Atkins R, Coresh J, et al. Chronic kidney disease as a global public health problem: approaches and initiatives - a position statement from Kidney Disease improving global outcomes. *Kidney Int*. 2007;72(3):247–259.
3 Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):1204–1222.
4 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351(13):1296–1305.
5 Li PK, Garcia-Garcia G, Lui SF, et al. Kidney health for everyone everywhere-from prevention to detection and equitable access to care. *J Ren Care*. 2020;46(1):4–12.
6 Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet*. 2018;392(10159):2052–2090.
7 Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. 2020;54(24):1451–1462.
8 Piercy KL, Troiano RP, Ballard RM, et al. The physical activity guidelines for Americans. *JAMA*. 2018;320(19):2020–2028.
9 Guo C, Tam T, Bo Y, Chang LY, Lao XQ, Thomas GN. Habitual physical activity, renal function and chronic kidney disease: a cohort study of nearly 200 000 adults. *Br J Sports Med*. 2020;54(20):1225–1230.
10 Jafar TH, Jin A, Koh WP, Yuan JM, Chow KY. Physical activity and risk of end-stage kidney disease in the Singapore Chinese Health Study. *Nephrology (Carlton)*. 2015;20(2):61–67.
11 Parvathaneni K, Surapaneni A, Ballew SH, et al. Association between midlife physical activity and incident kidney disease: the Atherosclerosis Risk In Communities (ARIC) study. *Am J Kidney Dis*. 2021;77(1):74–81.
12 Herber-Gast GC, Hulsegge G, Hartman L, et al. Physical activity is not associated with estimated glomerular filtration rate among young and middle-aged adults: results from the population-based longitudinal doetinchem study. *PLoS One*. 2015;10(10):e0133864.

13 Hawkins M, Newman AB, Madero M, et al. TV watching, but not physical activity, is associated with change in kidney function in older adults. *J Phys Activ Health*. 2015;12(4):561–568.
14 Seidu S, Abdool M, Almaqhawi A, et al. Physical activity and risk of chronic kidney disease: systematic review and meta-analysis of 12 cohort studies involving 1,281,727 participants. *Eur J Epidemiol*. 2023;38(3):267–280.
15 Bassett DR, Troiano RP, McClain JJ, Wolff DL. Accelerometer-based physical activity: total volume per day and standardized measures. *Med Sci Sports Exerc*. 2015;47(4):833–838.
16 White T, Westgate K, Hollidge S, et al. Estimating energy expenditure from wrist and thigh accelerometry in free-living adults: a doubly labelled water study. *Int J Obes*. 2019;43(11):2333–2342.
17 White T, Westgate K, Wareham NJ, Brage S. Estimation of physical activity energy expenditure during free-living from wrist accelerometry in UK adults. *PLoS One*. 2016;11(12):e0167472.
18 Strain T, Wijndaele K, Dempsey PC, et al. Wearable-device-measured physical activity and future health risk. *Nat Med*. 2020;26(9):1385–1391.
19 Lee J, Walker ME, Gabriel KP, Vasan RS, Xanthakis V. Associations of accelerometer-measured physical activity and sedentary time with chronic kidney disease: the Framingham Heart Study. *PLoS One*. 2020;15(6):e0234825.
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(3):e1001779.
21 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(9):1026–1034.
22 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(2):e0169649.
23 Khurshid S, Weng LC, Al-Alusi MA, et al. Accelerometer-derived physical activity and risk of atrial fibrillation. *Eur Heart J*. 2021;42(25):2472–2483.
24 Yoon SJ, Suh SY, Lee YJ, et al. Prospective validation of objective prognostic score for advanced cancer inpatients in South Korea: a multicenter study. *J Palliat Med*. 2017;20(1):65–68.
25 Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of physical activities: a second update of codes and MET values. *Med Sci Sports Exerc*. 2011;43(8):1575–1581.
26 Eknoyan G, Lameire N, Eckardt K, et al. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. 2013;3(1):5–14.
27 Honigberg MC, Zekavat SM, Pirruccello JP, Natarajan P, Vaduganathan M. Cardiovascular and kidney outcomes across the glycemic spectrum: insights from the UK Biobank. *J Am Coll Cardiol*. 2021;78(5):453–464.
28 Wuttke M, Li Y, Li M, et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat Genet*. 2019;51(6):957–972.
29 Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature*. 2018;562(7726):203–209.
30 Khera AV, Emdin CA, Drake I, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. *N Engl J Med*. 2016;375(24):2349–2358.
31 Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med*. 2021;385(19):1737–1749.
32 van Buuren S, Groothuis-Oudshoorn K. Mice: multivariate imputation by chained equations in R. *J Stat Software*. 2011;45(3):1–67.
33 Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika*. 1982;69:239–241.
34 Korthauer K, Kimes PK, Duvallet C, et al. A practical guide to methods controlling false discoveries in computational biology. *Genome Biol*. 2019;20(1):118.
35 White SL, Dunstan DW, Polkinghorne KR, Atkins RC, Cass A, Chadban SJ. Physical inactivity and chronic kidney disease in Australian adults: the AusDiab study. *Nutr Metab Cardiovasc Dis*. 2011;21(2):104–112.
36 Yamamoto S, Inoue Y, Kuwahara K, et al. Leisure-time, occupational, and commuting physical activity and the risk of chronic kidney disease in a working population. *Sci Rep*. 2021;11(1):12308.
37 Zhu Y, Bu Y, Zhang G, et al. Association of physical activity with chronic kidney disease: a systematic review and dose-response meta-analysis. *Aging*. 2020;12(19):19221–19232.
38 Bishop NC, Burton JO, Graham-Brown MPM, Stensel DJ, Viana JL, Watson EL. Exercise and chronic kidney disease: potential mechanisms underlying the physiological benefits. *Nat Rev Nephrol*. 2023;19(4):244–256.
39 Ito O, Nakamura T, Yamakoshi S, Mori N, Masahiro K. Effects of exercise training on renal damage and renin-angiotensin system in rats with chronic renal failure. *Ann Phys Rehabil Med*. 2018;61:e82.
40 Michou V, Nikodimopoulou M, Deligiannis A, Kouidi E. Metabolic and functional effects of exercise training in diabetic kidney transplant recipients. *World J Transplant*. 2022;12(7):184–194.
41 Di Francescomarino S, Sciartilli A, Di Valerio V, Di Baldassarre A, Gallina S. The effect of physical exercise on endothelial function. *Sports Med*. 2009;39(10):797–812.
42 Hambrecht R, Fiehn E, Weigl C, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation*. 1998;98(24):2709–2715.
43 Fu Q, Levine BD. Exercise and the autonomic nervous system. *Handb Clin Neurol*. 2013;117:147–160.
44 WHO. *Global action plan for the prevention and control of NCDs 2013–2020*. World Health Organization; 2013.
45 Dempsey PC, Rowlands AV, Strain T, et al. Physical activity volume, intensity, and incident cardiovascular disease. *Eur Heart J*. 2022;43(46):4789–4800.
46 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(1):e1003487.
47 Luo M, Yu C, Del Pozo Cruz B, Chen L, Ding D. Accelerometer-measured intensity-specific physical activity, genetic risk and incident type 2 diabetes: a prospective cohort study. *Br J Sports Med*. 2023;57(19):1257–1264.
48 Watts EL, Saint-Maurice PF, Doherty A, et al. Association of accelerometer-measured physical activity level with risks of hospitalization for 25 common health conditions in UK adults. *JAMA Netw Open*. 2023;6(2):e2256186.
49 Khurshid S, Al-Alusi MA, Churchill TW, Guseh JS, Ellinor PT. Accelerometer-Derived "weekend warrior" physical activity and incident cardiovascular disease. *JAMA*. 2023;330(3):247–252.
50 Feng H, Yang L, Liang YY, et al. Associations of the timing of physical activity with all-cause and cause-specific mortality in a prospective cohort study. *Nat Commun*. 2023;14(1):930.