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Sex differences in the association of wearable accelerometer-derived physical activity with coronary heart disease incidence and mortality

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Despite American Heart Association, European Society of Cardiology and World Health Organization (AHA/ESC/WHO) guidelines uniformly recommending 150 min week^{-1} of moderate-to-vigorous physical activity (MVPA) for both sexes, a substantial 'gender gap' persists in exercise capacity and guideline adherence, and its impact on coronary heart disease (CHD) development and prognosis remains underexplored. Here we analyzed the accelerometer-measured MVPA of 80,243 CHD-free participants to assess CHD incidence and 5,169 patients with CHD to evaluate all-cause mortality. Compared with non-adherent counterparts, guideline-adherent participants showed a 22% lower CHD risk in female individuals (hereinafter referred to as females) and a 17% lower CHD risk in male individuals (hereinafter referred to as males; ($P_{interaction}$ = 0.009). Notably, females achieved a CHD risk reduction of 30% (hazard ratio (HR) = 0.70) with 250 min week^{-1} of MVPA, whereas males required 530 min week^{-1} for comparable benefits. Among patients with CHD, active females experienced greater mortality risk reduction than males (HR = 0.30 versus 0.81; $P_{interaction}$ = 0.004). Similar sex differences were observed when analyzing guideline-adhering days ($P_{interaction}$ < 0.05). Our findings underscore the value of sex-specific tailored CHD prevention strategies using wearable devices, which may help bridge the 'gender gap' by motivating females to engage in physical activity.

Coronary heart disease (CHD) remains the predominant cause of morbidity and mortality worldwide[1]. Current guidelines from the American Heart Association[2], the European Society of Cardiology[3] and the World Health Organization[4] (AHA/ESC/WHO) all recommend at least 150 min week^{-1} of moderate-to-vigorous physical activity (MVPA) to prevent the development or progression of CHD. Despite these guidelines adopting a 'one-size-fits-all' approach for both sexes, a well-documented 'gender gap' exists[5], with males generally showing greater capacity than females[6]. Globally, the prevalence of insufficient physical activity (PA) was 5 percentage points higher among females than males (33.8% versus 28.7%)[7]. However, whether and to what extent sex disparities impact the development and prognosis of CHD remain underexplored. Understanding sex differences is crucial for tailored CHD prevention and has potential to bridge the 'gender gap' by tailoring PA recommendations.

Recently, the WHO Guideline Development Group endorsed the advancing surveillance of PA by using a wearable device[4], whereas previous studies mainly relied on self-reported questionnaires that are prone to recall bias and overestimation[8,9]. By contrast, wearable devices provide objective and continuous activity monitoring, enabling more

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Table 1 | Baseline characteristics of participants in the CHD incidence and mortality study

	CHD incidence study			CHD mortality study		
	Overall (*N*=80,243)	Female (*N*=45,986)	Male (*N*=34,257)	Overall (*N*=5,169)	Female (*N*=1,553)	Male (*N*=3,616)
Age (years)	61.54±7.84	61.16±7.75	62.05±7.94	66.93±5.90	66.36±6.25	67.17±5.73
Ethnicity						
Asian	3,148 (3.92%)	2,060 (4.48%)	1,088 (3.18%)	141 (2.73%)	63 (4.06%)	78 (2.16%)
Black	2,503 (3.12%)	1,394 (3.03%)	1,109 (3.24%)	172 (3.33%)	50 (3.22%)	122 (3.37%)
Mixed or other	403 (0.50%)	258 (0.56%)	145 (0.42%)	24 (0.46%)	12 (0.77%)	12 (0.33%)
White	74,189 (92.46%)	42,274 (91.93%)	31,915 (93.16%)	4,832 (93.48%)	1,428 (91.95%)	3,404 (94.14%)
Education						
College or university	35,525 (44.27%)	19,689 (42.82%)	15,836 (46.23%)	1,662 (32.15%)	480 (30.91%)	1,182 (32.69%)
Other	44,718 (55.73%)	26,297 (57.18%)	18,421 (53.77%)	3,507 (67.85%)	1,073 (69.09%)	2,434 (67.31%)
Center						
England	71,922 (89.63%)	41,236 (89.67%)	30,686 (89.58%)	4,657 (90.09%)	1,400 (90.15%)	3,257 (90.07%)
Scotland	5,256 (6.55%)	3,033 (6.60%)	2,223 (6.49%)	330 (6.38%)	100 (6.44%)	230 (6.36%)
Wales	3,065 (3.82%)	1,717 (3.73%)	1,348 (3.93%)	182 (3.52%)	53 (3.41%)	129 (3.57%)
Townsend deprivation index	−1.76±2.80	−1.72±2.80	−1.81±2.80	−1.69±2.83	−1.58±2.89	−1.74±2.81
BMI (kg m^{-2})	26.60±4.48	26.19±4.79	27.15±3.96	28.46±4.65	28.37±5.51	28.49±4.23
Sleep duration (h)						
< 7	17,371 (21.65%)	9,746 (21.19%)	7,625 (22.26%)	1,274 (24.65%)	425 (27.37%)	849 (23.48%)
7–8	57,891 (72.14%)	33,215 (72.23%)	24,676 (72.03%)	3,385 (65.49%)	972 (62.59%)	2,413 (66.73%)
>8	4,981 (6.21%)	3,025 (6.58%)	1,956 (5.71%)	510 (9.87%)	156 (10.05%)	354 (9.79%)
Smoking status						
Never	46,554 (58.02%)	28,233 (61.39%)	18,321 (53.48%)	2,237 (43.28%)	818 (52.67%)	1,419 (39.24%)
Previous	28,344 (35.32%)	15,126 (32.89%)	13,218 (38.58%)	2,548 (49.29%)	638 (41.08%)	1,910 (52.82%)
Current	5,345 (6.66%)	2,627 (5.71%)	2,718 (7.93%)	384 (7.43%)	97 (6.25%)	287 (7.94%)
Alcohol status						
Never	2,229 (2.78%)	1,641 (3.57%)	588 (1.72%)	191 (3.70%)	110 (7.08%)	81 (2.24%)
Previous	2,112 (2.63%)	1,225 (2.66%)	887 (2.59%)	203 (3.93%)	76 (4.89%)	127 (3.51%)
Current	75,902 (94.59%)	43,120 (93.77%)	32,782 (95.69%)	4,775 (92.38%)	1,367 (88.02%)	3,408 (94.25%)
Dietary health						
Ideal	28,145 (35.07%)	18,053 (39.26%)	10,092 (29.46%)	1,874 (36.25%)	663 (42.69%)	1,211 (33.49%)
Poor	52,098 (64.93%)	27,933 (60.74%)	24,165 (70.54%)	3,295 (63.75%)	890 (57.31%)	2,405 (66.51%)
Charlson comorbidity index	2.00 (1.00–2.00)	2.00 (1.00–2.00)	2.00 (1.00–3.00)	3.00 (2.00–4.00)	3.00 (2.00–4.00)	3.00 (2.00–4.00)
Hypertension	39,673 (49.44%)	19,904 (43.28%)	19,769 (57.71%)	4,522 (87.48%)	1,271 (81.84%)	3,251 (89.91%)
Diabetes	3,442 (4.29%)	1,373 (2.99%)	2,069 (6.04%)	834 (16.13%)	217 (13.97%)	617 (17.06%)
Dyslipidemia	47,672 (59.41%)	26,383 (57.37%)	21,289 (62.14%)	4,630 (89.57%)	1,325 (85.32%)	3,305 (91.40%)
Cholesterol-lowering medication	10,049 (12.52%)	4,054 (8.82%)	5,995 (17.50%)	3,308 (64.00%)	798 (51.38%)	2,510 (69.41%)
Blood pressure medication	13,140 (16.38%)	6,352 (13.81%)	6,788 (19.81%)	3,342 (64.65%)	868 (55.89%)	2,474 (68.42%)
Insulin therapy	1,743 (2.17%)	692 (1.50%)	1,051 (3.07%)	432 (8.36%)	97 (6.25%)	335 (9.26%)
Antiplatelet medication	7,712 (9.61%)	3,385 (7.36%)	4,327 (12.63%)	3,121 (60.38%)	711 (45.78%)	2,410 (66.65%)
Antianginal medication	5,982 (7.46%)	2,769 (6.03%)	3,213 (9.39%)	2,436 (47.13%)	602 (38.76%)	1,834 (50.72%)
MVPA (min week^{-1})	189.18±173.76	178.47±166.40	203.56±182.18	126.15±140.25	102.62±127.59	136.25±144.19
Average acceleration (mg)	208.93±84.56	202.52±77.58	217.55±92.41	180.48±78.53	170.36±71.78	184.82±80.87
Adherence to AHA/ESC/WHO standard[a]	38,887 (48.46%)	21,043 (45.76%)	17,844 (52.09%)	1,577 (30.51%)	340 (21.89%)	1,237 (34.21%)
Adherence to WHO extended recommendation[b]	16,066 (20.02%)	8,360 (18.18%)	7,706 (22.49%)	565 (10.93%)	120 (7.73%)	445 (12.31%)

Table 1 (continued) | Baseline characteristics of participants in the CHD incidence and mortality study

	CHD incidence study			CHD mortality study		
	Overall (*N*=80,243)	Female (*N*=45,986)	Male (*N*=34,257)	Overall (*N*=5,169)	Female (*N*=1,553)	Male (*N*=3,616)
Days met daily AHA/ESC/WHO standard[c]	2.92±2.28	2.81±2.30	3.06±2.25	1.98±2.12	1.59±1.95	2.15±2.17
Days met daily WHO extended recommendation[d]	1.57±1.89	1.47±1.86	1.71±1.92	0.95±1.56	0.71±1.39	1.05±1.62
Follow-up years	7.88 (7.31–8.39)	7.90 (7.35–8.40)	7.85 (7.26–8.37)	7.77 (7.24–8.31)	7.79 (7.29–8.31)	7.75 (7.20–8.31)
CHD events	3,764 (4.69%)	1,406 (3.06%)	2,358 (6.88%)	–	–	–
All-cause deaths	–	–	–	593 (11.47%)	117 (7.53%)	476 (13.16%)

[a]Defined as at least 150 min of MVPA per week. [b]Defined as at least 300 min of MVPA per week. [c]Defined as number of days with at least 150/7 min of MVPA. [d]Defined as number of days with at least 300/7 min of MVPA.

Table 2 | Sex-specific associations of accelerometer-derived PA with CHD risk in the CHD-free population and mortality risk in the CHD population

	Female		Male		$P_{interaction}$	*q*-FDR
	HR (95% CI)	*P* value	HR (95% CI)	*P* value		
CHD risk in the CHD-free population						
MVPA, per 30 min week^{-1}	0.971 (0.958–0.985)	3.31×10^{-5}	0.981 (0.973–0.990)	1.78×10^{-5}	8.41×10^{-4}	0.004
Adherence to the AHA/ESC/WHO standard[a]	0.780 (0.689–0.884)	9.36×10^{-5}	0.830 (0.760–0.906)	2.82×10^{-5}	0.009	0.016
Adherence to the WHO extended recommendation[b]	0.789 (0.658–0.947)	0.011	0.888 (0.792–0.994)	0.040	0.019	0.019
Days adhering to the average daily AHA/ESC/WHO standard[c]	0.940 (0.914–0.967)	1.56×10^{-5}	0.957 (0.938–0.977)	2.01×10^{-5}	0.002	0.005
Days adhering to the average daily WHO extended recommendation[d]	0.943 (0.908–0.979)	0.002	0.956 (0.932–0.980)	4.11×10^{-4}	0.016	0.019
Mortality risk in the CHD population						
MVPA, per 30 min week^{-1}	0.883 (0.804–0.970)	0.009	0.965 (0.940–0.989)	0.006	0.005	0.012
Adherence to the AHA/ESC/WHO standard[a]	0.300 (0.129–0.699)	0.005	0.808 (0.647–1.009)	0.060	0.004	0.012
Adherence to the WHO extended recommendation[b]	0.594 (0.185–1.909)	0.382	0.840 (0.602–1.170)	0.302	0.332	0.332
Days adhering to the average daily AHA/ESC/WHO standard[c]	0.850 (0.734–0.984)	0.030	0.922 (0.876–0.971)	0.002	0.052	0.065
Days adhering to the average daily WHO extended recommendation[d]	0.729 (0.552–0.963)	0.026	0.911 (0.847–0.980)	0.012	0.025	0.042

The HR and 95% CI were derived from multivariable Cox proportional hazard models adjusted for PA intensity, demographics, lifestyles and medical conditions, as well as the polygenetic risk score of CHD in the CHD incidence study, and the use of CHD treatment medicines (antiplatelet medication, antianginal medication) in the CHD mortality study. Likelihood ratio tests were used to test the interactions, by comparing models with and without interaction terms between sex and PA measures. All statistical tests were two sided, and FDR adjustments were used for multiple comparisons. [a]Defined as at least 150 min of MVPA per week. [b]Defined as at least 300 min of MVPA per week. [c]Defined as number of days with at least 150/7 min of MVPA. [d]Defined as number of days with at least 300/7 min of MVPA.

precision interventions[10]. In addition, with the growing popularity of consumer wearables, their roles in personalized health assessment and PA tracking are increasingly important[11]. Therefore, a prospective study using wearable accelerometer-derived data is essential to elucidate sex-specific benefits, further advance CHD precision management and modify the development or progression of CHD.

In our study, leveraging accelerometer-derived PA data of over 85,000 participants from the UK Biobank, we investigated sex differences in the association of PA with both the incidence risk of CHD in the CHD-free population and the all-cause mortality risk in patients with CHD.

Results

Population characteristics

In the CHD incidence study of 80,243 participants free of CHD (age: 61.54 ± 7.84 years; 57.3% female), there were 3,764 CHD events over a median follow-up of 7.88 years. In the CHD mortality study of 5,169 CHD-established participants (age: 66.93 ± 5.90 years; 30.0% female), 593 all-cause deaths occurred during a median follow-up of 7.77 years (Table 1). Comprehensive comparisons of participant characteristics across sexes and guideline-adherent groups are presented in Table 1 and Supplementary Tables 1 and 2. Overall, 48.46% of CHD-free participants met the minimum MVPA time (150 min week^{-1}) recommended by AHA/ESC/WHO, whereas only 30.51% of patients with CHD achieved this target. Furthermore, females lag behind males in both MVPA duration and intensity, and had a lower adherence to guidelines (Table 1 and Supplementary Figs. 1–3).

Sex differences in associations of PA measures with CHD incidence risk in the CHD-free population

In the CHD incidence study, per 30 min week^{-1} increase of MVPA duration was associated with a lower CHD risk in females (hazard ratio (HR) = 0.971, 95% confidence interval (CI): 0.958–0.985) and males (HR = 0.981, 95% CI: 0.973–0.990), indicating a stronger protective effect in females ($P_{interaction} < 0.001$) (Table 2). When stratified by guideline adherences, the cumulative incidence curves revealed a reduced risk for those adhering to guidelines across both sexes (both $P_{log\text{-}rank} < 0.001$) (Fig. 1a,b). The incidence rate of CHD was 703.53 per 100,000 person-years in physically active males adhering to AHA/ESC/WHO standard recommendations, compared with 1,143.62 for physically inactive males. A reduction in the CHD incidence rate was also observed in active females compared with inactive ones

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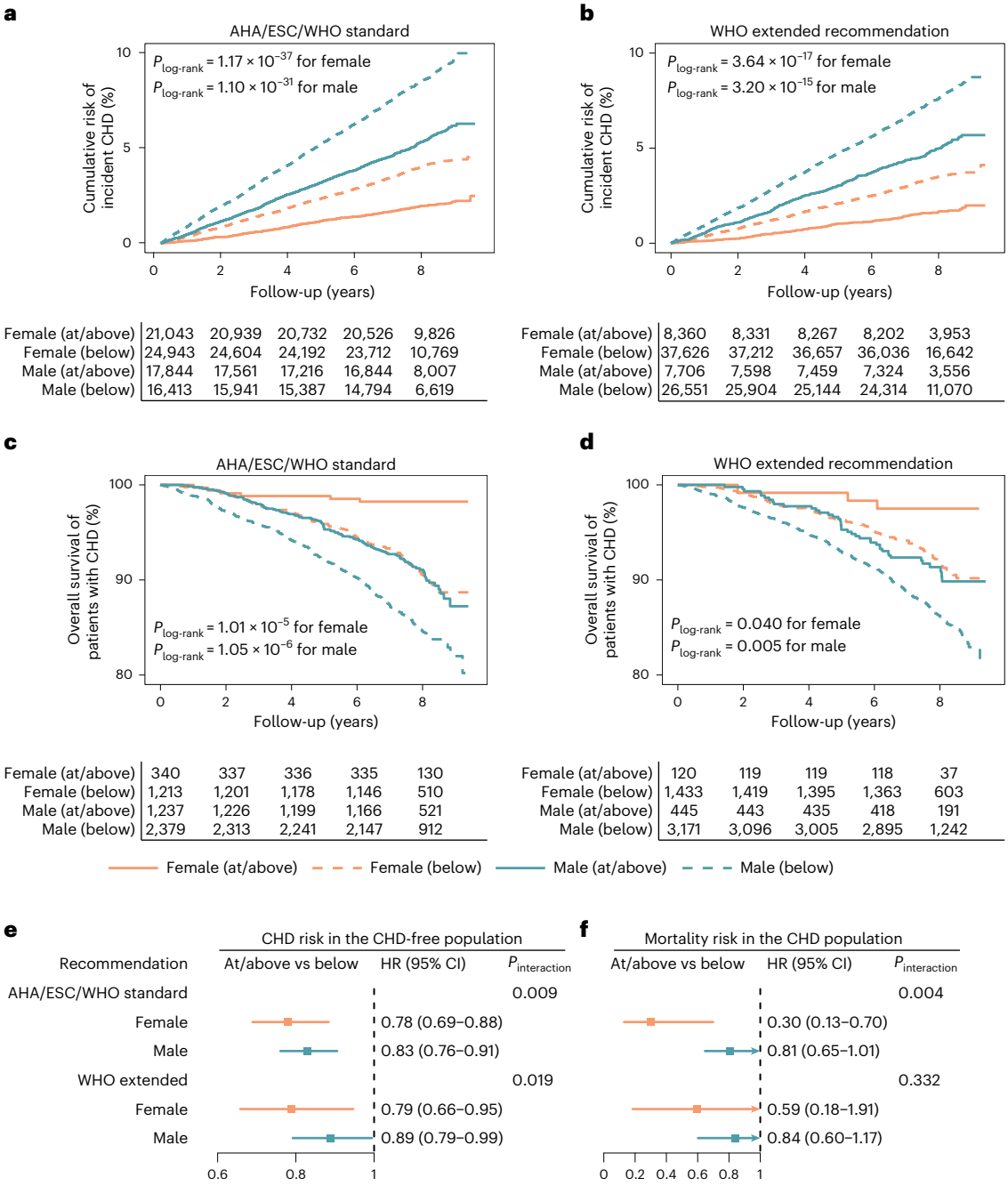

Fig. 1 | Sex-specific cumulative risks of CHD in the CHD-free population and overall survival in patients with CHD stratified by adherence to PA recommendations. a,**b**, Sex-specific cumulative risk of incident CHD in the CHD-free population stratified by adherence to the AHA/ESC/WHO standard recommendation (150 min week^{-1}) (**a**) and WHO extended recommendation (300 min week^{-1}) (**b**). **c**,**d**, Sex-specific overall survival of patients with CHD stratified by adherence to the AHA/ESC/WHO standard recommendation (150 min week^{-1}) (**c**) and WHO extended recommendation (300 min week^{-1}) (**d**). Cumulative risks and survival differences between groups were assessed using the two-sided log-rank test. **e**,**f**, Sex-specific associations and sex differences between PA guideline adherence and incident CHD risk in the CHD-free population (AHA/ESC/WHO standard: $N_{at/above\ versus\ below}$ = 21,043 versus 24,943 in females, and 17,844 versus 16,413 in males; WHO extended: 8,360 versus 37,626 in females, and 7,706 versus 26,551 in males) (**e**) and all-cause mortality in patients with CHD (AHA/ESC/WHO standard: $N_{at/above\ versus\ below}$ = 340 versus 1,213 in females, and 1,237 versus 2,379 in males; WHO extended: 120 versus 1,433 in females, and 445 versus 3,171 in males) (**f**). The point estimates and error bars represent the HR and 95% CI from multivariable Cox proportional hazard models. All statistical tests were two-sided.

(249.16 versus 519.28 per 100,000 person-years) (Supplementary Table 3). In addition, we compared the risk of CHD incidence across levels of guideline adherence using multivariable Cox proportional hazard models. Specifically, among participants who met the AHA/ESC/WHO standard recommendations, females experienced a 22% relative reduction in CHD incidence risk (HR = 0.780, 95% CI: 0.689–0.884), whereas males showed a 17% reduction (HR = 0.830, 95% CI: 0.760–0.906); a significant sex difference was observed ($P_{interaction}$ = 0.009) (Table 2 and Fig. 1e). A similar pattern was found while adhering to the extended recommendation of WHO (HR = 0.789, 95% CI: 0.658–0.947 for females; HR = 0.888, 95% CI: 0.792–0.994 for males; P = 0.019 for sex difference; Table 2 and Fig. 1).

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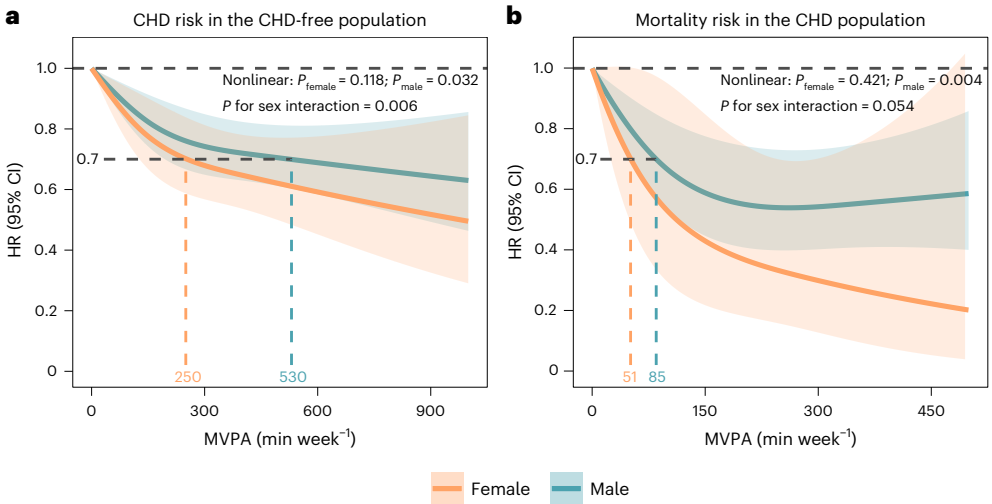

Fig. 2 | Dose–response associations of MVPA with CHD incidence and mortality by sex. a,**b**, The adjusted HRs for associations of MVPA duration with CHD incidence risk in the CHD-free population (N_{female} = 45,986, N_{male} = 34,257) (**a**) and all-cause mortality risk in patients with CHD (N_{female} = 1,553, N_{male} = 3,616) (**b**) by sex. The solid line depicts the estimated HR derived from restricted cubic spline models, and the shaded area indicates the corresponding 95% CI. Statistical tests were two sided.

The dose–response associations indicated that to achieve a reduction in CHD risk of 30% (HR = 0.70), males need to engage in 530 min week^{-1} of MVPA, while only 250 min week^{-1} was required for females (Fig. 2a). Compared with females, males needed twofold engagement of MVPA to achieve equivalent benefit in CHD risk.

An increase in number of days adhering to daily AHA/ESC/WHO guidelines (150/7 min d^{-1}) was also associated with a reduced risk of incident CHD for both sexes. For females, CHD incidence decreased from 5.2% in those with nonadherent days to 1.5% among participants engaged in PA every day of the week. Comparatively, a protective gradient was observed in males, with CHD incidence declining from 10.2% among inactive ones to 4.7% among those with regular PA engagement (Fig. 3a). The results of Cox models indicated that per 1 day of adhering to the daily AHA/ESC/WHO recommendation increment was related to a relatively lower risk of CHD in both females (HR = 0.940, 95% CI: 0.914–0.967) and males (HR = 0.957, 95% CI: 0.938–0.977). Sex significantly modified the effect of number of days adhering to the recommendation on CHD incidence risk ($P_{interaction}$ = 0.002) (Table 2 and Fig. 3e). Similar results were found when analyzing according to the WHO extended recommendation (HR = 0.943, 95% CI: 0.908–0.979 for females; HR = 0.956, 95% CI: 0.932–0.980 for males; P = 0.016 for sex interaction) (Fig. 3 and Table 2).

Sex differences in associations of PA measures with all-cause mortality risk in patients with CHD

In the CHD mortality study, protective effects of MVPA duration on the all-cause mortality of patients with CHD were present in both females (HR = 0.883, 95% CI: 0.804–0.970) and males (HR = 0.965, 95% CI: 0.940–0.989), while the benefits were different across sexes ($P_{interaction}$ = 0.005) (Table 2). Kaplan–Meier curves showed significant survival differences across PA-guideline-adherent groups for both sexes ($P_{log\text{-}rank}$ < 0.05 for both sexes) (Fig. 1c,d). For female patients with CHD, only 340 participants met the AHA/ESC/WHO standard recommendations, of whom 6 (1.76%) deaths were registered. In females with PA below the guidelines, 111 of 1,213 (9.15%) died during the follow-up period. Male patients with CHD showed similar but attenuated benefits; guideline-adherent patients (360 of 2,379, 15.13%) showed a substantially low mortality rate, compared with nonadherent counterparts (116 of 1,237, 9.38%) (Supplementary Table 3). In addition, multivariable Cox regression models indicated an HR of 0.300 (95% CI: 0.129–0.699) for females and 0.808 (95% CI: 0.647–1.009) for males, and this almost threefold sex-difference risk was also significant ($P_{interaction}$ = 0.004) (Table 2). Although unadjusted survival curves showed relatively modest disparities between patients with CHD stratified by adherence to WHO extended recommendations ($P_{log\text{-}rank}$ < 0.05) (Fig. 1d), no statistical evidence supports the significant association between mortality risk reduction and adherence to the WHO extended PA recommendation in patients with CHD, after adjusting for potential confounders in the multivariable Cox models (Table 2).

Figure 2b illustrates the sex-specific dose–response relationship between MVPA and all-cause mortality risk in patients with CHD. The results showed that, among patients with CHD, male patients required weekly MVPA engagement nearly 1.7-fold that of females to achieve a comparable relative reduction of mortality risk, with females having an MVPA of 51 min week^{-1} and males, 85 min week^{-1}.

The trends of mortality rate in patients with CHD suggested a potential inverse but slightly fluctuant relationship across number of days adhering to daily PA guidelines (Fig. 3c,d), probably owing to the relatively limited sample size (Supplementary Fig. 2d). Overall, per additional day meeting the AHA/ESC/WHO guidelines was related to a 15% (HR = 0.850, 95% CI: 0.734–0.984) relative reduction in mortality risk among female patients with CHD and 8% (HR = 0.922, 95% CI: 0.876–0.971) among male patients with CHD ($P_{interaction}$ = 0.052) (Table 2 and Fig. 3f). Furthermore, when examining the relationship between days meeting the WHO extended guidelines and mortality risk in patients with CHD, a greater benefit was noted in female patients (HR = 0.729, 95% CI: 0.552–0.963) versus males (HR = 0.911, 95% CI: 0.847–0.980) ($P_{interaction}$ = 0.025; Table 2 and Fig. 3f).

Sensitivity analyses

The sex differences in associations of PA measures with both CHD incidence and mortality remained consistent and robust across various sensitivity analyses. Multiple models incorporating different sets of covariate adjustments were applied to account for the influence of potential confounders (Supplementary Tables 4–7). Consistent and significant results were observed when accounting for the competing risk of death by using Fine and Gray subdistribution hazard models (Supplementary Table 8), considering alternative Cox proportional hazard models with age as the timescale (Supplementary Table 9), and accounting for sex-specific baseline hazards by using stratified Cox proportional hazard models (Supplementary Table 10). We excluded individuals who experienced

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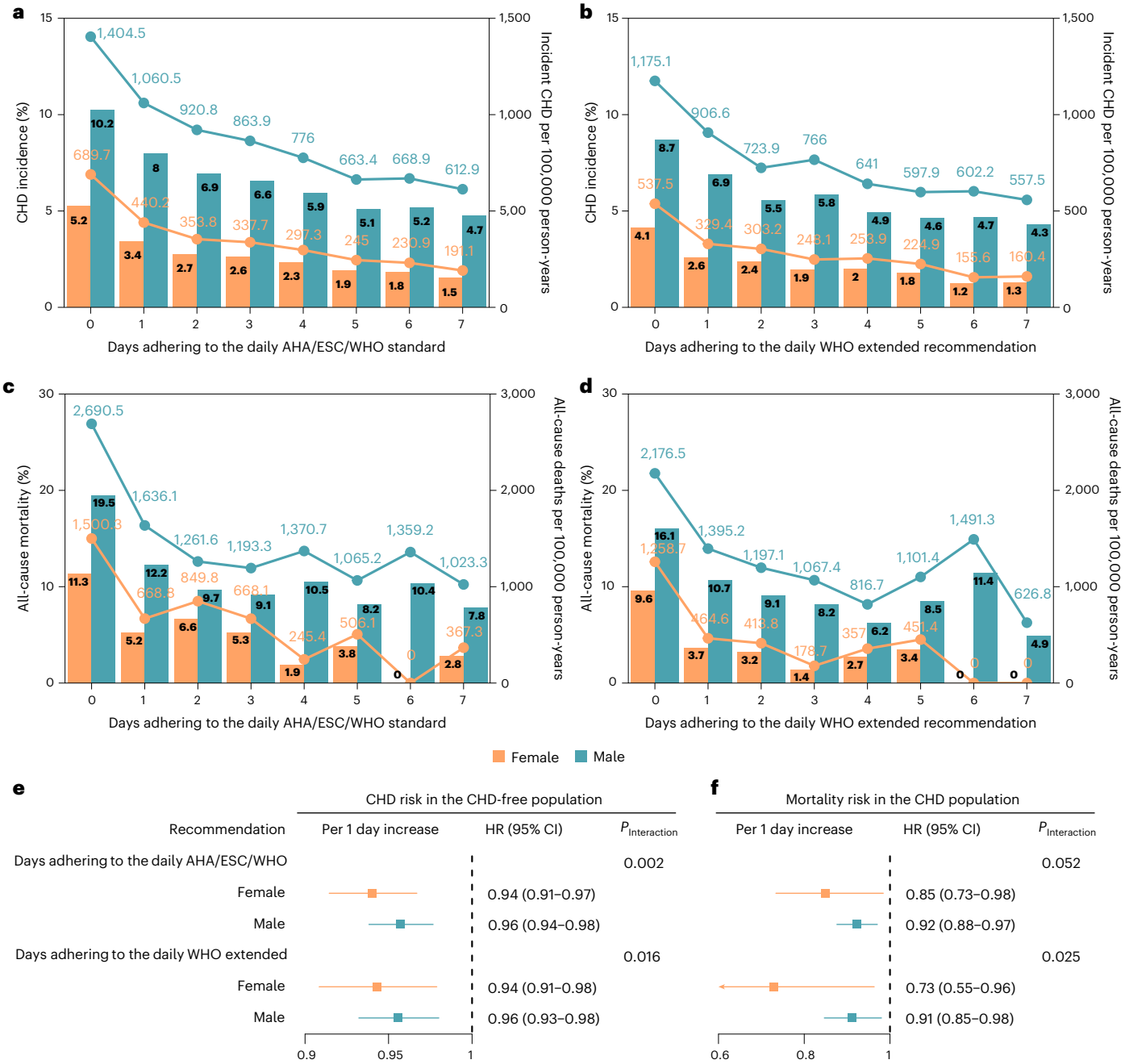

Fig. 3 | Sex-specific rates of CHD incidence and mortality stratified by days adhering to daily PA recommendations. a,**b**, Sex-specific CHD incidence rate in the CHD-free population stratified by days adhering to the AHA/ESC/WHO standard recommendation (150/7 min d^{-1}) (**a**) and WHO extended recommendation (300/7 min d^{-1}) (**b**). **c**,**d**, Sex-specific mortality rate in patients with CHD stratified by days adhering to the AHA/ESC/WHO standard recommendation (150/7 min d^{-1}) (**c**) and WHO extended recommendation (300/7 min d^{-1}) (**d**). **e**,**f**, Sex-specific associations and sex differences between days adhering to daily PA recommendations and CHD incidence risk in the CHD-free population (N_{Female} = 45,986, N_{Male} = 34,257) (**e**), and all-cause mortality in patients with CHD (N_{female} = 1,553, N_{male} = 3,616) (**f**). The point estimates and error bars represent the HR and 95% CI from multivariable Cox proportional hazard models. Statistical tests were two sided.

outcomes within the first year of follow-up period to mitigate reverse causality (Supplementary Figs. 4–6 and Supplementary Tables 11 and 12). Furthermore, sensitivity analyses using imputed datasets, comprising 88,611 participants in the CHD incidence study and 5,476 participants in the CHD mortality study, consistently revealed that females derived greater benefit in reducing CHD incidence among the CHD-free population and all-cause mortality among patients with CHD with equivalent doses of PA (Supplementary Figs. 7–9 and Supplementary Tables 13 and 14).

Discussion

In this large-scale prospective study using PA data measured by wrist-worn accelerometers among over 85,000 participants, we observed substantial sex differences in clinical benefits of PA with CHD incidence and mortality. Specifically, to achieve a 30% relative reduction in CHD incidence risk, males need to engage in 530 min of MVPA per week, whereas only half-time engagement (250 min $week^{-1}$) is needed for females to achieve a comparable benefit. For the all-cause mortality in patients with CHD, although

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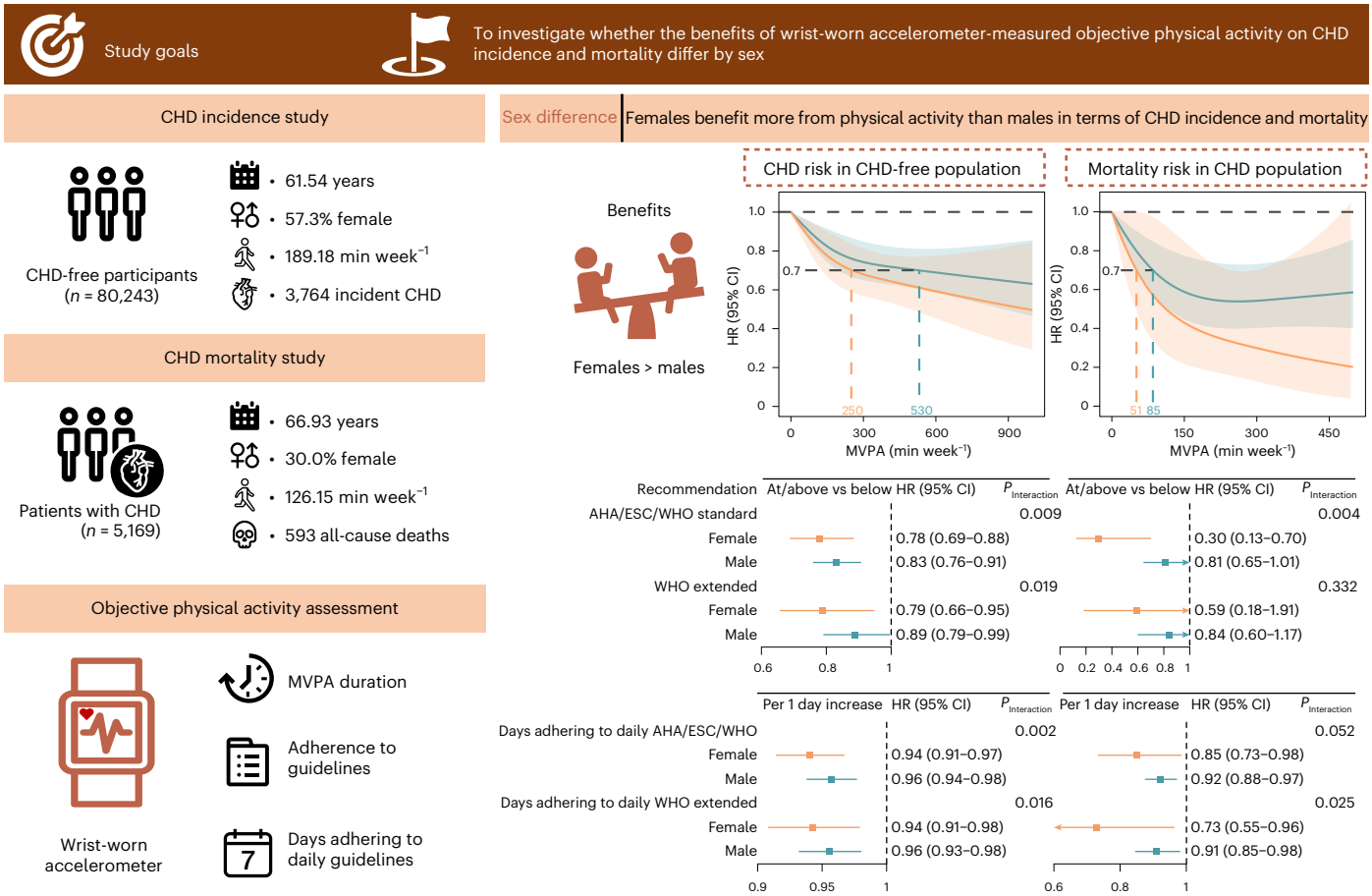

Fig. 4 | Central illustration of the study design and summary of findings. Wrist-worn accelerometer-derived PA data of 80,243 CHD-free participants and 5,169 patients with CHD were used to examine sex-specific dose–response associations between MVPA duration and CHD outcomes. HRs (solid line) and 95% CI (shaded area) were estimated from restricted cubic spline models. Sex-specific associations between guideline adherence and CHD outcomes were shown as HRs (point estimates) and 95% CIs (error bars), estimated from multivariable Cox proportional hazard models. Sex differences were assessed by two-sided likelihood ratio tests. Orange lines and areas represent females. Green lines and areas represent males.

both sexes adhere to equivalent MVPA recommended by AHA/ESC/WHO (150 min week^{-1}), female patients with CHD derived a substantial threefold reduction in mortality risk (Fig. 4). Our findings may provide insights into sex-specific prevention of CHD by using wearable devices, and encourage females to engage in PA.

Despite accumulating calls for sex-specific guidelines, few studies have focused on sex differences in risk stratification, prevention and prognosis of CHD[5,12]. A prospective study investigating the association of questionnaire-based MVPA with all-cause and cardiovascular mortality risk in a general population of US adults showed that females derived greater mortality reductions than males[13]. Regarding CHD-specific evidence, in a meta-analysis of 33 studies, the authors conducted an exploratory analysis based on 2 studies with sufficient data for interaction analysis, and reported a potential sex difference, but acknowledged biases induced by insufficient data collection and heterogeneity of study design and measures across studies[14]. Extending from previous work, our study used objective PA measures from wearable devices and confirmed similar sex interactions in both CHD risk prevention in the CHD-free population and mortality prevention in the established CHD population.

Some possible factors might contribute to sex differences in the beneficial effects of PA. Physiologically, circulating estrogen levels are much higher in females than in males, and estrogen can promote body fat loss during PA[15]. As shown in a randomized controlled trial, estrogen supplementation can increase lipid oxidation in men during exercise[16], which is established to improve clinical outcomes of CHD[17]. In addition, another possible reason could be the considerable sex disparities in the morphological composition of skeletal muscle[18]. Specifically, males have a greater percentage of type II muscle fibers, whereas the skeletal muscle of females is dominated by type I muscle fibers, leading to disparities in muscle metabolism[18]. Males have greater glycolytic capacity, while females are characterized with greater whole-muscle oxidative capacity[19]. These differences may contribute to the observed increased sensitivity to PA and greater clinical benefit in females. Nevertheless, the underlying mechanisms remain to be elucidated.

Our study has potential clinical implications and several strengths. Current 'one-size-fits-all' guidelines have uniform recommendations for females and males, assuming that PA amounts and benefits are the same for both sexes[2–4]. By contrast, females are more physically inactive and less likely to achieve management targets of CHD risk factors[20], and such a 'gender gap' might yield worse clinical outcomes in women. The landmark 2010 Institute of Medicine's publication called for attentions to sex differences in CHD management[21]. As reported, the focus on sex and gender research has successfully reduced 30% of CVD deaths in females[22]. Our study highlighted the necessity of sex-specific individualized management in CHD prevention. Compared with male individuals, females derive equivalent health benefits with only half the exercise time. The findings might have potential to encourage females to engage in PA. In addition, with the rising popularity of wrist-worn wearables revolutionizing PA monitoring[23], our results suggest the promise of smart wearable devices for future CHD management. Moreover, the large-scale population, prospective design, objective PA measures,

careful covariate consideration and comprehensive sensitivity analyses might strengthen our findings.

Several limitations should be considered when interpreting our findings. First, the generalizability of our findings might be limited by ancestry and geographics. The participants in UK Biobank were mostly white, had healthier lifestyles and lived in areas with less socioeconomic deprivation[24]. Further studies are warranted to explore the relationships between PA and both CHD incidence and mortality in diverse populations. Second, although our analyses included over 85,000 participants, the sample size of the CHD mortality study was relatively small and the number of documented CHD-specific deaths was relatively limited, which precluded robust analyses of CHD-specific mortality. Third, our results suggested a substantial reduction in mortality risk associated with PA among elderly females with established CHD, which was comparable to findings from previous accelerator-based studies in similar populations of elderly females with or without CHD[25,26]. Nevertheless, this result should be interpreted with caution owing to the limited sample size, and further validation in large-scale CHD cohorts, particularly those with objectively measured PA data from wearable devices, is warranted. Fourth, given the observational design, causality cannot be definitively established. Nevertheless, we conducted a series of sensitivity analyses by considering a broad range of covariates to address potential confounding, and excluding participants with events that occurred during the first year of follow-up to mitigate reverse causality. In addition, biological experiments are needed to explore the mechanisms underlying sex difference in PA benefits.

In conclusion, we observed significant sex differences in associations between accelerometer-measured PA with both CHD incidence risk in the CHD-free population and all-cause mortality risk in the established CHD population, based on a large-scale prospective cohort. Females compared with males derived greater benefits from the same level of PA engagement. Our findings might provide insights into sex-specific tailored management in the prevention of CHD incidence and mortality and advanced precision prevention using wearable devices, and have potential to bridge the 'gender gap' by encouraging female individuals to engage in PA.

Methods

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (Supplementary Table 15). All data field identifiers are listed in Supplementary Table 16.

Study population

The UK Biobank is extensively described online (www.ukbiobank.ac.uk). Briefly, over 500,000 participants aged 37–73 years were recruited between 2006 and 2010 from 22 assessment centers across England, Scotland and Wales. Each participant completed a touch-screen questionnaire, underwent a nurse-led interview, had physical measurements taken and provided biological samples[27]. This study was conducted under UK Biobank application number 134551. UK Biobank had ethical approval from the North West Multicenter Research Ethics Committee (ref: 11/NW/0382). All participants gave written informed consent.

Accelerometer-derived PA

In the PA sub-study conducted between February 2013 and December 2015, 103,695 participants provided the weekly wrist-worn triaxial accelerometer (Axivity AX3) data[28,29]. We excluded individuals who withdrew consent and had unreliable data size (field 90002), insufficient wear time (field 90015), poor calibration (field 90016, 90017) and implausible acceleration values (field 90012). We further excluded individuals with missing covariates or who developed CHD during the wearing period. Finally, 85,412 eligible participants were retained, among which 80,243 without CHD were included in the CHD incidence study to analyze the CHD incidence risk, and 5,169 with established CHD were included in the CHD mortality study for the mortality risk of CHD patients; see details in Supplementary Figs. 10 and 11.

As described previously, PA intensity was quantified as the average vector magnitude over 5-s epochs recorded by a wrist-worn triaxial accelerometer, expressed in milligravity (mg). Non-wear-time epochs were identified as consecutive stationary episodes ≥60 min in which all three axes had standard deviation <13.0 mg, which were imputed on the basis of the average of similar time-of-day vector magnitude and intensity distribution data points on different days[30]. Furthermore, MVPA duration was defined as the accumulation of 5-s epochs with mean acceleration ≥100 mg (refs. 30–32). To minimize the artifact misclassification of MVPA, we extracted MVPA data in bouts defined as 5-min periods in which more than 80% of epochs met the intensity threshold[30–32]. Additional measures derived from the quantified MVPA duration were as follows: (1) adherence to the standard recommendations of the AHA[2], ESC[3] and WHO[4] (AHA/ESC/WHO standard: ≥150 min week^{-1}); (2) adherence to the extended recommendation of WHO (WHO extended: ≥300 min week^{-1}); (3) number of days the average daily AHA/ESC/WHO standard (≥150/7 min d^{-1}) was met and (4) number of days the average daily WHO extended recommendation (≥300/7 min d^{-1}) was met.

Outcome ascertainment

For the CHD incidence study, the time-to-event outcome was defined as following-up years from the end of wear time to incident CHD in the CHD-free population, ascertained by the first occurrences of any code mapped to three-character International Classification of Diseases 10th Revision codes I20–I25 from primary care, hospital records, death registries and self-report fields. For the CHD mortality study, the outcome was following-up years from the end of wear time to the date of all-cause death in the established CHD population. Censoring was defined as death, withdrawal, loss to follow-up or the end of the follow-up period, whichever occurred first.

Covariates

Demographics including age, gender, center (England, Scotland or Wales), ethnicity (white or other), education (college, university or other), Townsend deprivation index and body mass index (BMI); lifestyles including smoking (never, ever or current), alcohol (never, ever or current), sleep duration (<7 h, 7–8 h or >8 h) and dietary health[33,34] (Supplementary Table 17); medical conditions including diabetes, hypertension, dyslipidemia, cholesterol-lowering medication, blood pressure medication, insulin therapy and Charlson comorbidity index[35]; and activity intensity measured by average acceleration were included as common covariates in the CHD incidence and mortality study. We further adjusted the polygenetic risk score of CHD in the CHD incidence study, and the use of CHD treatment medicines (antiplatelet medication, antianginal medication) in the CHD mortality study.

Cox proportional hazard models

Models with follow-up time as the timescale. For participant i at follow-up time t (years from the end of accelerometer wear to the event of interest or censoring), the hazard function was:

$$h_i(t) = h_0(t)\exp(\beta X_i + \gamma C_i)$$

where X_i represents the PA measures, C_i represents the covariates and $h_0(t)$ is the baseline hazard at time t. Sex-specific associations were estimated from separate Cox models for females ($g_i = 0$) and males ($g_i = 1$):

$$h_i(t \mid g_i) = h_{0,g_i}(t)\exp(\beta_{g_i} X_i + \gamma_{g_i} C_i)$$

where baseline hazard $h_{0,g_i}(t)$ varies by sex, and β_{g_i} denotes the sex-specific effects.

Interactions between sex and PA measures were tested using a likelihood ratio test, comparing the following two models with or without an interaction term.

$$\text{Model}_1 : h_i(t) = h_0(t)\exp(\beta_1 X_i + \beta_2 g_i + \gamma C_i + \theta(X_i \times g_i))$$
$$\text{Model}_2 : h_i(t) = h_0(t)\exp(\beta_1' X_i + \beta_2' g_i + \gamma' C_i)$$

Models with age as the timescale. When age was used as the timescale, the hazard for participant i at age a was:

$$h_i(a) = h_0(a)\exp(\beta X_i + \gamma C_i)$$

where $h_0(a)$ represents the baseline hazard at age a. Participants entered the risk set at their attained age and were followed until the age at the event or censoring. Sex-specific associations and sex–PA interactions were evaluated analogous to the follow-up time models.

Stratified Cox models by sex. In stratified Cox models[36], the baseline hazard $h_{0,g_i}(t)$ was allowed to differ by sex:

$$h_i(t \mid g_i) = h_{0,g_i}(t)\exp(\beta X_i + \gamma C_i)$$

To test sex difference, an interaction term between sex and PA measures was included:

$$h_i(t \mid g_i) = h_{0,g_i}(t)\exp(\beta X_i + \gamma C_i + \theta(X_i \times g_i))$$

For females ($g_i = 0$), the effect of PA measures is simply β. For males ($g_i = 1$), the effect is $\beta + \theta$. The significance of the sex difference was assessed by likelihood ratio test, comparing models with or without an interaction term.

$$\text{Model}_1 : h_i(t \mid g_i) = h_{0,g_i}(t)\exp(\beta X_i + \gamma C_i + \theta(X_i \times g_i))$$
$$\text{Model}_2 : h_i(t \mid g_i) = h_{0,g_i}(t)\exp(\beta' X_i + \gamma' C_i)$$

Statistical analyses

Descriptive characteristics were presented as mean ± s.d. or median with interquartile range for quantitative variables as appropriate; categorized variables were described by frequency (n) and proportion (%). The cumulative risk of incident CHD across guideline-adherent groups was illustrated using a cumulative incidence curve, and the overall survival for patients with CHD across groups was shown using a Kaplan–Meier survival curve. Event proportions over the follow-up period and event rates per 100,000 person-years were calculated to describe the outcome characteristics across groups. Cox proportional hazard models with follow-up time as timescale were used to examine sex-specific associations of all PA measures with both CHD incidence and mortality. HRs and 95% CIs were estimated from models to measure relative instantaneous risk of the outcome, and we reported the HR per 30 min week^{-1} on MVPA duration. Nonlinear relationships and dose–response associations between MVPA duration and CHD outcomes were evaluated through restricted cubic splines by using R package 'rms', with 0 min week^{-1} of MVPA as the reference. Sex differences in associations were assessed using likelihood ratio tests, comparing models with and without interaction terms between sex and PA measures[37]. Given the distinct populations and different hypotheses underlying the two outcomes, we applied false discovery rate (FDR) correction using the Benjamini and Hochberg method[38] for CHD incidence and mortality separately to account for multiple comparisons across five PA measures evaluated in each analysis.

We performed several sensitivity analyses. (1) We used Fine and Gray subdistribution hazard models[39] to account for the competing risk of death in the CHD incidence study; (2) we additionally fitted Cox proportional hazard models with age as the timescale to further control for potential confounding by age; (3) we used stratified Cox proportional hazard models by sex to account for sex-specific baseline hazards[36]; (4) we examined multiple PA measures with varying thresholds; (5) we used four models with progressively increasing covariate adjustment, and further conducted sensitivity analyses incorporating additional comorbidities (chronic kidney disease and arthritis) as well as family history (biological father, mother and siblings) of heart disease, to account for potential confounders; (6) we excluded participants with events occurring within the first year of the follow-up period to mitigate reverse causality; and (7) we imputed the missing data using the multiple imputation method with the R package 'mice'[40].

Statistical analyses were conducted using R v.4.3.3, and a two-sided $P \le 0.05$ was considered statistically significant.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

This research was conducted using the UK Biobank resource (application number 134551). The UK Biobank data are available upon application to the UK Biobank (https://www.ukbiobank.ac.uk/). Source data are provided with this paper.

Code availability

We used publicly available software for the analyses, and software used is described in Methods and Reporting Summary.

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Author contributions

J.C., Y.Z. and Yan Wang conceived and designed the study. J.C., Z.Z. and L.Z. contributed to data collection and processing. J.C., Yuliang Wang and Z.Z. performed statistical analyses using R. J.C. and X.C. contributed to data visualization. J.C. and L.J. contributed to data interpretation. J.C. and Yuliang Wang drafted the paper. Yuliang Wang, Y.Z. and Yan Wang revised the final paper. All authors approved the final version of the paper.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s44161-025-00732-z.

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Software and code

Policy information about availability of computer code

Data collection	The data this study were derived from UK Biobank, including questionnaires, clinical laboratories, genetic risk score, accelerometer-derived physical activity data using wrist-worn triaxial accelerometer (Axivity AX3), health and death outcome link to Primary Care, Hospital inpatient, and Death Register.
Data analysis	All the analyses were conducted using R (version 4.3.3). R packages: 'survival' (3.8.3), 'rms' (6.8.0), 'mice' (3.17.0). The codes for data analysis are available upon request from corresponding authors.

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This research was conducted using the UK Biobank resource (application number #134551). The UK Biobank data are available upon application to the UK Biobank (https://www.ukbiobank.ac.uk/). Source data are provided with this paper.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	The sex of participants was derived from UK Biobank data-field 31. Our study focused on the sex differences in association of wearable accelerometer-derived physical activity with coronary heart disease (CHD) incidence risk in CHD-free population and all-cause mortality risk in established CHD population.
Reporting on race, ethnicity, or other socially relevant groupings	The ethnicity of participants was derived from UK Biobank data-field 21000, which was incorporated as a covariate in the multi-variable Cox models. Participants self-identified their ethnic background during baseline period (2006-2010), with further details within the UK Biobank.
Population characteristics	80,243 participants free of CHD [age 61.54 ± 7.84 years; female: 57.3%] were included in the CHD incidence study, and 5,169 CHD-established participants (age: 66.93 ± 5.90 years; 30.0% female) were included in the CHD mortality study. Overall, 48.46% of CHD-free participants met the minimum moderate-to-vigorous physical activity (MVPA) time (150 min/week) recommended by AHA/ESC/WHO, whereas only 30.51% of CHD patients achieved this target. Furthermore, females lag behind males in both MVPA duration and intensity, and had a lower adherence to guidelines
Recruitment	The UK Biobank is a large prospective study with over 500,000 participants aged 37–73 years were recruited between 2006 and 2010 from 22 assessment centers across England, Scotland, and Wales. Each participant completed a touch-screen questionnaire, underwent a nurse-led interview, had physical measurements taken, and provided biological samples. In the physical activity sub-study conducted between February 2013 and December 2015, 103,695 participants provided the weekly wrist-worn triaxial accelerometer (Axivity AX3) data.
Ethics oversight	UK Biobank had ethical approval from the North West Multicenter Research Ethics Committee (Ref: 11/NW/0382). All participants gave written informed consent. This study was conducted under the UK Biobank application number 134551.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The sample size of this study was determined by the maximum number of eligible participants in the UK Biobank accelerometer-based physical activity sub-study. Among all 103,695 participants provided the weekly wrist-worn triaxial accelerometer (Axivity AX3) data, 83 withdraw consent, 4690 with unreliable data size, 4463 with insufficient wear time, 157 with poor calibration, 206 with implausible acceleration values, 8675 with missing covariates, and 8 developed CHD during the wearing period were excluded. Finally, 85,412 eligible participants were retained, among which, 80,243 without CHD were included in the CHD incidence study, and 5,169 with established CHD were included in the CHD mortality study.
Data exclusions	The exclusion criteria were shown in Figure S10, we excluded individuals who withdrawn consent, with unreliable data size, insufficient wear time, poor calibration, and implausible acceleration values. We further excluded individuals with missing covariates or who developed CHD during the wearing period.
Replication	This is a population-based cohort study using accelerometer-measured physical activity data. Due to the unavailability of suitable external data sources, we have not yet replicated our findings in an independent cohort. However, we conducted a series of sensitivity analyses to confirm the robustness of our results. Specifically, (a) we employed Fine and Gray subdistribution hazard models to account for the competing risk of death in CHD incidence study; (b) we additionally fitted Cox proportional hazards models with age as the time scale to further control for potential confounding by age; (c) we employed stratified Cox proportional hazards models by sex to account for sex-specific baseline

	hazards; (d) we examined multiple PA measures with varying thresholds; (e) we employed four models with progressively increasing covariate adjustment, and further conducted sensitivity analyses incorporating additional comorbidities (chronic kidney disease and arthritis) as well as family history (biological father, mother, and siblings) of heart disease, to account for potential confounders; (f) we excluded participants with events occurring within the first year of follow-up period to mitigate reverse causality; (g) we imputed the missing data using multiple imputation method with the R package mice.
Randomization	This is a population-based observational study, and randomization is not applicable. We employed multiple models with progressively increasing covariate adjustment to account for a wide range of potential covariates.
Blinding	This is a population-based observational study, and blinding is not applicable.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a