Joint non-linear dose–response associations of device-measured physical activity and cardiorespiratory fitness with cardiovascular disease: a cohort and Mendelian randomisation study

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ABSTRACT

Objectives To characterise the non-linear joint dose–response relationship of accelerometer-measured moderate-to-vigorous physical activity (MVPA) and cardiorespiratory fitness (CRF, estimated as maximal oxygen uptake (VO_2max)) with incident cardiovascular disease (CVD), and to assess causal consistency using Mendelian randomisation (MR).

Methods We conducted a cohort study in the UK Biobank using accelerometer data linked to hospital and death registries. A Cox generalised additive model characterised the joint MVPA–CRF association with incident CVD (atrial fibrillation, myocardial infarction, heart failure (HF) and stroke), adjusting for confounders. We derived a fitness-stratified matrix quantifying the weekly MVPA minutes associated with prespecified relative hazard reductions. Complementary two-sample MR analyses leveraged genome-wide association study summary statistics for device-measured physical activity (PA) traits and CRF to assess potential causal effects on cardiovascular outcomes.

Results Among 17 088 participants, 1233 incident CVD events occurred over a median follow-up of 7.85 years (IQR, 7.39–8.27). A significant non-linear interaction between MVPA and CRF was observed (p<0.001). Meeting the 150 min/week guideline yielded a modest ~8%–9% risk reduction across fitness levels, whereas achieving a >30% risk reduction required threefold to fourfold higher volumes (~560–610 min/week). Residual analysis indicated that fitness beyond what MVPA and covariates predicted retained a modest protective association with CVD risk (HR, 0.98 per 1 mL/kg/min; 95% CI 0.97 to 0.99; p<0.001). In MR analyses, genetically proxied higher CRF was associated with lower HF risk (OR, 0.79; 95% CI 0.63 to 0.99), whereas genetic evidence for PA traits was weaker and less consistent.

Conclusion Current MVPA guidelines provide a universal but modest safety margin, whereas optimal cardiovascular protection may require substantially higher activity volumes. The fitness-stratified prescription matrix offers quantitative behavioural targets, and genetic findings reinforce the independent importance of CRF in cardiovascular risk reduction.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Moderate-to-vigorous physical activity (MVPA) and cardiorespiratory fitness (CRF) are established, independent predictors of cardiovascular health.

⇒ Current guidelines universally recommend ≥150 min/week of MVPA, yet whether this generic threshold confers equivalent cardiovascular protection across different fitness levels remains unclear.

WHAT THIS STUDY ADDS

⇒ In a large accelerometer-based cohort with estimated CRF, meeting the current 150 min/week guideline was associated with a consistent but modest reduction in composite cardiovascular disease risk of approximately 8%–9% across low- to high-fitness strata.

⇒ Achieving substantial cardiovascular protection (>30% risk reduction) required MVPA volumes 3–4 times higher than current minimum recommendations (~560–610 min/week), with low-fitness individuals needing slightly more MVPA than high-fitness peers to attain comparable relative benefits.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The fitness-stratified prescription matrix complements universal guideline advice by enabling clinicians to set personalised, quantitative MVPA targets calibrated to an individual's fitness level.

⇒ Future guidelines and implementation strategies may need to differentiate between the minimal MVPA volume required for a basic safety margin and the substantially higher volumes necessary for optimal cardiovascular risk reduction.

INTRODUCTION

Regular physical activity (PA) is a cornerstone of cardiovascular disease (CVD) prevention and is associated with substantial reductions in CVD incidence and mortality.[1–4] Current public health guidelines therefore recommend that adults accumulate at least 150 min per week of moderate-to-vigorous physical activity (MVPA), a threshold associated with demonstrable cardiovascular benefits.[5 6] However, this generic threshold overlooks substantial interindividual heterogeneity. The same

MVPA dose does not necessarily confer equivalent cardiovascular protection across individuals.[7]

Variation in cardiorespiratory fitness (CRF), commonly indexed by maximal oxygen uptake (VO_2max), is a principal contributor to this heterogeneity.[8] CRF is a powerful predictor of cardiovascular health, and low CRF is strongly associated with an increased risk of CVD events and premature mortality in both general and clinical populations.[9 10] On the basis of this evidence, professional societies have advocated that CRF be regarded as a clinical vital sign and assessed routinely in clinical practice.[8] Importantly, CRF is not a simple surrogate for MVPA.[8 11] Rather, it is a complex physiological trait reflecting the combined influences of habitual PA, underlying genetic architecture and individual training responsiveness.[12 13]

An increasing number of studies have used wrist-worn accelerometers and other device-based measures to quantify PA objectively, thereby addressing the recognised limitations of self-reported questionnaires.[4 14 15] Nevertheless, several important analytical gaps persist. Most prior work has modelled MVPA or CRF as single exposures or has focused on their independent associations,[16 17] and few studies have quantified their joint effects on CVD risk within the same cohort using a two-dimensional non-linear dose–response framework. Furthermore, device-based studies have rarely delivered key translational outputs for clinical decision-making, such as iso-risk contour plots for the joint MVPA–CRF association or prescriptive matrices translating continuous risk surfaces into clinically actionable tables.[18] Although the predictive performance of device-measured PA has been explored for CVD mortality[19] or as an adjunct to established clinical risk scores,[20] systematic evaluation of competing risks, model calibration and discrimination within a joint dose–response framework remains limited, constraining the clinical transportability of existing findings.

From a causal inference perspective, two-sample Mendelian randomisation (MR) studies have begun to explore the PA–CVD relationship, but have often been constrained by weak instruments for device-measured PA or reliance on self-reported activity phenotypes.[21 22] Evidence regarding the causal effects of CRF remains sparse and pertains primarily to metabolic outcomes such as type 2 diabetes rather than CVD endpoints.[23 24] These gaps in quantitative observational evidence, clinical translation and causal inference collectively leave a key clinical question unanswered: how to provide an individualised, quantitative MVPA prescription that effectively reduces CVD risk while accounting for an individual's fitness level.

Therefore, we aimed to characterise the joint non-linear association of accelerometer-derived MVPA and CRF (VO_2max) with incident composite CVD in the UK Biobank (UKB) accelerometer cohort using a Cox generalised additive model (CoxGAM). We then sought to translate this two-dimensional risk surface into a fitness-stratified MVPA-risk reduction matrix to inform more personalised MVPA prescriptions. Finally, we used two-sample MR to triangulate observational findings and assess whether genetically proxied PA and CRF show associations consistent with causal effects, thereby mitigating potential residual confounding common in observational designs. The overarching aim of this work was to build on the established recommendation of 150 min per week by providing fitness-stratified, quantitatively refined MVPA dose targets for clinical and public health practice.

METHODS

This study combined a prospective cohort analysis of the UKB accelerometer subcohort with a two-sample MR design. Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and STROBE-MR guidelines.[25 26] Cohort analysis data were obtained from the UKB, a large prospective cohort that recruited approximately 500 000 community-dwelling adults aged 40–69 years across the UK between 2006 and 2010.[27] Baseline and follow-up phenotypic information was linked longitudinally to national hospital admission and death registries, thereby providing a resource for aetiological research on chronic diseases.

Prospective cohort study

The primary exposure was MVPA (minutes per week) derived from the UKB accelerometer substudy conducted between 2013 and 2015.[28] In this substudy, participants wore a wrist-mounted Axivity AX3 accelerometer at 100 Hz for seven consecutive days. Approximately 103 700 participants contributed data. Raw triaxial acceleration signals were processed using the official UKB pipeline.[28] Movement behaviours were classified into sleep, sedentary behaviour, light physical activity and MVPA using a balanced random forest (100 trees; 50 rotation-invariant features; 30 s epochs) trained on free-living, camera-annotated data from 152 adults (CAPTURE-24) and smoothed with a hidden Markov model. In leave-one-participant-out validation, mean accuracy was 88% (95% CI 87% to 89%) and Cohen's kappa was 0.80 (95% CI 0.79 to 0.82).[29] Using these classified epochs, we derived the daily proportion of time spent in MVPA and calculated the daily wear-time proportion from the accelerometer wear-duration information. Following the UKB-derived variable definitions, we multiplied the daily MVPA proportion by the corresponding wear-time proportion and converted the product to minutes. We then summed these values across the 7 days to derive total weekly MVPA in minutes.[4] We defined an effective accelerometer week as a 7-day period in which each day had a non-zero wear time proportion and non-missing MVPA minutes. If either condition was not met on any day, we considered the week invalid and excluded it. In the main analysis, MVPA was modelled as a continuous variable. For descriptive and competing risk analyses, MVPA was grouped into two categories based on guideline thresholds, namely <150 and ≥ 150 min per week. The second primary exposure was CRF, assessed at UKB baseline using an individually risk-stratified submaximal cycle ergometer test to estimate VO_2max. We applied basic quality control by restricting VO_2max to a prespecified plausible range of 15–55 mL/kg/min. The validity of this VO_2max estimation framework was evaluated in approximately 80 000 UKB participants and has been reported previously.[30]

Baseline covariates included age, sex, ethnicity, socioeconomic status (Townsend deprivation index), smoking status, alcohol intake (grams per week), self-rated health and a diet score ranging from 0 to 6, which was subsequently categorised into poor (0–2), intermediate (3–4) and good (5–6) diet quality for modelling. Anthropometric and clinical measures, including body mass index (BMI), resting heart rate and systolic blood pressure, were used primarily in robustness analyses.

The primary outcome was a composite CVD endpoint comprising four major events: atrial fibrillation or flutter (AF), myocardial infarction (MI), heart failure (HF) or stroke, defined as the first occurrence of any component. Incident events were ascertained through linkage to national Hospital Episode Statistics, covering inpatient diagnoses and relevant procedures, and national death registries. We excluded prevalent disease at or before the accelerometer wear period on the basis of hospital records and self-reports. Follow-up for the survival analysis

commenced individually on the end date of each participant's valid accelerometer wear period, which occurred between 2013 and 2015. Each participant was followed from this time origin until the earliest of: a first incident CVD event, death from any cause, or the administrative censoring date of 31 October 2022, derived from the latest available hospital and death registry linkage. This date was applied uniformly across all participants on the basis of the data release used for this analysis. We note that UKB provides region-specific data availability dates for England, Scotland and Wales, but the observed follow-up end dates in our dataset aligned with a common 31 October 2022 cut-off. In the primary Cox-GAM, non-CVD deaths were treated as censoring events, yielding cause-specific HRs that estimate the direct aetiological effect of the exposures on CVD among individuals still at risk.[31 32] In the complementary Fine-Gray analysis (online supplemental eTable 5), non-CVD deaths were modelled as competing events, yielding subdistribution HRs (SHRs) that capture the total effect on CVD cumulative incidence, including indirect pathways through non-CVD death. Detailed descriptions of variable derivations are provided in online supplemental eTables 1–3.

We used a Cox-GAM as the primary analytical framework, implemented via the mgcv package (V.1.9) in R with the cox.ph() family and restricted maximum likelihood (REML) estimation.[33 34] The joint non-linear effect of MVPA and CRF was modelled using a tensor product smooth (te()) constructed from thin plate regression spline marginal bases, each with a basis dimension of 4.[35] As with the univariate splines, knot placement was handled internally by mgcv and the effective complexity of the interaction surface was determined by REML penalisation. Continuous confounders were modelled with penalised splines implemented in mgcv. Age was specified as a thin plate regression spline (bs="tp") with a maximum basis dimension of k=5, and the Townsend deprivation index was specified as a thin plate regression spline with shrinkage (bs="ts", k=5), which allows the penalty to shrink the smooth toward zero if unsupported by data. For these mgcv splines, knot positions are not user-specified. Instead, the basis dimension k sets an upper bound on flexibility, and REML estimation determines the effective df (edf), yielding a fully data-driven smooth. In secondary models, BMI and systolic blood pressure were similarly specified as thin plate regression splines with shrinkage (bs="ts", k=4 each).[36] Categorical covariates (sex, ethnicity, smoking status, alcohol intake category, self-rated health and diet quality) entered the model as unpenalised parametric terms.[37] All models were adjusted for a minimal sufficient set of covariates derived from a prespecified directed acyclic graph (DAG), including age, sex, ethnicity, smoking, alcohol intake, self-rated health, diet score and the Townsend deprivation index, with the latter modelled using regression splines.[38] The proportional hazards assumption was evaluated using Schoenfeld residuals.[39] We first fitted a preliminary Cox model in which MVPA, CRF, age and the Townsend index were specified using natural cubic splines (ns()). MVPA and CRF were each modelled with df=4 using 3 internal knots placed at sample quartiles, and age and the Townsend index were each modelled with df=5 using 4 internal knots placed at sample quintiles. Complete knot positions are reported in online supplemental eTable 16. Schoenfeld residuals were then computed from this model to test the proportional hazards assumption. Median follow-up time and IQR were estimated using the reverse Kaplan-Meier method.[40]

A global χ^2 test was then used to assess the statistical significance of the MVPA×CRF interaction. To complement this multiplicative-scale test, we conducted a supplementary assessment of interaction on the additive scale following published recommendations.[41] We dichotomised MVPA at the WHO guideline threshold of 150 min per week and CRF (at or above vs below the sex-specific median VO_2max: 25.8 mL/kg/min for females, 32.4 mL/kg/min for males). We treated the combination of high MVPA and high CRF as the reference category to estimate the joint effects of the risk factors, that is, low MVPA and low CRF. A standard Cox proportional hazards model with a four-level joint exposure variable was fitted, adjusting for the same covariate set with natural cubic splines (ns() from the splines package) for age (df=5; 4 internal knots placed at the sample quintiles: 49, 56, 61 and 65 years; boundary knots at 40 and 75 years) and the Townsend deprivation index (df=5; 4 internal knots at the sample quintiles: −3.98, −2.87, −1.48 and 0.74; boundary knots at −6.26 and 8.74). We calculated the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP) and the synergy index (S) with bootstrap percentile 95% CIs based on 2000 resamples. The multiplicative interaction was quantified as the ratio of HRs ($HR_{11}/[HR_{10}\times HR_{01}]$).

Non-CVD deaths were treated as competing events and were analysed using Fine-Gray subdistribution hazard models.[42] Cumulative incidence functions were plotted across exposure groups. To aid interpretation of the exposure-response surface, we assessed the monotonicity of risk across CRF slices using a two-step procedure. First, sex-specific HR curves across the VO_2max range were estimated from the fitted Cox-GAM at a fixed MVPA of 150 min/week, with 95% CIs derived via the delta method using the linear predictor matrix and model covariance matrix.[43] Second, we evaluated monotonicity by computing Spearman correlation coefficients between the VO_2max grid and the predicted HRs across 400 parametric simulations by drawing coefficient vectors from the multivariate normal distribution of the fitted model parameters. Monotonicity was tested using a one-sided p value, defined as the proportion of simulations in which $\rho \geq 0$ (online supplemental eTable 7).[44] We then generated an out-of-fold, prediction-based residual CRF variable to evaluate whether residual variation in CRF at a given level of MVPA was associated with CVD risk. This variable was defined as the difference between observed VO_2max and its predicted value from MVPA and covariates.

To visualise the overall joint risk landscape, we modelled the HRs relative to a global reference anchor defined as 0 min per week of MVPA at the lowest fitness level, corresponding to approximately the 10th percentile of VO_2max. However, to derive the clinically actionable prescription matrix, we calculated the weekly MVPA minutes required to achieve relative risk reductions of 10%–30% using a fitness-specific reference anchor (ie, relative to 0 min per week at the same VO_2max level). As an exploratory prediction exercise, model discrimination and calibration were assessed using random survival forests (RSF), which provided 5-year C-index estimates and quantile-based calibration, with formal calibration testing via weighted linear regression of observed on predicted risk (testing intercept=0 and slope=1).[45 46] Within the Cox-GAM framework, we used factor-by-smooths to evaluate potential effect modification by sex, age (<60 vs ≥60 years) and BMI categories. Models were compared using the Akaike information criterion (AIC).[47] We note that model structure, including exposures, confounders and the tensor product interaction, was prespecified on the basis of a DAG, not selected by information criteria. AIC was used solely to evaluate whether adding stratum-specific deviation smooths (effect modification) improved relative fit. AIC was preferred over the Bayesian information criterion (BIC) because the

stronger sample-size penalty of BIC (log(n)≈9.75 vs 2 for AIC at N=17 088) can disproportionately penalise flexible smooth terms in a GAM framework, potentially favouring underfitting of genuinely non-linear effects.

In addition, we plotted sex-specific VO_2max-HR curves at an MVPA level of 150 min per week to visualise the associations. Multiple robustness analyses were performed, including exclusion of participants with follow-up of 2 years or less, winsorisation of exposure variables, sequential adjustment for BMI, resting heart rate and systolic blood pressure, and evaluation of alternative parametric model specifications.[48] Further analytical details and supplementary results are presented in online supplemental eTable 9.

Mendelian randomisation

We conducted two-sample MR analyses to investigate the potential causal effects of PA and CRF on major CVD components.[49] The primary PA exposure was accelerometer-derived average acceleration. Self-reported MVPA, derived from the same genome-wide association study (GWAS) of habitual PA, was used as an additional exposure in sensitivity analyses. Outcomes included coronary artery disease (CAD) or ischaemic heart disease (IHD), AF, HF, any stroke and transient ischaemic attack (TIA). Large GWAS consortia datasets were used for these endpoints.[50] When no suitable instrumental variables or harmonised single-nucleotide polymorphisms (SNPs) were available under stringent thresholds, the corresponding exposure-outcome effect was considered not estimable, consistent with standard MR practice.[51] The GWAS datasets used in this study, including identifiers, sources and selection rationale, are listed in online supplemental eTable 10.

Instrumental variables were selected using a genome-wide significance threshold of $p<5\times10^{-8}$ and were subjected to stringent linkage disequilibrium clumping with r^2 set to 0.001 and a window of 10 000 kb.[51] We then performed allele harmonisation and addressed palindromic variants. We applied Steiger directionality tests based on sample size information and preferentially retained SNP sets with at least three variants.[52] A DAG illustrating the MR framework and its three core assumptions namely relevance, independence and exclusion restriction, is presented in online supplemental eFigure 5. The main univariable MR estimator was the multiplicative random-effects inverse variance-weighted (IVW) method (online supplemental eTable 11).[53] We complemented this with several robust methods, including the weighted median, MR-Egger regression, simple mode and weighted mode estimators, as well as MR-RAPS (MR Robust Adjusted Profile Score).[53 54] In settings with a sufficient number of suitable instruments, we additionally performed multivariable MR (MVMR) to jointly estimate the independent causal effects of accelerometer-assessed PA and CRF on cardiovascular outcomes.[55]

Instrument strength was evaluated using F statistics, summarised as the mean, median, minimum and the proportion of variants with F values less than 10.[56] Cochran's Q statistics were used to assess heterogeneity in SNP-specific estimates (online supplemental eTable 12).[53] The MR-Egger intercept was examined to detect directional horizontal pleiotropy (online supplemental eTable 13).[57] We additionally assessed the distributional and structural assumptions underlying the IVW and MR-Egger regression models.[57] Linearity was evaluated by adding a quadratic term for the SNP-exposure association to the IVW regression and testing its significance. Residual normality was assessed using the Shapiro-Wilk test applied to the residuals of both IVW and MR-Egger regressions.[58] Influential variants were identified using Cook's distance, with a threshold of 4/n, where n is the number of SNPs.[59] Leave-one-out analyses were conducted and displayed graphically to evaluate the influence of individual variants.[53] A comprehensive summary of assumption verification across all 15 exposure-outcome pairs, including F statistics, Steiger directionality, MR-Egger intercept tests and Cochran's Q heterogeneity statistics, is provided in online supplemental eTable 17.

Patient and public involvement

Patients or members of the public were not involved in the design, conduct, reporting or dissemination plans of this research. This study is a secondary analysis of existing data from the UKB cohort.

Equity, diversity and inclusion

This study included both female and male participants across a wide age range, from middle to older adulthood. The authorship team comprises early-, mid- and senior-career researchers from a range of disciplines and institutions.

RESULTS

Prospective cohort study

The final analysis included 17 088 participants (table 1). The derivation of the analytic sample is detailed in online supplemental eFigure 1. Of the 103 567 UKB participants who provided valid accelerometer data during 2013–2015, we retained those with a complete 7-day wear period (ie, non-zero wear-time proportion and non-missing MVPA on each of the 7 days). We then restricted the sample to participants who had also completed the submaximal cycle ergometer test with an estimated VO_2max within the prespecified plausible range of 15–55 mL/kg/min. After further excluding individuals with prevalent CVD (ascertained through hospital records or self-report) and those with missing data on core covariates, 17 088 participants remained for the primary analysis. Before this exclusion, missingness across individual predictors ranged from 0% to 5.94%, the highest being alcohol intake category, and the proportion of participants with at least one missing predictor was 6.22% in the primary model (1133 of 18 221). Because missingness was marginal and concentrated in a single covariate (alcohol intake) while both exposures and the outcome were fully observed by design, a complete-case analysis was used for the primary models.[60] This sample yielded 1233 incident CVD events over a median follow-up of 7.85 years (IQR, 7.39–8.27), comprising 874 AF, 156 MI, 111 HF and 92 stroke events. The remaining 15 855 participants (92.8%) were censored: 558 (3.3%) died of non-CVD causes before experiencing a CVD event and 15 297 (89.5%) were administratively censored at the end of registry follow-up (31 October 2022) without a CVD event or death. The non-CVD deaths accounted for 31.2% of all failure events (CVD plus non-CVD death combined). These competing events were treated as censoring in the primary Cox-GAM and explicitly modelled in the complementary Fine-Gray analysis (online supplemental eTable 5). The cohort had a mean age of 57.4 years (SD: 8.1), and 56% were female. Participants who accumulated fewer than 150 min per week of MVPA (n=5484) were slightly older (mean 58.1 vs 57.1 years), more often female (67% vs 51%) and had higher BMI (median 26.8 vs 25.5 kg/m²) and lower estimated CRF (26.5 vs 30.4 mL/kg/min) than those meeting the guideline (n=11 604).

The primary Cox-GAM consumed 14.38 edf for the smooth terms, which included the MVPA×CRF tensor product

Table 1 Baseline characteristics overall and by MVPA 150 min threshold

Characteristic	Overall N=17 088*	<150 min/week N=5484*	≥150 min/week N=11 604*
Age, years, mean (SD)†	57.4 (8.1)	58.1 (8.0)	57.1 (8.1)
Sex, n (%)			
Female	9604 (56.2)	3677 (67.0)	5927 (51.1)
Male	7484 (43.8)	1807 (33.0)	5677 (48.9)
Ethnicity, n (%)‡			
Black/Asian	402 (2.4)	160 (2.9)	242 (2.1)
Other	281 (1.6)	86 (1.6)	195 (1.7)
White	16 405 (96.0)	5238 (95.5)	11 167 (96.2)
Townsend index, mean (SD)†	−1.6 (2.7)	−1.8 (2.7)	−1.5 (2.7)
BMI, kg/m^2, median (IQR)†	25.9 (23.5–28.7)	26.8 (24.2–30.3)	25.5 (23.3–28.0)
Body mass index ≥30, n (%)	3026 (17.7)	1463 (26.7)	1563 (13.5)
Self-rated health, n (%)			
Fair/poor	2833 (16.6)	1255 (22.9)	1578 (13.6)
Good	14 255 (83.4)	4229 (77.1)	10 026 (86.4)
Alcohol intake, g/week, median (IQR)§	83 (33–163)	74 (24–144)	93 (41–171)
Smoking status, n (%)			
Current	977 (5.7)	394 (7.2)	583 (5.0)
Former	6170 (36.1)	1998 (36.4)	4172 (36.0)
Never	9941 (58.2)	3092 (56.4)	6849 (59.0)
Educational attainment, n (%)			
A-level/college	2295 (13.4)	755 (13.8)	1540 (13.3)
Degree	7957 (46.6)	2059 (37.5)	5898 (50.8)
GCSE/none	3959 (23.2)	1514 (27.6)	2445 (21.1)
Missing	2877 (16.8)	1156 (21.1)	1721 (14.8)
Employment status, n (%)			
Employed	8994 (52.6)	2741 (50.0)	6253 (53.9)
Other/not working	794 (4.6)	255 (4.6)	539 (4.6)
Retired	5734 (33.6)	1941 (35.4)	3793 (32.7)
Missing	1566 (9.2)	547 (10.0)	1019 (8.8)
Healthy diet quality, n (%)			
Poor	4528 (26.5)	1541 (28.1)	2987 (25.7)
Intermediate	10 004 (58.5)	3197 (58.3)	6807 (58.7)
Good	2556 (15.0)	746 (13.6)	1810 (15.6)
Resting heart rate, bpm, mean (SD)†	67.4 (9.7)	69.3 (9.7)	66.5 (9.6)
Systolic BP, mm Hg, mean (SD)†	136.3 (16.3)	137.1 (16.4)	136.0 (16.3)
Systolic BP>140 mm Hg, n (%)			
No	10 350 (60.6)	3204 (58.4)	7146 (61.6)
Yes	6737 (39.4)	2280 (41.6)	4457 (38.4)
Missing	1 (0.0)	0 (0.0)	1 (0.0)
Diastolic BP, mm Hg, mean (SD)†	80.5 (9.1)	81.0 (9.2)	80.2 (9.1)
Diastolic BP>90 mm Hg, n (%)	2448 (14.3)	867 (15.8)	1581 (13.6)
Antihypertensive medication use, n (%)			
No	12 410 (72.6)	3686 (67.2)	8724 (75.2)
Yes	2633 (15.4)	1046 (19.1)	1587 (13.7)
Missing	2045 (12.0)	752 (13.7)	1293 (11.1)
CRF (VO_2max, mL/kg/min), mean (SD)†	29.1 (6.4)	26.5 (5.7)	30.4 (6.3)
Weekly MVPA, min, median (IQR)†	232 (115–400)	80 (43–115)	328 (230–475)

Denominators for educational attainment, employment status, antihypertensive medication use and systolic BP>140 mm Hg include missing observations; missing counts are shown as separate rows. These variables were included for descriptive purposes and were not used in the primary Cox-generalised additive model.
*Columns show overall cohort and subgroups defined by weekly MVPA: <150 versus ≥150 min.
†Continuous variables were summarised using a prespecified rule: |skewness|>1 indicates skewed distribution and is reported as median (IQR); otherwise mean (SD).
‡Race/ethnicity is self-reported and presented using model categories (black/Asian, other, white).
§Alcohol grams/week were derived from weekly/monthly glasses of each beverage (fields 1568–1608, 5364; 4407–4462), converted to UK units using standard drink factors and multiplied by 8 g/unit.
BMI, body mass index; BP, blood pressure; CRF, cardiorespiratory fitness; MVPA, moderate-to-vigorous physical activity.

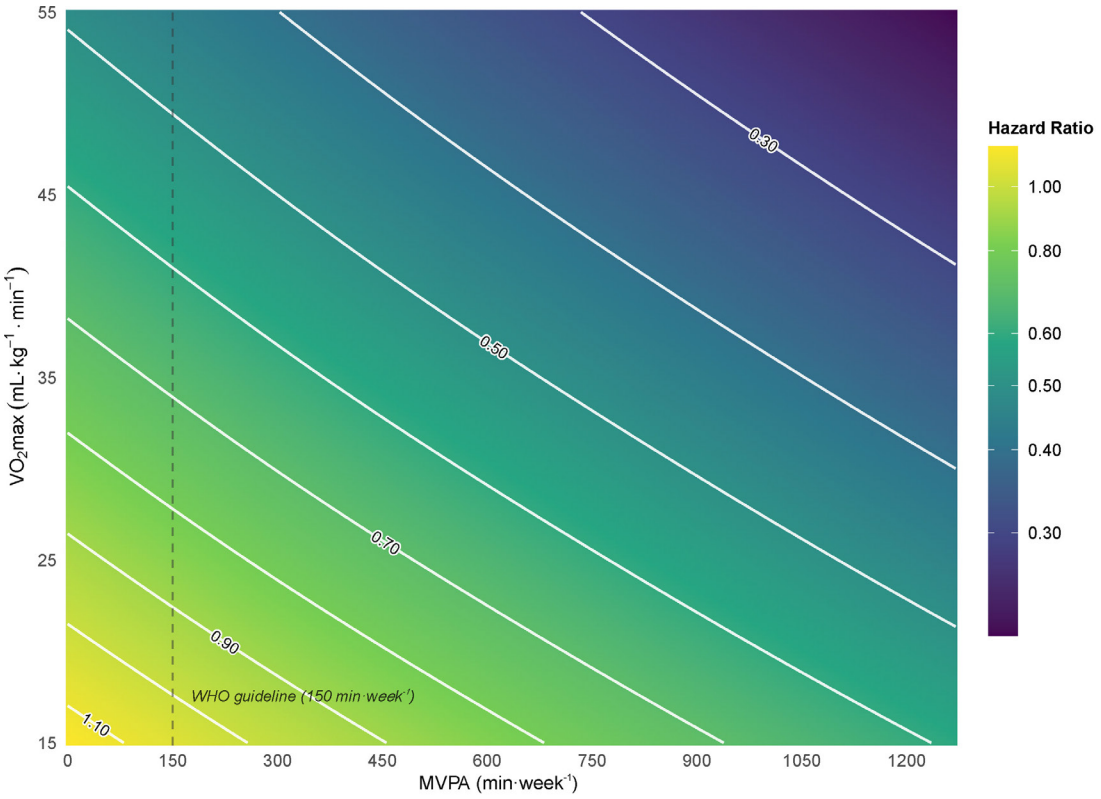

Figure 1 Joint non-linear dose–response association of device-measured physical activity and cardiorespiratory fitness with incident cardiovascular disease. The contour plot illustrates HRs for the composite cardiovascular disease outcome from a Cox generalised additive model with a tensor product smooth interaction between moderate-to-vigorous physical activity (MVPA) and cardiorespiratory fitness (CRF, VO_2max). The model is adjusted for age, sex, ethnicity, socioeconomic status (Townsend deprivation index), smoking status, alcohol intake, self-rated health and diet quality. The risk surface is anchored to a global reference point (HR=1.0) defined as 0 min/week MVPA at low fitness (approximately the 10th percentile of VO_2max, 21.5 mL/kg/min). Colour shading represents HRs on a $\log_{10}$ scale. White contour lines denote iso-risk levels. The dashed vertical line at 150 min/week indicates the current WHO physical activity guideline. A significant non-linear interaction was observed between MVPA and CRF (p<0.001). N=17 088; events=1233. HRs at selected MVPA and CRF grid points are provided in online supplemental eTable 19.

interaction (edf=3.07). Combined with 10 degrees of freedom for parametric covariates, this yielded a total of 24.38 effective model parameters. The resulting ratio of 50.6 events per effective parameter substantially exceeded the conventional minimum of 10 events per parameter recommended for stable Cox regression estimation.[61 62] We adjusted for the minimal sufficient covariate set derived from the DAG (online supplemental eFigure 2). In the Cox-GAM, the smooth MVPA×CRF interaction was highly significant on the multiplicative scale (χ^2=38.43; edf=3.07; p<0.001; online supplemental eTable 6), confirming that the joint dose–response surface was not reducible to the sum of independent marginal effects on the log-hazard scale. In a complementary binary analysis (online supplemental eTable 15), compared with the high MVPA and high CRF reference group, the HRs were 1.32 (95% CI 1.07 to 1.62) for low MVPA alone, 1.25 (95% CI 1.08 to 1.45) for low CRF alone and 1.48 (95% CI 1.26 to 1.73) for the combination of both risk factors. On the additive scale, the RERI was −0.09 (95% CI −0.45 to 0.22; p=0.57), the AP was −0.06 (95% CI −0.30 to 0.15), and the synergy index was 0.84 (95% CI 0.46 to 1.86). The multiplicative interaction ratio of HRs was 0.90 (95% CI 0.70 to 1.15; p=0.39). Thus, while the continuous non-linear interaction was highly significant in the Cox-GAM, the dichotomised analysis did not demonstrate statistically significant interaction on either the additive or multiplicative scale at these cut-points.

The two-dimensional risk surface (figure 1), anchored to a global sedentary low-fitness reference, illustrates that increasing MVPA progressively lowers risk, whereas higher CRF provides an independent safety margin. Consequently, lower-fitness individuals require substantially higher volumes of MVPA to reach the absolute low-risk levels observed in high-fitness groups. Figure 2A shows that meeting the guideline of 150 min per week yielded a consistent but modest relative protective effect across all fitness levels, with an HR of approximately 0.91–0.92 versus the sedentary reference. This corresponds to an overall baseline risk reduction of approximately 8%–9%. The prescription matrix (figure 2B) revealed a steep dose escalation: achieving a 20% risk reduction required approximately 340–370 min per week (more than double the guideline), whereas a 30% reduction required approximately 560–610 min per week. In sex-stratified analyses (figure 3), risk declined monotonically with higher CRF for both sexes (p<0.001 for trend; online supplemental eTable 7).

The proportional hazards assumption was met (p=0.21; online supplemental eTable 4), and the primary model showed acceptable discrimination (C-index=0.704; online supplemental eTable 9). Prespecified tests showed no significant effect modification by age or BMI (p>0.05). Although the sex-specific interaction was nominally significant (p=0.021), it did not improve model fit (ΔAIC=+2.9), suggesting that the joint dose–response shape was broadly generalisable (online supplemental eTable 8). Results remained robust in Fine-Gray competing-risk models (online supplemental eTable 5), in which MVPA≥150 min per week (SHR, 0.86; 95% CI 0.75 to 0.97) remained protective against CVD. Similarly, higher

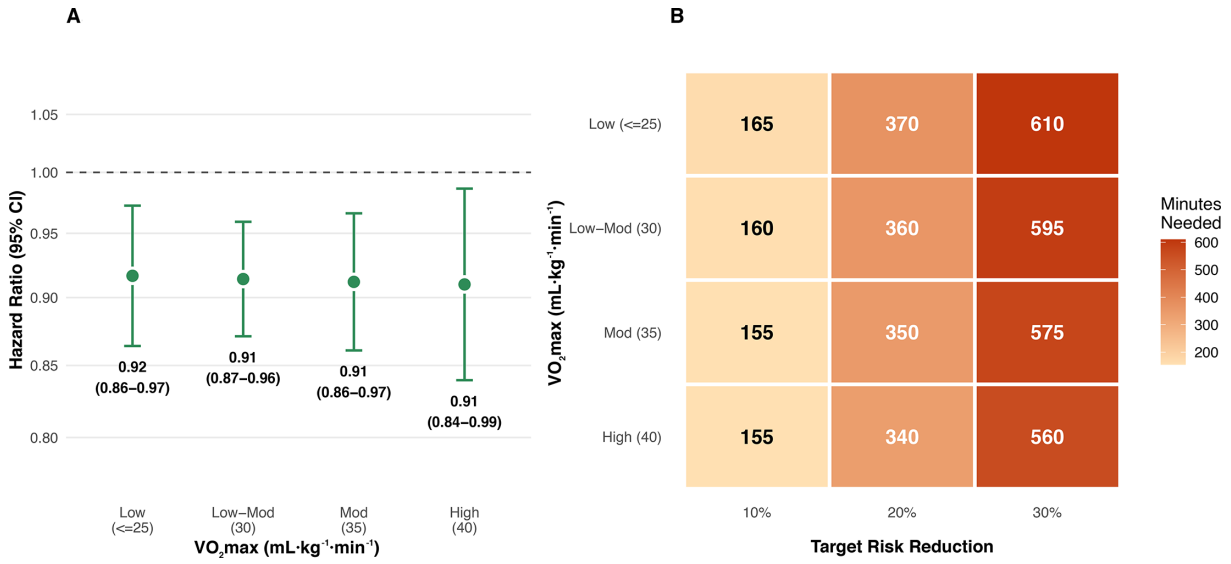

Figure 2 Efficacy of current guidelines and fitness-stratified dose requirements for cardiovascular prevention. (A) HRs (95% CI) for the composite cardiovascular disease outcome associated with meeting the WHO guideline of 150 min/week moderate-to-vigorous physical activity (MVPA), relative to a sedentary baseline (0 min/week) at the same fitness level. Estimates are derived from the primary Cox generalised additive model at four representative cardiorespiratory fitness levels: low (≤25), low-mod (30), mod (35) and high (40 mL/kg/min). The Y-axis is on a log scale. (B) Fitness-stratified, model-based matrix quantifying the weekly MVPA volume (min/week) required to achieve prespecified relative risk reductions (10%, 20% and 30%) compared with a sedentary baseline at the same fitness level. Colour intensity represents the volume of activity required; darker shading indicates a higher volume. Numbers inside cells indicate estimated minutes per week. Both panels are adjusted for age, sex, ethnicity, socioeconomic status (Townsend deprivation index), smoking status, alcohol intake, self-rated health and diet quality. N=17 088; events=1233.

CRF demonstrated a graded protective association (SHR, 0.75; 95% CI 0.65 to 0.86 for 30–40 mL/kg/min, and SHR, 0.70; 95% CI 0.52 to 0.95 for >40 mL/kg/min, compared with the <30 mL/kg/min reference group). The interaction persisted across robustness checks, including exclusion of early events and winsorisation of exposure variables (online supplemental eTable 9). Finally, prediction-based residual analysis using cross-fitted residual VO_2max, defined as the difference between observed and MVPA-predicted values in original units of mL/kg/min, indicated that surplus fitness retained a modest inverse association with CVD risk (HR, 0.98; 95% CI 0.97 to 0.99 per 1 mL/kg/min; p<0.001; online supplemental eFigure 3). This corresponded to an HR of 0.90 (95% CI 0.85 to 0.96) per 5 mL/kg/min, suggesting that a component of CRF-related

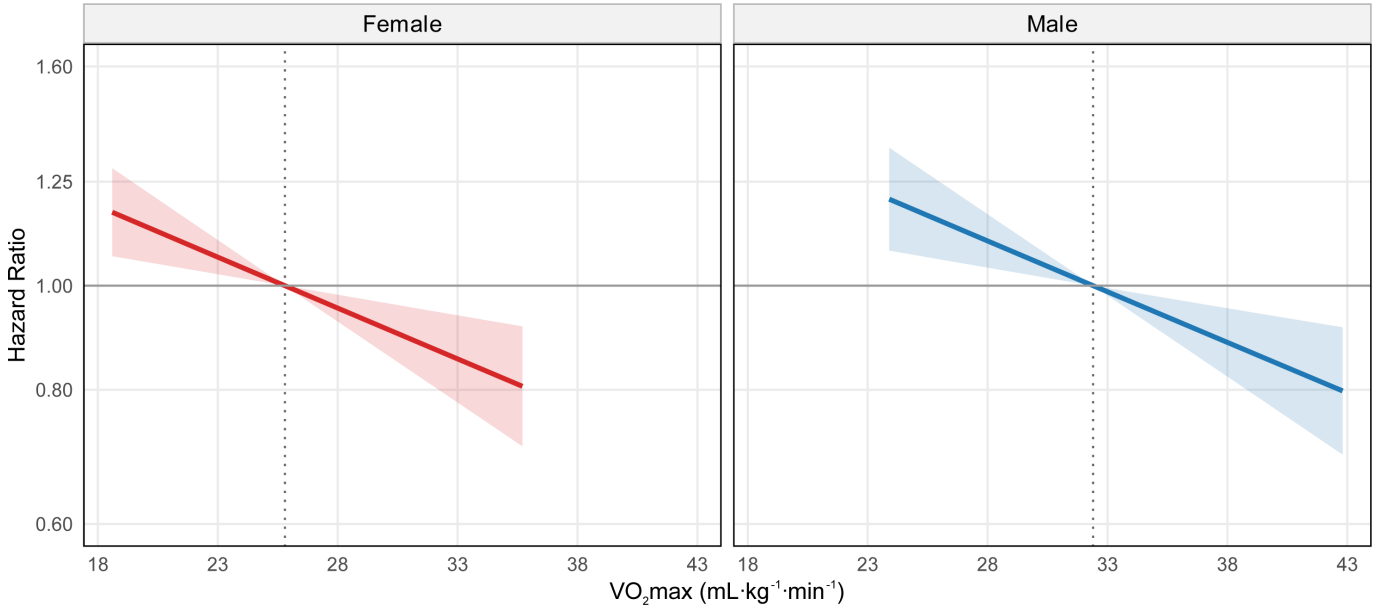

Figure 3 Sex-specific associations between cardiorespiratory fitness and cardiovascular disease risk at the guideline physical activity level. Panels show HRs for cardiorespiratory fitness (VO_2max) at a fixed moderate-to-vigorous physical activity level of 150 min/week, stratified by sex (females, left; males, right). HRs are relative to sex-specific median VO_2max (dotted vertical lines; 25.8 mL/kg/min for females, 32.4 mL/kg/min for males). The Y-axis is on a log scale. Shaded areas represent 95% CIs derived via the delta method. Covariates as in figure 1. P values for a monotone decreasing trend were obtained by parametric simulation of model coefficients (online supplemental eTable 7).

cardioprotection may operate through pathways not fully captured by MVPA volume alone.

Mendelian randomisation

In MVMR analyses adjusting for both PA and CRF, genetically proxied higher CRF was associated with lower HF risk (OR, 0.79; 95% CI 0.63 to 0.99; p=0.043; online supplemental eTable 14). Because two-sample MR estimates are derived from GWAS summary statistics on the log-odds scale, ORs are the natively estimable effect measure. Furthermore, given the low cumulative event incidence in our cohort, these ORs closely approximate risk ratios. This finding provides nominal evidence consistent with an independent protective effect. For AF, the multivariable estimate for genetically proxied CRF was directionally protective but imprecise (OR 0.73; 95% CI 0.49 to 1.09; p=0.12; online supplemental eTable 14), whereas several robust estimators in univariable sensitivity analyses (eg, weighted median OR 0.69; 95% CI 0.53 to 0.89; weighted mode OR 0.67; 95% CI 0.52 to 0.88) yielded statistically significant protective associations (online supplemental eTable 11). Taken together, these AF results are best viewed as suggestive rather than definitive. For CAD, IHD, any stroke and TIA, we found no consistent evidence of independent causal effects across any PA exposures (accelerometer-derived mean acceleration and self-reported MVPA; all MVMR p>0.05; online supplemental eTable 14; univariable sensitivity results in online supplemental eTable 11).

Across all 15 exposure-outcome pairs, median F statistics ranged from 31.0 to 39.3 (all >10), indicating adequate instrument strength (online supplemental eTable 17). Steiger directionality tests confirmed the expected causal direction for 12 of 15 pairs, with the remaining three pairs (involving TIA) lacking the sample size information required for the test. Diagnostic tests indicated substantial heterogeneity between instruments for several exposure-outcome pairs (Cochran's Q test p<0.05 for 8 of 15 pairs). Accordingly, we used multiplicative random-effects models throughout. MR-Egger intercept tests did not indicate strong directional pleiotropy (all p>0.05), consistent with the exclusion restriction assumption. Assessment of the regression assumptions underlying the IVW and MR-Egger models showed that linearity was supported across all 15 exposure-outcome pairs (all quadratic term p≥0.05). Residual normality (Shapiro-Wilk test) was met for 12 of 15 pairs in IVW and 13 of 15 in MR-Egger regressions. The three departures involved CAD/IHD and TIA pairs for which the main MR estimates were not statistically significant. Cook's distance analysis identified potentially influential variants in 7 of 15 pairs, but leave-one-out analyses (described above) did not reveal any single variant that substantially altered the primary conclusions (online supplemental eTable 18).

DISCUSSION

Principal findings

This study demonstrated a significant joint non-linear dose–response relationship between objectively measured MVPA and CRF and CVD risk. Using the UKB accelerometer cohort and a Cox-GAM two-dimensional spline model, we confirmed a highly significant smooth interaction between MVPA and CRF on the multiplicative scale via the tensor product smooth term. A complementary binary analysis following published recommendations for presenting interaction revealed no statistically significant additive interaction (RERI −0.09; 95% CI −0.45 to 0.22).[41] Beyond interaction testing, the primary model demonstrated acceptable discrimination (C-index=0.704), and exploratory RSF calibration showed adequate risk ranking, although with evidence of slope shrinkage (online supplemental eFigure 4), reflecting the robust prognostic value of integrating behavioural and physiological metrics. Importantly, this joint surface formed the basis for a quantifiable minutes–risk reduction matrix that prescribes, for each CRF level, the weekly MVPA dose required to achieve 10%–30% reductions in an individual's CVD risk relative to being sedentary at the same fitness level.

Interpretation of joint effects and mechanisms

The primary methodological contribution of this study lies in the simultaneous use of objectively measured MVPA and estimated CRF within the same population, which we modelled using a Cox-GAM two-dimensional spline to capture their structural interplay. This approach extends previous research that largely relied on single exposures or one-dimensional curves.[4 14 15 63 64] Regarding the conditional effects, we observed a remarkably consistent relative benefit of MVPA across the fitness spectrum.[65] This consistency is corroborated by the supplementary binary interaction analysis, where the absolute risk increases associated with insufficient MVPA and low CRF were approximately additive. These results indicate that, at guideline-based dichotomisation thresholds, neither strong synergism nor redundancy was evident on the absolute risk scale.[41] Consequently, the significant shape-level interaction detected by the continuous Cox-GAM likely captures subtler gradient changes, such as the steeper MVPA–risk slope at lower CRF levels, that are averaged away by dichotomisation.

Notably, large dose–response meta-analyses and cohort studies, which predominantly relied on self-reported PA without adjustment for CRF, have typically reported 20%–30% lower CVD risk at approximately 150 min per week.[1 66] In contrast, the more modest 8%–9% reduction observed at the guideline dose in the present study likely reflects the distinct analytical framework employed here. Unlike prior studies that estimated the total effect of MVPA, which implicitly captures benefits mediated through improved fitness, the joint model explicitly adjusts for CRF.[67] Consequently, these estimates represent the conditional effect of MVPA at a given fitness level, isolating the direct benefit of the behaviour itself independent of the physiological fitness reserve.[68] Despite this consistency in relative effects, our matrix (figure 2B) reveals a subtle absolute gradient, such that individuals with the lowest fitness require approximately 30–50 additional minutes per week compared with those with high fitness to achieve equivalent relative reductions, for example, a 20% reduction requires approximately 370 vs 340 min. This finding highlights the steeper challenge faced by deconditioned populations.[69]

Crucially, the prediction-based residual analysis refined the interpretation of these joint effects. Using cross-fitted residual VO_2max defined as observed minus MVPA-predicted values, we found that each 1 mL/kg/min increase in surplus fitness was associated with approximately 2% lower CVD hazard (HR, 0.98; 95% CI 0.97 to 0.99), corresponding to HR 0.90 (95% CI 0.85 to 0.96) per 5 mL/kg/min. This indicates that a modest component of CRF-related cardioprotection persists beyond what is explained by MVPA and the measured covariates. This residual association is consistent with contributions from genetic endowment, early-life cardiopulmonary development and training-induced physiological adaptations such as cardiac remodelling and improved endothelial function that are not fully captured by weekly MVPA volume.[12] Nevertheless, the effect size is small relative to the overall joint MVPA–CRF surface, suggesting

that the bulk of prognostic information carried by CRF for CVD is mediated through habitual activity, with surplus fitness providing a modest additional margin of protection.[70] Clinically, these findings support using CRF both to calibrate the amount of MVPA required to move a patient toward a lower-risk profile and as an independent marker that captures physiological cardioprotection not fully reflected by activity behaviour alone.[8]

Causal inferences from genetic evidence

The two-sample MR analyses provided distinct but generally supportive evidence for the prospective cohort findings, consistent with using MR as a natural experiment to strengthen causal inference in epidemiology.[71] Genetically predicted higher CRF was consistently associated with a reduced risk of HF at a nominal level of significance and remained significant in MVMR adjusting for PA, and showed a protective trend for AF. Although the primary IVW analysis for AF was not statistically significant, robust methods such as the weighted median and weighted mode provided consistent directional results, in line with recommended MR sensitivity strategies.[72 73] In contrast, genetic proxies for PA did not show stable and statistically significant associations with most CVD endpoints in either univariable or multivariable analyses. IVW results for CRF regarding CAD or any stroke were also largely not statistically significant, suggesting a pattern of CRF effect specificity similar to previous MR work in which CRF showed causal effects for selected metabolic or neurological outcomes rather than a uniform effect across all diseases examined.[74]

This pattern aligns with the broader MR literature, in which CRF, as an integrated physiological state, has stronger and more stable genetic instruments, whereas PA is a complex behavioural construct with weaker genetic instruments and greater heterogeneity, rendering overall estimates more susceptible to regression dilution toward the null.[12] Importantly, the Egger intercept test did not suggest significant directional pleiotropy, enhancing the credibility of the CRF-related causal estimates, although limitations regarding instrument strength and population consistency persist. Overall, the MR results echo the directional findings of the prospective cohort analysis and are consistent with higher CRF conferring a protective association with HF, although these estimates are imprecise and may be influenced by residual bias.[74 75] In contrast, current genetic instruments for PA and sedentary behaviour tend to yield weaker and more heterogeneous estimates for major cardiovascular outcomes. Their largely null or inconsistent associations should therefore be interpreted cautiously as reflecting limited instrument strength rather than an absence of biological relevance for PA.[12 76] Accordingly, the MR evidence in this study supports a tiered interpretation. Regarding CRF, genetically proxied associations provide suggestive evidence consistent with a causal protective effect on heart failure, although the precision of the estimate (OR 0.79, 95% CI 0.63 to 0.99) limits definitive conclusions. Conversely, for PA, current genetic instruments do not permit meaningful causal claims for most CVD endpoints. Therefore, the observational associations reported in this study remain the primary basis for informing activity-based recommendations.

Clinical implications

The integration of multidimensional cohort results with MR evidence provides a refined blueprint for precision exercise prescription. The two analytical approaches yielded notably different effect patterns. The prospective cohort analysis demonstrated consistent, graded associations for both MVPA and CRF with composite CVD, whereas MR provided suggestive support only for CRF on heart failure and largely null results for PA. Several factors are likely to contribute to this divergence. Genetic instruments for device-measured PA explain limited phenotypic variance and exhibit high heterogeneity, regression dilution is inherent in behavioural phenotypes with low heritability, and current MR designs cannot capture the cumulative, time-varying nature of habitual activity. Clinically, this pattern suggests that the observational MVPA-CVD associations, while potentially subject to residual confounding, remain the strongest available evidence for guiding activity-based prescriptions, and that MR in its current form is better suited to evaluating integrated physiological traits such as CRF than complex behavioural exposures. The MR findings, which suggest more stable genetic instruments for CRF than for behavioural PA,[21 23] complement our cohort-derived joint MVPA–CRF model. Within this framework, the residual fitness analysis indicated that surplus fitness retains a modest independent protective association with CVD (HR 0.98 per 1 mL/kg/min), suggesting that, while the cardioprotective role of CRF operates predominantly through the behavioural pathway of maintaining sufficient MVPA, a small but measurable physiological component persists independently of activity volume.

Importantly, these findings simultaneously reinforce the public health value of the current 150 min/week guideline. The remarkably consistent relative risk reduction across all fitness strata (HR, 0.91–0.92) and the broadly overlapping CIs in figure 2A confirm that this threshold functions as a robust universal minimum that does not require fitness-based modification. Given that large proportions of the population do not yet meet even this benchmark[77], the primary public health message remains straightforward: achieving 150 min/week of MVPA delivers meaningful cardiovascular protection regardless of fitness level. Beyond this population-level message, the minutes-to-target matrix offers a complementary individualised tool for clinical counselling, as the current guideline of 150 min per week is a vital entry point yet corresponds to only an approximately 8%–9% reduction in baseline risk. To achieve substantial protection (eg, >30% reduction) and likely drive the physiological adaptations supported by the genetic analyses, patients may need to progress toward MVPA volumes 3–4 times higher than the minimum guideline, approximately 560–610 min per week. In the analytic cohort, approximately 11.6% of participants, 1980 of 17 088, achieved at least 560 min per week, indicating that although such volumes are attainable, they represent a high behavioural threshold for most individuals. This is particularly critical for low-fitness populations, who face the dual challenge of high absolute risk and the need for rigorous adherence to accrue relative benefits. Implementation of these findings requires integrating wearable data into electronic health records to visualise patients' dose–response trajectories in real time.[78] Future research should validate these high-volume targets in randomised controlled trials to assess feasibility and safety, particularly in older adults, and employ multi-ancestry analyses to ensure generalisability beyond European-descent populations.

Strengths

The primary strength of this study lies in its methodological rigour and translational utility. We integrated objectively measured MVPA via accelerometry with physiological CRF estimates within the same cohort, using a DAG-guided Cox-GAM framework to map the complex joint risk surface. Robustness was confirmed through comprehensive sensitivity analyses,

including Fine-Gray competing risk models and random survival forest validation. Critically, we translated these high-dimensional data into a clinically actionable minutes-to-target prescription matrix, thereby bridging the gap between epidemiological observation and precision medicine. Parallel two-sample MR analyses provided complementary evidence, reinforcing the suggestive protective associations of CRF with cardiovascular outcomes.

Limitations

This study also has limitations. First, the stringent inclusion criteria required valid accelerometry, a completed submaximal cycle test and successful VO_2max quality control. This rigorous screening yielded a final cohort of 17 088 participants from the initial 103 567 accelerometer wearers, representing a retention rate of approximately 16.5%. The substantial attrition was driven primarily by the requirement for concurrent valid CRF data, which was available for only a subset of participants. Consequently, the resulting cohort is likely healthier and fitter than the general population, reflecting a healthy volunteer bias.[79] Although this rigorous selection prioritises internal validity, it may limit generalisability to frail older adults or those with contraindications to exercise. Second, measurement error remains a relevant consideration. CRF was estimated rather than directly measured via gas exchange, and prediction error may not be purely random if untrained individuals exhibit less predictable heart rate responses to submaximal exercise, potentially introducing systematic bias associated with habitual activity patterns. Single time-point assessments also cannot capture life-course trajectories or within-person variation over time. Third, despite rigorous DAG-based adjustment, residual confounding cannot be entirely excluded. The primary model did not adjust for sedentary time or light physical activity, both of which have been independently associated with CVD risk.[29] Because these behaviours share a fixed 24-hour time budget with MVPA, including them as conventional covariates risks inducing collinearity and overadjustment within the compositional time-use structure.[80] However, their omission means that any independent effects of prolonged sitting or insufficient light activity on CVD are not captured and may partly confound the estimated MVPA associations. Categorically measured confounders such as smoking status and self-reported alcohol intake are subject to measurement error that attenuates adjustment and introduces residual bias, even when the correct variables are included in the model. Furthermore, both exposures and confounders were assessed at a single time point, precluding adjustment for time-varying confounding. For instance, sustained engagement in MVPA, especially its vigorous component, would be expected to improve CRF within weeks to months through physiological adaptations such as increased cardiac stroke volume and enhanced mitochondrial capacity. Because our conditional estimates evaluate MVPA at a fixed CRF level, they do not fully capture this dynamic feedback and may therefore understate the total long-term cardiovascular benefit of activity volumes that progressively raise fitness. Similar feedback loops exist between physical activity and downstream mediators such as BMI, where PA lowers BMI, and BMI in turn influences future PA, constituting time-varying confounding affected by prior exposure. Conventional regression analysis cannot adequately adjust for this structure, which would require longitudinal data and methods such as marginal structural models or g-estimation.[81] Additionally, the cause-specific hazard approach used in our primary analysis assumes that competing events, specifically non-CVD deaths, are non-informative censoring, which may be violated if MVPA and CRF also influence non-CVD mortality.[31 32] The consistency between our cause-specific and Fine-Gray estimates (online supplemental eTable 5) mitigates this concern but does not fully resolve it. More broadly, HRs carry a built-in selection bias because the risk set at any time point is conditioned on prior survival, which can distort group comparability even after adequate confounding adjustment.[82] This structural limitation applies to all Cox-based analyses in the present study. Moreover, partial sample overlap between some exposure and outcome GWAS and the relatively modest instrument strength for accelerometer-based PA could have biased some MR estimates toward the null and reduced their precision. Finally, causal inferences from MR should be interpreted with caution, given the heterogeneity of PA instruments and the inherent assumptions of two-sample designs. The composite CVD endpoint pools conditions with distinct pathophysiology (AF, MI, HF, stroke), and the limited number of events for individual components (156 MI, 111 HF and 92 stroke) precluded reliable estimation of outcome-specific joint dose–response surfaces. Therefore, future studies with larger event counts should examine whether the MVPA–CRF interaction varies across CVD subtypes.

CONCLUSION

This study provides high-resolution mapping of the joint nonlinear dose–response relationship between objectively measured MVPA, CRF and CVD risk. The current guideline of 150 min per week offers a universal but modest safety margin of approximately 8%–9% risk reduction, whereas achieving larger relative risk reductions (eg, >30%) in this cohort appeared to require activity volumes 3–4 times higher than current minimums across fitness strata. The prediction-based analysis suggests that surplus fitness retains a modest independent protective association (HR, 0.98 per 1 mL/kg/min), complementing genetic evidence consistent with higher CRF being associated with lower HF risk. Collectively, these findings confirm that current guidelines provide a robust universal minimum threshold for cardiovascular protection while offering a quantifiable fitness-stratified prescription matrix as a complementary clinical tool to guide motivated patients from baseline adherence toward greater cardiovascular resilience.

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Patient consent for publication Not applicable.

Ethics approval This study was approved by the North West Multicentre Research Ethics Committee (reference 11/NW/0382), and all participants provided written informed consent. The present analysis was conducted within the UK Biobank resource application framework.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. Individual-level data from the UK Biobank are available to bona fide researchers upon application through the UK Biobank Access Management System (https://www.ukbiobank.ac.uk). This research was conducted under Application Number 1050630. Genome-wide association study summary statistics used in the Mendelian randomisation analyses were obtained from publicly available sources; full details including dataset identifiers and URLs are provided in online supplemental eTable 10. Summary-level analytical data and statistical code supporting the findings of this study are available from the corresponding author upon reasonable request and with permission of UK Biobank.

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