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Leisure-Time Physical Activity on Age-Modelled Trajectories of Body Mass Index and Obesity Risk Throughout Life: Multivariable Regression and Mendelian Randomization Analyses Using Electronic Health Record Data From the CORDELIA-Catalunya Study

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ABSTRACT

Aims: To assess whether self-reported leisure-time physical activity, moderate-to-vigorous leisure-time physical activity, and genetically determined cardiorespiratory fitness are associated with age-related BMI trajectories and incident obesity.

Methods: We pooled 14993 adults (30–90 years; 52.7% women; cohorts: REGICOR-ACRISC, ILERVAS, ARTPER) with estimated LTPA (moderate-to-vigorous LTPA [MVLTPA] in REGICOR-ACRISC), genotype, and 120352 repeated BMI measurements from electronic health records (1990–2024). LTPA was categorised into cohort-specific quartiles; MVLTPA in 0, <100, <200, and ≥200 METs-min/day. In one-sample Mendelian randomisation analyses, we categorised participants in quartiles of a cardiorespiratory fitness polygenic risk score derived from a large GWAS in UK Biobank. Group-dependent BMI trajectories were modelled using spline mixed-effects models. Obesity onset (first BMI ≥ 30 kg/m^2) was analysed with IPW-weighted Kaplan–Meier curves and Cox models.

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Results: Higher LTPA was associated with slower BMI increases in ages 30–60 (Q1: +0.120 vs. Q4: +0.075 kg/m^2·year), slower declines in ages 70–90 (Q1: −0.143 vs. Q4: −0.123 kg/m^2·year), and lower obesity risk (Q4 vs. Q1: HR 0.83, 95% CI 0.72–0.96). Similar trends were observed for MVLTPA. Higher genetically determined cardiorespiratory fitness showed parallel gradients (ages 30–60, Q1: +0.109 vs. Q4: +0.101 kg/m^2·year; ages 70–90, Q1: −0.130 vs. Q4: −0.102 kg/m^2·year) and lower obesity risk (Q4 vs. Q1: HR 0.66, 0.56–0.78). Associations were present for women and men separately, but were stronger in men.

Conclusions: Higher LTPA and MVLTPA were associated with more favourable lifelong BMI trajectories, delayed obesity risk, and convergent support from Mendelian randomisation analyses, supporting a causal protective role of physical activity (in both sexes but stronger in men).

1 | Introduction

High BMI is a major and growing global health concern, contributing substantially to morbidity, mortality, and disability across regions, sexes, and age groups. This burden is largely driven by major cardiometabolic and renal diseases, including diabetes mellitus, ischemic heart disease, hypertensive heart disease, chronic kidney disease, and stroke, together with disabling musculoskeletal conditions. In 2021, diabetes mellitus, ischemic heart disease, hypertensive heart disease, chronic kidney disease, low back pain, and stroke were the leading contributors to disability-adjusted life years attributable to high BMI [1, 2]. Population-level prevention through healthy lifestyle habits is therefore a central public health priority [3]. Leisure-time physical activity (LTPA) is widely recommended for weight management, particularly moderate-to-vigorous LTPA (MVLTPA) [4]. However, the causal role of LTPA on BMI has only been shown in short- or medium-term randomised controlled trials focusing on specific age groups [5–7]. The only evidence covering longer follow-up periods is observational, which is susceptible to residual and unmeasured confounding and does not demonstrate causality (individuals meeting LTPA recommendations often have healthier diets, smoke less, have higher socioeconomic status, and better underlying health), and has not covered the entire life course [8, 9]. In addition, reverse or bidirectional causation may contribute to this uncertainty, since higher BMI may itself lead to lower physical activity or greater sedentary behaviour over time [10, 11]. In the absence of long-term randomised trials specifically addressing lifelong effects of LTPA on adiposity, triangulation of observational evidence with other robust causal inference tools becomes essential [12]. In this context, data from electronic health records may serve beneficial to this purpose, as it has been previously used to characterise the worldwide epidemiologic landscape of overweight/obesity [13].

Mendelian randomisation (MR) uses genetic variants as instruments to estimate the unconfounded effects of modifiable exposures on outcomes [14]. When multivariable regression and MR results agree, this increases confidence that the association is causal [12]. Yet, applying MR directly to self-reported LTPA is challenging because physical activity is a complex behavioural trait that is not likely to be explained by genetic predisposition, raising concerns about instrument strength and MR assumptions [15]. Nevertheless, we could overcome this limitation by using physiological proxies that are tightly linked to habitual LTPA and have stronger genetic architecture, such as cardiorespiratory fitness (CRF) [16]. High CRF reflects the integrated response of cardiovascular and muscular systems to habitual exercise [17], can increase with higher LTPA, particularly moderate-to-vigorous [18, 19], as well as due to genetic predisposition, and is therefore suitable for MR analyses under our hypothesis. Thus, in this study we aimed to assess whether self-reported LTPA and MVLTPA levels and genetically determined CRF are associated with differences in estimated age-related BMI trajectories and the risk of incident obesity in the CORDELIA-Catalunya Study (in all participants, and in women and men separately).

2 | Materials and Methods

2.1 | Study Design and Population

We conducted a prospective observational study using data from the three existing Catalan cohorts with self-reported LTPA information, genotype data, and repeated measures of BMI included in the CORDELIA project: REGICOR-ACRISC, ILERVAS, and ARTPER [20]. Eligible participants were adults between 30 and 90 years and BMI range among 15–60 kg/m^2 with self-reported LTPA information at cohort recruitment time, available genotype data, and at least two valid BMI measurements recorded in electronic health records. The final analytical sample included 14 993 unique participants contributing 120 352 repeated BMI measurements (Figure 1).

2.2 | Leisure-Time Physical Activity

LTPA was assessed once, at the cohort recruitment visit, using self-reported questionnaires: the long version of Minnesota questionnaire in REGICOR-ACRISC [21, 22], the short version of Minnesota questionnaire in ARTPER [23], and the IPAQ questionnaire in ILERVAS [24]. The questionnaires registered the frequency and duration of 67 (Minnesota, long version), 27 (IPAQ, long version), and 6 activities (Minnesota, short version) undertaken by the participants during the previous year. Because these instruments differ in structure and recall frame, LTPA was harmonised as metabolic equivalents of task-minute per day (MET-min/day), calculated by multiplying the METs linked to each activity by its average minutes per day and summing across all activities. METs-min/day due to moderate and vigorous activities were used to estimate MVLTPA levels in REGICOR. These estimates were used to classify participants into physical activity groups for the BMI trajectory analyses; thus, LTPA/MVLTPA was modelled as an indicator of habitual physical activity rather than as a time-updated exposure.

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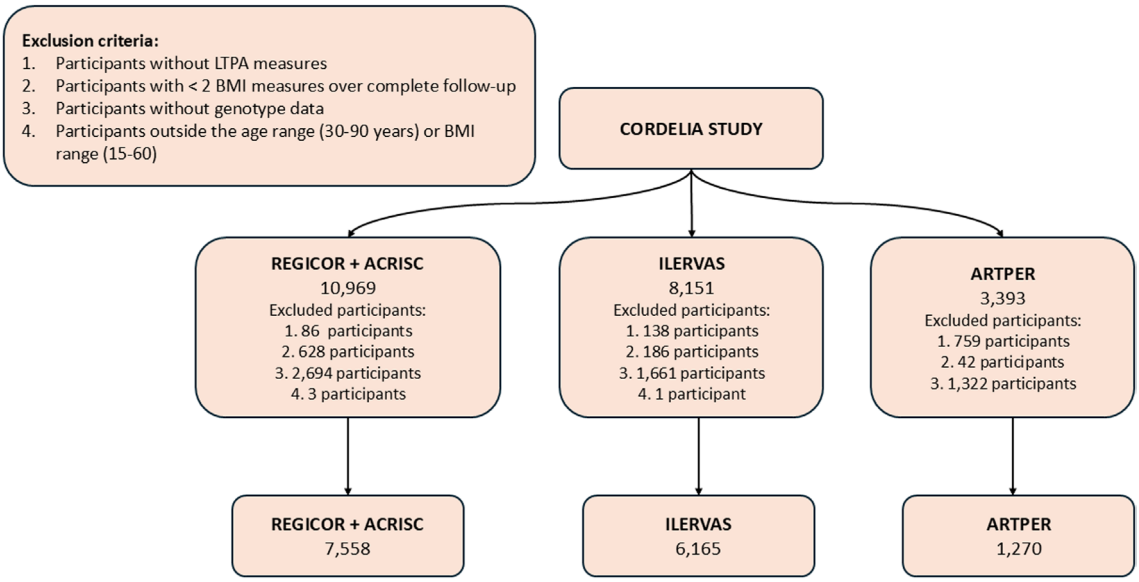

FIGURE 1 | Flow chart.

For the Mendelian randomisation analyses, CRF was selected as a fitness-related phenotype biologically linked to MVLTPA. This link is supported by interventional evidence showing that aerobic exercise improves CRF, with larger VO_2max gains observed at moderate-to-vigorous intensities and with increasing exercise dose [25, 26]. In our study, CRF was estimated using a non-exercise equation validated in Spanish adults that includes age, sex, resting heart rate, BMI, and self-reported MVPA as predictors of VO_2max [17].

2.3 | Genetic Predisposition for Cardiorespiratory Fitness

We used the results from the most recent genome-wide association study (GWAS) of objectively measured CRF that presented sex-stratified results to create the genetic instruments for our MR analyses [16]. This GWAS included 70 783 participants, aged 40–69, living in the United Kingdom (none of whom participated in the CORDELIA Study), with available genotype data and CRF measured as maximal oxygen consumption during a ramp test [16]. It identified genetic variants linked to CRF in all participants and in women and men separately. We computed participants' polygenic risk scores (PRS) for CRF using PRS-CS, which fits a Bayesian continuous-shrinkage model to GWAS summary statistics while incorporating an external linkage disequilibrium reference to jointly estimate the effect sizes of the genetic variants on CRF [27]. Each individual's PRS was calculated as the allele dosage-weighted sum of these effects and was directly proportional to the genetically determined CRF levels.

2.4 | Body Mass Index and First-Onset Obesity

BMI data was obtained from the Public Data Analysis for Health Research and Innovation Program of Catalonia (PADRIS) at the Agency for Health Quality and Assessment of Catalonia. PADRIS is focused on real-world data exploitation and routinely links individual-level demographic, socioeconomic, and healthcare data (including primary care and hospital visits) generated from consultations within the Catalan healthcare system [28]. All data were anonymized, de-identified, and accessed in accordance with applicable regulations, ethical guidelines, and transparency principles. BMI (in kg/m^2) was calculated for each participant from PADRIS height and weight values. We excluded specific BMI measurements that differed by more than $12\,kg/m^2$ from both the immediately preceding and the subsequent visit. Repeated BMI measures from 1990 to 2024 within the range $15–60\,kg/m^2$ were included. Each participant contributed repeated BMI measurements only within the ages captured during their individual follow-up. By stitching together these partially overlapping age segments across all participants, we assembled a longitudinal dataset that collectively spans ages 30–90 years. We restricted the analyses to individuals aged 30–90 due to the limited amount of BMI measures for participants aged 20–29 (1.1%) and 90–100 (0.03%).

We defined the first occurrence of obesity as the first recorded BMI $\geq 30\,kg/m^2$. For incidence analyses, participants with obesity (BMI $\geq 30\,kg/m^2$ at their first available BMI measurement) were excluded.

2.5 | Other Variables

The following information has been harmonised for all the participants of the participating cohorts in the beginning of their follow-up: age (continuous), prevalence of diabetes (yes/no), prevalence of hypertension (yes/no), prevalence of hypercholesterolemia (yes/no), smoking status (never smoker, current smoker, and former smoker [no smoking in the last 12 months]), and a proxy for socioeconomic status (area-level income indicator: median of the municipality-specific annual mean net per-capita income for the participant's municipality of residence, 2015–2023) [29]. The first 10 ancestry-informative genetic principal components (PCs) were also gathered to account for population stratification in MR analyses.

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2.6 | Ethical Aspects

This study was performed in line with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Parc de Salut Mar (reference 2024/11670/I; date: November 18, 2024). Approval for the CORDELIA Study was granted by the Ethics Committee of the Parc de Salut Mar (2023/10785/I, date: March 29, 2023). All cohorts obtained informed consent from their participants.

2.7 | Statistical Analysis

We described normally distributed continuous variables with means ± standard deviations (SD), and categorical variables with proportions.

2.8 | Multivariable Regression

We modelled BMI trajectories in the longitudinal, aggregated dataset spanning ages 30–90 using smoothed cubic spline mixed-effects regression models, with participants as random effects [30, 31]. In analyses with LTPA as the exposure, we modelled BMI trajectories across four cohort-specific quartiles of LTPA (to account for between-cohort differences in the distribution and measurement of LTPA) [32]. In analyses with MVLTPA, we modelled four categories (0 METs-min/d [null MVLTPA, reference], < 100 METs-min/d [insufficient MVLTPA], 100 to < 200 METs-min/d [adequate MVLTPA], and ≥ 200 METs-min/d [above-adequate]) among REGICOR-ACRISC participants. To allow different trajectories, models incorporated an interaction between age (the underlying time scale) and the LTPA/MVLTPA group. Analyses were adjusted for birth year, sex, and baseline prevalent diabetes, hypertension, hypercholesterolemia, smoking status, and socioeconomic status. Before the analyses, we imputed missing data using a nonparametric random forest-based approach in the following covariates: diabetes (0.16%), hypercholesterolemia (0.28%), hypertension (0.09%), and smoking status (0.56%). We graphed mean BMI trajectories by group using model-based predictions and estimated average between-group differences (with the lowest LTPA/MVLTPA group as the reference) at benchmark ages of 30, 40, 50, 60, 70, 80, and 90 via linear regressions. The trajectories shown in the figures represent model-predicted mean BMI values derived from all available repeated measurements rather than observed raw data. Predicted BMI values were estimated across the age range and then averaged within exposure groups to obtain the age-related trajectories displayed in the figures. As a sensitivity analysis, we assessed whether sex modified the associations by fitting models that added a 'sex × LTPA/MVLTPA group' interaction and compared them with the base models using likelihood ratio tests.

We also assessed the association between LTPA/MVLTPA and the incidence of obesity (first occurrence of BMI ≥ 30 kg/m^2). Using the same LTPA quartiles and MVLTPA categories defined for the trajectory analyses, we plotted cumulative incidence from ages 30–90 years for LTPA/MVLTPA groups using Kaplan–Meier curves. To reduce confounding in these curves, we applied inverse probability weighting based on a propensity score that included the same covariates as in the trajectory models, and we displayed weighted survival estimates with 95% confidence bands. Additionally, we estimated hazard ratios for obesity for LTPA/MVLTPA groups (relative to the lowest LTPA/MVLTPA group) using Cox proportional hazards models adjusted for the same covariates. As sensitivity analyses, we also investigated effects stratifying by sex.

2.9 | Mendelian Randomisation Analyses

We repeated the BMI trajectory and obesity incidence analyses using a one-sample MR framework with an externally weighted CRF-PRS. Participants were classified into CRF-PRS quartiles, which were used as the genetic proxy for CRF in both analyses. We used CRF as the genetically instrumented exposure because it is a fitness-related phenotype biologically linked to MVLTPA. All genetic-instrument models were adjusted only for the first 10 ancestry-informative genetic PCs.

We verified the three key MR assumptions in our analyses: (i) the genetic instrument is robustly associated with the exposure (relevance); (ii) there is no confounding of the instrument-outcome association by population stratification; and (iii) the instrument affects the outcome only through the exposure (lack of horizontal pleiotropy) [15]. Regarding the relevance assumption, we quantified the strength of association between the CRF-PRS and estimated CRF levels reporting the F-statistic and the magnitude of the association [15]. We minimised confounding of the genetic instrument-outcome association due to population stratification by adjusting all MR analyses for the first 10 ancestry-informative PCs [33]. We assessed the lack of horizontal pleiotropy using several checks [12, 34–37]. First, we evaluated the lack of association between the exposure in MR analyses (CRF-PRS quartiles) and the potential sources of horizontal pleiotropy, including baseline covariates in multivariable regression (sex, prevalent diabetes, prevalent hypertension, prevalent hypercholesterolemia, smoking status, and socioeconomic status), as well as age, using linear regressions and controlling for multiple comparisons with the Bonferroni method. Second, to examine whether any association between the CRF-PRS and BMI operated independently of the estimated CRF and MVLTPA, we fitted a model for the cumulative average BMI (mean of all available BMI measures per participant, as the outcome) that included CRF-PRS quartiles (main exposure) and estimated CRF quartiles (additional covariate). Attenuation towards the null supported the lack of horizontal pleiotropy. Finally, as a negative-control analysis, we verified the lack of association between the CRF-PRS and a variable theoretically unrelated to genetics (birth year), as an indication of no residual structure or broad pleiotropy.

All analyses were performed using R version 4.4.2. Code for data management and analysis is available at https://github.com/javifar/Lifelong-trajectories-of-BMI.

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3 | Results

3.1 | Participants

The study included 14 993 participants (mean age at cohort recruitment, 53.5 years; 52.7% women). Participant characteristics at cohort recruitment are shown in Table 1; cohort-stratified characteristics are provided in Table S2. The longitudinal dataset used for trajectory analyses comprised 120 352 repeated BMI measurements. The median number of BMI records per participant was 7 in REGICOR (interquartile range [IQR], 7), 4 in ACRISC (IQR, 5), 7 in ILERVAS (IQR, 5), and 10 in ARTPER (IQR, 8).

3.2 | Age-Related BMI Trajectories and Risk of Obesity According to LTPA and MVLTPA Groups

Participants in the groups with higher LTPA tended to increase BMI more slowly between ages 30–60 (Q1: +0.12 kg/m^2×year, 95% CI 0.118–0.121; Q2: +0.122 kg/m^2×year, 95% CI 0.121–0.124; Q3: +0.099 kg/m^2×year, 95% CI 0.097–0.101; Q4: +0.075 kg/m^2×year, 95% CI 0.073–0.077). Conversely, participants in the groups with higher LTPA tended to show a slower decline in BMI over time between ages 70 and 90, particularly among those above the median LTPA (Q1: −0.143 kg/m^2×year, 95% CI −0.145 to −0.140; Q2: −0.125 kg/m^2×year, 95% CI −0.128 to −0.122; Q3: −0.108 kg/m^2×year, 95% CI −0.111 to −0.105; Q4: −0.123 kg/m^2×year, 95% −0.126 to −0.120 CI) (Figure 2A). This translated into lower predicted BMI values in the groups with higher LTPA between ages 50 and 90 (Figure 2B). These differences also translated into lower incidence of first occurrence of obesity relative to Q1 (median age at first obesity event 66.9 years) in Q2 (HR 0.77, 95% CI 0.67–0.90; median age at first obesity event 72.5 years), Q3 (HR 0.82, 95% CI 0.71–0.95; median age at first obesity event 73.4 years), and Q4 (HR 0.83, 95% CI 0.72–0.96; median age at first obesity event 70.1 years) (Figure 2C).

Participants in groups with higher MVLTPA tended to increase BMI more slowly between ages 30–60, particularly at MVLTPA ≥100 METs-min/day (0 METs-min/day: +0.116 kg/m^2×year, 95% CI 0.114–0.118; >0 to <100 METs-min/day: +0.124 kg/m^2×year, 95% CI 0.122–0.126; ≥100 to <200 METs-min/day: +0.085 kg/m^2×year, 95% CI 0.083–0.088; ≥200 METs-min/day: +0.087 kg/m^2×year, 95% CI 0.085–0.089) (Figure 3A). This translated into lower predicted BMI values in the groups with adequate and above-adequate MVLTPA between ages 50–90 (Figure 3B). Kaplan–Meier curves also suggested adequate MVLTPA levels were linked to lower incidence of first occurrence of obesity relative to null MVLTPA (median age at first obesity event 65.41 years) in individuals with >0 to <100 METs-min/day (insufficient MVLTPA, HR 0.73, 95% CI 0.63–0.85; median age at first obesity event 71.8 years), ≥100 to <200 METs-min/day (adequate MVLTPA, HR 0.62, 95% CI 0.53–0.74; median age at first obesity event 81.6 years), and ≥200 METs-min/day (above-adequate MVLTPA, HR 0.66, 95% CI 0.56–0.78; median age at first obesity event 71.5 years) (Figure 3C).

3.3 | Genetically Determined Cardiorespiratory Fitness, BMI Trajectories, and Risk of Obesity

Participants with a genetic predisposition to higher CRF tended to show slower increases in BMI between ages 30 and

TABLE 1 | Main cardiovascular risk factors.

Variable	Whole population	Men	Women
Age at baseline, years (mean ± SD)	53.5 ± 11.0	53.0 ± 11.2	53.9 ± 10.9
Female sex (*n*, %)	7903 (52.7%)		
Baseline BMI, kg/m^2 (mean ± SD)	27.5 ± 4.61	27.8 ± 4.03	27.3 ± 5.06
Baseline BMI categories:			
Normal weight (< 25 kg/m^2) (*n*, %)	4616 (30.8%)	1721 (24.3%)	2895 (36.6%)
Overweight (25.0–29.9 kg/m^2) (*n*, %)	6512 (43.4%)	3562 (50.2%)	2950 (37.3%)
Obesity (≥ 30 kg/m^2) (*n*, %)	3865 (25.8%)	1807 (25.5%)	2058 (26%)
Baseline prevalence of diabetes (*n*, %)	1000 (6.67%)	556 (7.84%)	438 (5.54%)
Baseline prevalence of hypertension (*n*, %)	5342 (35.6%)	2988 (42.1%)	3275 (41.4%)
Baseline prevalence of hypercholesterolemia (*n*, %)	6269 (41.8%)	2992 (42.2%)	3277 (41.5%)
Smoking status:			
Current smoker (*n*, %)	3853 (25.7%)	2310 (32.6%)	1542 (19.5%)
Never smoked (*n*, %)	7134 (47.6%)	2002 (28.2%)	5134 (65.0%)
Former smoker (*n*, %)	4006 (26.7%)	2778 (39.2%)	1227 (15.5%)
Socioeconomic status, €/year (median, 1st-3rd quartile)	13 161 (11 949; 14 910)	13 161 (11 933; 14 755)	13 161 (11 949; 14 910)

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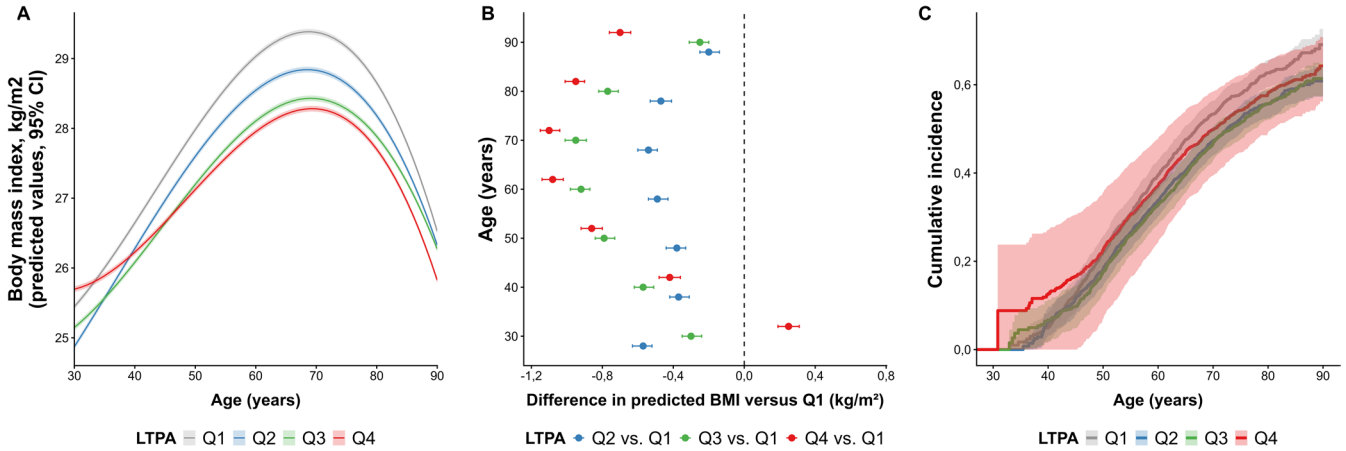

FIGURE 2 | BMI trajectories and incident obesity by cohort-specific quartiles of LTPA (Q1 in grey, Q2 in blue, Q3 in green, Q4 in red). (A) BMI trajectories per quartiles. (B) Inter-group differences in predicted mean BMI values between ages 30 and 90. (C) Weighted Kaplan–Meier curves for first obesity onset.

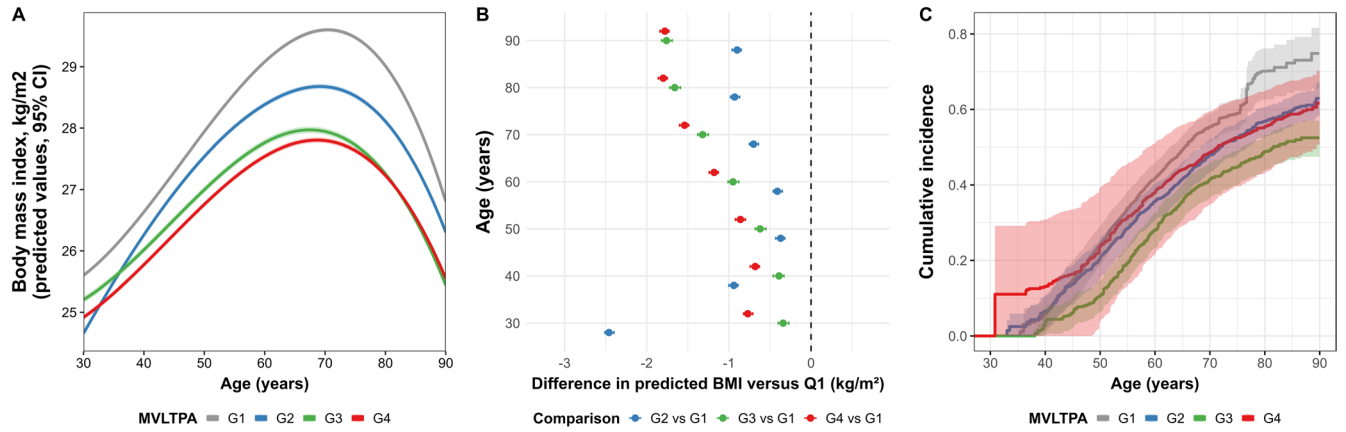

FIGURE 3 | BMI trajectories and incident obesity by MVLTPA levels in REGICOR-ACRISC (0 METs-min/day in grey, >0 to <100 METs-min/day in blue, ≥100 to <200 METs-min/day in green, ≥200 METs-min/day in red). (A) BMI trajectories per quartiles. (B) Inter-group differences in predicted mean BMI values between ages 30 and 90. (C) Weighted Kaplan–Meier curves for first obesity onset.

60 (Q1: +0.109 kg/m^2×year, 95% CI 0.109–0.110; Q2: +0.108 kg/m^2×year, 95% CI 0.107–0.109; Q3: +0.094 kg/m^2×year, 95% CI 0.093–0.095; Q4: +0.101 kg/m^2×year, 95% CI 0.100–0.102). In addition, participants with the highest genetically determined CRF showed an attenuated decrease in BMI over time between ages 70 and 90 (Q1: −0.130 kg/m^2×year, 95% CI −0.131 to −0.129; Q2: −0.119 kg/m^2×year, 95% CI −0.120 to −0.117; Q3: −0.144 kg/m^2×year, 95% CI −0.146 to −0.142; Q4: −0.102 kg/m^2×year, 95% CI −0.103 to −0.100) (Figure 4A). Thus, genetic predisposition to higher CRF was associated with lower predicted BMI among groups over time (Figure 4B). These differences were also associated with a lower incidence of first-onset obesity relative to Q1 (median age to first obesity event 65.0 years) in Q2 (HR 0.75, 95% CI 0.64–0.87; median age to first obesity event 72.5 years), Q3 (HR 0.67, 95% CI 0.56–0.80; median age to first obesity event 79.0 years), and Q4 (HR 0.66, 95% CI 0.56–0.78; median age to first obesity event 76.7 years) (Figure 4C).

The MR assumption checks supported the plausibility of the analytical framework, although the association between the CRF-PRS and estimated CRF indicated a modest instrument strength. The CRF-PRS was associated with estimated CRF, with an F-statistic of 7.66 and a positive association across PRS quartiles ($\beta = 0.32$, 95% CI 0.094–0.55). All MR analyses were adjusted for the first 10 ancestry-informative genetic principal components to reduce potential bias due to population stratification. Regarding horizontal pleiotropy, no meaningful associations were observed between CRF-PRS quartiles and the pre-identified sources of pleiotropy, or in the negative-control analysis (birth year) (p-values were >0.00714, considering the Bonferroni method for eight comparisons): age (p-value = 1), sex (p-value = 1), diabetes (p-value = 1), hypertension (p-value = 0.376), hypercholesterolemia (p-value = 1), socioeconomic status (p-value = 0.152), smoking (p-value = 0.224), and birth year (p-value = 0.728). In addition, adding CRF quartiles to the PRS-cumulative BMI mean showed the association's attenuation towards the null (unadjusted $\beta = -0.28$, 95% CI −0.36 to −0.20; adjusted $\beta = -0.17$, 95% CI −0.26 to −0.076; attenuation: 40%).

3.4 | Sex-Specific Analyses

LTPA analyses in women and men separately also showed a progressive attenuation in the BMI increase between ages 30–60, as

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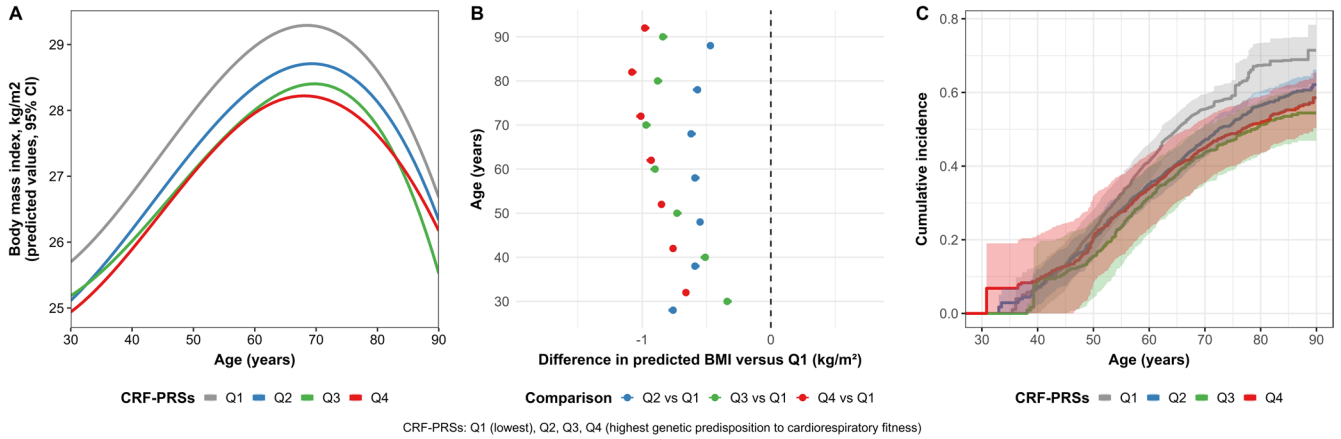

FIGURE 4 | BMI trajectories and incident obesity by genetically determined CRF levels (Q1 in grey, Q2 in blue, Q3 in green, Q4 in red). (A) BMI trajectories per quartiles. (B) Inter-group differences in predicted mean BMI values between ages 30 and 90. (C) Weighted Kaplan–Meier curves for first obesity onset.

well as a decreased risk of obesity in higher LTPA groups, with a stronger and more graded association in men (only women, Q4 vs. Q1: HR 0.85, 95% CI 0.73–0.99; only men, Q4 vs. Q1: HR 0.75, 95% CI 0.65–0.87) (Figures S1 and S2). MVLTPA analyses in women and men separately showed similar findings, as observed in obesity incidence analyses, again with a stronger association in men (only women, adequate vs. no MVLTPA: HR 0.64, 95% CI 0.51–0.80; above-adequate vs. no MVLTPA: HR 0.70, 95% CI 0.54–0.89; only men, adequate vs. no MVLTPA: HR 0.58, 95% CI 0.45–0.75; above-adequate vs. no MVLTPA: HR 0.60, 95% CI 0.47–0.76) (Figures S3 and S4). Sex-specific MR results also point in the same direction, with a lower risk of obesity in individuals with higher genetically determined CRF that is significant in both women and men separately but of greater magnitude among men (only women, Q4 vs. Q1: HR 0.73, 95% CI 0.56–0.94; only men, Q4 vs. Q1: HR 0.61, 95% CI 0.48–0.77) (Figures S5 and S6).

4 | Discussion

By integrating LTPA and MVLTPA data, genotype information, and long-term repeated BMI measurements, we were able to estimate trajectories and strengthen the evidence for a causal, protective role of physical activity against obesity over the lifespan. Across complementary analyses, higher LTPA and MVLTPA were consistently associated with a slower increase from early-to-mid adulthood, slower BMI decreases in older adults, lower predicted BMI from midlife onwards and a delayed and lower risk of first onset obesity in the general population. The concordant direction and shape of associations across multivariable regression models and one-sample Mendelian randomisation support the interpretation that physical activity causes a more favourable BMI evolution over time. These patterns were observed in women and men, with overall stronger associations in men.

Our findings align with prior observational work indicating that higher LTPA is linked to lower adiposity and healthier weight profiles over time [38], that physical activity is also associated with a slower BMI decline in ageing populations [39], and agree with longitudinal evidence considering more than baseline LTPA values [40]. Taken together with complementary MR evidence, our data support a causal role of LTPA/MVLTPA and its consequences (fitness) in shaping long-term BMI evolution and obesity risk. We extend current evidence of short- to medium-term effects of exercise training on reduced adiposity and improved weight-related phenotypes to longer term follow-up [5–7] supporting causality across the life course. MR studies of activity-related traits and objective fitness indicators generally support a causal role in lifelong lower BMI and fat body mass [41]. Besides previous evidence in twin studies pointing to a causal role of physical activity on lower BMI [42], our one-sample MR using genetically determined CRF adds to this causal triangulation: CRF is a plausible physiological proxy for habitual exercise exposure with stronger genetic architecture than self-reported activity [16], and the concordance between CRF-PRS gradients and both BMI trajectories and obesity incidence supports biological plausibility. Several lines of mechanistic evidence that also support this causal role, as higher activity/fitness: (i) increases total daily energy expenditure [43]; (ii) promotes maintenance and increases of lean muscle mass [44], which can contribute to higher basal energy expenditure over time and could also help explain the slower BMI decline in older populations due to sarcopenia; and (iii) activates AMP-mediated protein kinase, improving fatty acid oxidation and mitochondrial function in ways that limit long-term adiposity [45].

The moderately stronger associations we observed in men (together with beneficial associations in both women and men separately) are compatible with prior literature. Some large cohort analyses have reported slightly stronger associations in men between physical activity expenditure and other cardiometabolic health outcomes such as type-2 diabetes [46], whereas exercise trials suggest that, when prescribed energy expenditure is comparable, sex differences in body-weight change are often small [47]. Biologically, larger BMI separation in men in free-living settings could reflect (i) higher lean mass, so the same reported MET-min/day implies higher absolute energy expenditure; (ii) sex differences in fat distribution/mobilisation, with men tending to mobilise more visceral fat during negative energy balance [48]; and (iii) female life-course BMI evolution and menopause-related shifts in body composition that may moderate BMI-based differences in women despite similar metabolic benefits

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[48, 49]. Methodologically, self-reported LTPA/MVLTPA may be differentially misestimated by sex [50], BMI may not fully reflect beneficial changes in body composition (e.g., fat loss with preserved or increased muscle), and the same questionnaire-based activity may correspond to different energy expenditure in men and women [51].

Strengths of our study include the ability to integrate repeated BMI measures across three decades, sex-stratified analyses, and, critically, the triangulation of observational and genetic-proxy evidence within the same framework to suggest that residual confounding is not likely to explain the physical activity-associated benefits on BMI trajectories and obesity risk over time. However, our work also has several limitations. First, BMI trajectories were assembled by stitching partially overlapping age segments contributed by different individuals and time periods, creating potential temporal heterogeneity that could influence the reconstructed 'population trajectory'. Because each participant contributed data only during the age windows in which they had primary care encounters, rather than being observed continuously across the entire 30–90 year span, our approach implicitly assumes that missing BMI values are missing at random and that censoring/loss to follow-up is minimised after covariate adjustment. To mitigate potential bias, our spline mixed-effects models used all available repeated BMI measures without requiring every individual to contribute data at every age; analyses were restricted to individuals that contributed with at least two valid measures of BMI over time, age-as-time-scale survival models treat loss to follow-up as right censoring, adjustment for birth year aimed to minimise time heterogeneity, and we rebalanced obesity incidence curves using inverse probability weighting based on measured predictors. Nevertheless, prospective studies with more complete long-term follow-up and minimal attrition are needed to confirm these reconstructed life-course patterns. Second, BMI in routine care is measured at clinically driven encounters; if visit frequency depends on underlying weight change or health deterioration, it can imply an overrepresentation of individuals with more unfavourable BMI values and can bias trajectory estimation. Third, late-life estimates may be affected by selection and survivor biases because individuals who survive and remain under observation at older ages are likely healthier and therefore contribute more BMI measurements. This may partly influence the less steep BMI decline observed in the more active groups at older ages. In addition, obesity onset was defined from the first recorded BMI $\geq 30\,kg/m^2$, so the recorded onset may not coincide exactly with the true biological onset. Fourth, LTPA and MVLTPA were assessed only once, at cohort recruitment time, whereas BMI trajectories were reconstructed using repeated electronic health record measurements that could precede, coincide with, or follow the physical activity assessment. Thus, LTPA/MVLTPA was treated as a proxy marker of physical activity rather than as a time-varying exposure. This approach relies on the concept of persistence, or tracking, of physical activity behaviour over time. Previous longitudinal studies have shown that leisure-time physical activity and voluntary exercise habits display some degree of persistence across adulthood [52, 53], although tracking is imperfect and tends to decrease as follow-up duration increases. Therefore, baseline LTPA/MVLTPA may only partially capture long-term physical activity patterns, and changes in activity levels during follow-up may have introduced misclassification and likely bias estimates towards the null, while also complicating cross-cohort comparability (partly mitigated by cohort-specific quartiles). Fifth, our MR proxy has its own constraints: the CRF-PRS instrument strength appears modest, raising weak-instrument concerns; and while we performed multiple horizontal pleiotropy checks, it cannot be completely ruled out, particularly if genetic variants influence BMI through other pathways correlated with fitness. Therefore, the genetic analyses should be interpreted as analyses of genetically proxied CRF rather than as direct genetic instrumentation of physical activity behaviour.

Finally, our analyses were conducted in healthy individuals of a general population in a Mediterranean country, and generalizability of our findings to other populations and ancestries should be carefully evaluated. Due to the procedure to access BMI values, we may have also missed certain segments of the population, such as high-income individuals who primarily use private healthcare services, potentially limiting the representation of the highest socioeconomic strata.

In conclusion, higher LTPA and MVLTPA were consistently associated with more favourable estimated BMI trajectories (slower increases until mid-adulthood, slower decreases in older adults, lower values from midlife onwards), delayed risk of obesity, and convergent support from one-sample MR analyses, which are consistent with a protective causal contribution of physical activity on BMI trajectories throughout life (in both sexes and overall stronger in men). Our findings extend short/medium-term trial evidence to a life-course, incorporating routinely collected BMI measurements from the Catalan healthcare system and reinforce physical activity promotion as a scalable strategy for obesity prevention. Future work should validate these patterns in larger cohorts with repeated BMI measures, as well as in other ancestries and settings, incorporate repeated/objective activity and body composition measures, and evaluate implementation and cost-effectiveness of long-term activity-promotion interventions.

Author Contributions

Álvaro Hernáez: conceptualization and methodology. **Álvaro Hernáez:** project administration. **Javier Hernando-Redondo:** formal analysis. **Javier Hernando-Redondo:** visualisation. **Álvaro Hernáez:** supervision. **Javier Hernando-Redondo:** writing – original draft preparation. **Anna Camps-Vilaró**, **Roberto Elosua**, **Eleonora Fornara**, **Marcelino Bermúdez-López**, **Pere Torán-Monserrat**, **Ainara Jiménez-Navarro**, **José M. Valdivielso**, **Víctor M. López-Lifante**, **Tomàs Salas-Fernández**, **Serafí Cambray**, **Raquel Cruz**, **Jaume Marrugat**, and **Álvaro Hernáez:** writing – review and editing. **Javier Hernando-Redondo** and **Álvaro Hernáez** had full access to all the data in the study and take responsibility for its integrity and the data analysis. All authors read and approved the final manuscript.

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Ethics Statement

This study was performed in line with the principles of the Declaration of Helsinki. Approval for the study was granted by the Ethics Committee of the Parc de Salut Mar (2024/11670/I, date: November 18, 2024). Approval for the CORDELIA Study was granted by the Ethics Committee of the Parc de Salut Mar (2023/10785/I, date: March 29, 2023). All cohorts obtained written informed consent from their participants and were approved by the corresponding ethics committees.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Due to national data-protection legislation and ethical restrictions, and because participants did not provide explicit written consent for open data sharing, the underlying study dataset cannot be deposited in a public repository. However, access for the purposes of bona fide collaborative research may be granted to qualified investigators upon reasonable request and subject to appropriate approvals and data-sharing agreements. Requests should be addressed to the CORDELIA Principal Investigator (jmarrugat@researchmar.net). All code used for database construction, data management, and statistical analyses is publicly available at GitHub Repository.

Peer Review

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S2:** Baseline characteristics by cohort. **Figure S1:** BMI trajectories and incident obesity by cohort-specific quartiles of LTPA only in men (Q1 in grey, Q2 in blue, Q3 in green, Q4 in red). (A) BMI trajectories per quartiles. (B) Inter-group differences in predicted mean BMI values between ages 30 and 90. (C) Weighted Kaplan–Meier curves for first obesity onset. **Figure S2:** BMI trajectories and incident obesity by cohort-specific quartiles of LTPA only in women (Q1 in grey, Q2 in blue, Q3 in green, Q4 in red). (A) BMI trajectories per quartiles. (B) Inter-group differences in predicted mean BMI values between ages 30 and 90. (C) Weighted Kaplan–Meier curves for first obesity onset. **Figure S3:** BMI trajectories and incident obesity by MVLTPA levels in REGICOR-ACRISC only in men (0 METs-min/day in grey, >0 to <100 METs-min/day in blue, ≥ 100 to <200 METs-min/day in green, ≥ 200 METs-min/day in red). (A) BMI trajectories per quartiles. (B) Inter-group differences in predicted mean BMI values between ages 30 and 90. (C) Weighted Kaplan–Meier curves for first obesity onset. **Figure S4:** BMI trajectories and incident obesity by MVLTPA levels in REGICOR-ACRISC only in women (0 METs-min/day in grey, >0 to <100 METs-min/day in blue, ≥ 100 to <200 METs-min/day in green, ≥ 200 METs-min/day in red). (A) BMI trajectories per quartiles. (B) Inter-group differences in predicted mean BMI values between ages 30 and 90. (C) Weighted Kaplan–Meier curves for first obesity onset. **Figure S5:** BMI trajectories and incident obesity by genetically determined CRF levels only in men (Q1 in grey, Q2 in blue, Q3 in green, Q4 in red). (A) BMI trajectories per quartiles. (B) Inter-group differences in predicted mean BMI values between ages 30 and 90. (C) Weighted Kaplan–Meier curves for first obesity onset. **Figure S6:** BMI trajectories and incident obesity by genetically determined CRF levels only in women (Q1 in grey, Q2 in blue, Q3 in green, Q4 in red). (A) BMI trajectories per quartiles. (B) Inter-group differences in predicted mean BMI values between ages 30 and 90. (C) Weighted Kaplan–Meier curves for first obesity onset.

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