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Research Paper

Dose-response association of an accelerometer-measured physical activity with all-cause mortality and cardiovascular disease incidence: Prospective cohort with 76,074 participants

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ABSTRACT

Objective: To investigate the prospective dose-response association of accelerometer-measured moderate-to-vigorous physical activity (PA;MVPA) with all-cause mortality and cardiovascular disease (CVD) incidence.
Methods: This prospective cohort of 76,074 participants from the UK Biobank study contained one week of individual accelerometer-based PA data collected between June 1, 2013 and December 23, 2015. Using restricted cubic splines to allow for potential non-linearity, we examined dose-response associations of MVPA with all-cause mortality and incident CVD, respectively.
Results: The median follow-up time was 8.0 years (IQR 7.5–8.5). The dose-response association of MVPA with all-cause mortality and CVD showed a similar L-shaped association, with significant risk reductions already from 10 min of MVPA per week for all-cause mortality (hazard ratio [HR], 0.98 [95 % CI,0.98–0.99]) and 15 min per week for CVD incidence (HR, 0.99 [95 % CI,0.98–0.99]). Doing more MVPA was associated with further risk reduction, but beyond around 500 min per week the benefits levelled off at HR's around 0.6 to 0.7. The highest additional benefit of adding more minutes per week for all-cause mortality and CVD incidence were observed between 100 and 250 weekly minutes of MVPA. From this point forward, the mean risk reduction rates decreased and were close to 0 beyond 500 weekly minutes.
Conclusions: Significant, but small, risk reductions in all-cause mortality and CVD incidence can be achieved with as little as 10 and 15 min of MVPA per week, respectively. However, public health organizations should promote the attainment of 250 min of MVPA per week (with 100 min as a possible first target for inactive individuals), as these thresholds are associated with the greatest efficiency. Beyond that, less pronounced risk reductions can be achieved by accumulating additional MVPA, with hardly any additional benefits beyond 500 weekly minutes.

Introduction

Physical inactivity stands as a paramount public health concern worldwide, contributing to an estimated 3.2 million deaths per year and imposing a substantial economic burden.[1,2] Furthermore, it is intricately linked with a variety of chronic diseases, including cardiovascular disease (CVD),[3] which is the leading global cause of mortality.[4]

Nevertheless, the current evidence underpinning physical activity (PA) guidelines predominantly relies on self-reported PA, which is susceptible to reporting bias and measurement error.[5–7] These

Abbreviations: moderate-to-vigorous physical activity, MVPA; physical activity, PA; cardiovascular disease, CVD; Interquartile range, IQR; Hazard ratio, HR; confidence intervals, CIs; Standard deviation, SD; National Health and Nutrition Examination Survey, NHANES; Prospective Urban Rural Epidemiologic, PURE; Physical Activity Questionnaire, IPAQ; World Health Organization, WHO.

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questionnaire-based methods may not be adequate for capturing the entirety of PA conducted throughout the day.[8] By contrast, accelerometers allow the inclusion of all facets of physical activity, encompassing frequency, intensity, and duration, thereby validly capturing the entirety of physical activity undertaken.[8] However, a substantial variability exists in the units used by studies to report these data,[6,9–11] and there is a scarcity of studies providing data in a format than can facilitate public health recommendations and application, such as minutes per week.

Several investigations have examined the association between accelerometer-measured PA and all-cause mortality[12–16] as well as the incidence of CVD.[6,17,18] In general, these studies demonstrate that engaging in PA, irrespective of intensity level, and reducing total sedentary time, are linked to decreased risk of mortality and CVD. Nonetheless, there is a scarcity of prospective cohort studies examining the dose-response relationship of accelerometer-measured PA with all-cause mortality[9,15] and CVD incidence,[19] with the added problem that outcomes are self-reported in many cases. Importantly, none of the previous cohort studies provided information regarding the minimum and optimal quantity of PA required to achieve the greatest benefits, which would allow for specific guidelines and recommendations.

Therefore, the objective of our study was to investigate the prospective dose-response association of accelerometer-measured moderate-to-vigorous PA (MVPA) with all-cause mortality and CVD incidence.

Methods

Participants and design

The UK Biobank study is a prospective cohort of around 500,000 participants aged 40 to 69 years enrolled between 2006 and 2010.[20] Participants gave informed consent and underwent physical examinations by trained staff and touchscreen questionnaires in 22 assessment centers in the UK. Ethical approval was granted by the UK's National Health Service, National Research Ethics Service (Ethics Committee reference number: 11/NW/0382).

Accelerometer-measured PA

Data were collected from a cohort of 103,666 participants constituting the accelerometer subsample. These participants wore an Axivity AX3 wrist-based triaxial accelerometer for one week to assess MVPA. After the calibration of the acceleration signals, these accelerometers recorded continuous acceleration data at a sampling rate of 100 Hz, with a dynamic range of ±8 g, divided into 5-s epochs. Adequate accelerometer wear time was defined as wearing the device for more than 16 h per day. Participants with insufficient accelerometer wear time or incomplete covariate information were excluded from the study (eFigure 1). Furthermore, to ensure the robustness and representativeness of the measurements, only participants with a minimum of three valid measurement days, with at least one of those days falling on a weekend, were included in the subsequent analyses.

Outcome measures

CVD was identified as primary or secondary events using inpatient hospital records and data from the death registry, which were linked to the UK Biobank. For the present study, CVD encompassed coronary heart disease as defined by the International Classification of Diseases (ICD) 9th edition codes 410 to 411, 10th edition codes I20.0, I21, and I22, in addition to surgical codes pertaining to percutaneous transluminal coronary angioplasty and coronary artery bypass graft (codes K40-K46, K49-K50, and K75), stroke defined as either ischemic (ICD-9: 433–434; ICD-10: I63) or hemorrhagic stroke (ICD-9: 430–432; ICD-10: I60–I62), heart failure defined using ICD-9 code 428 and ICD-10 code I50, and atrial fibrillation denoted by ICD-9 code 427.3, ICD-10 code I48, along with surgical codes K50.1 and K62.2–K62.4.

Hospital registry-based follow-up was concluded on October 31, 2022, in England; August 31, 2022, in Scotland; and May 31, 2022, in Wales. CVD-related deaths were defined using the same ICD-10 codes for different end points, as indicated in the death registry. The death registry encompassed all fatalities that transpired prior to November 30, 2022, in England, Scotland, and Wales. Individuals were censored at these specified dates, upon experiencing the event of interest, or at the time of their demise, whichever occurred first.

Data analysis

Using restricted cubic splines to allow for potential non-linearity, we examined dose-response associations of MVPA with all-cause mortality and incident CVD, respectively. We used pre-specified knots placed at the 5th, 50th, and 95th percentiles of the exposure distribution. Departure from linearity was checked with a Wald test assessing the null hypothesis that the coefficient of the third spline was equal to zero. Models were adjusted for age, sex, racial and ethnic background, tobacco use, Townsend Deprivation Index, alcohol consumption, educational attainment, employment status, self-reported health, diet quality, family history of CVD and cancer, body mass index, medication use, and handgrip. Detailed information on these covariates has been published elsewhere.[9] A Wald test showed no interaction between MVPA and each of the aforementioned covariates. To reduce the risk of reverse causation we excluded participants with less than one-year follow-up and either prevalent CVD or cancer at baseline. We also estimated the rate of the adjusted mean risk reduction of all-cause mortality and CVD derived from a Cox regression using accumulated bouts of 50 weekly minutes of MVPA as exposure. We used complete case analysis. Estimates are presented with 95 % confidence intervals (CIs) if not otherwise stated. Analyses were conducted from September to October 2023 using Stata version 16.1 (StataCorp).

Results

We examined 76,074 individuals (mean [SD] age, 55.2 [7.8] years; 57 % women) who wore accelerometers for 1 week between any time between June 1, 2013, and December 23, 2015. The median follow-up time was 8.0 years (IQR 7.5–8.5). Detailed information on the characteristics of the study sample by recommended MVPA guidelines (i.e., meeting 150 weekly minutes of MVPA[21]) is shown in the Table 1.

Figs. 1 and 2 depict the dose-response association between MVPA and all-cause mortality and CVD incidence. Both showed a similar L-shape association which exhibited significant risk reductions within the range of 10 (hazard ratio [HR], 0.98 [95 % CI, 0.98–0.99]) and 2415 (HR, 0.53 [95 % CI, 0.29–0.99]) weekly minutes of MVPA for all-cause mortality, and 15 (HR, 0.99 [95 % CI, 0.98–0.99]) and 1795 (HR, 0.77 [95 % CI, 0.60–0.99]) weekly minutes of MVPA for CVD, respectively (reference: 0 MVPA minutes). In both cases the maximal significant risk reduction matched with the optimal risk reduction.

The greatest mean risk reduction rates for all-cause mortality were observed between 100 and 250 weekly minutes of MVPA for all-cause mortality and CVD. From this point forward, mean risk reductions rates were far lower (Figs. 3 and 4).

Discussion

We investigated the prospective dose-response association between accelerometer-measured MVPA and all-cause mortality or CVD incidence using data from the UK Biobank. Our primary and novel finding revealed an L-shaped association, indicating significant risk reductions for all-cause mortality with as little as 10 min of MVPA per week and 15 min of MVPA per week for CVD incidence. Interestingly, the greatest mean risk reduction rates were observed between 100 and 250 weekly minutes of MVPA for all-cause mortality and CVD, and beyond this

Table 1
Characteristics of the Study Sample by Recommended Levels of Moderate to Vigorous Physical Activity (MVPA).

Baseline Characteristic	No. (%)	
	Not meeting MVPA guidelines (n = 24,581)	Meeting MVPA guidelines (n = 51,493)
Age, mean (SD), y	56.0 (7.9)	54.9 (7.8)
Sex		
Female	16,707 (68.0)	26,956 (52.4)
Male	7874 (32.0)	24,537 (47.7)
Ethnic background[a]		
Asian	386 (1.6)	549 (1.1)
Black	98 (0.4)	150 (0.3)
Other	462 (1.9)	848 (1.7)
White	23,635 (96.2)	49,946 (97.0)
Tobacco use		
Never	13,931 (56.7)	30,602 (59.4)
Former	8557 (34.7)	17,867 (34.7)
Current	2093 (8.5)	3024 (5.9)
Townsend Deprivation Index[b]	−1.8 (2.8)	−1.7 (2.8)
Alcohol consumption		
Never	988 (4.0)	1213 (2.4)
Former	795 (3.2)	1278 (2.5)
Current	22,798 (92.8)	49,002 (95.2)
Educational attainment, mean (SD), y	13.7 (5.3)	15.0 (5.3)
Employed	14,725 (59.9)	34,003 (66.0)
Self-reported health		
Excellent	3582 (15.7)	13,552 (26.3)
Good	14,798 (60.2)	31,140 (60.5)
Fair	4947 (20.1)	6141 (11.9)
Poor	984 (4.0)	660 (1.3)
Diet quality		
Good	5130 (20.9)	12,262 (23.8)
Intermediate	13,237 (53.9)	27,583 (53.6)
Poor	6214 (25.3)	11,648 (22.6)
Family history of cardiovascular disease	17,694 (72.0)	36,308 (70.5)
Family history of cancer	7428 (30.2)	15,493 (30.1)
Body mass index, mean (SD), kg/m^2	28.0 (5.2)	26.0 (4.0)
Medication use		
Blood pressure	4682 (19.1)	6378 (12.4)
Cholesterol	3697 (15.0)	5274 (10.2)
Insulin	227 (0.9)	234 (0.5)
Handgrip, mean (SD), kg	30.4 (10.8)	33.8 (11.1)

SD = standard deviation.
[a] Represents self-reported "ethnic background." Race classification of "Other" defined as self-report of a race other than Asian, Black, or White.
[b] The Townsend Deprivation Index is a way to measure material deprivation standardized by geographic area. Greater values indicate more deprivation. The sample range is −6.3 to 10.6, with values around −2 and − 1 indicating somewhat less deprivation compared to average based on geographic location.

threshold, a decrease in the magnitude of risk is observed albeit less pronounced. Beyond 500 weekly minutes, there were hardly any additional benefits.

Our findings are in line with different European cohort studies, albeit only one explored a dose-response association. For instance, a cohort study utilizing the UK Biobank database, which included over 490,000 individuals with a mean age of 58 years, reported an inverse association between accelerometer-based physical activity and all-cause mortality in patients with and without multimorbidity.[9] Furthermore, the authors reported that 10 min of brisk walking a day were associated with an extended life expectancy. By contrast, the previously mentioned study did not provide information on CVD incidence and we documented benefits from as little as 10 min per week. In this regard, two additional cohort studies that did encompass CVD, conducted in Finland[22] and the UK,[10] found that accelerometer-measured MVPA was associated with reduced all-cause mortality and CVD incidence. Interestingly, Del Pozo et al.[10] conducted a similar dose-response analyses and found that 1147

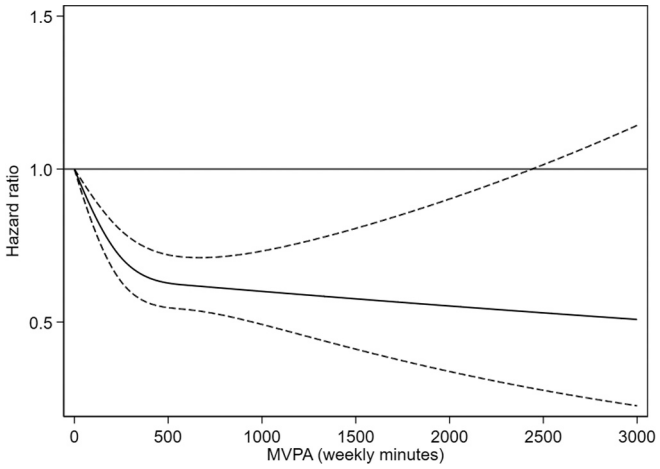

Fig. 1. Dose-Response Associations between Moderate to Vigorous Physical Activity (MVPA) and All-Cause Mortality. Fully adjusted model. Reference: 0 weekly minutes of MVPA. Dotted lines depict 95 %CIs.

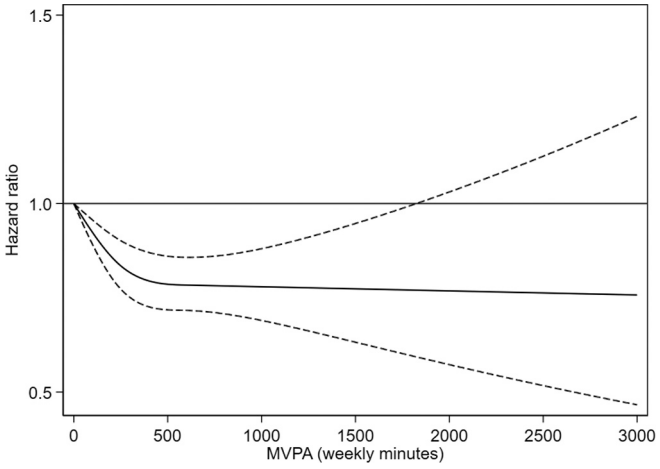

Fig. 2. Dose-Response Associations between Moderate to Vigorous Physical Activity (MVPA) and Cardiovascular Disease. Fully adjusted model. Reference: 0 weekly minutes of MVPA. Dotted lines depict 95 %CIs.

min/week were the maximal dose of MVPA for all-cause mortality reduction, while our maximum dose was 2415 min/week. Nevertheless, both of these upper thresholds are unrealistically high from a practical point of view in relation to public health guidelines. However, the aforementioned study included only individuals with hypertension, which likely explains the dose differences. Conversely, another study[6] involving over 25,000 adults aged 40 to 79 from UK, drawn from the EPIC-Norfolk study (European Prospective Investigation Into Cancer and Nutrition–Norfolk), failed in reporting an association between an accumulation of sedentary behavior and reduced physical activity with increased CVD incidence. Besides the fact that we did not analyze sedentary behavior, other divergences could potentially be attributed to a smaller sample size in comparison to our study, as well as the geographical specificity of the participants, who were drawn from a particular region of the UK. Additionally, it should be noted that participants used the accelerometer non-consecutively, removing it during sleep and aquatic activities, and they wore it on the hip, in contrast to the more common placement (wrist) used in most studies.

Considering studies focusing on non-European countries, the overall findings align with ours as well. For instance, a cohort study conducted in the US[23] using the National Health and Nutrition Examination Survey (NHANES), collected data from 3809 participants aged 40 years and

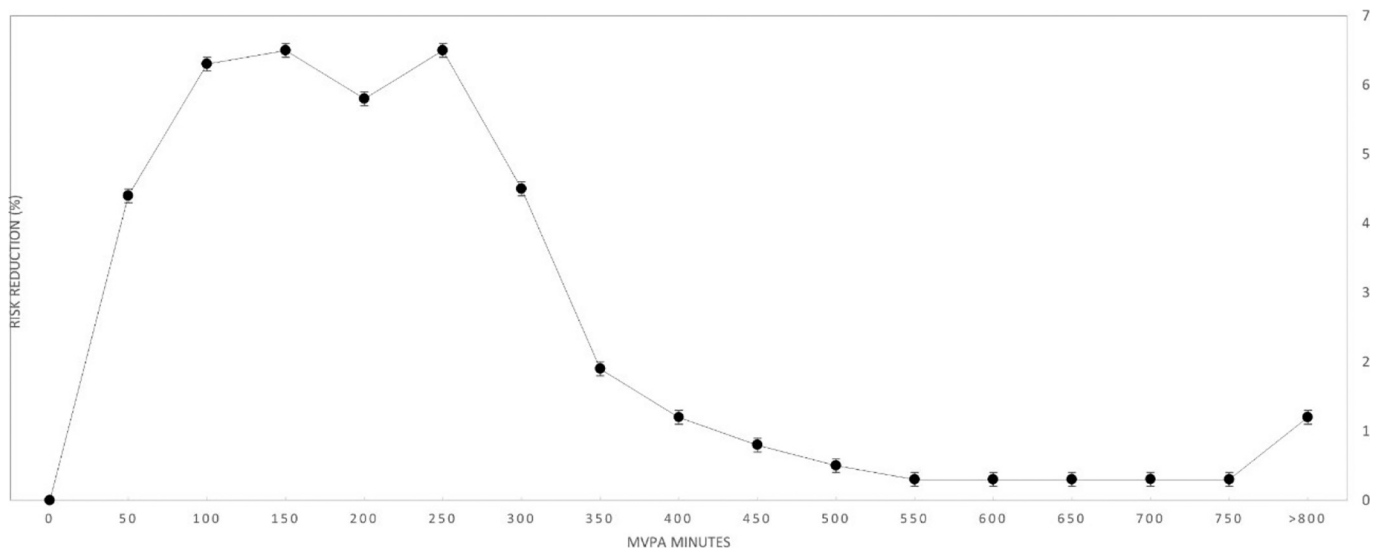

Fig. 3. Trends in Mean Risk Difference Rates for the Association between Moderate to Vigorous Physical Activity (MVPA) and All-Cause Mortality. Note: Error bars indicate Standard Deviation.

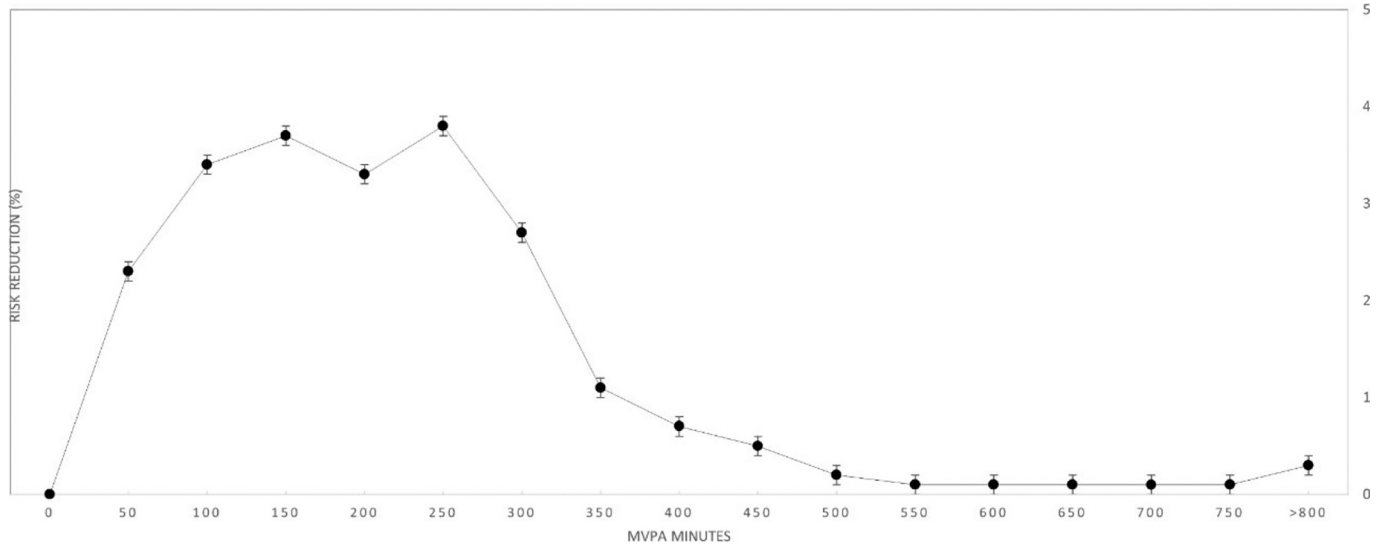

Fig. 4. Trends in Mean Risk Difference Rates for the Association between Moderate to Vigorous Physical Activity (MVPA) and Cardiovascular Disease Incidence. Note: Error bars indicate Standard Deviation.

found that accelerometer-measured MVPA was associated with reduced all-cause mortality and CVD incidence. In the same vein, the PURE (Prospective Urban Rural Epidemiologic) study,[24] which was conducted on four different continents and included participants aged 35 to 70 years from 17 countries, reported that higher levels of PA were associated with a lower risk of mortality and CVD events among individuals with low, medium, and high incomes. However, in this case, PA was assessed over a week using the International Physical Activity Questionnaire (IPAQ), which might introduce a range of self-report biases.

The current study represents, to date, the most comprehensive dose-response analysis pinpointing the specific minimum and optimal amounts of physical activity to mitigate the risk of mortality and CVD. Notably, a novel finding of this research reveals a significant risk reduction associated with physical activity levels as modest as 10–15 min per week, which would facilitate its practical application and reaffirm the message from the World Health Organization (WHO) that some physical activity is better than none.[21] In this sense, a previous meta-analysis reported the maximal risk reduction for all-cause mortality at about 24 min/day MVPA, congruent with the recommended level of physical activity for Americans.[25] Somewhat similar, we found that a range between 100 and 250 min of weekly MVPA, corresponding to 14 to 36 min/day, had the most pronounced mean risk reduction rates for mortality and CVD. Beyond this threshold, a reduction in the magnitude of risk is observed albeit less pronounced. In this vein, a previous study[9] reported greater, albeit less pronounced, reduction in mortality of 22 min/day or more of PA compared with 10 min/day. Interestingly, with only 100 min per week of MVPA, we found substantial risk reduction rates, which could be a relatively easy and appropriate initial target for inactive individuals, for example, as an active break during the workday.[26] Public health preventive strategies should encourage the attainment of 250 weekly minutes of MVPA when possible (which represents more than the recommended amount of moderate PA by the WHO[21]), since these thresholds provide further benefit. However, public health organizations should make it clear that the more MVPA, the better the risk reduction.

Limitations

This study should be interpreted in the light of several limitations. First, individuals may have modified their behavior during the period wearing accelerometers, which will lead to more conservative estimates and wider confidence intervals. Second, even though optimal MVPA thresholds using accelerometers are unclear,[27] our findings were consistent when using different thresholds below and well above current MVPA recommendations. Third, since the UK Biobank is not a representative sample of the UK adult population, generalizations over other populations should be cautiously made. Forth, the vast majority of the information on the covariates used was collected several years prior to accelerometry, which may lead to certain degree of misclassification bias. Fifth, MVPA measured through accelerometry does not account for stationary exercise such as strength training, yoga or similar, which may lead to underestimation of the actual amount of MVPA. Finally, we did not assess cardiorespiratory fitness, which may be an even more potent predictor of prognosis than PA.[28–33]

Conclusions

Significant but small, risk reductions in all-cause mortality and CVD incidence can be achieved with as little as 10 and 15 min of MVPA per week, respectively. However, public health organizations should promote the attainment of 250 min of MVPA per week (with 100 min as a possible first target for inactive individuals), as this threshold is associated with the greatest efficiency. Beyond that, less pronounced risk reductions can be achieved by accumulating additional MVPA, with hardly any additional benefits beyond 500 weekly minutes.

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CRediT authorship contribution statement

Ana Polo-López: Writing – original draft, Methodology, Conceptualization. **Joaquín Calatayud:** Writing – review & editing, Methodology, Conceptualization, Supervision. **Rodrigo Núñez-Cortés:** Methodology, Writing – review & editing. **Lars Louis Andersen:** Methodology, Writing – review & editing. **Laura López-Bueno:** Methodology, Writing – review & editing. **Rubén López-Bueno:** Conceptualization, Methodology, Formal analysis, Writing – review & editing.

Declaration of competing interest

All authors declare that they have no conflict of interest.

Data availability

Research was conducted using the UK Biobank Resource. The UK Biobank resource can be accessed by researchers on application.

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