The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries

the PURE study

The effect of physical activity on mortality and cardiovascular disease in 130,000 people from 17 high, middle and low income countries

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ABSTRACT

Background: It is not known whether the protective effects of physical activity (PA) on cardiovascular disease (CVD) reported in high income countries (mainly recreational PA) is also observed in lower income countries (mainly non-recreational PA). We examined whether different levels and types of PA are associated with lower mortality and cardiovascular disease (CVD) in countries at different economic levels.

Methods: In this prospective cohort study total PA was assessed using the International Physical Activity Questionnaire in 130 843 participants from 17 countries. Mortality and CVD were recorded during 6·9 years of follow-up. The effects of PA were adjusted for socio-demographic factors and other risk factors taking into account household, community and country clustering.

Findings: Compared to low PA levels (<600 METS per week or <150 minutes/week of moderate intensity PA), moderate (600 to 3000 or 150 to 750 minutes/week) and high PA levels (>3000 or >750 minutes/week) were associated with a graded reductions in mortality (hazard ratios =0·80 [0·74, 0·87] and 0·65 [0·60, 0·71], p<0·0001 for trend), and major CVD (myocardial infarction, stroke and heart failure; (0·86 [0·78, 0·93], p<0·001 for trend). Increasing PA was associated with lower risk of CVD and mortality in high, middle and low income countries. The adjusted population attributable fraction for not meeting the PA guidelines was 8·0% and 4·6%, and not meeting high PA levels was 13·0% and 9·5% for mortality and major CVD, respectively. Both recreational and non-recreational PA were associated with benefits.

Interpretation: Increasing recreational and non-recreational PA are associated with a lower risk of mortality and CVD events in low, middle and high income countries. Enhancing PA is a

simple, widely applicable, low cost global strategy which could avoid about 10% of deaths and CVD in middle age.

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KEY WORDS: physical activity, cardiovascular disease, global health, all-cause mortality

Cardiovascular disease (CVD) is the leading cause of death worldwide[1] and a major economic global burden.[2] Despite reductions in CVD mortality in high income countries (HIC), global CVD mortality increased by 41% between 1990 and 2013; largely driven by rises in low and lower-middle-income countries.[3] Indeed, 70% of global CVD deaths come from low and middle income countries where it is the largest cause of death.[4,5] It has been estimated that 23% of the world's population was insufficiently active[6] and the WHO has recommended a decrease in insufficient PA of 10% by 2020.[7]

Numerous studies from HIC have reported significant inverse associations of PA with mortality and CVD morbidity.[8] but such data from low and middle income countries are sparse and limited to a few small studies.[9-11] In addition, studies of PA have focused primarily on recreational PA (which is more common in HIC but less common in poorer countries),[8,11] with less evidence on the benefits of other forms of PA such as during transportation,[12] house work and occupational PA.[13]

In the Prospective Urban Rural Epidemiologic (PURE) study being conducted in 17 high, middle and low income countries, we examined whether PA is associated with lower risk of mortality and CVD in countries at varying economic levels and whether these associations differ by type of PA.

METHODS

The PURE study includes participants from three HICs (Canada, Sweden, United Arab Emirates); seven upper middle income countries ([UMIC] Argentina, Brazil, Chile, Poland, Turkey, Malaysia, South Africa); three lower middle income countries ([LMIC] China, Colombia, Iran); and four low income countries ([LIC] Bangladesh, India, Pakistan, Zimbabwe).[14] Country economic level was based on World Bank classifications in 2006. The choice and number of countries selected in PURE reflects a balance between involving a large number of communities in countries at different economic levels with substantial heterogeneity in social and economic circumstances versus the feasibility of centres to successfully achieve long-term follow-up.

Within each country, urban and rural areas in and around selected cities and towns were identified to reflect the geographical diversity of the countries. Communities were defined based on the geographical clustering of common characteristics (sharing culture [as people of a similar culture reside in close geographic proximity], socioeconomic status, and use of amenities, goods, and services) such as through a set of contiguous postal code areas or group of streets or a small village. The number of communities selected in each country varied. In some countries (eg, India, China, Canada, and Colombia), communities from several states/provinces were included to capture diversity, socioeconomic status, culture, and environments. In other countries (eg, Iran, Poland, Sweden, and Zimbabwe), fewer communities were selected. This strategy facilitated recruitment of individuals from different economic, cultural and geographical settings (rural and urban) around the globe.

Within each defined community, households were approached and individuals between 35 and 70 years of age who intended to live at their current address for at least another four years were invited to participate in the study. The method of approaching households differed between countries based on feasibility but was consistent across sites within each country. For example, in rural areas of India and China, a community announcement was made to the village through contact of a community leader, followed by in-person door-to-door visits of all households. In contrast in Canada, initial contact was by mail followed by telephone invitations to attend a central clinic. For each household at least three attempts at contact were made. All eligible residents of the household were invited and those who provided informed consent were recruited. Household participation rate was 86%. Recruitment started in a vanguard phase in Karnataka, India in January 2003; however most communities recruited between January 2005 and December 2010. See Supplementary Appendix provides more detail on sampling. The study was approved by local institutional research ethics boards.

Socio-demographic factors, medical history, lifestyle behaviours and risk factors were recorded using standardized measures and procedures.[11] One-week total PA was assessed using the long-form International Physical Activity Questionnaire (IPAQ)[15] and calculated as a total of occupation, transportation, housework and recreational activity reported in metabolic equivalents (MET) * minutes/ week. Physical activity is also reported in minutes/week of moderate intensity PA using the equation where minutes reported in each PA domain on the IPAQ by the participant are weighted relative to moderate intensity PA:

Minutes/week = 0.825*walking minutes + 1*moderate minutes + 1.375*garden minutes + 1.5*cycling minutes + 2*vigorous minutes

Total PA was categorized as low (<600 MET*minute/week), moderate (600-3000 MET*minute/week) and high (≥3000 MET*minute/week) PA levels, which corresponds to <150 minutes/week, 150-750 minutes/week and ≥750 minutes per week of moderate intensity PA.

Physical activity was also dichotomized as meeting or not meeting current PA guidelines (meeting guideline is PA ≥600MET*minute/week as per the IPAQ[15] or PA ≥150 minutes/week of moderate intensity PA as per the WHO[16]) with periods of less than 10 minutes of PA not included as per the IPAQ guidelines.[15 16]We also further categorized the high PA category into a lower-high PA level and an upper-high PA level by the median value of the high PA category of 6453 MET*minutes/week to investigate whether the effect of very high PA levels was graded. PA was categorized into recreational PA and non-recreational PA (occupational, transportation and housework).

The clinical outcomes of interest during follow-up were: mortality plus major CVD (CVD mortality plus incident MI, stroke, and heart failure), either as a composite or separately (Supplementary Appendix). In most low and middle income countries there was no central system of death or event registration. We therefore obtained information on prior medical illness and medically certified cause of death where available, and recorded best available information from close family or friends in order to arrive at a probable diagnosis or cause of death. Death certificates (available in 100% of deaths), medical records (MI: 49.4%, stroke 80.8% and heart failure: 76.2%), household interviews and other sources of information was used. We also used Verbal Autopsies to ascertain cause of death in addition to medical records which were reviewed by a health professional.[17] To ensure a standard approach and accuracy for classification of events across all countries and over time, a selection of cases from each country annually was adjudicated both locally and also by the adjudication chair, and if necessary further training was provided.

Statistical analyses

The primary analyses were conducted excluding participants who reported having CVD at baseline. Baseline characteristics were described for the entire cohort and stratified by low, moderate, and high level of total PA. Total and domain specific PA values were not normally distributed and are presented as median and inter-quartile range (IQR).[18] Kruskal-Wallis test and Jonckheere -Terpstra test[19,20] were used to test the heterogeneity and trend across the four country income levels (HIC, UMIC, LMIC, or LIC), respectively. For the two categorical PA variables: level of total PA and whether meeting PA guideline, we calculated frequencies and compared their difference and trend across the country income levels using Chi-square test and Cochrane-Armitage test,[21,22] as appropriate.

Age-sex-standardized incidence rates for all outcomes were calculated for levels of total PA and whether meeting PA guidelines.[23] To examine the association between PA variables and outcomes, we used the marginal Cox proportional hazard model .[24,25] Models were adjusted for age, sex, education, country income level, residency (urban vs. rural), family history of CVD and smoking status (current and ever smoker vs. never smoker- cigarette, cigar and pipe smoking) taking into account three levels of clustering. We conducted further analyses using wealth index and household income (in separate models) in place of education but these did not change the results. In addition, we further adjusted for body mass index (BMI).

Adjusted population attributable fractions related to not meeting PA guidelines and not achieving high PA levels were calculated to quantify the benefit of PA, using the method developed by Chen et al.[26] To minimize the potential for reverse causation, we conducted sensitivity analyses by excluding participants who experienced CVD events in the first two years of follow-up. Additional analyses were also conducted including PURE participants who had CVD at baseline (n=141 945) and these yielded similar results. We estimated the effect of total PA on the outcomes by country income level, sex, age (<50 or ≥50 years), BMI (<25 kg/m^2 or ≥25 kg/m^2), waist-hip-ratio (above 0·85 for female, 0·90 for male), and smoking, hypertension, and diabetes.

To assess and compare the effect of recreational PA vs. non-recreation PA, we fitted the adjusted marginal Cox model with restricted cubic spline with four knots at the 5th, 35th, 65th and 95th percentiles for overall and non-recreational PA.[27] Because 55% participants had no recreational PA, we chose 50th, 65th, 80th and 95th percentile as the knots. We also examined whether the association between PA and outcomes varied by country income and by type of PA (total, recreational or non-recreational) using tests of interaction to compare the effects between HIC and UMIC vs LMIC and LIC. All analyses were conducted using SAS 9.4, for UNIX operating system (SAS Institute, Cary, US) and R software, version 3.2.5, for Windows system.

RESULTS

A total of 168 916 participants were enrolled, of whom 141 945 had completed the IPAQ and the analyses were limited to the 130 843 participants without pre-existing CVD. Table 1 presents participant characteristics stratified by low, moderate, and high PA levels. Participant characteristics were not materially different in most features across the three groups with the exception of a lower proportion of males in the moderate PA group compared to the others and a greater proportion of family history of CVD in the high PA group. The prevalence of hypertension and diabetes were lower with higher PA. There was no association between diet score or body mass index with PA levels.

Table 2 presents PA by country income levels in both MET*minutes/week and minutes/week of moderate intensity PA. There was a trend towards lower total PA and recreational PA from HIC to LIC (p<0.0001 for both), but not for non-recreational PA. A large majority of participants met the PA guidelines, but fewer than half of the participants reached high levels of PA.

During the mean follow-up of 6·9 ± 3·0 years there were 5334 deaths,1294 CVD deaths and 4040 non-CVD deaths, 1987 individuals with incident MI, 2086 with incident stroke, and 386 with new heart failure (Supplemental Table 1). When stratified by PA level, there was a graded reduction in age and sex adjusted event rates for all outcomes from low to moderate to high PA (p<0·0001 for trend for all events except for stroke (p=0·0010)) except heart failure (Table 3). Those meeting the guidelines for minimal PA had lower age and sex adjusted rates of all outcomes (Table 3).

Participating in PA at or above the PA guidelines was associated with significant lower rates of outcomes compared to those participants not meeting the PA guidelines ≥600 MET*minute/week as per the IPAQ[15] or PA ≥150 minutes/week of moderate intensity PA as per the WHO[16]). In fully adjusted models, meeting PA guidelines was associated with hazard ratios (HR) [95% confidence interval] of 0·78 [0·74, 0·83] for mortality plus major CVD, 0·72 [0·67, 0·77] for mortality and 0·80 [0·74, 0·86] for major CVD (p<0·0001 for all).

In fully adjusted models increasing levels of PA (moderate and high) were associated with lower HR for mortality plus major CVD, mortality and major CVD compared to those with low levels of total PA ($p<0\cdot0001$ $p<0\cdot0001$ and $p=0\cdot0005$ for trend, respectively; Figure 1). When adjusted for either wealth index or household income in place of education, HR did not change (Supplemental Tables 2 and 3). In addition, high PA was associated with a lower HR compared to moderate PA for all outcomes. Dichotomizing high PA levels above or below the median value in this group off 6453 MET*minutes/week did not show further reductions in risk (Supplemental Table 4). Increasing PA was also associated with lower HR in CVD mortality, non-CVD mortality and MI (Supplemental Table 5). With further adjustment for BMI, the HR were slightly attenuated but remained significant (Supplemental Table 6). Excluding participants who had a CVD event within the first two years of follow-up (to account for potential reverse causality if sick individuals were less active), the results were consistent for all outcomes (Supplemental Table 7).

Survival curves (Supplemental Figure 1) for low, moderate, and high PA levels for our three primary outcomes of mortality plus major CVD, mortality and major CVD indicated a lower risk as PA increased ($p<0\cdot0001$).

The five-year adjusted population attributable fraction of not meeting the PA guidelines was 5·3%, 8·0% and 4·6% for mortality plus major CVD, mortality and major CVD, respectively (Supplemental Figure 2). These values were higher (10·3%, 13·0% and 9·5%, respectively), for not achieving high PA.

Increasing PA was associated with lower risk mortality in a range of subgroups (Figure 2). Compared to low levels of PA, moderate and high levels of PA were associated with a lower graded risk for mortality regardless of sex, age, and in the presence of risk factors.

Increasing PA was associated with significantly lower risk up to approximately 3000 MET*minutes/week (or 750 minutes/week of moderate intensity PA) with more modest benefits above that PA level ($p<0\cdot0001$). (Figure 3). For recreational PA, increasing PA was associated with significantly lower risk up to approximately 600 MET*minutes/week (or 150 minutes/week of moderate intensity PA) ($p=0\cdot01$) (as few had levels of PA higher than this), while for non-recreational PA, increasing PA was associated with significantly lower risk up to approximately 5000 MET*minutes/week (or 1250 minutes/week of moderate intensity PA) with more modest benefits above that PA level ($p<0\cdot0001$).

Increasing PA was associated with significantly lower risk for mortality plus major CVD in UMIC and LIC, mortality in UMIC, LMIC and LIC and major CVD in UMIC and LIC (Table 4). When stratified by country income level (HIC + UMIC versus LMIC + LIC) there was a significant interaction between country income level and PA levels for total ($p=0\cdot0012$) and recreational PA ($p=0\cdot0063$) such that the HIC + UMIC had a lower risk with increasing PA level (Figure 4). This was less clear for non-recreational PA ($p=0\cdot063$).

DISCUSSION

In this study involving 3 HIC, 7 UMIC, 3 LMIC, and 4 LIC countries, increasing PA was associated with a lower risk for mortality and incidence of major CVD. This lower risk was present even at moderate levels of PA compared to low levels of PA, and was more marked at higher PA levels . The benefit of PA was present independent of the type of PA (recreational or non-recreational), a range of socio-economic and CVD risk factors, and was similar in various countries with differing income levels.

In our study population of predominantly non-HIC residing participants, meeting the PA guidelines (150 minutes/week of moderate intensity of PA) was associated with a 22%, 28%, and 20% lower risk for all-cause mortality plus major CVD, mortality and major CVD, respectively, resulting in adjusted population attributable fractions of 5·3%, 8·0% and 4·6%, respectively. These attributable fractions are similar to those reported by Lee et al.; 9·4% for mortality and 5·8% for CVD in HIC.[9] In addition, we observed a graded effect such that participants at higher levels of PA had a lower risk than those participants engaging in moderate levels of PA. For example, compared to people at moderate levels of PA, participating in high levels of PA conferred an additional reduction in risk of 15%, 19% and 12% for mortality plus major CVD, mortality and major CVD, respectively. This benefit plateaued only at very high levels of PA (approximately 1250 minutes/week of moderate intensity of PA). Similar to previous studies of recreational PA in HIC,[28,29] we did not observe any adverse efforts of PA on our outcomes even in the approximately 9000 participants who reported over 2500 minutes/week of moderate intensity of PA (equivalent to 17 times that of the PA guidelines). Therefore while participating at even low levels of PA confers benefit (30 minutes per day for five days a week), the benefit continues to increase up to high levels of total PA. Given these findings and that the affordability of other CVD interventions such as consuming fruits and vegetables,[30] and taking generic CVD drugs is beyond the reach of many people in low and middle income countries,[31] participating in PA represents a low cost approach to CVD prevention .

When stratified by country income level there was a consistent reduction of risk with increasing PA. For HIC, meeting the PA guidelines was associated with a 30% lower risk for mortality, which is lower than the 11% reported in a meta-analysis of walking from a study conducted predominantly in HIC.[12] However, this earlier study did not include participants in the high PA level of >3000 MET*minutes/week as ours did in which we found a continued benefit with increasing PA levels. Studies in Iran and China also reported PA to be significantly associated with lower mortality in a dose-dependent manner.[32,33] Notably, Matthew et al. reported a HR of 0.61 [0.51-0.73] at the highest levels of PA of the Chinese women, which is similar to our HR of 0.65 [0.60, 0.71]. These findings are consistent with what we found in the LMIC category of countries of which Iran and China accounted for the overwhelming majority of participants in our LMIC group.

Increasing PA levels, was associated with a lower risk of mortality plus major CVD in higher and UMIC compared to lower middle and LIC for both total and recreational PA; there were less clear differences with respect to non-recreational PA. It is unclear why recreational PA may be less effective in the lower middle and LIC, however, very few participants from the countries participated in any recreational PA and so these findings may be swayed by a very small number of participants who are atypical of the general populations in poorer countries.

Few studies have assessed the association of non-recreational PA with outcomes. The available studies are relatively small and report inconsistent results.[12,34-38] We found that increasing levels of both recreational PA and non-recreational PA were independently associated with lower risk with our composite of all-cause mortality plus major CVD, indicating that PA of any type is beneficial. Of note, high levels of PA was only possible in those individuals participating in non-recreational PA. Indeed, only 2.9% of our study population participated in high level of PA (≥3000 MET*minutes per week or ≥750 minutes/week of moderate intensity of PA) derived exclusively from recreational PA compared to 37.9% of participants who attained this level through non-recreational PA. This reflects the challenges inherent with participating in high levels of recreational PA in that it is, by definition, conducted during discretionary hours of the day outside of occupational and domestic duties. In contrast, incorporating PA into one's daily lifestyle whether through active transportation, occupation and/or domestic duties has the potential to achieve higher levels of PA that are associated with even lower risk for mortality and CVD events.

To address concerns related to "reverse causality", we excluded those with known CVD and then conducted a sensitivity analysis further excluding those who had events within the first two years of follow-up. Our results were unchanged for our main study outcomes. In addition, we also conducted subgroup analyses stratified by sex, age, body mass index, smoking, presence of hypertension and presence of diabetes and observed consistent results. We also observed that increasing PA was associated with reduced CVD and non-CVD mortality. Regular PA has been reported to be associated with lower mortality from certain cancers[28,34,36,39] and respiratory conditions.[40] With continued follow-up, we anticipate accruing enough events to reliably investigate the effects of PA on specific categories of non-CVD mortality.

Limitations

While PA determined from the self-reported IPAQ has been found to modestly overestimate PA, it demonstrates good reliability and moderate validity compared to accelerometers such that higher IPAQ values correspond to higher levels of PA measured by accelerometers, thus providing good internal validity.[15,41,42] If PA is overestimated by the IPAQ, then the potential benefits of PA may be more marked and may occur at lower PA levels than reported here. In addition, the IPAQ has been tested across a range of countries similar to the PURE study[15] and the use of self-reported measures for assessing PA in large studies is considered acceptable in low resource settings.[43]

While it was not feasible to collect a proportionate sampling of the globe's population, our selection of countries and communities ensured that our population was typical of the regions from which participants were recruited with only modest differences compared to national data (Supplementary Appendix for comparative data).[44]Although we did not recruit a random sample of individuals, our approach minimized biases in selection of individuals once the communities were identified. Given the range of countries across five continents at different economic levels the large number of communities, and the large size of our study, our results are globally applicable. Given our method of event ascertainment, it is possible that some events may have been misclassified. However, we believe this to be of very limited numbers as the majority of events were ascertained using supporting documents, standardized definitions and adjudication using standardized definitions providing a high level of confidence in the validity. Lastly, in such a large study, it is not uncommon to report low p values that may not be clinically relevant, therefore p values should be interpreted with caution unless they are extreme ($p<0.001$). Given the magnitude and consistency of the effects observed across the different analyses, we can be confident in our main findings.

Conclusions

Our findings demonstrate that PA (both recreational and non-recreational) is associated with a lower risk for mortality and major CVD events., which was independent of the type of PA, other risk factors and seen in all major regions of the world and various country economic levels. In particular we demonstrate that increasing PA is associated with lower risk in LMIC and LIC for which limited data existed previously. . Even meeting the minimal PA guidelines such as walking for as little as 30 minutes on most days of the week had a substantial benefit, while higher levels of PA (up to and beyond 17 times the recommended PA guidelines) were associated with even lower risks. . As participating in PA (especially in daily life) is inexpensive, PA is a low cost approach to reducing deaths and CVD that is applicable globally with potential large impact. The results of our study provide robust evidence to support public health interventions to increase all forms of PA levels in countries of different socioeconomic circumstances.[45]

Table 1: Participant characteristics stratified by levels of total physical activity (data presented as means ± SD or counts and percentage).

	Overall (n = 130 843)	Low Physical Activity (n = 23 631)	Moderate Physical Activity (n = 49 348)	High Physical Activity (n = 57 864)
Age (years)	50·2 ± 9·7	51·0 ± 10·1	50·5 ± 9·7	49·7 ± 9·5
Male	54 621 (41·7%)	11 080 (46·9%)	18 224 (36·9%)	25 317 (43·8%)
Urban resident	69 993 (53·5%)	12 983 (54·9%)	28 525 (57·8%)	28 485 (49·2%)
Country Income Level				
High	13 546 (10·4%)	1435 (6·1%)	4991 (10·1%)	7120 (12·3%)
Upper Middle	34 625 (26·5%)	7479 (31·6%)	11 922 (24·2%)	15 224 (26·3%)
Lower Middle	53 841 (41·1%)	8620 (36·5%)	22 648 (45·9%)	22 573 (39·0%)
Low	28 831 (22·0%)	6097 (25·8%)	9787 (19·8%)	12 898 (22·4%)
Education				
None, Primary or Unknown	54 635 (41·9%)	10 642 (45·2%)	19 085 (38·8%)	24 908 (43·1%)
Secondary	50 500 (38·7%)	9035 (38·3%)	19 746 (40·1%)	21 719 (37·6%)
Trade, College or University	25 396 (19·5%)	3885 (16·5%)	10 412 (21·1%)	11 099 (19·2%)
Family History of Heart Disease or Stroke	36 812 (31·3%)	4911 (23·5%)	13 605 (30·5%)	18 296 (35·0%)
Hypertension	47 752 (39·0%)	9053 (42·6%)	18 364 (39·7%)	20 335 (36·9%)
Diabetes	12 740 (9·7%)	2898 (12·3%)	5102 (10·3%)	4740 (8·2%)
Smoker (current and former)	40 955 (31·5%)	7093 (30·3%)	13 695 (28·0%)	20 167 (35·0%)
Alternate Healthy Eating Index score	35.1 ±8.0	34.9 ±7.6	35.5 ±7.9	34.8 ±8.3
Body Mass Index (kg/m^2)	25·7 ±5·1	25·9 ±5·4	25·9 ±5·0	25·4 ±5·1

Low physical activity <600 MET*minute/week and <150 minutes/week of moderate intensity physical activity
Moderate physical activity 600-3000 MET*minute/week and 150-750 minutes/week of moderate intensity physical activity
High physical activity ≥3000 MET*minute/week and ≥750 minutes/week of moderate intensity physical activity
Column percentage presented for categorical variables.

Table 2: Physical activity by country income level).

	High Income Countries (n=13 546)	Upper Middle Income Countries (n=34 625)	Lower Middle Income Countries (n=53 841)	Low Income Countries (n= 28 831)	P value (for heterogeneity)	P value (for trend)
Total Physical Activity* MET*minutes/week Minutes/week	3227 [1485-6426] (807 [371-1607])	2436 [750-5979] (609 [188-1495])	2340 [960-5177] (585 [240-1294])	2520 [721-6442] (630 [180-1611])	<0·0001	<0·0001
Recreational Physical Activity* MET*minutes/week Minutes/week	518 [50-1386] (130 [12-347])	0 [0-320] (0 [0-80])	99 [0-693] (25 [0-173])	0 [0-0] (0 [0-0])	<0·0001	<0·0001
Non-Recreational Physical Activity* MET*minutes/week Minutes/week	2115 [806-4980] (529 [202-1245])	1983 [578-5400] (496 [144-1350])	1748 [693-4186] (437 [173-1047])	2297 [594-6222] (574 [149-1556])	<0·0001	0.7762
Low Physical Activity	1435 (10·6%)	7479 (21·6%)	8620 (16·0%)	6097 (21·1%)	<0·0001	
Moderate Physical Activity	4991 (36·8%)	11 922 (34·4%)	22 648 (42·1%)	9787 (33·9%)	.	
High Physical Activity	7120 (52·6%)	15 224 (44·0%)	22 573 (41·9%)	12 947 (44·9%)	.	
Meeting Physical Activity Guidelines †	12 111 (89·4%)	27 146 (78·4%)	45 221 (84·0%)	22 734 (78·9%)	<0·0001	<0·0001

* presented as median [inter-quartile range (IQR)] in MET*minutes/week and in minutes/week of moderate intensity physical activity
Low physical activity <600 MET*minute/week and <150 minutes/week of moderate intensity physical activity
Moderate physical activity 600-3000 MET*minute/week and 150-750 minutes/week of moderate intensity physical activity
High physical activity ≥3000 MET*minute/week and ≥750 minutes/week of moderate intensity physical activity
† meeting physical activity guidelines ≥600 MET*minute/week and ≥150 minutes/week of moderate intensity physical activity
P value for heterogeneity was calculated by Chisq test for categorical variable and Kruskal-Wallis for continuous variable. P value for trend was calculated by Cochrane-Armitage test for categorical variable and Jonckheere-Terpstra test for continuous variable.

Table 3: Summary of fatal and non-fatal events rates (per 1000 person years) and 95% CI stratified by different levels of physical activity, and those meeting, or not meeting, the recommended levels of physical activity.

	Mortality plus Major CVD^		Mortality		Major CVDˆ		CVD Mortality		Non-CVD Mortality		Myocardial Infarction		Stroke		Heart Failure	
	Events	Rate	Events	Rate	Events	Rate	Events	Rate	Events	Rate	Events	Rate	Events	Rate	Events	Rate
Low physical activity (n = 23 549)	1941	9·46 [8·99, 9·94]	1396	6·37 [5·99, 6·76]	1000	5·13 [4·78, 5·48]	377	1·75 [1·55, 1·94]	1019	4·63 [4·30, 4·96]	496	2·64 [2·39, 2·89]	427	2·09 [1·87, 2·31]	84	0·42 [0·32, 0·52]
Moderate physical activity (n = 49 245)	3002	7·14 [6·86, 7·43]	1881	4·25 [4·04, 4·47]	1682	4·13 [3·91, 4·34]	480	1·12 [1·01, 1·23]	1401	3·13 [2·95, 3·32]	730	1·86 [1·71, 2·00]	820	1·93 [1·79, 2·08]	144	0·34 [0·27, 0·40]
High physical activity (n = 57 725)	3233	6·60 [6·36, 6·84]	2057	4·11 [3·92, 4·30]	1718	3·53 [3·35, 3·70]	437	0·87 [0·78, 0·96]	1620	3·24 [3·07, 3·40]	761	1·58 [1·47, 1·70]	839	1·68 [1·56, 1·80]	158	0·30 [0·25, 0·36]
P value for trend		p<0·0001		p<0·0001		p<0·0001		p<0·0001		p<0·0001		p<0·0001		p=0·0010		p=0·0997
Not meeting guidelines (n=23 549)	1941	9·46 [8·99, 9·94]	1396	6·37 [5·99, 6·76]	1000	5·13 [4·78, 5·48]	377	1·75 [1·55, 1·94]	1019	4·63 [4·30, 4·96]	496	2·64 [2·39, 2·89]	427	2·09 [1·87, 2·31]	84	0·42 [0·32, 0·52]
Meeting guidelines (n=106 970)	6235	6·86 [6·68, 7·05]	3938	4·19 [4·05, 4·33]	3400	3·80 [3·66, 3·94]	917	0·98 [0·92, 1·05]	3021	3·21 [3·08, 3·33]	1491	1·71 [1·62, 1·81]	1659	1·79 [1·70, 1·88]	302	0·32 [0·28, 0·35]
P value for trend		p<0·0001		p<0·0001		p<0·0001		p<0·0001		p<0·0001		p<0·0001		p=0·0088		p=0·0376

Event rates are standardized for age and sex.

Low physical activity <600 MET*minutes/week; moderate physical activity 600-3000 MET*minutes/week; high physical activity ≥3000 MET*minutes/week

CVD = cardiovascular disease

ˆMajor CVD = CVD mortality plus incident myocardial infarction, stroke, and heart failure

A maximum of one event per participant is tabulated for each outcome.

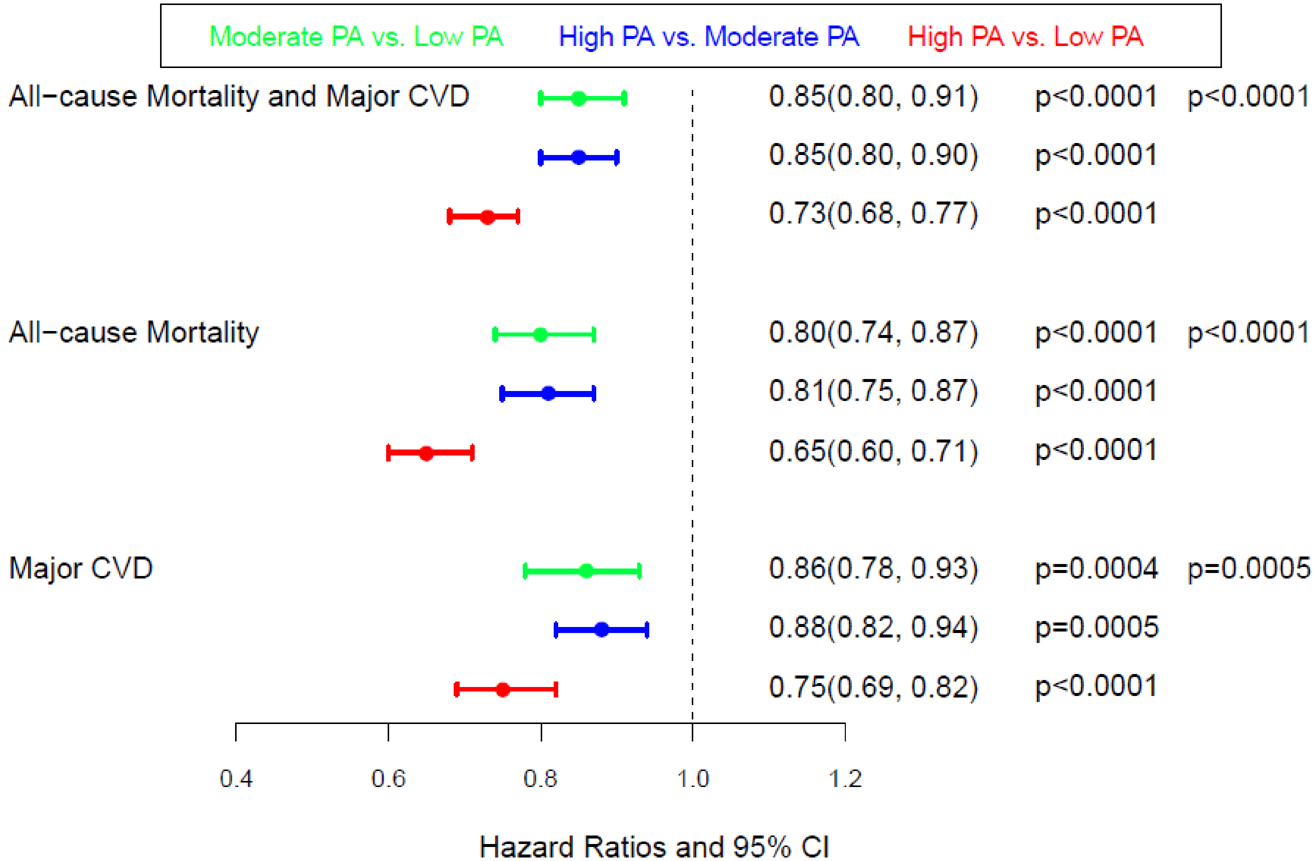


Figure 1: Hazard ratios and 95% CI for the pairwise comparison between levels of total physical activity, adjusted for age, sex, education, country income level, urban/rural residency, family history of CVD and smoking status taking into account household, community and country clustering. There were 3155, 2041 and 1723 events for all-cause mortality and major CVD, all-cause mortality, and major CVD, respectively.

Low physical activity level <600 MET*minute/week; moderate physical activity 600-3000 MET*minute/week; high physical activity ≥3000 MET*minute/week

CVD = cardiovascular disease

ˆMajor CVD = CVD mortality plus incident MI, stroke, and heart failure. The p values of the first column show the significance of each comparison. P-values of the second column show the significance of the overall effect of PA level.

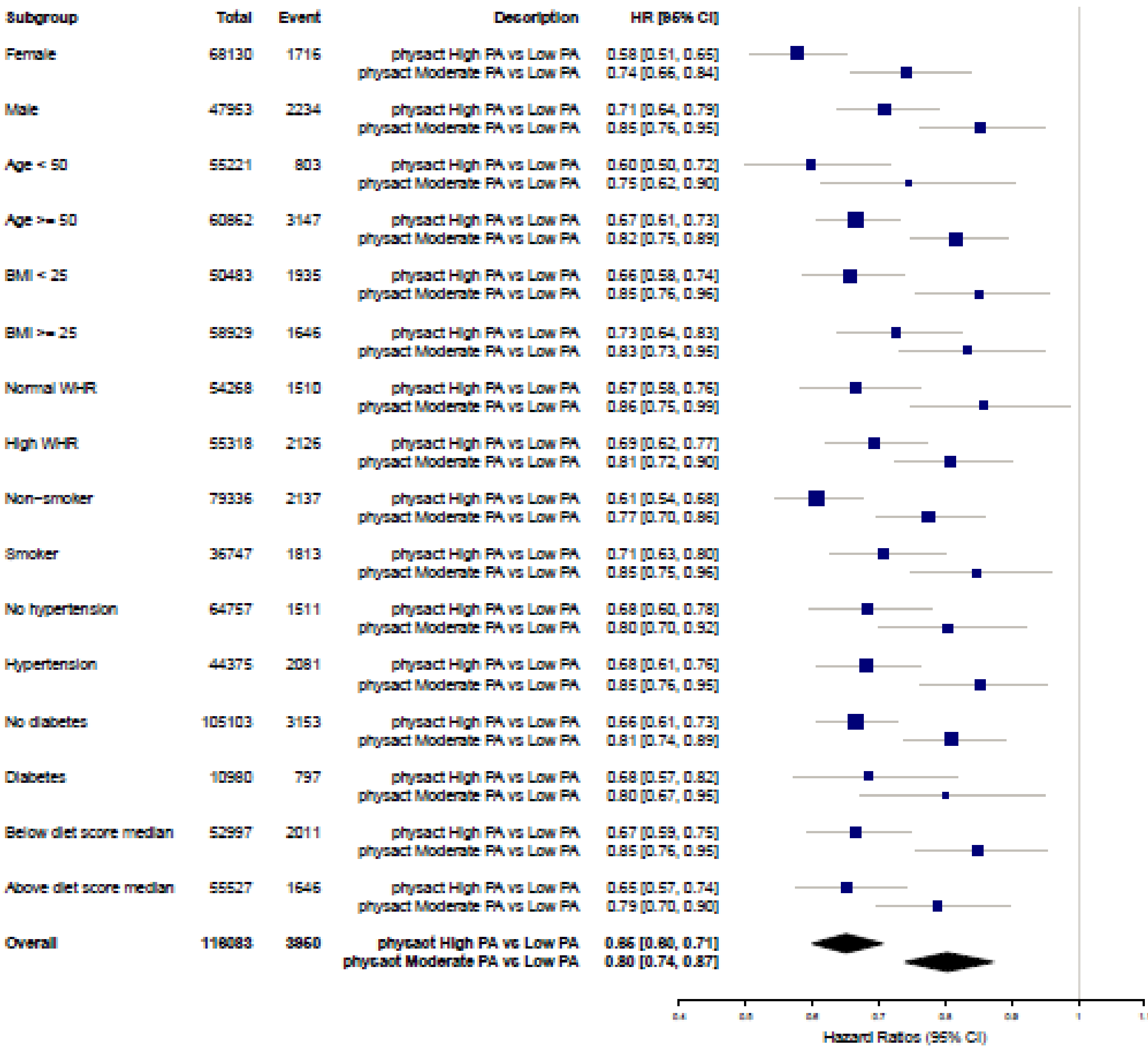


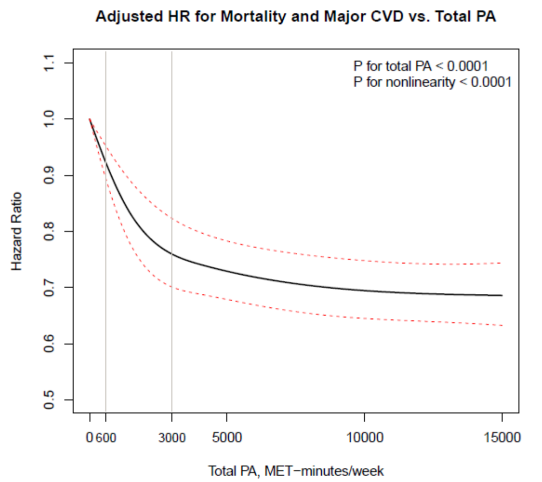
Figure 2: Hazard ratios and 95% CI of level of total physical activity for mortality (adjusted for age, sex, education, country income level, urban/rural residency, family history of cardiovascular disease and smoking status taking into account household, community and country clustering). Based on data for 115 436 participants with complete data.

Note: Low physical activity level (<600 MET*minute/week) is the reference group.

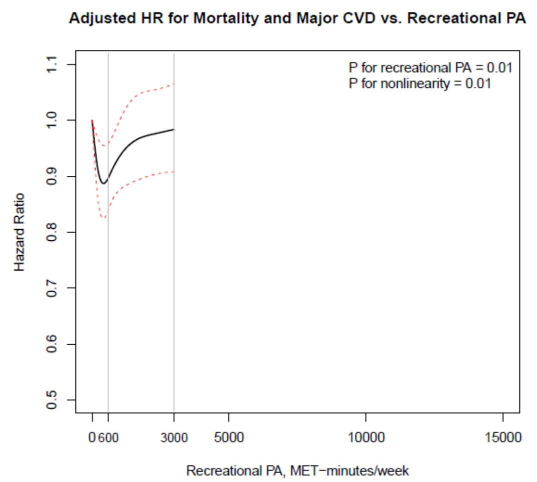
Moderate physical activity 600-3000 MET*minute/week; high physical activity ≥3000 MET*minute/week

BMI = body mass index; WHR = waist to hip ratio (high WHR was defined as above 0.85 for female and above 0.9 for male)

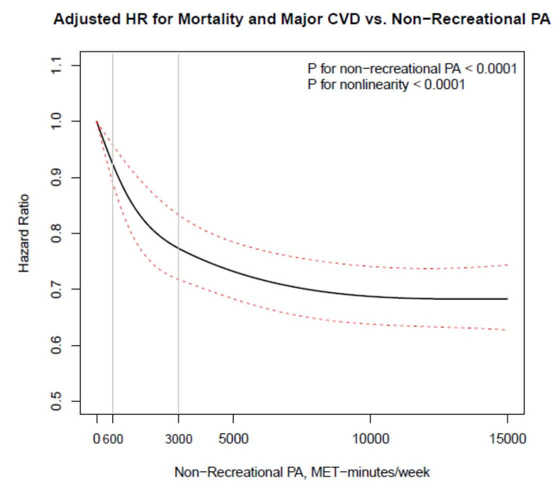
Relationship between PA Type with Mortality and Major CVD expressed MET*min/week



Interval	[0, 600)	[600,3000]	(3000,5000]	(5000,10000]	(10000,15000]	>15000
Total	21690	46409	18781	20801	8566	6420
# of event	1941	3007	1028	1247	507	446

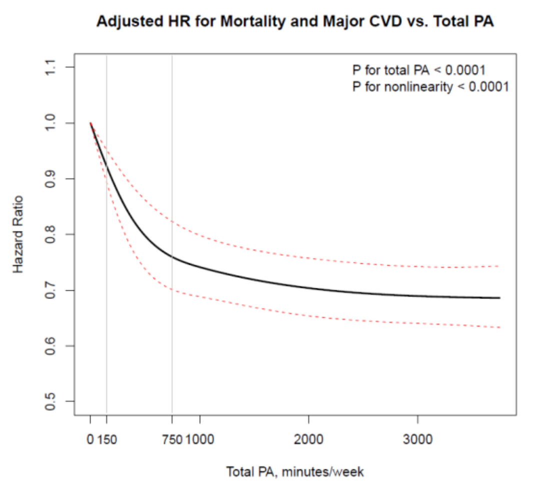


Interval	[0, 600)	[600,3000]	>3000
Total	94893	24177	3597
# of event	6647	1342	187

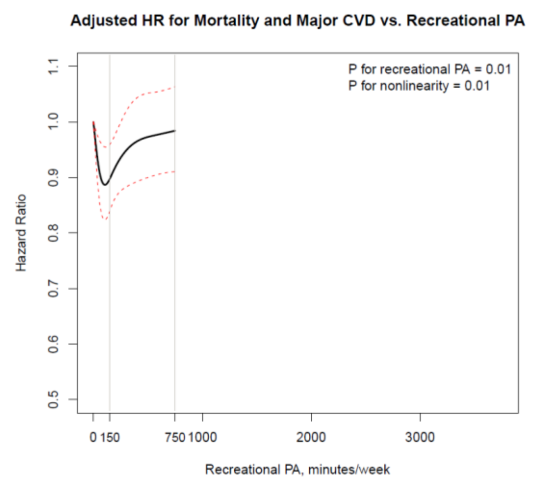


Interval	[0, 600)	[600,3000]	(3000,5000]	(5000,10000]	(10000,15000]	>15000
Total	27968	47964	15571	17547	7597	6020
# of event	2384	2964	873	1077	459	419

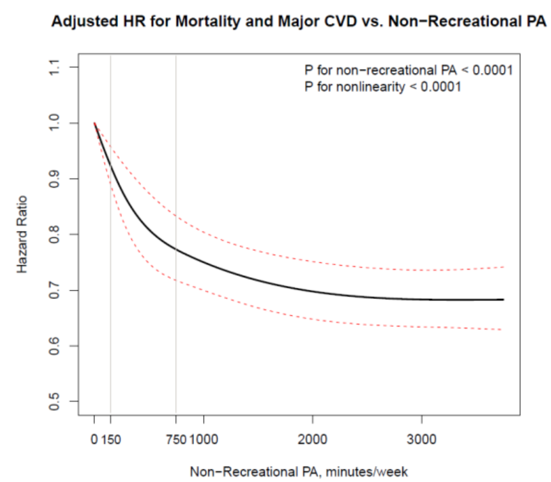
Relationship between PA Type with Mortality and Major CVD expressed min/week of Moderate Intensity PA



Interval	[0, 150)	[150,750]	(750,1250]	(1250,2500]	(2500,3750]	>3750
Total	21690	46409	18781	20801	8566	6420
# of event	1941	3007	1028	1247	507	446



Interval	[0, 150)	[150,750]	>750
Total	94893	24177	3597
# of event	6647	1342	187



Interval	[0, 150)	[150,750]	(750,1250]	(1250,2500]	(2500,3750]	>3750
Total	27968	47964	15571	17547	7597	6020
# of event	2384	2964	873	1077	459	419

Figure 3: Relationship between increasing total physical activity (PA; left panels), recreational PA (middle panels) and non-recreational PA (occupational, transportation and housework PA; right panels) with mortality and major cardiovascular disease (CVD) presented in MET*minutes/week (top panels) and minutes/week of moderate intensity PA (bottom panels). Models were adjusted for age, sex, education, country income level, urban/rural residency, family history of CVD and smoking status, taking into account household, community and country clustering. Recreational PA was truncated at 3000 MET*minutes/week and 750 minutes/week of moderate intensity PA due to sparse observation above that level.

ˆMajor CVD = CVD mortality plus incident MI, stroke, and heart failure

HR = hazard ratio

Table 4. Summary of risk (hazards ratio) of mortality and major CVD events stratified by country income level and physical activity levels.

		Mortality plus Major CVD^	Mortality	Major CVDˆ
High Income Countries	Events	548	259	335
	Moderate PA	0·70 [0·54, 0.91]	0·69 [0·48, 1·00]	0·62 [0·44, 0·86]
	High PA	0·58 [0·45, 0·76]	0·54 [0·38, 0·78]	0·53 [0·38, 0·72]
	P value	0.0550	0.0818	0.1891
Upper Middle Income Countries	Events	1665	1150	836
	Moderate PA	0·82 [0·72, 0·93]	0·77 [0·66, 0·89]	0·86 [0·72, 1·03]
	High PA	0·65 [0·57, 0·74]	0·63 [0·54, 0·73]	0·64 [0·54, 0·77]
	P value	<0·0001	0.0056	0.0004
Lower Middle Income Countries	Events	2811	1343	1852
	Moderate PA	0·99 [0·89, 1.10]	0·94 [0·81, 1·08]	0·94 [0·82, 1.07]
	High PA	0·92 [0·82, 1.02]	0·79 [0·68, 0·92]	0·94 [0·83, 1.08]
	P value	0.0741	0.0043	0.8913
Low Income Countries	Events	1579	1203	804
	Moderate PA	0·76 [0·67, 0·87]	0·73 [0·63, 0·85]	0·83 [0·69, 1.00]
	High PA	0·61 [0·53, 0·69]	0·58 [0·50, 0·66]	0·63 [0·53, 0·75]
	P value	0.0002	0.0010	0.0013

Hazard ratios (and 95% CI) were adjusted for age, sex, education, country income level, urban/rural residency, family history of CVD and smoking status taking into account household, community and country clustering.

Note: Low physical activity level (<600 MET*minute/week) is the reference group.

Moderate physical activity 600-3000 MET*minute/week; high physical activity ≥3000 MET*minute/week

CVD = cardiovascular disease

ˆMajor CVD = CVD mortality plus incident MI, stroke, and heart failure

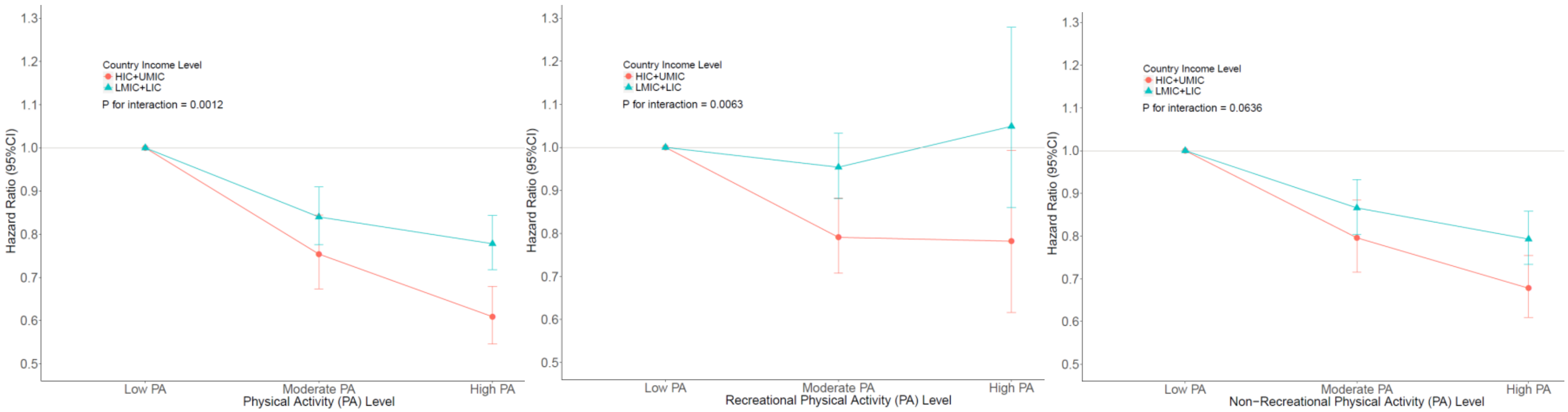


Figure 4: Relationship between increasing levels of total physical activity (PA; left panel), recreational PA (middle panel) and non-recreational PA (occupational, transportation and housework PA; right panel) with mortality and major cardiovascular disease (CVD) stratified by country income level. Models were adjusted for age, sex, education, country income level, urban/rural residency, family history of CVD and smoking status, taking into account household, community and country clustering.
HIC+UMIC = high income countries plus upper middle income countries
LMIC+LIC = lower middle income countries plus low income countries
ˆMajor CVD = CVD mortality plus incident MI, stroke, and heart failure

Supplemental Table 1: Summary of fatal and non-fatal events rates (per 1000 person years) and 95% CI stratified by country income level.

	Mortality plus Major CVD^		Mortality		Major CVDˆ		CVD Mortality		Non-CVD Mortality		Myocardial Infarction		Stroke		Heart Failure	
	Events	Rate	Events	Rate	Events	Rate	Events	Rate	Events	Rate	Events	Rate	Events	Rate	Events	Rate
High Income Countries	548	4·06 [3·67, 4·45]	259	1·79 [1·53, 2·04]	335	2·57 [2·25, 2·88]	30	0·22 [0·13, 0·32]	229	1·56 [1·33, 1·80]	155	1·24 [1·02, 1·46]	142	1·03 [0·84, 1·23]	50	0·34 [0·22, 0·45]
Upper Middle Income Countries	1690	7·08 [6·71, 7·44]	1171	4·65 [4·36, 4·94]	843	3·66 [3·40, 3·92]	270	1·07 [0·94, 1·21]	901	3·57 [3·32, 3·83]	407	1·79 [1·61, 1·98]	311	1·33 [1·17, 1·48]	139	0·57 [0·47, 0·68]
Lower Middle Income Countries	2863	6·23 [5·98, 6·48]	1371	2·92 [2·75, 3·09]	1884	4·11 [3·91, 4·31]	293	0·64 [0·56, 0·72]	1078	2·28 [2·13, 2·43]	583	1·31 [1·19, 1·42]	1206	2·59 [2·43, 2·74]	127	0·27 [0·21, 0·32]
Low Income Countries	3075	10·75 [10·34, 11·16]	2533	8·49 [8·13, 8·86]	1338	4·87 [4·59, 5·15]	701	2·37 [2·18, 2·57]	1832	6·12 [5·81, 6·43]	842	3·12 [2·89, 3·34]	427	1·48 [1·33, 1·63]	70	0·24 [0·18, 0·30]
Total	8176	7·32 [7·15, 7·49]	5334	4·57 [4·44, 4·71]	4400	4·03 [3·90, 4·16]	1294	1·12 [1·05, 1·19]	4040	3·46 [3·34, 3·57]	1987	1·87 [1·79, 1·96]	2086	1·84 [1·76, 1·93]	386	0·33 [0·30, 0·37]

Event rates are standardized for age and sex.
CVD = cardiovascular disease
ˆMajor CVD = CVD mortality plus incident myocardial infarction, stroke, and heart failure
A maximum of one event per participant is tabulated for each outcome.

Supplemental Table 2: Summary of risk (hazard ratios) for mortality and major CVD events compared by physical activity (PA) levels (adjusted for wealth index in place of education).

	Mortality plus Major CVD^		Mortality		Major CVDˆ	
	HR	P value	HR	P value	HR	P value
Moderate PA vs. Low PA	0.85 [0.80,0.91]	<0·0001	0.80 [0.74,0.87]	<0·0001	0.86 [0.79,0.94]	0·0008
High PA vs. Low PA	0.73 [0.68,0.78]	<0·0001	0.66 [0.60,0.71]	<0·0001	0.76 [0.69,0.83]	<0·0001
High PA vs. Moderate PA	0.85 [0.81,0.90]	<0·0001	0.82 [0.76,0.88]	<0·0001	0.88 [0.82,0.95]	0·0007

Hazard ratios (and 95% CI) were adjusted for age, sex, wealth index, country income level, urban/rural residency, family history of CVD and smoking status taking into account household, community and country clustering.
Low PA level <600 MET*minute/week; Moderate PA 600-3000 MET*minute/week; High physical activity ≥3000 MET*minute/week
CVD = cardiovascular disease
ˆMajor CVD = CVD mortality plus incident MI, stroke, and heart failure

Supplemental Table 3: Summary of risk (hazard ratios) for mortality and major CVD events compared by physical activity (PA) levels (adjusted for household income in place of education).

	Mortality plus Major CVD^		Mortality		Major CVDˆ	
	HR	P value	HR	P value	HR	P value
Moderate PA vs. Low PA	0.85 [0.80,0.91]	<0·0001	0.80 [0.74,0.88]	<0·0001	0.87 [0.79,0.95]	0·002
High PA vs. Low PA	0.72 [0.68,0.78]	<0·0001	0.64 [0.59,0.70]	<0·0001	0.77 [0.70,0.84]	<0·0001
High PA vs. Moderate PA	0.85 [0.80,0.90]	<0·0001	0.80 [0.74,0.87]	<0·0001	0.88 [0.82,0.95]	0·0013

Hazard ratios (and 95% CI) were adjusted for age, sex, household income, country income level, urban/rural residency, family history of CVD and smoking status taking into account household, community and country clustering.
Low PA level <600 MET*minute/week; Moderate PA 600-3000 MET*minute/week; High physical activity ≥3000 MET*minute/week
CVD = cardiovascular disease
ˆMajor CVD = CVD mortality plus incident MI, stroke, and heart failure

Supplemental Table 4: Summary of risk (hazard ratios) for mortality and major CVD events compared by physical activity (PA) levels.

	Mortality plus Major CVD^		Mortality		Major CVDˆ	
	HR	P value	HR	P value	HR	P value
Moderate PA vs. Low PA	0·85 [0·80, 0·91]	<0·0001	0·80 [0·74 ,0·87]	<0·0001	0·86 [0·79, 0·93]	0·0004
Lower high PA vs. Moderate PA	0·88 [0·82 ,0·94]	0·0002	0·83 [0·76 ,0·91]	<0·0001	0·92 [0·84, 1·00]	0·0528
Upper high PA vs. Lower high PA	0·93 [0·86, 1·01]	0·0807	0·95 [0·85, 1·05]	0·2896	0·91 [0·82, 1·01]	0·0817

Hazard ratios (and 95% CI) were adjusted for age, sex, education, country income level, urban/rural residency, family history of CVD and smoking status taking into account household, community and country clustering.
Low PA level <600 MET*minute/week; Moderate PA 600-3000 MET*minute/week; Lower high PA 3000-6453 MET*minute/week; Higher high PA ≥6453 MET*minute/week
CVD = cardiovascular disease
ˆMajor CVD = CVD mortality plus incident MI, stroke, and heart failure

Supplemental Table 5: Summary of risk (hazard ratios) for major CVD events stratified by physical activity (PA) level.

	CVD Mortality	Non-CVD Mortality	Myocardial Infarction	Stroke	Heart Failure
Moderate PA	0·75 [0·64, 0·88]	0·83 [0·75, 0·91]	0·78 [0·68, 0·89]	0·93 [0·82, 1·06]	0·83 [0·63, 1·11]
High PA	0·58 [0·49, 0·68]	0·68 [0·62, 0·75]	0·67 [0·59, 0·76]	0·85 [0·75, 0·96]	0·76 [0·58, 1·01]
P value for trend	p=0·0010	p<·0001	p=0·0100	p=0·0716	p=0·4794

Hazard ratios (and 95% CI) were adjusted for age, sex, education, country income level, urban/rural residency, family history of CVD and smoking status taking into account household, community and country clustering.

Note: Low physical activity level (<600 MET*minute/week) is the reference group.

Moderate physical activity 600-3000 MET*minute/week; high physical activity ≥3000 MET*minute/week CVD = cardiovascular disease

Supplemental Table 6: Summary of risk (hazard ratios) for mortality and major CVD events stratified by physical activity (PA) level with the additional adjustment for body mass index.

	Mortality plus Major CVD^	Mortality	Major CVD ^	CVD Mortality	Non-CVD Mortality	Myocardial Infarction	Stroke	Heart Failure
Moderate PA	0·88 [0·82, 0·94]	0·84 [0·77, 0·92]	0·88 [0·80, 0·96]	0·80 [0·67, 0·96]	0·85 [0·77, 0·94]	0·81 [0·71, 0·93]	0·96 [0·84, 1·09]	0·83 [0·62, 1·12]
High PA	0·76 [0·71, 0·81]	0·69 [0·63, 0·75]	0·79 [0·72, 0·86]	0·64 [0·54, 0·76]	0·71 [0·64, 0·78]	0·71 [0·62, 0·82]	0·87 [0·77, 0·99]	0·81 [0·61, 1·08]
P value for trend	p<0·0001	p<0·0001	p=0·0056	p=0·0059	p<0·0001	p=0·0358	p=0·0926	p=0·8712

Hazard ratios (and 95% CI) were adjusted for age, sex, education, country income level, urban/rural residency, family history of CVD, body mass index and smoking status taking into account household, community and country clustering.

Note: Low physical activity level (<600 MET*minute/week) is the reference group.

Moderate physical activity 600-3000 MET*minute/week; high physical activity ≥3000 MET*minute/week

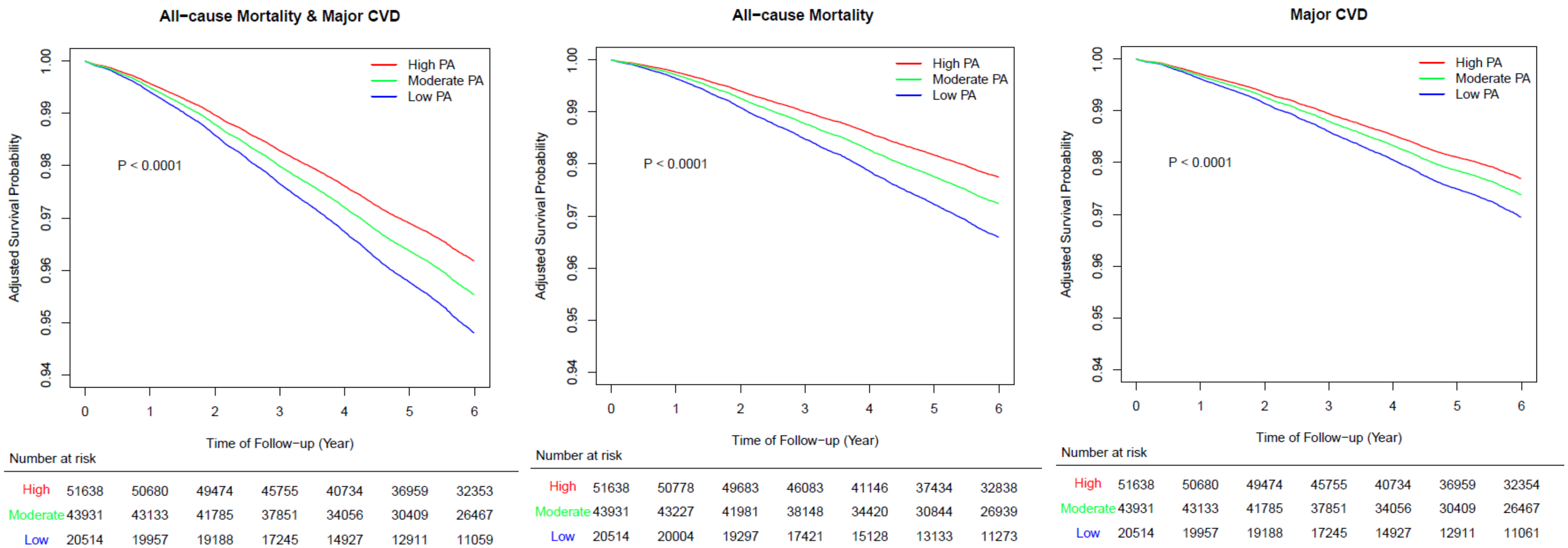
CVD = cardiovascular disease

^Major CVD = CVD mortality plus incident MI, stroke, and heart failure

Supplemental Table 7: Summary of risk (hazard ratios) for mortality and major CVD events stratified by physical activity (PA) level (***excluding*** *participants with CVD events in first two years of follow-up*).

	Mortality plus Major CVD^	Mortality	Major CVD ˆ	CVD Mortality	Non-CVD Mortality	Myocardial Infarction	Stroke	Heart Failure
Moderate PA	0·89 [0·83, 0·96]	0·85 [0·78, 0·93]	0·87 [0·79, 0·96]	0·76 [0·63, 0·93]	0·88 [0·79, 0·98]	0·80 [0·69, 0·93]	0·95 [0·83, 1·09]	0·77 [0·56, 1·06]
High PA	0·77 [0·71, 0·83]	0·69 [0·63, 0·76]	0·80 [0·73, 0·89]	0·64 [0·53, 0·77]	0·71 [0·64, 0·79]	0·75 [0·65, 0·87]	0·88 [0·77, 1·02]	0·78 [0·57, 1·06]
P value for trend	p<0·0001	p<0·0001	p=0·0492	p=0·0533	p<0·0001	p=0·3588	p=0·1996	p=0·9531

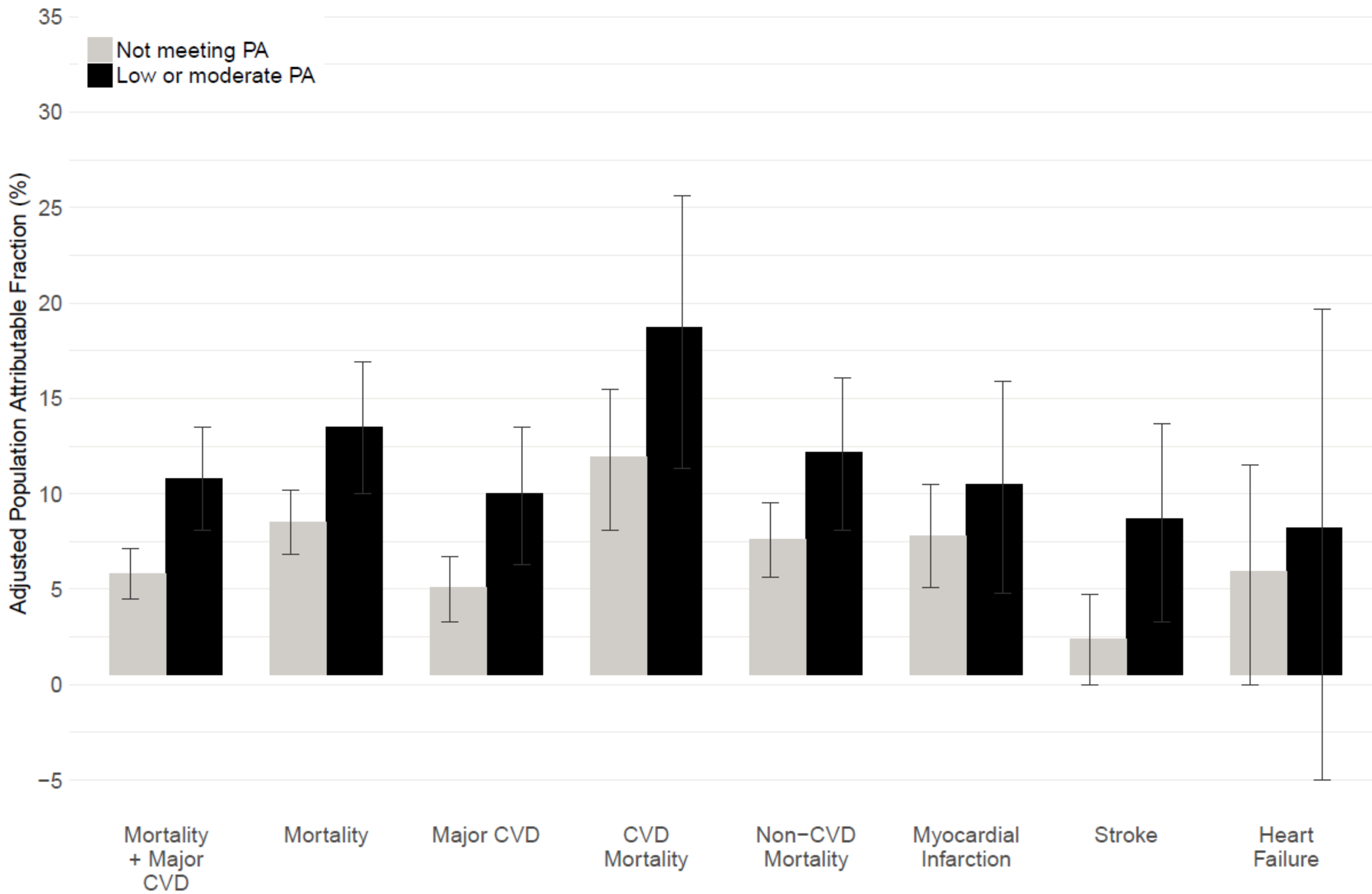
Hazard ratios (and 95% CI) were adjusted for age, sex, education, country income level, urban/rural residency, family history of CVD and smoking status taking into account household, community and country clustering.
Note: Low physical activity level (<600 MET*minute/week) is the reference group.
Moderate physical activity 600-3000 MET*minute/week; high physical activity ≥3000 MET*minute/week CVD = cardiovascular disease
ˆMajor CVD = CVD mortality plus incident MI, stroke, and heart failure



Supplemental Figure 1: Adjusted survival curves for mortality and major cardiovascular disease (CVD) (left panel), mortality (middle panel) and major CVD (CVD mortality plus incident MI, stroke, and heart failure; right panel) stratified by level of physical activity (PA). All models adjusted for age, sex, education, country income level, urban/rural residency, family history of CVD and smoking status, taking into account household, community and country clustering.

Low physical activity <600 MET*minute/week; moderate physical activity 600-3000 MET*minute/week; high physical activity ≥3000 MET*minute/week

P values corresponding to testing heterogeneity of the three curves in each panel



Supplemental Figure 2. Adjusted 5-year population attributable fraction and 95% CI of not meeting physical activity (PA) guideline (gray bars) and of not participating high PA (black bars). Meaning a proportion reduction in the outcomes by 5 years if the entire population met PA guidelines (gray bars) and if entire population achieved high physical activity (≥3000 MET*minute/week; black bars). (Adjusted for age, sex, education, country income level, urban/rural residency, family history of CVD and smoking status, taking into account household, community and country clustering).

CVD = cardiovascular disease

ˆMajor CVD = CVD mortality plus incident MI, stroke, and heart failure

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AUTHOR CONTRIBUTIONS
S Lear wrote the analysis plans and had the primary responsibility for writing this paper
S Yusuf designed and supervised the study, data analysis, interpreted the data & reviewed and commented on drafts
K Teo reviewed and commented on the data analysis and drafts
S Rangarajan coordinated the worldwide study & reviewed and commented on drafts
W Hu conducted the analysis & reviewed and commented on drafts
A Casanova reviewed and commented on the data analysis and drafts
D Leong reviewed and commented on the data analysis and drafts
D Gasevic reviewed and commented on the data analysis and drafts
All other authors coordinated the study in their respective countries and provided comments on drafts of the manuscript.

CONFLICT OF INTEREST
The authors declare no conflicts.

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