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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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56

57 **ABSTRACT**

58

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

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

68 **Findings:** Compared to low PA levels (<600 METS per week or <150 minutes/week of
69 moderate intensity PA), moderate (600 to 3000 or 150 to 750 minutes/week) and high PA levels
70 (>3000 or >750 minutes/week) were associated with a graded reductions in mortality (hazard
71 ratios =0·80 [0·74, 0·87] and 0·65 [0·60, 0·71], $p<0\cdot0001$ for trend), and major CVD
72 (myocardial infarction, stroke and heart failure; 0·86 [0·78, 0·93], $p<0\cdot001$ for trend).

73 Increasing PA was associated with lower risk of CVD and mortality in high, middle and low
74 income countries. The adjusted population attributable fraction for not meeting the PA guidelines
75 was 8·0% and 4·6%, and not meeting high PA levels was 13·0% and 9·5% for mortality and
76 major CVD, respectively. Both recreational and non-recreational PA were associated with
77 benefits.

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

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

82 **Funding:** Funding sources listed at end of paper.

83

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

85

86 Cardiovascular disease (CVD) is the leading cause of death worldwide¹ and a major economic
87 global burden.² Despite reductions in CVD mortality in high income countries (HIC), global
88 CVD mortality increased by 41% between 1990 and 2013; largely driven by rises in low and
89 lower-middle-income countries.³ Indeed, 70% of global CVD deaths come from low and middle
90 income countries where it is the largest cause of death.^{4,5} It has been estimated that 23% of the
91 world's population was insufficiently active⁶ and the WHO has recommended a decrease in
92 insufficient PA of 10% by 2020.⁷

93
94 Numerous studies from HIC have reported significant inverse associations of PA with mortality
95 and CVD morbidity.⁸ but such data from low and middle income countries are sparse and limited
96 to a few small studies.⁹⁻¹¹ In addition, studies of PA have focused primarily on recreational PA
97 (which is more common in HIC but less common in poorer countries),^{8,11} with less evidence on
98 the benefits of other forms of PA such as during transportation,¹² house work and occupational
99 PA.¹³

100
101 In the Prospective Urban Rural Epidemiologic (PURE) study being conducted in 17 high, middle
102 and low income countries, we examined whether PA is associated with lower risk of mortality
103 and CVD in countries at varying economic levels and whether these associations differ by type
104 of PA.

105

106 **METHODS**

107 The PURE study includes participants from three HICs (Canada, Sweden, United Arab
108 Emirates); seven upper middle income countries ([UMIC] Argentina, Brazil, Chile, Poland,

109 Turkey, Malaysia, South Africa); three lower middle income countries ([LMIC] China,
110 Colombia, Iran); and four low income countries ([LIC] Bangladesh, India, Pakistan,
111 Zimbabwe).¹⁴ Country economic level was based on World Bank classifications in 2006. The
112 choice and number of countries selected in PURE reflects a balance between involving a large
113 number of communities in countries at different economic levels with substantial heterogeneity
114 in social and economic circumstances versus the feasibility of centres to successfully achieve
115 long-term follow-up.

116
117 Within each country, urban and rural areas in and around selected cities and towns were
118 identified to reflect the geographical diversity of the countries. Communities were defined based
119 on the geographical clustering of common characteristics (sharing culture [as people of a similar
120 culture reside in close geographic proximity], socioeconomic status, and use of amenities, goods,
121 and services) such as through a set of contiguous postal code areas or group of streets or a small
122 village. The number of communities selected in each country varied. In some countries (eg,
123 India, China, Canada, and Colombia), communities from several states/provinces were included
124 to capture diversity, socioeconomic status, culture, and environments. In other countries (eg,
125 Iran, Poland, Sweden, and Zimbabwe), fewer communities were selected. This strategy
126 facilitated recruitment of individuals from different economic, cultural and geographical settings
127 (rural and urban) around the globe.

128
129 Within each defined community, households were approached and individuals between 35 and
130 70 years of age who intended to live at their current address for at least another four years were
131 invited to participate in the study. The method of approaching households differed between

132 countries based on feasibility but was consistent across sites within each country. For example,
133 in rural areas of India and China, a community announcement was made to the village through
134 contact of a community leader, followed by in-person door-to-door visits of all households. In
135 contrast in Canada, initial contact was by mail followed by telephone invitations to attend a
136 central clinic. For each household at least three attempts at contact were made. All eligible
137 residents of the household were invited and those who provided informed consent were recruited.
138 Household participation rate was 86%. Recruitment started in a vanguard phase in Karnataka,
139 India in January 2003; however most communities recruited between January 2005 and
140 December 2010. See Supplementary Appendix provides more detail on sampling. The study was
141 approved by local institutional research ethics boards.

142
143 Socio-demographic factors, medical history, lifestyle behaviours and risk factors were recorded
144 using standardized measures and procedures.¹¹ One-week total PA was assessed using the long-
145 form International Physical Activity Questionnaire (IPAQ)¹⁵ and calculated as a total of
146 occupation, transportation, housework and recreational activity reported in metabolic equivalents
147 (MET) * minutes/ week. Physical activity is also reported in minutes/week of moderate intensity
148 PA using the equation where minutes reported in each PA domain on the IPAQ by the participant
149 are weighted relative to moderate intensity PA:

$$\begin{aligned} 150 \text{ Minutes/week} &= 0.825 * \text{walking minutes} + 1 * \text{moderate minutes} + 1.375 * \text{garden minutes} + \\ 151 &1.5 * \text{cycling minutes} + 2 * \text{vigorous minutes} \end{aligned}$$

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

155 Physical activity was also dichotomized as meeting or not meeting current PA guidelines
156 (meeting guideline is $PA \geq 600 \text{ MET} \cdot \text{minute/week}$ as per the IPAQ¹⁵ or $PA \geq 150 \text{ minutes/week}$
157 of moderate intensity PA as per the WHO¹⁶) with periods of less than 10 minutes of PA not
158 included as per the IPAQ guidelines.^{15 16}We also further categorized the high PA category into a
159 lower-high PA level and an upper-high PA level by the median value of the high PA category of
160 6453 MET*minutes/week to investigate whether the effect of very high PA levels was graded.
161 PA was categorized into recreational PA and non-recreational PA (occupational, transportation
162 and housework).

163
164 The clinical outcomes of interest during follow-up were: mortality plus major CVD (CVD
165 mortality plus incident MI, stroke, and heart failure), either as a composite or separately
166 (Supplementary Appendix). In most low and middle income countries there was no central
167 system of death or event registration. We therefore obtained information on prior medical illness
168 and medically certified cause of death where available, and recorded best available information
169 from close family or friends in order to arrive at a probable diagnosis or cause of death. Death
170 certificates (available in 100% of deaths), medical records (MI: 49.4%, stroke 80.8% and heart
171 failure: 76.2%), household interviews and other sources of information was used. We also used
172 Verbal Autopsies to ascertain cause of death in addition to medical records which were reviewed
173 by a health professional.¹⁷ To ensure a standard approach and accuracy for classification of
174 events across all countries and over time, a selection of cases from each country annually was
175 adjudicated both locally and also by the adjudication chair, and if necessary further training was
176 provided.

177

178 **Statistical analyses**

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

188
189 Age-sex-standardized incidence rates for all outcomes were calculated for levels of total PA and
190 whether meeting PA guidelines.²³ To examine the association between PA variables and
191 outcomes, we used the marginal Cox proportional hazard model.^{24,25} Models were adjusted for
192 age, sex, education, country income level, residency (urban vs. rural), family history of CVD and
193 smoking status (current and ever smoker vs. never smoker- cigarette, cigar and pipe smoking)
194 taking into account three levels of clustering. We conducted further analyses using wealth index
195 and household income (in separate models) in place of education but these did not change the
196 results. In addition, we further adjusted for body mass index (BMI).

197
198 Adjusted population attributable fractions related to not meeting PA guidelines and not achieving
199 high PA levels were calculated to quantify the benefit of PA, using the method developed by
200 Chen et al.²⁶ To minimize the potential for reverse causation, we conducted sensitivity analyses

201 by excluding participants who experienced CVD events in the first two years of follow-up.
202 Additional analyses were also conducted including PURE participants who had CVD at baseline
203 (n=141 945) and these yielded similar results. We estimated the effect of total PA on the
204 outcomes by country income level, sex, age (<50 or ≥50 years), BMI (<25 kg/m² or ≥25 kg/m²),
205 waist-hip-ratio (above 0·85 for female, 0·90 for male), and smoking, hypertension, and diabetes.

206
207 To assess and compare the effect of recreational PA vs. non-recreation PA, we fitted the adjusted
208 marginal Cox model with restricted cubic spline with four knots at the 5th, 35th, 65th and 95th
209 percentiles for overall and non-recreational PA.²⁷ Because 55% participants had no recreational
210 PA, we chose 50th, 65th, 80th and 95th percentile as the knots. We also examined whether the
211 association between PA and outcomes varied by country income and by type of PA (total,
212 recreational or non-recreational) using tests of interaction to compare the effects between HIC
213 and UMIC vs LMIC and LIC. All analyses were conducted using SAS 9.4, for UNIX operating
214 system (SAS Institute, Cary, US) and R software, version 3.2.5, for Windows system.

215

216 **RESULTS**

217 A total of 168 916 participants were enrolled, of whom 141 945 had completed the IPAQ and the
218 analyses were limited to the 130 843 participants without pre-existing CVD. Table 1 presents
219 participant characteristics stratified by low, moderate, and high PA levels. Participant
220 characteristics were not materially different in most features across the three groups with the
221 exception of a lower proportion of males in the moderate PA group compared to the others and a
222 greater proportion of family history of CVD in the high PA group. The prevalence of

223 hypertension and diabetes were lower with higher PA. There was no association between diet
224 score or body mass index with PA levels.

225

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

230

231 During the mean follow-up of 6.9 ± 3.0 years there were 5334 deaths, 1294 CVD deaths and
232 4040 non-CVD deaths, 1987 individuals with incident MI, 2086 with incident stroke, and 386
233 with new heart failure (Supplemental Table 1). When stratified by PA level, there was a graded
234 reduction in age and sex adjusted event rates for all outcomes from low to moderate to high PA
235 ($p < 0.0001$ for trend for all events except for stroke ($p = 0.0010$)) except heart failure (Table 3).
236 Those meeting the guidelines for minimal PA had lower age and sex adjusted rates of all
237 outcomes (Table 3).

238

239 Participating in PA at or above the PA guidelines was associated with significant lower rates of
240 outcomes compared to those participants not meeting the PA guidelines ≥ 600
241 MET*minute/week as per the IPAQ¹⁵ or PA ≥ 150 minutes/week of moderate intensity PA as per
242 the WHO¹⁶). In fully adjusted models, meeting PA guidelines was associated with hazard ratios
243 (HR) [95% confidence interval] of 0.78 [0.74, 0.83] for mortality plus major CVD, 0.72 [0.67,
244 0.77] for mortality and 0.80 [0.74, 0.86] for major CVD ($p < 0.0001$ for all).

245

246 In fully adjusted models increasing levels of PA (moderate and high) were associated with lower
247 HR for mortality plus major CVD, mortality and major CVD compared to those with low levels
248 of total PA ($p < 0.0001$ $p < 0.0001$ and $p = 0.0005$ for trend, respectively; Figure 1). When adjusted
249 for either wealth index or household income in place of education, HR did not change
250 (Supplemental Tables 2 and 3). In addition, high PA was associated with a lower HR compared
251 to moderate PA for all outcomes. Dichotomizing high PA levels above or below the median
252 value in this group off 6453 MET*minutes/week did not show further reductions in risk
253 (Supplemental Table 4). Increasing PA was also associated with lower HR in CVD mortality,
254 non-CVD mortality and MI (Supplemental Table 5). With further adjustment for BMI, the HR
255 were slightly attenuated but remained significant (Supplemental Table 6). Excluding participants
256 who had a CVD event within the first two years of follow-up (to account for potential reverse
257 causality if sick individuals were less active), the results were consistent for all outcomes
258 (Supplemental Table 7).

259
260 Survival curves (Supplemental Figure 1) for low, moderate, and high PA levels for our three
261 primary outcomes of mortality plus major CVD, mortality and major CVD indicated a lower risk
262 as PA increased ($p < 0.0001$).

263
264 The five-year adjusted population attributable fraction of not meeting the PA guidelines was
265 5.3%, 8.0% and 4.6% for mortality plus major CVD, mortality and major CVD, respectively
266 (Supplemental Figure 2). These values were higher (10.3%, 13.0% and 9.5%, respectively), for
267 not achieving high PA.

268

269 Increasing PA was associated with lower risk mortality in a range of subgroups (Figure 2).

270 Compared to low levels of PA, moderate and high levels of PA were associated with a lower
271 graded risk for mortality regardless of sex, age, and in the presence of risk factors.

272

273 Increasing PA was associated with significantly lower risk up to approximately 3000

274 MET*minutes/week (or 750 minutes/week of moderate intensity PA) with more modest benefits

275 above that PA level ($p < 0.0001$). (Figure 3). For recreational PA, increasing PA was associated

276 with significantly lower risk up to approximately 600 MET*minutes/week (or 150 minutes/week

277 of moderate intensity PA) ($p = 0.01$) (as few had levels of PA higher than this), while for non-

278 recreational PA, increasing PA was associated with significantly lower risk up to approximately

279 5000 MET*minutes/week (or 1250 minutes/week of moderate intensity PA) with more modest

280 benefits above that PA level ($p < 0.0001$).

281

282 Increasing PA was associated with significantly lower risk for mortality plus major CVD in

283 UMIC and LIC, mortality in UMIC, LMIC and LIC and major CVD in UMIC and LIC (Table

284 4). When stratified by country income level (HIC + UMIC versus LMIC + LIC) there was a

285 significant interaction between country income level and PA levels for total ($p = 0.0012$) and

286 recreational PA ($p = 0.0063$) such that the HIC + UMIC had a lower risk with increasing PA level

287 (Figure 4). This was less clear for non-recreational PA ($p = 0.063$).

288

289 **DISCUSSION**

290 In this study involving 3 HIC, 7 UMIC, 3 LMIC, and 4 LIC countries, increasing PA was

291 associated with a lower risk for mortality and incidence of major CVD. This lower risk was

292 present even at moderate levels of PA compared to low levels of PA, and was more marked at
293 higher PA levels . The benefit of PA was present independent of the type of PA (recreational or
294 non-recreational), a range of socio-economic and CVD risk factors, and was similar in various
295 countries with differing income levels.

296
297 In our study population of predominantly non-HIC residing participants, meeting the PA
298 guidelines (150 minutes/week of moderate intensity of PA) was associated with a 22%, 28%, and
299 20% lower risk for all-cause mortality plus major CVD, mortality and major CVD, respectively,
300 resulting in adjusted population attributable fractions of 5·3%, 8·0% and 4·6%, respectively.
301 These attributable fractions are similar to those reported by Lee et al.; 9·4% for mortality and
302 5·8% for CVD in HIC.⁹ In addition, we observed a graded effect such that participants at higher
303 levels of PA had a lower risk than those participants engaging in moderate levels of PA. For
304 example, compared to people at moderate levels of PA, participating in high levels of PA
305 conferred an additional reduction in risk of 15%, 19% and 12% for mortality plus major CVD,
306 mortality and major CVD, respectively. This benefit plateaued only at very high levels of PA
307 (approximately 1250 minutes/week of moderate intensity of PA). Similar to previous studies of
308 recreational PA in HIC,^{28,29} we did not observe any adverse effects of PA on our outcomes even
309 in the approximately 9000 participants who reported over 2500 minutes/week of moderate
310 intensity of PA (equivalent to 17 times that of the PA guidelines). Therefore while participating
311 at even low levels of PA confers benefit (30 minutes per day for five days a week), the benefit
312 continues to increase up to high levels of total PA. Given these findings and that the affordability
313 of other CVD interventions such as consuming fruits and vegetables,³⁰ and taking generic CVD

314 drugs is beyond the reach of many people in low and middle income countries,³¹ participating in
315 PA represents a low cost approach to CVD prevention .

316

317 When stratified by country income level there was a consistent reduction of risk with increasing
318 PA. For HIC, meeting the PA guidelines was associated with a 30% lower risk for mortality,
319 which is lower than the 11% reported in a meta-analysis of walking from a study conducted
320 predominantly in HIC.¹² However, this earlier study did not include participants in the high PA
321 level of >3000 MET*minutes/week as ours did in which we found a continued benefit with
322 increasing PA levels. Studies in Iran and China also reported PA to be significantly associated
323 with lower mortality in a dose-dependent manner.^{32,33} Notably, Matthew et al. reported a HR of
324 0.61 [0.51-0.73] at the highest levels of PA of the Chinese women, which is similar to our HR of
325 0.65 [0.60, 0.71]. These findings are consistent with what we found in the LMIC category of
326 countries of which Iran and China accounted for the overwhelming majority of participants in
327 our LMIC group.

328

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

335

336 Few studies have assessed the association of non-recreational PA with outcomes. The available
337 studies are relatively small and report inconsistent results.^{12,34-38} We found that increasing levels
338 of both recreational PA and non-recreational PA were independently associated with lower risk
339 with our composite of all-cause mortality plus major CVD, indicating that PA of any type is
340 beneficial. Of note, high levels of PA was only possible in those individuals participating in non-
341 recreational PA. Indeed, only 2.9% of our study population participated in high level of PA
342 (≥ 3000 MET*minutes per week or ≥ 750 minutes/week of moderate intensity of PA) derived
343 exclusively from recreational PA compared to 37.9% of participants who attained this level
344 through non-recreational PA. This reflects the challenges inherent with participating in high
345 levels of recreational PA in that it is, by definition, conducted during discretionary hours of the
346 day outside of occupational and domestic duties. In contrast, incorporating PA into one's daily
347 lifestyle whether through active transportation, occupation and/or domestic duties has the
348 potential to achieve higher levels of PA that are associated with even lower risk for mortality and
349 CVD events.

350
351 To address concerns related to “reverse causality”, we excluded those with known CVD and
352 then conducted a sensitivity analysis further excluding those who had events within the first two
353 years of follow-up. Our results were unchanged for our main study outcomes. In addition, we
354 also conducted subgroup analyses stratified by sex, age, body mass index, smoking, presence of
355 hypertension and presence of diabetes and observed consistent results. We also observed that
356 increasing PA was associated with reduced CVD and non-CVD mortality. Regular PA has
357 been reported to be associated with lower mortality from certain cancers^{28,34,36,39} and respiratory

358 conditions.⁴⁰ With continued follow-up, we anticipate accruing enough events to reliably
359 investigate the effects of PA on specific categories of non-CVD mortality.

360

361 Limitations

362 While PA determined from the self-reported IPAQ has been found to modestly overestimate PA,
363 it demonstrates good reliability and moderate validity compared to accelerometers such that
364 higher IPAQ values correspond to higher levels of PA measured by accelerometers, thus
365 providing good internal validity.^{15,41,42} If PA is overestimated by the IPAQ, then the potential
366 benefits of PA may be more marked and may occur at lower PA levels than reported here. In
367 addition, the IPAQ has been tested across a range of countries similar to the PURE study¹⁵ and
368 the use of self-reported measures for assessing PA in large studies is considered acceptable in
369 low resource settings.⁴³

370

371 While it was not feasible to collect a proportionate sampling of the globe's population, our
372 selection of countries and communities ensured that our population was typical of the regions
373 from which participants were recruited with only modest differences compared to national data (
374 Supplementary Appendix for comparative data).⁴⁴ Although we did not recruit a random sample
375 of individuals, our approach minimized biases in selection of individuals once the communities
376 were identified. Given the range of countries across five continents at different economic levels
377 the large number of communities, and the large size of our study, our results are globally
378 applicable. Given our method of event ascertainment, it is possible that some events may have
379 been misclassified. However, we believe this to be of very limited numbers as the majority of
380 events were ascertained using supporting documents, standardized definitions and adjudication

381 using standardized definitions providing a high level of confidence in the validity. Lastly, in such
382 a large study, it is not uncommon to report low p values that may not be clinically relevant,
383 therefore p values should be interpreted with caution unless they are extreme ($p < 0.001$). Given
384 the magnitude and consistency of the effects observed across the different analyses, we can be
385 confident in our main findings.

386

387 Conclusions

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

Table 1: Participant characteristics stratified by levels of total physical activity (data presented as means \pm 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 \pm 9.7	51.0 \pm 10.1	50.5 \pm 9.7	49.7 \pm 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 \pm 8.0	34.9 \pm 7.6	35.5 \pm 7.9	34.8 \pm 8.3
Body Mass Index (kg/m ²)	25.7 \pm 5.1	25.9 \pm 5.4	25.9 \pm 5.0	25.4 \pm 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 \geq 3000 MET*minute/week and \geq 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	3227 [1485-6426]	2436 [750-5979]	2340 [960-5177]	2520 [721-6442]	<0.0001	<0.0001
Minutes/week	(807 [371-1607])	(609 [188-1495])	(585 [240-1294])	(630 [180-1611])		
Recreational Physical Activity* MET*minutes/week	518 [50-1386]	0 [0-320]	99 [0-693]	0 [0-0]	<0.0001	<0.0001
Minutes/week	(130 [12-347])	(0 [0-80])	(25 [0-173])	(0 [0-0])		
Non-Recreational Physical Activity* MET*minutes/week	2115 [806-4980]	1983 [578-5400]	1748 [693-4186]	2297 [594-6222]	<0.0001	0.7762
Minutes/week	(529 [202-1245])	(496 [144-1350])	(437 [173-1047])	(574 [149-1556])		
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 Cochran-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 CVD [^]		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

[^]Major CVD = CVD mortality plus incident myocardial infarction, stroke, and heart failure

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

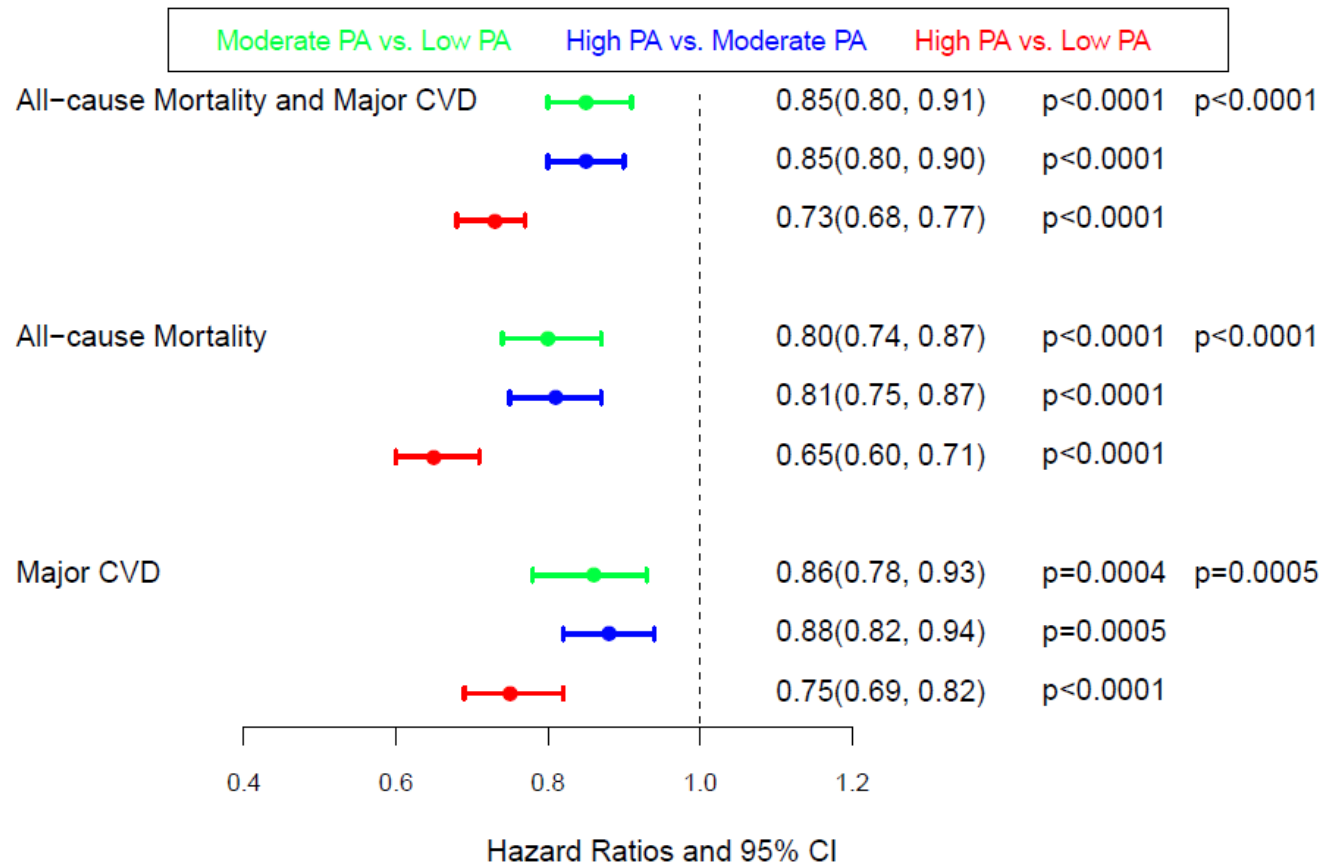


Figure 1: Hazard ratios and 95% CI for the pairwise comparison between levels of total physical activity, adjusted for age, sex, education, country income level, urban/rural residency, family history of CVD and smoking status taking into account household, community and country clustering. There were 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 \geq 3000 MET*minute/week

CVD = cardiovascular disease

^Major 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.

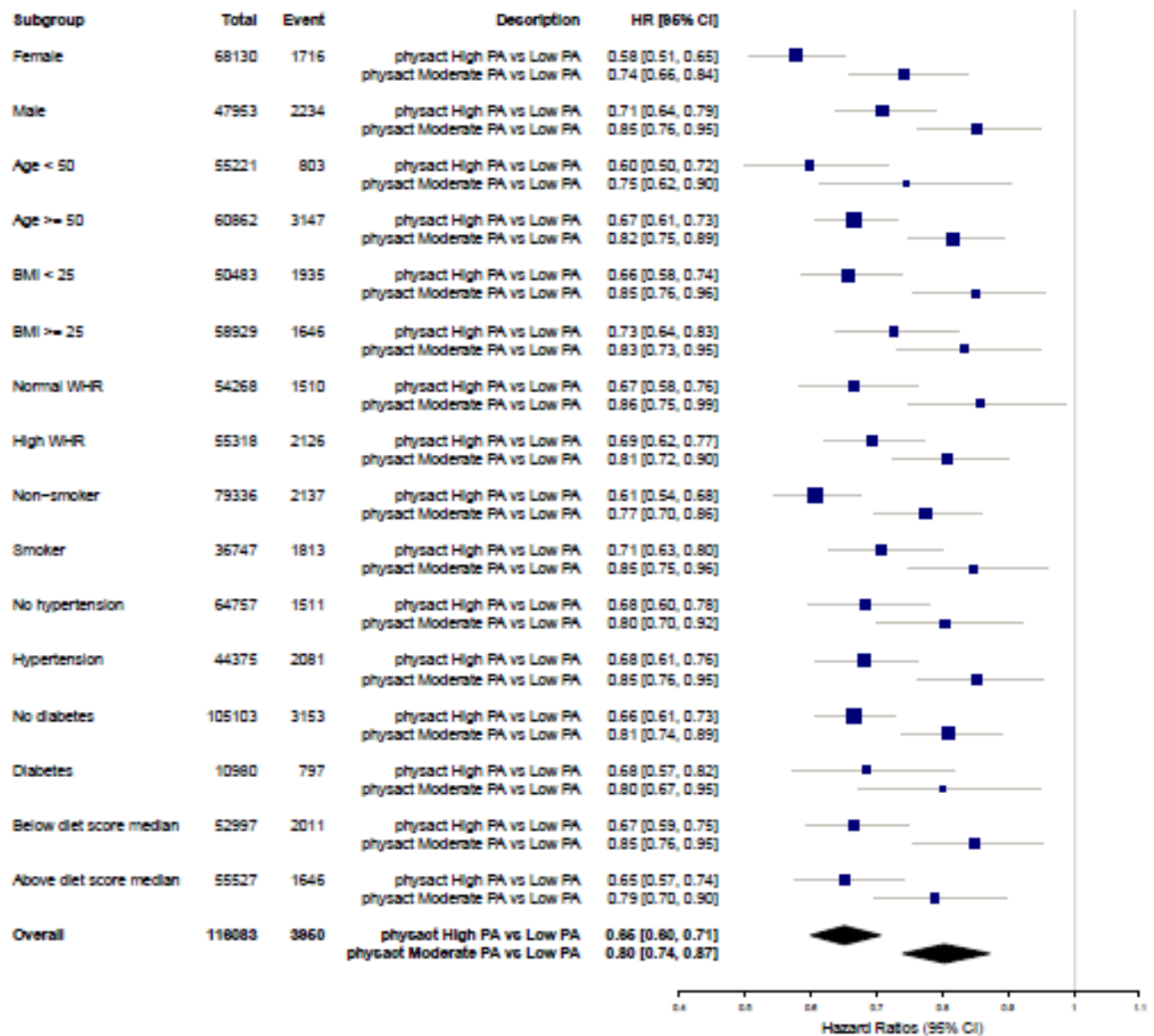


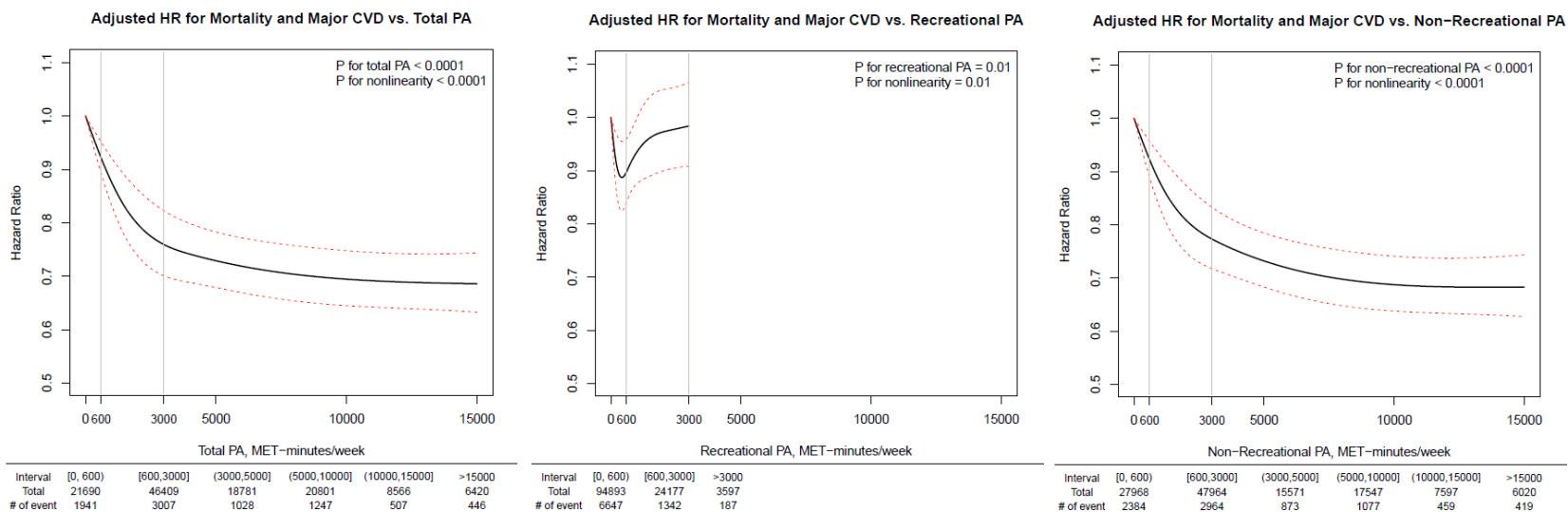
Figure 2: Hazard ratios and 95% CI of level of total physical activity for mortality (adjusted for age, sex, education, country income level, urban/rural residency, family history of cardiovascular disease and smoking status taking into account household, community and country clustering). Based on data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



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

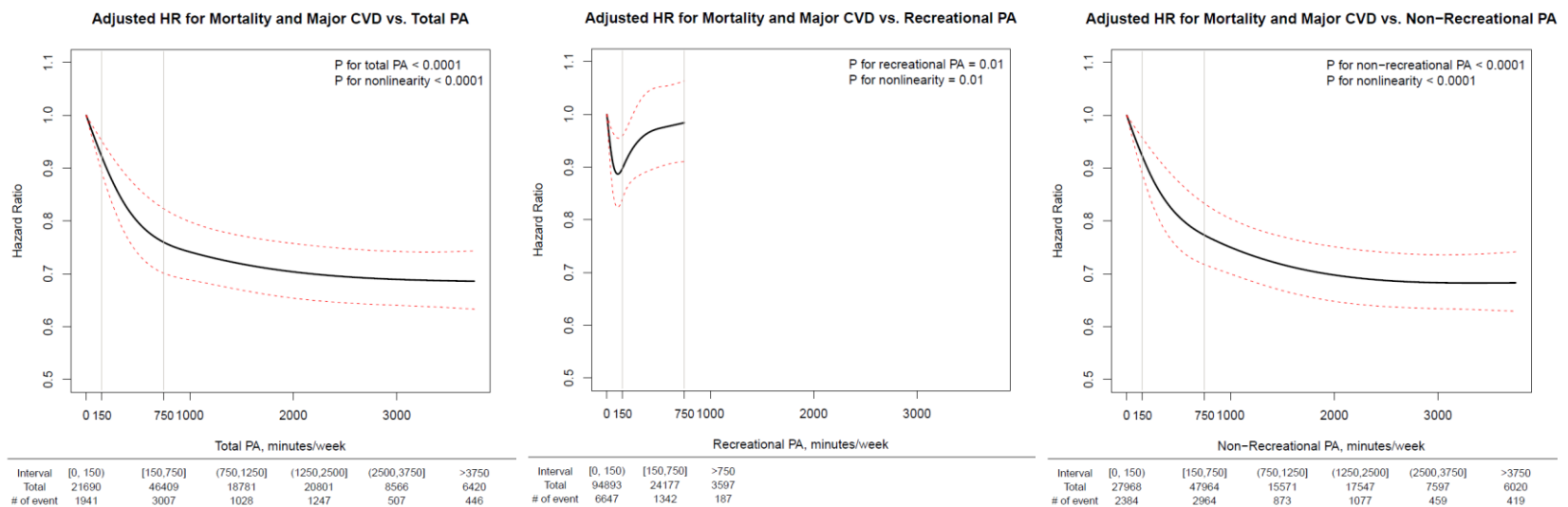


Figure 3: Relationship between increasing total physical activity (PA; left panels), recreational PA (middle panels) and non-recreational PA (occupational, transportation and housework PA; right panels) with mortality and major cardiovascular disease (CVD) presented in MET*minutes/week (top panels) and 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.

^Major 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 CVD [^]
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 \geq 3000 MET*minute/week

CVD = cardiovascular disease

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

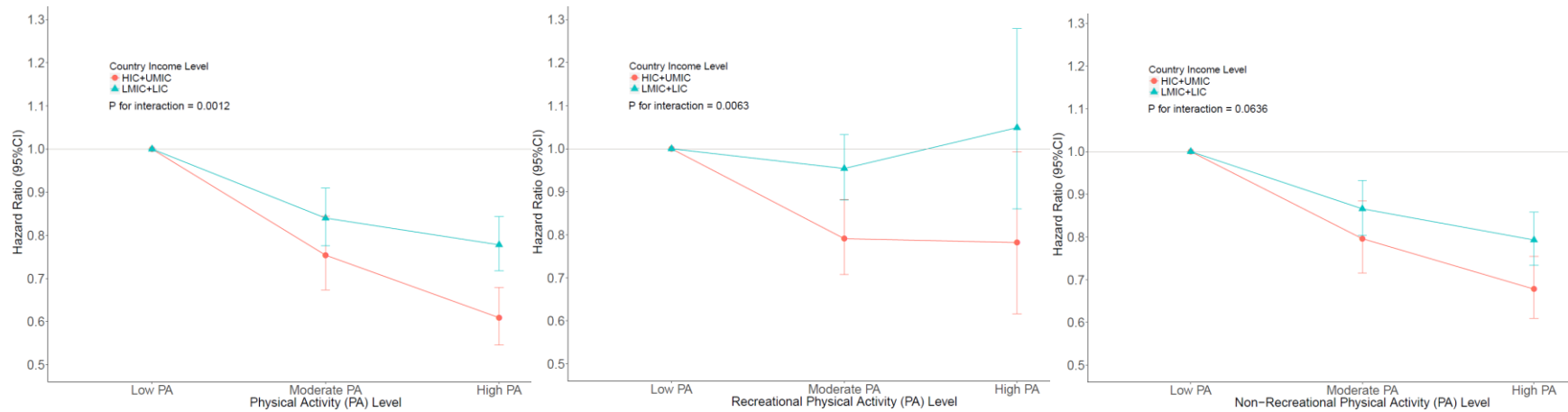


Figure 4: Relationship between increasing levels of total physical activity (PA; left panel), recreational PA (middle panel) and non-recreational PA (occupational, transportation and housework PA; right panel) with mortality and major cardiovascular disease (CVD) stratified by country income level. Models 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

^Major 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 CVD [^]		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

[^]Major 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 CVD [^]	
	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

[^]Major 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 CVD [^]	
	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

[^]Major 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 CVD [^]	
	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

[^]Major 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*).

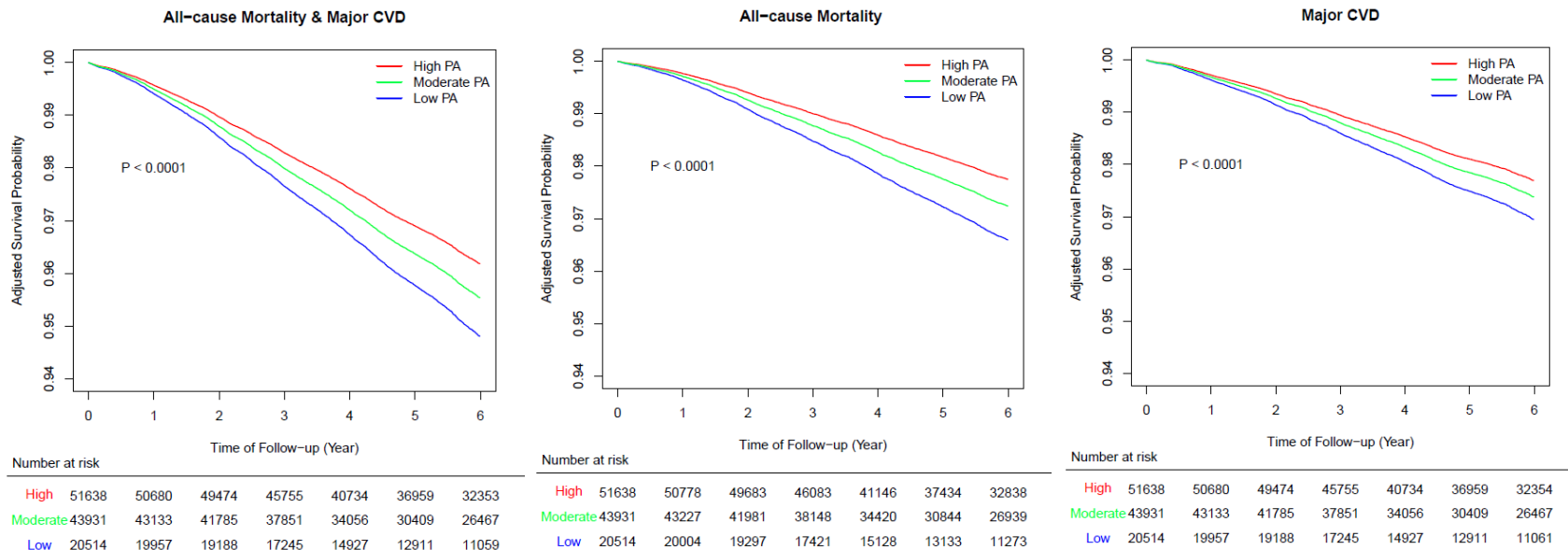
	Mortality plus Major CVD [^]	Mortality	Major CVD [^]	CVD Mortality	Non-CVD Mortality	Myocardial Infarction	Stroke	Heart Failure
Moderate PA	0.89 [0.83, 0.96]	0.85 [0.78, 0.93]	0.87 [0.79, 0.96]	0.76 [0.63, 0.93]	0.88 [0.79, 0.98]	0.80 [0.69, 0.93]	0.95 [0.83, 1.09]	0.77 [0.56, 1.06]
High PA	0.77 [0.71, 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

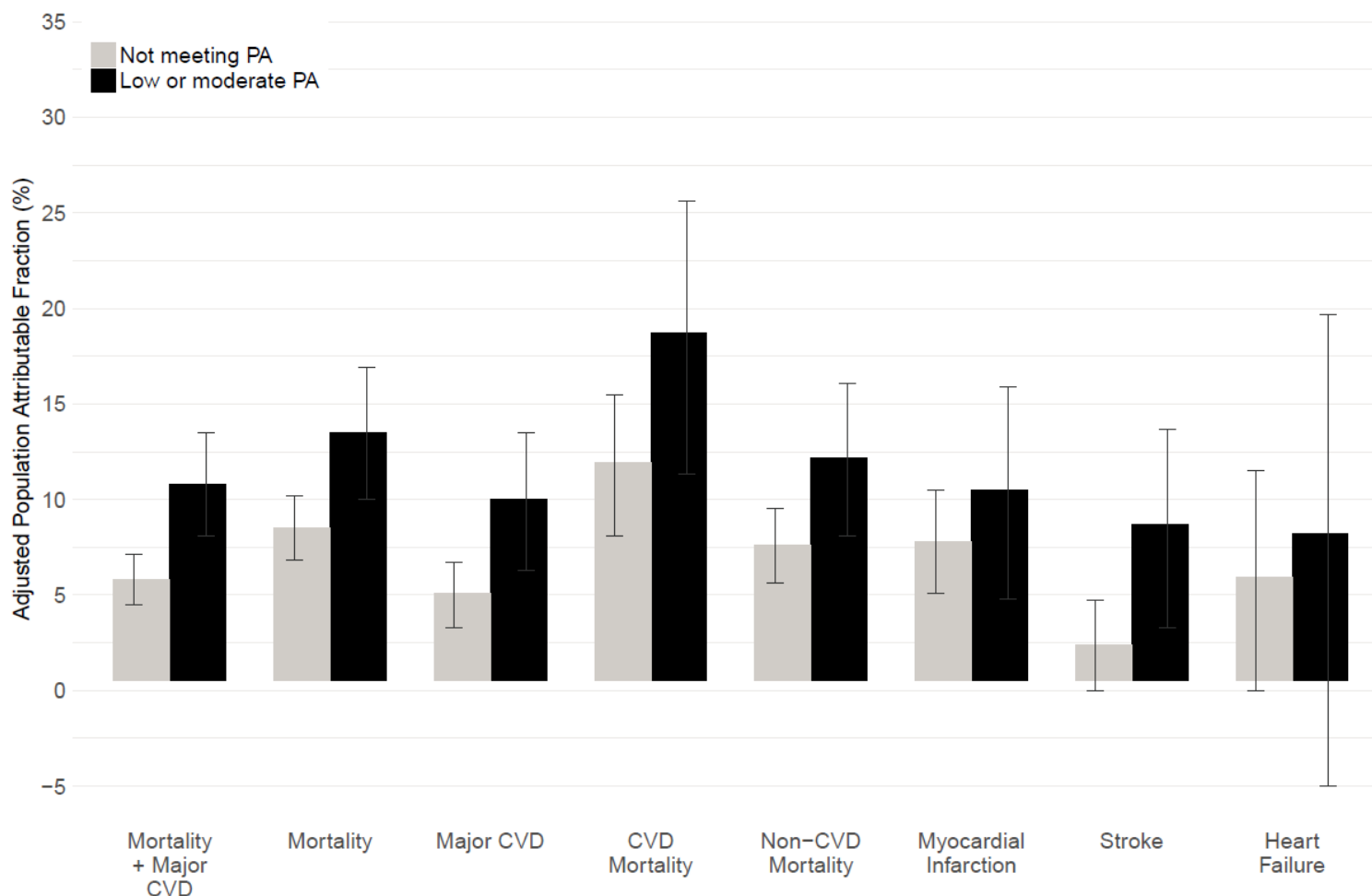
[^]Major CVD = CVD mortality plus incident MI, stroke, and heart failure



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 \geq 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

^Major 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

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CONFLICT OF INTEREST

The authors declare no conflicts.

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