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

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Summary

Background **Physical activity has a protective effect against cardiovascular disease (CVD) in high-income countries, where physical activity is mainly recreational, but it is not known if this is also observed in lower-income countries, where physical activity is mainly non-recreational. We examined whether different amounts and types of physical activity are associated with lower mortality and CVD in countries at different economic levels.**

Methods **In this prospective cohort study, we recruited participants from 17 countries (Canada, Sweden, United Arab Emirates, Argentina, Brazil, Chile, Poland, Turkey, Malaysia, South Africa, China, Colombia, Iran, Bangladesh, India, Pakistan, and Zimbabwe). Within each country, urban and rural areas in and around selected cities and towns were identified to reflect the geographical diversity. Within these communities, we invited individuals aged between 35 and 70 years who intended to live at their current address for at least another 4 years. Total physical activity was assessed using the International Physical Activity Questionnaire (IPQA). Participants with pre-existing CVD were excluded from the analyses. Mortality and CVD were recorded during a mean of 6·9 years of follow-up. Primary clinical outcomes during follow-up were mortality plus major CVD (CVD mortality, incident myocardial infarction, stroke, or heart failure), either as a composite or separately. The effects of physical activity on mortality and CVD were adjusted for sociodemographic factors and other risk factors taking into account household, community, and country clustering.**

Findings **Between Jan 1, 2003, and Dec 31, 2010, 168916 participants were enrolled, of whom 141945 completed the IPAQ. Analyses were limited to the 130 843 participants without pre-existing CVD. Compared with low physical activity (<600 metabolic equivalents [MET]×minutes per week or <150 minutes per week of moderate intensity physical activity), moderate (600–3000 MET×minutes or 150–750 minutes per week) and high physical activity (>3000 MET×minutes or >750 minutes per week) were associated with graded reduction in mortality (hazard ratio 0·80, 95% CI 0·74–0·87 and 0·65, 0·60–0·71; p<0·0001 for trend), and major CVD (0·86, 0·78–0·93; p<0·001 for trend). Higher physical activity was associated with lower risk of CVD and mortality in high-income, middle-income, and low-income countries. The adjusted population attributable fraction for not meeting the physical activity guidelines was 8·0% for mortality and 4·6% for major CVD, and for not meeting high physical activity was 13·0% for mortality and 9·5% for major CVD. Both recreational and non-recreational physical activity were associated with benefits.**

Interpretation **Higher recreational and non-recreational physical activity was associated with a lower risk of mortality and CVD events in individuals from low-income, middle-income, and high-income countries. Increasing physical activity is a simple, widely applicable, low cost global strategy that could reduce deaths and CVD in middle age.**

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Introduction

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, global CVD mortality increased by 41% between 1990 and 2013, largely driven by rises in low-income and lower-middle-income countries.[3] Indeed, 70% of global CVD deaths come from low-income and middle-income countries, where it is the commonest cause of death.[4,5] 23% of the world's population is estimated to be insufficiently active[6] and WHO has recommended a decrease in insufficient physical activity of 10% (of the aforementioned 23%) by 2020.[7]

Many studies from high-income countries have reported significant inverse associations of physical activity with mortality and CVD morbidity,[8] but such data from low-

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Research in context

Evidence before this study

We searched the MEDLINE database for articles regarding the role of physical activity and exercise on mortality and cardiovascular disease across countries at various economic levels. We used the terms "physical activity", "exercise", "mortality", "cardiovascular disease" in English but without date restrictions. We screened papers by title and abstract to identify full-text papers that were relevant to the study aims. We also screened citation lists from these full-text papers to identify other relevant research. The papers cited in this report were selected to be representative of the existing evidence base, and are not an exhaustive list of relevant research.

Added value of this study

Studies investigating the role of physical activity in preventing death from cardiovascular disease have been primarily from high-income countries, and focused on recreational or leisure time physical activity. In low-income and middle-income countries, physical activity is predominantly from non-recreational activities such as transportation, occupation, and housework, and therefore findings in high-income countries might not apply to other countries. A few studies have reported on the role of physical activity in low-income and middle-income countries, but these were cross-sectional or used inconsistent methods and are therefore not robust. Our investigation looks at the relationship between recreational and non-recreational physical activity and incident events in countries from all regions of the world.

Implications of all the available evidence

Physical activity is associated with reduced risk of mortality and incident cardiovascular disease in all regions of the world. The greatest reductions occurred at the lowest and continued to be present at very high levels of physical activity with no indication of a ceiling effect. In addition, both recreational and non-recreational physical activity were associated with lower risks. Physical activity is a low-cost approach to reducing deaths and cardiovascular disease that is applicable globally with potential large impact.

income and middle-income countries are sparse and limited to a few small studies.[9–11] Moreover, studies of physical activity have focused primarily on recreational physical activity (which is common in high-income countries but less common in poorer countries),[8,11] with less evidence on the benefits of other forms of physical activity such as during transportation,[12] housework, and occupational physical activity.[13]

In the Prospective Urban Rural Epidemiologic (PURE) study done in 17 countries of various income levels, we examined whether physical activity is associated with lower risk of mortality and CVD in countries at varying economic levels and whether these associations differ by type of physical activity.

Methods

Study design and participants

The PURE study includes participants from three high-income countries (Canada, Sweden, United Arab Emirates); seven upper-middle-income countries (Argentina, Brazil, Chile, Poland, Turkey, Malaysia, South Africa); three lower-middle-income countries (China, Colombia, Iran); and four low-income-countries (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 many 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 geographical 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 and 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 aged 35–70 years who intended to live at their current address for at least another 4 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 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 (appendix). The study was approved by local institutional research ethics boards.

Sociodemographic factors, medical history, lifestyle behaviours, and risk factors were recorded using standardised measures and procedures.[11] 1-week total physical activity 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 per week. Physical activity was also reported in minutes per week of moderate intensity physical activity using the equation where minutes reported in each physical activity domain on the IPAQ by the participant are weighted relative to moderate intensity physical activity:

$$\text{Min per week} = 0{\cdot}825 \times \text{walking min} + 1 \times \text{moderate min} + 1{\cdot}375 \times \text{garden min} + 1{\cdot}5 \times \text{cycling min} + 2 \times \text{vigorous min}$$

Total physical activity was categorised as low (<600 MET×minutes per week), moderate (600–3000 MET×minutes per week), and high (>3000 MET×minutes per week) physical activity, corresponding to less than 150 minutes per week, 150–750 minutes per week, and more than 750 minutes per week of moderate intensity physical activity. Physical activity was also dichotomised as meeting or not meeting current physical activity guidelines (≥600 MET×minutes per week as per the IPAQ[15] or physical activity ≥150 minutes per week of moderate intensity physical activity as per WHO[16]) with periods of less than 10 minutes of physical activity not included as per the IPAQ guidelines.[15,16] We further categorised the high physical activity category into lower-high physical activity and an upper-high physical activity by the median value of the high physical activity category of 6453 MET×minutes per week to investigate whether the effect of very high physical activity was graded. Physical activity was categorised into recreational physical activity and non-recreational physical activity (occupational, transportation, and housework).

Outcomes

Primary clinical outcomes during follow-up were mortality plus major CVD (CVD mortality plus incident myocardial infarction, stroke, or heart failure), either as a composite or separately (appendix). In most low-income and middle-income countries there was no central system of death or event registration. We therefore obtained information on history of illness and medically certified cause of death where available, and recorded best available information from close family or friends to arrive at a probable diagnosis or cause of death. Death certificates (available in 100% of deaths), medical records (percentage of availability of medical records for the following conditions: myocardial infarction 49·4%, stroke 80·8%, and heart failure 76·2%), household interviews, and other sources of information were used. We also used verbal autopsies to ascertain cause of death in addition to medical records that 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 further training was provided if necessary.

See Online for appendix

Statistical analyses

Sample size was not predetermined; we aimed to use as many participants as possible with no maximum limit. The primary analyses were done excluding participants who reported having CVD at baseline. Baseline characteristics were described for the entire cohort and stratified by low, moderate, and high total physical activity. Total and domain-specific physical activity values were not normally distributed and are presented as median and IQR.[18] The Kruskal-Wallis test and Jonckheere-Terpstra test[19,20] were used to test the heterogeneity and trend across the four country income levels (high-income countries, upper-middle-income countries, lower-middle-income countries, or low-income countries), respectively. For the two categorical physical activity variables: total physical activity and whether meeting physical activity guideline, we calculated frequencies and compared their difference and trend across the country income levels using the χ^2 test and Cochran-Armitage test,[21,22] as appropriate.

Age-sex-standardised incidence rates for all outcomes were calculated for total physical activity and whether meeting physical activity guidelines.[23] To examine the association between physical activity 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 or ever smoker *vs* never smoker; cigarette, cigar, and pipe smoking) taking into account three levels of clustering. We did further analyses using wealth index and household income (in separate models) in place of education but these did not change the results. We further adjusted for body-mass index (BMI).

Adjusted population attributable fractions that were related to not meeting physical activity guidelines and not achieving high physical activity were calculated to quantify the benefit of physical activity, using the method developed by Chen and colleagues.[26] To minimise the potential for reverse causation, we did sensitivity analyses by excluding participants who had CVD events in the first 2 years of follow-up. Additional analyses were also done including PURE participants who had CVD at baseline (n=141 945), which yielded similar results. We estimated the effect of total physical activity on the outcomes by country income level; sex; age (<50 or ≥50 years); BMI (<25 kg/m² or ≥25 kg/m²); waist-to-hip ratio (above 0·85 for women and girls, 0·90 for men and boys); and smoking, hypertension, and diabetes.

	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/m²)	25·7 (5·1)	25·9 (5·4)	25·9 (5·0)	25·4 (5·1)

Data are mean (SD) or n (%). MET=metabolic equivalents. *Low physical activity=<600 MET × min per week and <150 min per week of moderate intensity physical activity. †Moderate physical activity=600–3000 MET × min per week and 150–750 min per week of moderate intensity physical activity. ‡High physical activity=>3000 MET × min per week and >750 min per week of moderate intensity physical activity.

***Table 1*: Participant characteristics stratified by total physical activity**

	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*	..	..	..	..	<0·0001	<0·0001
MET × min per week	3227 (1485–6426)	2436 (750–5979)	2340 (960–5177)	2520 (721–6442)	..	..
Min per week	807 (371–1607)	609 (188–1495)	585 (240–1294)	630 (180–1611)	..	..
Recreational physical activity*	..	..	..	..	<0·0001	<0·0001
MET × min per week	518 (50–1386)	0 (0–320)	99 (0–693)	0 (0–0)	..	..
Min per week	130 (12–347)	0 (0–80)	25 (0–173)	0 (0–0)	..	..
Non-recreational physical activity*	..	..	..	..	<0·0001	0.7762
MET × min per week	2115 (806–4980)	1983 (578–5400)	1748 (693–4186)	2297 (594–6222)	..	..
Min per 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

Data are median (IQR) or n (%). p value for heterogeneity was calculated by χ^2 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.[15,16] MET=metabolic equivalents. *Moderate intensity physical activity. †Low physical activity <600 MET × min per week and <150 min per week of moderate intensity physical activity. ‡Moderate physical activity 600–3000 MET × min per week and 150–750 min per week of moderate intensity physical activity. §High physical activity >3000 MET × min per week and >750 min per week of moderate intensity physical activity. ¶Meeting physical activity guidelines ≥600 MET × min per week and ≥150 min per week of moderate intensity physical activity.

***Table 2*: Physical activity by country income level**

To assess and compare the effect of recreational physical activity versus non-recreation physical activity, 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 physical activity.[27] Because 55% of participants had no recreational physical activity, we chose 50th, 65th, 80th, and 95th percentile as the knots. We also examined whether the association between physical activity and outcomes varied by country income and by type of physical activity (total, recreational, or non-recreational) using tests of interaction to compare the effects between high-income countries and upper-middle-income countries versus lower-middle-income countries and low-income countries. All analyses were done using SAS 9.4, for UNIX operating system (SAS Institute, Cary, USA) and R software, version 3.2.5, for Windows system.

Role of the funding source

The funders and sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; in the preparation, review, or approval of the manuscript; or in the decision to submit the manuscript for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 1, 2003, and Dec 31, 2010, we enrolled 168916 participants, of whom 141945 completed the IPAQ. Analyses were limited to the 130 843 participants without pre-existing CVD. Table 1 presents participant characteristics stratified by low, moderate, and high physical activity. 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 physical activity group compared with the others and a greater proportion of family history of CVD in the high physical activity group. The prevalence of hypertension and diabetes were lower with higher physical activity. There was no association between diet score or BMI and physical activity.

Table 2 presents physical activity by country income level in both MET × minutes per week and minutes per week of moderate intensity physical activity. There was a trend towards lower total physical activity and recreational physical activity from high-income countries to low-income countries (p<0·0001 for both), but not for non-recreational physical activity. Most participants met the physical activity guidelines, but fewer than half of the participants reached high physical activity.

During the mean follow-up of 6·9 years (SD 3·0) there were 5334 deaths in total (1294 deaths from CVD and 4040 deaths from non-CVD causes), 1987 individuals with incident myocardial infarction, 2086 individuals with incident stroke, and 386 individuals with new heart failure (appendix). When stratified by 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 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 recommendations (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 recommendations (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 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 standardised for age and sex. Data are n, or n per 1000 person-years (95% CI). A maximum of one event per participant is tabulated for each outcome. CVD=cardiovascular disease. MET=metabolic equivalents. *Major CVD=CVD mortality plus incident myocardial infarction, stroke, or heart failure. †Low physical activity=<600 MET × min per week and <150 min per week of moderate intensity physical activity. ‡Moderate physical activity=600–3000 MET × min per week and 150–750 min per week of moderate intensity physical activity. §High physical activity=>3000 MET × min per week and >750 min per week of moderate intensity physical activity.

***Table 3*: Summary of fatal and non-fatal events by physical activity**

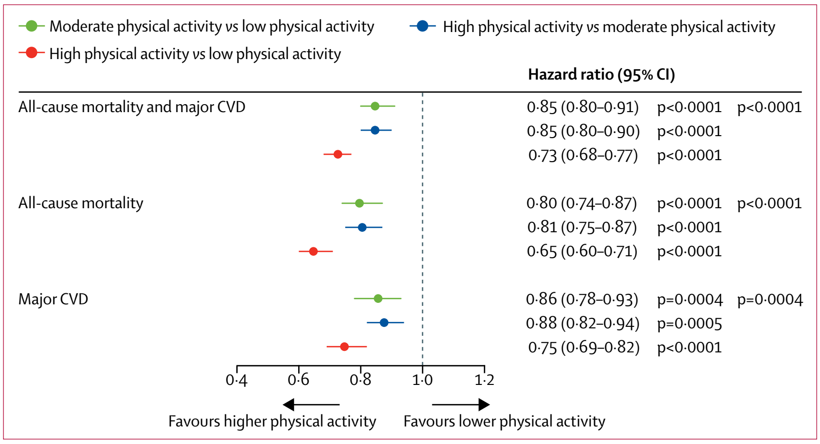


***Figure 1*: Hazard ratios and 95% CI for all-cause mortality and major CVD, all-cause mortality, or major CVD by level of physical activity**

Data adjusted for age, sex, education, country income level, urban or rural residency, family history of CVD, and smoking status; taking into account household, community, and country clustering. There were 3155 events for all-cause mortality and major CVD, 2041 events for all-cause mortality, and 1723 events for major CVD. 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 physical activity. Low physical activity=<600 MET × min per week. Moderate physical activity=600–3000 MET × min per week. High physical activity=>3000 MET × min per week. CVD=cardiovascular disease. Major CVD=CVD mortality plus incident myocardial infarction, stroke, or heart failure. MET=metabolic equivalents.

there was a graded reduction in age and sex adjusted event rates for all outcomes except heart failure from low to moderate to high physical activity (table 3). Participants meeting the guidelines for physical activity had lower age and sex adjusted rates of all outcomes (table 3).

Participating in physical activity at or above the physical activity guidelines was associated with significantly lower rates of outcomes compared with those participants not meeting the physical activity guidelines (≥600 MET×minutes per week as per IPAQ,[15] or physical activity ≥150 minutes per week of moderate intensity physical activity as per WHO[16]). In fully adjusted models, meeting physical activity guidelines was associated with hazard ratios (HRs) of 0·78 for mortality plus major CVD (95% CI 0·74–0·83), 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, moderate and high physical activity were associated with lower HRs for mortality plus major CVD (p<0·0001 for trend), mortality (p<0·0001 for trend), and major CVD (p=0·0005 trend) compared with those with low total physical activity (figure 1). When adjusted for either wealth index or household income in place of education, HRs did not change (appendix).

	Total	Event	Description	HR (95% CI)
Female	68 130	1716	High PA vs low PA	0·58 (0·51–0·65)
			Moderate PA vs low PA	0·74 (0·66–0·84)
Male	47 953	2234	High PA vs low PA	0·71 (0·64–0·79)
			Moderate PA vs low PA	0·85 (0·76–0·95)
Age <50 years	55 221	803	High PA vs low PA	0·60 (0·50–0·72)
			Moderate PA vs low PA	0·75 (0·62–0·90)
Age ≥50 years	60 862	3147	High PA vs low PA	0·67 (0·61–0·73)
			Moderate PA vs low PA	0·82 (0·75–0·89)
BMI <25	50 483	1935	High PA vs low PA	0·66 (0·58–0·74)
			Moderate PA vs low PA	0·85 (0·76–0·96)
BMI ≥25	58 929	1646	High PA vs low PA	0·73 (0·64–0·83)
			Moderate PA vs low PA	0·83 (0·73–0·95)
Normal WHR	54 268	1510	High PA vs low PA	0·67 (0·58–0·76)
			Moderate PA vs low PA	0·86 (0·75–0·99)
High WHR	55 318	2126	High PA vs low PA	0·69 (0·62–0·77)
			Moderate PA vs low PA	0·81 (0·72–0·90)
Non-smoker	79 336	2137	High PA vs low PA	0·61 (0·54–0·68)
			Moderate PA vs low PA	0·77 (0·70–0·86)
Smoker	36 747	1813	High PA vs low PA	0·71 (0·63–0·80)
			Moderate PA vs low PA	0·85 (0·75–0·96)
No hypertension	64 757	1511	High PA vs low PA	0·68 (0·60–0·78)
			Moderate PA vs low PA	0·80 (0·70–0·92)
Hypertension	44 375	2081	High PA vs low PA	0·68 (0·61–0·76)
			Moderate PA vs low PA	0·85 (0·76–0·95)
No diabetes	105 103	3153	High PA vs low PA	0·66 (0·61–0·73)
			Moderate PA vs low PA	0·81 (0·74–0·89)
Diabetes	10 980	797	High PA vs low PA	0·68 (0·57–0·82)
			Moderate PA vs low PA	0·80 (0·67–0·95)
Below diet score median	52 997	2011	High PA vs low PA	0·67 (0·59–0·75)
			Moderate PA vs low PA	0·85 (0·76–0·95)
Above diet score median	55 527	1646	High PA vs low PA	0·65 (0·57–0·74)
			Moderate PA vs low PA	0·79 (0·70–0·90)
Total	**116 083**	**3950**	**High PA vs low PA**	**0·65 (0·60–0·71)**
			Moderate PA vs low PA	**0·80 (0·74–0·87)**

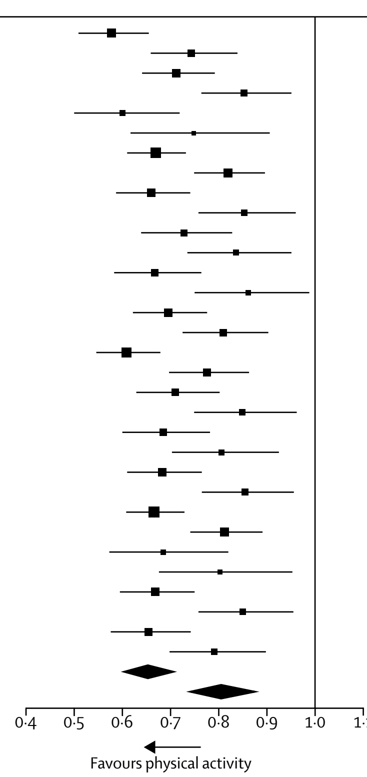


***Figure 2*: Hazard ratios and 95% CI of total physical activity for mortality**

Adjusted for age, sex, education, country income level, urban or 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. Low physical activity (<600 MET × min per week) is the reference group. Moderate physical activity=600–3000 MET × min per week. High physical activity=>3000 MET × min per week. PA=physical activity. HR=hazard ratio. MET=metabolic equivalents. BMI=body-mass index. WHR=waist-to-hip ratio (high WHR was defined as above 0·85 for women and girls and above 0·9 for men and boys).

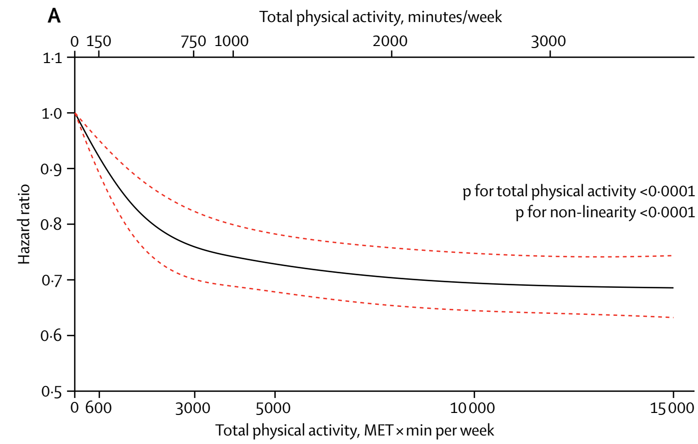
High physical activity was associated with a lower HR than was moderate physical activity for all outcomes. Dichotomising high physical activity above or below the median value in this group of 6453 MET × minutes per week did not show further reductions in risk (appendix). Higher physical activity was also associated with lower HRs in CVD mortality, non-CVD mortality, and myocardial infarction (appendix). With further adjustment for BMI, the HRs were slightly attenuated but remained significant (appendix). Excluding participants who had a CVD event within the first 2 years of follow-up (to account for potential reverse causality if sick individuals were less active), the results were consistent for all outcomes (appendix).

Survival curves for low, moderate, and high physical activity for our three primary outcomes of mortality plus major CVD, mortality, and major CVD indicated a lower risk as physical activity increased ($p<0\cdot0001$; appendix).

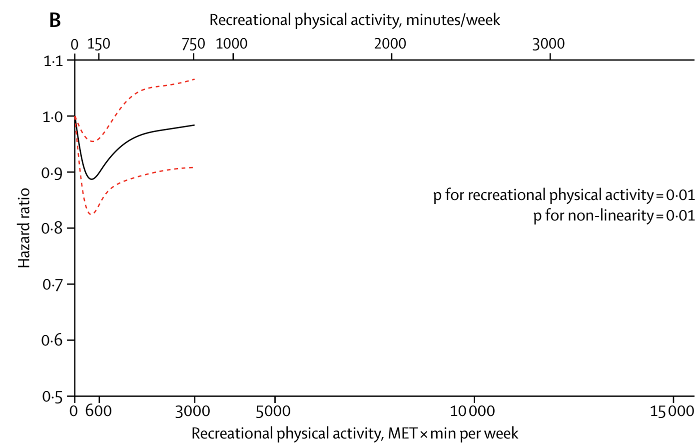
The 5-year adjusted population attributable fraction of not meeting the physical activity guidelines was 5·3% for mortality plus major CVD, 8·0% for mortality, and 4·6% for major CVD (appendix). These values were higher (10·3% for mortality plus major CVD, 13·0% for mortality, and 9·5% for major CVD) in participants who did not achieve high physical activity (appendix).

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

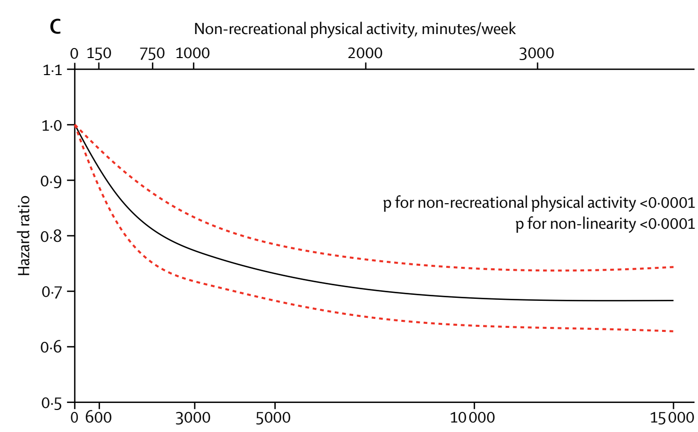
Higher physical activity was associated with significantly lower risk up to approximately 3000 MET × minutes per week (or 750 minutes per week of moderate intensity physical activity) with more modest benefits above that physical activity ($p<0\cdot0001$; figure 3). For recreational physical activity, higher physical activity was associated with significantly lower risk up to approximately 600 MET × minutes per week (or 150 minutes per week of moderate intensity physical activity, $p=0\cdot01$; as few had physical activity higher than this), and for non-recreational physical activity, higher physical activity was associated with significantly lower risk up to approximately 5000 MET × minutes per week (or 1250 minutes per week of moderate intensity physical



Interval (MET × min per week)	0–600	600–3000	3000–5000	5000–10 000	10 000–15 000	>15 000
Total	21 690	46 409	18 781	20 801	8566	6420
Number of events	1941	3007	1028	1247	507	446



Interval (MET × min per week)	0–600	600–3000	>3000
Total	94 893	24 177	3597
Number of events	6647	1342	187



Interval	0–600	600–3000	3000–5000	5000–10 000	10 000–15 000	>15 000
(MET × min per week)	27 968	47 964	15 571	17 547	7597	6020
Total	2384	2964	873	1077	459	419
Number of events						

***Figure 3:* Comparison of physical activity and mortality and major CVD**
(A) Adjusted HR (black line) and 95% CI (red lines) for mortality and major CVD compared with total physical activity. (B) Adjusted HR for mortality and major CVD compared with recreational physical activity. (C) Adjusted HR for mortality and major CVD compared with non-recreational physical activity. Models were adjusted for age, sex, education, country income level, urban or rural residency, family history of CVD, and smoking status, taking into account household, community, and country clustering. Recreational physical activity was truncated at 3000 MET × min per week and 750 min per week of moderate intensity physical activity because of sparse observations above that point. CVD=cardiovascular disease. MET=metabolic equivalents. HR=hazard ratio. Major CVD=CVD mortality plus incident myocardial infarction, stroke, or heart failure.

	Mortality plus major CVD*	Mortality	Major CVD*
High-income countries			
Events	548	259	335
Moderate physical activity†	0·70 (0·54–0·91)	0·69 (0·48–1·00)	0·62 (0·44–0·86)
High physical activity‡	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 physical activity†	0·82 (0·72–0·93)	0·77 (0·66–0·89)	0·86 (0·72–1·03)
High physical activity‡	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 physical activity†	0·99 (0·89–1.10)	0·94 (0·81–1·08)	0·94 (0·82–1.07)
High physical activity‡	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 physical activity†	0·76 (0·67–0·87)	0·73 (0·63–0·85)	0·83 (0·69–1.00)
High physical activity‡	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

Data are n or hazard ratio (95%CI). Hazard ratios (and 95% CI) were adjusted for age, sex, education, country income level, urban or rural residency, family history of CVD, and smoking status taking into account household, community, and country clustering. Low physical activity (<600 MET × min per week) is the reference group. CVD=cardiovascular disease. MET=metabolic equivalents. *CVD mortality plus incident myocardial infarction, stroke, or heart failure. †Moderate physical activity=600–3000 MET × min per week and 150–750 min per week of moderate intensity physical activity. ‡High physical activity=>3000 MET × min per week and >750 min per week of moderate intensity physical activity.

Table 4: **Summary of risk of mortality and major CVD events stratified by country income level and physical activity**

activity) with more modest benefits above that level of physical activity (p<0·0001).

Higher physical activity was associated with significantly lower risk for mortality plus major CVD in upper-middle-income countries and low-income countries; mortality in upper-middle-income countries, lower-middle-income countries, and low-income countries; and major CVD in upper-middle-income countries and low-income countries (table 4). When stratified by country income level (high-income countries and upper-middle-income countries *vs* lower-middle-income countries and low-income countries) there was a significant interaction between country income level and physical activity for total (p=0·0012) and recreational physical activity (p=0·0063) such that the high-income countries and upper-middle-income countries had a lower risk with increasing physical activity (figure 4). This was less clear for non-recreational physical activity (p=0·063).

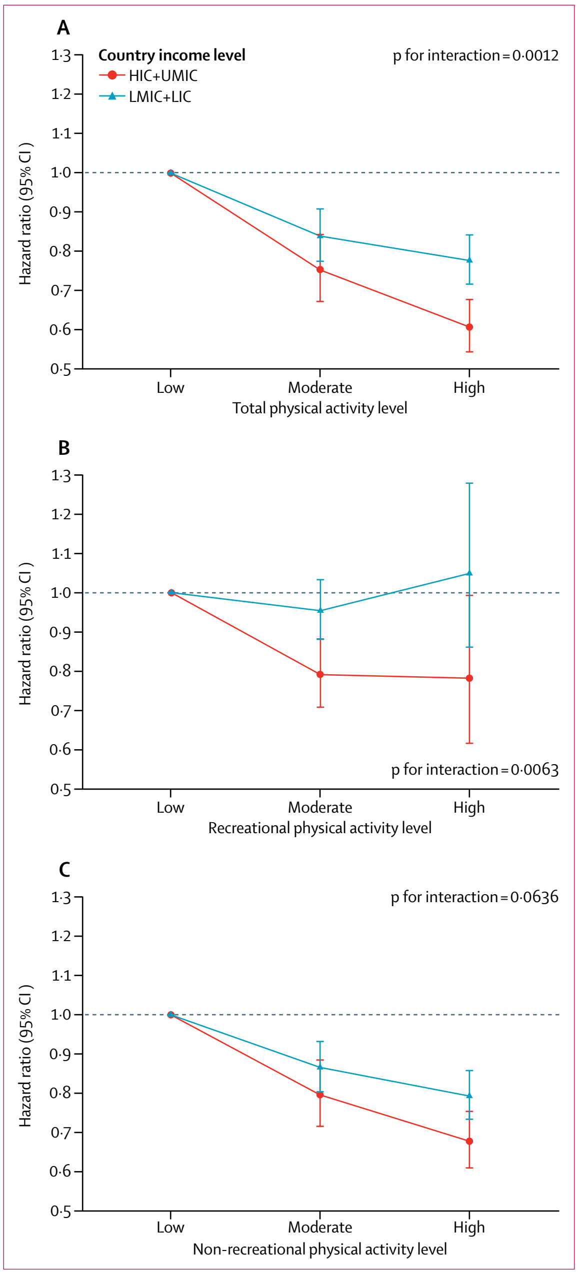


Figure 4: **Comparison of physical activity with mortality and major CVD stratified by country income level**
(A) Total physical activity. (B) Recreational physical activity. (C) Non-recreational physical activity. Models were adjusted for age, sex, education, country income level, urban or rural residency, family history of CVD, and smoking status, taking into account household, community, and country clustering. CVD=cardiovascular disease. 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 myocardial infarction, stroke, or heart failure.

Discussion

In this study involving three high-income countries, seven upper-middle-income countries, three lower-middle-income countries, and four low-income countries, higher physical activity was associated with a lower risk for mortality and incidence of major CVD. This lower risk was present even at moderate physical activity compared with low physical activity, and was more marked at higher physical activity. The benefit of physical activity was independent of the type of physical activity (recreational or non-recreational), a range of socioeconomic and CVD risk

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factors, and was similar in various countries with differing income levels.

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

When stratified by country income level, there was a consistent reduction of risk with increasing physical activity. In high-income countries, meeting the physical activity 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 done predominantly in high-income countries.[12] However, this earlier study did not include participants in the high physical activity range (>3000 MET×minutes per week), in whom we found a continued benefit with increasing physical activity. Studies in Iran and China[32,33] also reported physical activity to be significantly associated with lower mortality in a dose-dependent manner. Notably, Matthews and colleagues[33] reported an HR of 0·61 (95% CI 0·51–0·73) at the highest physical activity 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 lower-middle-income category of countries, of which Iran and China accounted for by far the most participants in our lower-middle-income countries.

Higher physical activity was associated with a lower risk of mortality plus major CVD in higher-income and upper-middle-income countries compared with lower-middle-income and low-income countries for both total and recreational physical activity; differences with respect to non-recreational physical activity were less clear. It is unclear why recreational physical activity might be less effective in the lower-middle-income and low-income countries; however, few participants from the countries participated in any recreational physical activity and so these findings could be swayed by a few participants who are atypical of the general populations in poorer countries.

Few studies have assessed the association of non-recreational physical activity with outcomes. The available studies are small and report inconsistent results.[12,34–38] Higher recreational and non-recreational physical activity were independently associated with lower risk with our composite of all-cause mortality plus major CVD, indicating that physical activity of any type is beneficial. Of note, high physical activity was only possible in those individuals participating in non-recreational physical activity. Indeed, only 2·9% of our study population participated in high physical activity (≥3000 MET×minutes per week or ≥750 minutes per week of moderate intensity physical activity) that derived exclusively from recreational physical activity compared with 37·9% of participants who attained this through non-recreational physical activity. This reflects the challenges inherent with participating in high recreational physical activity in that it is, by definition, done during discretionary hours of the day outside of occupational and domestic duties. By contrast, incorporating physical activity into a daily lifestyle whether through active transportation, occupation, or domestic duties has the potential to achieve higher physical activity that is associated with even lower risk for mortality and CVD events.

To address concerns related to reverse causality, we excluded individuals with known CVD and then did a sensitivity analysis further excluding those who had events within the first 2 years of follow-up. Our results were unchanged for our main study outcomes. We also did subgroup analyses stratified by sex, age, BMI, smoking, presence of hypertension, and presence of diabetes, and observed consistent results. We also observed that increasing physical activity was associated with reduced CVD and non-CVD mortality. Regular physical activity is associated with lower mortality from some cancers[28,34,36,39] and respiratory conditions.[40] With continued follow-up, we anticipate accruing enough events to reliably investigate the effects of physical activity on specific categories of non-CVD mortality.

Our study had several limitations. Although physical activity defined from the self-reported IPAQ modestly overestimates physical activity, it demonstrates good reliability and moderate validity compared with accelerometers such that higher IPAQ values correspond to higher physical activity measured by accelerometers, thus providing good internal validity.[15,41,42] If physical activity is overestimated by the IPAQ, then the potential benefits of physical activity could be more marked and might occur at lower physical activity than reported here. 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 physical activity in large studies is considered acceptable in low-resource settings.[43]

Although it was not feasible to collect a proportionate sampling of the world'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 with national data (appendix).[44] Although we did not recruit a random sample of individuals, our approach minimised 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 might have been misclassified. However, we believe this potential misclassification to include few events, as most events were ascertained using supporting documents, standard definitions, and adjudication using standard definitions providing high confidence in the validity. Lastly, in such a large study, it is not uncommon to report low p values that might 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 are confident in our main findings.

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

Contributors

SAL wrote the analysis plans and had the primary responsibility for writing this paper. SY designed and supervised the study, data analysis, interpreted the data and reviewed and commented on drafts. SR coordinated the worldwide study and reviewed and commented on drafts. WH did the analysis. KT, WH, AC, DL, and DG 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.

Declarations of interest

We declare no competing interests.

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