The burden of cardiovascular events according to cardiovascular risk profile in adults from high-income, middle-income, and low-income countries (PURE): a cohort study

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Summary

Background Current strategies to prevent adverse cardiovascular outcomes focus primary prevention in high-risk groups and secondary prevention in people with known cardiovascular disease. We aimed to determine the proportion of events occurring in lower-risk groups globally.

Methods We included people aged 40 years to younger than 75 years who were enrolled in the Prospective Urban Rural Epidemiology (PURE) study, which is an ongoing, international, prospective, population-based cohort study that started recruiting adults from households selected to be broadly representative of the sociodemographic composition of their communities. We prospectively documented fatal or non-fatal myocardial infarction, stroke, heart failure, or any other fatal cardiovascular event stratified by history of cardiovascular disease and by the 10-year predicted disease risk scores based on WHO 2019 laboratory risk tables (<10% [low], 10% to <20% [intermediate], and ≥20% [high]) in people without previous cardiovascular disease from 26 high-income, middle-income, and low-income countries. Outcome event rates were standardised for the cohort's age and sex distribution.

Findings Between July 11, 2000, and May 6, 2019, 128 973 participants were included from 26 countries (mean age 53·6 years [SD 8·2]; 75 858 [58·8%] were female and 53 115 [41·2%] were male). We observed 11 483 outcome events affecting 8·9% of the cohort during a median follow-up of 12·3 years (IQR 9·8–14·6). Among participants, 89 508 (69·4%) had a low cardiovascular disease risk, 22 363 (17·3%) had an intermediate cardiovascular disease risk, and 5529 (4·3%) had a high cardiovascular disease risk, while 11 573 (9·0%) had known cardiovascular disease. The age-standardised and sex-standardised cardiovascular disease incidence rates per 1000 person-years was 4·1 (95% CI 4·0–4·2) in the low-risk group, 17·7 (15·2–20·2) in the intermediate-risk group, and 40·8 (25·1–56·4) in the high-risk group. Overall, 41% of outcome events occurred in cardiovascular disease-naive participants at low risk. The proportion of adverse cardiovascular outcomes occurring in this low-risk group was inversely related to country income level (32% in high-income, 38% in middle-income, and 54% in low-income countries) and was higher in women (51%) than in men (32%).

Interpretation To achieve a substantial population-level reduction in cardiovascular disease, a fundamental change is needed, so that preventive strategies for cardiovascular disease extend beyond those at high or even intermediate predicted risk to include those at considered to be at low risk.

Funding The funding bodies are listed in the appendix (p 29).

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Introduction

Currently, strategies for the prevention of adverse cardiovascular outcomes focus on secondary prevention in people with known cardiovascular disease[1] and primary prevention in high-risk groups.[2] However, in European populations, most cardiovascular events occur in people with no history of cardiovascular disease and without established cardiovascular risk factors because most of the population falls into this category.[3] Therefore, it has been postulated that population-wide approaches to preventing cardiovascular events would lead to greater reductions in these outcomes than the current approach of targeting only people who are at high risk of or have established cardiovascular disease.[4,5]

Most cardiovascular events globally occur in low-income and middle-income countries.[6] However, there is a paucity of data from these countries on the occurrence of cardiovascular events in people with established

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Research in context

Evidence before this study

We searched PubMed using the search strategy "low-risk" AND "cardi*" AND "primary prevention" on Feb 5, 2025, to identify original research in which cardiovascular event rates were reported stratified by baseline cardiovascular risk as determined by a published risk score. We reviewed all the abstracts identified since inception irrespective of language. Few studies specifically described the burden of cardiovascular events occurring in adults considered to be at low risk versus high risk. Data extracted from cohort studies show considerable variation depending on cohort age and nationality. Individuals at low risk account for a fifth to three-fifths of cardiovascular events in these studies.

Added value of this study

To our knowledge, there are no studies including data from countries across all income levels to inform the burden of cardiovascular events in adults at low risk. Therefore, the present study represents novel data to inform the use of resources to reduce the population burden of cardiovascular disease.

Implications of all the available evidence

According to current recommendations, adults without established cardiovascular disease and who are considered at lower risk are not treated with risk-reducing pharmacotherapies. However, we found that nearly half of cardiovascular events occur in these individuals. To mitigate the population burden of cardiovascular disease, strategies to reduce the incidence of cardiovascular events in this lower-risk group need to be developed and implemented.

cardiovascular disease or at high risk of cardiovascular disease versus those at low risk. Therefore, in this analysis of the Prospective Urban Rural Epidemiology (PURE) study, we aimed to describe the proportion of incident adverse cardiovascular events stratified by baseline cardiovascular risk in adults from low-income countries (LICs), middle-income countries (MICs), and high-income countries (HICs).

Methods

Overview

The PURE study is an ongoing, international, prospective, population-based cohort study, and its design has previously been described.[7] The study is conducted in HICs, MICs, and LICs, which are categorised based on gross national income per capita according to the World Bank classification in 2006 when most countries started recruiting participants.[8] This analysis included adults aged 40 years to younger than 75 years who had a history of cardiovascular disease or baseline evaluation of cardiovascular risk using WHO's 2019 laboratory risk tables (which provide region-specific risk estimates based on sex, tobacco use, systolic blood pressure, diabetes, and cholesterol)[9] and who had at least one follow-up visit.

The PURE study received approval from the ethics committees at each centre, and all participants provided written informed consent.

Data collection

At baseline, standardised questionnaires produced by investigators were used to collect information on participant characteristics and medical history. Participants were considered to have a history of cardiovascular disease if they reported being diagnosed with angina, myocardial infarction, coronary artery disease, stroke, or heart failure. Further detail on baseline data collection is provided in the appendix (p 16).

In participants without a history of cardiovascular disease, we calculated the laboratory WHO cardiovascular risk score, which is a validated measure of 10-year risk of future cardiovascular disease based on age, sex, smoking, diabetes, systolic blood pressure, and cholesterol.[10] We categorised the cardiovascular disease risk of these individuals as less than 10% (low-risk group), 10% to less than 20% (intermediate-risk group), and 20% or higher (high-risk group) corresponding to WHO intervention thresholds.[9]

Participants were contacted at least every 3 years to ascertain their vital status and the occurrence of specific non-fatal events. Where possible, detailed information on cause of death was obtained from verbal autopsies or medical records, and on non-fatal events from hospital or physician reports and standardised questionnaires.

Outcomes

The primary outcome of this analysis was a new cardiovascular disease event, defined as fatal or non-fatal myocardial infarction, stroke, heart failure, or any other fatal event determined to be of cardiovascular cause. These events were adjudicated centrally in each country by trained physicians using standardised definitions (appendix p 17).

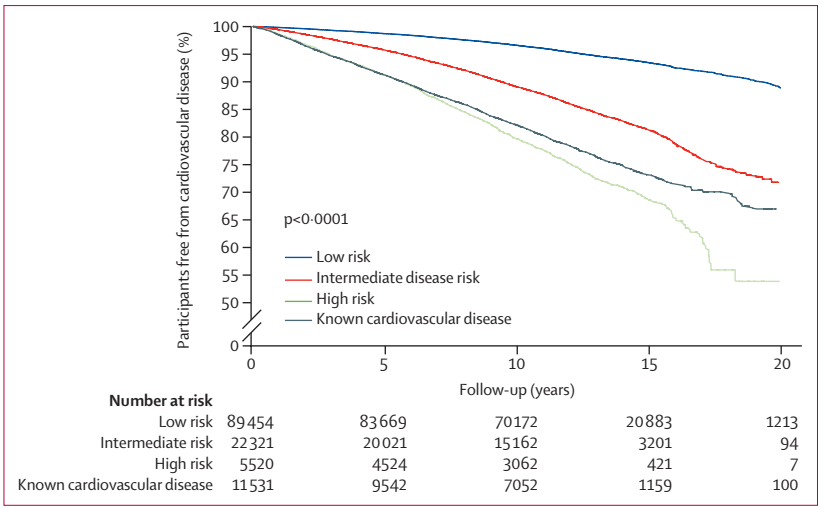
Statistical analysis

Under a null hypothesis that most cardiovascular events occur in adults with either a history of cardiovascular disease or at intermediate or greater predicted risk, our sample size and cardiovascular risk distribution had 82% power to determine that only 46% of events occur in this group (intermediate and high risk or past cardiovascular disease) and at least 54% of events occur in participants at low predicted risk. Participants were stratified into four mutually exclusive groups: those with a baseline history of cardiovascular disease, and in those without a history of cardiovascular disease, using the

	Cardiovascular risk group*				Country income level†			Total (n=128 973)
	Low (n=89 508)	Intermediate (n=22 363)	High (n=5529)	Known cardiovascular disease (n=11 573)	High (n=15 146)	Middle (n=95 332)	Low (n=18 495)	
Age, years	50·7 (7·0)	60·5 (6·3)	63·4 (5·6)	58·0 (7·6)	54·1 (8·2)	53·7 (8·0)	52·5 (8·9)	53·6 (8·2)
Sex								
Female	58 302 (65·1%)	9228 (41·3%)	1780 (32·2%)	6548 (56·6%)	7993 (52·8%)	57 543 (60·4%)	10 322 (55·8%)	75 858 (58·8%)
Male	31 206 (34·9%)	13 135 (58·7%)	3749 (67·8%)	5025 (43·4%)	7153 (47·2%)	37 789 (39·6%)	8173 (44·2%)	53 115 (41·2%)
Country income level								
High	10 437 (11·7%)	3147 (14·1%)	611 (11·1%)	951 (8·2%)	..	..	..	15 146 (11·7%)
Middle	64 662 (72·2%)	16 580 (74·1%)	4566 (82·6%)	9524 (82·3%)	..	..	..	95 332 (73·9%)
Low	14 409 (16·1%)	2636 (11·8%)	352 (6·4%)	1098 (9·5%)	..	..	..	18 495 (14·3%)
Education								
Primary	31 385/81 333 (38·6%)	9245/20 253 (45·6%)	2491/4939 (50·4%)	4262/9789 (43·5%)	1874/15 125 (12·4%)	36 671/82 764 (44·3%)	8838/18 425 (48·0%)	47 383/116 314 (40·7%)
Secondary	31 432/81 333 (38·6%)	6667/20 253 (32·9%)	1416/4939 (28·7%)	3293/9789 (33·6%)	4440/15 125 (29·4%)	31 416/82 764 (38·0%)	6952/18 425 (37·7%)	42 808/116 314 (36·8%)
University or trade school	18 516/81 333 (22·8%)	4341/20 253 (21·4%)	1032/4939 (20·9%)	2234/9789 (22·8%)	8811/15 125 (58·3%)	14 677/82 764 (17·7%)	2635/18 425 (14·3%)	26 123/116 314 (22·5%)
Tobacco								
Former	13 226 (14·8%)	3849 (17·2%)	864 (15·6%)	13 226 (14·8%)	5242 (34·6%)	14 311 (15·1%)	1008 (5·5%)	20 561 (16·0%)
Current	14 458 (16·2%)	6964 (31·1%)	2454 (44·4%)	14 458 (16·2%)	2071 (13·7%)	19 735 (20·8%)	3959 (21·4%)	25 765 (20·0%)
Never	61 824 (69·1%)	11 550 (51·6%)	2211 (40·0%)	61 824 (69·1%)	7830 (51·7%)	61 030 (64·2%)	13 510 (73·1%)	82 370 (64·0%)
Alcohol								
Former	4211/88 700 (4·7%)	1371/22 069 (6·2%)	408/5399 (7·6%)	1206/11 178 (10·8%)	951/15 114 (6·3%)	5650/93 785 (6·0%)	595/18 447 (3·2%)	7196/127 346 (5·7%)
Current	30 414/88 700 (34·3%)	8452/22 069 (38·3%)	2128/5399 (39·4%)	3454/11 178 (30·9%)	10 458/15 114 (69·2%)	31 969/93 785 (34·1%)	2021/18 447 (11·0%)	44 448/127 346 (34·9%)
Never	54 075/88 700 (61·0%)	12 246/22 069 (55·5%)	2863/5399 (53·0%)	6518/11 178 (58·3%)	3705/15 114 (24·5%)	56 166/93 785 (59·9%)	15 831/18 447 (85·8%)	75 702/127 346 (59·4%)
Diabetes (self-report)								
No	86 098/89 428 (96·3%)	18 428/22 340 (82·5%)	3632/5521 (65·8%)	9071/11 547 (78·6%)	13 663/2835 (90·3%)	87 589/97 221 (92·0%)	15 977/18 483 (86·4%)	117 229/128 836 (91·0%)
Yes	3330/89 428 (3·7%)	3912/22 340 (17·5%)	1889/5521 (34·2%)	2476/11 547 (21·4%)	1469/2835 (9·7%)	7632/97 221 (8·0%)	2506/18 483 (13·6%)	11 607/128 836 (9·0%)
Blood glucose, mmol/L	5·1 (1·5)	6·0 (2·5)	7·0 (3·1)	5·8 (2·4)	5·6 (1·6)	5·4 (1·8)	5·6 (2·9)	5·4 (2·0)
Hypertension (self-report)								
No	73 305/89 412 (82·0%)	14 154/22 339 (63·4%)	2656/5519 (48·1%)	4585/11 498 (39·9%)	11 671/15 129 (77·1%)	68 592/95 156 (72·1%)	14 437/18 483 (78·1%)	94 700/128 768 (73·5%)
Yes	16 107/89 412 (18·0%)	8185/22 339 (36·6%)	2863/5519 (51·9%)	6913/11 498 (60·1%)	3458/15 129 (22·9%)	26 564/95 156 (27·9%)	4046/18 483 (21·9%)	34 068/128 768 (26·5%)
Systolic blood pressure, mm Hg	128·1 (18·1)	147·6 (21·1)	167·0 (24·0)	139·8 (23·5)	130·7 (18·5)	135·5 (22·2)	130·3 (22·8)	134·2 (22·0)
BMI, kg/m²	26·1 (5·4)	26·8 (5·4)	27·3 (5·3)	27·8 (5·7)	27·9 (5·6)	26·7 (5·3)	23·8 (5·3)	26·4 (5·4)
Waist-to-hip ratio	0·9 (0·1)	0·9 (0·1)	0·9 (0·1)	0·9 (0·1)	0·9 (0·1)	0·9 (0·1)	0·9 (0·1)	0·9 (0·1)
Alternate Healthy Eating Index score	34·5 (8·5)‡	34·7 (8·6)‡	34·7 (8·5)‡	35·5 (8·6)‡	34·6 (10·2)	34·5 (8·4)	35·1 (7·2)	34·6 (8·5)
Physical activity								
Low	12 094/83 395 (14·5%)	3878/21 148 (18·3%)	1141/5322 (21·4%)	2053/11 055 (18·6%)	2025/13 982 (14·5%)	13 619/91 125 (14·9%)	3522/15 813 (22·3%)	19 166/120 920 (15·9%)
Medium	31 211/83 395 (37·4%)	8198/21 148 (38·8%)	2068/5322 (38·9%)	4502/11 055 (40·7%)	4937/13 982 (35·3%)	35 430/91 125 (38·9%)	5612/15 813 (35·5%)	45 979/120 920 (38·0%)
High	40 090/83 395 (48·1%)	9072/21 148 (42·9%)	2113/5322 (39·7%)	4500/11 055 (40·7%)	7020/13 982 (50·2%)	42 076/91 125 (46·2%)	6679/15 813 (42·2%)	55 775/120 920 (46·1%)
Handgrip strength, kg	30·4 (11·1)	31·3 (11·3)	31·4 (10·6)	28·8 (10·9)	35·7 (12·3)	30·6 (10·8)	25·1 (9·2)	30·5 (11·1)

Data are mean (SD), n (%), or n/N (%). Percentages might not sum to 100 because of rounding. p values across the four mutually exclusive cardiovascular disease risk groups and across country income levels were all less than 0·0001, except where indicated. *10-year cardiovascular disease risk according to the WHO risk score.[9] †Country income levels are categorised based on gross national income per capita according to the World Bank classification in 2006 when most countries were recruiting participants.[8] ‡p=0·036.

Table 1: **Participant baseline characteristics stratified by baseline cardiovascular disease versus no cardiovascular disease and by country income level**



Number at risk					
Low risk	89454	83669	70172	20883	1213
Intermediate risk	22321	20021	15162	3201	94
High risk	5520	4524	3062	421	7
Known cardiovascular disease	11531	9542	7052	1159	100

Figure 1: **Kaplan–Meier curves for cardiovascular events (myocardial infarction, stroke, heart failure, or cardiovascular death) stratified by the presence of known cardiovascular disease and predicted 10-year cardiovascular risk according to the WHO model[9] in those without known cardiovascular disease**
The four mutually exclusive cardiovascular risk groups were history of non-fatal cardiovascular disease and in those with no history of cardiovascular disease, according to strata of cardiovascular disease risk (ie, low [<10%], intermediate [10% to <20%], and high [≥20%] 10-year risk) according to WHO.[9]

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See Online for appendix

WHO cardiovascular risk predictor, into those with a 10-year predicted low, intermediate, or high risk of a fatal or non-fatal cardiovascular event based on their baseline risk factors.[9] Groups were compared using linear regression to estimate mean differences and 95% CIs for continuous variables and logistic regression for categorical variables.

Differences in time to cardiovascular disease (defined as the time from baseline visit to the first primary outcome event or the participant's most recent study visit in the absence of a primary outcome event) among the four groups were evaluated using Kaplan–Meier curves and Cox models adjusted for country income level,[11] education,[12] BMI,[13] Alternative Health Eating Index,[14] physical activity,[15] and handgrip strength.[16] These covariates have all been demonstrated to have strong associations with cardiovascular disease and death, and with components of the WHO risk score. The proportional hazards assumption was evaluated by visual inspection of log–log plots stratified by cardiovascular disease risk groups. The functional form of continuous covariates was evaluated by visual inspection of Martingale residual plots, which indicated that it was appropriate to include these variables untransformed in the model.

Our primary analysis was based on counts of cardiovascular disease events in each stratum expressed as a percentage of the total number of events. Analyses were also stratified by sex and by the presence of hypertension, diabetes, or smoking, by age older than 55 years versus 55 years or younger, at baseline, and by country income level.

In addition, to account for differences in length of follow-up among the four groups, we estimated the numbers of events in each stratum using Poisson regression with the logarithmic link function adjusting for follow-up duration.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Between July 11, 2000, and May 6, 2019, 128 973 participants were included from 26 countries (appendix p 4). Baseline characteristics are shown in table 1 and the appendix (p 5; in which data are presented as row percentages). Mean age was 53·6 years (8·2), and 75 858 (58·8%) participants were female and 53 115 (41·2%) were male. Higher-risk groups were older, while participants from LICs were younger. Females had lower cardiovascular disease risk scores than males and at baseline, and 6548 (8·6%) of 75 858 females had a history of cardiovascular disease, as compared with 5025 (9·5%) of 53 115 males (p<0·0001). Individuals from LICs had lower cardiovascular disease risk scores than those in MICs or HICs at baseline.

Baseline cardiovascular disease was present in 951 (6·3%) of 15 146 participants in HICs, 9524 (10·0%) of 95 332 participants in MICs, and 1098 (5·9%) of 18 495 participants in LICs (p<0·0001). In LICs, fewer individuals were at high baseline cardiovascular risk (352 [1·9%]) than in MICs (4566 [4·8%]) and in HICs (611 [4·0%]). Participants with lower levels of education had more cardiovascular disease and cardiovascular disease risk factors than individuals with higher education, and participants from LICs had lower education levels than those from MICs and HICs. Baseline cardiovascular disease was present in 6518 (8·2%) of 75 702 alcohol never drinkers, 3454 (7·8%) of 44 448 current drinkers, and 1206 (16·8%) of 7196 former drinkers (p<0·0001), and current and former drinkers had higher cardiovascular disease risk than never drinkers.

At baseline, cardiovascular disease was present in 6785 (8·2%) of 82 370 never smokers, 1889 (7·3%) of 25 765 current smokers, and 2622 (12·8%) of 20 561 former smokers (p<0·0001). Of individuals with versus without diabetes, 2855 (18·0%) of 15 823 versus 8718 (7·7%) of 113 150 had known cardiovascular disease (p<0·0001). Of individuals with versus without hypertension, 7607 (12·5%) of 60 642 versus 3448 (5·1%) of 67 682 had known cardiovascular disease (p<0·0001). Respective BMIs in participants with versus without baseline cardiovascular disease were 27·8 kg/m² (SD 5·7) versus 26·3 kg/m² (5·4; p<0·0001)—a clinically relevant difference—and there was a positive relationship between BMI and WHO risk. There was also a positive relationship between BMI country income level.

The difference in diet quality among the different cardiovascular disease risk groups was not clinically

	Participants	Number of cardiovascular disease events per 1000 participants standardised for age, sex, and follow-up duration	Cardiovascular disease event rate per 1000 person-years standardised for age and sex	Number of cardiovascular disease events adjusted for age, sex, and follow-up duration	Proportion of cardiovascular disease events
Overall					
Low cardiovascular disease risk*	89 508	39·4 (39·1–39·8)	4·1 (4·0–4·2)	4738 (4738–4738)	41%
Intermediate cardiovascular disease risk*	22 363	28·0 (27·8–28·1)	17·7 (15·2–20·2)	3205 (3205–3205)	27%
High cardiovascular disease risk*	5529	11·3 (11·2–11·3)	40·8 (25·1–56·4)	1272 (1272–1272)	11%
Known cardiovascular disease	11 573	21·8 (21·7–21·9)	17·7 (16·9–18·6)	2415 (2415–2415)	21%
High-income countries					
Low cardiovascular disease risk*	10 437	22·9 (22·6–23·1)	3·2 (2·4–4·0)	339 (339–339)	32%
Intermediate cardiovascular disease risk*	3147	22·0 (21·8–22·2)	7·3 (6·2–8·5)	332 (332–332)	32%
High cardiovascular disease risk*	611	8·3 (8·3–8·3)	15·7 (10·7–20·8)	123 (123–123)	12%
Known cardiovascular disease	951	16·5 (16·5–16·5)	30·9 (26·5–35·2)	247 (247–247)	24%
Middle-income countries					
Low cardiovascular disease risk*	64 662	33·0 (32·6–33·3)	4·1 (3·9–4·3)	2994 (2994–2994)	38%
Intermediate cardiovascular disease risk*	16 580	25·1 (25·0–25·3)	14·6 (12·9–16·3)	2167 (2167–2167)	27%
High cardiovascular disease risk*	4566	11·4 (11·4–11·5)	28·6 (23·4–33·8)	980 (980–980)	12%
Known cardiovascular disease	9524	21·5 (21·4–21·6)	18·0 (17·1–19·0)	1818 (1818–1818)	23%
Low-income countries					
Low cardiovascular disease risk*	14 409	76·2 (75·7–76·7)	6·7 (6·3–7·0)	1405 (1405–1405)	54%
Intermediate cardiovascular disease risk*	2636	38·4 (38·2–38·7)	39·3 (32·8–45·9)	706 (706–706)	27%
High cardiovascular disease risk*	352	9·2 (9·2–9·2)	116·3 (89·3–143·3)	169 (169–169)	6%
Known cardiovascular disease	1098	19·0 (19·0–19·0)	27·4 (24·3–30·6)	350 (350–350)	13%

Estimates are presented with 95% CIs, except the proportion of cardiovascular disease events, which was calculated by dividing the predicted number of events in each risk stratum by the sum of the predicted number of events across all risk strata. Country income levels are categorised based on gross national income per capita according to the World Bank classification in 2006 when most countries were recruiting participants.[8] *10-year cardiovascular disease risk according to the WHO risk score (low was <10%, intermediate was 10% to <20%, and high was ≥20%).[9]

Table 2: **Numbers of cardiovascular disease events and rates**

important. However, those with a history of cardiovascular disease were less physically active than those who did not have known cardiovascular disease, among whom there was a clinically important inverse association between physical activity and WHO risk. Participants in HICs were more physically active than those in LICs, who also had less handgrip strength. Individuals with known cardiovascular disease had less handgrip strength than those without known cardiovascular disease, although the size of the difference is of uncertain clinical significance and causal relationship.

During a median follow-up of 12·3 years (IQR 9·8–14·6), 8255 (6·4%) of participants died from non-cardiovascular causes, 11 483 (8·9%) of participants had a major adverse cardiovascular event (myocardial infarction, stroke, heart failure, or fatal cardiovascular disease), and 109 235 (84·7%) were censored on the date of their most recent study visit. Among participants, 89 508 (69·4%) had a low predicted 10-year cardiovascular disease risk, 22 363 (17·3%) had an intermediate risk, and 5529 (4·3%) had a high risk, while 11 573 (9·0%) had known cardiovascular disease. As expected, increasing cardiovascular disease risk at baseline was associated with increased cardiovascular disease during follow-up (figure 1; table 2).

Adjusting for country income level, education, BMI, Alternate Healthy Eating Index score, physical activity levels, and handgrip strength, as compared with the low-risk group, the hazard ratio for cardiovascular disease was 3·11 (95% CI 2·96–3·27) in the intermediate-risk group, 6·08 (5·68–6·51) in the high-risk group, and 5·38 (5·08–5·69) in the known cardiovascular disease group.

We evaluated the calibration of the WHO cardiovascular disease risk score by plotting predicted versus observed cardiovascular disease probabilities. This analysis demonstrated that the risk score overestimated cardiovascular disease risk overall (appendix p 11). However, there was heterogeneity in calibration according to country income level. Calibration appeared to be best in HICs, whereas in MICs the risk score overestimated cardiovascular disease risk and in LICs it underestimated cardiovascular disease risk (appendix p 11).

The proportion of incident cardiovascular disease events occurring in four mutually exclusive groups—those with baseline cardiovascular disease, and those without baseline cardiovascular disease stratified by WHO cardiovascular disease risk score—is shown in figure 2 and table 2. Overall, two in every five cardiovascular disease events occurred in individuals with no history of cardiovascular disease and considered to be at low

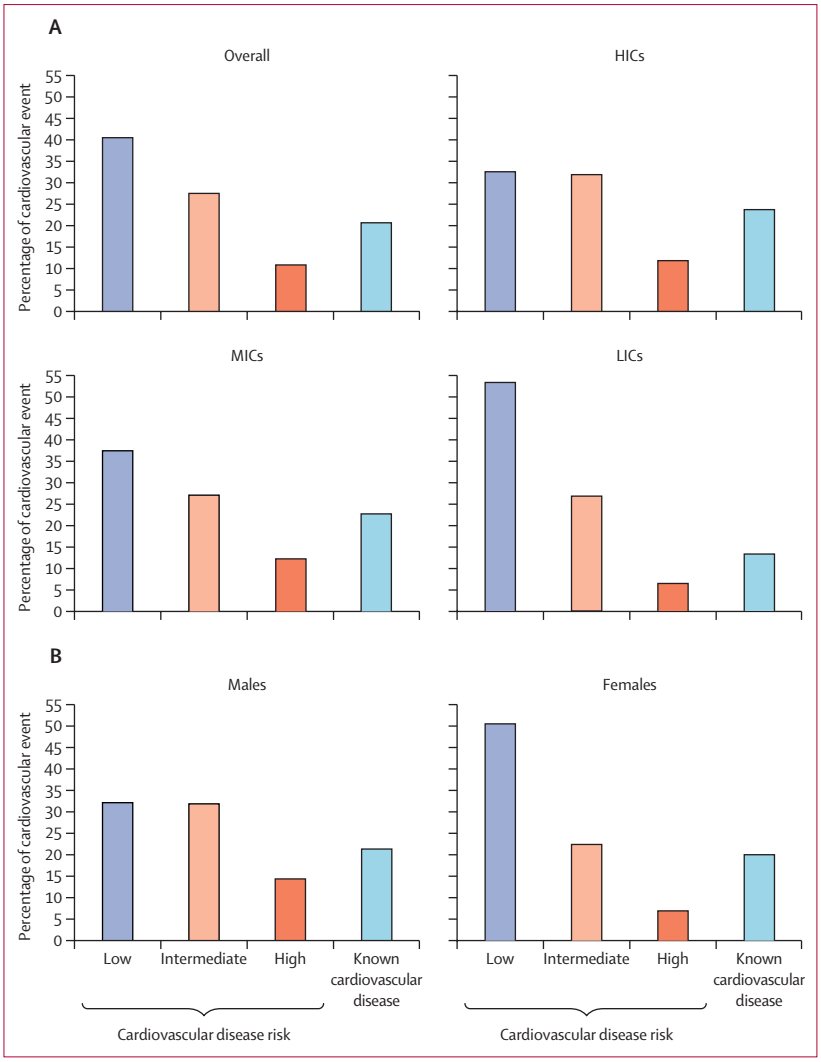

Figure 2: **Proportion of incident cardiovascular disease events occurring in different cardiovascular risk groups overall and stratified by country income level (A) and by sex (B)**

Incident cardiovascular disease includes myocardial infarction, stroke, heart failure, or other fatal cardiovascular event. The four mutually exclusive cardiovascular risk groups were history of non-fatal cardiovascular disease and in those with no history of cardiovascular disease, according to strata of cardiovascular disease risk (ie, low [<10%], intermediate [10% to <20%], and high [≥20%] 10-year risk) according to WHO.[9] HICs=high-income countries. LICs=low-income countries. MICs=middle-income countries.

cardiovascular disease risk, while only one in ten cardiovascular disease events occurred in those with no history of cardiovascular disease and considered at high cardiovascular disease risk. There was a progressive increase in the proportion of cardiovascular disease occurring in low-risk or intermediate-risk groups from HICs to MICs to LICs (figure 2A). In HICs, a third of cardiovascular disease events occurred in participants with no known cardiovascular disease and a low cardiovascular disease risk score. This proportion was higher in MICs, whereas in LICs most cardiovascular disease events occurred in this group; in LICs, only one in five cardiovascular disease cases occurred in individuals with previous cardiovascular disease or with a high risk.

In both males and females, about one in five new cardiovascular disease events occurred in those with a history of cardiovascular disease (figure 2B). We observed differences between males and females in the proportions of cardiovascular disease events occurring in low-risk groups (figure 2B). In females, half of cardiovascular disease events developed in those with no known cardiovascular disease who were classified as low risk, as compared with males, among whom a third of cardiovascular disease occurred among individuals with low risk and nearly a half occurred in those with no history of cardiovascular disease but estimated to have more than 10% 10-year risk. Among females, the proportion of cardiovascular disease events occurring in those with no known cardiovascular disease who were classified as low risk was highest in LICs, with 51%, 47%, and 63% of events occurring in low-risk individuals in HICs, MICs, and LICs, respectively. A similar pattern was seen in males, with 23%, 29%, and 45% of cardiovascular disease events occurring in those at low risk with no known cardiovascular disease in HICs, MICs, and LICs, respectively.

We examined the proportion of adverse cardiovascular events occurring in the presence of the major individual cardiovascular disease risk factors. Of all incident cardiovascular disease events, 24% developed in those with diabetes (self-reported, on blood glucose-lowering medications or with fasting plasma glucose concentration ≥7 mmol/L) and 26% developed in current smokers.

In total, 42% of cardiovascular disease events occurred in those with self-reported hypertension. However, of 94 700 participants who reported not having hypertension, 29 365 (31·0%) had baseline systolic blood pressure of 140 mm Hg or higher and/or diastolic blood pressure of 90 mm Hg or higher. Overall, 66% of cardiovascular disease events occurred in individuals with self-reported hypertension, taking blood pressure-lowering medications, or with blood pressure of 140/90 mm Hg or higher.

Overall, 62% of cardiovascular disease events occurred in individuals older than 55 years. The respective proportions of cardiovascular disease events occurring in individuals older than 55 years in HICs, MICs, and LICs were 66%, 70%, and 56%.

We undertook exploratory analyses to identify baseline characteristics associated with the development of cardiovascular disease among individuals considered to be at low risk at baseline. The Cox model analysis demonstrated that lower country income, lower attained education, lower physical activity, and lower handgrip strength (and BMI ≥30 kg/m² in males) were independently associated with incident cardiovascular disease in this subgroup, with country income and education demonstrating particularly strong associations (table 3).

Discussion

The main findings from this analysis of adults from 26 HICs, MICs, and LICs during 2000–19 are that, overall,

	Overall		Males		Females	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Country income level						
High	1 (ref)	..	1 (ref)	..	1 (ref)	..
Middle	1·40 (1·23–1·60)	<0·0001	1·31 (1·07–1·59)	0·0080	1·42 (1·19–1·70)	0·0001
Low	1·57 (1·35–1·82)	<0·0001	1·55 (1·24–1·94)	0·0001	1·45 (1·19–1·77)	0·0002
Education						
> Secondary	1 (ref)	..	1 (ref)	..	1 (ref)	..
Secondary	1·27 (1·15–1·41)	<0·0001	1·27 (1·11–1·47)	0·0007	1·37 (1·18–1·60)	<0·0001
< Secondary	1·67 (1·51–1·85)	<0·0001	1·53 (1·32–1·78)	<0·0001	2·00 (1·73–2·32)	<0·0001
BMI						
20 to <30 kg/m²	1 (ref)	..	1 (ref)	..	1 (ref)	..
<20 kg/m²	1·10 (0·99–1·21)	0·07	1·01 (0·87–1·17)	0·89	1·12 (0·97–1·29)	0·11
≥30 kg/m²	1·04 (0·96–1·00)	0·36	1·36 (1·18–1·56)	<0·0001	0·96 (0·86–1·06)	0·42
Alternative Health Eating Index	1·000 (0·996–1·004)	0·85	0·994 (0·988–1·000)	0·053	1·004 (0·999–1·010)	0·091
Physical activity						
High	1 (ref)	..	1 (ref)	..	1 (ref)	..
Medium	1·14 (1·06–1·22)	0·0002	1·10 (0·99–1·23)	0·082	1·21 (1·11–1·33)	<0·0001
Low	1·29 (1·18–1·41)	<0·0001	1·15 (1·01–1·30)	0·039	1·39 (1·23–1·57)	<0·0001
Handgrip strength by quartile						
Highest	1 (ref)	..	1 (ref)	..	1 (ref)	..
3rd	1·15 (1·05–1·27)	0·0034	1·20 (1·04–1·39)	0·016	1·15 (1·02–1·31)	0·025
2nd	1·17 (1·06–1·29)	0·0017	1·33 (1·15–1·55)	0·0002	1·11 (0·97–1·26)	0·12
Lowest	1·50 (1·36–1·65)	<0·0001	1·79 (1·54–2·09)	<0·0001	1·40 (1·24–1·59)	<0·0001

Estimates were derived from Cox models with all listed characteristics included simultaneously.

Table 3: **Hazard ratios (95% CIs) for an incident cardiovascular event (myocardial infarction, stroke, heart failure, or cardiovascular death) in participants with low (<10%) predicted 10-year cardiovascular risk according to the WHO cardiovascular disease risk score[9]**

about 40% of severe cardiovascular disease events develop in individuals with no history of cardiovascular disease and who are considered to be at low cardiovascular disease risk; the proportion of cardiovascular disease events occurring in these individuals who are at low risk increases from 32% in HICs to 54% in LICs; and the burden of cardiovascular disease events developing in individuals with lower risk is greater among females than males.

Our analysis demonstrates higher cardiovascular disease event rates in individuals at higher predicted cardiovascular risk according to the WHO risk calculator. These findings indicate clinically important increases in cardiovascular disease risk among groups predicted to be at higher risk. Targeting people at higher predicted cardiovascular risk with preventive strategies would therefore be expected to lead to the largest absolute risk reductions in incident cardiovascular disease events. However, from a population health perspective, most of the population do not fall into the high predicted risk category. Therefore, a substantial proportion of cardiovascular disease events occur among adults who are not projected to be at high risk simply because there are more such individuals in whom events might occur. In this study, we have quantified these different perspectives on cardiovascular disease burden.

Previous research describing the burden of cardiovascular disease in adults with low versus high risk has produced different findings. In a cohort of Italian adults without cardiovascular disease aged 35–69 years at enrolment, the overwhelming majority (89%) of incident cases of stroke occurred in those with a high burden of cardiovascular risk factors.[17] By contrast, other European and US population-based cohort data suggest that most major cardiovascular disease events occur in individuals who are not considered to be at high cardiovascular risk based on traditional cardiovascular disease risk factors.[18] Our findings are consistent with the latter data. Several reasons might account for these divergent findings. In the Italian study, baseline data collection occurred between 1983 and 1997 versus post-2001 in the PURE study. There have been some (albeit modest) improvements in the uptake of cardiovascular medications during the past four decades. Consistent with this, 11% of the Italian cohort were taking antihypertensive medication compared with 21% in HICs in the PURE cohort. Improvements in the treatment of cardiovascular risk factors might reduce the risk of major cardiovascular disease in individuals with a high risk. Therefore, we might be witnessing an epidemiological transition, in that as individuals at high risk increasingly receive preventive treatments, the relative burden of adverse cardiovascular events might shift towards individuals at low risk who do not receive these treatments.

The findings from our study might have important implications for strategies to prevent cardiovascular disease globally. Contemporary recommendations indicate that individuals at low cardiovascular risk should only be counselled on healthy lifestyle, while the addition of pharmacotherapy to lifestyle advice should be reserved for those at higher cardiovascular risk.[19,20] These recommendations are axiomatic. However, Wald and Law argued that, as 96% of deaths from ischaemic heart disease and stroke occur in adults aged 55 years or older, and the risks of preventive medications such as statins, antihypertensive medications, and aspirin are small, all adults aged 55 years or older should receive a polypill containing these medications.[5] We found that nearly two-thirds of fatal and non-fatal cardiovascular disease events occurred in those aged 55 years or older. These data might be helpful in modelling the effects of Wald and Law's hypothesis, which is supported by evidence indicating that treatments such as statins reduce cardiovascular events even in people at lower risk.[21,22]

The World Heart Federation declared a target of 30 by 30—ie, a 30% decrease in cardiovascular disease and death by 2030. Although cardiovascular death is to a large extent preventable, major new strategies will need to be implemented to achieve this goal. Unless a reduction in cardiovascular disease events occurs in those at low-risk, it is unlikely that 30 by 30 will be realised.

In this analysis, we confirm our previous finding that lower country income, lower education, lower physical activity, and lower handgrip strength are associated with higher risks of subsequent cardiovascular events.[12] Addressing risk factors not encapsulated by cardiovascular disease risk scores might be important approaches to decreasing the global burden of cardiovascular disease. In this study, we demonstrated that these other risk factors were distributed in a pattern that was consistent with predicted cardiovascular disease risk. For example, individuals at high predicted cardiovascular disease risk had lower education levels and lower physical activity levels than those at low predicted cardiovascular disease risk. Our findings suggest that incorporating them into cardiovascular disease risk scores might enhance the discrimination of those who will experience a future cardiovascular event. The totality of cardiovascular disease risk factors that individuals are exposed to has been termed the exposome.[23] A greater emphasis on individuals' exposome rather than limiting treatments to the traditional cardiovascular disease risk factors, which only account for half of the global population burden of cardiovascular disease,[24] is likely to impact overall event rates. Such an approach is increasingly being promoted in more recent guidelines.[25]

Our study delivered important insights for cardiovascular disease prevention in women. Among females with no known cardiovascular disease in the Chicago Heart Association Detection Project in Industry Study, only 15% of cardiovascular deaths occurred in those at lower cardiovascular disease risk.[26] Our study extends on these results by demonstrating that in females from countries of different income levels, low cardiovascular disease risk groups accounted for approximately half of major cardiovascular disease events.

We have previously shown that females in the PURE study have a lower cardiovascular disease risk factor burden than males and among those without established cardiovascular disease, more primary prevention medication use.[27] The present analysis extends on this to demonstrate that despite these favourable characteristics, a larger burden of adverse cardiovascular outcomes was observed in females at lower cardiovascular disease risk. These findings suggest that other non-traditional or sex-specific risk factors might account for the excess of cardiovascular events in females considered to be low risk.

Our study has important limitations and strengths. One limitation of this analysis is that cardiovascular risk was only evaluated at baseline; we did not account for change in cardiovascular risk during follow-up. Competing risks might have influenced our findings. However, we would expect proportionally more non-cardiovascular deaths to occur in the low cardiovascular disease risk group, thus reducing the proportion of cardiovascular disease events occurring in this group compared with a hypothetical scenario in which the competing risk did not exist. Therefore, in the absence of the competing risk, the proportion of cardiovascular disease events occurring in the low WHO risk group might even be higher. A further limitation of our study is that the cohort might not be nationally or globally representative. For example, rates of diabetes in the LICs in our study were higher than reported in other literature.[28] Another plausible bias that might result is that individuals from lower socioeconomic classes might be under-represented. As we expect those from lower socioeconomic groups to have higher cardiovascular risk and cardiovascular disease event rates, this could lead to an underestimation of the proportion of cardiovascular disease occurring in higher-risk groups. We observed that the WHO risk calculator overestimated cardiovascular disease risk in our cohort, which is consistent with this possible bias. Other reasons for the modest calibration of the WHO risk estimates include the need for more data to enable better calibration. It is likely that a risk calculator that incorporates a wider range of risk factors or that was recalibrated would increase the proportion of cardiovascular events attributable to individuals at high risk. Furthermore, differences in calibration patterns according to country income level might have led to heterogeneity in the bias with which cardiovascular disease burden was estimated. We expect that these differences might have exerted a downward bias on the proportion of cardiovascular events observed in high-risk groups in MICs and an upward bias in the proportion of events seen in low-risk groups in LICs.

In conclusion, approximately 40% of major cardiovascular disease events occur in adults with no history of cardiovascular disease and who are not considered at high cardiovascular risk. Therefore, to achieve a substantial population-level reduction in cardiovascular disease, we need a fundamental change that focuses on preventive strategies for cardiovascular disease extend beyond those at high or even intermediate predicted risk to include those considered to be at low risk.

Contributors

DPL designed and implemented the statistical analysis and drafted the manuscript. SY conceptualised the study and revised the manuscript. All other authors collected study data and revised the manuscript. No authors were prohibited from accessing the data; however, for reasons of practicality, only DPL and SR directly accessed the full data and verified the analyses reported in the manuscript. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

SG reports honoraria from AstraZeneca, Boehringer Ingelheim, Novartis, Novo Nordisk, Nobel, and Servier. All other authors declare no competing interests.

Data sharing

Individual-level participant data are not publicly available. Summary statistics and statistical code will be made available on reasonable request to the corresponding author. The study protocol and data collection forms will be shared on request to the corresponding author.

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