Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: the Prospective Urban Rural Epidemiologic (PURE) study

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Summary

Background Socioeconomic status is associated with differences in risk factors for cardiovascular disease incidence and outcomes, including mortality. However, it is unclear whether the associations between cardiovascular disease and common measures of socioeconomic status—wealth and education—differ among high-income, middle-income, and low-income countries, and, if so, why these differences exist. We explored the association between education and household wealth and cardiovascular disease and mortality to assess which marker is the stronger predictor of outcomes, and examined whether any differences in cardiovascular disease by socioeconomic status parallel differences in risk factor levels or differences in management.

Methods In this large-scale prospective cohort study, we recruited adults aged between 35 years and 70 years from 367 urban and 302 rural communities in 20 countries. We collected data on families and households in two questionnaires, and data on cardiovascular risk factors in a third questionnaire, which was supplemented with physical examination. We assessed socioeconomic status using education and a household wealth index. Education was categorised as no or primary school education only, secondary school education, or higher education, defined as completion of trade school, college, or university. Household wealth, calculated at the household level and with household data, was defined by an index on the basis of ownership of assets and housing characteristics. Primary outcomes were major cardiovascular disease (a composite of cardiovascular deaths, strokes, myocardial infarction, and heart failure), cardiovascular mortality, and all-cause mortality. Information on specific events was obtained from participants or their family.

Findings Recruitment to the study began on Jan 12, 2001, with most participants enrolled between Jan 6, 2005, and Dec 4, 2014. 160 299 (87·9%) of 182 375 participants with baseline data had available follow-up event data and were eligible for inclusion. After exclusion of 6130 (3·8%) participants without complete baseline or follow-up data, 154 169 individuals remained for analysis, from five low-income, 11 middle-income, and four high-income countries. Participants were followed-up for a mean of 7·5 years. Major cardiovascular events were more common among those with low levels of education in all types of country studied, but much more so in low-income countries. After adjustment for wealth and other factors, the HR (low level of education *vs* high level of education) was 1·23 (95% CI 0·96–1·58) for high-income countries, 1·59 (1·42–1·78) in middle-income countries, and 2·23 (1·79–2·77) in low-income countries ($p_{interaction}$<0·0001). We observed similar results for all-cause mortality, with HRs of 1·50 (1·14–1·98) for high-income countries, 1·80 (1·58–2·06) in middle-income countries, and 2·76 (2·29–3·31) in low-income countries ($p_{interaction}$<0·0001). By contrast, we found no or weak associations between wealth and these two outcomes. Differences in outcomes between educational groups were not explained by differences in risk factors, which decreased as the level of education increased in high-income countries, but increased as the level of education increased in low-income countries ($p_{interaction}$<0·0001). Medical care (eg, management of hypertension, diabetes, and secondary prevention) seemed to play an important part in adverse cardiovascular disease outcomes because such care is likely to be poorer in people with the lowest levels of education compared to those with higher levels of education in low-income countries; however, we observed less marked differences in care based on level of education in middle-income countries and no or minor differences in high-income countries.

Interpretation Although people with a lower level of education in low-income and middle-income countries have higher incidence of and mortality from cardiovascular disease, they have better overall risk factor profiles. However, these individuals have markedly poorer health care. Policies to reduce health inequities globally must include strategies to overcome barriers to care, especially for those with lower levels of education.

Lancet Glob Health 2019; 7: e748–60

Published **Online** April 23, 2019 http://dx.doi.org/10.1016/S2214-109X(19)30045-2

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Funding Full funding sources are listed at the end of the paper (see Acknowledgments).

Introduction

In high-income countries, low socioeconomic status is associated with an increased risk of cardiovascular disease and mortality.[1–3] Whether this association also applies to low-income and middle-income countries, which have the highest burden of cardiovascular disease,[4,5] has been less well studied, and findings on the association between socioeconomic status and cardiovascular health have been inconsistent.[6,7] Clarifying the nature of the association between socioeconomic status and cardiovascular disease in low-income and middle-income countries, and understanding the underlying reasons or related factors, is necessary for the development of contextually appropriate strategies to mitigate health disparities. However, socioeconomic status is a multidimensional construct[8] related to both adequacy of financial resources and educational attainment. Therefore, the meaning and effects of socioeconomic status on cardiovascular disease might vary according to context, indicating the need for research in different settings. Specifically, with rapid urbanisation and societal change in low-income and middle-income countries, as well as increasing rates of cardiovascular disease, there is a need for up-to-date studies that can capture the current situation. Although some data exist on socioeconomic gradients in cardiovascular disease in low-income and middle-income countries,[9–14] to our knowledge no study has used consistent methods to compare cardiovascular disease or death by socioeconomic status, nor has any study explored potential reasons for any observed differences. Furthermore, to our knowledge, existing studies have not used consistent methods or studied a large number of countries at different levels of economic development.

The Prospective Urban Rural Epidemiologic (PURE) study is a large-scale prospective cohort study that

Research in context

Evidence before this study

We searched PubMed for articles published up to Feb 13, 2018, with the search terms (MESH and All Fields) "socioeconomic status", "cardiovascular disease", and "epidemiologic, comparison" and no language limits and identified 266 abstracts; after addition of the term "management" another 42 abstracts were returned. Furthermore, we used the Journal/Author Name Estimator search engine on the abstract of this manuscript to identify similar publications and found another 20 abstracts. Two authors (KBB, AR) searched all abstracts for cross-sectional and cohort studies that compared cardiovascular morbidity and mortality between countries of different socioeconomic levels (high-income, middle-income, and low-income countries) and between urban and rural communities. Altogether, we identified 49 relevant abstracts. We found several studies in high-income countries, but only altogether eight in other countries, that addressed disparities in socioeconomic position and cardiovascular complications and made comparisons between urban and rural areas. However, we found no studies that compared countries of high-income, low-income, and middle-income socioeconomic status in these respects. Therefore, although some data on socioeconomic gradients in cardiovascular disease in low-income and middle-income countries exist, we did not identify any that used consistent methods or compared findings across several countries at different levels of economic development.

Added value of this study

In high-income countries, low socioeconomic status is associated with an increased risk of cardiovascular disease. Whether this association also applies in low-income and middle-income countries, which have the largest burden of cardiovascular disease, has been less well studied and the results of existing studies are inconsistent. We found that low education was a stronger marker for cardiovascular disease and mortality than was wealth. This association was most marked in low-income countries (mainly India, Pakistan, and Bangladesh), less marked in middle-income countries, and least evident in high-income countries (mainly Canada and Sweden). Differences in risk factor proportions, which to a large extent were lower in individuals living in low-income countries, did not explain the different risks of cardiovascular disease in different educational groups. By contrast, less educated individuals in low-income countries received fewer medications for hypertension, diabetes, or secondary prevention and were less likely to quit smoking or have a healthy diet.

Implications of all the available evidence

Education, rather than wealth, was the factor most strongly associated with the study primary outcomes, with low education being associated with an increased risk of major cardiovascular disease and higher case fatality, despite lower proportions of cardiovascular risk factors in low-income countries than in high-income countries. Improved education and access to effective health care might mitigate some of the substantial excess burden of cardiovascular disease and mortality in low-income countries and narrow global health inequalities.

	Total patients	Education		
		None or primary only	Secondary	Trade school, college, or university
High-income countries				
Total number of people	17 241 (100·0%)	2137 (12·4%)	4995 (29·0%)	10 109 (58·6%)
Age (years)	52·2 (9·4)	55·1 (9·7)	52·4 (9·3)	51·5 (9·3)
Sex				
Women	9241 (53·6%)	1289 (60·3%)	2739 (54·8%)	5213 (51·6%)
Men	8000 (46·4%)	848 (39·7%)	2256 (45·2%)	4896 (48·4%)
Urban	13 320 (77·3%)	1351 (63·2%)	3584 (71·8%)	8385 (82·9%)
Current use of at least one tobacco product per day	2307 (13·4%)	321 (15·0%)	896 (17·9%)	1090 (10·8%)
INTERHEART risk score	13·08 (6·1)	13·95 (6·2)	13·79 (6·3)	12·54 (5·9)
INTERHEART risk score without smoking	11·41 (5·4)	12·28 (5·6)	11·68 (5·5)	11·09 (5·3)
Hypertension*	6594/16 647 (39·6%)	1101/1915 (57·5%)	2051/4836 (42·4%)	3442/9896 (34·8%)
Diabetes, self-reported or on glucose-lowering agent (known diabetes)†	1609 (9·3%)	484 (22·6%)	458 (9·2%)	667 (6·6%)
Diabetes, self-reported or fasting glycaemia ≥7 mmol/L or no-fasting glucose >7·7 mmol/L	1867 (10·8%)	536 (25·1%)	544 (10·9%)	787 (7·8%)
Cardiovascular disease‡	1345 (7·8%)	246 (11·5%)	399 (8·0%)	700 (6·9%)
Middle-income countries				
Total number of people	102 843 (100·0%)	45 820 (44·6%)	41 862 (40·7%)	15 161 (14·7%)
Age (years)	51·0 (9·6)	53·4 (9·6)	48·7 (8·9)	49·9 (9·8)
Sex				
Women	60 397 (58·7%)	29 152 (63·6%)	23 564 (56·3%)	7681 (50·7%)
Men	42 446 (41·3%)	16 668 (36·4%)	18 298 (43·7%)	7480 (49·3%)
Urban	53 206 (51·7%)	15 920 (34·7%)	24 030 (57·4%)	13 256 (87·4%)
Current use of at least one tobacco product per day	21 610 (21·0%)	8955 (19·5%)	9816 (23·4%)	2839 (18·7%)
INTERHEART risk score	10·52 (5·8)	10·99 (5·8)	9·88 (5·6)	10·91 (5·9)
INTERHEART risk score without smoking	8·62 (5·1)	9·21 (5·2)	7·81 (4·9)	9·05 (5·2)
Hypertension*	41 932/96 628 (43·4%)	21 019/43 350 (48·5%)	15 234/38 701 (39·4%)	5679/14 577 (39·0%)
Diabetes, self-reported or on glucose-lowering agent (known diabetes)†	8229 (8·0%)	4234 (9·2%)	2721 (6·5%)	1274 (8·4%)
Diabetes, self-reported or fasting glycaemia ≥7 mmol/L or no-fasting glucose >7·7 mmol/L	10 709 (10·4%)	5354 (11·7%)	3753 (9·0%)	1602 (10·6%)
Cardiovascular disease‡	8950 (8·7%)	4488 (9·8%)	2922 (7·0%)	1540 (10·2%)
Low-income countries				
Total number of people	34 085 (100·0%)	18 095 (53·1%)	11 653 (34·2%)	4337 (12·7%)
Age (years)	48·6 (10·3)	49·3 (10·7)	47·8 (9·8)	47·9 (9·9)
Sex				
Women	19 446 (57·1%)	11 925 (65·9%)	5856 (50·3%)	1665 (38·4%)
Men	14 639 (42·9%)	6170 (34·1%)	5797 (49·7%)	2672 (61·6%)
Urban	15 514 (45·5%)	5096 (28·2%)	6680 (57·3%)	3738 (86·2%)
Current use of at least one tobacco product per day	7755 (22·8%)	5027 (27·8%)	2237 (19·2%)	491 (11·3%)
INTERHEART risk score	7·86 (5·0)	6·98 (4·6)	8·77 (5·3)	9·12 (5·4)
INTERHEART risk score without smoking	6·95 (4·8)	6·00 (4·4)	7·83 (5·0)	8·52 (5·1)
Hypertension*	10 122/31 233 (32·4%)	4598/16 085 (28·6%)	3906/11 017 (35·5%)	1618/4131 (39·2%)
Diabetes, self-reported or on glucose-lowering agent (known diabetes)†	3195 (9·4%)	1007 (5·6%)	1536 (13·2%)	652 (15·0%)
Diabetes, self-reported or fasting glycaemia ≥7 mmol/L or no-fasting glucose >7·7 mmol/L	4343 (12·7%)	1474 (8·1%)	2040 (17·5%)	829 (19·1%)
Cardiovascular disease‡	1530 (4·5%)	760 (4·2%)	583 (5·0%)	187 (4·3%)

Data are n (%), mean (SD), or n/N (%). *Self-reported or on medications, or blood pressure ≥140/≥90 mm Hg. †Plasma glucose concentrations were available in 122 711 participants. ‡Diagnosed with stroke, coronary heart disease, heart failure, or other heart disease before baseline visit.

Table 1: **Participant characteristics stratified by education in high-income, middle-income, and low-income countries**

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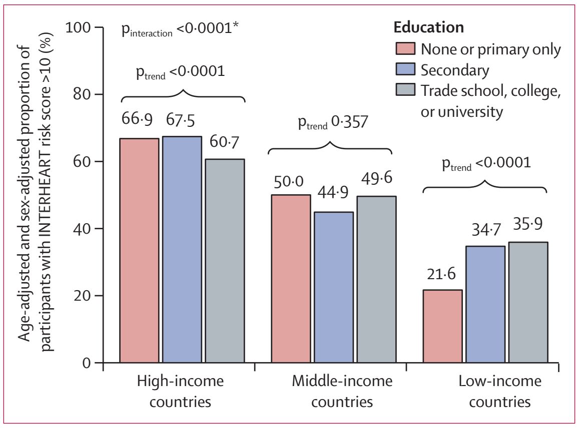


Figure 1: **Age-standardised and sex-standardised proportion of participants with INTERHEART risk score >10 in high-income, middle-income, and low-income countries by education**
Data are adjusted for age and gender. *Testing the interaction between country income and education.

recruited individuals from high-income, low-income, and middle-income countries, providing an opportunity to explore associations between socioeconomic status and cardiovascular disease across settings at varying economic levels. In this Article, we describe the association between two markers of socioeconomic status (education and household wealth) and cardiovascular disease and mortality to assess which marker is the stronger predictor of outcomes. We also examined whether any differences in cardiovascular disease by socioeconomic status paralleled differences in risk factor levels or differences in management (using markers of health care such as hypertension control, diabetes care, and use of secondary prevention strategies).

Methods

Study design and participants

The design, methods (including sampling, information gathered, and follow-up strategy), and participant characteristics of the PURE study have been published previously.[15] Briefly, adults aged between 35 years and 70 years from 367 urban and 302 rural communities in 20 countries (Tanzania, Zimbabwe, Bangladesh, Pakistan, India, occupied Palestinian territory, China, Colombia, Iran, South Africa, Malaysia, Argentina, Turkey, Brazil, Poland, Chile, Saudi Arabia, United Arab Emirates, Canada, and Sweden) were included. Details of sampling, information gathered, and follow-up strategy have been previously reported in several publications.[15,16]

See **Online** for appendix

For the present study, follow-up event data were available until Sept 20, 2017. The countries were grouped according to the 2006 World Bank income classifications[17] based on gross national product per capita at the time when data collection began (appendix). Men and women aged between 35 years and 70 years, who were expected to remain in their community for at least 4 years, were eligible for inclusion. The response rate was 72%. Although modest differences exist between the PURE household population and national data, these differences are unlikely to have much of an effect on the exposure–disease associations derived in PURE, and demographics and mortality were generally similar to national statistics.[18]

Ethics committees at each centre approved the protocol and all participants provided written informed consent.

Procedures

We collected data on families and households in two questionnaires, the first recording sociodemographic information on all inhabitants of the household and the second recording information on house structure and amenities. Data on cardiovascular risk factors (tobacco use, history of hypertension, diabetes, psychosocial factors, diet, physical activity, and physical measures) were recorded using standardised questions and methods in a third questionnaire, which was supplemented by physical examination, including blood pressure, anthropometric measures, spirometry, and an electrocardiogram. Further questionnaires assessed diet (food frequency) and physical activity by use of standardised instruments. Consenting participants also provided a fasting blood sample (appendix). The non-cholesterol INTERHEART risk score,[19] which integrates information on age, sex, smoking, diabetes (self-report or fasting glucose >7·0 mmol/L), high blood pressure (blood pressure >140/>90 mm Hg or self-report), family history of heart disease, waist to hip ratio, psychosocial factors, diet (healthy eating score), and physical activity, was used to describe overall risk factor levels (appendix).[15,16] The quality of data collection was maintained by the use of standardised protocols, centralised training, and stringent quality control at the project office.

We assessed socioeconomic status using education and a household wealth index. Education was categorised as no or primary school education only (lowest), secondary school education (intermediate), or higher education, defined as completion of trade school, college, or university (highest). Household wealth, calculated at the household level and with household data, was defined by an index on the basis of ownership of assets and housing characteristics,[20] validated in several countries, and documented to be a robust measure of wealth, consistent with measures of income and expenditure.

Outcomes

Primary outcomes were major cardiovascular disease (a composite of cardiovascular deaths, strokes, myocardial infarction, and heart failure; appendix), cardiovascular mortality, and all-cause mortality.

Information on specific events was obtained from participants or their family, who were contacted at regular intervals after the questionnaires were delivered. Follow-up of participants was done at 3-year intervals and information on clinical events was obtained from participants or family members for deceased participants.

	High-income countries		Middle-income countries		Low-income countries	
	Number of events	Age-standardised and sex-standardised event rate per 1000 person-years (95% CI)	Number of events	Age-standardised and sex-standardised event rate per 1000 person-years (95% CI)	Number of events	Age-standardised and sex-standardised event rate per 1000 person-years (95% CI)
All-cause mortality						
By education						
None or primary only	101	5·3 (4·2–6·4)	2683	8·1 (7·7–8·4)	2149	16·0 (15·0–17·0)
Secondary	116	2·9 (2·3–3·4)	1140	4·7 (4·4–5·0)	872	10·8 (10·0–12·0)
Trade school, college, or university	199	2·6 (2·2–3·0)	332	3·2 (2·9–3·6)	152	5·3 (4·2–6·5)
By wealth						
Poorest third	168	3·8 (3·2–4·4)	1807	8·1 (7·7–8·5)	1471	16·4 (16·0–17·0)
Middle third	116	2·5 (2·0–3·0)	1327	5·6 (5·2–5·9)	974	13·7 (13·0–15·0)
Richest third	132	3·0 (2·4–3·6)	1021	4·6 (4·3–4·9)	728	8·7 (8·0–9·4)
Cardiovascular mortality						
By education						
None or primary only	25	1·3 (0·8–1·8)	841	2·4 (2·2–2·6)	627	4·6 (4·3–5·0)
Secondary	21	0·6 (0·3–0·8)	304	1·3 (1·1–1·5)	320	3·9 (3·4–4·4)
Trade school, college, or university	36	0·4 (0·3–0·6)	98	1·0 (0·8–1·2)	52	1·6 (1·1–2·2)
By wealth						
Poorest third	41	1·0 (0·7–1·3)	566	2·5 (2·3–2·8)	366	4·1 (3·7–4·6)
Middle third	14	0·3 (0·1–0·4)	394	1·6 (1·4–1·7)	348	4·9 (4·4–5·5)
Richest third	27	0·6 (0·3–0·9)	283	1·3 (1·1–1·5)	285	3·3 (2·9–3·7)
Major cardiovascular disease						
By education						
None or primary only	127	7·3 (5·7–8·9)	2551	7·3 (6·9–7·6)	1038	7·5 (7·0–8·0)
Secondary	171	4·5 (3·8–5·3)	1493	5·8 (5·4–6·1)	645	7·7 (7·0–8·4)
Trade school, college, or university	293	3·7 (3·2–4·2)	506	4·9 (4·5–5·4)	112	3·5 (2·7–4·3)
By wealth						
Poorest third	228	5·5 (4·7–6·3)	1748	7·4 (7·0–7·7)	587	6·3 (5·8–6·8)
Middle third	161	3·2 (2·6–3·7)	1506	6·1 (5·8–6·5)	614	8·5 (7·8–9·2)
Richest third	202	4·8 (4·0–5·5)	1296	5·6 (5·2–5·9)	594	6·9 (6·3–7·5)

For standardisation, the 2015 UN population data was used as the reference.

Table 2: **Age-standardised and sex-standardised event rates per 1000 person-years by education and by country income**

For **UN population data** see https://population.un.org/wpp/DataQuery/

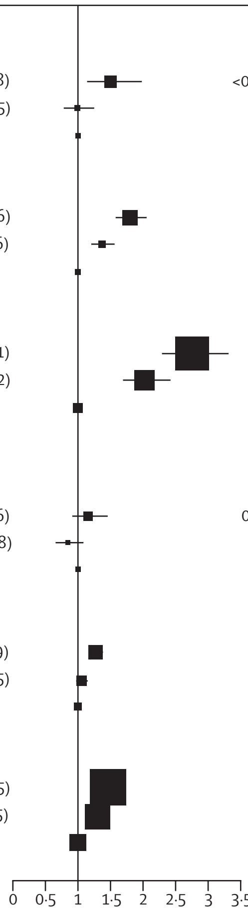
All follow-up visits were done either by visiting households or by telephone calls from participants, or, in countries such as Canada, the participants were invited to the central office to complete the follow-up visit. Events were adjudicated centrally in each country by trained physicians by use of standardised definitions, verbal autopsies, and review of documents.[16]

Statistical analysis

We used direct standardisation to calculate the age-standardised and sex-standardised incidence rates (per 1000 person-years) for cardiovascular events and deaths. We used multi-level Cox proportional hazard models to obtain the hazard ratios (HRs) for all-cause mortality, fatal cardiovascular disease, and major cardiovascular disease. In the multi-level structure models, we considered individual participants nested in centres and considered centres as a random intercept effect. We mutually adjusted HRs for education and wealth, in addition to age, sex, urban versus rural, baseline cardiovascular disease, and INTERHEART risk score. We included the interaction terms of region and education and region and wealth, where region denoted high-income, middle-income, or low-income countries. We tested the assumption of proportional hazard with log of the negative log of Kaplan-Meier estimates of the survival function versus the log time for evidence of non-parallelism.

Defining countries according to country income might not adequately capture inequalities across the entire distribution of education or wealth. Consequently, we also used the Wagstaff index, which has been proposed as an alternative to the concentration index when the health variable is bounded (ie, has an upper and lower

	All-cause mortality: Events/total	All-cause mortality: Adjusted HR (95% CI)	$p_{interaction}$ value	Major cardiovascular disease: Events/total	Major cardiovascular disease: Adjusted HR (95% CI)	$p_{interaction}$ value*
Association of events by education						
High-income countries						
None or primary only	101/2135	1·50 (1·14–1·98)	<0·0001	127/2135	1·23 (0·96–1·58)	<0·0001
Secondary	116/4985	0·99 (0·78–1·25)		171/4985	1·01 (0·83–1·22)	
Trade school, college, or university	199/10 065	1·00 (ref)		293/10 065	1·00 (ref)	
p_{trend}		0·0149			0·1079	
Middle-income countries						
None or primary only	2682/45 110	1·80 (1·58–2·06)		2549/45 110	1·59 (1·42–1·78)	
Secondary	1134/41 135	1·37 (1·20–1·56)		1490/41 135	1·29 (1·16–1·43)	
Trade school, college, or university	331/14 967	1·00 (ref)		505/14 967	1·00 (ref)	
p_{trend}		<0·0001			<0·0001	
Low-income countries						
None or primary only	2145/16 472	2·76 (2·29–3·31)		1034/16 472	2·23 (1·79–2·77)	
Secondary	872/10 975	2·02 (1·69–2·42)		645/10 975	2·01 (1·63–2·48)	
Trade school, college, or university	152/3974	1·00 (ref)		112/3974	1·00 (ref)	
p_{trend}		<0·0001			<0·0001	
Association of events by wealth						
High-income countries						
Poorest third	168/4747	1·15 (0·91–1·46)	0·0119	228/4747	1·11 (0·91–1·35)	0·0021
Middle third	116/6213	0·84 (0·66–1·08)		161/6213	0·81 (0·66–1·00)	
Richest third	132/6225	1·00 (ref)		202/6225	1·00 (ref)	
p_{trend}		0·1279			0·4193	
Middle-income countries						
Poorest third	1805/33 071	1·27 (1·16–1·39)		1745/33 071	1·07 (0·98–1·17)	
Middle third	1324/33 829	1·06 (0·97–1·15)		1505/33 829	0·99 (0·92–1·07)	
Richest third	1018/34 312	1·00 (ref)		1294/34 312	1·00 (ref)	
p_{trend}		<0·0001			0·0486	
Low-income countries						
Poorest third	1470/10 388	1·46 (1·29–1·65)		586/10 388	1·10 (0·95–1·28)	
Middle third	973/9945	1·30 (1·17–1·45)		613/9945	1·18 (1·04–1·33)	
Richest third	726/11 088	1·00 (ref)		592/11 088	1·00 (ref)	
p_{trend}		<0·0001			0·3534	



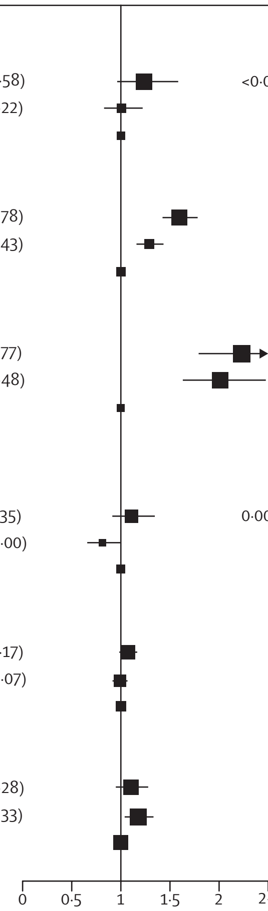


Figure 2: **HRs (95% CI) for all-cause mortality and major cardiovascular disease by country income and level of education**
We included the interaction terms region and education, as well as region and wealth, where region denoted high-income, middle-income, or low-income countries. HR=hazard ratio. *Testing the interaction between country income and education or wealth.

limit).[21,22] The Wagstaff index is the concentration index divided by 1 minus the mean of the health variable, producing a value between –1 and 1.

We calculated case fatality rates in the 28 days following myocardial infarction, stroke, and heart failure adjusted for age and sex. We calculated age-adjusted and sex-adjusted case fatality rates by education or wealth and stratified by country income with the method of least squares to fit general linear models. Reported p_{trend} values on the figures are for case fatality rates within each country income grouping using the χ^2 test for trend. Given the multiple comparisons, p values should be interpreted with caution, unless very small (eg, p<0·0001). All analyses were done with SAS version 9.4 and all figures were drawn in R version 3.2.5.

Role of the funding source

The funders and sponsors of the study had no role in the study design and conduct, data collection, data analysis, data interpretation, writing of the report, or 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

Recruitment to the study began on Jan 12, 2001, with most participants enrolled between Jan 6, 2005, and Dec 4, 2014. 160 299 (87·9%) of 182 375 participants with baseline data had available follow-up event data, and were aged between 35 and 70 years and from 20 countries (other countries and participants were enrolled too recently to have had a follow-up visit). After exclusion of 6130 (3·8%) participants without complete baseline or follow-up data, 154 169 remained for analysis (appendix). Populations had diverse sizes, with India contributing 81% of the low-income population, and China 45% of the middle-income population, whereas Canada contributed 60% of the high-income population.

4337 (12·7%) of 34 085 participants from low-income countries had a university, college, or trade school education, compared with 15 161 (14·7%) of 102 843 participants in middle-income countries and 10 109 (58·6%) of 17 241 participants in high-income countries (table 1). Corresponding proportions for primary education or less were 18 095 (53·1%) for low-income countries, 45 820 (44·6%) in middle-income countries, and 2137 (12·4%) in high-income countries. Across all countries, participants with a high level of education were younger, and less likely to be women. In high-income countries, individuals with a low level of education had higher INTERHEART risk scores than did those with higher levels of education, and more frequently had hypertension, diabetes, and previous cardiovascular disease, whereas the opposite was true for low-income countries, with the exception of previous cardiovascular disease, which was similar across all education categories (table 1). We recorded the proportion of participants with INTERHEART risk scores score greater than 10 (figure 1). With respect to the findings for individual countries, India and Bangladesh, which constituted 88% of the low-income population, both had higher INTERHEART risk scores among people with higher levels of education, although findings for the smaller samples in the other three low-income countries were heterogeneous (data not shown). Characteristics by wealth categories and individual components of the INTERHEART risk score by education are shown in the appendix.

Over a mean follow-up duration of 7·5 years until Sept 20, 2017, we recorded 7744 deaths and 6936 cases of major cardiovascular disease. Mortality varied substantially by education and country income (table 2), with the highest mortality in low-income countries and in those with the lowest levels of education across country income categories. The group with the lowest level of education in low-income countries had an age-standardised and sex-standardised mortality rate of 16·0 (95% CI 15·0–17·0) per 1000 person years—more than five times that of people with the highest level of education in high-income countries (2·6 per 1000 person-years, 95% CI 2·2–3·0). Similar results were also seen for cardiovascular mortality (table 2). When stratified by household wealth, total and cardiovascular mortality rates varied from 16·4 (95% CI 16·0–17·0) and 4·1 (3·7–4·6) per 1000 person-years, respectively, among the poorest third of participants in low-income countries to 3·0 (2·4–3·6) and 0·6 (0·3–0·9) per 1000 person-years, respectively, among the richest third of participants in high-income countries. Incidence of major cardiovascular disease was similar for people with the lowest levels of education across low-income, middle-income, and high-income countries (7·5 per 1000 person-years, 95% CI 7·0–8·0, in low-income countries, 7·3 per 1000 person-years, 6·9–7·6, in middle-income countries, and 7·3 per

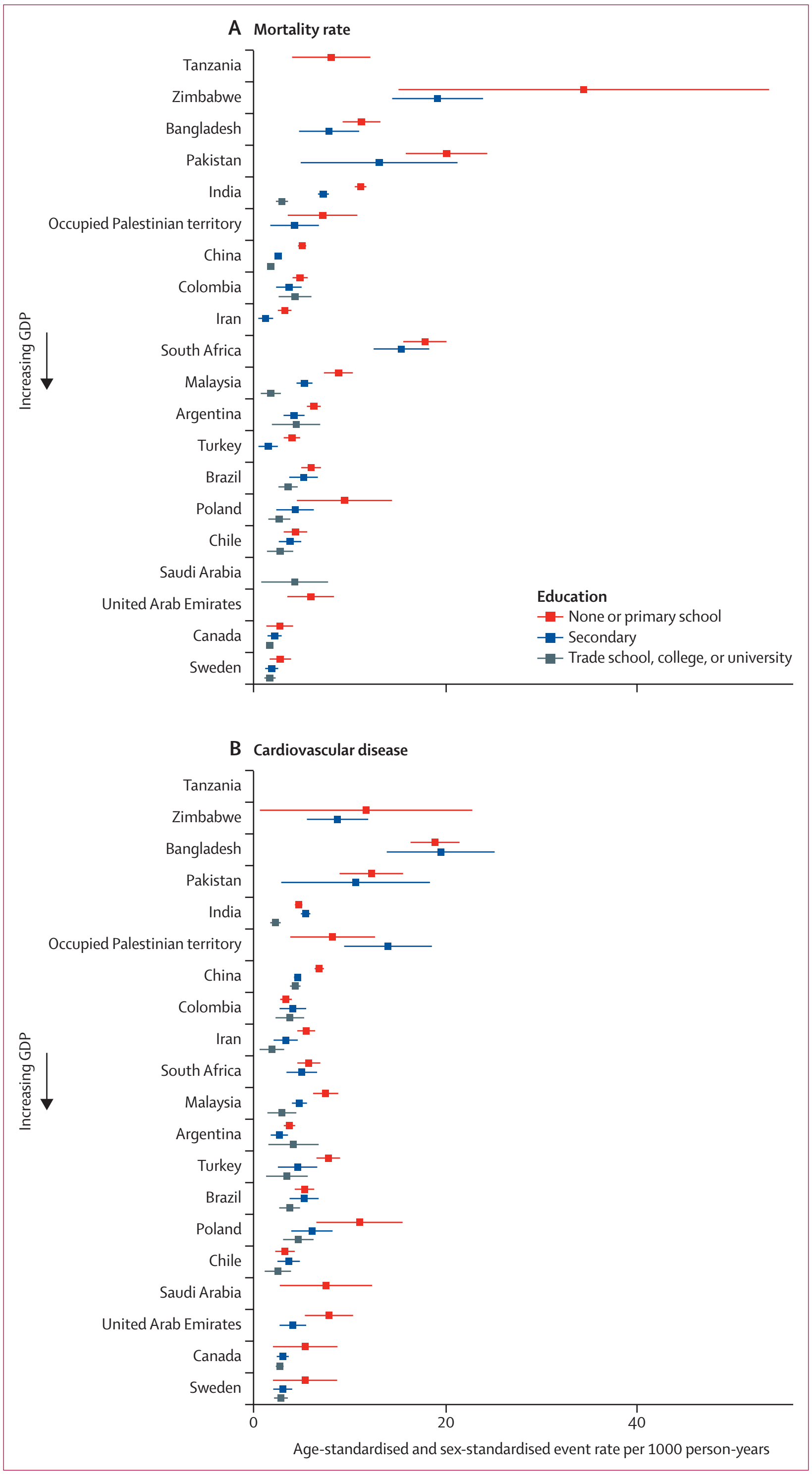
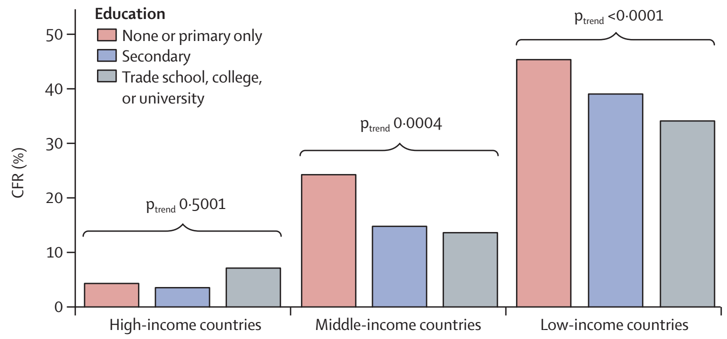


Figure 3: **Age-standardised and sex-standardised mortality (A) and cardiovascular disease incidence (B) per 1000 person-years by level of education**

Data are stratified by country and arranged by increasing GDP (data for categories with fewer than eight events not shown). GDP=gross domestic product.



	High-income countries			Middle-income countries			Low-income countries		
Case fatality rate	4·32	3·55	7·13	24·22	14·77	13·61	45·27	38·98	34·05
OR (95% CI)	0·66 (0·2–1·9)	0·53 (0·2–1·4)	1·00 (ref)	1·9 (1·4–2·7)	1·25 (0·9–1·8)	1·00 (ref)	2·23 (1·4–3·4)	1·49 (0·9–2·3)	1·00 (ref)

Figure 4: **28-day CFR after a first cardiovascular event and OR by country income and level of education among participants without previous cardiovascular disease**
$p_{interaction}$<0·0001 for country income and education. We adjusted ORs for age and sex. CFR=case fatality rate. OR=odds ratio.

1000 person-years, 5·7–8·9, in high-income countries). The incidence rates for those with the highest level of education were 3·5 per 1000 person-years (95% CI 2·7–4·3) in low-income countries, 4·9 per 1000 person-years (4·5–5·4) in middle income countries, and 3·7 per 1000 person-years (3·2–4·2) in high-income countries. The association between wealth and outcomes was weaker than the same comparisons between education and outcomes, and this was consistently observed among men and women (data not shown).

In multivariable models that simultaneously adjusted for education and wealth, in addition to age, sex, urban versus rural setting, baseline cardiovascular disease, and INTERHEART risk score, education was a strong independent predictor for total mortality (HR 2·76, 95% CI 2·29–3·31, in low-income countries, 1·80, 1·58–2·06, in middle-income countries, and 1·50, 1·14–1·98, in high-income countries) when comparing the lowest level of education with the highest level of education ($p_{interaction}$<0·0001; figure 2). We observed similar results for major cardiovascular disease (2·23, 1·79–2·77, for low-income countries, 1·59, 1·42–1·78, for middle-income countries, and 1·23, 0·96 to 1·58, for high-income countries; $p_{interaction}$<0·0001). Level of education was a far stronger predictor for major cardiovascular disease and all-cause mortality than was wealth. We also calculated mutually adjusted HRs by education and wealth, stratified by countries grouped by income, but adjusted for separate risk factors rather than the composite INTERHEART risk score (appendix). Sensitivity analyses from which subjects with previous cardiovascular disease were excluded provided similar results (appendix).

Cardiovascular event rates and death rates by individual country ranked by their gross domestic product (GDP) are shown in figure 3. The only low-income country with a sufficient number of events for analysis in people with a high level of education was India, but we observed similar patterns in the other low-income countries, for which we were able to compare middle and low levels of education.

The Wagstaff index results reaffirmed our conclusions, specifically that although the patterns of inequality were broadly similar for education and the wealth index, the strength of the association between education and outcomes was stronger than the corresponding association between the wealth index and outcomes, as indicated by the relatively lower index estimates for wealth (appendix). Importantly, the index estimates were consistent with our conclusions from figure 2 and table 2.

5509 (79·4%) of 6936 major cardiovascular disease events recorded occurred in participants with no previous cardiovascular disease at baseline, of whom 1407 (25·5%) died within 28 days. We observed substantial differences between countries at different income levels with respect to absolute case fatality rates (CFRs), and in the association between level of education and CFR ($p_{interaction}$<0·0001 for country income and education; figure 4). The gradients in CFRs between the highest and the lowest levels of education were steepest in low-income and middle-income countries, and we observed no gradient in high-income countries, where there were fewer overall fatalities. Corresponding data for wealth are shown in the appendix.

Hypertension and diabetes are among the most important risk factors for cardiovascular disease and related mortality and treating them is proven to reduce complications, as does secondary prevention in people with known cardiovascular disease. Therefore, we examined variations in the medical treatment of hypertension and diabetes, and in secondary prevention, by education and country income as a marker of management of these conditions (table 3). 27 327 (46·6%) of 58 642 participants with hypertension were aware of their condition. In the high-income countries included in our study, medical treatment did not vary by education, whereas we found a consistent and significant inverse association between level of education and treatment in low-income and middle-income countries ($p_{interaction}$<0·0001).

13 207 (8·6%) of 153 934 participants had known diabetes—1609 (9·3%) in high-income countries, 8224 (8·0%) in middle-income countries, and 3194 (9·4%) in low-income countries (table 3). 1198 (74·5%) of 1609 people with known diabetes in high-income countries used hypoglycaemic drugs, with no differences by education, and 4349 (52·9%) of 8224 people with known diabetes in middle-income countries used hypoglycaemic drugs, with slightly lower use with lower levels of education. Among those with the highest level of education in low-income countries, 248 (38·0%) of 652 participants were on medication for their diabetes, but only 232 (23·1%) of 1006 participants with low levels of education also took such medication (odds ratio [OR] 0·43, 95% CI 0·34–0·54; $p_{interaction}$<0·0001; table 3).

We also examined differences in use of secondary prevention medications as a potential explanation of the

	High-income countries (n=17 236)			Middle-income countries (n=102 640)			Low-income countries (n=34 058)			p value*
	n/N (%)	OR (95% CI)	p_{trend}	n/N (%)	OR (95% CI)	p_{trend}	n/N (%)	OR (95% CI)	p_{trend}	
People with hypertension† and aware of their condition	3281/6594 (49·8%)	..	..	19 999/41 926 (47·7%)	..	..	4047/10 122 (40·0%)	..	..	..
Proportion treated	2971/3281 (90·6%)	..	..	16 799/19 999 (84·0%)	..	..	3017/4047 (74·5)	..	..	..
None or primary only	547/588 (93·0%)	1·15 (0·77–1·72)	0·9774	8828/10 520 (83·9%)	0·66 (0·58–0·75)	<0·0001	922/1442 (63·9%)	0·28 (0·22–0·36)	<0·0001	<0·0001
Secondary	924/1035 (89·3%)	0·83 (0·64–1·08)	..	5509/6607 (83·4%)	0·89 (0·78–1·01)	..	1420/1808 (78·5%)	0·56 (0·44–0·72)	..	..
Trade school, college, or university	1500/1658 (90·5%)	1·00 (ref)	..	2462/2872 (85·7%)	1·00 (ref)	..	675/797 (84·7%)	1·00 (ref)	..	..
People with known diabetes‡	1609/17 236 (9·3%)	..	..	8224/102 640 (8·0%)	..	..	3194/34 058 (9·4%)	..	..	..
Proportion treated with hypoglycaemic agents	1198/1609 (74·5%)	..	..	4349/8224 (52·9%)	..	..	926/3194 (29·0%)	..	..	..
None or primary only	394/484 (81·4%)	1·14 (0·80–1·62)	0·6854	2236/4231 (52·8%)	0·77 (0·66–0·89)	<0·0001	232/1006 (23·1%)	0·43 (0·34–0·54)	<0·0001	<0·0001
Secondary	328/458 (71·6%)	0·90 (0·68–1·18)	..	1417/2719 (52·1%)	0·94 (0·81–1·08)	..	446/1536 (29·0%)	0·64 (0·52–0·79)	..	..
Trade school, college, or university	476/667 (71·4%)	1·00 (ref)	..	696/1274 (54·6%)	1·00 (ref)	..	248/652 (38·0%)	1·00 (ref)	..	..
People with cardiovascular disease at baseline	1345/17 236 (7·8%)	..	..	8950/102 640 (8·7%)	..	..	1530/34 058 (4·5%)	..	..	..
Proportion medically treated§	1040/1345 (77·3%)	..	..	3617/8950 (40·4%)	..		240/1530 (15·7%)	..	..	..
None or primary only	207/246 (84·1%)	1·82 (1·14–2·89)	0·0256	1948/4488 (43·4%)	1·10 (0·95–1·28)	0·6632	67/760 (8·8%)	0·26 (0·17–0·41)	<0·0001	<0·0001
Secondary	308/399 (77·2%)	1·06 (0·78–1·45)	..	1084/2922 (37·1%)	1·28 (1·10–1·48)	..	113/583 (19·4%)	0·76 (0·50–1·16)	..	..
Trade school, college, or university	525/700 (75·0%)	1·00 (ref)	..	585/1540 (38·0%)	1·00 (ref)	..	60/187 (32·1%)	1·00 (ref)	..	..
Smoking cessation (among former and current smokers)	559/771 (72·5%)	..	..	1469/3055 (48·1%)	..	..	158/494 (32·0%)	..	..	..
None or primary only	82/125 (65·6%)	0·57 (0·35–0·92)	0·0061	676/1408 (48·0%)	0·81 (0·65–1·01)	0·0245	57/252 (22·6%)	0·35 (0·17–0·72)	0·0008	0·0387
Secondary	182/265 (68·7%)	0·63 (0·43–0·91)	..	477/1057 (45·1%)	1·03 (0·83–1·29)	..	80/197 (40·6%)	0·66 (0·33–1·32)	..	..
Trade school, college, or university	295/381 (77·4%)	1·00 (ref)	..	316/590 (53·6%)	1·00 (ref)	..	21/45 (46·7%)	1·00 (ref)	..	..
Healthy eating¶	260/962 (27·0%)	..	..	3180/7973 (39·9%)	..	..	285/1280 (22·3%)	..	..	..
None or primary only	23/160 (14·4%)	0·30 (0·18–0·49)	<0·0001	1364/4020 (33·9%)	0·50 (0·43–0·58)	<0·0001	112/590 (19·0%)	0·36 (0·24–0·55)	<0·0001	0·0044
Secondary	64/334 (19·2%)	0·40 (0·28–0·55)	..	1148/2545 (45·1%)	0·75 (0·65–0·86)	..	121/516 (23·4%)	0·66 (0·44–1·01)	..	..
Trade school, college, or university	173/468 (37·0%)	1·00 (ref)	..	668/1408 (47·4%)	1·00 (ref)	..	52/174 (29·9%)	1·00 (ref)	..	..
High level of physical activity‖	458/857 (53·4%)	..	..	3372/8325 (40·5%)	..	..	365/1192 (30·6%)	..	..	..
None or primary only	61/127 (48·0%)	0·80 (0·53–1·21)	0·4695	1605/4176 (38·4%)	1·11 (0·97–1·27)	0·2709	181/548 (33·0%)	1·52 (0·98–2·34)	0·0659	0·2941
Secondary	168/305 (55·1%)	1·05 (0·78–1·42)	..	1144/2682 (42·7%)	1·16 (1·01–1·33)	..	148/477 (31·0%)	1·34 (0·86–2·08)	..	..
Trade school, college, or university	229/425 (53·9%)	1·00 (ref)	..	623/1467 (42·5%)	1·00 (ref)	..	36/167 (21·6%)	1·00 (ref)	..	..

Participants who had missing information on history of cardiovascular disease at baseline were excluded from this analysis (235 individuals). All ORs are adjusted for age, sex, and centre as a random effect, and treatment for hypertension and treatment for diabetes were additionally adjusted for baseline history of cardiovascular disease. OR=odds ratio. *Interaction between education and country income. †Self-reported or on medications, or blood pressure ≥140/≥90 mm Hg. ‡Self-reported diabetes or on glucose-lowering agent. §At least one of antiplatelet, β blockers, angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers, or statins. ¶Alternative Healthy Eating Index score in the third tertile. ‖Metabolic equivalent score >3000.

Table 3: **Proportions of patients with hypertension treatment, diabetes treatment, and secondary prevention treatment by education adjusted for age and sex**

high mortality among people with low levels of education in low-income and middle-income countries. 11825 (7·7%) of 153934 study participants had a previous cardiovascular disease event at baseline (table 3). Use of at least one medication was reported by 1040 (77·3%) of 1345 participants in high-income countries, 3617 (40·4%) of 8950 participants in middle-income countries, and 240 (15·7%) of 1530 participants in low-income countries. In high-income countries, people with low education had higher use of any secondary prevention medication (OR 1·82, 95% CI 1·14–2·89), whereas there was no systematic variation in middle-income countries (OR for lowest level *vs* highest level of education 1·10, 95% CI 0·95–1·28). In low-income countries, 60 (32·1%) of 187 participants with the highest level of education and 67 (8·8%) of 760 participants with no or primary education only used any secondary preventive drug (OR 0·26, 95% CI 0·17–0·42; $p_{interaction}$<0·0001).

Overall, quitting smoking was more common in those with higher education in all types of country—295 (77·4%) of 381 participants in high-income countries, 316 (53·6%) of 590 participants in middle-income countries, and 21 (46·7%) of 45 participants in low-income countries with trade school, college, or university level education, compared with 82 (65·6%) of 125 participants in high-income countries, 676 (48·0%) of 1408 participants in middle-income countries, and 57 (22·6%) of 252 participants in low-income countries with no or primary only education ($p_{interaction}$ 0·0387; table 3). A higher healthy diet score (alternative healthy eating index; appendix) was less common with lower levels of education across high-income, middle-income, and low-income countries (table 3). High levels of physical activity were more common among those with low education in low-income countries, but we found no significant interaction between country income and education (p=0·2941; table 3).

Discussion

We found that socioeconomic gradients with respect to cardiovascular disease and mortality varied between high-income, middle-income, and low-income countries, with inverse gradients that were steepest in poorer countries. Variations in traditional risk factors, as captured by the INTERHEART risk score, did not explain the differences in outcomes by socioeconomic status, because risk factors were generally lower in those with lower levels of education in low-income countries. Education, rather than wealth, was the socioeconomic indicator most consistently associated with outcomes, and people with low levels of education in low-income and middle-income countries had a markedly higher risk of major cardiovascular events compared with those with higher levels of education. Socioeconomic differences in primary and secondary prevention were also pronounced, with the least advantaged people (ie, those with low levels of education in low-income countries) receiving very poor secondary prevention, and markedly poorer diabetes and hypertension treatment compared with all other groups. We also observed large differences in CFRs after an acute cardiovascular event across both income level of countries and education level, as well as the household wealth of people within each country; however, details of care during or immediately after an acute event were not available.

The inverse gradient between low socioeconomic status and cardiovascular disease in high-income countries has been well documented.[1–3,23,24] However, although cardiovascular disease mortality has decreased rapidly in high-income countries, low-income and middle-income countries now face the greatest burden of cardiovascular disease.[25] Discussion of the changing patterns in cardiovascular disease has been informed by the concept of the epidemiological transition—the shift from malnutrition and infectious diseases to degenerative or non-communicable diseases, such as cardiovascular disease, as major causes of death and disability, resulting in an increasing average life expectancy and brought about by industrialisation and urbanisation[26,27]—but what is currently happening is unclear.[7] Although there are data on differences in risk factors by socioeconomic status in low-income and middle-income countries, there are sparse data on whether the incidence and mortality after a cardiovascular disease event vary by socioeconomic status in these countries.

In this study, education was the marker of socioeconomic status that we found to be most clearly linked with cardiovascular outcomes, consistent with our previous report from the INTERHEART study.[28] Low education is a proxy for broader social disadvantage but might directly impair an individual's ability to obtain effective care in several ways, including low awareness of the importance of seeking timely care or reduced access to information on how and where to obtain care and to overcome barriers that exist, both through formal channels and social networks. Lower education also reduces life opportunities more generally, meaning that individuals might not be able to afford necessary health care or might live in neighbourhoods with worse access to health-care facilities, especially in countries without universal health coverage.[29–31] These factors act throughout a person's life. The effects of social and behavioural factors are important, particularly where health-care systems are unable to compensate for social and economic disadvantages among the poor and less educated. These factors are in line with our finding that, in low-income countries, individuals with lower levels of education with hypertension have a cumulative disadvantage from detection to treatment and control, as previously reported in Colombia.[32] Consistent with this finding, we also showed that those with the lowest levels of education in low-income countries were disadvantaged in access to primary and secondary prevention, and, as previously noted, overall use of these medicines is also alarmingly low in low-income and middle-income countries.[33] Given these findings, it is unsurprising that we observed large differences by education in CFRs in low-income countries. This finding is also consistent with evidence from studies in India, where use of key treatments (thrombolytics, β blockers, lipid-lowering drugs, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, percutaneous coronary intervention, and coronary artery bypass graft surgery) in patients with acute myocardial infarction differed substantially by socioeconomic status.[34] Although the mechanisms that cause inequalities in access to health care might lead to differences in CFRs, the association with differences in incidence of cardiovascular disease might be less intuitive. However, we do know that most of a sizeable proportion of those enrolled in PURE who had either hypertension, diabetes, or cardiovascular disease were either suboptimally treated or not treated at all, particularly in low-income countries. Thus, there is potential for preventing many events by improving the use of simple proven treatments, especially in individuals with a lower level of education.

In addition to differences in medical management, other factors should be considered, because many people will be healthy before an event and not in need of medication. For example, differences in wealth might affect an individual's ability to afford a healthier diet if certain components of a healthy diet, such as fruits and vegetables, are relatively more expensive and thus unaffordable to many, particularly in poorer countries.[35] People with low levels of education in low-income and middle-income countries had lower risk factor levels but a higher risk of cardiovascular disease compared to those with higher levels of education. This apparent paradox could be due to epigenetics,[36] or weight gain during critical periods in childhood,[37,38] adolescence, and adulthood,[39] all areas for which systematic information, especially from middle-income and low-income countries, is lacking. Other unmeasured factors might include working conditions,[40] other psychosocial stress factors,[41] and poverty in early life.[42]

The main strengths of our study are the inclusion of many communities from several countries at different economic levels, a standardised and systematic approach to data collection, and use of both wealth and education as markers of socioeconomic status. Limitations of our study include grouping together of countries (within the broad categories of low-income or high-income) that are culturally and socially diverse, potentially also with respect to quality of education—the quality of education in low-income countries might be very different to that in high-income countries. However, PURE, like most other surveys on similar topics, did not collect data on the quality of education. Thus, although participants in PURE are broadly similar to the populations of the countries concerned,[18] the effect of education and wealth on health might vary between different countries within the same region. This could reflect the mediating effect of welfare policies, or differences between ethnic groups, where belief systems or social networks might confer differing levels of resilience. For example, research in Europe shows that the adverse health effects of unemployment differ among different models of the welfare state,[43] and the association between wealth and self-rated health differs in ethnic groups in the USA.[44] Furthermore, the magnitude of ethnic differences in mortality in some countries, including the USA, varies with independent measures of racism[45] and with measures of political culture.[46] However, disentangling these relationships is extremely complicated in a multinational study because of the very different national contexts.

Another limitation of this study is that the documentation of cardiovascular events, which to a large extent depended on admissions to hospital, might have been less complete for people with scarce financial resources. Therefore, event rates might have been even higher in those with the lowest levels of education or lowest wealth. However, it is possible that CFRs in low-income and middle-income countries could have been inflated if non-fatal events were incompletely reported. Although we collected information from 20 countries, the results might not necessarily be applicable to other countries in the same income category that were not included. Our study is not intended to be globally representative, but instead the diversity of countries in the study reflects the patterns of different associations between socioeconomic status and risk factors, treatments, and events. To our knowledge, PURE is the largest prospective study to date with in-depth data on socioeconomic status, risk factors, treatments, and fatal and non-fatal events. Nevertheless, our findings might not be applicable to some countries within a specific economic category—for example, the USA—where the social and health-care systems differ substantially from other high-income countries. Our findings should stimulate similar studies to PURE that involve additional countries. However, our data show considerable consistency in cardiovascular disease and mortality by education group within each of the 20 countries, which indicates our results are likely to be widely applicable.

In conclusion, cardiovascular disease in low-income countries is a problem predominantly among people with lower levels of education, whereas the situation in middle-income countries is more variable. Despite a lower risk factor burden among people with lower levels of education in low-income countries, we found higher rates of major cardiovascular disease. We observed marked differences between those with the highest levels of education and those with the lowest levels of education in the treatment of hypertension and diabetes, secondary prevention, and CFRs, as markers of substandard management. Given the increasing prevalence of cardiovascular disease, diabetes, and hypertension in low-income and middle-income countries, these findings are important. The findings of this study emphasise the importance of better education, which in turn can lead to better care and more use of proven pharmacological therapies. Therefore, measures to address the reasons underlying why so many people struggle to obtain education, and to assist them to remedy this situation, are likely to mitigate some of the substantial excess burden of cardiovascular disease and mortality, especially among the least privileged in low-income countries.

Contributors

AR wrote the analysis plan and had primary responsibility for writing the paper. SY designed and supervised the study and data analysis, interpreted the data, and reviewed and commented on all drafts of the manuscript. SR coordinated the worldwide study and reviewed and commented on drafts of the manuscript. CR did the analysis. MM, AS, and SIB reviewed and commented on the data analysis and drafts of the manuscript. KBB and AR coordinated the literature search for the research in context panel. 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.

Acknowledgments

SY is supported by the Mary W Burke endowed chair of the Heart and Stroke Foundation of Ontario. The PURE study is an investigator-initiated study that is funded by the Population Health Research Institute, the Canadian Institutes of Health Research, Heart and Stroke Foundation of Ontario, Support from the Canadian Institutes of Health Research Strategy for Patient Oriented Research, through the Ontario SPOR Support Unit, as well as the Ontario Ministry of Health and Long-Term Care, and through unrestricted grants from several pharmaceutical companies (with major contributions from AstraZeneca [Canada], Sanofi-Aventis [France and Canada], Boehringer Ingelheim [Germany and Canada], Servier, and GlaxoSmithKline), and additional contributions from Novartis and King Pharma and various national or local organisations in participating countries. These various national or local organisations include: Argentina: Fundacion ECLA (Estudios Clínicos Latino America); Bangladesh: Independent University, Bangladesh and Mitra and Associates; Brazil: Unilever Health Institute, Brazil; Canada: Public Health Agency of Canada and Champlain Cardiovascular Disease Prevention Network; Chile: Universidad de la Frontera; China: National Center for Cardiovascular Diseases and ThinkTank Research Center for Health Development; Colombia: Colciencias (grant nos 6566-04-18062 and 6517-777-58228); India: Indian Council of Medical Research; Malaysia: Ministry of Science, Technology and Innovation of Malaysia (grant no 100-IRDC/BIOTEK 16/6/21 [13/2007 and 07-05-IFN-BPH 010), Ministry of Higher Education of Malaysia (grant no 600-RMI/LRGS/5/3 [2/2011]), Universiti Teknologi MARA, Universiti Kebangsaan Malaysia (UKM-Hejim-Komuniti-15-2010); occupied Palestinian territory: the United Nations Relief and Works Agency for Palestine Refugees in the Near East, occupied Palestinian territory; International Development Research Centre, Canada; Philippines: Philippine Council for Health Research and Development; Poland: Polish Ministry of Science and Higher Education (grant no 290/W-PURE/2008/0), Wroclaw Medical University; Saudi Arabia: Saudi Heart Association, Dr Mohammad Alfagih Hospital, The Deanship of Scientific Research at King Saud University, Riyadh, Saudi Arabia (research group no RG-1436-013); South Africa: The North-West University, SA and Netherlands Programme for Alternative Development, National Research Foundation, Medical Research Council of South Africa, The South Africa Sugar Association, Faculty of Community and Health Sciences; Sweden: grants from the Swedish state under the agreement concerning research and education of doctors; the Swedish Heart and Lung Foundation; the Swedish Research Council; the Swedish Council for Health, Working Life and Welfare, King Gustaf V's and Queen Victoria Freemason's Foundation, AFA Insurance; Turkey: Metabolic Syndrome Society, AstraZeneca, Sanofi-Aventis; United Arab Emirates: Sheikh Hamdan Bin Rashid Al Maktoum Award For Medical Sciences and Dubai Health Authority, Dubai.

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