Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): a prospective cohort study

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Summary

Background To our knowledge, no previous study has prospectively documented the incidence of common diseases and related mortality in high-income countries (HICs), middle-income countries (MICs), and low-income countries (LICs) with standardised approaches. Such information is key to developing global and context-specific health strategies. In our analysis of the Prospective Urban Rural Epidemiology (PURE) study, we aimed to evaluate differences in the incidence of common diseases, related hospital admissions, and related mortality in a large contemporary cohort of adults from 21 HICs, MICs, and LICs across five continents by use of standardised approaches.

Methods The PURE study is a prospective, population-based cohort study of individuals aged 35–70 years who have been enrolled from 21 countries across five continents. The key outcomes were the incidence of fatal and non-fatal cardiovascular diseases, cancers, injuries, respiratory diseases, and hospital admissions, and we calculated the age-standardised and sex-standardised incidence of these events per 1000 person-years.

Findings This analysis assesses the incidence of events in 162 534 participants who were enrolled in the first two phases of the PURE core study, between Jan 6, 2005, and Dec 4, 2016, and who were assessed for a median of 9·5 years (IQR 8·5–10·9). During follow-up, 11 307 (7·0%) participants died, 9329 (5·7%) participants had cardiovascular disease, 5151 (3·2%) participants had a cancer, 4386 (2·7%) participants had injuries requiring hospital admission, 2911 (1·8%) participants had pneumonia, and 1830 (1·1%) participants had chronic obstructive pulmonary disease (COPD). Cardiovascular disease occurred more often in LICs (7·1 cases per 1000 person-years) and in MICs (6·8 cases per 1000 person-years) than in HICs (4·3 cases per 1000 person-years). However, incident cancers, injuries, COPD, and pneumonia were most common in HICs and least common in LICs. Overall mortality rates in LICs (13·3 deaths per 1000 person-years) were double those in MICs (6·9 deaths per 1000 person-years) and four times higher than in HICs (3·4 deaths per 1000 person-years). This pattern of the highest mortality in LICs and the lowest in HICs was observed for all causes of death except cancer, where mortality was similar across country income levels. Cardiovascular disease was the most common cause of deaths overall (40%) but accounted for only 23% of deaths in HICs (*vs* 41% in MICs and 43% in LICs), despite more cardiovascular disease risk factors (as judged by INTERHEART risk scores) in HICs and the fewest such risk factors in LICs. The ratio of deaths from cardiovascular disease to those from cancer was 0·4 in HICs, 1·3 in MICs, and 3·0 in LICs, and four upper-MICs (Argentina, Chile, Turkey, and Poland) showed ratios similar to the HICs. Rates of first hospital admission and cardiovascular disease medication use were lowest in LICs and highest in HICs.

Interpretation Among adults aged 35–70 years, cardiovascular disease is the major cause of mortality globally. However, in HICs and some upper-MICs, deaths from cancer are now more common than those from cardiovascular disease, indicating a transition in the predominant causes of deaths in middle-age. As cardiovascular disease decreases in many countries, mortality from cancer will probably become the leading cause of death. The high mortality in poorer countries is not related to risk factors, but it might be related to poorer access to health care.

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Introduction

Understanding contemporary variations in the incidence of common diseases and deaths across countries at different economic levels is crucial to develop strategies to improve global health. Two epidemiological transitions might have affected global patterns of disease and death. First, previous studies have noted a reduction in deaths from communicable diseases and an increase in non-communicable diseases.[1] Second, prevention and treatment of some non-communicable diseases have

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Research in context

Evidence before this study

Information on the differences in rates and causes of death, disease incidence, and disease outcomes have previously been based on data collected with non-standardised approaches. Although projects such as the Global Burden of Disease (GBD) study and the International Association of Cancer Registries GLOBOCAN database summarise the available evidence, comparison between regions is restricted by heterogeneous approaches to data collection and inadequate information on factors that could confound the relationships observed. The existing data suggest that there has been an epidemiological transition from communicable to non-communicable diseases (NCDs) as the leading cause of death in adults, first in high-income countries (HICs), then in middle-income countries (MICs), and later in low-income countries (LICs). Cardiovascular disease is now the leading cause of death overall. However, the number of deaths associated with cardiovascular disease has decreased, particularly in HICs, because of implementation of preventive and therapeutic measures. By contrast, there have been fewer such reductions in other NCDs, including cancer, and effective therapies for several of these NCDs are only in early stages of development or implementation. These changes in the incidence of diseases and related deaths have been less studied in MICs and LICs. Furthermore, data on resources for the management of disease, including hospital admissions and medication use, have been scarce in countries with different incomes, and they have not been collected with standardised methods. We did no formal systematic review of the literature. However, in our informal review of the literature, which consulted the GBD study and the WHO MONICA project—two of the largest and most comprehensive epidemiological studies undertaken—we found no similar report to ours, either in English or in French.

Added value of this study

We found that, among 162 534 individuals aged 35–70 years who were living in 21 countries and who we followed up for a median of 9·5 years (IQR 8·5–10·9), mortality rates were highest in the LICs and lowest in the HICs. Cardiovascular disease was the leading cause of death overall. However, in the HICs that we included, death from cancer was twice that from cardiovascular disease whereas, in our included LICs, death from cardiovascular disease was three times that from cancer, suggesting a transition in the main cause of death within the NCDs. This finding has not previously been well described, and it was independent of differences in age, sex, education, alcohol and tobacco use, diabetes, hypertension, physical activity, body-mass index, and rural versus urban location. Rates of hospital admission and of medication use were inversely associated with death, suggesting that lower health-care availability or accessibility might be contributing factors to higher mortality in the poorer countries.

Implications of all the available evidence

Although ongoing strategies to address cardiovascular disease in adults in HICs remain important, enhanced efforts to prevent and successfully treat cancer are crucial to reduce mortality rates. Cardiovascular disease is the major cause of death in adults aged 35–70 years in MICs and LICs, and strategies to prevent and treat cardiovascular disease, such as better availability of and access to hospitals and cardiovascular disease medications are likely to reduce the proportion of deaths associated with cardiovascular disease. If patterns of disease and related deaths in MICs and LICs follow those in HICs, cancer could become the most common cause of death in these countries in the next few decades.

improved, particularly cardiovascular disease in high-income countries (HICs), which has led to marked reductions in deaths from cardiovascular disease.[2] However, fewer advances have been made in the treatment of other non-communicable diseases, such as cancers, and these advances have been more recent.[1,3–7] Thus, the incidence of and mortality from different non-communicable diseases might be changing. Although there are reliable data on mortality rates by cause from several HICs, there is a paucity of similar data from most low-income countries (LICs) and middle-income countries (MICs). Further, there are scant data on disease incidence or hospital admissions and medication use in most countries in the world. In our analysis of the Prospective Urban Rural Epidemiology (PURE) study, we aimed to evaluate differences in the incidence of common diseases, related hospital admissions, and related mortality in a large contemporary cohort of adults from 21 HICs, MICs, and LICs across five continents by use of standardised approaches to enrolment, follow-up, and event reporting.

Methods

Study design and participants

The design of the PURE study has previously been reported (appendix p 1).[8–10] Briefly, the PURE study is an ongoing, prospective, population-based cohort study. During the first and second phases of the study, 132 977 households (comprising a population of 506 087 individuals) living in 21 countries were approached, to participate in the study. We classified countries into income groups (ie, HICs, MICs, or LICs) by use of gross national income per capita according to their World Bank classification for 2006, when the study was initiated. The HICs were Canada, Saudi Arabia, Sweden, and the United Arab Emirates. The MICs were Argentina, Brazil, Chile, China, Columbia, Iran, Malaysia, Palestine, Philippines, Poland, Turkey, and South Africa. The LICs were Bangladesh, India, Pakistan, Tanzania, and Zimbabwe.

This analysis was done on findings of the first two phases of the PURE core study, in which individuals were recruited from these 21 countries and had

completed at least one follow-up visit. The phases of the study are described in the appendix (p 1). Follow-up of participants enrolled in the third phase of the PURE study is ongoing, so these individuals are not included in this analysis. To qualify for study inclusion, we required participants to be aged 35–70 years. In all phases of baseline enrolment, all participants who met the age eligibility criterion could consent to participate in either the core study, which collected detailed data, or the surveillance study, which only collected data on deaths during the study period; the core and surveillance studies were run concurrently.

In each country, we recruited individuals from urban and rural communities, but we aimed to ensure feasibility of data collection and long-term follow-up. We selected households to be broadly representative of the socio-demographic composition of communities. Although not designed to be nationally representative, the socio-demographic characteristics and mortality rates of men and women of phase 1 of the PURE study (which included participants from 17 countries) were broadly similar to their national populations.[9]

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

Procedures

We contacted participants at least every 3 years, to ascertain their vital status, the occurrence of specific non-fatal events, and all hospital admissions. We used standardised questionnaires to collect information on participant characteristics and medical history. Where possible, further details on deaths were obtained from verbal autopsies or medical records, and further details on non-fatal events were obtained from hospital or physician reports and standardised questionnaires. The INTERHEART risk score,[11,12] which is a validated measure of risk for future cardiovascular disease that integrates information on health behaviours and risk factors, was calculated at baseline for all participants. The INTERHEART score is measured on a scale of 0 to 48, with higher scores indicating a higher risk of cardiovascular disease. The cardiovascular medications that we recorded included blood pressure lowering drugs, cholesterol lowering drugs, antiplatelet drugs, anticoagulants, and glucose lowering drugs.

Deaths, cancers, myocardial infarctions, strokes, and heart failure were adjudicated centrally in each country by trained physicians with standardised definitions. All other events were documented at each site with study definitions (appendix pp 3–12), but they were not adjudicated centrally. All events were also classified by a trained nosologist according to the International Classification of Diseases (tenth revision).[13] Data were collected from all countries and checked and analysed at the Population Health Research Institute (Hamilton, ON, Canada).

If a participant did not respond to requests for follow-up, their neighbours and relatives were approached to obtain updated contact details or, if unavailable, their vital status. Sites were instructed to continue attempts to contact participants or their relatives on an ongoing basis if vital status was unknown at a scheduled study visit. Bias related to loss to follow up was considered unlikely to substantially affect our findings, owing to the high ascertainment of vital status that we achieved.

Outcomes

The events that we evaluated in our analyses were deaths (by cause), myocardial infarctions, strokes, heart failure, cancers (excluding non-melanoma skin cancers; pre-cancerous lesions and polyps of the colon that were detected during screening were not reported as cancer), injuries requiring hospital admission, chronic obstructive pulmonary disease (COPD), and hospital admissions (including the primary reason for the hospital admission). Hospital admission was defined as a stay in a hospital, emergency room, or clinic for a procedure or for at least 12 h. For each category of non-fatal event, we only included its first occurrence in the analysis. Event definitions are shown in the appendix (pp 3–12). We included all reported events until July 3, 2019. Cardiovascular disease was defined as death from cardiovascular disease, myocardial infarction, stroke, or heart failure.

Statistical analysis

Continuous variables are presented as means with SDs. Categorical variables are presented as counts and proportions. Disease incidence and mortality rates were standardised according to the age and sex distribution of the PURE cohort, and they are expressed per 1000 person-years. Cox proportional hazards models were constructed for mortality, with community included as a random effect, to account for within-community clustering of characteristics. The proportionality of hazards was evaluated by visual inspection of log-log plots. For all outcome events, we considered the first occurrence of the event of interest. For hospital admissions, we did additional analyses with all hospital admissions. For cause-specific mortality and first hospital admission, a competing risks regression was done, with death in the absence of the event of interest regarded as the competing risk. Results from competing risks regression are expressed as sub-distribution hazard ratios (HRs) with 95% CIs. In time-to-event models, we adjusted for age, sex, education, alcohol and tobacco use, diabetes, hypertension, physical activity, body-mass index, and rural versus urban location. 1-year case-fatality rates were calculated as the proportion of individuals with a specific event who died within 1 year of the event. To explore the reasons underlying differences in patterns of deaths across countries, we did several analyses to compare indicators of country wealth or access to health care, with event rates stratified

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See **Online** for appendix

For the **protocol for the Prospective Urban and Rural Epidemiological Study** see www.phri.ca/pure

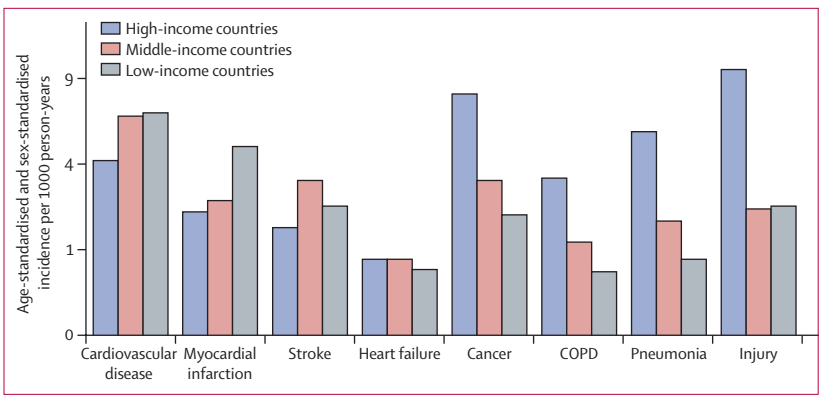

Figure 1: **Age-standardised and sex-standardised incidence of disease, stratified by country income level**
The *y*-axis represents a squared scale. COPD=chronic obstructive pulmonary disease.

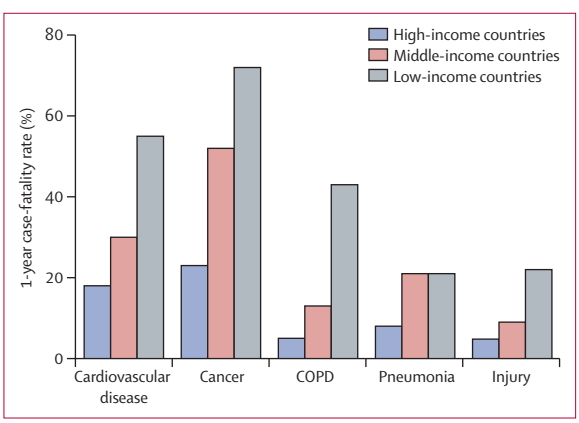

Figure 2: **1-year case-fatality rates after an event, stratified by country income level**
COPD=chronic obstructive pulmonary disease.

by country. Specifically, we evaluated the relationship between hospital admission rate and mortality rate; the administration of medication for cardiovascular disease over time and death; and gross domestic product per capita in 2017 and the ratio of deaths from cardiovascular disease to deaths from cancer across countries. We used an exponential regression, assuming one asymptote, according to the models:

$$\text{Mortality rate} = b_1 \times (b_2)^{\text{hospital admission rate}};$$

$$\text{Mortality rate} = b_1 \times (b_2)^{\text{medication rate}}; \text{ and}$$

$$\sqrt{\text{Ratio of cardiovascular disease to cancer mortality}} = (b_1 \times (b_2)^{\text{gross domestic product}})$$

where b_1 and b_2 are coefficients determined by the regression model. An asymptotic model was chosen rather than a linear model because a linear model has an intercept at which the mortality rate or ratio of cardiovascular disease to cancer is modelled as 0, which is implausible. The model fit was assessed by the Akaike Information Criterion, where the Akaike Information Criterion=(–2×LnL)+2k, where LnL is the maximised log-likelihood of the model and k is the number of parameters estimated. We used Stata version 16.0 for our analyses.

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. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 12, 2001, and Dec 4, 2016, 506 087 individuals were approached for inclusion in the first two phases of the PURE study, of whom 47 653 (9·4%) individuals declined to participate (appendix p 17). Of the remaining 458 434 (90·6%) individuals, 235 180 (46·5%) individuals were aged 35–70 years. Of these eligible individuals, 167 068 (71·0%) participated in the PURE core study, in which detailed baseline and follow-up data were collected, and the remaining 68 112 (29·0%) individuals participated in the surveillance cohort, in which only deaths were documented. Before final analysis of the core study participants, 2805 (1·7%) participants were excluded because of missing baseline data (eg, on age and sex), and 306 (0·2%) participants were excluded because they were not due a follow-up visit yet. This report includes 162 534 (97·3%) participants from the first two phases of the PURE core study, comprising individuals from 883 communities (397 urban and 486 rural) in 21 countries who had completed at least one follow-up visit. Events were reported until July 3, 2019, for a median follow-up of 9·5 years (IQR 8·5–10·9; median 10·8 years in LICs, 9·2 years in MICs, and 9·2 years in HICs).

The baseline characteristics of the 162 534 participants are shown in the appendix (p 13) and were similar to those of the 155 722 individuals described in our companion Article (which does not include those with previous cardiovascular disease).[14] We achieved a high participation rate of eligible individuals in the detailed core study, 94·1% of individuals completed at least one cycle of follow-up, and information on vital status was available in 98·4% of participants. At baseline, 94 144 (58%) participants were female and they had a mean age of 50·6 years (SD 9·9). Baseline INTERHEART risk scores were 13·1 (6·2) in HICs, 10·5 (5·8) in MICs, and 7·9 (5·0) in LICs (p=0·0001), representing a 20–30% difference between successive country income groups. This finding indicates the highest burden of cardiovascular disease risk factors among participants from HICs and the lowest burden in LICs.

During follow-up, 9329 (5·7%) participants had cardiovascular disease, 5151 (3·2%) participants had a cancer, 4386 (2·7%) participants had injuries requiring

hospital admission, 2911 (1·8%) participants had pneumonia, and 1830 (1·1%) participants had COPD. Incident cancers, injuries, COPD, and pneumonia were most common in HICs and least common in LICs (figure 1). The same pattern of incidence was observed when the five most common cancers (breast, lung, colon, prostate, and gynaecological) were analysed separately (data not shown). By contrast, cardiovascular disease occurred more often in LICs (7·1 cases per 1000 person-years) and in MICs (6·8 cases per 1000 person-years) than in HICs (4·3 cases per 1000 person-years). After adjustment, the sub-distribution HRs for cardiovascular disease were 1·14 (95% CI 1·04–1·24) in MICs and 1·15 (1·04–1·27) in LICs compared with HICs. These differences were driven by a higher incidence of myocardial infarction in LICs and a higher incidence of stroke in MICs than in HICs. When China was analysed separately, the age-standardised and sex-standardised incidences of cardiovascular disease were 4·3 cases per 1000 person-years in HICs, 6·1 cases per 1000 person-years in MICs, 7·1 cases per 1000 person-years in LICs, and 7·5 cases per 1000 person-years in China. The incidence of heart failure was similar in HICs, MICs, and LICs.

1-year case-fatality rates for all conditions were consistently highest in LICs and lowest in HICs (figure 2). For cardiovascular disease, cancer, pneumonia, and hospital admissions for injury, the 1-year case-fatality rate was 3–4 times higher in LICs than in HICs, whereas the 1-year case fatality rate for COPD was about 8 times higher in LICs than in HICs.

During follow-up, 38 334 individuals were admitted to hospital (table 1). Age-standardised and sex-standardised rates of hospital admission, stratified by country income level, are shown in the appendix (p 18). Cardiovascular disease was the most common cause of hospital admission globally, and this condition was the primary reason for hospital admission in 23·9% of all hospital admissions (22% of admissions in LICs, 27% in MICs, and 17% in HICs). We observed a contrasting pattern when comparing the rates of hospital admission for cardiovascular disease with the incidence of cardiovascular disease: LICs reported the highest incidence of cardiovascular disease but the lowest rates of hospital admissions for cardiovascular disease (5·0 admissions per 1000 person-years), whereas HICs reported the lowest incidence of cardiovascular disease but the highest rates of hospital admissions for cardiovascular disease (9·4 admissions per 1000 person-years). The low rate of hospital admissions in LICs was also observed for all other conditions, except for infections: hospital admission for infections was more common in LICs than in HICs or MICs. This pattern of a low rate of hospital admissions in LICs compared with HICs was unchanged after adjustment for age, sex, education, alcohol and tobacco use, diabetes, hypertension, physical activity, body-mass index, and rural versus urban location. Medications for cardiovascular disease were used most frequently in HICs and least frequently in LICs (age-standardised and sex-standardised rates of use of 29% in HICs, 23% in MICs, and 17% in LICs).

	All admissions	First admissions		
		High-income countries (n=18 073)	Middle-income countries (n=108 291)	Low-income countries (n=36 170)
All				
Number admitted (%)	60 736 (100·0%)	7435 (41·1%)	23 583 (21·8%)	7316 (20·2%)
Sub-distribution HR	..	1 (ref)	0·52 (0·51–0·54)	0·53 (0·51–0·55)
Cardiovascular				
Number admitted (%)	14 492 (23·9%)	1664 (9·2%)	7386 (6·8%)	1694 (4·7%)
Sub-distribution HR	..	1 (ref)	0·77 (0·72–0·82)	0·62 (0·57–0·67)
Gastrointestinal				
Number admitted (%)	8169 (13·5%)	1658 (9·2%)	4291 (4·0%)	863 (2·4%)
Sub-distribution HR	..	1 (ref)	0·57 (0·53–0·61)	0·40 (0·36–0·45)
Cancer				
Number admitted (%)	5558 (9·2%)	1058 (5·9%)	2702 (2·5%)	613 (1·7%)
Sub-distribution HR	..	1 (ref)	0·55 (0·50–0·60)	0·43 (0·48–0·49)
Respiratory				
Number admitted (%)	5133 (8·5%)	889 (4·9%)	2571 (2·4%)	697 (1·9%)
Sub-distribution HR	..	1 (ref)	0·48 (0·43–0·52)	0·39 (0·34–0·44)
Musculoskeletal				
Number admitted (%)	4701 (7·7%)	1496 (8·3%)	1998 (1·9%)	309 (0·9%)
Sub-distribution HR	..	1 (ref)	0·31 (0·29–0·34)	0·18 (0·16–0·21)
Injury				
Number admitted (%)	4599 (7·6%)	1295 (7·2%)	2172 (2·0%)	756 (2·1%)
Sub-distribution HR	..	1 (ref)	0·30 (0·27–0·33)	0·33 (0·29–0·37)
Genito-urinary				
Number admitted (%)	4445 (7·3%)	924 (5·1%)	2326 (2·2%)	694 (1·9%)
Sub-distribution HR	..	1 (ref)	0·58 (0·52–0·64)	0·58 (0·51–0·66)
Infection				
Number admitted (%)	2569 (4·2%)	260 (1·4%)	1016 (0·9%)	1104 (3·1%)
Sub-distribution HR	..	1 (ref)	0·53 (0·45–0·63)	1·66 (1·39–1·98)

Data are the number admitted (%) with the eight most common reasons for admission or the number of first hospital admissions (%) attributable to these causes, and the sub-distribution HRs (95% CIs), indicating the risk of a first hospital admission attributable to these eight causes in middle-income and low-income countries relative to high-income countries. HR=hazard ratio.

Table 1: **The eight most common reasons for hospital admission**

During follow-up, 11 307 (7·0%) participants died (table 2). Age-standardised and sex-standardised mortality rates in LICs (13·3 deaths per 1000 person-years) were double those in MICs (6·9 deaths per 1000 person-years) and four times higher than in HICs (3·4 deaths per 1000 person-years; appendix p 19). We also noted this pattern in deaths by country income among the 68 112 individuals who only participated in the surveillance cohort during follow-up: the age-standardised and sex-standardised mortality rates in the surveillance cohort were 9·6 deaths per 1000 person-years in LICs, 4·0 deaths per 1000 person-years in MICs, and 3·9 deaths per 1000 person-years in HICs (appendix p 13). The age-standardised and sex-standardised mortality rates in the 227 539 individuals

	Overall (n=162 534)	High-income countries (n=18 073)	Middle-income countries (n=108 291)	Low-income countries (n=36 170)
Overall mortality				
Number of deaths (%)	11 307 (7·0%)	604 (3·3%)	6251 (5·8%)	4452 (12·3%)
HRs	..	1 (ref)	1·42 (1·21–1·66)	2·56 (2·15–3·06)
Cardiovascular disease				
Number of deaths (%)	3398 (2·1%)	110 (0·6%)	1944 (1·8%)	1344 (3·7%)
Sub-distribution HRs	..	1 (ref)	2·21 (1·78–2·73)	4·18 (3·34–5·24)
Cancer				
Number of deaths (%)	2265 (1·4%)	293 (1·6%)	1495 (1·4%)	477 (1·3%)
Sub-distribution HRs	..	1 (ref)	0·90 (0·77–1·05)	0·71 (0·58–0·86)
Injury-related				
Number of deaths (%)	755 (0·5%)	41 (0·2%)	357 (0·3%)	357 (1·0%)
Sub-distribution HRs	..	1 (ref)	1·06 (0·74–1·51)	2·38 (1·62–3·49)
Respiratory				
Number of deaths (%)	738 (0·5%)	31 (0·2%)	409 (0·4%)	298 (0·8%)
Sub-distribution HRs	..	1 (ref)	1·50 (1·00–2·25)	1·97 (1·27–3·05)
Infection-related				
Number of deaths (%)	643 (0·4%)	11 (0·1%)	324 (0·3%)	308 (0·9%)
Sub-distribution HRs	..	1 (ref)	2·56 (0·91–7·19)	9·97 (3·52–28·3)

Data are number of deaths (%) attributable to each cause and HRs (95% CIs) compared across high-income, middle-income, and low-income countries. HRs and sub-distribution HRs were adjusted for age, sex, education level, tobacco and alcohol use, urban versus rural location, baseline diabetes and hypertension, physical activity, and body-mass index. Because the absolute numbers of deaths attributable to gastrointestinal (n=223) and genito-urinary (n=48) causes were low, these causes were not modelled as outcomes. HRs=hazard ratios.

Table 2: **Overall deaths and cause-specific deaths across high-income, middle-income, and low-income countries**

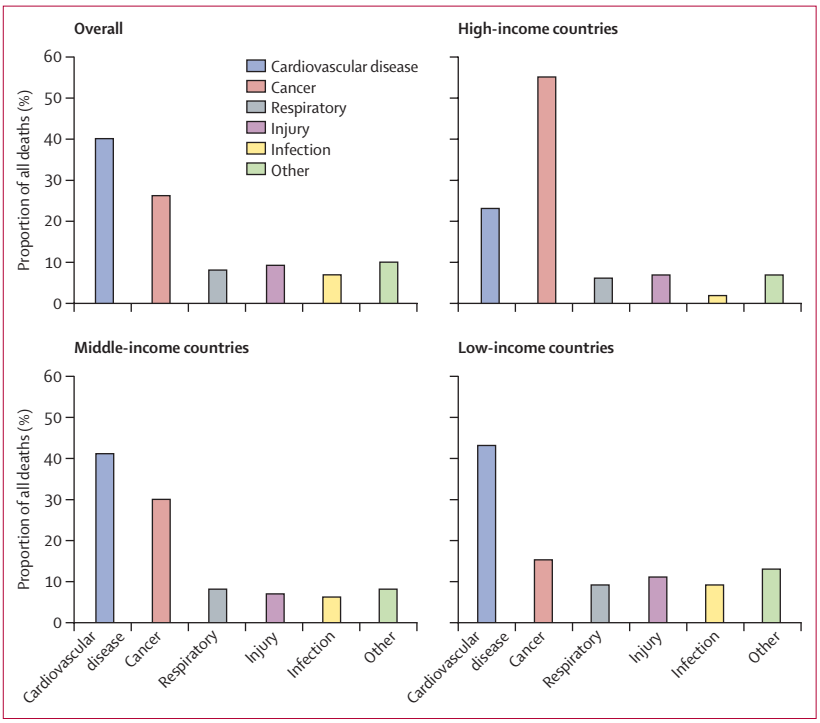

Figure 3: **The most common causes of death as proportions of all deaths, overall and stratified by country income level**

with pooled data from the core and surveillance cohorts were 12·7 deaths per 1000 person-years in LICs, 6·3 deaths per 1000 person-years in MICs, and 3·7 deaths per 1000 person-years in HICs.

Cardiovascular disease and cancer were the most common causes of death overall (unadjusted data, 40% and 26% of deaths; figure 3). We found marked differences in the most common causes of death by country income levels. In HICs, deaths from cancer (1·7 deaths per 1000 person-years) were about 2·5 times more common than those from cardiovascular disease (0·6 deaths per 1000 person-years; appendix p 16). In MICs, deaths from cardiovascular disease (2·0 deaths per 1000 person-years) were slightly more common than those from cancer (1·6 deaths per 1000 person-years) whereas, in LICs, deaths from cardiovascular disease (4·2 deaths per 1000 person-years) were three times more common than those from cancer (1·4 deaths per 1000 person-years). Therefore, the ratio of deaths from cardiovascular disease to those from cancer was 0·4 in HICs, 1·3 in MICs, and 3·0 in LICs. In LICs, cardiovascular disease accounted for 43% of deaths and cancer accounted for 15% of deaths. In MICs, cardiovascular disease accounted for 42% of deaths and cancer for 30% of deaths. In HICs, 55% of deaths were due to cardiovascular disease and 23% of deaths were due to cancer. More deaths from cancer than from cardiovascular disease were also reported in four upper-MICs (Argentina, Chile, Turkey, and Poland) but not in other MICs (appendix p 14). We found a strong inverse relationship between each country's gross domestic product per capita in 2017 and the ratio of deaths from cardiovascular disease to those from cancer—ie, a higher country gross domestic product is associated with a lower incidence of deaths from cardiovascular disease compared with those from cancer (figure 4).

The adjusted risk of death from cardiovascular disease was more than four times higher in LICs than in HICs (table 2). The risk of death from cancer was 1·4 times higher in HICs than in LICs, whereas the risk of death related to injuries or respiratory conditions in LICs was around double that in HICs. The risk of death from infections was ten times higher in LICs than in HICs. Compared with HICs, the adjusted risk of any death related to the conditions reported was 1·4 times higher in MICs, mostly driven by the doubling in risk of death from cardiovascular disease. However, the adjusted risks of death due to cancers, injuries, respiratory disease, and infections in MICs were not significantly different to those in HICs. We found a strong inverse association between rates of all hospital admissions and mortality rates across countries and a similar association between rates of cardiovascular disease medication use and of death (figure 5).

Discussion

In our study of 162 534 adults aged 35–70 years (complemented with data on 68 112 individuals in the

surveillance cohort, to a total of 227 649 people) from four HICs, 12 MICs, and five LICs, we reported four major findings. First, among the countries studied, we found a larger proportion of deaths and hospital admissions associated with non-communicable diseases versus infectious diseases. Second, we found a higher proportion of deaths associated with cancers than with cardiovascular disease in HICs and several upper-MICs, with the opposite trend in LICs. Third, we found a higher incidence of cardiovascular disease and related death in poorer countries than in richer countries (despite a lower burden of cardiovascular disease risk factors in poorer countries). Fourth, we found an inverse association between markers of health care (hospital admissions or medication use) and deaths, suggesting that poorer access to health care could be responsible, at least in part, for the higher mortality in poorer countries.

Our study confirms that non-communicable diseases are the most common cause of deaths and illnesses globally among adults aged 35–70 years, and that cardiovascular disease is more common in MICs and LICs than in HICs. We have previously reported,[15] and we have confirmed in the companion Article,[14] a paradox in that usual cardiovascular disease risk factors are markedly lower in LICs compared with HICs but cardiovascular disease incidence and related mortality rates are higher in LICs than in HICs, suggesting that the higher cardiovascular disease incidence and higher related mortality rates in LICs are not likely to be due to risk factors. The higher case-fatality rates, lower use of medications, lower rates of risk factor control, and secondary prevention in MICs and LICs (and low-income and MICs [LMICs]) than in HICs, which we have previously reported,[10,16] suggest that poorer access to health care in LMICs than in HICs might be responsible for the higher mortality in LMICs. Further, other risk factors, such as household and ambient air pollution, lower educational attainment, and poor diet are more common in LMICs and might be responsible for the higher mortality in LMICs compared with HICs.

Although cardiovascular disease occurs more frequently and causes more deaths than cancer in LMICs, we observed a higher incidence of death from cancer than from cardiovascular disease in HICs and some upper-MICs. This epidemiological transition might be due to improved prevention and treatment of cardiovascular disease in HICs, whereas successful strategies (other than tobacco control) to prevent and treat cancers are yet to lead to large reductions in most cancers.

The cardiovascular disease conditions (myocardial infarction, stroke, and heart failure) share many common risk factors.[16,17] In HICs, cardiovascular disease has been recognised to be the primary cause of disease and deaths for about 50 years. This recognition has led to the development and implementation of strategies to control common cardiovascular disease risk factors and better treatments for myocardial infarction, stroke, and heart failure, to reduce the health-care burden from cardiovascular disease.[4,18,19] Consequently, the incidence of cardiovascular disease and death have declined markedly in several HICs in the last two decades.[2,20] Although the use of effective prevention and treatment strategies in HICs is far from optimal, this trend suggests that increasing adoption of these measures should lead to even greater reductions in cardiovascular disease and related death in HICs.

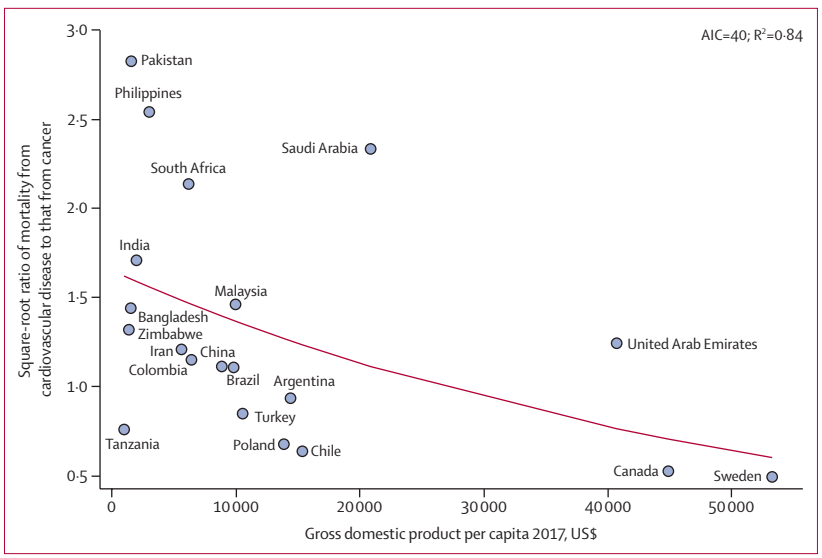

Figure 4: **The relationship between gross domestic product per capita in 2017 and the square root of the ratio of deaths from cardiovascular disease to those from cancer, by country**
AIC=Akaike's information criterion.

Compared with cardiovascular disease, which is largely explained by a handful of risk factors, cancers are more varied, and their causes can also be more diverse. Although there have been advances in the prevention of some cancers, such as reductions in incidence of oral and lung cancer by tobacco avoidance, other effective approaches to preventing specific cancers are relatively recent, although they could have important effects in the future (such as vaccination against human papillomavirus to prevent cervical cancer, or hepatitis B vaccination to prevent liver cancers).[1,6,21] However, for common cancers such as breast, prostate, or bowel cancer, few modifiable risk factors have been identified that have a large effect on cancer risk. This paucity of known risk factors might have led to the low change in overall cancer incidence in most countries and, combined with fewer deaths associated with cardiovascular disease, cancer has emerged as the most common disease and cause of death in the HICs and some MICs that we have evaluated in PURE.

Our findings are consistent with the Global Burden of Disease (GBD) Study, which found that, among adults aged 50–69 years from wealthy countries, cancers were the leading cause of death in 2017, whereas cardiovascular disease was the leading cause of death among adults

For **Global Burden of Disease data** see https://vizhub.healthdata.org/gbd-compare/#

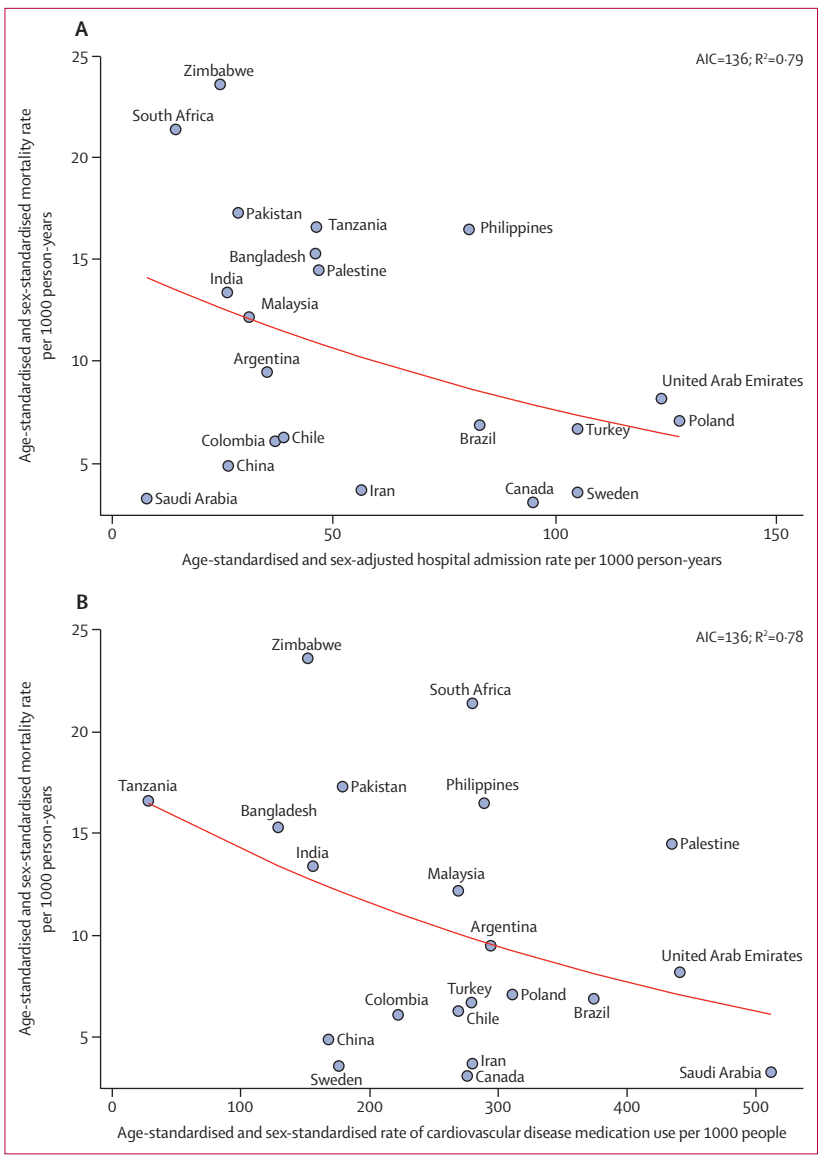

Figure 5: **The relationship between country hospital admission rates (all admissions) and mortality rates (A), and between country rate of cardiovascular disease medication use and mortality rates (B)**
AIC=Akaike's information criterion.

aged 50–69 years from countries with low social development indices. Our international findings are also consistent with a large US study,[22] which demonstrated an epidemiological transition from cardiovascular disease as the main cause of death in poorer countries to cancer as the main cause of death in richer countries.

The numbers of countries and deaths recorded in PURE are much smaller than those in the GBD. However, PURE also provides data on disease incidence, hospital admissions, and treatments, which were collected with a standardised approach, which is a unique strength. Therefore, GBD and PURE are complementary, and these data should inform future estimates of the global patterns and burden of diseases.

Notably, we observed higher rates of hospital admissions for pneumonia and COPD in HICs compared with LMICs, whereas death from these conditions is highest in LMICs. This finding might be due to higher rates of diagnosis and earlier treatment for these respiratory conditions in HICs compared with LMICs, an explanation that is consistent with the few data that suggest low pneumonia hospital admission rates in LMICs.[23] Similar patterns were observed with higher rates of hospital admissions and fewer deaths from injuries in HICs than in LMICs.

Rates of hospital admission and use of medications to treat or prevent cardiovascular disease are general indicators of access to health care. These rates were lowest in LICs and highest in HICs. Less frequent use of proven medications and lower rates of hospital admissions were associated with more deaths and 1-year case fatality from several diseases in the poorer countries. Our findings are consistent with those from the WHO MONICA Project,[24] which was mainly done in Europe and which reported that the use of cardiovascular disease medications and revascularisation explained a larger proportion of the reduction in mortality rates associated with coronary heart disease than changes in exposure to risk factors.[24] These findings suggest that mortality rates in LMICs could be reduced by improving access to essential health-care services.[25] In most HICs, these reductions have been achieved by greater government investment in health care and the provision of universal health coverage, such that most of the population have access to essential health-care interventions and services. Similar strategies could have a major effect in reducing mortality rates in LMICs.

Our findings have several implications. In HICs, intensification of current efforts to prevent and treat cardiovascular disease should further reduce cardiovascular disease incidence and associated mortality rates. Further, identifying new and effective strategies to prevent and treat cancers will be necessary to reduce deaths from cancers. By contrast, MICs are likely to face challenges relating to death from several non-communicable diseases, including cardiovascular disease, with some upper-MICs already showing increasing numbers of deaths from cancers. If the approaches that have been successful at reducing deaths from cardiovascular disease in HICs are implemented widely in LMICs, large future reductions in deaths from cardiovascular disease would be expected in LMICs. Over time, we might also expect cancer to become an increasingly important cause of death in LICs, as already observed in many MICs.[25] Therefore, it is desirable to implement both cardiovascular disease and cancer prevention and treatment strategies in countries at all economic levels worldwide.

The major strength of our study is that, to our knowledge, it is the only study that has prospectively recorded information on individual-level risk factors, characteristics, treatments, diseases, hospital admissions, and deaths from several HICs, MICs, and LICs with standardised approaches. Therefore, the PURE study

is uniquely positioned to inform comparisons of risk factors, morbidity, and mortality between countries at different income levels. A potential limitation of our study is that participating countries and communities within each country were not selected at random because this design was not considered feasible in a long-term large cohort study. Therefore, caution must be exercised in extrapolating our findings to all countries globally and, ideally, it will be important to confirm our findings in more countries. However, participants within each community were screened with strategies that were aimed at minimising any selection biases. We achieved a high participation rate of eligible individuals in the detailed core study, 94·1% of individuals completed at least one cycle of follow-up, and information on vital status was available in 98·4% of participants.

Those enrolled in the detailed core study had a higher cardiovascular disease risk factor burden, and higher mortality rates than those who entered the surveillance cohort (appendix p 13). However, the mortality rates across groups of countries and when stratified by sex and age were similar between the core and the surveillance cohorts. Therefore, we found no evidence that there were systematic biases or differences between countries in their patterns of participation in the core study that would have accounted for the observation of higher event rates in poorer countries in this analysis.

Although the absolute mortality rates noted in this cohort were slightly lower than those reported in the surveillance cohort (which represents an additional 27% of the population aged 35–70 years in the households contacted), the patterns of deaths across HICs, MICs, and LICs were comparable to that of the core cohort (which provided more detailed information), such that the overall data show consistent patterns. The markedly higher incidence of cardiovascular disease that we observed in LICs compared with MICs and HICs provides evidence against systematic ascertainment biases in detection or classification of outcomes and parallels our findings with respect to deaths. Our report only includes data from 21 countries, but the PURE study has enrolled individuals from an additional six countries (Russia, Kyrgyzstan, Kazakhstan, Ecuador, Uruguay, and Peru) and additional participants from Poland, Argentina, and Chile; we expect to report follow-up data from 27 countries in future. Even with this expanded effort, PURE will have no data from north or west Africa and relatively modest representation from HICs, so it will be important to complement the information in PURE with data from additional countries. Also, some outcomes (especially injury requiring hospital admission) might be more frequent in HICs owing to more accessible and affordable hospitals. Additionally, more research is needed to understand the specific factors associated with differences in national incomes between countries that could account for the differences in the risk of death and disease that we observed.

In conclusion, our study showed that, in the countries studied, although cardiovascular disease continues to be the primary cause of death overall in adults aged 35–70 years globally, this disease is no longer the most common cause of death in HICs and several upper-MICs, where deaths from cancer are now more common than those from cardiovascular disease. Whether similar patterns occur in other HICs and MICs needs to be explored, but this finding appears to indicate a new epidemiological transition among the different categories of non-communicable diseases. If the pattern of disease incidence and deaths that we found in HICs and some MICs also occurs in other countries, substantial reductions in cardiovascular disease and related deaths can be expected to occur in most countries. It is also likely that cancer will become the most common cause of deaths globally in a few decades.

Contributors

GRD chaired the event adjudication committee and is the principal investigator at the Quebec site. GRD and DPL wrote the draft manuscript. DPL did all study analyses. SR coordinated the worldwide study. SR and PJ reviewed and commented on all the drafts. SY designed and supervised the study, obtained funding, interpreted the data, and reviewed and commented on all the drafts. All other authors coordinated the study in their respective countries and provided comments on drafts of the paper.

Declaration of interests

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