Variations in risks from smoking between high-income, middle-income, and low-income countries: an analysis of data from 179 000 participants from 63 countries

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Summary

Background Separate studies suggest that the risks from smoking might vary between high-income (HICs), middle-income (MICs), and low-income (LICs) countries, but this has not yet been systematically examined within a single study using standardised approaches. We examined the variations in risks from smoking across different country income groups and some of their potential reasons.

Methods We analysed data from 134 909 participants from 21 countries followed up for a median of 11·3 years in the Prospective Urban Rural Epidemiology (PURE) cohort study; 9711 participants with myocardial infarction and 11 362 controls from 52 countries in the INTERHEART case-control study; and 11 580 participants with stroke and 11 331 controls from 32 countries in the INTERSTROKE case-control study. In PURE, all-cause mortality, major cardiovascular disease, cancers, respiratory diseases, and their composite were the primary outcomes for this analysis. Biochemical verification of urinary total nicotine equivalent was done in a substudy of 1000 participants in PURE.

Findings In PURE, the adjusted hazard ratio (HR) for the composite outcome in current smokers (*vs* never smokers) was higher in HICs (HR 1·87, 95% CI 1·65–2·12) than in MICs (1·41, 1·34–1·49) and LICs (1·35, 1·25–1·46; interaction p<0·0001). Similar patterns were observed for each component of the composite outcome in PURE, myocardial infarction in INTERHEART, and stroke in INTERSTROKE. The median levels of tar, nicotine, and carbon monoxide displayed on the cigarette packs from PURE HICs were higher than those on the packs from MICs. In PURE, the proportion of never smokers reporting high second-hand smoke exposure (≥1 times/day) was 6·3% in HICs, 23·2% in MICs, and 14·0% in LICs. The adjusted geometric mean total nicotine equivalent was higher among current smokers in HICs (47·2 μM) than in MICs (31·1 μM) and LICs (25·2 μM; ANCOVA p<0·0001). By contrast, it was higher among never smokers in LICs (18·8 μM) and MICs (11·3 μM) than in HICs (5·0 μM; ANCOVA p=0·0001).

Interpretation The variations in risks from smoking between country income groups are probably related to the higher exposure of tobacco-derived toxicants among smokers in HICs and higher rates of high second-hand smoke exposure among never smokers in MICs and LICs.

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

Introduction

Tobacco use is one of the most preventable causes of premature deaths globally and an important risk factor for cardiovascular disease, cancers, and respiratory diseases.[1] Estimates of the global burden of death and diseases have implicitly assumed that the risks associated with smoking are similar across countries,[1] but this has never been systematically examined within a single study involving several countries and using similar methods. Although meta-analyses of cohort studies done in several regions of the world have been reported,[2,3] none have examined whether the risks from smoking vary between countries at different economic levels. In the Prospective Urban Rural Epidemiology (PURE),[4] INTERHEART,[5] and INTERSTROKE[6] studies, we recorded self-reported smoking and clinical events using standardised and similar methods in individuals from 63 high-income (HICs), middle-income (MICs), and low-income (LICs) countries. In this study, we have examined the variations in risks from current smoking compared with never smoking across different country income groups and some of their potential reasons.

Lancet Glob Health 2022; 10: e216–26

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Research in context

Evidence before this study

We systematically searched PubMed for relevant articles published in English from June 1, 1954, to Oct 1, 2021. Our key search terms included "smoking", "tobacco use", "death", "cardiovascular disease", "cancer", and "respiratory disease". Our search was restricted to studies done in adults (aged ≥18 years). The harmful health effects of smoking have been extensively studied in high-income countries (HICs), but fewer data are available from low-income (LICs) and middle-income (MICs) countries. Thus, the estimates of the global burden of death and diseases attributable to smoking are currently largely based on pooled relative risks from studies done in HICs. Risk estimates from previous separate studies suggest that the hazards of smoking might be higher in HICs than in MICs and LICs. However, indirect comparisons might not be reliable, as these studies differ in their study design, adjustment of confounders, ascertainment of outcomes, and follow-up periods. Thus, there is a need for studies with standardised approaches involving many countries at different economic levels.

Added value of this study

This analysis of data from the Prospective Urban Rural Epidemiology (PURE), INTERHEART, and INTERSTROKE studies involving approximately 179 000 participants from 63 countries shows that the hazards of smoking for all-cause mortality, major cardiovascular disease, cancers, and respiratory diseases are higher in HICs than in MICs and LICs. These variations in risks are not fully explained by the differences in smoking patterns and other risk factors, the tobacco products used, and competing risks between country income groups. The median levels of tar, nicotine, and carbon monoxide displayed on the cigarette packs in PURE HICs were higher than those on the packs in MICs. In PURE, the proportion of never smokers reporting high second-hand smoke exposure (≥1 times/day) was higher in MICs (23·2%) and LICs (14·0%) than in HICs (6·3%). In a substudy among 1000 PURE participants, the average urinary total nicotine equivalent (a composite of seven nicotine metabolites) concentrations were significantly higher among current smokers in HICs than in MICs and LICs. In contrast, the mean total nicotine equivalent was significantly higher among never smokers in LICs and MICs compared with HICs.

Implications of all the available evidence

The variations in risks from smoking between country income groups are probably related to the higher exposure of tobacco-derived toxicants among smokers in HICs and higher rates of high second-hand smoke exposure among never smokers in MICs and LICs. Our study also emphasises the need to develop region-specific estimates of the number of deaths, cardiovascular disease events, cancers, and respiratory diseases, which might lead to revisions in the global estimates of the burden of death and diseases caused by smoking. This should be complemented by urinary biomarkers of tobacco exposure to obtain more reliable estimates.

Methods

Study design and participants

Details of the studies' design have been described previously,[4–6] and are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (appendix pp 7–15). Briefly, PURE is a population-based cohort study that enrolled 166 762 participants (aged 35–70 years) from 21 countries between Jan 12, 2001, and April 23, 2017. We included 134 909 never and current smokers with no history of cardiovascular disease, cancer, or respiratory disease at baseline and who had completed one or more follow-up visits in the analyses (appendix p 19). We excluded participants who were using only smokeless tobacco from the analyses. Participants were contacted every 3 years to document clinical events that were adjudicated using standardised definitions, supplemented with information from household interviews, medical records, death certificates, verbal autopsies, and other sources.[4] INTERHEART was a case-control study of 12 461 first cases of acute myocardial infarction and 14 637 controls matched for age and sex from 52 countries recruited between Feb 13, 1999, and March 11, 2003.[5] INTERSTROKE was a case-control study of 13 447 first cases of acute stroke and 13 472 controls matched for age and sex from 32 countries enrolled between Jan 11, 2007, and Aug 8, 2015.[6] We included 21 073 never and current smokers in the INTERHEART study analyses and 22 911 never and current smokers in the INTERSTROKE study analyses. In all three studies, we categorised countries into HICs, MICs, and LICs, according to World Bank's Gross National Income per capita[7] at study enrolment.

In PURE, a substudy was initiated to assess biomarkers of tobacco exposure in urine samples of 8073 participants from 14 countries who were selected from 55 246 eligible participants using a nested case-cohort design (appendix p 20). Overnight fasting urine samples were collected and frozen (–20°C to –70°C) locally and then shipped at –160°C to Hamilton (ON, Canada). For this study, from 8073 participants, urine samples of 1000 were randomly selected in approximately equal proportions of never (n=335), light (<10 tobacco products/day; n=324), and heavy (≥10 tobacco products/day; n=341) current smokers (appendix p 20). Light and heavy smokers were combined for analyses. All three studies were approved by the ethics committees at each participating centres and at the Hamilton Health Sciences. All participants provided written informed consent.

Procedures

We used identical questionnaires to collect data on tobacco use at baseline and follow-up visits in the PURE study, at recruitment in the INTERHEART and INTERSTROKE studies (appendix pp 16–18).[4–6] Participants were asked if they smoked cigarettes, bidis, pipes, cigars, or sheesha. Current smokers were those who smoked at least one tobacco product daily in the past 12 months and included those who had quit within the past 1 year. Never smokers were those who reported having never used any tobacco products (smoked or smokeless tobacco products [chewing tobacco, snuff, paan, or rolled tobacco leaves]). Information on the age of smoking initiation, numbers smoked per day, and duration of smoking was recorded. Non-cigarette smoked products were converted to cigarette-equivalents to calculate pack-years using previously described methods.[1,8] Demographics, geographical location, alcohol use, diet, physical activity, frequency of second-hand smoke (SHS) exposure, and medications used were recorded.[4–6] We also collected commonly sold cigarette packs from stores in PURE communities to assess the tar, nicotine, and carbon monoxide content displayed on those packs. Physical measurements (height, weight, and blood pressure) were recorded, and fasting blood samples were analysed for glucose and lipids using standard protocols.[4–6] In PURE, we also collected data on the primary use of fuels for cooking as a proxy for household air pollution[4] and outdoor air pollution (derived from a combination of ground monitor measurements, satellite retrievals of aerosol optical depth, and chemical transport models).[9]

Urine samples were analysed centrally in a core laboratory in Hamilton (ON, Canada). We did an analysis of seven nicotine metabolites and their glucuronide conjugates to determine the total nicotine equivalent (TNE).[10] TNE is a robust measure of nicotine intake and is not affected by sex, genetic factors, or dietary habits.[10] The stored frozen urine samples were thawed slowly, aliquoted, and diluted in deionized water before analysis. Multisegment injection-capillary electrophoresis-mass spectrometry[11] was used to measure nicotine metabolites with a 6230 time-of-flight mass spectrometer (Agilent Technologies, Santa Clara, CA, USA). The limit of quantification for TNE was 0·48 µM, and lower concentrations were imputed using the k-nearest neighbours method[12] for analyses. Overall, good technical precision was achieved for TNE determination as reflected by a mean coefficient of variation of 14% with repeated analyses of quality control samples (n=158).

Outcomes

In PURE, all-cause mortality, major cardiovascular disease, cancers, respiratory diseases, and their composite were the primary outcomes for this analysis. Major cardiovascular disease included myocardial infarction, stroke, heart failure, and cardiovascular deaths. Cancers were those known to be related to smoking (cancers of the oral cavity and pharynx, larynx, lung, oesophagus, stomach, pancreas, colon and rectum, kidney and renal pelvis, bladder and liver, and acute myeloid leukaemia).[13] Respiratory diseases were a composite of tuberculosis, asthma, chronic obstructive pulmonary disease, pneumonia, influenza, chronic bronchitis, and interstitial lung disease.[13] We included all events recorded up to March 23, 2021, from PURE. Acute myocardial infarction and acute stroke were the primary outcomes in INTERHEART and INTERSTROKE, respectively.

Statistical analysis

Categorical variables are summarised as frequency and percentages and continuous variables as median (IQR). In PURE, Cox frailty models with centre specified as a random intercept to account for within-centre clustering of participants (that also adjusts for region and country) were used to estimate hazard ratios (HRs) and 95% CIs for the associations between current smoking (*vs* never smoking) and outcomes. The models included age, sex, education, household wealth index, cooking fuel, urban or rural location, alcohol use, diet quality, physical activity, obesity, hypertension, diabetes, dyslipidaemia, and outdoor fine particulate matter ($PM_{2·5}$). Additionally, we adjusted for pack-years to assess whether variations in smoked tobacco products and cumulative dose of smoking between country income groups affected associations with the outcomes. The proportionality of hazards was assessed by visual inspection of the log-log survival plots. We did a competing risks regression[14] for smoking-related deaths (cardiovascular, respiratory, and neoplastic deaths),[15,16] with death unrelated to smoking regarded as the competing risk. Results are presented as sub-distribution HRs and 95% CIs.

In INTERHEART and INTERSTROKE, we estimated odds ratios (ORs and 95% CIs) for the association between current smoking (*vs* never smoking) and myocardial infarction and stroke, respectively, using unconditional logistic regression after adjusting for the matching criteria, covariates, and pack-years. We used unconditional logistic regression because perfect matching was not possible for 14% (1763 of 12 461) of cases and 5% (738 of 14 637) of controls in INTERHEART, leading to a loss of information if unmatched participants had to be dropped. Further, the results from unconditional analyses were similar to those from conditional analyses in both the case-control studies (<5% variation).[5,6]

In all three studies, pack-years were included as a quadratic term in the models, as the log-linearity assumption was not met (based on martingale residuals and lowess plots).[17] Interaction terms between smoking status (never or current smoking) and country income group (HICs, MICs, or LICs) were included in the

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See **Online** for appendix

	HICs		MICs		LICs	
	Never smokers (n=9260)	Current smokers (n=2334)	Never smokers (n=69 240)	Current smokers (n=22 028)	Never smokers (n=25 377)	Current smokers (n=6670)
Age, years	49·0 (42·0 to 57·0)	50·0 (44·0 to 57·0)	50·0 (42·0 to 58·0)	49·0 (43·0 to 57·0)	46·0 (39·0 to 55·0)	48·0 (40·0 to 56·0)
Sex						
Women	5538/9260 (59·8%)	987/2334 (42·3%)	51 576/69 240 (74·5%)	4860/22 028 (22·1%)	18 070/25 377 (71·2%)	926/6670 (13·9%)
Men	3722/9260 (40·2%)	1347/2334 (57·7%)	17 664/69 240 (25·5%)	17 168/22 028 (77·9%)	7307/25 377 (28·8%)	5744/6670 (86·1%)
Education						
None or primary	1448/9244 (15·7%)	303/2330 (13·0%)	30 296/69 131 (43·8%)	8878/21 978 (40·4%)	12 805/25 287 (50·6%)	4061/6639 (61·2%)
Secondary or high school	2280/9244 (24·7%)	910/2330 (39·1%)	28 482/69 131 (41·2%)	10 104/21 978 (46·0%)	8734/25 287 (34·5%)	2130/6639 (32·1%)
Trade, college, or university	5516/9244 (59·7%)	1117/2330 (47·9%)	10 353/69 131 (15·0%)	2996/21 978 (13·6%)	3748/25 287 (14·8%)	448/6639 (6·8%)
Location						
Urban	6733/9260 (72·7%)	1706/2334 (73·1%)	35031/69 240 (50·6%)	10 856/22 028 (49·3%)	13 369/25 377 (52·7%)	2482/6670 (37·2%)
Rural	2527/9260 (27·3%)	628/2334 (26·9%)	34 209/69 240 (49·4%)	11 172/22 028 (50·7%)	12 008/25 377 (47·3%)	4188/6670 (62·8%)
Household wealth index*	1·4 (1·2 to 1·5)	1·3 (1·0 to 1·5)	0·2 (–0·4 to 0·7)	0·1 (–0·4 to 0·6)	–1·2 (–1·7 to -0·4)	–1·5 (–2·0 to –0·9)
Dirty cooking fuel (kerosene or solid fuels)	2/9260 (0·02%)	0/2334 (0·0%)	15 280/65 190 (23·4%)	5653/20 715 (27·3%)	11 539/23 629 (48·8%)	3791/5858 (64·7%)
Alcohol use						
Never drinker	4061/9235 (44·0%)	536/2329 (23·0%)	57 978/69 127 (83·9%)	10 100/21 982 (46·0%)	23 831/25 327 (94·1%)	4225/6652 (63·5%)
Former drinker	305/9235 (3·3%)	186/2329 (8·0%)	1658/69 127 (2·4%)	1349/21 982 (6·1%)	283/25 327 (1·1%)	359/6652 (5·4%)
Current drinker	4869/9235 (52·7%)	1607/2329 (69·0%)	9491/69 127 (13·7%)	10 533/21 982 (47·9%)	1213/25 327 (4·8%)	2068/6652 (31·1%)
AHEI score†	36·7 (29·4 to 43·9)	29·4 (23·2 to 37·0)	35·0 (29·4 to 40·4)	34·5 (28·8 to 40·0)	34·4 (30·3 to 38·5)	33·8 (29·4 to 37·4)
Physical activity‡						
Low	2019/8734 (23·1%)	349/2093 (16·7%)	11 518/65 978 (17·5%)	3890/20 352 (19·1%)	4604/22 123 (20·8%)	1205/5621 (21·4%)
Moderate	3165/8734 (36·2%)	650/2093 (31·1%)	26 520/65 978 (40·2%)	7195/20 352 (35·4%)	7910/22 123 (35·8%)	1414/5621 (25·2%)
High	3550/8734 (40·7%)	1094/2093 (52·3%)	27 940/65 978 (42·4%)	9267/20 352 (45·5%)	9609/22 123 (43·4%)	3002/5621 (53·4%)
Obesity§	2682/9058 (29·6%)	549/2301 (23·9%)	12241/64 820 (18·9%)	2884/20 598 (14·0%)	2654/23 330 (11·4%)	180/5893 (3·1%)
Hypertension¶	3314/9251 (35·8%)	895/2332 (38·4%)	29 440/69 193 (42·6%)	8486/22 008 (38·6%)	8961/25 360 (35·3%)	1694/6667 (25·4%)
Diabetes‖	1094/9249 (11·8%)	221/2331 (9·5%)	6726/69 177 (9·7%)	1702/22 003 (7·7%)	3270/25 354 (12·9%)	629/6666 (9·4%)
Dyslipidaemia**	6305/9260 (68·1%)	1775/2334 (76·1%)	45 199/69 240 (65·3%)	12 927/22 028 (58·7%)	12 726/25 377 (50·2%)	2633/6670 (39·5%)
Outdoor fine particulate matter ($PM_{2·5}$), μg/m³	8·8 (8·0 to 35·3)	8·7 (8·1 to 11·3)	41·4 (20·6 to 74·9)	42·5 (21·3 to 72·5)	42·8 (26·0 to 80·8)	45·8 (39·4 to 87·8)
Tobacco type††						
Cigarette	..	2174/2301 (94·5%)	..	20 959/21 219 (98·8%)	..	2903/6107 (47·5%)
Bidi	..	2/2301 (0·1%)	..	50/21 219 (0·2%)	..	3737/6107 (61·2%)
Cigar	..	80/2301 (3·5%)	..	105/21 219 (0·5%)	..	83/6107 (1·4%)
Pipe	..	71/2301 (3·1%)	..	107/21 219 (0·5%)	..	80/6107 (1·3%)
Water pipe or sheesha	..	100/2301 (4·4%)	..	80/21 219 (0·4%)	..	206/6107 (3·4%)
Chewing tobacco	..	7/2301 (0·3%)	..	11/21 219 (0·1%)	..	297/6107 (4·9%)
Snuff	..	235/2301 (10·2%)	..	37/21 219 (0·2%)	..	83/6107 (1·4%)
Rolled tobacco leaves	..	0/2301 (0·0%)	..	31/21 219 (0·2%)	..	0/6107 (0·0%)
Age of smoking initiation, years	..	17·0 (15·0 to 20·0)	..	20·0 (17·0 to 24·0)	..	24·0 (18·0 to 32·0)
Numbers smoked per day	..	16·0 (10·0 to 20·0)	..	15·0 (8·0 to 20·0)	..	10·0 (5·0 to 20·0)

(Table 1 continues on next page)

models, and their statistical significance was tested using the Wald test.[18]

In PURE, Cox frailty models were also run for the numbers smoked (1–19/day and ≥20/day), duration of smoking (≤35 years and >35 years), pack-years of smoking (<35 and ≥35), and age of smoking initiation (≤15 years and >15 years). These cutoffs were chosen such that there was an adequate number of events of each type and in each subgroup to provide stable models. We assessed the consistency in reporting of

	HICs		MICs		LICs	
	Never smokers (n=9260)	Current smokers (n=2334)	Never smokers (n=69 240)	Current smokers (n=22 028)	Never smokers (n=25 377)	Current smokers (n=6670)
(Continued from previous page)						
Duration of smoking, years	..	33·0 (25·0 to 40·0)	..	29·0 (22·0 to 36·0)	..	22·0 (15·0 to 33·0)
Pack-years of smoking‡‡	..	24·0 (13·5 to 38·8)	..	19·0 (9·5 to 30·0)	..	10·5 (4·5 to 22·5)
Frequency of second-hand smoke exposure§§						
Never	7785/9229 (84·4%)	..	42 423/68 428 (62·0%)	..	12 685/16 578 (76·5%)	..
Low (1–6 times/week)	860/9229 (9·3%)	..	10 146/68 428 (14·8%)	..	1569/16 578 (9·5%)	..
High (≥1 times/day)	584/9229 (6·3%)	..	15 859/68 428 (23·2%)	..	2324/16 578 (14·0%)	..

Data are median (IQR) or n/N (%). AHEI=Alternate Healthy Eating Index. HIC=high-income country. LIC=low-income country. MET=metabolic equivalent task. MIC=middle-income country. PURE=Prospective Urban Rural Epidemiology. *Household wealth index is the non-monetary aspect of wealth based on the number and type of household items owned, whereby a higher value indicates greater wealth. †AHEI score is a measure of dietary quality, whereby a higher score indicates better quality. ‡Low physical activity was defined as less than 600 MET/min per week, moderate physical activity as 600–3000 MET/min per week, and high physical activity as more than 3000 MET/min per week. §Body-mass index of 30 kg/m² or more. ¶Self-reported hypertension or systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher or taking anti-hypertensive medications. ||Self-reported diabetes or fasting plasma glucose 126 mg/dL or higher, or taking glucose lowering medications. **High total cholesterol (≥200 mg/dL) or low HDL cholesterol (<40 mg/dL in men, <50 mg/dL in women) or high LDL cholesterol (≥130 mg/dl) or high triglycerides (≥150 mg/dl), or taking lipid lowering medications. ††Percentages do not total 100 as the categories are not mutually exclusive. ‡‡Pack-years=(number of cigarettes smoked per day × duration of smoking in years)/20. §§Exposed refers to self-reported history of regular exposure (at least once a week) to other people's tobacco smoke for a minimum of 5 consecutive min during the past 12 months. Data on second-hand smoke exposure are not available from 4 of 5 centres in India, Chile, Argentina, and Poland, as the earlier version of the questionnaire did not collect this information.

Table 1: **Characteristics of never and current smokers by country income groups in the PURE study**

smoking status (never or current) between baseline and 3-year follow-up visit (appendix p 30) using Cohen's kappa.[19]

Since the distribution of TNE concentrations was positively skewed, log-transformation was done before analysis. Analysis of covariance (ANCOVA) was used to compare mean TNE concentrations between groups, adjusting for age, sex, education, body-mass index, numbers smoked per day, and duration of smoking (or self-reported SHS exposure in models for never smokers). Log-transformed marginal means (and 95% CIs) estimated from ANCOVA models were exponentiated to derive adjusted geometric means and their 95% CIs. All reported p values are two-sided. We did all the statistical analyses using Stata (version 15.1).

Role of the funding source

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

Results

In PURE, the proportion of current smokers was 14·4% (2334 of 16 181) in HICs, 21·9% (22 028 of 100 466) in MICs, and 20·0% (6670 of 33 290) in LICs. The median age at baseline was 49·0 (IQR 41·0–57·0) years, and 81 957 (60·8%) participants were female. During a median follow-up of 11·3 (IQR 8·6–12·4) years, 9744 deaths and 7817 incident cases of major cardiovascular disease, 1778 cancers, 5972 respiratory diseases, and 19 049 composite events were recorded.

Table 1 shows the characteristics of PURE participants by country income groups. Current smokers in all three country income groups were more likely than never smokers to be male, have a lower socio-economic status, be current alcohol drinkers, eat a less healthy diet, and be physically more active, and less likely to be obese and have diabetes. Most of the smokers in HICs (94·5%) and MICs (98·8%) were smoking cigarettes, whereas the majority (61·2%) were smoking bidis in LICs. 10·5% of current smokers in HICs were also using smokeless tobacco, whereas 0·4% of current smokers in MICs and 5·9% of current smokers in LICs used smokeless tobacco. Current smokers in HICs started smoking at a younger age and smoked more products per day and longer than those in MICs and LICs. The proportion of never smokers reporting high SHS exposure (≥1 times/day) was 6·3% in HICs, 23·2% in MICs, and 14·0% in LICs.

In PURE, the risks associated with current smoking were consistently higher for all outcomes in HICs than in MICs and LICs (table 2). For example, the HR for the composite outcome in current smokers compared with never smokers was 1·87 (95% CI 1·65–2·12) in HICs, whereas the HR was 1·41 (1·34–1·49) in MICs and 1·35 (1·25–1·46) in LICs (interaction p<0·0001), after adjusting for risk factors and pack-years. Similar patterns were observed for all-cause mortality, major cardiovascular disease, cancers, and respiratory diseases. Sensitivity analyses did not materially alter our findings (appendix pp 31–35). The adjusted sub-distribution HR from competing risks regression for mortality from smoking was higher in HICs (3·07, 95% CI 2·28–4·13) than in MICs (1·66, 1·51–1·82) and LICs (1·36, 1·19–1·54; appendix p 36).

In INTERHEART, the proportion of current smokers in HICs, MICs, and LICs was 34·6%, 36·2%, and 31·8%, and for INTERSTROKE the proportion was 19·7%,

	HICs		MICs		LICs		p for interaction*
	Never smokers	Current smokers	Never smokers	Current smokers	Never smokers	Current smokers	
PURE							
Number of participants	9260	2334	69 240	22 028	25 377	6670	..
All-cause mortality							
Events	230 (2·5%)	142 (6·1%)	3490 (5·0%)	1938 (8·8%)	2625 (10·3%)	1319 (19·8%)	..
HR†	1·00	2·62 (2·08–3·32)	1·00	1·61 (1·51–1·72)	1·00	1·24 (1·13–1·36)	<0·0001
HR† adjusted for pack-years of smoking	1·00	2·58 (1·97–3·37)	1·00	1·51 (1·40–1·62)	1·00	1·22 (1·11–1·34)	<0·0001
Major cardiovascular disease‡							
Events	275 (3·0%)	150 (6·4%)	3551 (5·1%)	1647 (7·5%)	1500 (5·9%)	694 (10·4%)	..
HR†	1·00	2·17 (1·74–2·71)	1·00	1·52 (1·41–1·63)	1·00	1·37 (1·21–1·54)	0·0004
HR† adjusted for pack-years of smoking	1·00	2·19 (1·70–2·83)	1·00	1·43 (1·32–1·54)	1·00	1·38 (1·21–1·56)	0·0012
Cancers§							
Events	99 (1·1%)	82 (3·5%)	751 (1·1%)	531 (2·4%)	203 (0·8%)	112 (1·7%)	..
HR†	1·00	3·12 (2·26–4·31)	1·00	1·85 (1·61–2·12)	1·00	1·56 (1·13–2·15)	0·0004
HR† adjusted for pack-years of smoking	1·00	2·85 (1·97–4·12)	1·00	1·60 (1·38–1·86)	1·00	1·50 (1·08–2·08)	0·0044
Respiratory diseases¶							
Events	831 (9·0%)	374 (16·0%)	2441 (3·5%)	1116 (5·1%)	804 (3·2%)	406 (6·1%)	..
HR†	1·00	1·95 (1·71–2·23)	1·00	1·50 (1·38–1·63)	1·00	1·64 (1·39–1·93)	<0·0001
HR† adjusted for pack-years of smoking	1·00	1·78 (1·53–2·08)	1·00	1·40 (1·27–1·53)	1·00	1·53 (1·29–1·82)	<0·0001
Composite outcome‖							
Events	1237 (13·4%)	575 (24·6%)	7969 (11·5%)	3790 (17·2%)	3720 (14·7%)	1758 (26·4%)	..
HR†	1·00	2·00 (1·80–2·23)	1·00	1·52 (1·45–1·59)	1·00	1·37 (1·26–1·47)	<0·0001
HR† adjusted for pack-years of smoking	1·00	1·87 (1·65–2·12)	1·00	1·41 (1·34–1·49)	1·00	1·35 (1·25–1·46)	<0·0001
INTERHEART							
Number of participants	2122	1980	7672	6222	1918	1159	..
Acute myocardial infarction	731 (34·5%)	1249 (63·1%)	2857 (37·2%)	3579 (57·5%)	635 (33·1%)	660 (57·0%)	..
OR**	1·00	3·52 (3·03–4·10)	1·00	3·13 (2·88–3·41)	1·00	2·95 (2·47–3·51)	0·0012
OR** adjusted for pack-years of smoking	1·00	3·32 (2·78–3·97)	1·00	2·45 (2·22–2·70)	1·00	2·55 (2·10–3·10)	0·0110
INTERSTROKE							
Number of participants	1931	847	8932	4195	4953	2053	..
Acute stroke	833 (43·1%)	590 (69·7%)	4263 (47·7%)	2381 (56·8%)	2406 (48·6%)	1107 (53·9%)	..
OR**	1·00	2·76 (2·25–3·40)	1·00	1·64 (1·48–1·81)	1·00	1·50 (1·32–1·71)	<0·0001
OR** adjusted for pack-years of smoking	1·00	2·40 (1·89–3·05)	1·00	1·41 (1·26–1·58)	1·00	1·46 (1·28–1·67)	<0·0001

Data are n (%), HR (95% CI), or OR (95% CI). HIC=high-income country. HR=hazard ratio. LIC=low-income country. MIC=middle-income country. OR=odds ratio. PURE=Prospective Urban Rural Epidemiology. *Refers to the p value of the interaction term between smoking status (never or current smoking) and country income group (HICs, MICs, or LICs) in Cox frailty models or logistic regression models. †Adjusted for age, sex, education, household wealth index, cooking fuel, urban or rural location, alcohol use, diet quality, physical activity, obesity, hypertension, diabetes, dyslipidaemia, and outdoor fine particulate matter ($PM_{2·5}$) in Cox frailty models. Centre was specified as a random intercept to account for within-centre clustering of participants. ‡Includes myocardial infarction, stroke, heart failure, and cardiovascular deaths. §Includes cancers of the oral cavity and pharynx, larynx, lung, oesophagus, stomach, pancreas, colon and rectum, kidney and renal pelvis, bladder and liver, and acute myeloid leukaemia. ¶Includes asthma, tuberculosis, chronic obstructive pulmonary disease, pneumonia, influenza, chronic bronchitis, and interstitial lung disease. ‖Includes all-cause mortality, major cardiovascular disease, cancers, and respiratory diseases. **Adjusted for age, sex, geographical region, education, occupation, alcohol use, fruit and vegetable intake, physical activity, obesity, hypertension, diabetes, and dyslipidaemia in unconditional logistic regression.

Table 2: **Hazards of current smoking by country income groups in the PURE, INTERHEART, and INTERSTROKE studies**

27·5%, and 27·8%, respectively. The characteristics of participants in these two studies by country income group are given in the appendix (pp 37–40). Consistent with PURE, the fully adjusted OR for myocardial infarction (in INTERHEART) and stroke (in INTERSTROKE) in current smokers compared with never smokers was higher in HICs than in MICs and LICs (table 2).

In each country income group in PURE, within each stratum of pack-years, the adjusted HRs for current smoking (*vs* never smoking) in HICs for all outcomes were consistently higher than in MICs and LICs (figure 1). For example, in HICs, the adjusted HR for the composite outcome was 1·74 (95% CI 1·53–1·98) for current smokers with less than 35 pack-years, whereas the HR was 1·42 (1·35–1·50) in MICs and 1·36 (1·26–1·48) in LICs. The corresponding HRs for smokers with 35 or more pack-years were 2·54 (2·20–2·94) in HICs, 1·84 (1·71–1·97) in MICs, and 1·49 (1·30–1·71) in LICs (figure 1E). Similar patterns were observed in

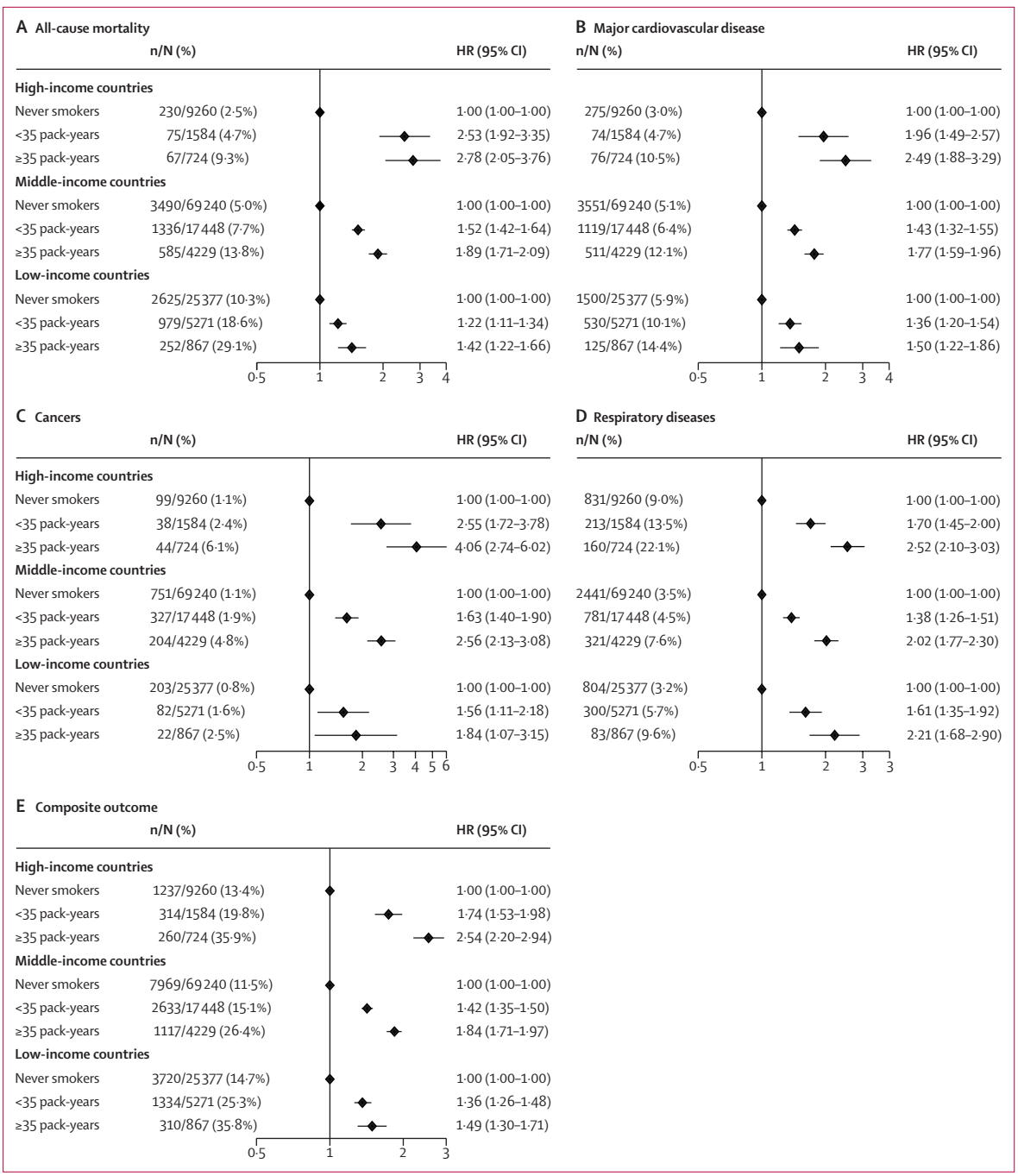

Figure 1: **Hazard ratios for pack-years of current smoking (*vs* never smoking) and all-cause mortality, major cardiovascular disease, cancers, respiratory diseases, and composite outcome by country income groups in PURE**

HRs were adjusted for age, sex, education, household wealth index, cooking fuel, urban or rural location, alcohol use, diet quality, physical activity, obesity, hypertension, diabetes, dyslipidaemia, and outdoor fine particulate matter ($PM_{2·5}$) in Cox frailty models. Centre was specified as a random intercept to account for within-centre clustering of participants. HR=hazard ratio. PURE=Prospective Urban Rural Epidemiology.

separate analyses for quantity, duration, and age at initiation of smoking (appendix pp 21–29).

The median levels of tar, nicotine, and carbon monoxide displayed on the cigarette packs from PURE HICs were higher than those on the packs from MICs (14·7 mg *vs* 10·7 mg per cigarette for tar; 1·2 mg *vs* 0·8 mg per cigarette for nicotine; 14·3 mg *vs* 11·6 mg per cigarette for carbon monoxide, respectively; table 3). The Cohen's kappa for self-reported smoking status (never or current) was 0·99 (95% CI 0·98–1·00)

	Number of cigarette packs collected from PURE communities	Number of cigarette packs with tar content recorded	Median tar per cigarette, mg	Number of cigarette packs with nicotine content recorded	Median nicotine per cigarette, mg	Number of cigarette packs with carbon monoxide content recorded	Median carbon monoxide per cigarette, mg
HICs	100	75	14·7 (8·0–23·5)	75	1·2 (0·6–1·9)	75	14·3 (8·0–22·0)
MICs	243	163	10·7 (10·0–12·0)	163	0·8 (0·6–1·0)	158	11·6 (10·0–14·0)

Data are n or median (IQR). Of the 81 cigarette packs collected from LICs, only three packs had information on tar and nicotine content, and none had information on carbon monoxide content, and so the data from LICs are unreliable. HIC=high income country. LIC=low-income country. MIC=middle income country. PURE=Prospective Urban Rural Epidemiology.

Table 3: **Amounts of tar, nicotine, and carbon monoxide displayed on the cigarette packs collected from PURE communities in HICs and MICs**

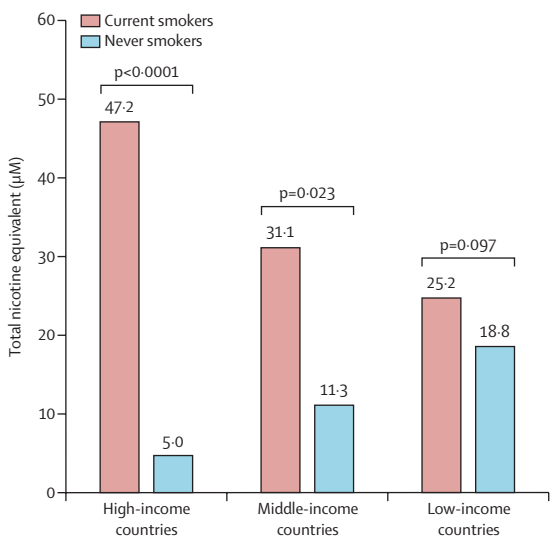

Figure 2: **Adjusted geometric mean urinary total nicotine equivalent concentrations in current and never smokers by country income groups in PURE**

Analysis of covariance models were adjusted for age, sex, education, body-mass index, numbers smoked per day, and duration of smoking (or self-reported second-hand smoke exposure in models for never smokers). The p values represent the difference in the mean total nicotine equivalent between current and never smokers. PURE=Prospective Urban Rural Epidemiology.

in HICs, 0·95 (0·94–0·95) in MICs, and 0·93 (0·92–0·94) in LICs.

The characteristics of participants in the PURE urinary biomarker substudy are given in the appendix (p 41). The proportion of never smokers reporting high SHS exposure (≥1 times/day) was 6·3% in HICs, 14·2% in MICs, and 39·6% in LICs. The adjusted geometric mean TNE was higher among current smokers in HICs (47·2 μM, 95% CI 41·3–53·9) than in MICs (31·1 μM, 27·5–35·2) and LICs (25·2 μM, 21·1–30·1; ANCOVA p<0·0001). By contrast, the adjusted geometric mean TNE was higher among never smokers in LICs (18·8 μM, 13·2–26·8) and MICs (11·3 μM, 8·2–15·6) than in HICs (5·0 μM, 3·2–7·9; ANCOVA p=0·0001) (figure 2). The adjusted geometric mean TNE was significantly higher among current smokers than never smokers in HICs (p<0·0001) and MICs (p=0·023), but this difference was less marked in LICs (p=0·097).

Discussion

In three large studies involving approximately 179 000 participants from 63 countries, the risks of tobacco-related diseases from current smoking are higher in HICs than in MICs and LICs. The levels of nicotine and toxicants were higher in cigarettes from PURE HICs (based on the labels of the packs) than in those from MICs. The consistency in reporting of smoking status (never or current) between baseline and follow-up was very high and similar in all three country income groups in PURE. The average urinary TNE concentrations were significantly higher among current smokers in HICs than in MICs and LICs, whereas they were significantly higher among never smokers in LICs and MICs compared with HICs.

No previous study has compared the hazards of smoking simultaneously in countries at different economic levels using standardised approaches. However, indirect comparisons of the results from previous separate studies[16,20,21] support our observations. In studies done in HICs, the risks of all-cause mortality were about 2–3 times higher in current than in never smokers. For example, in the British Doctors' Study of 34 439 men, followed up from 1951 to 2001, the relative risk (RR) was 2·19 for the cohort (aged ≥60 years) born in the 20th century.[20] In the UK's Million Women Study of 1 180 652 women (median age 55 years), followed up from 1996 to 2011, the RR was 2·76 (95% CI 2·71–2·81).[21] In the US National Health Interview Survey of 216 917 individuals (aged ≥18 years), followed up from 1997 to 2006, the HR was 2·8 (99% CI 2·4–3·1) in men and 3·0 (2·7–3·3) in women.[16] By contrast, studies[15,22,23] in MICs and LICs have reported lower hazards for all-cause mortality than those seen in HICs. For example, in a cohort study of 224 500 men (aged ≥40 years) in China, followed up from 1990 to 1996, the RR was 1·19 (95% CI 1·13–1·25).[22] In a prospective study of 118 840 adults (aged 30–69 years) in Cuba, followed up from 1996 to 2017, the RR was 1·66 (95% CI 1·58–1·74).[23] In a nationally representative case-control study of 152 058 adults (aged ≥20 years) done in India from 2001 to 2003, the risk ratio was 1·7 (99% CI 1·6–1·8) in men and 2·0 (1·8–2·3) in women.[15]

The variations in risks associated with smoking between country income groups are not fully explained

by the differences in risk factors, smoking patterns (ie, age at initiation, quantity, duration, and pack-years of smoking), the tobacco products used, or competing risks. In our analyses, we accounted for heterogeneity in smoked tobacco products by adjusting for pack-years, which included converting non-cigarette smoked products to cigarette-equivalents using standard methods.[1,8] In PURE, bidi smoking was more common in LICs than in MICs and HICs, and smokeless tobacco use was more frequent in HICs (mostly snuff) and LICs (mostly chewing tobacco) than in MICs (table 1; appendix p 42). However, compared with never smokers, exclusive bidi smokers and exclusive cigarette smokers had similar risks in LICs (appendix p 43). Furthermore, the exclusion of smokers who were also using smokeless tobacco did not alter the main results (appendix p 35). The cumulative incidence of the competing event for mortality from smoking was low over 11 years in all three country income groups (appendix p 36), and so the results were similar to those from Cox models.[24]

The variations in risks observed could be due to differences in the amounts of toxicants in tobacco products[25] or from SHS exposure[26] or smoking behaviours[27] between country income groups. The PURE urinary biomarker data shows that the adjusted mean TNE concentrations in current smokers from HICs were significantly higher than in those from MICs and LICs. This difference could be because cigarettes might be more toxic in HICs or smokers in HICs could be smoking products in different ways than those in MICs and LICs. The median levels of tar, nicotine, and carbon monoxide displayed on the cigarette packs from PURE HICs were higher than the levels displayed on those from MICs. Very few cigarette packs (3 of 81) collected from LICs had this information, and so the data from LICs are too scarce to be reliable. We know that exposure to toxins, both in absolute amounts and their distribution within the respiratory system, could be influenced by product design and associated compensatory smoking behaviour (eg, taking more puffs per cigarette).[27] One factor is whether the cigarettes have filters but there are other less easily identified aspects of design that could play a part. However, we do not have relevant data to explore these issues, which might explain some of the differences in risks from smoking between country income groups. In the PURE urinary biomarker sub study, the adjusted mean TNE concentrations were significantly higher among never smokers in LICs and MICs than in HICs. Furthermore, the difference in mean TNE was less marked between never and current smokers in LICs. These are likely due to the higher rates of high self-reported SHS exposure in LICs and MICs. This is possibly resulting from poor enforcement of smoking bans in public places and lack of voluntary rules for smoke-free homes in many of these countries.[26,28]

PURE, INTERHEART, and INTERSTROKE are large-scale studies that used standardised and systematic approaches to enrol participants and collect data on self-reported smoking and outcomes simultaneously from many countries at different economic levels. Thus, the studies included in this report permit more direct and likely more reliable comparisons of the hazards of smoking across different country income groups. The median follow-up in PURE was prolonged (11·3 years), with information on vital status and non-fatal events available for 98·4% of participants, and 94·1% completing at least one follow-up visit. Since the tests for interaction have low power, the large sample size of the studies included in our analyses could robustly detect significant differences in the HRs between country income groups.[29] Finally, we have adjusted for an extensive list of potential confounders measured at the individual, household, and community levels, and these are more extensive than those used in almost all large observational studies relating smoking to disease.

Our study has a few potential limitations. In PURE or the other two case-control studies, we did not aim for a strict proportionate sampling of the population in each country because this was not feasible. However, our sampling approaches minimise material biases that could affect our results.[4–6] Furthermore, we have previously shown that the sociodemographic characteristics and the death rates of PURE participants were generally similar to their national populations.[30] For the PURE analyses, we only used smoking data collected at baseline, and so changes in smoking habits over time could affect the assessment of long-term risks. However, this was not an issue for INTERHEART and INTERSTROKE. We are not able to validate self-reported smoking status and SHS exposure with TNE, as there is no established optimal cut off point for TNE to distinguish true smokers from true non-smokers (and for SHS exposure). Additionally, only 111 of 335 self-reported never smokers in the urinary biomarker substudy reported a history of SHS exposure. This small number, when subdivided by HICs, MICs, and LICs, will result in too small groups to provide reliable estimates. We did not assess the hazards of smoking and the benefits of quitting among former smokers, as the reasons for quitting varied considerably between those in HICs, MICs, and LICs in PURE (appendix p 44). Finally, urine samples were collected from PURE participants on a single occasion at baseline, which captures only a narrow time window of exposure to TNE from recent tobacco exposure (<3 days). However, since smoking habits tend to be generally consistent in the medium term, a single urine sample will likely be a reasonable reflection of current smoking habits.

In conclusion, there are substantial variations in risks associated with smoking among individuals in different

country income groups. These are probably related to higher exposure of tobacco-derived toxicants among smokers in HICs and higher rates of high SHS exposure among never smokers in MICs and LICs. These findings emphasise the need for separate assessments of the risks of tobacco in different regions of the world, complemented by urinary biomarkers of tobacco use to obtain more reliable estimates.

Contributors

SY was the principal investigator and designed all three studies included in this paper, obtained funding, and oversaw their conduct, analyses, and revisions of this manuscript. TS wrote the first draft of the manuscript and did data analyses. TS and SY assume responsibility for analyses and data interpretation. SI supervised all analyses. SR coordinated the studies included in this paper. PB-M, SY, GP, and TS conceived the PURE biomarker substudy. BG did the urine preparation, data acquisition, data processing and calibration, and preliminary data analyses for the PURE urinary biomarker substudy. MJO designed the INTERSTROKE study along with SY. MM contributed to the interpretation of the findings. All other authors coordinated the PURE study in their countries, and all commented on drafts of the manuscript. TS, SI, PB-M, BG, SR, MJO, and SY had full access to the data in the three studies and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The Population Health Research Institute (PHRI) believes that the dissemination of research results is vital and sharing of data is important. PHRI prioritises access to data to researchers who have worked on the research study for a substantial duration, have played intellectual and operational roles, and have participated in raising the funds to conduct the study. Data will be disclosed only upon request to the corresponding author and approval of the proposed use of the data by a review committee. Specific collaborative projects can be developed with groups with similar data for joint analyses. Data are available to the journal for the evaluation of reported analyses. Data requests from other investigators will not be considered until 5 years after the date of publication.

Acknowledgments

The PURE study was funded by the Population Health Research Institute, Hamilton Health Sciences Research Institute, the Canadian Institutes of Health Research (including through the Ontario's Strategy for Patient-Oriented Research Support Unit), the Heart and Stroke Foundation (ON, Canada), and the Ontario Ministry of Health and Long-Term Care. It was also funded by unrestricted grants from several pharmaceutical companies, with major contributions from AstraZeneca (Canada), Sanofi (France and Canada), Boehringer Ingelheim (Germany and Canada), Servier Laboratories, and GlaxoSmithKline, and additional contributions from Novartis, King Pharma, and from several national and local organisations in participating countries. TS received funding for the PURE urinary biomarker substudy from the Hamilton Health Sciences New Investigator Fund (NIF-20504), Hamilton (ON, Canada). PB-M acknowledges support from the Natural Sciences and Engineering Research Council, Genome Canada, and Canada Foundation for Innovation. This support assisted in infrastructure purchase or maintenance and basic method development as related to our exposomics research programme. The INTERHEART study was funded by the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Ontario, the International Clinical Epidemiology Network (INCLEN), and through unrestricted grants from several pharmaceutical companies (with major contributions from AstraZeneca, Novartis, Hoechst Marion Roussel [now Aventis], Knoll Pharmaceuticals [now Abbott], Bristol Myers Squibb, King Pharma, and Sanofi-Sythelabo), and by various national bodies in different countries. The INTERSTROKE study was funded by the Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada, Canadian Stroke Network, Swedish Research Council, Swedish Heart and Lung Foundation, The Health & Medical Care Committee of the Regional Executive Board, Region Vastra Gotaland (Sweden), and through unrestricted grants from several pharmaceutical companies with major contributions from AstraZeneca, Boehringer Ingelheim (Canada), Pfizer (Canada), MSD, Swedish Heart and Lung Foundation, Chest, Heart and Stroke Scotland, and The Stroke Association, with support from The UK Stroke Research Network.

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