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Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies

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Summary

Background Several studies reported a U-shaped association between urinary sodium excretion and cardiovascular disease events and mortality. Whether these associations vary between those individuals with and without hypertension is uncertain. We aimed to explore whether the association between sodium intake and cardiovascular disease events and all-cause mortality is modified by hypertension status.

Methods In this pooled analysis, we studied 133 118 individuals (63 559 with hypertension and 69 559 without hypertension), median age of 55 years (IQR 45–63), from 49 countries in four large prospective studies and estimated 24-h urinary sodium excretion (as group-level measure of intake). We related this to the composite outcome of death and major cardiovascular disease events over a median of 4·2 years (IQR 3·0–5·0) and blood pressure.

Findings Increased sodium intake was associated with greater increases in systolic blood pressure in individuals with hypertension (2·08 mm Hg change per g sodium increase) compared with individuals without hypertension (1·22 mm Hg change per g; $p_{interaction}$<0·0001). In those individuals with hypertension (6835 events), sodium excretion of 7 g/day or more (7060 [11%] of population with hypertension: hazard ratio [HR] 1·23 [95% CI 1·11–1·37]; p<0·0001) and less than 3 g/day (7006 [11%] of population with hypertension: 1·34 [1·23–1·47]; p<0·0001) were both associated with increased risk compared with sodium excretion of 4–5 g/day (reference 25% of the population with hypertension). In those individuals without hypertension (3021 events), compared with 4–5 g/day (18 508 [27%] of the population without hypertension), higher sodium excretion was not associated with risk of the primary composite outcome (≥7 g/day in 6271 [9%] of the population without hypertension; HR 0·90 [95% CI 0·76–1·08]; p=0·2547), whereas an excretion of less than 3 g/day was associated with a significantly increased risk (7547 [11%] of the population without hypertension; HR 1·26 [95% CI 1·10–1·45]; p=0·0009).

Interpretation Compared with moderate sodium intake, high sodium intake is associated with an increased risk of cardiovascular events and death in hypertensive populations (no association in normotensive population), while the association of low sodium intake with increased risk of cardiovascular events and death is observed in those with or without hypertension. These data suggest that lowering sodium intake is best targeted at populations with hypertension who consume high sodium diets.

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Introduction

Several prospective cohort studies[1–7] have reported that the association between sodium consumption and cardiovascular disease or mortality is U-shaped, with increased risk at both high and low sodium intake. This finding has been reported in studies done in different countries, in studies using different methods to estimate sodium intakes, and in different types of populations (ie, people with diabetes, those with vascular disease, and in the general population). A meta-analysis of 23 epidemiological studies (n=274 683) also reported a U-shaped relation.[8] Subsequently, findings from the PURE study[7] were consistent with findings from this previous meta-analysis, such that the collective data for 376 628 people involving more than 15 000 clinical events, showing a U-shaped association, are robust. In view that increasing sodium intake is related to increased blood pressure, and that this is steeper in those individuals with hypertension compared with in those without hypertension,[9,10] we hypothesised that there might be differences in the association between sodium intake and cardiovascular disease outcomes in individuals with hypertension compared with in those without hypertension. In this analysis, we explore whether the association between sodium intake and cardiovascular disease events and all-cause mortality is modified by hypertension status. We also compare the observed magnitude (and pattern) of association between sodium intake and clinical events with the predicted hazard ratio (HR) derived

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Research in context

Systematic review

We searched PubMed for relevant research published between Jan 1, 1960, and April 1, 2016, using the term "sodium" or "salt" AND "mortality" OR "cardiovascular" OR "myocardial" OR "stroke" OR "heart failure" OR "sudden cardiac death" in English. We screened papers by title and abstract to identify full-text reports that were relevant to the study aims. We also screened citation lists from these full-text reports to identify other relevant research. We considered papers if they contained an evaluation of the relation between sodium intake and at least one of the outcomes of interest. The papers cited in this report were selected to be representative of the existing evidence base, and are not an exhaustive list of relevant research.

Added value of this study

Several prospective cohort studies have recently reported that the association between sodium consumption and cardiovascular disease or mortality is U-shaped, with increased risk at both high and low sodium intake. Subsequently, the PURE study showed similar results in 101 945 people worldwide. Whether these associations vary between those individuals with and without hypertension is unknown. In this analysis of four international prospective studies with 9856 events and based on an analysis of 133 118 people (63 559 with hypertension and 69 559 without hypertension) selected from 49 countries in six continents, we assess whether the association between sodium intake and cardiovascular disease events and all-cause mortality is modified by hypertension status. To our knowledge, this is the largest individual-level data study of any kind relating sodium intake to cardiovascular disease events and mortality.

Interpretation

The results showed that cardiovascular disease and death are increased with low sodium intake (compared with moderate intake) irrespective of hypertension status, whereas there is a higher risk of cardiovascular disease and death only in individuals with hypertension consuming more than 6 g of sodium per day (representing only 10% of the population studied). These data indicate that lowering sodium is best targeted at those individuals with hypertension who also consume high sodium.

from modelling the association between sodium intake and blood pressure, and assuming that all reductions in blood pressure should translate into cardiovascular disease reduction, with no other off-target effects (eg, activation of the renin system or increases in blood lipids).

Methods

Study design and participants

Details of the studies' designs and population characteristics have been published before and are described in the appendix (pp 2–6). In brief, the Prospective Urban Rural Epidemiological Study (PURE Study)[11–15] is an ongoing large-scale epidemiological cohort study that has enrolled 156 424 individuals between 35 years and 70 years from the population in 628 communities in 17 low-income, middle-income, and high-income countries on five continents. The sampling strategy used in PURE ensures representation from urban and rural communities from different geographical areas.[11–15] For this analysis, we included 101 511 participants from PURE who collected morning fasting urine samples suitable for analysis and with baseline blood pressure measurements. The EPIDREAM trial was a prospective cohort study of 17 453 individuals, aged 18–85 years, who were screened for eligibility to enter the DREAM clinical trial (a randomised, double-blind trial with a 2×2 factorial design that assigned participants at high risk for type 2 diabetes to receive either ramipril [15 mg/day] *vs* placebo or rosiglitazone [8 mg/day] *vs* placebo).[16] The EPIDREAM cohort included participants who were screened for the study and includes those who entered DREAM and those who were not included in the trial and agreed to a long-term prospective follow-up.[16,17] For this analysis, to conserve power and at the same time to be efficient on resources, we used a case-cohort design to select all individuals who developed a cardiovascular disease event (n=478) during the follow-up of the EPIDREAM cohort and a control group comprised of a random sample of individuals (n=2372; five controls per case) who did not develop a cardiovascular disease event. ONTARGET was a randomised, double-blind, parallel trial comparing the effects of ramipril (10 mg/day), telmisartan (80 mg/day), and combination therapy of ramipril (10 mg/day) and telmisartan (80 mg/day) in 25 620 patients, aged 55 years or older, with vascular disease or high-risk patients with diabetes. TRANSCEND was a randomised controlled trial comparing telmisartan (80 mg/day) with placebo in 5926 participants who were intolerant to angiotensin converting enzyme (ACE) inhibitors.[18,19] For this analysis, we included 28 757 participants from ONTARGET and TRANSCEND with morning fasting urine samples and with baseline blood pressure measures. All studies were coordinated by the Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, ON, Canada, and the studies were approved by the ethics committees at participating centres and at the Hamilton Health Sciences, Hamilton, ON, Canada. All participants provided written informed consent.

Procedures

A morning fasting urine sample was collected from every participant and shipped in ambient packaging (Saf-T-Pak) for analysis at the Clinical Research and Clinical Trials Laboratory at Hamilton General Hospital in Hamilton, ON, Canada (the central laboratory), or the regional laboratory in Beijing, Bangalore, India, or Kocaeli, Turkey, for analyses with the use of validated and standardised methods. A description of the methods used for urinary analyses has been described previously.[7,9]

We used the Kawasaki formula[20] to estimate 24-h urinary excretion of sodium and potassium from a fasting morning specimen and used these estimates as surrogates for daily sodium and potassium intake (in grams). Previous studies have reported that this method provides a reliable estimate of sodium intake in healthy Japanese participants (r=0·73)[20] and this was replicated later in Japanese participants with hypertension (r=0·69 in those on blood pressure medication, r=0·66 in those not medicated),[21,22] and more recently in Chinese participants with hypertension (r=0·64).[23] We did further validation of the method in 1083 people from 11 countries,[24] and showed that the estimated sodium excretion from the morning urine specimen shows a good correlation with direct measures of sodium excretion from the actual 24-h urine collection (intraclass correlation coefficient of 0·70 [95% CI 0·61–0·77] among individuals with hypertension and 0·71 [0·61 to 0·78] among those without hypertension). Further, the blood pressure change per g of sodium was 2·11/0·78 mm Hg,[9] which is consistent with the results of a meta-analysis of sodium lowering randomised controlled trials (appendix pp 7, 8).[25]

Weight, height, and two recordings of blood pressure after 5 min of rest in a sitting position with the use of an Omron automatic digital monitor (Omron HEM-757 used in all studies) were recorded in all participants. Individuals were considered hypertensive if their untreated baseline blood pressure was 140/90 mm Hg or greater or if they were prescribed antihypertensive drugs at baseline.

The information about study variables was collected with similar approaches to measure risk factor variables and data collection forms in each of the studies. Information about personal medical history and use of drugs were recorded. Standardised case-report forms was used to capture data for major cardiovascular disease events and death during follow-up. Events were classified according to the definitions used in each study, but they were broadly similar. For this analysis, we included data from the PURE study (which is ongoing) through to March, 2015, the complete data from ONTARGET/TRANSCEND,[18,19] and case-cohort data from EPIDREAM.

Statistical analysis

Mean estimated 24-h urinary excretion values of sodium were computed overall and by hypertension status. Multivariable linear regression was used to obtain estimates of the slope describing the relation between estimated sodium excretion (exposure) and blood pressure measurements (outcome variable), within each subpopulation, with adjustment for age, sex, body-mass index, education, alcohol intake, current smoking, and geographical region.[9] We examined the association between an estimated so-called usual level of sodium excretion (ie, accounting for the degree of correlation between sodium levels in urine when measured after 30 days and 90 days in 448 individuals; this also allows adjustment for regression dilution bias)[26] and blood pressure. Analysis of covariance was done, with tests for linear trend, to compare the adjusted mean blood pressure according to sodium excretion level.

The primary outcome was defined as the composite of death, myocardial infarction, stroke, and heart failure. We used restricted cubic-spline plots with four knots (at the 5th, 35th, 65th, and 95th percentiles) to explore the shape of the association between the estimated sodium excretion and the outcomes.[27] Participants were categorised into urinary sodium excretion groups, based on 1 g/day increments of excretion. Because few individuals had excretion values less than 2 g/day or more than 8 g/day, we truncated excretion values at less than 3 g/day and >7 g/day to avoid small numbers of individuals at the extreme ends of the distribution (about 10% of participants in the lowest and highest excretion categories within each subgroup). We calculated HRs of time to event with Cox proportional hazards models, with shared frailty models. The clustering variable was the study cohort. The proportional hazards assumption was checked by visual inspection of log-log plots. The primary model included age, sex, ethnicity, BMI, smoking status, diabetes, educational level, alcohol consumption, physical activity, past cardiovascular disease events, and treatment allocation (ramipril, telmisartan, or both, and treatment with statins, β blockers, diuretic therapy, calcium antagonist, and antidiabetes medication), as in our previously published papers.[4,7] Separate analyses were done that excluded those individuals who had had previous cardiovascular events. Interaction tests were done to assess whether the slopes of the associations between estimated sodium excretion level and blood pressure, cardiovascular disease events, or deaths differed between those individuals with and without hypertension.

We modelled the estimated effect of changes in sodium intake on risk of incident cardiovascular disease events, based on the observed associations between sodium excretion and systolic blood pressure, and between systolic blood pressure and cardiovascular events (appendix p 9). For this modelling, we focused on 98 612 participants (3733 cardiovascular disease events; median 3·7 years of follow-up (IQR 2·9–5·0) without baseline cardiovascular disease, because this subcohort is comprised of generally healthy people from the population among whom few were receiving drugs. We compared these simulated blood

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See **Online** for appendix

pressure-based estimates with directly observed HR of sodium excretion versus clinical outcomes to assess the consistency between estimates derived overall and in those individuals with and without hypertension. Cox regression was used to calculate HRs and 95% CIs of cardiovascular disease events (total cardiovascular disease, stroke, and myocardial infarction) per 1 mm Hg increment in systolic blood pressure, within each subgroup of hypertension status.

Data were analysed with SAS version 9.3 (SAS, Cary, NC, USA).

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

133 118 individuals, (63 559 with hypertension and 69 559 without hypertension), were included in the study. 98 612 (74%) individuals were without previous cardiovascular disease, and 118 232 (89%) were without diabetes. Baseline characteristics the of study participants are shown in the appendix (pp 9, 10). The mean age was 58·6 years (SD 10·3) in individuals with hypertension and 50·5 (10·7) in those without hypertension. Individuals with hypertension were more likely to be men, heavier, less physically active, and had more previous cardiovascular disease and diabetes (appendix pp 10, 11).

	Estimated sodium excretion					
	<3 g/day (N=14 553)	3·00–3·99 g/day (N=27 463)	4·00–4·99 g/day (N=34 208)	5·00–5·99 g/day (N=27 670)	6·00–6·99 g/day (N=15 893)	≥7·00 g/day (N=13 331)
All participants (N=133 118)						
Death or cardiovascular event	1323 (9%)	1996 (7%)	2487 (7%)	1965 (7%)	1148 (7%)	937 (7%)
Univariable analysis†	1·26 (1·17–1·36)	1·04 (0·98–1·11)	1·00	1·00 (0·93–1·06)	1·09 (1·01–1·18)	1·28 (1·18–1·39)
Multivariable analysis‡§	1·31 (1·21–1·42)	1·08 (1·01–1·16)	1·00	0·98 (0·91–1·05)	1·04 (0·96–1·13)	1·18 (1·08–1·29)
Excluding CVD at baseline	1·38 (1·23–1·55)	1·14 (1·03–1·26)	1·00	1·02 (0·92–1·13)	1·02 (0·91–1·16)	1·14 (1·003–1·30)
Excluding events in year 1 and year 2	1·27 (1·15–1·40)	1·09 (1·002–1·19)	1·00	1·00 (0·92–1·09)	1·06 (0·96–1·17)	1·17 (1·05–1·31)
Major CVD events	1001 (7%)	1472 (5%)	1852 (5%)	1461 (5%)	857 (5%)	725 (5%)
Univariable analysis†	1·27 (1·17–1·38)	1·03 (0·96–1·11)	1·00	1·00 (0·93–1·07)	1·10 (1·01–1·21)	1·37 (1·25–1·50)
Multivariable analysis‡§	1·34 (1·23–1·47)	1·06 (0·98–1·15)	1·00	0·96 (0·88–1·04)	1·03 (0·94–1·13)	1·21 (1·10–1·34)
Excluding CVD at baseline	1·36 (1·18–1·57)	1·14 (0·98–1·29)	1·00	1·03 (0·91–1·17)	1·04 (0·89–1·20)	1·15 (0·98–1·35)
Excluding events in year 1 and year 2	1·30 (1·16–1·46)	1·05 (0·95–1·16)	1·00	0·95 (0·86–1·05)	1·03 (0·92–1·16)	1·21 (1·06–1·37)
All-cause mortality	812 (6%)	1177 (4%)	1377 (4%)	1102 (4%)	644 (4%)	573 (4%)
Univariable analysis†	1·38 (1·27–1·51)	1·11 (1·03–1·20)	1·00	1·01 (0·93–1·09)	1·10 (1·00–1·22)	1·42 (1·28–1·58)
Multivariable analysis‡§	1·41 (1·28–1·54)	1·15 (1·06–1·24)	1·00	1·00 (0·91–1·09)	1·05 (0·95–1·17)	1·31 (1·17–1·47)
Excluding CVD at baseline	1·52 (1·32–1·74)	1·18 (1·05–1·32)	1·00	1·02 (0·89–1·18)	1·03 (0·88–1·22)	1·28 (1·08–1·51)
Excluding events in year 1 and year 2	1·34 (1·19–1·51)	1·15 (1·04–1·27)	1·00	1·01 (0·91–1·15)	1·06 (0·93–1·22)	1·28 (1·11–1·48)
Participants without hypertension (N=69 559)						
Number of individuals	7547	15 166	18 508	14 240	7827	6271
Death or cardiovascular event	393 (5%)	668 (4%)	837 (5%)	632 (4%)	293 (4%)	198 (3%)
Univariable analysis†	1·23 (1·08–1·40)	1·04 (0·94–1·16)	1·00	1·00 (0·90–1·12)	0·95 (0·82–1·09)	0·95 (0·81–1·12)
Multivariable analysis‡§	1·26 (1·10–1·45)	1·05 (0·94–1·18)	1·00	0·99 (0·88–1·11)	0·92 (0·79–1·07)	0·90 (0·76–1·08)
Excluding CVD at baseline	1·38 (1·15–1·66)	1·10 (0·94–1·29)	1·00	1·03 (0·87–1·21)	0·81 (0·65–1·00)	0·81 (0·64–1·03)
Excluding events in year 1 and year 2	1·22 (1·02–1·44)	1·07 (0·93–1·23)	1·00	1·00 (0·87–1·16)	0·91 (0·76–1·09)	0·91 (0·73–1·13)
Major CVD events	262 (3·47)	452 (2·98)	573 (3·10)	409 (2·87)	209 (2·67)	131 (2·09)
Univariable analysis†	1·18 (1·01–1·38)	1·03 (0·91–1·17)	1·00	0·95 (0·83–1·08)	1·02 (0·86–1·20)	0·98 (0·80–1·20)
Multivariable analysis‡§	1·28 (1·09–1·51)	1·05 (0·91–1·21)	1·00	0·92 (0·79–1·06)	0·97 (0·81–1·15)	0·90 (0·72–1·11)
Excluding CVD at baseline	1·34 (1·04–1·71)	1·16 (0·94–1·43)	1·00	0·99 (0·79–1·23)	0·89 (0·67–1·17)	0·69 (0·49–0·96)
Excluding events in year 1 and year 2	1·31 (1·07–1·61)	1·07 (0·90–1·27)	1·00	0·95 (0·80–1·14)	0·94 (0·75–1·18)	0·90 (0·70–1·18)
All-cause mortality	257 (3%)	403 (3%)	475 (3%)	374 (3%)	166 (2%)	122 (2%)
Univariable analysis†	1·42 (1·21–1·67)	1·11 (0·97–1·28)	1·00	1·05 (0·91–1·20)	0·95 (0·79–1·14)	1·04 (0·84–1·27)
Multivariable analysis‡§	1·39 (1·17–1·66)	1·10 (0·95–1·28)	1·00	1·04 (0·90–1·21)	0·95 (0·78–1·15)	1·00 (0·80–1·24)
Excluding CVD at baseline	1·50 (1·19–1·90)	1·10 (0·90–1·36)	1·00	1·03 (0·83–1·28)	0·78 (0·59–1·04)	0·93 (0·69–1·24)
Excluding events in year 1 and year 2	1·18 (0·94–1·48)	1·06 (0·88–1·27)	1·00	1·02 (0·85–1·23)	0·91 (0·71–1·16)	0·96 (0·73–1·26)

(Table continues on next page)

	Estimated sodium excretion					
	<3 g/day (N=14 553)	3·00–3·99 g/day (N=27 463)	4·00–4·99 g/day (N=34 208)	5·00–5·99 g/day (N=27 670)	6·00–6·99 g/day (N=15 893)	≥7·00 g/day (N=13 331)
(Table continued from previous page)						
Participants with hypertension (N=63 559)						
Number of individuals	7006	12 297	15 700	13 430	8066	7060
Death or cardiovascular event	930 (13%)	1328 (11%)	1650 (11%)	1333 (10%)	855 (11%)	739 (11%)
Univariable analysis†	1·28 (1·17–1·41)	1·05 (0·97–1·14)	1·00	0·97 (0·90–1·05)	1·11 (1·01–1·21)	1·31 (1·19–1·45)
Multivariable analysis‡§	1·34 (1·23–1·47)	1·09 (1·002–1·19)	1·00	0·97 (0·89–1·05)	1·07 (0·97–1·18)	1·23 (1·11–1·37)
Excluding CVD at baseline	1·37 (1·19–1·58)	1·16 (1·01–1·32)	1·00	0·99 (0·87–1·14)	1·12 (0·96–1·30)	1·26 (1·08–1·47)
Excluding events in year 1 and year 2	1·29 (1·14–1·45)	1·10 (0·99–1·23)	1·00	0·99 (0·89–1·10)	1·11 (0·98–1·25)	1·24 (1·09–1·41)
Excluding users of antihypertension medication	1·70 (1·39–2·06)	1·26 (1·07–1·50)	1·00	1·02 (0·86–1·20)	1·07 (0·88–1·29)	1·13 (0·93–1·37)
Major CVD events	739 (11%)	1020 (8%)	1279 (8%)	1052 (8%)	648 (8%)	594 (8%)
Univariable analysis†	1·30 (1·18–1·44)	1·03 (0·95–1·13)	1·00	1·00 (0·91–1·09)	1·08 (0·97–1·19)	1·37 (1·24–1·53)
Multivariable analysis‡§	1·35 (1·21–1·50)	1·06 (0·97–1·17)	1·00	0·97 (0·88–1·06)	1·02 (0·92–1·14)	1·26 (1·12–1·42)
Excluding CVD at baseline	1·36 (1·14–1·63)	1·13 (0·96–1·32)	1·00	1·03 (0·88–1·21)	1·06 (0·89–1·27)	1·27 (1·06–1·52)
Excluding events in year 1 and year 2	1·29 (1·12–1·47)	1·05 (0·93–1·18)	1·00	0·95 (0·84–1·07)	1·04 (0·91–1·20)	1·26 (1·09–1·45)
Excluding users of antihypertension medication	1·64 (1·30–2·08)	1·21 (0·99–1·48)	1·00	1·04 (0·85–1·27)	0·96 (0·76–1·21)	1·15 (0·91–1·45)
All-cause mortality	555 (8%)	774 (6%)	902 (6%)	728 (5%)	478 (6%)	451 (6%)
Univariable analysis†	1·37 (1·23–1·54)	1·12 (1·01–1·24)	1·00	0·98 (0·88–1·08)	1·13 (1·01–1·28)	1·50 (1·33–1·70)
Multivariable analysis‡§	1·39 (1·23–1·58)	1·17 (1·05–1·31)	1·00	0·97 (0·87–1·08)	1·08 (0·95–1·23)	1·39 (1·22–1·59)
Excluding CVD at baseline	1·52 (1·25–1·86)	1·25 (1·05–1·49)	1·00	1·00 (0·84–1·20)	1·17 (0·95–1·43)	1·43 (1·17–1·75)
Excluding events in year 1 and year 2	1·43 (1·23–1·68)	1·22 (1·06–1·40)	1·00	1·01 (0·88–1·16)	1·12 (0·96–1·32)	1·39 (1·17–1·64)
Excluding users of antihypertension medication	1·77 (1·38–2·27)	1·37 (1·11–1·70)	1·00	1·00 (0·80–1·24)	1·11 (0·86–1·42)	1·27 (0·99–1·63)

Data are hazard ratios (95% CI) or n of individuals (%). CVD=cardiovascular disease. *Major cardiovascular events included death from cardiovascular causes, myocardial infarction, stroke, and heart failure. †The univariable model included age, sex, and ancestry (Asian *vs* non-Asian). ‡The primary model included age, sex, ancestry (Asian *vs* non-Asian), educational level, alcohol intake, body-mass index, current smoking, physical activity, status with respect to diabetes mellitus and a history of cardiovascular events, treatment allocation (ramipril, telmisartan, or both, and treatment with statins, β blockers, diuretic therapy, calcium antagonist, and antidiabetes medication). §Additional sensitivity analyses with estimated potassium excretion included in the model or exclusion of participants from the EPIDREAM study (case-cohort design) did not materially alter estimates of association.

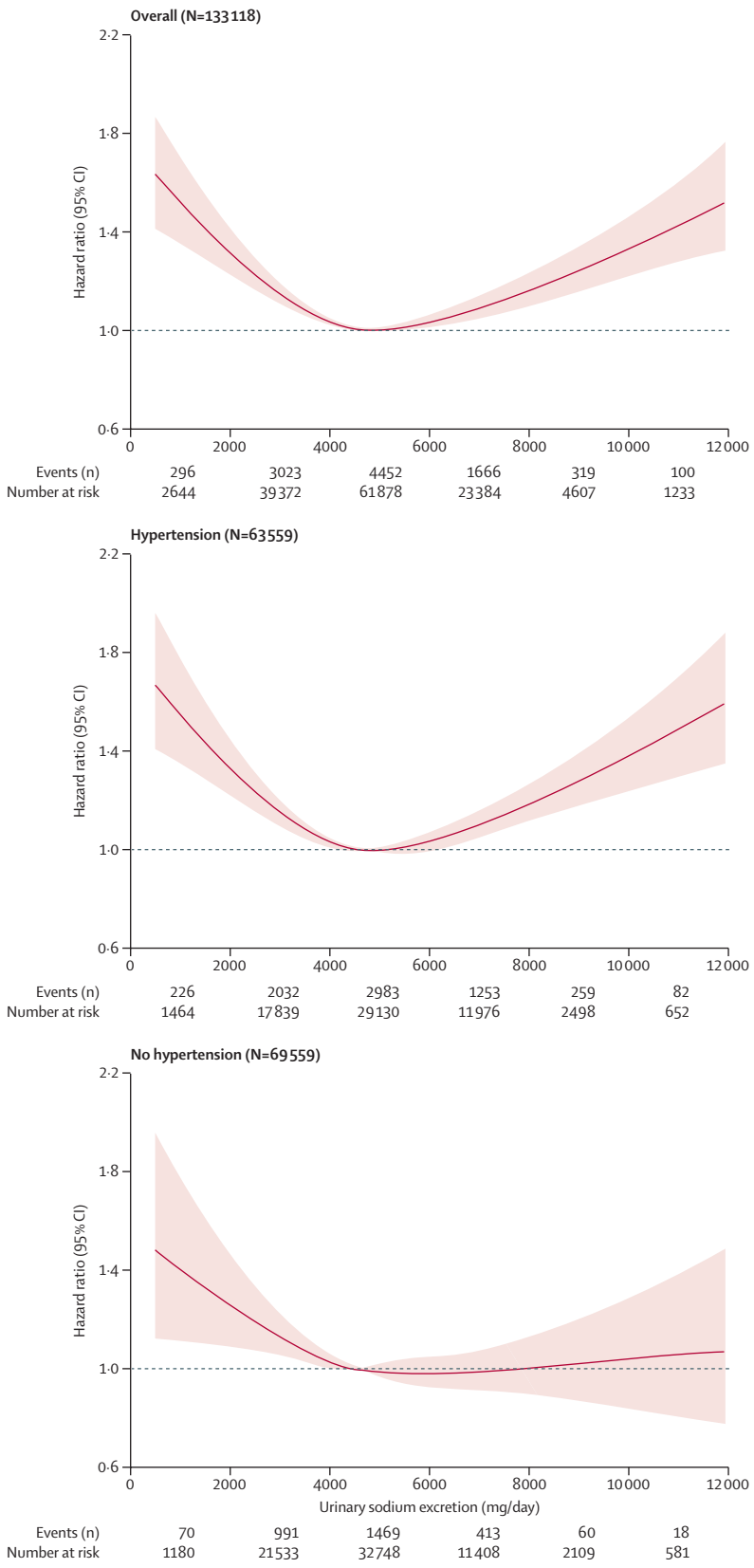
Table: **Association of estimated urinary sodium excretion with death and major cardiovascular events***

Mean estimated sodium excretion was 4956 g/day (SD 1747) in individuals with hypertension and 4823 g/day (1647) in those without hypertension (p<0·0001).

Among those individuals with hypertension, 7006 (11%) had an estimated sodium excretion of less than 3·0 g/day and 15 126 (24% of those with hypertension, or 11% of the overall population) had an estimated sodium excretion of 6 g or more (7060 [11% of those with hypertension, or 5% of the overall population] 7 g or more), and 41 427 (65%) had an estimated sodium excretion between 3 g/day and 6 g/day. In those individuals without hypertension, 7547 (11%) had an estimated sodium excretion of less than 3·0 g/day and 14 098 (20%) had an estimated sodium excretion of more than 6 g/day (6271 [9%] more than 7 g), and 47 914 (69%) had an estimated sodium excretion between 3 g/day and 6 g/day. After adjustment for regression dilution bias, 3039 (<3%) participants had a sodium excretion of less than 3 g/day and 21 240 (16%) had an estimated sodium excretion of 6 g/day or more (11 146 [18%] of those individuals with hypertension and 10 094 [15%] of those without hypertension; p<0·0001).

133 118 (96%) participants had completed follow-up, with a median follow-up of 4·2 years (IQR 3·0–5·0). The primary composite outcome of all-cause death or a major cardiovascular disease event occurred in 6835 individuals (11%) with hypertension and 3021 (4%) without hypertension (table). Those participants with 4–5 g of sodium excretion had the lowest risk and this was used as the reference category.

The association between sodium excretion and the primary composite outcome varied significantly by hypertension status ($p_{heterogeneity}$=0·0342; figure 1). In the hypertension group, a U-shaped association between sodium excretion and cardiovascular events and mortality was apparent. Compared with sodium excretion of 4–5 g/day (reference category), sodium excretion of 7 g/day or more (HR 1·23 [95% CI 1·11–1·37]; p<0·0001) and less than 3 g/day (1·34 [1·23–1·47]; p<0·0001) were both associated with increased risk of the composite outcome (table; figure 1). After adjustment for blood pressure, the associations between high sodium excretion and the composite outcome (HR 1·21 [95% CI 1·09–1·34]; p=0·0006), and the association between low



sodium excretion and the composite outcome were unaltered (1·35 [1·23–1·49]; p<0·0001).

In those individuals without hypertension, compared with 4–5 g/day, sodium excretion of 7 g/day or more was not associated with risk of the primary composite outcome (HR 0·90 [95% CI 0·76–1·08]; p=0·2547), whereas an excretion of less than 3 g/day was associated with a significantly increased risk (1·26 [1·10–1·45]; p=0·0009; table; figure 1). After adjustment for blood pressure, the association between low sodium excretion and the composite outcome remained significant (p=0·0011).

Similar results were noted for death from any cause ($p_{heterogeneity}$=0·0135) and major cardiovascular disease ($p_{heterogeneity}$=0·0432; table).

The results described above of a U-shaped association in those participants with hypertension were consistent in those participants with and without vascular disease (appendix p 12). Among those participants without hypertension, an increased risk with sodium excretion of less than 3 g/day compared with 4–5 g/day was consistent in those with and without vascular disease, whereas a sodium excretion of 7 g/day or more was associated with an increased risk only in those with known vascular disease (appendix p 12). When we exclude data from the EPIDREAM study from the analysis (which is a case-cohort study of 2850 individuals), the results of the study overall and by subgroup do not change and the estimates from the PURE study report the same findings (appendix pp 14–16). Further, the data from the ONTARGET and TRANSCEND trials are consistent with the data from the two observational studies.

Exclusion of those participants who had an event in the first 2 years of follow-up did not affect the estimates (table). Further, in those with hypertension, exclusion of 35 027 individuals who were taking antihypertensive medication did not change the findings (table).

Sodium excretion was more strongly associated with increased systolic blood pressure in individuals with hypertension (2·08 mm Hg increment in systolic pressure per g [95% CI 1·96–2·21]) than in those without hypertension (1·22 mm Hg [1·13–1·30]; p<0·0001 for interaction; figure 2). Similar results were noted for diastolic blood pressure (0·72 mm Hg increment in diastolic pressure per g [95% CI 0·65–0·80] and 0·52 mm Hg [0·46–0·58], respectively; p<0·0001 for interaction; figure 2).

Figure 1: **Sodium excretion versus composite outcome events**
Cubic splines for the association between sodium excretion and composite outcome events (risk of death and major cardiovascular events), overall and by hypertension status in the four included studies (N=133 118). The analyses were adjusted for the variables in the primary model which included age, sex, ancestry (Asian *vs* non-Asian), body-mass index, educational level, alcohol intake, current smoking, physical activity, status with respect to diabetes mellitus, a history of cardiovascular events, treatment allocation (ramipril, telmisartan, or both, and treatment with statins, β blockers, diuretic therapy, calcium antagonist, and antidiabetes medication).

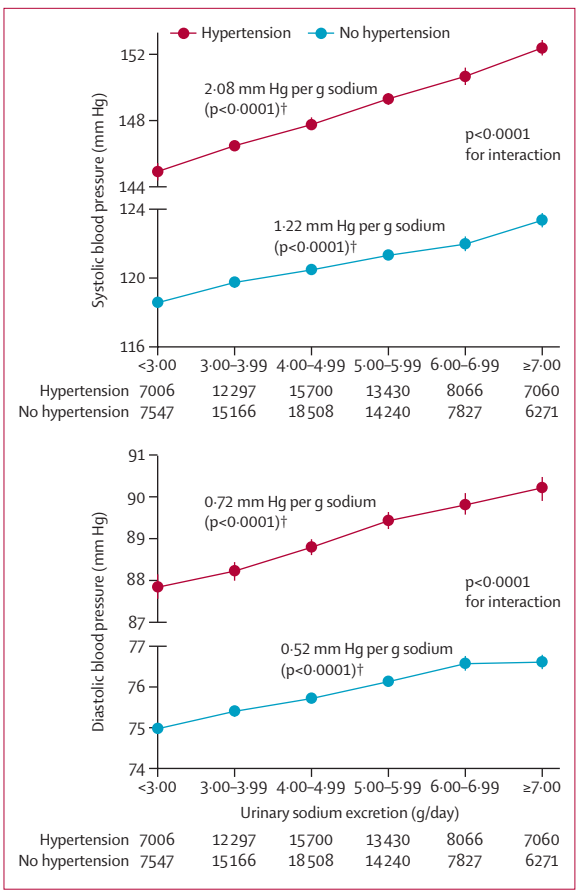


Figure 2: **Blood pressure by sodium excretion**
Mean (95% CI) systolic and diastolic blood pressure by sodium excretion and hypertension status, with adjustment for age, sex, body-mass index, education, alcohol intake, current smoking, and geographical region (N=133 118). These covariates were selected because they were included in the INTERSALT study and in our previous PURE analysis.[18] Linear regression assumptions were checked with standard plots (residuals vs predicted values plots, residual time-series plots, and normal probability plots), with no detected violations. *Slope estimates are based on linear regression models with adjustment for covariates and regression dilution bias.

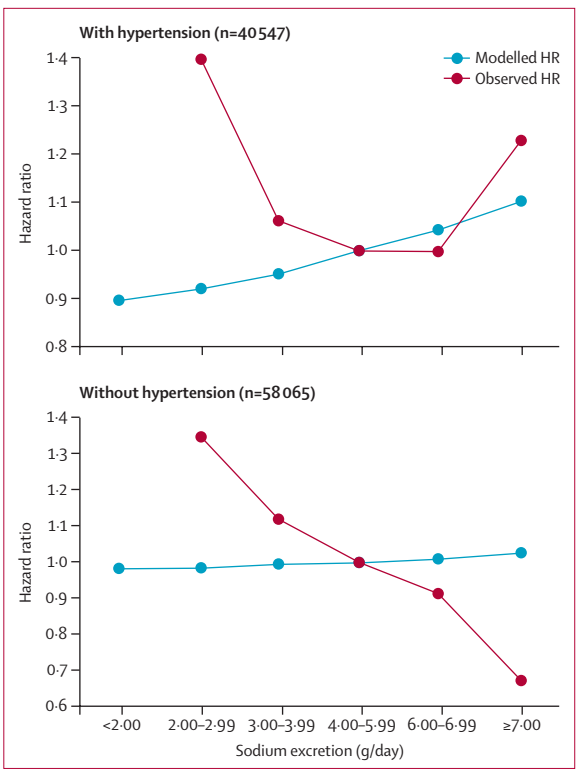


Figure 3: **Simulation modelled versus observed hazard ratio (HR) estimates of the association between sodium excretion and cardiovascular disease events in those without cardiovascular disease (N=98 612), overall and stratified by hypertension status**

In the simulation models, in which we assumed that the effect of sodium intake on cardiovascular disease events was solely related to its association through systolic blood pressure, the projected HR of cardiovascular disease events, stroke, and myocardial infarction increased in a graded fashion. However, there was a greater increase in risk in individuals with hypertension, and a more modest association in those without hypertension (p<0·0001 for heterogeneity; figure 3; appendix p 18).

The modelled estimates differed from the observed HR of cardiovascular disease events both in individuals with hypertension and those without hypertension. This discordance was marked at lower levels of sodium excretion (ie, <3 g/day). The projection model shows lower HR estimates with lower sodium excretion, whereas the observed HR estimates show an increased risk of events with lower sodium excretion. In individuals with hypertension, the observed HR was similar to the modelled HR at average or higher levels of sodium excretion (>4 g/day; figure 3; appendix pp 19–21).

Discussion

In this analysis of four international prospective studies with 9856 events and based on an analysis of 133 118 people selected from 49 countries in six continents (appendix pp 5, 6), we noted significant heterogeneity in the association between sodium excretion and the composite outcome by hypertension status. In both individuals with or without hypertension, there is an increased risk of cardiovascular disease events and deaths associated with 24-h urinary sodium excretion of less than 3 g/day. However, an increase in risk of cardiovascular disease associated with high sodium excretion (surrogate for intake) was only seen in individuals with hypertension (which represents 24% of those with hypertension but only about 10% of the overall populations enrolled in the four cohorts included in this analysis), but not in those without hypertension.

Our results are consistent with another recently published cohort study (PREVEND study;[10] n=7543), which reported an association between increased sodium intake and cardiovascular disease, that was confined to participants with baseline hypertension ($p_{interaction}$=0·08)

and in those with baseline pro-BNP (brain natriuretic peptide) concentrations above the median. Other studies have not reported a significant modifying effect of previous hypertension, but these studies have been smaller than our study. In our analysis, the association between low sodium intake (<3 g/day) and increased cardiovascular disease and mortality was consistent, irrespective of baseline hypertension status and after further adjustment for blood pressure level indicating that mechanisms unrelated to blood pressure might be operational. Our findings are also in keeping with a previous meta-analysis of prospective cohort studies showing a U-shaped association between sodium intake and cardiovascular disease events, in both healthy and high-risk populations (eg, those individuals with cardiovascular disease or diabetes), with consistency across different methods of sodium estimation.[1–8] Although the meta-analysis[8] included previous analyses from the ONTARGET/TRANSCEND cohort, it did not include the PURE study and EPIDREAM cohorts, and the PURE study accounts for most of the current study population. Our findings replicate previous reports and extend these observations to populations based on baseline hypertension status. Further, they suggest that although there is a limit below which sodium intake would be unsafe, the harm associated with high sodium consumption seems to be confined to those individuals with hypertension. Only about 10% of the population in our study had both hypertension and high sodium consumption (6 g/day or more). This argues against a population-wide approach to reduce sodium intake in most countries, except in those where the mean sodium intake is high (eg, some in central Asia or some parts of China).

We noted that most of the world's population (about 95%) studied consumes more than 3 g/day of sodium, regardless of hypertension status and only 22% consume 6 g/day or more of sodium—the threshold above which we note an increase in mortality and cardiovascular disease risk. Sodium is an essential cation and is crucial to the action potential of all cells in the body.[28] Sodium homoeostasis is under tight physiological regulation. Further, emerging evidence suggests that inflammatory responses with infections involve mobilising high concentrations of sodium to the local tissues that are involved, and this ability might be part of an essential defence mechanism to external infections.[29–31] Sodium intake is governed by neural mechanisms that regulate intake of sodium and related homoeostatic mechanisms,[32] and so although extreme reductions in sodium intake are possible in controlled settings for short periods, this is unlikely to be sustainable in free living individuals in the long term.[33]

Previous modelling studies[34] that have estimated the effect of reducing sodium intake globally on cardiovascular mortality are based on the assumption that the blood pressure-lowering effects of sodium reduction seen in short-term trials will translate into reductions in cardiovascular disease in the long term. However, it is unknown that whether lowering blood pressure results in reductions in cardiovascular disease is dependent on the baseline blood pressure of the population, the mechanism of blood pressure lowering, and presence or absence of cardiovascular disease. Although the SPRINT trials did report a reduction in heart failure and cardiovascular death when lowering blood pressure to a mean of 121 mm Hg systolic blood pressure in a primary prevention population,[35] several other randomised controlled trials have failed to show a benefit of lowering systolic blood pressure below 130 mm Hg in a primary prevention population (HOPE-3)[36] and secondary prevention populations (ACCORD, SPS3, PRoFESS),[37–39] and some have shown harm.[40] Three independent meta-analyses of large randomised trials of blood pressure lowering with antihypertensive drugs in individuals with diabetes[41–43] show that the benefits of blood pressure lowering in reducing clinical events is noted only in those with a systolic blood pressure of higher than 140 mm Hg. This finding is also supported by the results of the recent HOPE 3 trial,[36] which showed that reducing systolic blood pressure by 6 mm Hg reduced cardiovascular disease risk by about 25% only in those with increased baseline levels (systolic blood pressure >143 mm Hg), but not in those with lower initial systolic blood pressure, despite similar reductions in blood pressure. These data are consistent with our finding that the association of high sodium intake and cardiovascular disease is confined to those with baseline blood pressure higher than 140/90 mm Hg. The mechanism of blood pressure lowering is also important and non-blood pressure effects might be beneficial or harmful. Although high-risk people—eg, those with previous myocardial infarction or stroke—have benefited from ACE inhibitors or β blockers, the benefits seem to be not exclusively due to blood pressure lowering,[44] and other drugs that lower blood pressure in high risk people might not necessarily reduce cardiovascular disease events in such populations.[37,45] Further, some drugs that were shown to reduce blood pressure to similar extents differed in their effect on cardiovascular disease or its individual cardiovascular disease outcomes.[46,47] Our data suggest that although a persuasive case can be made to reduce sodium intake in individuals with hypertension and high sodium intake, it is unclear whether the remaining more than 90% of the population will benefit from dietary sodium reduction.

Our analyses indicate the limitations of estimates from modelled calculations based only on projected changes in blood pressure from sodium lowering. This is apparent in view that the results differ compared with the directly observed data relating sodium to cardiovascular disease events and supported by an absence of cardiovascular disease reduction with blood pressure lowering in people without cardiovascular

disease. This suggests that the effect of a given level of sodium intake on clinical outcomes is only partly mediated through its effects on blood pressure and that other mechanisms might also be at play. This is supported by observations of activation of the renin system and of catecholamines with low sodium intake.[48,49] High renin concentrations have been reported in studies of the Yanomamo Indians who reportedly consume very little sodium.[50] Several studies have shown that increases of renin, aldosterone, and catecholamines are all associated with increased cardiovascular disease events and mortality.[51–56] Therefore, predicting the net clinical effect based on only considering the effects of sodium on blood pressure might not provide a comprehensive understanding of its effects on cardiovascular disease and mortality, especially within the range of sodium intake that affects the renin system (<4 g/day).

We noted that the association of sodium intake with cardiovascular disease remained strong even when adjusted for blood pressure levels. This indicates that the association between sodium and cardiovascular disease might also be related to non-blood pressure mechanisms. Exploration of why individuals with hypertension with high sodium intake have a higher risk of cardiovascular disease whereas no such relation is noted in those without hypertension requires mechanistic investigation in careful physiological studies. Randomised trials have shown that sodium lowering has only a small effect on blood pressure in individuals without hypertension[49] and that such individuals might be less sensitive to the blood pressure effects of salt consumption.[57] Furthermore, understanding of why low sodium intake is associated with increased event rates, despite slightly lower blood pressure, is also of importance. As sodium is an essential cation, it should not be surprising that there is an optimal range for its intake. This mirrors the situation of most biological systems and it is only with external toxins (eg, tobacco or environmental pollutants) that a linear association is likely.

Despite careful design, follow-up, and analyses, observational analyses cannot definitively prove causality. Therefore, ideally large and long-term randomised controlled trials (RCTs) of sodium reduction to various levels to assess the effect on clinical outcomes are essential to guide public policy. In view of the absence of such RCTs, large prospective observational studies (despite their inherent limitations) relating sodium intake to cardiovascular disease should be considered the best available evidence. Further, we have initiated a pilot RCT to assess feasibility as a prelude to establishing a larger and long-term study to definitively address this question (NCT02458248). In the absence of large definitive RCTs showing a clear reduction in cardiovascular disease, the weight of the substantial epidemiological studies describing a potentially adverse effect of low sodium should urge caution in making broad public health recommendations. Further, the observation that high sodium intake is only associated with increased cardiovascular disease in individuals with hypertension raises questions whether public health policies targeted at reducing sodium in the entire population are appropriate. Therefore, until new robust data emerge from large trials,[58] it might be prudent to recommend reduction in sodium intake only in those with high sodium intake and with hypertension. Some might consider large randomised trials of sodium reduction impractical to assess their effect on cardiovascular disease, but they are essential to definitively resolve the controversy.

Strengths of our study include the large size, the international nature of our cohorts, use of validated urinary measure of sodium intake, standardised methods to measure a large number of covariates, and careful and standardised measurement of blood pressure. These rigorous methods make our study both valid and generalisable. Our analyses include participants with established cardiovascular disease recruited into an RCT (ONTARGET/TRANSCEND) as well as those without vascular disease identified from the population (PURE) or those screened for a trial (EPIDREAM). This broad range of individuals from 49 countries indicates that our findings are widely applicable and robust because similar findings were noted across all four studies. Although the collection of one overnight urine sample to estimate the 24-h urinary sodium excretion might be considered a limitation, it has been validated against 24-h urine collections in previous studies of healthy individuals[20] and those with hypertension[21–23] and in our international validation study,[24] with correlations similar to that noted with a blood pressure measured at a clinic visit versus 24-h ambulatory monitoring. Further, our analyses take into account the day to day variability of sodium intake in individuals by estimating the correlation of two measures taken 30–90 days apart and then using statistical adjustments to assess the degree of regression dilution. Adjustments for day to day variability and the absence of perfect correlation with 24-h urinary estimates of sodium would steepen all the associations (both at the low and high ends of sodium intake) and so would not qualitatively affect the pattern of our results.[59] With our method, there is about a 10% overestimation of 24-h sodium excretion, indicating that the true intake range at which risk of cardiovascular events and death changes might occur at a slightly lower level of sodium intake. Residual confounding cannot be completely ruled out in any epidemiological study but extensive multivariable analyses did not change our results. Further sensitivity analyses to minimise the potential for reverse causality (in which sicker people reduce sodium intake) by excluding in turn those with known cardiovascular disease, hypertension, or diabetes or by confining analyses to events beyond 2 years, did not change the pattern of our findings. Therefore our results are robust to different forms of analyses.

In summary, our results show an association between low sodium intake (*vs* moderate intake) and increased risk of clinical outcomes in those individuals with and without hypertension, whereas high sodium intake (greater than 6 g/day) was associated with an increased risk in individuals with hypertension. Our findings suggest that sodium reduction should be confined to only those individuals with hypertension and high sodium intake; this represents only about 10% of the population studied.

Contributors

AM designed the study, did the statistical analysis, and wrote the first draft of the report. SY designed the study, conceived and initiated the Prospective Urban Rural Epidemiology (PURE) study, supervised its conduct and data analysis, and provided critical comments on all drafts of the report. MO'D reviewed and provided critical comments on drafts. SR coordinated the worldwide PURE study and reviewed and commented on drafts. KT was the coprincipal investigator of the PURE study and reviewed and commented on drafts. All other authors coordinated the study and collected data in their respective countries and provided comments on drafts of the report. SSA and SY lead the EPIDREAM study and SY and KT lead the ONTARGET and TRANSCEND trials.

Declaration of interests

We declare no competing interests. AM is a recipient of a Research Early Career Award from Hamilton Health Sciences Foundation. SY is funded by the Marion Burke Chair of the Heart and Stroke Foundation of Canada. SSA holds a Canada Research Chair in Ethnic Diversity and Cardiovascular Disease, and is the Michael G DeGroote and Heart and Stroke Foundation of Ontario Chair in Population Health, McMaster University. HG holds the Population Health Research Institute Chair in Diabetes Research sponsored by Aventis. SY is currently the President of the World Heart Federation (WHF), but this paper does not necessarily reflect the position of the WHF or any other organisation.

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