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on behalf of the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group

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The Global Cardiovascular Risk Transition Associations of Four Metabolic Risk Factors with National Income, Urbanization, and Western Diet in 1980 and 2008

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Background—It is commonly assumed that cardiovascular disease risk factors are associated with affluence and Westernization. We investigated the associations of body mass index (BMI), fasting plasma glucose, systolic blood pressure, and serum total cholesterol with national income, Western diet, and, for BMI, urbanization in 1980 and 2008.

Methods and Results—Country-level risk factor estimates for 199 countries between 1980 and 2008 were from a previous systematic analysis of population-based data. We analyzed the associations between risk factors and per capita national income, a measure of Western diet, and, for BMI, the percentage of the population living in urban areas. In 1980, there was a positive association between national income and population mean BMI, systolic blood pressure, and total cholesterol. By 2008, the slope of the association between national income and systolic blood pressure became negative for women and zero for men. Total cholesterol was associated with national income and Western diet in both 1980 and 2008. In 1980, BMI rose with national income and then flattened at \approx Int\$7000; by 2008, the relationship resembled an inverted U for women, peaking at middle-income levels. BMI had a positive relationship with the percentage of urban population in both 1980 and 2008. Fasting plasma glucose had weaker associations with these country macro characteristics, but it was positively associated with BMI.

Conclusions—The changing associations of metabolic risk factors with macroeconomic variables indicate that there will be a global pandemic of hyperglycemia and diabetes mellitus, together with high blood pressure in low-income countries, unless effective lifestyle and pharmacological interventions are implemented. (*Circulation*. 2013;127:1493-1502.)

Key Words: blood pressure ■ cholesterol ■ diabetes mellitus ■ epidemiology ■ obesity

Cardiovascular diseases (CVDs) are the leading cause of death and disease burden worldwide. Population aging leads to an increase in CVD deaths because CVD mortality rises with age. Beyond aging, age-specific mortality rates may increase or decline over time. Age-specific CVD death rates are themselves affected by exposure to risk factors such as excess weight; smoking; high blood pressure, cholesterol, and glucose; and by treatment availability and quality.

Access to treatment tends to rise with income.¹ Although the association between CVD risk factors and socioeconomic status has been studied within countries,¹ few studies have assessed the cross-country association of CVD risk factors with national macroeconomic variables.²⁻⁴ Some studies have postulated that CVD risk factors may rise with national income or urbanization, due to a Westernized diet and lifestyle,^{5,6} referred to as diseases of affluence or Western diseases paradigm; others have concluded that higher income and urban infrastructure may help reduce CVD risk factors

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through healthier lifestyle or better access to preventive interventions and primary care.⁷ Even less is known about how these associations have changed over time with the availability of new public health and clinical programs and with the globalization of medicines and foods.^{8,9} Knowledge of the relationship between socioeconomic factors and CVD risk factors at the population level is essential to understanding the role of risk factors in the epidemiological transition and to informing national and global policies and priorities. Individual-level studies that provide evidence on causal effects cannot assess with population-level patterns and dynamics.

We investigated the population-level associations of major metabolic risk factors—body mass index (BMI), fasting plasma glucose (FPG), systolic blood pressure (SBP), and serum total fasting cholesterol (TC)—with national income, Western diet, and, for BMI only, urbanization in 1980 and 2008. Although some of the associations reported here may be causal, they should not be generally interpreted as such, because factors like national income and urbanization may themselves be correlated, making inferences about causal effects neither feasible nor possibly relevant. Rather, population-level analysis demonstrates how risk factors, whose causal effects on CVD are established in individual-level epidemiological studies, are distributed across countries in relation to the degree of social and economic development, and how these patterns have changed over time.

Methods

Risk Factor Levels by Sex, Country, and Year

Mean BMI, FPG, SBP, and TC were from a systematic analysis of population-based data, by sex, for 199 countries and territories, as described in detail in previous publications.^{10–13} In brief, we reviewed and accessed published and unpublished health examination surveys and population-based epidemiological studies to collate comprehensive data on these 4 risk factors between 1980 and 2008. There were 960 data sources across countries and years for BMI, 786 for SBP, 321 for TC, and 370 for FPG. Data in some sources were gathered in a single year, whereas others covered 1 year or more. Counting each source as 1 country-year, these numbers are equivalent to 17% of all 5771 country-years for which estimates were made for BMI, 14% for SBP, 5.5% for TC, and 6.5% for FPG. These figures should be compared with a recommended survey frequency of ≈ 1 in 5 years, ie, 20% of all country-years¹⁴; to our knowledge, only Japan has an annual health examination survey. The number of countries with no data ranged from 30 (ie, 15%) for BMI to >100 (ie, >50%) for TC.

For each risk factor, we developed and applied a Bayesian statistical model to impute missing data. The model incorporated the hierarchical nature of the data, nonlinear time trends and age associations, and national versus subnational and community representativeness of data. With the use of these data and methods, we estimated mean risk factor levels and their uncertainties by age and sex for each country-year. The uncertainties are larger for risk factors, countries, and years without data or with data that were not from a nationally representative survey (see online-only Data Supplement Materials for statistical details on how uncertainty was incorporated in all analyses). We estimated age-standardized means by using the World Health Organization standard population to account for the fact that the age composition varies across countries and over time.

National Income, Urbanization, and Western Diet

National income was measured as per capita gross domestic product (GDP) converted to international dollars and adjusted for inflation with a base year of 2005.¹⁵ Urbanization was measured as the proportion of a country's population who live in urban areas by the use of

data from the Population Division of the Department of Economic and Social Affairs of the United Nations.

We used data on the availability of multiple food types for human consumption from the food balance sheets of the Food and Agriculture Organization of the United Nations. The food balance sheets report the availability of 24 food types for human consumption, in kilocalories per capita per day. We used 22 of 24 food types because one (sugar crops) was missing in >70% of country-years, and another (miscellaneous) may not be defined consistently across countries. For the remaining 22 food types, missing values were imputed by using Imputation by Chained Equations (Stata 10.1 software command *ice*). The average of 100 imputed values was used. We defined outlier values for a single country-year as values that were larger or smaller than both the previous and the subsequent year's values by 3 standard deviations or 300% and set these outlier values to the average of the 3 previous and 3 subsequent years. There was an abrupt change in the reported values for all food types in the Occupied Palestinian Territory around 1993 and in the values of 1 food type in 1 year in Mongolia, Maldives, Cyprus, and the Netherlands. These discontinuities were likely due to changes in reporting. We adjusted the earlier estimates by the difference between pre- and postdiscontinuity values, resulting in a smooth trend.

To identify major dietary patterns with the use of all 22 food types, we used principal component analysis, an approach commonly used in dietary pattern studies to objectively aggregate food items based on the correlation structure within the data set.¹⁶ We used the first principal component in our analysis. This component explained >28% of the variance of data¹⁰ and had relatively large positive coefficients for alcoholic beverages, animal fats and animal products, eggs, meat, milk, offals, stimulants, sugar and sweeteners, and total calories; and negative coefficients for pulses and cereals (Table). Consistent with studies of dietary patterns in individuals, we considered this pattern

Table. Coefficients of 22 Food Types from Principal Component Analysis, representing a Western Dietary Pattern

Food Type	Principal Component Coefficients
Animal products	0.39
Meat	0.36
Animal fats	0.34
Milk, excluding butter	0.34
Offals	0.30
Alcoholic beverages	0.29
Sugar and sweeteners	0.25
Eggs	0.24
Stimulants	0.23
Total calories	0.20
Vegetable oils	0.08
Fish and seafood	0.05
Vegetables	0.03
Tree nuts	0.02
Fruits, excluding wine	−0.05
Other aquatic products	−0.06
Spices	−0.07
Vegetal products	−0.09
Oil crops	−0.10
Starchy roots	−0.10
Cereals, excluding beer	−0.16
Pulses	−0.19

Food types with large coefficients are the ones that are common in the dietary pattern, and those with small coefficients are uncommon.

as representing a Western diet (WD). Because a principal component does not have a directly interpretable scale, we used percentiles for presentation. Percentiles were calculated by using the distribution of data pooled over all 29 years of analysis. Therefore, as diet in a country westernizes over time, its percentile of WD increases.

Statistical Methods

We investigated the univariate associations of age-standardized mean risk factor levels with national income, Western diet, and urbanization (for BMI only) with countries as the units of observation. We did not weight the mean risk factor values by country population because our aim was to investigate the associations between mean risk factors and macroeconomic characteristics across countries as opposed to in the global population. We present the scatter plots and the estimated Pearson correlation coefficient and its 95% confidence interval for 1980 and 2008 (Figures 1 through 3). In each graph, we fitted a nonparametric (Loess) regression to visualize the association. We also fitted univariate regression models to each pair of variables in Figures 1 through 3 separately by year (1980 and 2008) and report the slopes in these figures. In addition, we analyzed the associations of mean FPG, SBP, and TC with mean BMI (Figure 4), because BMI causally affects the other 3 metabolic risk factors, which also have other determinants, eg, dietary salt and saturated fats and medication use.

All analyses were based on a Bayesian multiple imputation approach as described in online-only Data Supplement Material. We estimated the uncertainties of the correlation and regression coefficients as described in online-only Data Supplement Material. Analyses were performed in R (v. 2.15.0) and Stata (10.1 StataCorp).

Results

In 1980, population mean BMI, SBP, and TC were positively associated with national income, with correlation coefficients ranging between 0.34 and 0.50 (Figure 1). The relationship between BMI and national income flattened at a per capita GDP of \approx Int\$7000. The association between national income and FPG in 1980 was weaker than those of the other 3 risk factors, with correlation coefficients below 0.15 and regression slopes close to zero.

In 2008, the relationship between natural logarithm of GDP [Ln(GDP)] and BMI resembled an inverted U for women, peaking at middle-income levels. Middle- and upper-middle-income countries in Oceania, Middle East, and North Africa had higher BMIs than countries with similar incomes in other regions, whereas women living in high-income countries in Asia-Pacific and Western Europe had lower BMIs than women in countries with similar incomes in other regions. The slope of the BMI-Ln(GDP) association and the correlation coefficient in 2008 were about one-third smaller than their 1980 levels for women.

The association between income and SBP reversed between 1980 and 2008, with the slopes becoming negative for women (from 2.76 [95% uncertainty interval (2.36, 3.62)] mm Hg per Ln(GDP) in 1980 to -1.85 [-2.24 , -1.27] in 2008) and virtually zero for men. In 2008, TC was still strongly correlated with national income (correlation coefficients of 0.60 [0.53, 0.70] for women and 0.62 [0.53, 0.67] for men). Although the slope of TC-Ln(GDP) association declined slightly between 1980 and 2008, the declines were not statistically significant. The association between mean FPG and income remained weak in 2008.

The associations of risk factors with the percentage of population in urban areas, and how they changed between 1980

and 2008, mostly had the same patterns as associations with national income (detailed results available from the authors by request). The exception was the association between BMI and urbanization. The associations between mean BMI and urban population were positive and statistically significant in both 1980 and 2008, with slopes ranging between 0.54 and 0.7 kg/m² per 10 percentage point increase in urbanization.

In 1980, BMI was associated with WD, with some flattening for men and reversal of association at approximately the 80th percentile for women (Figure 3). In 2008, the BMI-WD curve for men maintained its linear-then-flat shape but was shifted upward, showing higher BMI levels at the same value of WD. For women, the reversal of association occurred at approximately the 60th WD percentile. The association between SBP and WD shifted from positive to negative for women and was substantially weakened for men over the 3 decades of analysis. TC was positively and significantly associated with Western diet in both 1980 and 2008 with slopes remaining positive and only slightly declining (Figure 3) and correlation coefficients >0.6 .

TC was positively associated with BMI in both 1980 and 2008, but there was more flattening of the curve in 2008, and the slope of the TC-BMI relationship declined in both men and women; The SBP-BMI association disappeared in both men and women over time (Figure 4). Although mean FPG had weak associations with national income and Western diet, it was positively correlated with BMI, with correlation coefficients increasing from 0.22 (0.02, 0.34) and 0.25 (0.14, 0.43) in 1980 in men and women, respectively, to 0.54 (0.42, 0.64) and 0.52 (0.40, 0.59) in 2008. The FPG-BMI slope ranged between 0.06 and 0.10 mmol/L per kg/m² over the analysis period for both men and women.

Discussion

Randomized and observational epidemiological studies have established elevated blood pressure and cholesterol, excess body weight, hyperglycemia, and smoking as some of the most important risk factors for CVD. Until now, little has been known about the associations of these risk factors with macroeconomic characteristics of countries and how the associations have changed over time. Our analysis suggests that the associations of metabolic risk factors with affluence and Western diet are complex and dynamic. In 1980, 3 major metabolic risk factors for CVD, SBP, TC, and BMI, were positively associated with national income and Western diet at the national level. By 2008, only TC retained a strong positive association with national income, whereas the other associations changed qualitatively. Interestingly, BMI remained positively associated with urbanization over the nearly 3 decades of the analysis in both men and women, suggesting that urbanization may have effects on BMI apart from income and Western diet.

Comparable country data for smoking, the other key CVD risk factor, are available only for recent years and hence do not allow analysis for 1980.¹⁴ Analysis using 2008 data, which were available, shows that correlation between adult per capita number of cigarettes smoked per day and Ln(GDP) was 0.24 in men and 0.53 in women (Figure 5). The absence of a linear association with income in men could be due to effective tobacco control in high-income

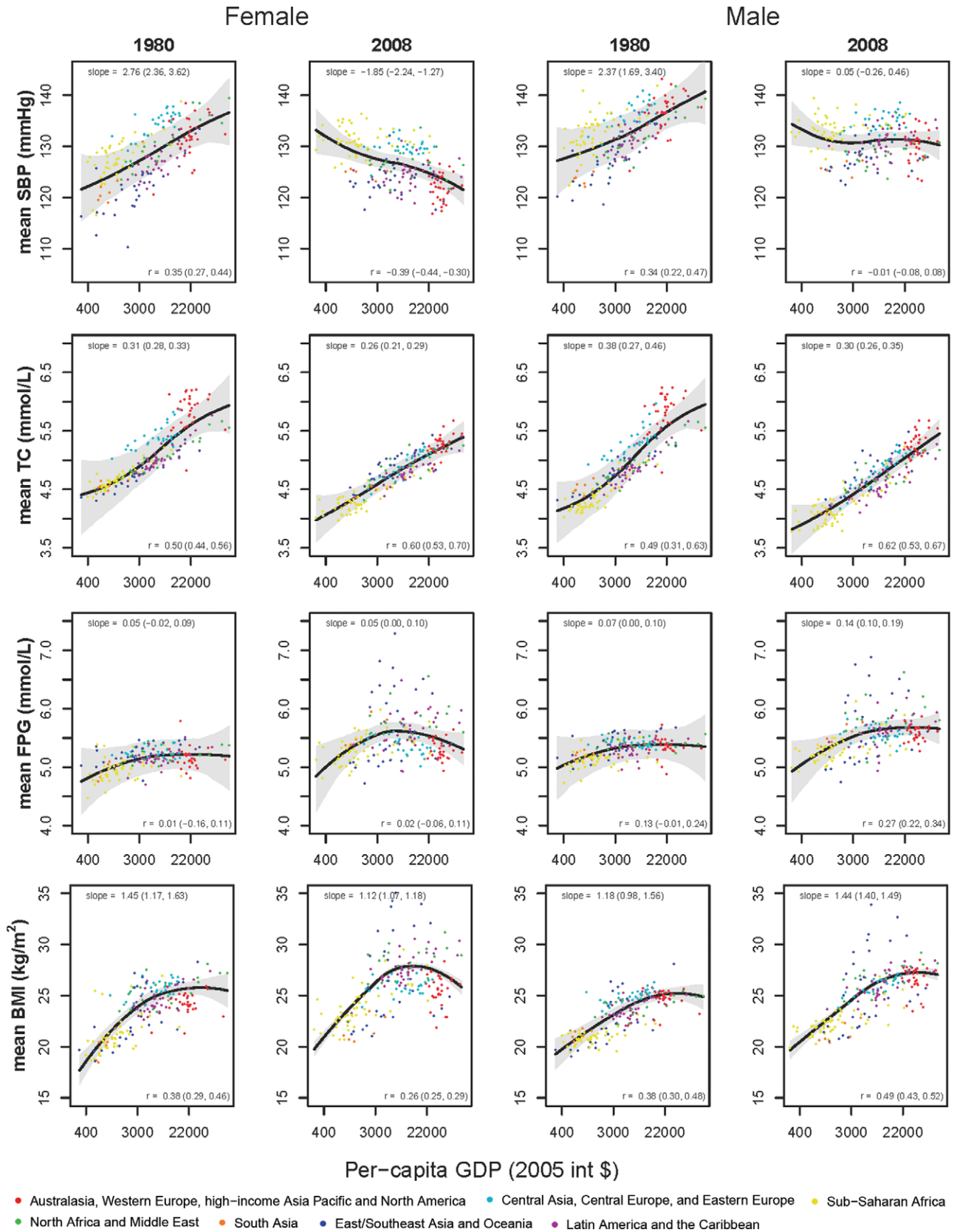


Figure 1. Mean age-standardized levels of metabolic risk factors in relation to per capita gross domestic product (GDP). GDP is in international dollars, which accounts for differences in purchasing power across countries, and is adjusted for inflation. The thick line shows the mean association and the gray area the 95% uncertainty interval of this relationship, calculated by using a nonparametric (Loess) regression as described in Methods and online-only Data Supplement Material. Individual data points show country means. See online-only Data Supplement Table for country data. BMI indicates body mass index; FPG, fasting plasma glucose; SBP, systolic blood pressure; and TC, serum total cholesterol.

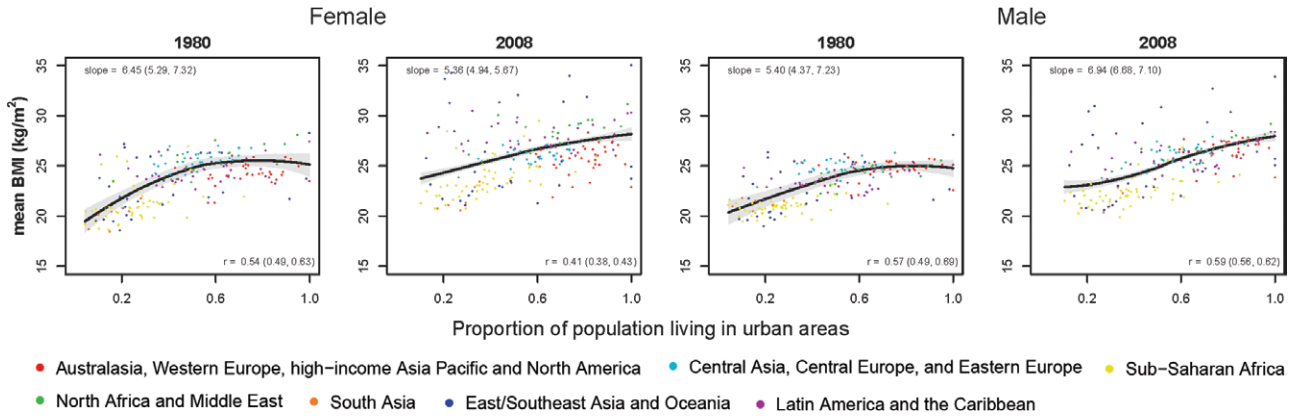


Figure 2. Mean age-standardized BMI in relation to the proportion of a country’s population that live in urban areas. Associations of other risk factors with urbanization are available from the authors by request. See online-only Data Supplement Table for country data. BMI indicates body mass index.

countries and high smoking prevalence in middle-income countries in Eastern Europe and East and Southeast Asia.

The strengths and innovations of this study include the analysis of associations with multiple macroeconomic variables in both 1980 and 2008; the use of a Bayesian hierarchical model for estimating risk factor levels that incorporated their important features such as nonlinear trends and age associations; and systematic analysis of uncertainty. The main limitation of our study is that, despite extensive data seeking, many country-years still lacked data, especially in the 1980s and for FPG and TC. As reported elsewhere, our model performed well in external predictive validity tests, ie, in estimating risk factor levels in countries and years that had data, but whose data were held back from the analysis to test the model’s predictions.^{10–13} Furthermore, in the current analysis, this shortage of data is reflected in larger uncertainty intervals in 1980 in comparison with 2008, and in larger uncertainty for the associations of FPG and TC in comparison with BMI. Our results were similar and our conclusions were unchanged in a sensitivity analysis using those countries with at least 1 data point over time.

There are several potential reasons for the changing associations of metabolic risk factors with affluence and Western diet. The VA Cooperative Studies and subsequent randomized trials demonstrated the benefits of lowering blood pressure at prehypertension levels and led to lower clinical thresholds for treatment with antihypertensives. This may have differentially advantaged high-income countries.¹⁷ Lower salt intake and higher intake of fresh fruits and vegetables may also be responsible for lower blood pressure in some high-income countries.^{17,18} There is further evidence from within-country studies that the decline in blood pressure has been even larger in individuals with higher BMI,^{19,20} which is consistent with the decoupling of these 2 causally-related factors at the population level.

The large rise in BMI in middle-income and lower-middle-income countries may be occurring because food cost has become (at least until a recent rise in food prices) an increasingly smaller share of household expenditure in these countries. The fact that the association of BMI with Western diet has weakened indicates that the rise in BMI in developing

countries may be as much due to increased caloric intake from traditional sources as from a shift to a Western diet. In addition, the persistent positive association of BMI with urbanization, especially for men, is consistent with a role of physical inactivity in urban populations and in urbanizing countries. The differences in associations of BMI with macroeconomic variables between men and women is consistent with the faster rise in female BMI in low- and middle-income countries in comparison with male BMI.^{13,21} The continued positive association between serum TC and national income may be due to the relatively high cost of animal products in low- and even middle-income countries. Nonetheless, TC declined in Western countries,¹² possibly because of changes in diet and the wider use of statins.²²

The changes in metabolic risk factors, especially in relation to national income, may help explain some of the trends in CVD mortality. Age-standardized cardiovascular disease mortality in high-income countries has declined substantially over the past few decades.^{23,24} Faster emergency response times; the use of medicines such as antiplatelet agents, angiotensin-converting-enzyme inhibitor, β -blockers, and statins after heart attack or stroke; and medical advances such as angioplasty, defibrillation, and thrombolysis have improved the survival of people with a cardiovascular event.²⁵ However, the contribution of postevent treatment to lower CVD mortality is estimated as <50%.²⁶ Rather, the mortality decline is largely a result of lower disease incidence, itself due to preventive interventions, especially population-level improvements in blood pressure and cholesterol and reduction in smoking²⁶ that have occurred despite rising BMI levels. There are fewer data on CVD trends in low- and middle-income countries. The available data nonetheless indicate that relatively soon after the decline in infectious diseases, CVD mortality also declined even in low- and middle-income countries^{27,28}; where this decline has been documented, it has accompanied a decline in blood pressure.²⁹

Given this evidence, the dynamic global epidemiology of metabolic risk factors has important implications for CVD prevention worldwide. First, a key focus of global CVD prevention should be to reverse the shifting burden of SBP to low-income countries seen in Figure 1. Lowering salt intake

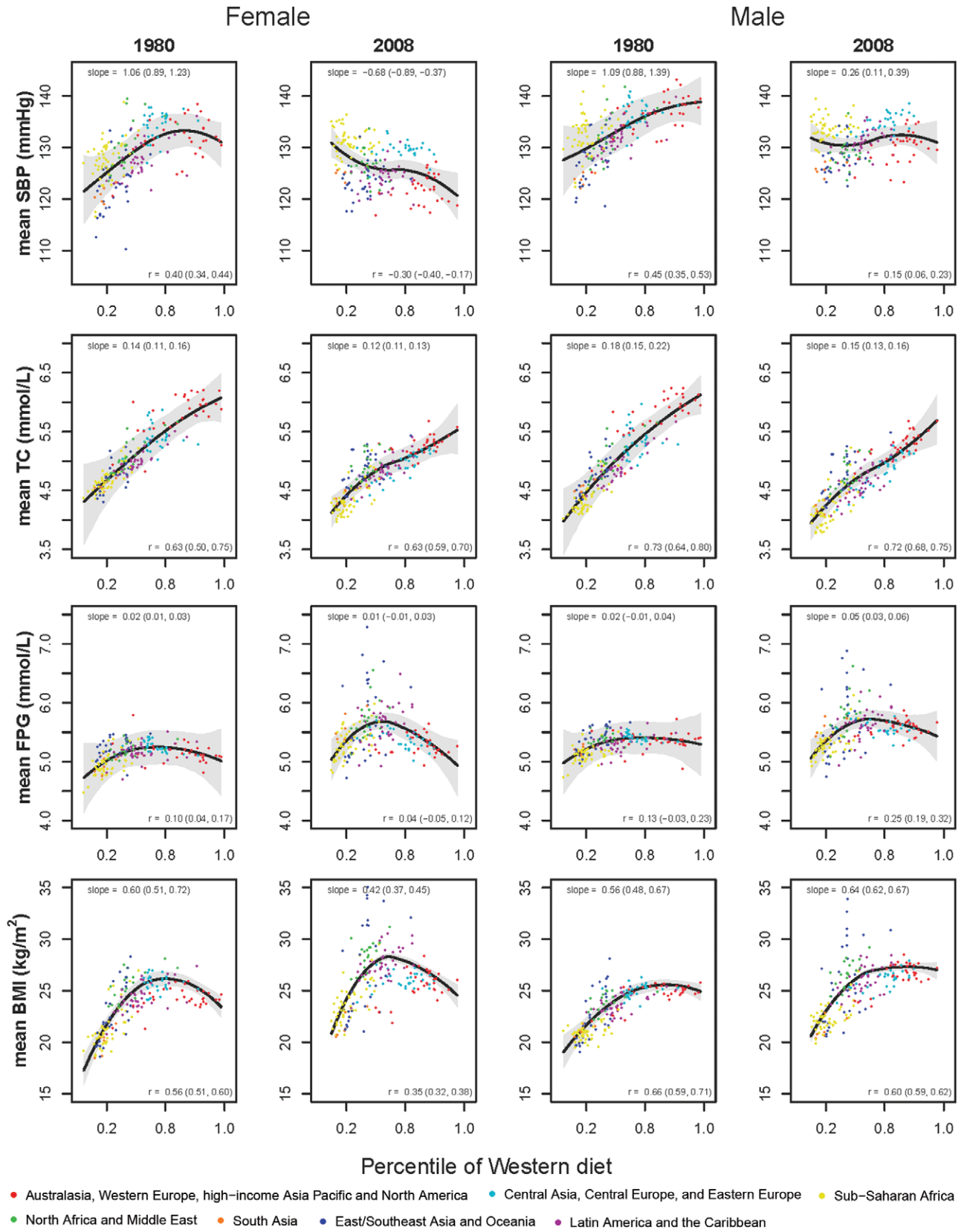


Figure 3. Mean age-standardized levels of metabolic risk factors in relation to Western diet (WD). See Methods for how percentiles were calculated. See online-only Data Supplement Table for country data. BMI indicates body mass index; FPG, fasting plasma glucose; SBP, systolic blood pressure; and TC, serum total cholesterol.

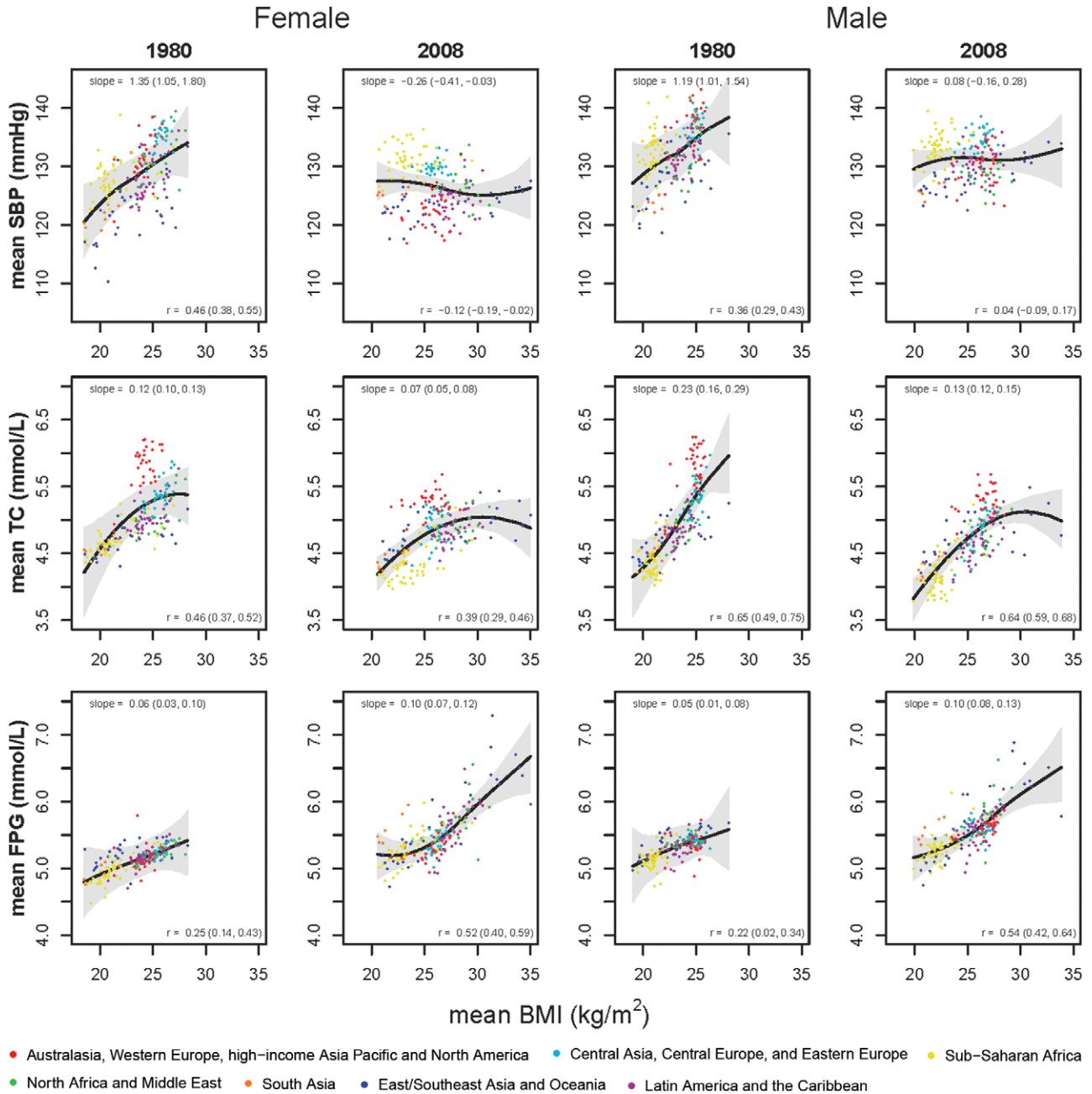


Figure 4. Mean age-standardized SBP, TC, and FPG in relation to mean age-standardized BMI. See online-only Data Supplement Table for country data. BMI indicates body mass index; FPG, fasting plasma glucose; SBP, systolic blood pressure; and TC, serum total cholesterol.

through regulation and well-designed health education, improving access to fresh fruits and vegetables, and strengthening primary care to better detect and manage high blood pressure can help lower blood pressure worldwide, replicating the decline in high-income nations.^{24,30} Second, low- and middle-income countries could implement food policies that encourage the use of polyunsaturated fats instead of saturated fats,²² avoiding the high cholesterol levels experienced in Western countries and the rise in Japan and China. Third, high- and middle-income countries can increase the coverage of statins for lowering serum cholesterol.³¹ The cost of medicines and screening and follow-up tests may be too high for low-income countries. The availability of generic

drugs and lower-cost tests will help make statins affordable even in low-income settings, but their implementation requires investment in an equitable and high-quality primary care system. Currently, high- and middle-income countries spend significant healthcare resources on treatment of CVD, diabetes mellitus, and their complications.^{32–35} Redirecting some of these resources to primary prevention of high blood pressure and cholesterol may lead to a net cost saving.^{36,37} In low-income countries, additional strengthening and investment in primary care³⁸ and regulatory infrastructures, eg, establishing and enforcing limits on salt in more commonly used packaged foods and staples such as flour and bread, may be needed.

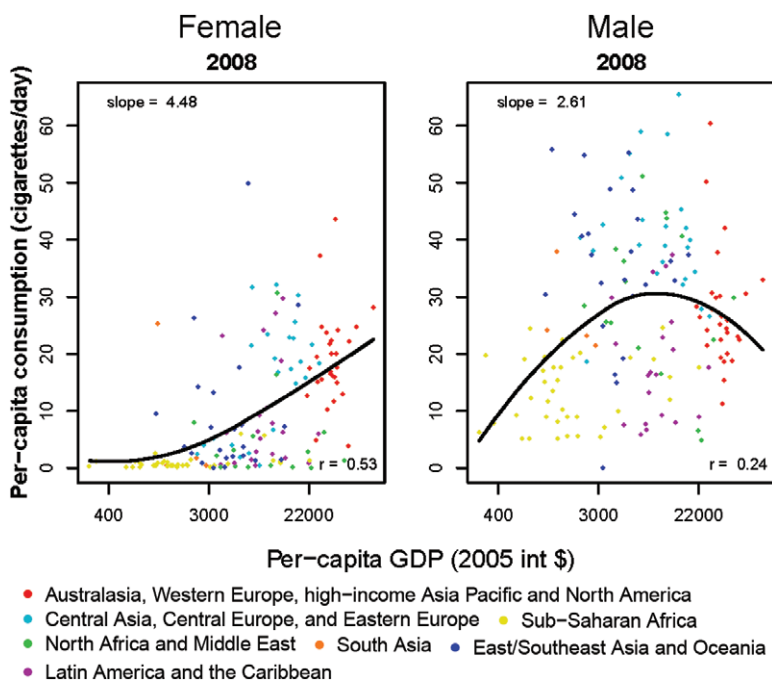


Figure 5. Age-standardized per-capita cigarette consumption in relation to per capita gross domestic product (GDP) in 2008. Smoking data are from the World Health Organization Global Status Report on Noncommunicable Diseases 2010.¹⁴

In contrast to blood pressure, which has become increasingly disassociated from BMI at the population level, the persistent association between BMI and FPG and the rising BMI levels mean that, unless effective interventions for weight control or improvements in diet and other lifestyle factors are designed and implemented to prevent diabetes mellitus, health systems worldwide will face an increasing burden of hyperglycemia and diabetes mellitus and will have to develop mechanisms for better detection and management of diabetes mellitus. A costly global epidemic of hyperglycemia and diabetes mellitus, together with high blood pressure in low-income countries, may be the most salient feature of the global cardiovascular risk transition in the coming decades.

Appendix

Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group

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Drs Danaei and Ezzati developed the study concept, and Dr Paciorek developed the statistical approach for the analysis of associations. Dr Ezzati wrote the first draft of the article, and Dr Paciorek wrote the first draft of the Statistical Methods. Drs Singh and Finucane and J. K. Lin analyzed data. Other members of the Writing and Global Analysis Group contributed to study design, analysis, and writing of article. The members of the Country Data Group analyzed health examination survey and epidemiological study data. Drs Danaei and Singh had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr Ezzati oversaw the research and is the study guarantor.

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Dr Paciorek holds stock in Pfizer. M. Cowan, Dr Stevens, and L. Riley are staff members of the World Health Organization. They alone are responsible for the views expressed in this publication, and they do not necessarily represent the decisions, policy, or views of the World Health Organization. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

The diseases of affluence paradigm suggests that noncommunicable diseases are the modern scourges of the world and are hence more common in developed countries. But until now, little has been known about the associations of these risk factors with the macroeconomic characteristics of countries, and how the associations have changed over time. We examined this paradigm by using data from a global analysis of body mass index, systolic blood pressure (SBP), serum total cholesterol, and fasting plasma glucose. We found that in 1980, body mass index, SBP, and serum total cholesterol were in fact higher in wealthier countries. By 2008, there was either no relationship between SBP and national income (for men) or SBP was lower in wealthier countries (for women). This may be partly due to improved diagnosis and treatment in wealthier countries and perhaps subtle improvements in diet and lifestyle, for example, lower salt intake and year-round availability of fresh fruits and vegetables. The relationship between body mass index and national income in more recent years resembled an inverted U, in part, because overweight and obesity increased substantially in many middle-income countries. Unlike SBP and fasting plasma glucose, serum total cholesterol was associated with both income and Western diet throughout this period. We also found that fasting plasma glucose was positively correlated with body mass index but had little association with other national characteristics. If the observed trends continue, developed countries will continue to face an obese population with a high prevalence of diabetes mellitus and hypercholesterolemia, whereas developing countries will be confronted by a combination of obesity, hypertension, and diabetes mellitus. The diseases of affluence paradigm seems inadequate for explaining these nuances in the global epidemiology of cardiovascular risk factors and should be replaced with a more refined framework that better informs both policy and intervention.

Supplemental Material

Supplementary Text

The association of metabolic risk factors with income, urbanization, and western diet: statistical methods and considerations

All of our graphical and statistical analyses are based on a Bayesian multiple imputation approach. Specifically, the Bayesian statistical model for estimating risk factor levels borrowed information based on a hierarchy of countries within subregions and regions, across time and age groups, and using a small set of country-specific covariates. These covariates included the country-level characteristics considered in this paper's analyses, namely metrics of national income, urbanization, and western diet. This may appear to introduce circularity and potentially overestimate the association. Below, we provide the statistical justification for this approach and specify how we took into consideration the fact that the risk factor data were estimated using a Bayesian statistical model with covariates. In our explanation below, we conceptually divide our risk factor estimates into those that are essentially "known" based on good data for a given country-year and those that are imputed in the absence of such data; in reality there is a continuum of uncertainty.

First, we note that the covariates in the Bayesian model were chosen with the goal of best predicting country risk factor levels. The predicted risk factor levels used here are based on the posterior predictive distribution from the Bayesian hierarchical model, which conditions on all available information, both risk factor data and explanatory variables. As such, the posterior draws of country risk factor levels are a Bayesian multiple imputation. It is well known in the statistical literature that a correct multiple imputation procedure should condition on all available

information¹. Further, we note that the imputed country risk factor levels are based on the estimated relationship with covariates and the variability of country risk factor levels around the relationship, hence incorporating the variation around the estimated relationship. In other words, we draw from the posterior predictive distribution, which is the model's estimate of the distribution of the country risk factor levels, and therefore includes all of the appropriate sources of variation.

We can motivate the approach further by considering an example of why it would be incorrect to exclude the country-level characteristics of interest from the Bayesian hierarchical model.

Suppose that we exclude a country covariate that is correlated with the risk factor of interest, and that none of the other covariates in the model are correlated with that characteristic. The result will be that our imputed values for missing country risk factor levels will not be correlated with the characteristic. When we produce figures such as Figures 1-3, those countries with data-driven, essentially-known risk factor levels would show a correlation with the characteristic but the imputed values would not, so the overall association would appear weaker than if we knew the true country risk factor levels. Now suppose that the characteristic of interest is not correlated with the risk factor of interest but that we include it in the Bayesian model. In the Bayesian model, we will estimate a near-zero coefficient based on the available country data, and the imputed values will be uncorrelated with the characteristic. Then in the subsequent analyses, neither the data-driven risk factor levels nor the imputed values will be correlated with the characteristic, and there will not be a circularity problem.

Given the uncertainty in the country-specific risk factor levels, including in relation to the covariates, our assessment of associations takes a missing data perspective and is based on a Bayesian multiple imputation approach^{1,2}. Specifically, we present the Loess fits, and the correlation and regression coefficients, in Figures 1-4 based on 500 posterior draws from the Bayesian model. Uncertainty intervals were calculated as the 2.5th to 97.5th percentiles of these 500 draws.

Supplementary Table

Table S1: Country data used in Figures 1-4 of the main paper. Data are from a systematic analysis of population-based data, by sex, for 199 countries and territories, as described in detail in previous publications³⁻⁶ and in the main paper.

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