Global Variation in the Prevalence of Elevated Cholesterol in Outpatients With Established Vascular Disease or 3 Cardiovascular Risk Factors According to National Indices of Economic Development and Health System Performance

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Background—Elevated serum cholesterol accounts for a considerable proportion of cardiovascular disease worldwide. An understanding of the relationship between country-level economic and health system factors and elevated cholesterol may provide insight for prioritization of cardiovascular prevention programs.

Methods and Results—Using hierarchical models, we examined the relationship between elevated total cholesterol (>200 mg/dL) in 53,570 outpatients from 36 countries, and tertiles of several country-level indices: (1) gross national income, (2) total expenditure on health as percentage of gross domestic product, (3) government expenditure on health as percentage of total expenditure on health, (4) out-of-pocket expenditures as percentage of private expenditure on health, and the World Health Organization indices of (5) Health System Achievement and (6) Performance/Efficiency. Overall, 38% of outpatients had total cholesterol >200 mg/dL (>5.18 mmol/L), and 9.3% of the total variability in elevated cholesterol was at the country level; this proportion was higher for patients with (12.1%) versus without (7.4%) history of hyperlipidemia. Among patients with history of hyperlipidemia, countries in the highest tertile of gross national income or World Health Organization Health System Achievement had lower odds of elevated cholesterol than lower tertiles (P<0.001, for both). Countries in the highest tertile of out-of-pocket health expenditures had higher odds of elevated cholesterol than those in the lowest tertile (P<0.001). No significant associations were found for patients without history of hyperlipidemia.

Conclusions—Global variations in the prevalence of elevated cholesterol among patients with history of hyperlipidemia are associated with country-level economic development and health system indices. These results support the need for strengthening efforts toward effective cardiovascular disease prevention and control and may provide insight for health policy setting at the national level. (Circulation. 2012;125:1858-1869.)

Key Words: cardiovascular disease ■ hypercholesterolemia ■ global trends ■ health system performance ■ national health expenditures

The World Health Organization (WHO) proposed the 2008 to 2013 Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Diseases to establish and strengthen initiatives for the surveillance, prevention, and management of chronic diseases around the world.1 The core objective of this effort was to “raise the priority accorded to chronic diseases while encouraging governments and health agencies to integrate preventive and...
treatment efforts into healthcare policies.” According to global estimates from WHO, nearly 1 of every 3 deaths in 2004 was attributed to cardiovascular disease with nearly 80% of these deaths occurring in low- and middle-income countries. In an effort to guide the National Heart, Lung, and Blood Institute in setting priorities for investment in global cardiovascular health, the Institute of Medicine recently outlined key barriers to and evidence-based solutions for the control of cardiovascular disease across the world. An improved understanding of the relationship between levels of national economic development, healthcare investment, health system characteristics, and key modifiable cardiovascular risk factors may provide insights for the prioritization of cardiovascular disease prevention programs.

Clinical Perspective on p 1869

Elevated serum cholesterol is a modifiable risk factor that is associated with an estimated 4.4 million deaths each year and accounts for a considerable proportion of ischemic stroke and heart disease worldwide. Therapeutic lifestyle changes (reduced dietary intake of saturated fats and cholesterol, weight control, and increased physical activity) form the core of all cholesterol-lowering initiatives. Supplemental therapy with lipid-lowering medications has been shown to safely reduce the long-term incidence of major cardiovascular events in secondary prevention and, more recently, high-risk primary prevention trials, and is universally recommended in patients with established or at high predicted risk of cardiovascular disease. Numerous reports have documented the underrecognition and undertreatment of elevated cholesterol levels in developed and developing countries. Whereas most studies have examined the patient- and physician-level factors responsible for these variations, associations with country-level factors have not been systematically explored.

A primary objective of the international Reduction of Atherothrombosis for Continued Health (REACH) Registry was to describe the global distribution and management of risk factors for atherothrombotic events across the spectrum of patients with established atherosclerotic vascular disease. As such, REACH provides a unique source for gaining insight into country-level factors that might influence effective cardiovascular risk factor control. We used data from REACH to examine the relationship between established national indices of overall health system expenditure and performance and country-specific prevalence rates of elevated total cholesterol at baseline. Our analyses allowed the effect of country-level factors to differ for patients with versus without a history of hyperlipidemia, because factors influencing the prevalence of elevated cholesterol may differ between these 2 populations.

Methods

Study Population

The rationale, design, and baseline characteristics of the REACH Registry have been previously published. In brief, REACH is an international, prospective registry of 68,236 outpatients, aged 45 years or older, at risk of atherothrombosis due to established coronary artery disease (CAD), cerebrovascular disease (CVD), or peripheral arterial disease (PAD), or ≥3 cardiovascular risk factors. Patients from 39 countries were enrolled between December 2003 to 2004. Presence of established CAD, CVD, and PAD was ascertained by physicians using well-defined criteria (see online-only Data Supplement Methods for definitions). Patients without established CAD, CVD, or PAD could be enrolled given the presence of 3 or more of the following risk factors: treated diabetes mellitus, diabetic nephropathy, ankle-brachial index <0.9, asymptomatic carotid stenosis ≥70%, carotid intima media thickness that exceeds twice the mean at neighboring sites, systolic blood pressure ≥150 mm Hg despite therapy for at least 3 months, hypercholesterolemia treated with medication, current smoking of at least 15 cigarettes per day, men aged 65 years or older, or women aged 70 years or older. Patients already in a clinical trial, hospitalized patients, or those who might have difficulty returning for a follow-up visit were excluded from enrolment in REACH.

With the goal of yielding a representative sample of patients at the national level, the selection of sites was based on the best available data regarding the burden of atherothrombosis in at-risk populations within each country, and healthcare delivery settings most typically used by those patients. Site characteristics considered in the site selection process included overall patient profiles (eg, CAD, CVD, or PAD, or primary prevention), physician profiles (general practitioners, internists, cardiologists, neurologists, endocrinologists, vascular surgeons), healthcare environments (rural, suburban, urban), and medical practices (office-based, hospital-based). Data for patients enrolled in the registry were collected centrally via use of a standardized international case report form, completed at the study visit. The REACH protocol was submitted to the institutional review board in each country according to local requirements, and signed informed consent was obtained for all patients.

The analysis cohort was derived from the patients enrolled in REACH. Of the 68,236 patients from 39 countries enrolled in REACH, 1576 patients from 3 countries (Taiwan, Hong Kong, and Panama), for which national health system and economic indices were unavailable, were excluded from the current analysis. Of the remaining 66,660 patients, 13,020 (20%) did not have total cholesterol values (16% and 32% of patients with and without a history of hyperlipidemia, respectively), and an additional 70 patients were missing documentation regarding history of hypercholesterolemia. The remaining 53,570 patients (80.4%) from 36 countries formed the analytic cohort for this study.

Elevated Total Blood Cholesterol and History of Hyperlipidemia

Total blood cholesterol levels available at the time of enrollment (measurements must have been taken within the preceding 12 months) were recorded. For this analysis, elevated cholesterol was defined as total cholesterol >200 mg/dL (>5.18 mmol/L). History of hyperlipidemia was defined as a documented past diagnosis of hyperlipidemia or reported use of lipid-lowering therapy at study enrollment.

Country-Level Indices

Information on national health expenditures for the year 2001 was obtained from the 2004 World health report for the following indices: total expenditure on health as percentage of gross domestic product (GDP), general government expenditure on health as percentage of total expenditure on health, and out-of-pocket expenditure as percentage of private expenditure on health. For country-level income, we used the 2003 gross national income (GNI) per capita (Atlas method) as developed by the World Bank. For country-level data pertaining to health system performance, we used 2 indices developed by WHO: overall Health System Achievement (HAI), and Health System Performance/Efficiency (HPEI). HAI is a weighted linear aggregate of measures of health level, health inequality, responsiveness, responsiveness inequality, and fairness of financial contribution that ranges from 0 to 100, with 100 being the highest possible level of achievement. HPEI is a ratio of the observed level of population health (healthy life expectancy) to the maximum that could be achieved with the observed resources (function of average years of schooling and per capita health expenditure) and ranges.
### Table. Patient Characteristics Among Those With (First Entry) Versus Without (Second Entry) History of Hyperlipidemia,* by Region/Country

<table>
<thead>
<tr>
<th>Region Country</th>
<th>Total</th>
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<th>Latin America</th>
<th>Eastern Europe</th>
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<tr>
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**Age, y‡**

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<td>9.7</td>
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**Men, %‡**

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<tr>
<td>Latin America</td>
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**College or technical education, %‡**

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<tr>
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**History of hypertension, %‡**

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<td>Latin America</td>
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**BMI ≥30 kg/m², %‡**

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</tr>
<tr>
<td>Latin America</td>
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<td>34.9</td>
</tr>
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<td>Eastern Europe</td>
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<td>17.4</td>
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**Current smoking, %‡**

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<th>17.1</th>
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</tr>
<tr>
<td>Latin America</td>
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<td>16.3</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>9.7</td>
<td>12.3</td>
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**Documented vascular disease at baseline, %‡**

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<th>Region Country</th>
<th>78.9</th>
<th>86.0</th>
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<td>71.9</td>
<td>80.1</td>
</tr>
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<td>Latin America</td>
<td>81.2</td>
<td>89.1</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>86.3</td>
<td>97.9</td>
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</table>

**Cholesterol-related characteristics**

**Total cholesterol at baseline, mg/dL†‡**

<table>
<thead>
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<th>Region Country</th>
<th>Mean</th>
<th>SD</th>
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</thead>
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<td>North America</td>
<td>191.7</td>
<td>48.0</td>
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<tr>
<td>Latin America</td>
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<tr>
<td>Eastern Europe</td>
<td>174.1</td>
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**Among patients with history of hyperlipidemia***

**Past diagnosis of hyperlipidemia, %**

<table>
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<td>97.3</td>
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<tr>
<td>Latin America</td>
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<td>39.9</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>89.7</td>
<td>35.3</td>
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**On lipid-lowering therapy at baseline, %**

<table>
<thead>
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<th>41.1</th>
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<tbody>
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<td>39.1</td>
</tr>
<tr>
<td>Latin America</td>
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</tr>
<tr>
<td>Eastern Europe</td>
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**Statins**

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<tbody>
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<td>Latin America</td>
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<tr>
<td>Eastern Europe</td>
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**Others**

<table>
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<td>26.9</td>
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<td>Latin America</td>
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<td>35.5</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>8.4</td>
<td>27.2</td>
</tr>
</tbody>
</table>

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*History of hyperlipidemia was defined as a documented past diagnosis of hyperlipidemia or use of lipid-lowering medications before study entry at baseline.

†To convert mg/dL to mmol/L, please divide by 39.

‡Data provided in the second row relate to patients without history of hyperlipidemia.

UAE indicates United Arab Emirates; UK, United Kingdom; USA, United States of America; CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease; TC, total cholesterol.
<table>
<thead>
<tr>
<th>Region</th>
<th>Country</th>
<th>Austria</th>
<th>Belgium</th>
<th>Denmark</th>
<th>Finland</th>
<th>France</th>
<th>Germany</th>
<th>Greece</th>
<th>Netherlands</th>
<th>Portugal</th>
<th>Spain</th>
<th>Switzerland</th>
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<td>n=2842</td>
<td>n=3454</td>
<td>n=485</td>
<td>n=185</td>
<td>n=169</td>
<td>n=1484</td>
<td>n=46</td>
<td>n=364</td>
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<tr>
<td>No History of Hyperlipidemia*</td>
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<td>n=94</td>
<td>n=79</td>
<td>n=37</td>
<td>n=522</td>
<td>n=890</td>
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<td>n=36</td>
<td>n=27</td>
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<td>n=103</td>
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<tr>
<td>Age, y‡</td>
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<tr>
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<tr>
<td>Men, %‡</td>
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<tr>
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Among patients with history of hyperlipidemia†

| Past diagnosis of hyperlipidemia, % | 98          | 90.7       | 96.4       | 92          | 96.8        | 73.8    | 89.4        | 91.9  | 95        |
| On lipid-lowering therapy at baseline, % | 98          | 100        | 98.2       | 100         | 99.8        | 100    | 100         | 100   | 100       |
| Statins               | 96.7        | 84.9       | 96.4       | 99          | 98          | 85.7   | 92.4        | 87.2  | 94.7      |
| Others                | 8.9         | 20.9       | 6.6        | 4           | 3.5         | 19.5   | 16.2        | 19    | 9.1       |
from 0 to 1 (fully efficient). Estimates of average country-level total fat consumption (grams per person per day) were obtained from the Food and Agricultural Organization for the year 2003 and were available for all countries with the exception of Singapore.19

Statistical Analysis
Baseline characteristics of participants in REACH according to history of hyperlipidemia, both overall and by country, are summarized as means and standard deviations for continuous variables, and percentages for categorical variables. To estimate the proportion of total variability in elevated cholesterol (>200 mg/dL) that is at the country level, we obtained the intraclass correlation coefficient from a hierarchical logistic regression model in which the individual patient is considered level 1 and country is considered level 2.20 This analysis was performed for the overall study cohort, and separately for patients with and without history of hyperlipidemia, as well.

Cubic spline modeling were used to estimate smooth curves describing the associations between country-level health system and economic indices (continuous variables) and country-specific prevalence of elevated cholesterol. Hierarchical generalized mixed-effects (logistic) regression models, with individual patient at the first level and country (treated as a random effect) at the second level, were used to estimate the association between the country-level economic/health system indices and odds of elevated cholesterol. We explored the use of site as a third possible level, but the level, were used to estimate the association between the country-level health system indices and odds of elevated cholesterol. For these analyses, the national indices of health-related expenditures and performance were categorized into low, medium, and high levels, approximately according to tertiles (see online-only Data Supplement Figure 1A through 1F). For GNI per capita, previously established cut points reflecting variation in GNI across countries were used.21 These analyses were performed on the overall analytic population, with the inclusion of interaction terms between the country-level indices and the indicator for history of hyperlipidemia. Two models were fit for each of the country-level indices, with elevated total cholesterol (>200 mg/dL) as the outcome measure. The first model adjusted for patient-level factors, assessed at the time of enrollment, including age, sex, educational level, smoking status, obesity (BMI >30 kg/m2), established CAD, CVD, or PAD, history of congestive heart failure, carotid surgery, atrial fibrillation/flutter, aortic valve stenosis, diabetes mellitus, and treated hypertension, and current use of antiplatelet and antihypertensive medications; covariates significant at P<0.20 were retained in the model. In the second model, we further adjusted for average country-level fat consumption (as continuous variable)19 to account for the potential influence of regional variation in dietary patterns on cholesterol levels. An interaction between fat consumption and history of hyperlipidemia was also included, and eliminated if nonsignificant (P>0.05). From each of the final models, the relative impact of different levels of each health system/economic index on elevated cholesterol was estimated separately for history versus no history of hyperlipidemia subgroups, and associated odds ratios and corresponding 95% confidence limits were generated. All analyses were performed by use of SAS version 9.2 statistical software (SAS Institute Inc, Cary, NC). P values of ≤0.05 were considered statistically significant.

Results
In the overall analytic cohort, 20,469 (38%) patients had baseline total cholesterol >200 mg/dL. The prevalence of elevated cholesterol varied widely across countries and ranged from 73% in Bulgaria to 24% in Finland. Among 42,955 patients with a history of hyperlipidemia, 37% had elevated cholesterol reported at baseline; among the remaining 10,615 patients without history of hyperlipidemia, 43% had elevated cholesterol (Table). Overall, 9.3% of the total variability in elevated cholesterol was at the country level. This proportion was higher for patients with (12.1%) versus without (7.4%) history of hyperlipidemia.

Figure 1A through 1F show scatter plots of the country-level economic/health system indices versus percentage of patients with elevated cholesterol, stratified by history of hyperlipidemia, respectively. For patients with history of hyperlipidemia, country-specific elevated cholesterol percentages tended to increase with decreasing total expenditure on health as percentage of GDP spent on health, GNI, and WHO HAI and PEI indices, and increasing levels of out-of-pocket expenditures. For patients without history of hyperlipidemia, these graphs suggest somewhat different associations, with trends toward high prevalence of elevated cholesterol with both increasing percentage of GDP spent on health and increasing percentage of governmental expenditure as a function of total expenditure on health.

A high prevalence of elevated cholesterol was observed in patients from eastern European countries (Bulgaria, Lithuania, Romania, Ukraine, Hungary, and Russia); these countries also ranked relatively low on health system/economic indices. A relatively low prevalence of elevated cholesterol, similar to that for the United States, was seen for countries (eg, Finland, United Kingdom, Israel, Australia, and Canada) with considerably lower total expenditure on health as percentage of GDP and comparable or slightly more favorable WHO health system indices.

Figure 2A through 2F presents odds ratios and associated 95% confidence intervals for the relative effect of different levels of the country-level indices on the risk of elevated cholesterol, for patients with (top panel) and without (bottom panel) history of hyperlipidemia at baseline. Within each panel, results from 2 models (adjusted for patient-level factors only [blue] and adjusted for both patient-level factors and country-level fat consumption [red]) are presented. Further details relating to the model results, including probability values for the estimated effects of each of the country-level indices are presented in online-only Data Supplement Table I. For the history of hyperlipidemia subgroup, countries in the highest tertile of GNI had significantly lower odds of elevated cholesterol than countries in the lowest tertile (P<0.001). Similar results were seen for the WHO HAI. Countries in the lowest tertile of WHO HPEI had significantly higher odds of elevated cholesterol than those in the intermediate or highest tertile (P<0.001 for both). Countries in the highest tertile of out-of-pocket health expenditures had significantly higher odds of elevated cholesterol than countries in the lowest tertile (P<0.001). No statistically significant associations between country-level factors and odds of elevated cholesterol were found for patients without history of hyperlipidemia.

Higher fat consumption at the country level (average grams per person per day) was associated with a significant increase in the odds of elevated cholesterol in the model examining the association with GNI. For none of the other models was the estimated effect of fat consumption statistically significant, and no significant interactions between fat consumption and history of hyperlipidemia was found in any of the models. As shown in Figure 2A, adjustment for country-level fat consumption in addition to patient-level factors increased the magnitude of association between GNI and the odds of...
elevated cholesterol. Estimated coefficients for all covariates for both GNI models (with and without fat consumption) are included in the online-only Data Supplement Table II. Estimated coefficients describing the association between patient-level covariates and the odds of elevated cholesterol varied little across models for different country-level indices.

**Discussion**

The exponential rise in noncommunicable chronic diseases over the past decade has placed a tremendous burden on the health and economic development of countries worldwide, with unprecedented demands for an effective response from governments and other stakeholders in global health. An understanding of how country-level economic and healthcare indices are associated with disease-specific, modifiable risk factors may be of potential value for strategic planning and evaluation of related public health policies and programs. In this study, we examined data from a large, multinational registry of individuals with or at high risk of atherothrombotic events to provide insight into the relationship between indices of national health systems and economic development, and elevated total cholesterol, a key risk factor for cardiovascular disease. The significant associations observed at the country level between these national indices and prevalence of elevated cholesterol underscore the importance for countries to maintain, improve, or establish effective surveillance of chronic disease risk factors such as cholesterol levels, while also prioritizing population-based efforts aimed at the prevention and management of chronic diseases.

**Comparison With Previous Studies**

Numerous reports have consistently demonstrated a substantial gap between evidence-based guidelines and actual clinical practice across geographic regions, among different physician specialties, and independent of the arterial bed affected. Data from the multinational WHO MONICA Project demonstrated wide variations in the prevalence and treatment of hypercholesterolemia between 1989 and 1997 across 32 populations from 19 countries. Subsequently, using data from European national surveys conducted during 1995 and 2007,
Kotseva et al. documented dramatic improvements in cholesterol control over time; however, less than half of the patients on lipid-lowering therapy reached the recommended target level. In a recent study of ~80,000 adults from 8 high- and middle-income countries, the proportion of “undiagnosed” individuals with elevated cholesterol (≥6.2 mmol/L or 240 mg/dL) varied 5-fold (16% in the United States to 78% in Thailand), whereas the rates of effective cholesterol control among patients on lipid-lowering medication ranged from 4% in Germany to 58% in Mexico. In our study, which includes patients from primary care and specialty practices, ~4 in 10 individuals had elevated cholesterol at baseline; this proportion differed significantly across countries, with country-level factors explaining an appreciable proportion of variability in elevated cholesterol in the overall cohort.

Recruitment of patients to the REACH Registry was designed to yield a representative sample of patients, based on the burden of atherothrombosis in at-risk populations within each country and healthcare delivery settings most typically used by those patients. A comparison of the prevalence rates of elevated total cholesterol observed in 9 countries included in both the REACH Registry and the EUROASPIRE II survey revealed a high correlation between the 2 studies (r=0.72; see online-only Data Supplement Figure II for details). To the extent that the patterns of risk factors observed for patients enrolled in REACH are representative of national patterns for these high-risk populations, findings from our study reveal the degree to which the prevalence of elevated cholesterol at the country level may be related to macroeconomic and healthcare system factors. Moreover, the association between elevated cholesterol and GNI for patients with a history of hypercholesterolemia is consistent with patterns revealed in a recent analysis of data from the multinational Prospective Urban and Rural Epidemiological (PURE) study, in which a 20-fold difference in the use of statins for secondary prevention between low- and high-income countries was found.

The significant associations found between prevalence rates of elevated cholesterol and total and out-of-pocket health expenditures, and WHO indices, as well, for patients...
with, but not without, a history of hyperlipidemia suggest differential influence of these country-level factors in these patient subsets. Although the exact reasons for these differences cannot be determined in this study, the sample of patients without history of hyperlipidemia in REACH is small (20% of the overall cohort) and likely comprises patients who were either never screened or who had been screened but were found not to be hyperlipidemic before enrollment in the registry. The potential inclusion of the latter category of patient may contribute to the lack of association between the prevalence of elevated cholesterol and country-level indices in this seemingly underdiagnosed subgroup. In contrast, elevated cholesterol in patients with history of hyperlipidemia may be due to prescription of suboptimal therapy (undertreatment) or medication nonadherence related to availability or affordability issues.

Global Challenges for Cholesterol Management

Optimal management of cardiovascular disease is complex and country-level variations in risk factor control may arise from variability in guidelines, and whether, and the extent to which, specific initiatives are effectively implemented, as well. Ferket et al.27 reviewed 27 professional guidelines for cardiovascular risk assessment from Western countries and documented marked differences in the definition of target populations, specific screening tests used, and thresholds for initiating pharmacological treatment.5,6,28 In our study, based on the National Cholesterol Education Program Adult Treatment Panel III guidelines for risk assessment,5 we considered total cholesterol ≥200 mg/dL to be elevated. This cut point is, for instance, higher than the thresholds used in guidelines from the European Society of Cardiology6 and WHO.28 Such variability in the threshold used to identify elevated cholesterol may explain some of the variation in the prevalence rates of elevated cholesterol across countries and, to the extent that it is correlated with the country-level factors used in this analysis, may underlie some of the associations found.

Wide variations in procurement prices across countries and public versus private health sectors have also been demon-
strated to impact use of recommended medications across regions.29–31 The association between the prevalence of elevated cholesterol and out-of-pocket expenditure seen for patients with history of hyperlipidemia in our study is noteworthy, because it may reflect an inability or unwillingness on the part of some patients in countries with higher out-of-pocket healthcare expenses to be consistently compliant with prescribed chronic lipid-lowering therapy. The recent availability of generic statin therapy should make out-of-pocket expense less of an impediment to use. Recent results from the United States-based Post-Myocardial Infarction Free Rx and Economic Evaluation (MI-FREEE) trial demonstrated that the elimination of copayments for medications prescribed after myocardial infarction significantly improved adherence rates and rates of major cardiovascular events, without increasing overall health costs, although, even with full coverage, adherence rates remained far from optimal, at 55% overall.32 Barriers to achieving adequate cholesterol control at the population level may also be linked to agricultural and economic policies that increase access to low-cost, unhealthy diets.33 In our study, adjustment for differences in country-level dietary fat consumption increased the estimated magnitude of association between elevated cholesterol and some country-level indices, suggesting a complex interplay between access to diets rich in highly saturated fats, national level of economic development, and cholesterol levels.

Limitations

Because this analysis was based on data from an observational registry, causal mechanisms underlying the associations described in this report cannot be determined. For example, although the prevalence of elevated cholesterol tended to increase with country-level out-of-pocket healthcare expenditures, explicit recommendations for national healthcare coverage should not be based on these data alone. Nonetheless, a contemporary study of US outpatients with established CAD found that patients’ lack of medical insurance is significantly associated with statin underuse.14

The summary WHO indices of health system achievement and performance examined in this analysis have drawn criticism relating to the data on and methods by which they were derived.34,35 In addition, these indices were derived at an earlier time period than REACH Registry enrolment and may have limited relevance in more contemporary settings. Nevertheless, the observed relationship of these indices to objective disease-specific risk factors in high-risk patients suggests their potential validity for assessing health system performance with respect to effective cardiovascular disease prevention and management.

By design, the REACH Registry recruited participants with access to health care; as a result, the prevalence of elevated cholesterol in this study may underestimate the overall prevalence in the countries included in this study, and the associations found may not be generalizable to individuals without access to medical care. However, these patterns of variation in statin use according to country-level income are similar to those found in the PURE study,26 which used a community-based sampling scheme.

Total cholesterol measurements were unavailable for proportionately more patients without a history of hyperlipidemia than patients with such history; this was the case for almost all participating countries; and no evidence of systematic differences across countries with respect to other baseline variables was apparent. The extent to which the lower sample size for the no history of hyperlipidemia subgroup, and any systematic bias associated with the availability of total cholesterol measurements, accounts for the lack of significant associations found for that group, cannot be determined. Our models evaluating the association between country-level indices and elevated total cholesterol, however, adjusted for all patient-level risk factors. Other limitations include that fact that information related to lipid-lowering therapy was abstracted from medical records and may not reflect true patient compliance. In addition, details related to dosing strategies, contraindications to the use of, or adverse effects from lipid-lowering medications were not collected in REACH, nor were side effects that may have precluded specific medication use. Finally, whereas other components of the lipoprotein profile might be considered more optimal measures of cardiovascular risk, only total cholesterol measurements were recorded in the REACH Registry.

Implications

The above limitations notwithstanding, these results could serve as impetus for continued national and international dialogue and targeting of efforts toward improving cardiovascular risk factor control. In the past decade, several countries have made progress in their efforts to strengthen national capacity for prevention and control of noncommunicable diseases; yet, much of these advancements are seen in high-income countries.36 WHO has recently proposed a framework of several cost-effective or low-cost population-based strategies and individual-level interventions aimed at reducing behavioral and physiological risk factors for chronic diseases that may help reduce such disparities between low/middle- and high-income countries.1 In recognition of the extent to which patients, physicians, and healthcare systems all influence adherence to preventive therapies, a framework for the integration of healthcare system-based approaches with community-based health promotion efforts within the United States has also been proposed.37 In addition, as part of the Million Hearts initiative, the US Centers for Medicare and Medicaid Services has expanded coverage for CVD prevention.38 Efforts such as these, in combination with ensuring adequate infrastructure for surveillance of risk factors and health outcomes, are crucial for controlling the rising, yet preventable, burden of cardiovascular diseases and may serve as a template for other countries to build upon.

Conclusions

Global variations in the prevalence of elevated cholesterol among patients with history of hyperlipidemia are associated with country-level economic and health expenditure indices, and WHO indices of healthcare system achievement and performance/efficiency, as well. These results support the need for maintaining and strengthening healthcare system efforts toward effective cardiovascular disease prevention.
and control and may provide potential insights for strategic public health policy settings at the national level.

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References
The exponential rise in cardiovascular disease over the past decade has placed a tremendous burden on the health and economic development of countries worldwide, with unprecedented demands for an effective response from governments and other stakeholders in global health. From a large, multinational registry of outpatients with established cardiovascular disease or ≥3 risk factors, we used data from 53 570 individuals from 36 countries to examine the relationship between country-level economic and health system factors and the risk of elevated cholesterol (total cholesterol levels >200 mg/dL). The analysis was performed separately for patients with versus without previous history of hyperlipidemia; a higher proportion of the total variability in elevated cholesterol was at the country level for patients with (12.1%) versus without (7.4%) history of hyperlipidemia. Among patients with history of hyperlipidemia, after adjusting for patient-level demographic and clinical characteristics and average fat consumption at the country level, countries in the highest tertile of gross national income or World Health Organization index of health system achievement were found to have significantly lower odds of elevated cholesterol than those in each of the lower 2 tertiles, and the odds of elevated cholesterol was higher for countries in higher versus lower tertile of out-of-pocket health expenditures. No significant associations between country-level factors and elevated cholesterol were found for patients without history of hyperlipidemia. These results support the need for strengthening efforts toward effective cardiovascular disease prevention and control and may provide insight for health policy setting at the national level.
Global Variation in the Prevalence of Elevated Cholesterol in Outpatients With Established Vascular Disease or 3 Cardiovascular Risk Factors According to National Indices of Economic Development and Health System Performance


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SUPPLEMENTAL MATERIALS
SUPPLEMENTAL METHODS

Medical record documentation was required for establishment of the presence of CAD, CVD, or PAD. Documented CAD consisted of 1 or more of the following criteria: stable angina with documented CAD, history of unstable angina with documented CAD, history of percutaneous coronary intervention, history of coronary artery bypass graft surgery, or previous myocardial infarction. Documented CVD consisted of a hospital or neurologist report with the diagnosis of transient ischemic attack or ischemic stroke. Documented PAD consisted of 1 or both criteria: current intermittent claudication with ankle brachial index of less than 0.9 or a history of intermittent claudication together with a previous and related intervention, such as angioplasty, stenting, atherectomy, peripheral arterial bypass graft, or other vascular intervention including amputation.
SUPPLEMENTAL TABLE 1: Univariate and multivariable models for relationship between tertiles of country-levels indices of economic development and WHO health system achievement and performance/efficiency

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**A) GROSS NATIONAL INCOME PER CAPITA**

### With history of hyperlipidemia

- **High (> $9000) vs. Low (< $2900)**
  - **Unadjusted:** 0.41 (0.27, 0.63) < 0.001
  - **Adjusted:** 0.40 (0.26, 0.61) < 0.001
  - **Interaction:** 0.22 (0.12, 0.41) < 0.001

- **High vs. Medium ($2900-$9000)**
  - **Unadjusted:** 0.56 (0.35, 0.90) 0.015
  - **Adjusted:** 0.52 (0.32, 0.84) 0.008
  - **Interaction:** 0.36 (0.21, 0.62) < 0.001

- **Medium ($2900-$9000) vs. Low (< $2900)**
  - **Unadjusted:** 0.73 (0.43, 1.25) 0.250
  - **Adjusted:** 0.76 (0.44, 1.33) 0.337
  - **Interaction:** 0.62 (0.36, 1.07) 0.083

### Without history of hyperlipidemia

- **High (> $9000) vs. Low (< $2900)**
  - **Unadjusted:** 1.00 (0.66, 1.54) 0.990
  - **Adjusted:** 1.05 (0.67, 1.64) 0.832
  - **Interaction:** 0.59 (0.31, 1.11) 0.100

- **High vs. Medium ($2900-$9000)**
  - **Unadjusted:** 1.41 (0.85, 2.32) 0.180
  - **Adjusted:** 1.34 (0.80, 2.25) 0.268
  - **Interaction:** 0.93 (0.52, 1.66) 0.807

- **Medium ($2900-$9000) vs. Low (< $2900)**
  - **Unadjusted:** 0.71 (0.41, 1.25) 0.236
  - **Adjusted:** 0.78 (0.44, 1.40) 0.409
  - **Interaction:** 0.63 (0.35, 1.13) 0.119

**B) % TOTAL EXPENDITURE ON HEALTH AS % GROSS DOMESTIC PRODUCT**

### With history of hyperlipidemia

- **High (> 8) vs. Low (< 6)**
  - **Unadjusted:** 0.61 (0.38, 0.98) 0.043
  - **Adjusted:** 0.60 (0.36, 0.98) 0.041
  - **Interaction:** 0.46 (0.20, 1.05) 0.064

- **High vs. Medium (6-8)**
  - **Unadjusted:** 0.81 (0.50, 1.29) 0.363
  - **Adjusted:** 0.81 (0.50, 1.31) 0.388
  - **Interaction:** 0.74 (0.42, 1.31) 0.303

- **Medium (6-8) vs. Low (< 6)**
  - **Unadjusted:** 0.76 (0.46, 1.24) 0.264
  - **Adjusted:** 0.74 (0.44, 1.22) 0.237
  - **Interaction:** 0.61 (0.33, 1.16) 0.132

### Without history of hyperlipidemia

- **High (> 8) vs. Low (< 6)**
  - **Unadjusted:** 1.48 (0.91, 2.42) 0.117
  - **Adjusted:** 1.53 (0.92, 2.54) 0.102
  - **Interaction:** 1.19 (0.52, 2.76) 0.679

- **High vs. Medium (6-8)**
  - **Unadjusted:** 1.47 (0.91, 2.36) 0.113
  - **Adjusted:** 1.46 (0.89, 2.38) 0.135
  - **Interaction:** 1.33 (0.75, 2.37) 0.326

- **Medium (6-8) vs. Low (< 6)**
  - **Unadjusted:** 1.01 (0.61, 1.66) 0.974
  - **Adjusted:** 1.05 (0.63, 1.76) 0.852
  - **Interaction:** 0.50 (0.47, 1.70) 0.734

**C) GOVERNMENT EXPENDITURE ON HEALTH AS % OF TOTAL EXPENDITURE ON HEALTH**

### With history of hyperlipidemia

- **High (>72) vs. Low (≤50)**
  - **Unadjusted:** 1.16 (0.70, 1.91) 0.563
  - **Adjusted:** 1.23 (0.74, 2.04) 0.435
  - **Interaction:** 1.36 (0.78, 2.36) 0.285

- **High (>72) vs. Medium (50-72)**
  - **Unadjusted:** 0.96 (0.61, 1.51) 0.863
  - **Adjusted:** 0.91 (0.57, 1.45) 0.692
  - **Interaction:** 0.89 (0.56, 1.42) 0.623

- **Medium (50-72) vs. Low (≤50)**
  - **Unadjusted:** 1.21 (0.76, 1.93) 0.432
  - **Adjusted:** 1.35 (0.84, 2.17) 0.222
  - **Interaction:** 1.52 (0.89, 2.61) 0.127

### Without history of hyperlipidemia

- **High (>72) vs. Low (≤50)**
  - **Unadjusted:** 1.11 (0.67, 1.84) 0.692
  - **Adjusted:** 1.20 (0.71, 2.00) 0.499
  - **Interaction:** 1.31 (0.75, 2.31) 0.341

- **High (>72) vs. Medium (50-72)**
  - **Unadjusted:** 0.88 (0.55, 1.39) 0.571
  - **Adjusted:** 0.87 (0.54, 1.39) 0.559
  - **Interaction:** 0.85 (0.53, 1.37) 0.501

- **Medium (50-72) vs. Low (≤50)**
  - **Unadjusted:** 1.27 (0.79, 2.04) 0.331
  - **Adjusted:** 1.38 (0.85, 2.24) 0.199
  - **Interaction:** 1.55 (0.90, 2.67) 0.118

**D) OUT-OF-POCKET EXPENDITURES AS % OF PRIVATE EXPENDITURE ON HEALTH**
<table>
<thead>
<tr>
<th></th>
<th>High (≥90) vs. Low (&lt;70)</th>
<th>Medium (≥70–&lt;90) vs. Low (&lt;70)</th>
<th>Medium (≥70–&lt;90) vs. Low (&lt;70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (≥90) vs. Low (&lt;70)</td>
<td>2.15 (1.37, 3.37)</td>
<td>0.001</td>
<td>2.19 (1.37, 3.51)</td>
</tr>
<tr>
<td>High (≥90) vs. Medium (≥70–&lt;90)</td>
<td>1.40 (0.87, 2.25)</td>
<td>0.170</td>
<td>1.50 (0.91, 2.47)</td>
</tr>
<tr>
<td>Medium (≥70–&lt;90) vs. Low (&lt;70)</td>
<td>1.54 (0.98, 2.42)</td>
<td>0.060</td>
<td>1.46 (0.91, 2.33)</td>
</tr>
</tbody>
</table>

**E) WORLD HEALTH ORGANIZATION (WHO) HEALTH SYSTEM ACHIEVEMENT INDEX**

<table>
<thead>
<tr>
<th></th>
<th>High (≥90) vs. Low (&lt;70)</th>
<th>Medium (≥70–&lt;90) vs. Low (&lt;70)</th>
<th>Medium (≥70–&lt;90) vs. Low (&lt;70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (≥90) vs. Low (&lt;70)</td>
<td>0.77 (0.49, 1.22)</td>
<td>0.266</td>
<td>0.74 (0.46, 1.19)</td>
</tr>
<tr>
<td>High (≥90) vs. Medium (≥70–&lt;90)</td>
<td>0.73 (0.45, 1.19)</td>
<td>0.213</td>
<td>0.71 (0.43, 1.18)</td>
</tr>
<tr>
<td>Medium (≥70–&lt;90) vs. Low (&lt;70)</td>
<td>1.05 (0.67, 1.66)</td>
<td>0.833</td>
<td>1.04 (0.65, 1.68)</td>
</tr>
</tbody>
</table>

**F) WHO HEALTH SYSTEM PERFORMANCE/EFFICIENCY INDEX**

<table>
<thead>
<tr>
<th></th>
<th>High (&gt;0.85) vs. Low (≤0.75)</th>
<th>Medium (≥0.75–&lt;0.85) vs. Low (≤0.75)</th>
<th>Medium (≥0.75–&lt;0.85) vs. Low (≤0.75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (&gt;0.85) vs. Low (≤0.75)</td>
<td>0.47 (0.32, 0.69)</td>
<td>0.47 (0.31, 0.70)</td>
<td>0.42 (0.26, 0.68)</td>
</tr>
<tr>
<td>High (&gt;0.85) vs. Medium (≥0.75–&lt;0.85)</td>
<td>1.49 (1.02, 2.17)</td>
<td>0.039</td>
<td>1.46 (0.98, 2.18)</td>
</tr>
<tr>
<td>Medium (≥0.75–&lt;0.85) vs. Low (≤0.75)</td>
<td>0.32 (0.21, 0.47)</td>
<td>0.001</td>
<td>0.32 (0.21, 0.49)</td>
</tr>
</tbody>
</table>

**History of hyperlipidemia**

* P Interaction: the p-value for interaction term between global indices and group indicator (with and without history of hyperlipidemia); Note: Fat consumption data was not available for Singapore, therefore, the fat-adjusted estimates were derived from 35 countries; † History of hyperlipidemia refers to documented past diagnosis of hyperlipidemia or use of lipid-lowering medications at baseline.
SUPPLEMENTAL TABLE 2. Results from hierarchical generalized mixed effect (logistic) regression models, estimating the impact of gross national income (GNI) level on the odds of elevated cholesterol, with and without country-level fat consumption as an adjustment factor (in addition to patient-level factors)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Model with Fat Consumption</th>
<th>Model without Fat Consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.5986</td>
<td>1.3915</td>
</tr>
<tr>
<td>GNI: low</td>
<td>-0.5331</td>
<td>0.0481</td>
</tr>
<tr>
<td>GNI: medium</td>
<td>-0.4606</td>
<td>-0.2450</td>
</tr>
<tr>
<td>GNI: high</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>History of hyperlipidemia†</td>
<td>0.8297</td>
<td>0.8305</td>
</tr>
<tr>
<td>History of hyperlipidemia*GNI low</td>
<td>-0.9836</td>
<td>-0.9773</td>
</tr>
<tr>
<td>History of hyperlipidemia*GNI medium</td>
<td>-0.0241</td>
<td>-0.0249</td>
</tr>
<tr>
<td>History of hyperlipidemia*GNI high</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.0115</td>
<td>-0.0115</td>
</tr>
<tr>
<td>Male Sex</td>
<td>-0.6658</td>
<td>-0.6606</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.3010</td>
<td>0.3012</td>
</tr>
<tr>
<td>College or technical education</td>
<td>-0.0424</td>
<td>-0.0447</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>-0.1722</td>
<td>-0.1745</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>0.1377</td>
<td>0.1379</td>
</tr>
<tr>
<td>CAD</td>
<td>-0.4284</td>
<td>-0.4290</td>
</tr>
<tr>
<td>CVD</td>
<td>0.1125</td>
<td>0.1160</td>
</tr>
<tr>
<td>PAD</td>
<td>0.1035</td>
<td>0.1070</td>
</tr>
<tr>
<td>History of carotid surgery</td>
<td>-0.1441</td>
<td>-0.1454</td>
</tr>
<tr>
<td>History of CHF</td>
<td>0.0468</td>
<td>0.0453</td>
</tr>
<tr>
<td>History of atrial fibrillation/flutter</td>
<td>-0.1869</td>
<td>-0.1866</td>
</tr>
<tr>
<td>History of aortic valve stenosis</td>
<td>0.1597</td>
<td>0.1605</td>
</tr>
<tr>
<td>Antiplatelet drug therapy</td>
<td>-0.2468</td>
<td>-0.2506</td>
</tr>
<tr>
<td>Antihypertensive drug therapy</td>
<td>-0.2465</td>
<td>-0.2422</td>
</tr>
<tr>
<td>Country-level fat consumption</td>
<td>0.0100</td>
<td></td>
</tr>
</tbody>
</table>

† History of hyperlipidemia refers to documented past diagnosis of hyperlipidemia or use of lipid-lowering medications at baseline; CAD: Coronary artery disease; CVD: Cerebrovascular disease; PAD: Peripheral vascular disease; GNI: Gross national income
Supplemental Figure 1A-F:

A: Gross National Income (Atlas method)

B: Total Health Expenditure as % of Gross Domestic Product
C: Government Expenditure as % of Total Expenditure on Health

D: Out-of-pocket Expenditures as % of Private Expenditures on Health
E: WHO Health System Achievement Index

Low (<80)
Intermediate (≥80-<90)
High (≥90)

F: WHO Health System Performance/Efficiency Index

Low (≤.75)
Intermediate (.75-≤.85)
High (> .85)
Supplemental Figure 2:

Pearson's correlation coefficient: 0.72
SUPPLEMENTAL FIGURE LEGENDS

**Figure 1A-F:** Distribution of indices of economic development, healthcare investment and health system performance in the REACH Registry

**Figure 2:**
Correlation between rates of elevated total cholesterol reported in nine countries included in REACH Registry (>200 mg/dL or 5.18 mmol/L) and EUROASPIRE Survey II (≥190 mg/dL or ≥5.0 mmol/L).\(^1\)
Supplemental Reference

Variations de la prévalence de l’hypercholestérolémie à travers le monde,
chez les patients présentant une maladie vasculaire avérée ou 3 facteurs de risque cardiovasculaire, en fonction des indices nationaux de développement économique et de performance des systèmes de santé

Lakshmi Venkitachalam, PhD ; Kajjun Wang, PhD ; Avi Porath, MD ; Ramon Corbalan, MD ; Alan T. Hirsch, MD ; David J. Cohen, MD, MSc ; Sidney C. Smith, Jr, MD ; E. Magnus Ohman, MD ; Ph. Gabriel Steg, MD ; Deepak L. Bhatt, MD, MPH ; Elizabeth A. Magnuson, ScD ; au nom des investigateurs du registre REACH

Contexte—L’hypercholestérolémie est à l’origine d’une très large part des événements cardiovasculaires survenant de par le monde. La connaissance du lien unissant les facteurs économiques et sanitaires à l’hypercholestérolémie au sein d’un pays donné pourrait permettre de mieux définir les actions à mener en priorité dans le cadre des programmes de prévention des maladies cardiovasculaires.

Méthodes et résultats—En nous appuyant sur des modèles hiérarchiques, nous avons examiné, chez 53 570 patients ambulatoires répartis dans 36 pays, les relations existant entre l’hypercholestérolémie (taux supérieur à 2,0 g/l) et les tertiles de plusieurs indices nationaux, à savoir (1) le produit intérieur brut (PIB), (2) le pourcentage du PIB consacré aux dépenses globales de santé, (3) la part de ces dernières assumée par les pouvoirs publics, (4) le reste à charge des frais médicaux pour les patients en pourcentage de leurs dépenses privées ainsi que les indicateurs utilisés par l’Organisation Mondiale de la Santé (OMS) pour évaluer les systèmes de santé en termes (5) de niveau de développement et (6) d’efficacité. Globalement, 38 % des patients avaient une cholestérolémie totale supérieure à 2,0 g/l (5,18 mmol/l), 9,3 % de la variabilité totale de l’hypercholestérolémie s’étant révélée liée au pays d’appartenance ; le pourcentage était toutefois plus élevé pour les patients qui avaient des antécédents d’hyperlipidémie (12,1 %) que pour ceux qui en étaient exempts (7,4 %). En limitant l’analyse aux patients ayant des antécédents d’hyperlipidémie, le risque d’hypercholestérolémie est apparu plus faible dans les pays dont le PIB ou le niveau de développement du système de santé tel que défini par l’OMS s’inscrivait dans le tertile le plus haut que dans ceux pour lesquels ces indicateurs se situaient dans les tertiles les plus bas (p<0,001, pour les deux indices). De même, le risque d’hypercholestérolémie était plus élevé pour les pays dans lesquels le reste à charge des frais médicaux pour les patients se situait dans le tertile le plus élevé que pour ceux dans lesquels cet indice relevait du tertile le plus faible (p<0,001). Aucune corrélation significative n’a été mise en évidence pour les patients qui n’avaient pas d’antécédent d’hyperlipidémie.


Mots clés : maladie cardiovasculaire ■ hypercholestérolémie ■ tendances mondiales ■ performance des systèmes de santé ■ dépenses de santé nationales

Indice de masse corporelle, chirurgie et risque d’événement thromboembolique veineux chez la femme d’âge moyen

Une étude de cohorte

Lianne Parkin, MB, ChB, PhD ; Siân Sweetland, DPhil ; Angela Balkwill, MSc ; Jane Green, MB, ChB, DPhil ; Gillian Reeves, PhD ; Valerie Beral, MD, FRS, pour les investigateurs du Million Women Study

Contexte—L’obésité et la chirurgie sont des facteurs de risque connus d’événement thromboembolique veineux (ETV), mais peu de données sont disponibles sur l’influence spécifique exercée par l’obésité sur le survenu d’un ETV postopératoire. Nous avons donc confronté les données fournies par le questionnaire de la Million Women Study (étude sur un million de femmes) aux comptes rendus d’hospitalisation et aux certificats de décès afin d’évaluer le risque d’ETV encouru en fonction de l’indice de masse corporelle (IMC) en l’absence d’intervention chirurgicale et dans les 12 premières semaines qui suivent une opération.

Méthodes et résultats—Au total, 1 170 495 femmes (âge moyen : 56,1 ans) incluses dans l’étude entre 1996 et 2001 par l’intermédiaire du programme de dépistage du cancer du sein mis en place par le National Health Service britannique en Angleterre et en Ecosse ont été suivies pendant une durée moyenne de 6 ans, période pendant laquelle 6 438 de ces femmes ont été hospitalisées pour un ETV ou sont décédées des suites d’un tel événement. Nous avons pu établir que le risque relatif ajusté d’ETV avait augmenté proportionnellement à l’IMC et qu’il avait été 3 ou 4 fois plus élevé chez les femmes dont l’IMC atteignait 35 kg/m² ou plus que chez celles qui avaient un IMC compris entre 22,5 et 24,9 kg/m² (risque relatif : 3,45 [IC à 95 % : 3,09–3,86]). Les femmes en surcharge pondérale ou obèses se sont révélées plus exposées que les femmes minces à être hospitalisées en vue d’être opérées mais aussi à présenter un ETV postopératoire. Sur une période de 12 semaines libre d’intervention chirurgicale, les taux d’ETV pour 1 000 femmes ont été de 0,10 (0,09–0,10) lorsque l’IMC était inférieur à 25 kg/m² et de 0,19 (0,18–0,20) lorsque l’IMC atteignait 25 kg/m² ou plus ; les taux correspondants enregistrés au cours des 12 semaines ayant suivi un acte chirurgical pratiqué en ambulatoire ou dans le cadre d’une hospitalisation ont été, respectivement, près de 4 et 40 fois plus élevés.


Mots clés : obésité ■ chirurgie ■ thrombose veineuse profonde ■ embolie pulmonaire ■ étude de cohorte