

Discussion

The serum cholesterol concentrations of the local (mainly rural) population samples in the Seven Countries Study appear to have truly reflected the national differences (though not necessarily the national averages), since they correlate so remarkably well with the national differences in mortality. The high correlations also vindicate the use of national mortality rates, since errors in the data would tend to weaken the correlation estimates rather than create false-positive associations. Laboratory biases are excluded by using a central laboratory, and a false-positive correlation would seem possible only if there had been a tendency in countries with a high incidence of coronary heart disease to select population samples with unrepresentatively high cholesterol concentrations or vice versa in countries with a low incidence of the disease. Nevertheless, the strong inverse correlation of cholesterol concentration with senility and ill-defined causes of death indicates that this is also a broad marker of medicosocial conditions and not only of dietary fat.

The results support and extend the conclusion from the Seven Countries Study that differences in serum cholesterol concentration account for most of the difference in mortality from coronary heart disease between these countries. Differences in blood pressure might also contribute, but any such effect is overshadowed by the strength of the cholesterol prediction; furthermore, the comparison might be confused by measurement biases.

All the correlations (for cholesterol concentration and both systolic and diastolic blood pressures) grew steadily stronger with time, and the cholesterol concentrations in the late 1950s gave an almost perfect prediction of the international differences in mortality from coronary heart disease in the mid-1970s. With data from only seven countries it would be unwise to put too much reliance on the time trend, which was consistent with a delay of 10 years or more between exposure of a population to given concentrations of cholesterol or blood

pressure and the maximum effect on mortality from coronary heart disease; the decline in American rates in the 1970s brought them into line with what would have been predicted by the cholesterol concentration more than a decade earlier. The situation is, however, complicated by continuing changes in the levels of these and other coronary risk factors. This makes it all the more surprising that a single examination can permit such accurate long-term prediction.

Longitudinal surveys such as the Framingham study⁵ have found that in individuals the predictive ability of the serum cholesterol concentration is much less in older than in younger people, which seems to be at variance with the present findings. Possibly the determination of individual risk has a different basis from the determination of rates in populations. Some clarification might come from comparing short-term and long-term predictive power within the same individuals.

The results do not support the view that low mean concentrations of cholesterol imply a higher national risk of cancer: the trend is in fact rather strongly in the reverse direction.

Data extraction and computing were undertaken by Miss Linda Colwell.

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Commentary: Insights from cross-population studies: Rose revisited

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Using data across different populations (ecological studies) to understand disease aetiology is uncommon, partly because it is

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difficult to establish standardized measurements of exposure or risk factors and obtain reliable and comparable outcome statistics, but also because such studies are difficult to establish. However, an even bigger obstacle has been the theoretical concerns (some may even say prejudices) held in relation to ecological studies. The argument goes that unknown or unmeasured factors that cosegregate with the exposure of interest may confound the relationship, or worse that the specific exposure being studied

may be only a surrogate marker of exposure (something that tracks with the exposure variable but has no direct or indirect link to the processes that lead to disease). Although these concerns may be valid in some circumstances, they are applied in varying degrees to all types of observational studies. A rigid adherence to these beliefs may blind us to circumstances in which comparing information across countries or populations (ecological or cross-population analyses) suggests unusual insights that other study designs do not provide.

There are several potential strengths of cross-population analyses. First, the estimate of exposure in a population is generally more precise than for measurements in individuals if the selection of the population is not systematically biased. This is because these measures are derived from large numbers of observations. Although measurements in individuals within the population are subject to measurement errors and chance variations, the overall parameter estimate of an exposure in a population is more precise. Similarly, using outcome rates derived from an overall population sample, or even an entire country, provides more stable (and 'representative') estimates of a particular type of event, for example, coronary heart disease (CHD) or death, than does using rates derived from a subgroup of individuals within a cohort. Second, when the variation in the exposure across populations is large, estimates derived from large, representative samples of several different populations (for example, urban and rural communities, or different countries) are more likely to capture this variation than a nonrandom, homogeneous sample such as is typically chosen for prospective followup in cohort studies such as the British doctors¹ or US nurses studies.²

Therefore, a combination of more precise estimates of exposure and outcomes in a population and larger variation in exposure across populations allows for more accurate characterization of the relationship between the exposure and a specific outcome (as long as there is other information that suggests strongly that such links are causal). In a sense, for certain questions, the cross-population strategy is likely to have advantages over the alternative study designs typically used for more homogeneous populations, such as cohort or case-control studies. This was the basis of Ancel Keys's Seven Countries Study, which led to a number of important insights into heart disease in the 1960s.³

Rose exploited these characteristics in a brilliantly simple analysis to demonstrate the strength of the relationship of serum cholesterol and blood pressure (BP) to CHD mortality using data from the Seven Countries Study.^{3,4} He correlated the mean values of cholesterol and BP measured in 1958–64 in a population of men from seven countries with national CHD mortality data for the same age cohorts derived from an average of four 3-yr periods (1951–61, 1964–66, 1969–71, and 1974–76). The correlation for cholesterol measured at baseline and subsequent CHD improved from an r of 0.86 in the initial period (1951–61) to 0.90 after 5 yr, 0.93 after 10 yr, and 0.96 after 15 yr.⁵ A moderate correlation between BP and CHD mortality was observed with a similar pattern: a stronger relationship emerging over time (for systolic BP the r values were 0.48, 0.56, 0.57, and 0.64).⁵

What are the implications of these observations? First, differences in mean population levels of cholesterol appear to account for most of the variations in CHD mortality rates among

countries, with only a modest contribution from differences in blood pressure. Presumably this implies that differences in other factors among populations will also have only a minor effect. Second, with the increasingly strong correlation between cholesterol and CHD over time (another brilliant stroke in the study design, which addresses the issue of temporality in an investigation that started with a cross-sectional data collection), Rose suggested that the full impact of differences in exposure would take time to manifest (incubation period). How plausible are these implications? The slope of the cholesterol-CHD relationship derived from Figure 1 of Rose's paper suggests that a 1 mmol reduction in mean cholesterol (for example, from 7 to 6 mmol) is associated with one-third lower CHD mortality rates. Larger reductions (say from 7 to 5 or even 4 mmol) are likely to be associated with much larger benefits (a relative risk of $0.66 \times 0.66 \times 0.66 = 0.29$, or ~70% lower risk). Further, if the process of reversing the risks using cholesterol-lowering strategies parallels the time frame of the incubation period that leads to elevated cholesterol causing CHD, then the full benefits of cholesterol-lowering in individuals will increase over time, as demonstrated in the randomized trials⁶ and in populations, such as the North Karelia observational cohort.⁷ Most randomized trials of cholesterol-lowering⁶ support both the quantitative estimate derived from the relationship of cholesterol to CHD predicted from the Seven Countries Study,³ and a moderate lag before observing benefits, so that there is very little impact on CHD or mortality in the first year of trials, but increasing differences over time. Indeed, one is surprised at how similar the predictions derived from Rose's paper are to the results of the recent cholesterol-lowering trials with statins.

Does Rose's study mean that cholesterol is the overwhelmingly dominant risk factor for CHD, and that other risk factors have only minor roles? Not necessarily. Closer perusal of the data indicate that mean cholesterol varied from 4 to 7 mmol but that a much smaller variation in systolic BP was present across countries. Therefore, even if the strength of the relationships between two separate risk factors and CHD is similar, their relative importance will depend on which factor has larger variation. For example, if cholesterol levels were similar in all of the populations, one would not observe any relationship between cholesterol and CHD.⁸ The impact of other risk factors would dominate.

These observations have important implications for the design of future epidemiological studies of various chronic diseases (cardiovascular disease, diabetes, cancers, etc.). First, future studies should try to include heterogeneous populations (that is, populations with substantial variations in their settings, culture, and surroundings) so that large variations in both risk factors and outcomes in such populations can be exploited.

Second, for scientists aiming to study interactions involving common gene polymorphisms and environmental exposure (lifestyles), choosing populations with markedly different lifestyles (identified by ethnicity, geographic region, or levels of urbanization) may provide the range of exposures that will facilitate the discovery of even moderate interactions, since there is very little heterogeneity in genetic makeup between different populations. Therefore, it is important to rely on having variability in environments and related exposures. A greater emphasis on establishing large cross-population studies is needed. Such studies include MONICA (Multinational

Monitoring of Trends and Determinants in Cardiovascular Disease; mostly developed countries),⁹ INTER-SALT,¹⁰ INTER-HEART,¹¹ and the Prospective Urban and Rural Epidemiologic Study (PURE)—the last two involving low-, middle-, and high-income countries. These studies will complement the more traditional cohort studies generally conducted within relatively homogenous populations.

Acknowledgements

SY holds a Heart and Stroke Foundation of Ontario Chair in Cardiovascular Research. ATM has the Hirsch Research Career Award, Hamilton Health Sciences. SSA holds a CIHR Career Investigator Award.

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Commentary: Geoffrey Rose's thinking about coronary artery disease

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Two decades ago, Geoffrey Rose was clear about the essentials of atherosclerotic coronary disease. It is insidious, treatable, the source of endless puzzlement and, most importantly, eradicable.

In 1982 he related measurements of cholesterol and blood pressure which had been made in 40- to 59-year-old men in the Seven Countries Study (Finland, Greece, Holland, Italy, Japan, the USA, and Yugoslavia) to rates of death from coronary heart disease 5, 10 and 15 years later in the corresponding but much larger age cohorts identifiable from national mortality statistics.¹ He showed persuasively that the closeness of the correlation about the regression line increased with time so that measurements of cholesterol in particular, made in the late 1950s predicted almost perfectly international differences in mortality from coronary heart disease in the mid-1970s. He argued, therefore, that the data were consistent with a delay of

10 years or more between exposure to hypercholesterolaemia or hypertension and the maximum effect of these risk factors on coronary death rates. In passing, he noted that a delay of this magnitude was not inconsistent with a rapidly appearing benefit of reduction of cholesterol or blood pressure.

This understanding of the time course of coronary artery disease, based on epidemiological data, accords well with pathology and data from clinical studies. A myriad complexities notwithstanding, atherosclerosis can be ascribed to gradual (over decades) deposition in the artery wall of cholesterol from the low-density lipoproteins (LDLs) of plasma, and lowering of LDL cholesterol by diet, drugs, or surgery is rapidly followed (in months) by a reduced risk of myocardial infarction.

In contemporary cardiology we still seem to be puzzled by the dual concept of the rapid salutary effects of removal of a slowly working agent of disease. For example, the rapid reduction in risk demonstrated in clinical trials of lowering LDL cholesterol with statins was thought to require an explanation in addition

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