Half of all adult deaths (and much severe disability) are caused by cardiovascular diseases, and most of these deaths involve ischemic heart disease or stroke. The Asia-Pacific region accounts for about half of the global burden of cardiovascular disease and the proportion is likely to increase during the next few decades.\textsuperscript{1,2} Smoking and elevated levels of systolic blood pressure (SBP) and total blood cholesterol are major causes of cardiovascular disease,\textsuperscript{3} yet much of our knowledge about the associations between these risk factors and cardiovascular diseases comes from studies carried out in North American and western European countries. In most Asian countries, however, the mean levels of total cholesterol are lower than those found in Western countries and the incidence of coronary heart disease (CHD) is also lower, whereas the incidence of stroke, particularly hemorrhagic stroke, is higher.

The Asia Pacific Cohort Studies Collaboration report in this issue of \textit{Circulation} investigates the combined effects of SBP and total cholesterol on risk of cardiovascular disease in a meta-analysis of 36 cohort studies (29 conducted in Asia and 7 from Australia and New Zealand) involving 380,000 individuals.\textsuperscript{4} This meta-analysis differs from previous studies in several ways: It is the largest study from this region, involving $\geq$3000 CHD events and 4000 stroke events; individual records were available for each of the participants in each study, with cause and age of death (if applicable); and information on several thousand repeat measurements of blood pressure and cholesterol made during prolonged follow-up allowed correction for “regression dilution.” These features of the study allowed detailed analyses of the combined effects of SBP and cholesterol on CHD and stroke by age at risk and sex.

The major findings of this study were 2-fold. First, there was clear evidence of hazards of higher SBP at all levels of cholesterol, and hazards of higher cholesterol at all levels of SBP, as previously reported in Western populations.\textsuperscript{5-7} For people in the highest categories of both total cholesterol and SBP (ie, with measured total cholesterol $\geq$6.25 mmol/L and measured SBP $\geq$160 mm Hg), CHD risk was 7 times higher and ischemic stroke risk 8 times higher than among people in the lowest categories of both (ie, measured values of total cholesterol and SBP of $<$4.75 mmol/L and 130 mm Hg, respectively). Furthermore, there was no abrupt increase in risk at levels of SBP or cholesterol above some arbitrary threshold value for either risk factor. Whether these patterns were truly similar for men and women and in those above or below 70 years of age is uncertain. Even in this large collaboration there were too few events in the extreme categories, particularly for stroke, to provide reliable estimates.

Second, it is widely believed that the effects of the major risk factors for cardiovascular disease are “multiplicative” (ie, if 1 factor doubles risk and another triples it, then their joint effects increase risk 6-fold).\textsuperscript{8} The present study is consistent with results reported previously for Western populations\textsuperscript{5-7} that the effects of SBP and total cholesterol, although being more than additive, are less than multiplicative (in terms of relative risks). Had the associations been genuinely multiplicative in the present study, there would have been an $\approx$12-fold higher risk of CHD and a 15-fold higher risk of ischemic stroke among people in the highest categories of both total cholesterol and SBP compared with people in the lowest categories of both. Moreover, the slopes of the associations with 1 risk factor would have been the same at all levels of the other risk factor; however, the slopes of the risk associations with SBP were moderately steeper at lower levels of total cholesterol and vice versa for both CHD and ischemic stroke (but not for hemorrhagic stroke because there was no association with total cholesterol). Although the relative risks for 1 risk factor tended to decline at higher levels of the other risk factor, the corresponding absolute risks may well have increased because of the higher cardiovascular event rates at higher levels of SBP and total cholesterol.

In cohort studies, disease rates during follow-up are typically analyzed with respect to the values of risk factors measured at an initial baseline survey. Because of the combined effects of measurement errors and longer-term fluctuations in risk factors such as SBP or cholesterol, such analyses will systematically underestimate the true strength of the association of disease with “usual” (ie, long-term average) levels of the risk factors—the so-called regression dilution bias. Previous studies have demonstrated that the magnitude of regression dilution bias is greater at longer intervals between measurements.\textsuperscript{9,10} So replicate measurements of the risk factors in a sample of the study participants recorded at later intervals are required to appropriately correct for regression dilution bias. In this analysis, a simultaneous adjustment of risk estimates for the effects of regression dilution biases in both blood pressure and cholesterol measurements (including simultaneous correction for measurement errors in the same model) was performed.\textsuperscript{11} Interestingly, these simultaneous
adjustments did not differ substantially from the simpler analysis involving independent corrections for SBP and cholesterol, possibly because SBP and total cholesterol were only weakly correlated.

What are the implications of these findings for lipid-lowering and blood pressure–lowering treatment? The findings certainly seem to provide a rationale for simultaneous lowering of both SBP and total cholesterol. There have been many large-scale randomized trials of either lipid lowering12 or blood pressure lowering13 for the prevention of cardiovascular diseases. In the Cholesterol Treatment Trials’ collaborative overview of 90,000 participants in randomized trials of cholesterol-lowering treatment, a 1 mmol/L reduction in low-density lipoprotein (LDL) cholesterol was associated with a 23% reduction in coronary events, regardless of whether the initial diastolic blood pressure was above or below 90 mm Hg.12 The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) was designed specifically to investigate the benefits of lipid lowering in primary prevention of CHD among people with high blood pressure (defined as SBP ≥ 160 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg) but only average to below average cholesterol levels (nonfasting total cholesterol of ≤ 6.5 mmol/L).14 The investigators found that lowering LDL-cholesterol by 1 mmol/L reduced the risk of nonfatal myocardial infarction and fatal CHD by 36% (95% confidence interval 17% to 50%). Therefore, although the benefits of lowering LDL-cholesterol among people with high blood pressure are now abundantly clear, the benefits of blood pressure reduction at different levels of cholesterol remain uncertain.

In both predominantly Western and Asian populations, there is already compelling epidemiological evidence of strong direct continuous associations between usual blood pressure and the risks of major cardiovascular diseases15,16 and of strong direct continuous associations between usual total cholesterol and risks of CHD17 and ischemic stroke,15 both in middle and old age and among both men and women. This association suggests that the benefits of blood pressure and cholesterol lowering on cardiovascular disease risk are not likely to be restricted to patients with nonoptimal levels. Hence, population-wide strategies to promote physical activity, reduce obesity, and achieve sustained reductions in intake of dietary salt, saturated fat, and trans fatty acids could have a much greater impact on reducing cardiovascular disease in the population than antihypertensive or cholesterol-lowering therapy targeted at threshold levels of blood pressure or cholesterol.15,19 In conclusion, this report from the Asia Pacific Studies Collaboration adds to the growing evidence of the truly independent but not quite multiplicative effects of blood pressure and cholesterol, emphasizing the hazards of high blood pressure among people with high cholesterol levels and vice versa.

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References

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