Models of Effects of Low Blood Cholesterol on the Public Health
Implications for Practice and Policy

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In this issue of Circulation, Manolio et al report on the epidemiology of low blood total cholesterol (TC) levels in older adults and respond to a need to define the physical and disease characteristics of persons with low TC. Associations are established between low TC and mortality from hemorrhagic stroke,3 some cancers, and some noncancer/noncardiovascular diseases.2,4-6 The associations raise questions of whether low TC is causally related to a variety of nonatherosclerotic diseases or is a manifestation of confounding. The answer is important to the public health because the causal role in atherosclerosis of elevated TC or its components is unquestioned, and preventive practice and public policy are based on this fact. The answer is also vital to understanding human biology because cholesterol is so fundamental to structure and function.

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The answer is not obvious, however, despite progress made toward elimination of several potential sources of confounding in the low-TC-disease associations. Analyses suggest that confounding is not involved for age, sex, cigarette smoking, diastolic blood pressure, body mass index, or habitual alcohol intake.2 Notably, these analyses also reveal that most of the low-TC-mortality relations persist even after early deaths are eliminated, within 5, 10, or more years of entry TC measurement. That finding is critical because “reversed causality” is a leading hypothesis: that is, the observed low-TC-mortality associations are not causal; rather, undetected disease causes the low TC. The persistence of significant associations after elimination of deaths during 10 years weakens but does not refute this hypothesis. For example, it is conceivable that undetected disease lowers TC many years before death in such long-term conditions as chronic obstructive pulmonary disease, chronic hepatitis, diseases of intestinal malabsorption, paralytic diseases, eating disorders, and other gradually debilitating diseases. Manolio et al point to the powerful TC-lowering effects of cytokines, produced in response to chronic inflammation, as one way in which early stages of disease might lower TC. However, occult disease causing low TC does not rule out the possibility that low TC is an aggravating factor in disease processes. The hypothesis of Manolio et al and of Harris et al,8 that there are two groups of people with low TC, one healthy and the other diseased, is conceptually attractive yet difficult to address because there is no sure way to identify the source of a given individual’s low TC. Iribarren et al found elevated total mortality at low TC levels in the Honolulu Heart Program only in the 23% of participants who at baseline were heavy drinkers or smokers or had medical conditions such as gastrectomy, liver cirrhosis, colectomy, or intestinal disease (Iribarren C, Dwyer JH, Burchfiel CM, Reed DM: Can the U-shaped relation between mortality and serum cholesterol be explained by confounding? Submitted to the American Heart Association’s 33rd Annual Conference on Cardiovascular Disease Epidemiology, March 17–20, 1993, Santa Fe, N.M.).

Another approach to understanding the observed low-TC-disease associations is to consider plausible mechanisms. Konishi and colleagues7,9 make a cogent argument that low TC plays a causal role in hemorrhagic stroke; they propose that low TC fosters degenerative change in intracerebral arterioles through increased fragility of media muscle cells. Low TC can modify levels of cell membrane cholesterol7-9 and thereby modify membrane permeability to toxins and influence cell and membrane products. One cell product, for example, pulmonary surfactant, may be susceptible to modification at low TC levels because it derives much of its cholesterol from plasma low and high density lipoprotein.8,31 Cell membrane abnormalities occur in many diseases, but it is not clear whether low TC contributes. A causal role for low TC in some diseases, therefore, remains a plausible but unproven hypothesis.

It may be that TC–disease associations differ between the elderly versus the middle-aged. Manolio et al present Cardiovascular Health Study data from an older group (age, 65–100 years). In contrast, most of the Bethesda Conference evidence was for people with average age about 50 years (range, 35–69 years) followed for 15 or 20 years to average age 65 or 70 years.2 Although several studies have found greater short-term mortality among elderly nursing home residents, the possibility is stronger in older than in younger persons that low TC is the result rather than the cause of disease.
processes.\textsuperscript{12} Manolio et al add “fuel to the fire” by finding that low TC in the elderly is related to self-rating of poor health and to the number of coexisting diseases. At the same time, they find that low TC is not related to other measures of occult disease such as past smoking or heavy drinking, recent weight loss, or impaired cognition. Thus, the study by Manolio et al provides important new information characterizing people with low TC. It does not resolve, however, whether the observed low-TC-disease associations are a product of confounding or causality. We think it likely that the associations are explained by a combination of confounding and causality. But wide recognition of the low-TC-disease associations has clouded public health policy regarding TC lowering.\textsuperscript{13,14} We address here the potential health outcomes of major shifts in population TC.

**Observed Population Shifts in TC**

As a first step, we examine the manner in which the TC distribution changes over time in whole communities. Metabolic ward feeding studies suggest that TC responsiveness to dietary change is less at higher than at lower TC levels.\textsuperscript{15} On this basis, we hypothesize that the distribution of TC changes proportionately under conditions of population-wide change. One source of data bearing on this issue is the 10-year upward shift of TC between the 1960s and 1970s among Japanese men and women 50–59 years old.\textsuperscript{16} In Japanese cross-sectional surveys separated by 10 years, population-wide mean TC increased 20 mg/dl in men and 23 mg/dl in women. But proportionate change occurred in the Japanese TC distribution in that the 10th percentile in Japanese men increased only 17 mg/dl (from 115 to 132 mg/dl), whereas the 90th percentile increased 27 mg/dl (from 182 to 209 mg/dl) over the 10-year period. TC change in Japanese women was similar to that in men.

A smaller effect in the opposite direction was observed in unpublished data from 25–74-year-old men and women in Minnesota Heart Health Program population surveys between 1980 and 1989.\textsuperscript{17} Men experienced a decrease in mean TC of 5 mg/dl, women of 10 mg/dl. The 10th percentile in Minnesota men decreased by 5 mg/dl (from 159 to 154 mg/dl), whereas the 90th percentile decreased by 8 mg/dl (from 260 to 252 mg/dl). Proportionate change was somewhat more pronounced in Minnesota women. Thus, in both Japanese and Minnesotans, population-wide TC change is proportionate to level and selectively affects absolute levels at the upper end of the TC distribution.

**Models of Proportionate TC Change and Its Causal Effects**

Four scenarios of population change were constructed, represented by four possible TC distributions, specifying a mean level of TC in each of 10 TC categories. First, the observed categories were those of 350,977 men 35–57 years old screened for the Multiple Risk Factor Intervention Trial.\textsuperscript{3} These categories ranged from TC <140 up to ≥300 mg/dl and were represented by mean levels of 130, 150, . . . , 310 mg/dl. Next, the mean TC was decreased rigidly by 20 mg/dl for each cell; for example, people originally in the ≤140 mg/dl category shifted from a mean of 130 to 110 mg/dl. The third distribution represented proportionate change in observed TC, that is, the lower the TC level, the less the absolute TC change. For example, mean TC decreased by 10 mg/dl in the lowest category (130–120 mg/dl), but this was augmented by 2.5 mg/dl per step up to 32.5 mg/dl change in the highest TC category. The final model followed the same strategy of proportionate change in the six highest TC categories, but in the three lowest categories, the TC means were increased proportionately by 10 (e.g., from 130 to 140 mg/dl), 12.5, and 15 mg/dl, modeling a medical strategy to elevate levels among those having low TC.

Mortality change for middle-aged men was modeled under these four possible shifts of the population TC distribution and under several assumptions about the causal effects of TC change, using the cardiovascular disease, noncardiovascular disease, and total mortality rates (per 10,000 in 6 years) for the 10 classes of TC observed in the men screened.\textsuperscript{3} Rates were smoothed and extrapolated to a TC level of 110 mg/dl. Modeled mortality rates were computed as a weighted average of the death rate at the new TC level (after the change represented by one of the four distributions) and the death rate at the observed TC level. The death rate at the new TC level was weighted by the causality proportion (for example, 0.2 representing 20% causality), and the death rate at the observed TC level was weighted by its complement, (1 − the causality proportion). The causality proportion was taken to be 1 for cardiovascular disease.

We examined the predicted effects of each of these population shifts in TC distribution on cardiovascular, noncardiovascular, and total mortality under these several scenarios with added assumptions of different degrees of causality for low TC level and noncardiovascular diseases (100%, 50%, and 20%).

**Modeled Public Health Impact**

All models predicted similar substantial decreases in cardiovascular disease mortality. The “worst-case” model predicted an increase of 0.2% in total mortality, assuming full causality of lowered TC on noncardiovascular deaths and a uniform shift downward of 20 mg/dl in TC across the entire distribution. An assumption of less than full causality for noncardiovascular disease death reduced the estimated increase in noncardiovascular mortality associated with TC lowering and yielded a 3.1% decline in total mortality. However, models that do not take into account proportionate change in TC levels when average population levels fall exaggerate the potential untoward effects of TC-lowering strategies. Modeling a proportionate shift downward in population TC levels damps the predicted increase in noncardiovascular disease death, resulting in estimated net reductions in total mortality of 4.2% under the 100% low-TC causality assumption and 5.8% or 6.9% reductions under the 50% or 20% causality assumptions, which we consider more realistic.

Noncardiovascular mortality rates increased slightly, however, even under the conservative assumption of a proportionate shift downward in TC level at 20% causality. But when TC level is modeled to increase in people with lowest values and decrease in those with highest values, total mortality reduction is estimated as 8.1%, 7.2%, and 6.7% in the 100%, 50%, and 20% low-TC causality models, respectively. Note that when 20% causality of TC for noncardiovascular disease is
assumed, the total mortality reduction of 6.7% in the model in which people with low TC levels increase their values is somewhat less favorable than the 6.9% reduction in the corresponding model in which people with low TC levels experience a proportionate decrease in TC level. All these models were based on a sample of middle-aged men having mean TC of 215 mg/dl. A cautionary note is that the lower the population TC among men, the less is the predicted overall population benefit from TC lowering.

We consider closest to reality the models of proportionate decline in TC level along with 50% or 20% causality of TC lowering on noncardiovascular deaths. These models predict declines in total mortality rate consistent with the declines actually observed in recent decades in the United States as population means of TC and other cardiovascular risk factors have declined.19,20

Such models may be helpful in thinking about future public health strategies for reduction of atherosclerotic diseases. The proportionate TC change and partial causality models imply that little harm is done to those having low TC by the current, population-wide TC lowering strategies, because already low TC levels are relatively little changed by such population strategies and because only part of the association between low TC and mortality is likely to be causal. Models that do not further alter a low TC level imply that a slight improvement in overall mortality rate might be achieved if people with such levels make no further eating pattern changes or relax changes already made. Models in which TC is actually increased in those with low TC represent a medical strategy that has a strong advantage only if 100% causality holds. Individual efforts to actively increase a low TC are unlikely to undermine the current effective population strategy of gradual TC lowering. But neither are they likely, at this stage of knowledge, to be deemed an appropriate medical strategy.

Women

For women, the evidence suggests that the pattern of the relation between TC and various noncardiovascular diseases is similar to that in men, although absolute rates for women are lower; to this extent, these models apply to women. The important exception, however, is the flat relation between TC and mortality from total cardiovascular disease in women despite an equally strong relation among sexes of coronary heart disease mortality to TC. Furthermore, premenopausal women have lower TC than men of similar age. We acknowledge that consideration of TC alone may mask the important influences of both low and high density lipoprotein cholesterol on total cardiovascular disease risk in women.21 On the other hand, the more frequent manifestation of angina pectoris in women than in men may conceivably reflect differences between the sexes in cardiovascular pathology. We find the data generally inadequate to model effects of TC lowering in women.

Finally, we find ourselves increasingly uncomfortable with the current heavy reliance on medications as a population-wide TC lowering strategy, particularly in women and the elderly, who have been little studied.14 In contrast, there are many positive aspects for women as well as for men in the widely recommended healthy eating patterns for individuals, families, and whole populations, irrespective of diet effects on TC itself.22,23

For example, there are diet effects on obesity, and many conditions are likely to be affected favorably by the recommended increased intake of antioxidants and fibers. Because current population-wide efforts to lower high average TC levels in Western nations clearly have benefit in reducing cardiovascular disease morbidity and mortality and, as we show here, have relatively little estimated impact on noncardiovascular disease mortality, those public health strategies for lowering TC will probably continue to benefit populations having mass (relative) hypercholesterolemia. Although there are no clinical data indicating harm from lowering already low TC levels, the theoretically greater risk for nonatherosclerotic diseases could outweigh the small absolute reduction in coronary heart disease risk. Therefore, it appears reasonable that individuals found to have low TC values take no specific steps to further lower their personal levels.

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