Primary Prevention of High Blood Cholesterol Concentrations in the United States

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Background: Mean concentrations of total cholesterol (TC) among adults have declined in the United States for decades. Whether the decline has been owing to prevention of high TC levels or treatment of high TC levels once present is not known.

Objective: To determine whether population-wide influences and/or the high-risk approach have been operating to produce the well-known decline in mean TC concentration in the US population.

Methods: We examined changes in the distribution of TC levels across US birth cohorts as sampled in the National Health Examination Survey and the National Health and Nutrition Examination Surveys I, II, and III. We tested the hypotheses that the age-adjusted 10th, 25th, 50th, 75th, and 90th percentiles of TC levels were lower in more recent US birth cohorts than in earlier cohorts.

Results: Data were analyzed for 49,536 participants born between 1887 and 1975 and examined at ages 18 through 74 years between 1959 and 1994. The 10th, 25th, 50th, 75th, and 90th percentiles of TC levels (adjusted for age, race, and sex) were estimated to be lower by 3.4, 3.9, 4.7, 5.7, and 7.1 mg/dL (0.09, 0.10, 0.12, 0.15, and 0.18 mmol/L), respectively, for every successive 10 years in date of birth (P<.001 for each estimate).

Conclusions: The declines in TC levels associated with successive birth cohorts were greater at the upper aspect of the distribution, probably because of the combination of population influences and treatment effects. The differences seen at the lower percentiles support the contention that a strong prevention effect occurred in the US population from 1959 through 1994. Greater understanding of this dramatic shift in the distribution of TC levels could support future prevention efforts.

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Mean serum total cholesterol (TC) concentrations have declined in the United States during the past several decades. It has not been apparent whether this shift in mean TC concentration has been owing to reductions in blood TC concentrations through broadly occurring behavioral or environmental changes in the population, treatment of clinically recognized high blood cholesterol concentrations, or a combination of these influences. Rose contrasted the expected changes in the population distribution of a risk factor in response to either (1) population-wide influences, such as effective prevention efforts, or (2) treatment of the subgroup of the population with the risk factor present. According to this paradigm, population-wide influences would shift the entire cholesterol distribution to lower levels by reducing contemporaneous cholesterol concentrations and/or by reducing the rate of increase in cholesterol concentrations with aging. The approach of treating those at the highest risk, with selective attention to persons with high blood cholesterol levels, could affect only the upper aspect of the cholesterol distribution (by reducing the cholesterol concentrations of only those persons selected for treatment).

The mean population level of cholesterol would be lower by either (or both) a downward shift in the entire distribution or a decrease in the upper extreme of the cholesterol distribution. However, a reduction in mean cholesterol concentration because of a shift in the population distribution would be expected to have much greater impact on population mortality than would a reduction in mean cholesterol owing to treatment of persons with high blood cholesterol levels alone. Therefore, to understand the observed temporal changes in cardiovascular disease mortality, it is important to determine the nature of shifts that
METHODOLOGICAL APPROACH

POPULATION

Data for this report came from the National Health Examination Survey (NHES) and the National Health and Nutrition Examination Surveys (NHANES) I, II, and III. The designs of the NHES and NHANES series have been published previously.6,7 In brief, these surveys represent repeated, independent cross-sectional surveys of representative samples of the civilian, noninstitutionalized population of the United States, 18 through 74 years of age.6,7 In NHANES III, there was no upper age cutoff point; however, since persons older than 74 years were excluded from the earlier surveys, those participants were excluded from the present analyses. All racial and ethnic groups and both sexes were included. These data were collected to represent cross-sections of the population of the United States. We constructed a series of birth cohorts from approximately 1887 through 1975, the birth years that would meet age eligibility criteria for at least one in the series of surveys.

VARIABLES

The NHES and NHANES series included data describing the participant’s date of birth, date of examination, age, sex, race, and TC concentration. Lipoprotein cholesterol concentrations were available in only the 2 most recent surveys; hence, these data were not examined in the present analyses. The date of birth and age at examination were used as 2 primary factors that predict TC concentration. Given these 2 variables, the distribution of cholesterol levels at a fixed age could be described as a function of the year of birth (or “birth cohort”) of the participants. For the NHES and NHANES III, neither year of birth nor exact date of examination were available. Thus, for those 2 surveys, we estimated year of birth by subtracting the participant’s age from the midyear of the examination period (1961 for NHES, 1989 for NHANES III phase 1, and 1993 for NHANES III phase 2). Data regarding Hispanic ethnicity were not collected before NHANES III; therefore, analyses to differentiate persons of Hispanic ethnicity could not be performed.

In all surveys, serum TC concentration was scheduled to be measured on all examined adults, regardless of fasting status. A description of the procedures used for blood sample collection and measurement of TC has been published previously.1

Cholesterol measurements from each of the 4 surveys were standardized according to the criteria of the Centers for Disease Control and Prevention (CDC) or the CDC–National Heart, Lung, and Blood Institute Lipid Standardization Program.8 The NHES I measurements were performed by the CDC Lipid Standardization Laboratory using a modified ferric chloride reference method, and the values were corrected to the subsequently adopted CDC reference cholesterol method that is based on the method of Abell et al.9 The rationale and factors used to make the adjustments have been discussed previously.10 The NHANES I measurements were made in the CDC Lipid Standardization Laboratory, but with a newer reference method.11 In NHANES II, serum samples were analyzed in the George Washington University Lipid Research Clinic Laboratory using a Liebermann-Burchard reaction method.12,13 This method used serum calibration pools to adjust measured values to equivalent CDC reference values.12,13 In NHANES III, cholesterol levels were measured enzymatically in The Johns Hopkins University Lipid Research Clinic Laboratory using a commercially available reagent mixture (Cholesterol/HP, catalog No. 816302; Boehringer Mannheim Diagnostics, Indianapolis, Ind) based on the method of Allain et al.14

ANALYTIC PLAN

We examined age-related changes in the distribution of TC concentration across birth cohorts as sampled in the series of surveys to determine whether more recent birth cohorts were attaining lower blood cholesterol distributions than earlier birth cohorts. We tested the hypotheses that the age-adjusted 10th, 25th, 50th, 75th, and 90th percentiles of TC concentration were lower in successively more

have occurred in the cholesterol distribution of the US population beyond an exclusive focus on either the arithmetic mean or the upper extreme of the distribution. From a public health perspective, reliance on cholesterol-lowering medications cannot be a long-term solution for the control of epidemic high blood cholesterol levels that affect millions of US adults. Population-wide preventive strategies promoting appropriate behavior change are in principle much preferred, if they can be shown to be effective.2 Therefore, understanding the forces that determine the observed distributions of serum TC concentrations in human populations is necessary for the soundest development of long-range public health approaches to prevention of high blood cholesterol levels. The goal of the present epidemiologic investigation is to determine whether population-wide influences and/or the high-risk approach have been operating to produce the well-known decline in mean TC concentration in the US population.
recent US birth cohorts than in earlier cohorts. We contend that changes at the 10th, 25th, and 50th percentiles reflect population-wide influences alone, whereas changes at the 75th and 90th percentiles could reflect the combined effects of population-wide influences and high-risk approaches. For use in graphical presentations, 8 birth cohorts were constructed (1887-1899, 1900-1909, 1910-1919, 1920-1929, 1930-1939, 1940-1949, 1950-1959, and 1960-1969). Persons born in 1970 through 1975 were excluded from the graphical presentations because this birth cohort would have contributed a single point. The 5 specified percentile values of the distribution of TC were determined for the 8 birth cohorts across 6 age groups (18-24, 25-34, 35-44, 45-54, 55-64, and 65-74 years). Plotting these percentile values within each stratum defined by age and birth cohort displays the unadjusted birth cohort patterns of association between age and the percentile for TC.

The primary goal of these analyses was to determine whether there were differences in the selected percentiles of TC across birth cohorts at a fixed age. An analysis of covariance approach was used, wherein the expected value for a percentile of the TC distribution was modeled as a function of the birth year, age, and nonlinear and interaction terms, specifically:

$$TC_x = \beta_0 + \beta_1 (Age) + \beta_2 (Age^2) + \beta_3 (BY) + \beta_4 (Age \times BY) + \epsilon,$$

where $TC_x$ is the x-th percentile (10th, 25th, 50th, 75th, or 90th) of the TC distribution, Age is the birth year of the participant at the time of the survey, BY is the birth year of the participant, and $\beta$ are the regression parameters. The goal of this analysis was to assess whether there were differences in the age-related pattern of TC across birth years. These differences were assessed in the full model described herein and in a simplified model excluding age-by-birth year interaction terms. The Age\(^2\) term was included in the model to account for the curvilinear nature of the age-related pattern of TC concentration. The Age \times BY and Age\(^2\) \times BY interaction terms were included in the models to test whether the age-related pattern of TC differed across birth cohorts, that is, whether the slope of the age-related “change” in TC was more or less steep across birth cohorts. These models were fit using the asymmetric square error loss approach used by Efron.\(^b\) In ordinary regression (or least squares), the relationship between predictor variables and the mean value for the outcome variable is estimated by providing equal weight to residuals above and below the estimated regression line. Efron\(^b\) suggested that the relationship between predictor variables and percentiles of the distribution can be estimated by “shifting” the regression line by assigning differential weight to residuals above the regression line relative to those below the regression line. By more heavily weighting residuals above (relative to below) the regression line, the line that minimizes the weighted sum of squares will shift the regression line upward. For any specific weight, the slope and intercept defining a unique regression line can be found by Newton-Raphson methods.\(^c\) The percentile associated with the regression line can be determined by tabulating the number of observations above and below the estimated line. Specific percentiles of interest for these analyses (10th, 25th, 50th, 75th, and 90th) were found by an additional Newton-Raphson search. The variances of the estimated parameters were provided by bootstrap methods with 100 replications.\(^d,e\) Analyses were adjusted for sex and ethnicity. Additional percentile regression analyses were performed to estimate the 1st, 5th, 15th, 20th, 30th, 35th, 40th, 45th, 55th, 60th, 65th, 70th, 80th, 85th, 95th, and 99th percentiles. These percentiles were used in developing a graphical display of the estimated TC distributions of 50-year-old persons born in 1910 (measured in 1960) and 1940 (measured in 1990).

Complex sampling strategies were used in the individual surveys to enable the estimation of population characteristics such as prevalence of high blood cholesterol levels that were applicable to the noninstitutionalized adult population of the United States. The incorporation of these sampling weights in the current analyses was not feasible because appropriate statistical techniques have not been developed for weighted percentile regression. These sampling weights would have a major impact on the estimation of the prevalence of high blood cholesterol levels in the US population, but in general have a lesser impact on the estimation of associations between TC and other variables, such as year of birth. All analyses were conducted using STATA 5.0 statistical software (Stata Corp, College Station, Tex).

### Distribution of Participants With Serum Total Cholesterol Concentrations in the National Health Examination Survey and the National Health and Nutrition Examination Surveys I, II, and III by Year of Birth and Age at Examination

<table>
<thead>
<tr>
<th>Year of Birth</th>
<th>18-24</th>
<th>25-34</th>
<th>35-44</th>
<th>45-54</th>
<th>55-64</th>
<th>65-74</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1887-1899</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1361</td>
</tr>
<tr>
<td>1900-1909</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6090</td>
</tr>
<tr>
<td>1910-1919</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6907</td>
</tr>
<tr>
<td>1920-1929</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7602</td>
</tr>
<tr>
<td>1930-1939</td>
<td>389</td>
<td>1463</td>
<td>3457</td>
<td>966</td>
<td>1346</td>
<td></td>
<td>7621</td>
</tr>
<tr>
<td>1940-1949</td>
<td>1285</td>
<td>4465</td>
<td>1350</td>
<td>1376</td>
<td></td>
<td></td>
<td>8476</td>
</tr>
<tr>
<td>1950-1959</td>
<td>2958</td>
<td>1897</td>
<td>2146</td>
<td></td>
<td></td>
<td></td>
<td>6801</td>
</tr>
<tr>
<td>1960-1969</td>
<td>1005</td>
<td>2313</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3318</td>
</tr>
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<td>1970-1975</td>
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<td></td>
<td></td>
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<td>1360</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>6997</td>
<td>10396</td>
<td>8934</td>
<td>6847</td>
<td>7233</td>
<td>9129</td>
<td>49536</td>
</tr>
</tbody>
</table>

*Ellipses indicate data not applicable.*
data for the earliest birth cohorts were limited necessarily to the older age groups. Likewise, those participants in the most recent birth cohorts could not have achieved an advanced age by the time of the final examination, and as such the data for the most recent birth cohorts were limited necessarily to the younger age groups.

**TC CONCENTRATION AND AGE**

Observed and estimated percentile curves for TC concentrations of persons aged 18 through 74 years are shown by birth cohort in Figure 1. At each percentile shown, TC concentration was greater at successively older ages except for a plateau or decrease for persons older than 60 years. In the regression analyses of TC percentiles that included age, age<sup>2</sup>, race, sex, and year of birth, the coefficients for the linear age terms were positive (higher TC levels at older ages) and significant (P<.001). Conversely, the coefficients for the age<sup>2</sup> (quadratic) term were negative (because of a declining rate of increase across the whole age range and a decrease in TC concentration at the oldest ages) and significant (P<.001).
TC CONCENTRATION AND BIRTH YEAR

At each percentile shown, more recent birth cohorts attained lower TC concentrations than did earlier birth cohorts (Figure 1). The differences between the birth cohorts were larger the higher the percentile considered; nevertheless, the observed declining pattern with more recent birth cohorts was significant ($P < .001$) for all percentiles considered. Adjusted for age, sex, and ethnicity, the 10th, 25th, 50th, 75th, and 90th percentiles of TC concentrations were estimated to be 3.4, 3.9, 4.7, 5.7, and 7.1 mg/dL (0.09, 0.10, 0.12, 0.15, and 0.18 mmol/L) lower, respectively, for every successive 10 years later in date of birth. Additional models (results not shown) were examined to assess differences in this birth cohort effect between sex and ethnic groups. Decreasing TC concentrations were observed at all 5 percentiles in both men and women, with greater decreases observed in women than in men (for sex–by–birth year interaction term, $P < .001$ in all 5 models). No ethnic difference was observed at the 75th and 90th percentiles.

The rate of the estimated decrease in the percentiles of TC also varied by age as shown in Figure 1. Not only were TC concentrations lower for more recent birth cohorts than for earlier birth cohorts but also the apparent increase in TC concentration with age was less rapid (for interaction terms, $P < .001$ in all 5 models). That is, the apparent rate of increase in TC concentrations attributable to aging was slower in more recent cohorts than in earlier cohorts. This finding is indicated by the divergence of the estimated curves shown in Figure 1, at least through the end of middle age. (These patterns of change in TC concentration by age are based on observations made in independent samples of persons belonging to any particular birth cohort at successive surveys.)

The birth cohort changes shown in Figure 1 have an impact on the estimated distribution of TC concentration at any given age for 2 or more contrasting birth cohorts. Thus, the estimated distributions of TC concentration for 50-year-olds born in 1910 and 1940 are shown in Figure 2. The entire distribution of TC concentrations was shifted to lower levels in the 1940
Adverse trends in physical activity and obesity have occurred during this century until the mid-1960s. As levels of these other risk factors, including cigarette smoking, diabetes mellitus, dietary imbalance, and physical inactivity, have stabilized or declined, it is likely that the declining trend in the coronary heart disease mortality during the same period. A previously demonstrated downward shift in blood pressure may also have contributed to the decline in coronary heart disease mortality. Coronary heart disease has a complex risk factor structure that prominently includes other risk factors, including cigarette smoking, diabetes mellitus, dietary imbalance, and physical inactivity. The pattern of increasing coronary heart disease mortality until the mid-1960s may reflect changes in these other risk factors, most notably the increase in smoking rates during the early part of this century until the mid-1960s. As levels of these other risk factors, including smoking rates, have stabilized or declined, it is likely that the declining trend in the entire cholesterol distribution has played an important role in the decrease in coronary heart disease mortality observed in the United States during the past 40 years.

A limitation inherent in the data available through these surveys is the lack of repeated measures of cholesterol concentrations with increasing age for specific individuals. Rather, these data represent repeated independent samples from these birth cohorts. Thus, the use of these data to describe age-related changes in cholesterol concentrations is similar to the use of cross-sectional data to construct growth charts for children. In the analogous scenario involving the construction of growth charts, the tempo of growth in a typical child is markedly blunted in cross-sectional data. Thus, growth charts constructed from cross-sectional data do not adequately reveal the typical growth pattern of an indi-
vidual. Nevertheless, if growth charts constructed based on cross-sectional data from different birth cohorts of children differed substantially, one would be able to identify the fact that some birth cohorts of children were growing faster (or slower) or taller (or shorter) than other birth cohorts. Likewise, although the tempo of cholesterol change with age for a typical individual cannot be accurately described using these data, substantial differences in the change of cholesterol with age between birth cohorts are equally compelling as representing a cohort effect as the analogous example regarding growth in children.

The alternative (and in principle stronger) study design, a series of population-based cohort studies following persons born between 1887 and 1974 from ages 18 through 74 years, can no longer be performed. Establishing and following current birth cohorts would be of great interest but would address the question of future changes in the distributions of cholesterol rather than previous changes. Thus, the present epidemiologic approach was the only means available for the stated purposes of gaining greater insight relevant to population-level changes in cholesterol distributions during the past several decades.

Techniques for cholesterol concentration measurement differ across surveys.1 The most likely effect of this change on the analyses reported herein would be to introduce random error or “noise” and thereby to decrease the likelihood of observing a consistent change across birth cohorts. Furthermore, if the quality of cholesterol measurements improved with successive surveys, the expected effect of this change in method would be a reduction in the number of extreme measurements caused by measurement error. As the proportion of extreme measurements due to error decreased, there would be an associated increase in the lower percentiles (10th and 25th) of cholesterol in the absence of other influences. Therefore, if temporal changes in measurement error were important influences, we would at worst have underestimated the true decline in these lower percentiles.

The nature of the shift in the cholesterol distribution demonstrated herein supports the contention that changes in population-wide behavior and environmental conditions have contributed to the decline in mean cholesterol concentrations observed in the United States. As a result, these findings support the potential utility of planned population approaches to risk factor reduction and chronic disease prevention.

Efforts aimed at preventing the development of high blood cholesterol levels (ie, primary prevention of hyperlipidemia) through changes in health behaviors at the population level should go forward simultaneously with intervention and chronic disease prevention. This knowledge could enhance greatly our prospects for the prevention of cardiovascular diseases.

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REFERENCES


