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.1 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. Rose2 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 entire 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.3 Therefore, to understand the observed temporal changes in cardiovascular disease mortality, it is important to determine the nature of shifts that
METHODS

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. 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. 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 serial 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.

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. 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. The rationale and factors used to make the adjustments have been discussed previously. The NHANES I measurements were made in the CDC Lipid Standardization Laboratory, but with a newer reference method. In NHANES II, serum samples were analyzed in the George Washington University Lipid Research Clinic Laboratory using a Liebermann-Burchard reaction method. This method used serum calibration pools to adjust measured values to equivalent CDC reference values. 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.

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

RESULTS

POPULATION CHARACTERISTICS

Across the 4 surveys, 52646 men and women met year of birth and age eligibility criteria to be included in this analysis, including 6530 participants from NHES, 16704 from NHANES I, 12504 from NHANES II, and 16908 from NHANES III. This composite data file included 29145 women and 23501 men, 41430 white participants, 10053 black participants, and 1163 persons of other or unknown race or ethnicity. Data regarding TC concentration were missing for 3110 persons (5.9%), leaving 49536 participants for analysis. The distribution of these participants by year of birth (as reported or estimated) and age is shown in the Table. Because those born in the earliest birth cohorts were old at the time of the first examination, the

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recent US birth cohorts than in earlier cohorts. We con-
tend 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 com-
combined effects of population-wide influences and high-risk
approaches. For use in graphical presentations, 8 birth co-
horts 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 ex-
cluded from the graphical presentations because this birth
cohort would have contributed a single point. The 5 speci-
fied percentile values of the distribution of TC were de-
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 interac-
tion terms, specifically:

\[ TC_i = \beta_0 + \beta_1 \times (\text{Age}) + \beta_2 \times (\text{Age}^2) + \beta_3 \times (\text{BY}) + \beta_4 \times (\text{Age} \times \text{BY}) + \beta_5 \times (\text{Age}^2 \times \text{BY}), \]

where \( TC_i \) is the \( i \)-th percentile (10th, 25th, 50th, 75th, or
90th) of the TC distribution, \( \text{Age} \) is the age of the partici-

dant at the time of the survey, \( \text{BY} \) is the birth year of the par-
ticipant, and \( \beta_i \) 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 dif-
erences were assessed in the full model described herein and
in a simplified model exclusive of age-by-birth year interac-
tion terms. The \( \text{Age}^2 \) term was included in the model to ac-
count for the curvilinear nature of the age-related pattern
of TC concentration. The \( \text{Age} \times \text{BY} \) and \( \text{Age}^2 \times \text{BY} \) 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. In ordinary regression (or least squares), the rela-
tionship 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 suggested that the relationship between predictor vari-
bles 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 mini-
mizes the weighted sum of squares will shift the regression
line upward. For any specific weight, the slope and inter-
cept defining a unique regression line can be found by Newton-
Raphson methods. The percentile associated with the re-
gression line can be determined by tabulating the number of
observations above and below the estimated line. Specific per-
centiles 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 pro-
vided by bootstrap methods with 100 replications. 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 percentile
terms were used in developing a graphical display of the es-
timated 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 indi-

cidual surveys to enable the estimation of population char-
acteristics such as prevalence of high blood cholesterol lev-
els 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 be-
cause appropriate statistical techniques have not been devel-
oped 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 popu-
lation, 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 sta-
tistical 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>
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<tr>
<td>1900-1909</td>
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<td></td>
<td></td>
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<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>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7602</td>
</tr>
<tr>
<td>1930-1939</td>
<td></td>
<td></td>
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<td></td>
<td>7621</td>
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<td>1940-1949</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8476</td>
</tr>
<tr>
<td>1950-1959</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6801</td>
</tr>
<tr>
<td>1960-1969</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3318</td>
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<tr>
<td>1970-1975</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1360</td>
</tr>
<tr>
<td>Total</td>
<td>6897</td>
<td>10396</td>
<td>8934</td>
<td>6847</td>
<td>7233</td>
<td>9129</td>
<td>49536</td>
</tr>
</tbody>
</table>
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, age², 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 age² (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<.01 in all 3 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 persons born in 1910 and 1940 are shown in Figure 2. The entire distribution of TC concentrations was shifted to lower levels in the 1940
birth cohort relative to the 1910 birth cohort, with a greater shift in the upper range of the TC distribution. This view of the changing distribution illustrates clearly the effects described by Rose and addressed herein.

These analyses demonstrate that the entire distribution of TC concentrations has shifted to lower levels in the United States. This downward shift, previously described primarily for the mean, is present at even the lower percentiles (10th and 25th) of blood pressure, where pharmacologic management can be assumed to have had virtually no impact. Thus, this shift in the overall distribution cannot be attributed solely to treatment effects but must have resulted to an important degree from population-wide behavioral and environmental influences on TC concentrations. The finding that the shift was observed among women and men and among black and white populations supports the contention that population-wide behavioral and environmental influences are operating to cause this birth cohort effect.

Previously, populations have been shown to differ in the slope of cholesterol increase with age. In this report, the slope of cholesterol increase with increasing age was less steep for more recent birth cohorts than for earlier cohorts. This finding indicates that the forces that influence the slope of the cholesterol increase with age may be dynamic and may therefore be modifiable through planned prevention strategies. If this pattern were to continue, we could expect more recent birth cohorts to develop clinically defined high blood cholesterol concentrations less commonly in the future than have earlier birth cohorts. Such a finding would be strongly supportive of an effect of primary prevention of high blood cholesterol levels in the US population.

The population influences responsible for this substantial change in cholesterol development are not yet known. Adverse trends in physical activity and obesity have been reported; however, important beneficial dietary changes may have occurred, for example, increased consumption of fruits and vegetables and decreased consumption of foods containing saturated fatty acids. A recent report from the CARDIA Study documented birth cohort-related reductions in TC and low-density lipoprotein cholesterol concentrations in association with reductions in dietary saturated fatty acid and cholesterol intake. It is also instructive to note that pellagra was endemic in much of the United States during the early 1900s, an observation that underscores the magnitude of the dietary changes that have occurred during the past century.

The shift to lower blood cholesterol concentrations was more pronounced in the upper range of the distribution. The larger decrease in the upper range could in theory reflect the combined effects of prevention and treatment, with the prevention effect seen at the lower percentiles complemented by the specific treatment effect on those with recognized and treated high blood cholesterol levels. However, use of effective cholesterol-lowering medications was not widespread during the period covered by these surveys. Alternatively, the greater decline at the upper aspect of the cholesterol distribution could reflect a greater cholesterol-lowering effect of societal and behavioral changes among persons with high cholesterol concentrations whether due to genetic differences in response to behavior change or more extreme initial behavior patterns with correspondingly greater latitude for improvement.

The US mortality from coronary heart disease increased during this century until the mid-1960s and has been declining since. One may speculate that since high blood cholesterol levels stand as one of the most important risk factors for coronary heart disease, the downward shift in the distribution of cholesterol since the middle of the 20th century may be playing a central role in the more than 50% decline in 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. 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 changes in health behaviors at the population level through pharmacologic intervention and chronic disease prevention.

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