Age-related changes in total and high-density-lipoprotein cholesterol in elderly Dutch men.

Age-Related Changes in Total and High-Density–Lipoprotein Cholesterol in Elderly Dutch Men

ABSTRACT

Objectives. This study investigated changes in total and high-density–lipoprotein cholesterol (HDL) concentrations with age and time in elderly men.

Methods. A cohort of men born between 1900 and 1920 from the Dutch town of Zutphen was examined in 1977 and 1978 (n = 571), 1985 (n = 885), 1990 (n = 555), and 1993 (n = 345). Linear regression analysis and random-effects models were used to assess cross-sectional and longitudinal age- and time-related changes in cholesterol concentrations.

Results. In both cross-sectional and longitudinal analyses, total cholesterol decreased by 0.04 mmol/L a year with age. The longitudinal change was observed in the entire population as well as in men who participated in all four examinations (n = 135) and in a subgroup of men who were free of common chronic diseases, were not on cholesterol-lowering medication or a prescribed diet, and rated themselves as being "healthy" (n = 64). HDL cholesterol did not change significantly with age neither on a cross-sectional nor on a longitudinal basis.

Conclusions. Among elderly men, total cholesterol diminishes with age both on a cross-sectional and on a longitudinal basis; HDL cholesterol does not vary with age in any way. (*Am J Public Health.* 1996;86: 798–803)

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Introduction

The importance of total and high-density–lipoprotein (HDL) cholesterol concentrations for coronary heart disease in the elderly is still a subject of debate.[1–9] Part of the controversy may be due to changing cholesterol concentrations with advancing age.[10] Concentrations measured in old age may not be representative of a lifetime exposure and may therefore attenuate associations. Total cholesterol declines with advancing age in elderly men both on a cross-sectional and on a longitudinal basis.[10–15] It is still unclear whether this observed decline is a consequence of selective survival,[16] clinical or subclinical disease,[12–14] other unknown factors associated with age and cholesterol concentrations,[17,18] or the aging process itself. HDL cholesterol concentrations do not seem to vary with age on a cross-sectional basis in elderly men.[19–21] Longitudinal changes in HDL cholesterol have not specifically been reported for elderly subjects.

We studied changes in total and HDL cholesterol concentrations with age in older Dutch men both in a cross-sectional and a longitudinal setting and investigated whether these changes were independent of secular trends, selective mortality, loss to follow-up, or changes in health status.

Methods

Study Cohort

The Zutphen Study is a longitudinal investigation of chronic-disease risk factors initiated in 1960 among middle-aged men, born between 1900 and 1919, as the Dutch contribution to the Seven Countries Study.[22] In 1985, 555 men from the 1960 cohort were still alive. In addition to this group, a new random sample (two out of three) of all men who were born between 1900 and 1920, who lived in Zutphen, and who were not part of the 1960 cohort were selected to take part in the study. Both total and HDL cholesterol concentrations were measured four times between 1977/78 and 1993 (Table 1).

Lipid Measurements

Clinical examinations took place between March and June of each examination year. During the 1977/78 examination, information from the participants was collected during the same months in one of either of the years. In all examination years, nonfasting venous blood samples were taken for the analysis of total and HDL cholesterol. Analyses were carried out in the standardized lipid laboratory of the Department of Human Nutrition, Agricultural University, Wageningen, The Netherlands. HDL cholesterol was isolated after precipitation of apo-lipoprotein B–containing particles by heparin-Mn^{2+} in 1977/78[23] and by dextran sulphate-Mg^{2+} in the other years.[24] In 1977/78, cholesterol was determined with Huang's method,[25] which was calibrated on Abell–Kendall standardized sera. In 1985, 1990, and 1993, cholesterol

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was determined enzymatically with the CHOD-PAP mono-testkit from Boehringer Mannheim, Germany.[26,27] For total cholesterol, standardization was realized by using calibration sera from the Lipid Standardization Laboratory, Centers for Disease Control and Prevention (Atlanta, Ga, USA) in 1977/78 and from the Foundation of Chemical Analysis Quality Control (The Netherlands) since 1985. For HDL cholesterol, calibration sera prepared according to van der Haar and coworkers[28] were used since 1985. In all four examination rounds the deviations of total cholesterol concentrations from the control sera were below the international norm of 3%. For HDL cholesterol the deviations from control sera were always lower than 10%. The combined within- and between-run coefficient of variation for control sera was lower than 3% for both total and high-density cholesterol at the time of the analyses in all four examination periods. In 1977/78, 1985, and 1990 cholesterol concentrations were measured in serum and in 1993 in EDTA plasma. Plasma values were multiplied by 1.030[29] to make them comparable to the serum values in the other examination years, because plasma may be diluted by the addition of the anticoagulant EDTA.[29] Because of the systematic lower concentrations of total cholesterol in 1993 compared with the concentrations in the other examination years, even after adjustment of the values, plasma from a random sample of 50 men was reanalyzed in July 1994 with the same method used in the 1985, 1990, and 1993 examinations.

TABLE 1—Population Size and Participation Rate, by Examination Year: The Zutphen Study, 1977/78 through 1993

	1977/78	1985	1990	1993
No. men invited	671	1266	721	544
No. participated	611	939	560	390
Participation rate, %	91	74	78	72
No. men with total and HDL cholesterol measurements	571[a]	885	555	345

[a]HDL cholesterol concentrations were available for 570 men.

TABLE 2—Mean Values for Baseline Characteristics in All Men and in Subgroups of the Total Study Population, by Examination Period: The Zutphen Study, 1977/78 through 1993

Examination Year	Maximum No. Men	Mean (SD) Values: All Men[a]	Men Who Participated in Each Examination (n = 135)	"Healthy" Men Who Participated in Each Examination[b] (n = 64)
Age, y				
1977/78	571	66.3 (5.2)	63.7 (4.1)	63.5 (4.2)
1985	885	71.5 (5.3)	70.7 (4.1)	70.5 (4.2)
1990	555	75.1 (4.7)	75.7 (4.1)	75.5 (4.2)
1993	345	77.8 (4.4)	78.7 (4.1)	78.5 (4.2)
Total cholesterol, mmol/L				
1977/78	571	5.90 (1.06)	5.94 (0.97)	5.96 (1.00)
1985	885	6.10 (1.11)	6.10 (0.99)	6.13 (1.06)
1990	555	6.07 (1.13)	6.08 (1.01)	6.07 (1.05)
1993	345	5.56 (1.06)	5.43 (1.06)	5.47 (1.00)
HDL cholesterol, mmol/L				
1977/78	570	1.23 (0.31)	1.20 (0.28)	1.26 (0.29)
1985	885	1.12 (0.29)	1.10 (0.27)	1.12 (0.27)
1990	555	1.16 (0.31)	1.10 (0.30)	1.13 (0.31)
1993	345	1.20 (0.35)	1.13 (0.35)	1.18 (0.36)

[a]Mean values are based on the maximum number of men.
[b]These men did not have and had never had angina pectoris, myocardial infarction, diabetes mellitus, or cancer; did not use and had never used cholesterol-lowering medication or been on a prescribed diet; and rated themselves to be "healthy" or "rather healthy."

Measurement of Other Variables

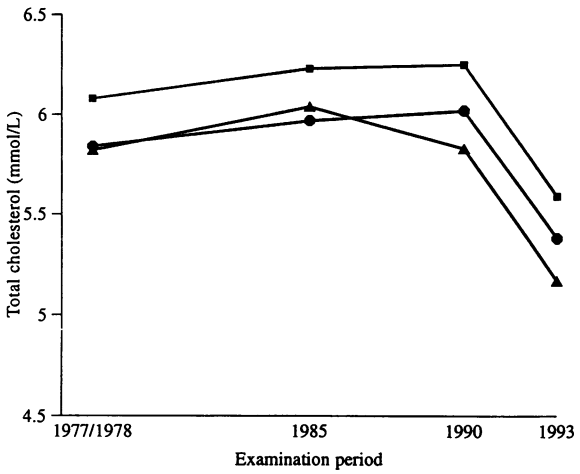
In 1985 and 1990 extensive information on use of cholesterol-lowering medication and prescribed diets for a high cholesterol concentration was obtained through a standardized questionnaire. In 1993 information was only collected on prescribed diets. In 1977/78, no such information was collected. Note that only very few men were on cholesterol-lowering therapy during the examinations (25 in 1985, 10 in 1990, and 8 in 1993).

In 1977/78, 1985, and 1990 information on the presence or a history of angina pectoris or myocardial infarction was obtained through the Dutch translation of the Rose questionnaire.[30] History of diabetes mellitus and any form of cancer was reported with a standardized questionnaire. All the information was verified with hospital discharge data and information from the subjects' general practitioners. In 1993 additional information on the presence or history of these diseases was obtained with a self-administered questionnaire.

Information on self-rated health was collected in 1985, 1990, and 1993 with the question: "How do you feel?" The four answer categories were "healthy," "rather healthy," "moderately healthy," and "not healthy." This information was not collected in 1977/78. Low self-rated health has been associated with an increased risk of mortality independent of traditional risk factors and a history of chronic diseases.[31] It is thought to be an indicator of underlying (subclinical) disease, which may in turn be accompanied by lowered total cholesterol concentrations.

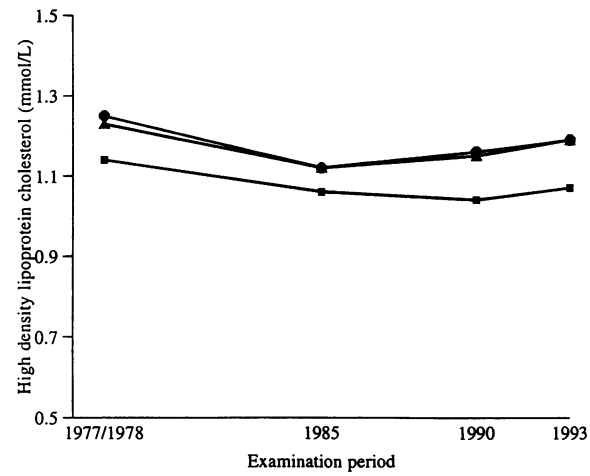
Statistical Methods

To account for selective survival or selective participation and the possibility that the total cholesterol concentration is lowered in diseased people,[12] we analyzed three subgroups of participants. The first group comprised the total population of men who participated in at least one



Note. ■ = 1915 through 1920 (n = 59); ● = 1910 through 1914 (n = 50); ▲ = 1900 through 1909 (n = 26).

FIGURE 1—Total cholesterol concentrations, by examination year and by birth cohort (n = 135).



Note. ■ = 1915 through 1920 (n = 59); ● = 1910 through 1914 (n = 50); ▲ = 1900 through 1909 (n = 26).

FIGURE 2—High-density lipoprotein cholesterol concentrations, by examination year and by birth cohort (n = 135).

of the examination periods (n = 1118). Another group consisted of those men who participated in each examination (n = 135). Finally we selected a "healthy" group, defined as those men from the former group who did not have a history of myocardial infarction, angina pectoris, diabetes mellitus, or cancer; had never been on cholesterol-lowering medication or a prescribed diet; and rated themselves as "healthy" or "rather healthy" (n = 64).

Statistical analyses were carried out with the SAS program (version 6.09, 1989). All tests were two sided. A paired *t* test was conducted to evaluate the difference between newly analyzed total cholesterol values and the original values from the random sample of 50 men. Cross-sectional analyses were performed with linear regression analysis of total or HDL cholesterol on age in each of the examination years. The assumption of linearity was checked visually by using the plots of the residuals by age. To perform the longitudinal analyses the repeated measures of cholesterol were related to age and time effects with a model that allowed for two sources of error: (1) within subjects between occasions and (2) between subjects. Age- and time-related changes in total and HDL cholesterol were estimated from the model. This was done with the SAS Proc Mixed Procedure, which deals with unbalanced data and assumes missing observations are missing at random.[32]

Results

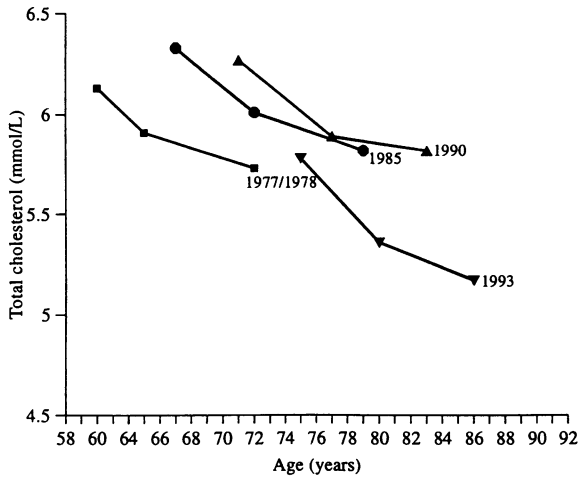
Total cholesterol concentrations increased between 1977/78 and 1985 and thereafter decreased with the largest drop observed in the last 3 years (Table 2). This progression was observed for all men, as well as for men who participated in each examination and for the healthy men who participated in each examination. The drop in total cholesterol between 1990 and 1993 was not due to measurement error. New analyses for plasma total cholesterol from a random sample of 50 men in 1994 revealed that the mean concentration in 1994 was not significantly different from the mean concentration of total cholesterol analyzed in 1993 (5.54 mmol/L [SD = 0.90] in 1994 vs 5.51 mmol/L [SD = 0.88] in 1993; $P = .15$). HDL cholesterol exhibited a decrease between 1977/78 and 1985 and a slight increase over the later examination years (Table 2). These results were similar among the three groups of men. When the birth cohorts were examined separately, the changes in total and HDL cholesterol between examination years were generally similar with the exception of an earlier drop in total cholesterol for the oldest birth cohort compared with the two younger cohorts (Figures 1 and 2). Whether this is an age-related change or a secular change with time cannot be deducted from the figure.

On a cross-sectional basis, total cholesterol diminished significantly with age in every examination year (Figures 3 and 4 and Table 3). The decrease tended to be stronger in the more recent examinations; it ranged from a decrease of 0.04 mmol/L a year in 1977/78 to a decrease of 0.06 mmol/L a year in 1993. High-density-lipoprotein cholesterol did not change consistently with age in any of the examination rounds.

On a longitudinal basis, total cholesterol decreased by 0.04 mmol/L a year with increasing age of the men (Table 4). There was no evidence for a stronger age-related change in the older birth cohorts compared with the younger ones (not shown). Total cholesterol increased between 1977/78 and 1985 and between 1985 and 1990. Between 1990 and 1993 total cholesterol decreased by 0.14 mmol/L a year solely due to a period effect. HDL cholesterol did not change with age. Between 1977/78 and 1985 HDL cholesterol decreased by 0.02 mmol/L a year. These results were essentially the same for the healthy men who participated in every examination period.

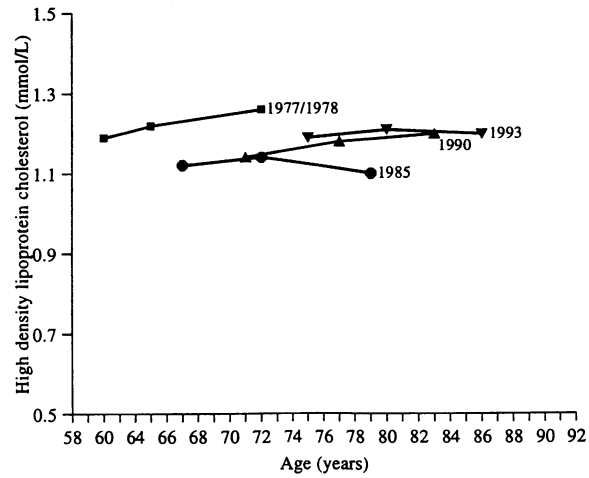
Discussion

Among men aged 58 to 91 years in our study, total cholesterol decreased with age by 0.04 mmol/L a year, and this decrease was observed in both cross-sectional and longitudinal analyses even



Note. ■ = 1977/78 (n = 571); ● = 1985 (n = 885); ▲ = 1990 (n = 555); ▼ = 1993 (n = 345).

FIGURE 3—Total cholesterol concentrations, by mean age of 5-year birth cohort (the oldest two combined) and by examination year.



Note. ■ = 1977/78 (n = 571); ● = 1985 (n = 885); ▲ = 1990 (n = 555); ▼ = 1993 (n = 345).

FIGURE 4—High-density lipoprotein cholesterol concentrations, by mean age of 5-year birth cohort (the oldest two combined) and by examination year.

after the effects of selective mortality, loss to follow-up, and impaired health had been taken into account. A considerable secular drop in total cholesterol was observed between 1990 and 1993. HDL cholesterol did not vary with age, but showed a secular drop between the first and second examination periods.

Secular Changes in Total and HDL Cholesterol

The change in the method of cholesterol determination between 1977/78 and 1985 probably did not lead to systematic differences in cholesterol concentrations between the years. Huang's method,[25] which was used in 1977/78, was calibrated on Abell–Kendall standardized sera, and the enzymatic determinations with the CHOD-PAP mono-testkit used in 1985 through 1994 were proven to agree rigidly with the method of Abell et al.[26,33] However, the change in the method of precipitating apo-lipoprotein B–containing particles between 1977/78 and 1985 may have led to systematic differences in the HDL cholesterol concentrations between the examination years. Warnick et al. found that the heparin-Mn^{2+} method of precipitation generally overestimates the cholesterol concentrations of HDL compared with the dextran sulphate-Mg^{2+} method.[24] Their regression equation can be used to estimate the expected HDL cholesterol concentration in 1977/78 if dextran sulphate-Mg^{2+} had been used (0.023 mmol/L + 0.955 × heparin-Mn^{2+} value [mmol/L]). The mean expected HDL cholesterol value was 1.17 mmol/L (SD = 0.27) for the men who participated in every examination. This value is 2.5% lower than the original value and is still significantly higher than the value measured in 1985 ($P < .001$). Thus, the change in precipitation method cannot fully explain the secular drop in HDL cholesterol observed between 1977/78 and 1985.

The drop in total cholesterol between 1990 and 1993 was unexpected. Because the newly analyzed plasma total cholesterol concentrations from the random sample of men in 1994 were not different from the concentrations determined in 1993, this drop cannot be due to measurement error. However, the laboratory analyses were generally higher than the true cholesterol content of the control sera in 1990 (mean = 0.9%) and were generally lower than the true cholesterol content of the control sera in 1993 (mean = 1.7%). These deviations from the control sera suggest that total cholesterol may have dropped by 2.6% between

TABLE 3—Linear Regression of Total or HDL Cholesterol on Age and Expected Concentrations in a Man of Mean Age in Each Examination Year, among Men Aged 58 to 91 Years: The Zutphen Study, 1977/78 through 1993

Examination Year	Regression Coefficient for Age (95% Confidence Interval)	Mean Age, y	Expected Concentration in a Man of Mean Age, mmol/L
	Total cholesterol		
1977/78	−0.038 (−0.054, −0.022)	66.3	5.89
1985	−0.043 (−0.056, −0.029)	71.5	6.07
1990	−0.043 (−0.063, −0.024)	75.1	6.11
1993	−0.058 (−0.083, −0.033)	77.8	5.55
	HDL cholesterol		
1977/78	0.004 (−0.001, 0.009)	66.3	1.24
1985	−0.002 (−0.006, 0.001)	71.5	1.14
1990	0.004 (−0.002, 0.009)	75.1	1.18
1993	−0.002 (−0.010, 0.007)	77.8	1.16

TABLE 4—Estimated Mean Changes in Total and HDL Cholesterol per Year with Age and between Examination Rounds, for All Men Aged 58 to 91 Years and "Healthy" Men: The Zutphen Study, 1977/78 through 1993

Period of Change	Mean Change (95% Confidence Interval)	
	All Men Who Participated in at Least One Examination[a]	"Healthy" Men Who Participated in Each Examination (n = 64)[b]
Total cholesterol		
With age	−0.043 (−0.054, −0.032)	−0.040 (−0.094, 0.014)
Between 1977/78 and 1985	0.066 (0.052, 0.081)	0.065 (0.005, 0.124)
Between 1985 and 1990	0.029 (0.012, 0.045)	0.028 (−0.037, 0.092)
Between 1990 and 1993	−0.135 (−0.164, −0.106)	−0.159 (−0.239, −0.079)
HDL cholesterol		
With age	−0.000 (−0.003, 0.003)	0.010 (−0.007, 0.026)
Between 1977/78 and 1985	−0.016 (−0.020, −0.011)	−0.029 (−0.047, 0.011)
Between 1985 and 1990	0.007 (0.003, 0.012)	−0.007 (−0.027, 0.190)
Between 1990 and 1993	0.011 (0.003, 0.019)	0.007 (−0.018, 0.032)

[a]For number of participants, see Table 2.
[b]For definition of "healthy," see Table 2.

1990 and 1993 due to measurement error alone. The cholesterol determinations for the high-density lipoproteins were susceptible to the same measurement errors as the total cholesterol determinations. Because there were no changes in HDL cholesterol concentrations between 1990 and 1993, this implies that measurement error alone cannot explain the drop in total cholesterol concentrations in the same period. Dietary changes among men of the cohort during 1990 and 1993 may also partly explain the decline in the total cholesterol concentration in the men. In 1991, 1992, and 1993 Fat Watch campaigns were carried out on a national level in The Netherlands.[34] Although it remains difficult to establish the effect of such mass media community intervention programs, it has been estimated that this program may have caused a drop of 3.5% in total cholesterol from 5.7 mmol/L to 5.5 mmol/L in the Dutch population between 1987 and 1992.[35] If we assume that possible changes in diet in the present cohort also resulted in a 3.5% decline in total cholesterol, together with the possible difference in measurement of total cholesterol (3.5% + 2.6% = 6.1%), this may explain most of the 6.7% (0.135 mmol/L per year) secular drop in the total cholesterol concentration observed in just 3 years in the present study.

Age-Related Changes in Total and HDL Cholesterol

Our cross-sectional analyses revealed that among men over 58 years of age total cholesterol diminished with increasing age. The percent decline in total cholesterol estimated from regression analysis amounted to 20% for men aged 72 to 92 years. Newschaffer et al. observed a 21% drop among both men and women between 75 and 95 years of age.[15] An increased age-related drop with advancing age was observed in other studies among elderly men.[15,19–21,36] In the present study, the effect also tended to be stronger in the later examination periods and possibly with increasing age of the population. These cross-sectional observations of declining total cholesterol concentrations with age may, however, have been confounded by selective survival of older men with lower cholesterol concentrations.[16]

Our longitudinal analyses also showed that total cholesterol decreases with age. The magnitude of the decline was comparable to the cross-sectional one (0.04 mmol/L per year), and the percent decline was 15%. The results were similar for men who participated in at least one examination and for men who participated in every examination, which shows that selective survival or participation did not affect our results. Newschaffer et al. reported a longitudinal decline of 9% among men and women between 75 and 95 years of age.[15]

Total cholesterol concentrations are known to be reduced in people with clinical or subclinical disease, and there is evidence that this is a consequence of a host's inflammatory response.[12] Because there is generally increasing morbidity with advancing age in older people,[13,37] it is plausible that clinical or subclinical disease led to the decrease in total cholesterol with age in this study. However, the decline in total cholesterol with age was still of the same magnitude in the subgroup of men who appeared to be and felt healthy, were not on cholesterol-lowering medication or prescribed diet, and participated in every examination year. Similar observations were made in the Honolulu Heart Program cohort of men aged 70 to 90 years.[10] Possibly other factors are involved. Metabolic and hormonal changes with advancing age may play a role by reducing the absorption of dietary determinants of cholesterol, thus leading to reduced cholesterol concentrations in the blood.[18]

Confirming earlier findings from cross-sectional studies,[19–21,36,38] HDL cholesterol did not vary with age in the cross-sectional analyses. Wilson and coworkers[39] recently reported that HDL cholesterol declined by 0.07 mmol/L between 1979 and 1983 among men initially aged 65 to 79 years in the Framingham Study. However, they did not take into account possible time-related changes in cholesterol concentrations. Moreover, the aim of their study was to investigate the determinants of change in cholesterol concentrations and not to specifically described longitudinal changes with advancing age. Our report is the first on longitudinal changes in HDL cholesterol concentrations with age in elderly men in which time- and age-related changes have been disentangled. It shows no longitudinal changes in HDL cholesterol with increasing age.

Conclusion

Our study shows that total cholesterol diminishes with age in elderly men both on a cross-sectional and on a longitudinal basis, whereas HDL cholesterol does not vary with age in any way. A secular drop in total cholesterol was observed between 1990 and 1993, and this group will be followed to see whether this secular reduction is sustained. □

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