5000 (n=30) except in one sample. Thus there was practically no overlapping between these groups. In the intermediate range there was more variation.

Measurement of blood echogenicity could be developed into a fast method for monitoring certain inflammatory diseases and is fairly independent of packed cell volume; the information obtained is similar to that given by the erythrocyte sedimentation rate. Measuring blood echogenicity also allows study of the tendency for erythrocyte aggregation in relation to shear rate, which may be a potentially important variable of blood rheology. A further advantage is that, in theory, blood echogenicity can be measured non-invasively in vivo.

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1 Fåhraeus R. The suspension stability of the blood. *Acta Med Scand* 1921;55: 1-228.
2 Rampling MW, Whittingstall P. A comparison of five methods for estimating red cell aggregation. *Klin Wochenschr* 1986;**64**:1084-8.
3 Stuart J, Lewis SM. Monitoring the acute phase response. *BMJ* 1988;**297**: 1143-4.
4 Sigel B, Machi J, Beitler JC, Justin JR. Red cell aggregation as a cause of blood-flow echogenicity. *Radiology* 1983;**148**:799-802.
5 Shung KK. Physics of blood echogenicity. *Journal of Cardiovascular Ultrasonography* 1983;2:401-6.
6 Shung KK. Ultrasonic characterization of biological tissues. *J Biomech Eng* 1985;**107**:309-14.
7 Alanen A, Kormano M. Ultrasonic echoes registered from erythrocytes. *Invest Radiol* 1985;**20**:521-4.
8 Kallio T, Alanen A. A new ultrasonic technique for quantifying blood echogenicity. *Invest Radiol* 1988;**23**:832-5.
9 Neijadlik DC, Engelhardt C. An evaluation of the Guest method for determining erythrocyte sedimentation rate. *Am J Clin Pathol* 1977;**68**: 766-8.
10 The ESR—an outdated test? [editorial]. *Lancet* 1982;i:377.
11 International Committee for standardization in haematology (expert panel on blood rheology). Guidelines on selection of laboratory tests for monitoring the acute phase response. *J Clin Pathol* 1988;**41**:1203-12.
12 Borders SE, Fronek A, Kemper WS, Franklin D. Ultrasonic energy backscattered from blood. An experimental determination of the variation of sound energy with hematocrit. *Ann Biomed Eng* 1978;6:83-92.
13 Wolverson MK, Nouri S, Joist JH, Sundaram M, Heiberg E. The direct visualization of blood flow by real-time ultrasound: clinical observations and underlying mechanisms. *Radiology* 1981;**140**:443-8.
14 Yuan YW, Shung KK. Ultrasonic backscatter from flowing whole blood. I: Dependence on shear rate and hematocrit. *J Acoust Soc Am* 1988;**84**:52-8.
15 Sigel B, Coelho JCU, Schade SG, Justin J, Spigos DG. Effect of plasma proteins and temperature on echogenicity of blood. *Invest Radiol* 1982;**17**: 29-33.

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Does plasma cholesterol concentration predict mortality from coronary heart disease in elderly people? 18 year follow up in Whitehall study

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Abstract

***Objective*—To explore the extent to which the relation between plasma cholesterol concentration and risk of death from coronary heart disease in men persists into old age.**

***Design*—18 year follow up of male Whitehall civil servants. Plasma cholesterol concentrations and other risk factors were determined at first examination in 1967-9 when they were aged 40-69. Death of men up to 31 January 1987 was recorded.**

***Subjects*—18 296 male civil servants, 4155 of whom died during follow up.**

***Main outcome measures*—Cause and age of death. Cholesterol concentration in 1967-9 and number of years elapsed between testing and death.**

***Results*—1676 men died of coronary heart disease. The mean cholesterol concentration in these men was 0·32 mmol/l higher than that in all other men (95% confidence interval 0·26 to 0·37 mmol/l). This difference in cholesterol concentrations fell 0·15 mmol/l with every 10 years' increase in age at screening. The risk of raised cholesterol concentration fell with age at death. Compared with other men cholesterol concentration in those who died of coronary heart disease was 0·44 mmol/l higher in those who died aged <60 and 0·26 mmol/l higher in those aged 60-79 (p=0·03). For a given age at death the longer the gap between cholesterol measurement and death the more predictive the cholesterol concentration, both for coronary heart disease and all cause mortality (trend test p=0·06 and 0·03 respectively).**

***Conclusion*—Reducing plasma cholesterol concentrations in middle age may influence the risk of death from coronary heart disease in old age.**

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Introduction

Much international effort is being put into changing plasma cholesterol concentrations of whole populations to prevent coronary heart disease.[1] There is therefore much interest in whether total cholesterol concentration in plasma predicts coronary heart disease in elderly people. In the Framingham study serum cholesterol concentration became less important as a risk factor as the population aged,[1] although other studies do not agree with this finding.[2] If risk factors do not predict disease in elderly people there is little justification for attempting to reduce these risk factors in elderly people.

Most studies examining the predictive value of cholesterol concentration in older people had short follow up so that the age at which cholesterol concentration was measured and the age at death were close. The 18 year follow up of civil servants in the Whitehall study[3] enables us to examine how cholesterol concentrations at younger age predict death from coronary disease occurring considerably later.

Subjects and methods

In the Whitehall study 19 018 male civil servants aged 40 to 69 were examined during 1967-9.[3] The plasma cholesterol concentrations of 18 309 men were measured at entry to the study in a capillary blood sample by using the then standard Technicon method N 24a.[4] These cholesterol measurements may have been too low for technical reasons, and the overall mean of 5·10 mmol/l in these men is probably an underestimate by 10-15%. The records of the men held at the NHS Central Register were flagged and we were notified of deaths of these men up to 31 January 1987. During this period 13 men died of unknown causes, and we therefore excluded them from all cause-specific analyses. The remaining 18 296 men, who have been followed for a minimum of 18 years since the initial screening, formed the basis for our analysis.

To distinguish between age at screening and age at risk (age at death) during the subsequent follow up, each subject's total follow up period was partitioned

into single years of observation. For each of these individual years of observation a new record was created consisting of each subject's current age at risk together with their initial cholesterol concentration and their length of follow up during that year. Deaths were allocated to the appropriate current age and year of follow up category. In analyses of mortality from coronary heart disease subjects who died from other causes were included in the follow up until the year of their death at which point they were censored. We then cross classified the data into five year groups according to age at screening, age at risk, and interval of follow up and calculated mortality from coronary heart disease using the person years at risk. We compared the mean plasma cholesterol concentrations of men who had died of coronary heart disease with those of other men in the same groups.

Proportional hazards analyses[5] relating mortality from coronary heart disease to plasma cholesterol concentration and current age at risk were computed for each combination of age at risk and interval of follow up. These cholesterol proportional hazards coefficients and their standard errors were then used to calculate, independently for various ages at risk and intervals of follow up, the change in risk of coronary heart disease associated with a given change in plasma cholesterol concentration. We performed similar analyses for mortality from other causes and total mortality.

Results

During the follow up 1676 men (9%) died of coronary heart disease. Figure 1 shows the distribution of these deaths by age at screening and by interval of follow up. Mortality from coronary heart disease increased with age both cross sectionally (with age at screening) and longitudinally (with follow up interval within each age cohort). Only 44% of the men who died of coronary heart disease died before the age of 65, even though 84% of the men were aged under 60 at screening. More men aged over 75 died of coronary heart disease (216) than did men under 55 (128). Thus we can relate the risk of death from coronary heart disease in elderly people to risk factors measured at younger ages.

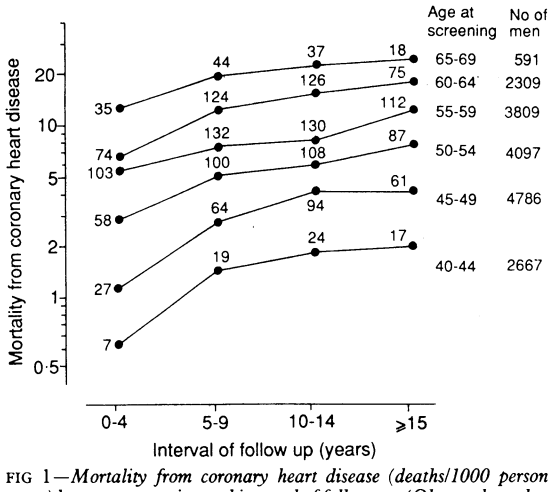

FIG 1—*Mortality from coronary heart disease (deaths/1000 person years) by age at screening and interval of follow up. (Observed number of deaths from coronary heart disease are given by each point)*

TOTAL CHOLESTEROL CONCENTRATION AND AGE AT SCREENING

The total cholesterol concentration in plasma was not associated with age. Men screened when aged 45-49 had the highest mean concentration 1·6% higher than the overall mean, and men screened aged 65-69 had the lowest mean concentration, 3·7% lower than the overall mean. The mean total cholesterol concentration in the 1676 men who died of coronary heart disease was 0·32 mmol/l higher than that in all other men (95% confidence interval 0·26 to 0·37 mmol/l). The mean difference in the total cholesterol concentration in plasma between the men who died of coronary heart disease and other men, fell with age at screening (fig 2). Linear regression showed that this difference decreased by 0·15 mmol/l for every increase of 10 years in age at screening.

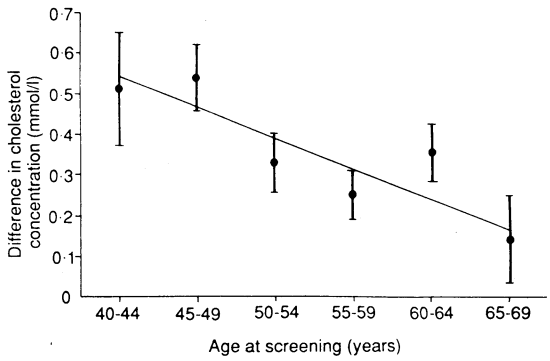

FIG 2—*Mean (SE) difference in plasma cholesterol concentration (mmol/l) between men who died of coronary heart disease and other men by age at screening*

TABLE I—*Mean (SE) mortality and mean (SE) difference in plasma cholesterol concentration between men who died of coronary heart disease and all other men according to age at death and interval of follow up**

Age at death	Interval of follow up (years) 0-4	5-9	10-14	≥15	All intervals
	Difference in mean total cholesterol (mmol/l)				
50-54	0·27 (0·28)	0·58 (0·20)			0·42 (0·15)
55-59	0·35 (0·14)	0·37 (0·13)	0·67 (0·15)		0·44 (0·08)
60-64	0·18 (0·13)	0·36 (0·10)	0·35 (0·12)	0·26 (0·17)	0·29 (0·06)
65-69	0·14 (0·22)	0·20 (0·11)	0·18 (0·11)	0·31 (0·15)	0·20 (0·07)
70-74		0·04 (0·12)	0·36 (0·10)	0·27 (0·12)	0·23 (0·07)
75-79			0·24 (0·13)	0·40 (0·15)	0·32 (0·10)
	Mortality from coronary heart disease (deaths/1000 person years)				
50-54	1·8 (40)	2·1 (41)			2·0 (96)
55-59	4·4 (86)	3·7 (80)	3·0 (57)		3·5 (231)
60-64	6·1 (88)	7·0 (130)	4·9 (101)	4·1 (55)	5·6 (374)
65-69	10·0 (58)	10·3 (134)	6·8 (116)	6·8 (82)	8·1 (390)
70-74		16·0 (79)	13·4 (151)	11·2 (109)	13·0 (347)
75-79			18·6 (70)	16·0 (85)	17·2 (166)

*Only cells based on at least 40 coronary heart disease deaths are shown.

The relative risk of coronary heart disease for a given rise in cholesterol concentration decreases with age at screening, and this is confirmed by a proportional hazards analysis on our data. Despite this the absolute risk attributable to raised cholesterol concentration increased with age, because mortality from coronary heart disease increases considerably with age.

RISK OF RAISED CHOLESTEROL CONCENTRATION AND CURRENT AGE

An alternative and informative approach is to compare cholesterol concentrations at the initial screen in the men who died of coronary heart disease with those in other men of the same current age group and follow up time as those who died.

Table I shows the mean differences in plasma cholesterol concentration between men who died of coronary heart disease and other men, for each current age group and interval of follow up. Proportional hazards analysis (not shown) produced the same relation with current age and interval of follow up.

For every current age group at every follow up interval there was a positive association between plasma cholesterol concentration and death from coronary heart disease. In general, for a given interval of follow up, the association between cholesterol and

death from coronary heart disease falls with current age (age at death). For a given current age, the association between coronary heart disease and cholesterol concentration was weakest when the interval between cholesterol measurement and death was shortest—that is, for the men who were oldest when cholesterol concentrations were measured. The mean rise in plasma cholesterol concentration in men who died of coronary heart disease aged under 60 was 0·44 (SE 0·07) mmol/l, which is significantly higher than the mean increase of 0·26 (0·04) mmol/l in men who died of coronary heart disease aged 60-79 (p=0·03). Figure 3 summarises the relation between cholesterol concentration and death from coronary heart disease at different current ages (age at death). It gives the relative risk (strictly the hazard ratio) of death from coronary heart disease associated with a difference of 2 mmol/l in plasma cholesterol concentration, adjusted for interval of follow up. The relative risk fell with current age (test for trend; p=0·04), though the fall was not linear.

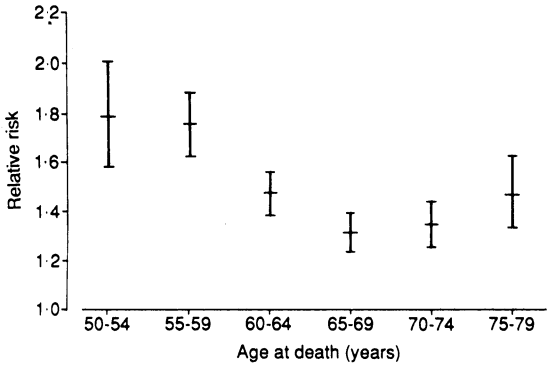

FIG 3—*Relative risk and standard error of mortality from coronary heart disease associated with difference of 2 mmol/l in plasma cholesterol concentration by age at death. Relative risks are adjusted for interval of follow up*

Within each current age group there was a tendency for the relation between cholesterol concentration and death from coronary heart disease to increase with increasing time since measurement of cholesterol concentration. For instance, for each current age group between 50 and 69, the association was weaker at 0-4 years follow up than at any subsequent follow up interval. In particular, the mean difference in cholesterol concentration between men who had died of coronary heart disease and other men, standardised for age at death, was 0·12 (0·11) mmol/l greater when cholesterol concentration had been measured 5-9 years previously than when it had been measured 0·4 years previously.

Although the overall test for trend was marginally significant (p=0·06), the relative risks in figure 4 indicate that for a given age at risk, the earlier the age at which cholesterol was measured, the stronger the relation with coronary heart disease. Adjusted for age at death, the longer the interval between measurement of cholesterol concentration and death, and hence the earlier the age at which it was measured, the stronger the relation between cholesterol concentration and coronary heart disease.

The secular trend in mortality from coronary heart disease during the study must also be accounted for. Every man was examined in 1967-9. Therefore deaths occurring, for example, among 65 year olds in years 0-4 of follow up happened in the late 1960s and early 1970s. Deaths occurring in this age group at 15 years' follow up occurred in 1982-4. Figure 1 shows that mortality in later years was lower than that earlier in the study—consistent with the national fall in mortality from coronary heart disease, particularly among people in non-manual occupations.[6] Since comparable relations between cholesterol concentration and death from coronary heart disease are known to persist in different populations with very different mortalities from coronary heart disease we do not consider the fall to have any effect on the trends described above.

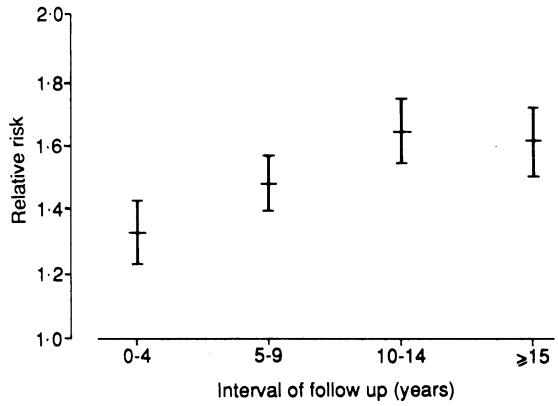

FIG 4—*Relative risk and standard error of mortality from coronary heart disease associated with a difference of 2 mmol/l in plasma cholesterol concentration by interval of follow up. Relative risks are adjusted for age at death*

DEATHS FROM OTHER CAUSES AND TOTAL MORTALITY

We did analyses similar to those described above to examine the relation between plasma cholesterol concentration and mortality from non-cardiac causes and total mortality (table II). For mortality from non-cardiac causes there was an inverse relation with plasma cholesterol concentration for the first five years after measurement of cholesterol (relative risk for 2 mmol/l increase in cholesterol concentration=0·76). No relation was found with longer follow up, though the risk of death from non-cardiac causes when aged over 70 was higher in subjects who had had low cholesterol concentrations at screening.

For mortality from all causes the strength of the cholesterol relation fell significantly with age at death. The relation was strong for those who died aged under 60 (around a 40% increase in risk for a 2 mmol/l increase in cholesterol concentration), but there was no evidence of association beyond age 70. However, for a given age at death the relation between cholesterol concentration and total mortality is stronger if cholesterol concentration was measured over 10 years before (test for trend p=0·03).

For instance, if we consider all men who died aged 60-69 there was no association if plasma cholesterol concentration had been measured within the past five

TABLE II—*Relative risk* of death from coronary heart disease, other causes, and all causes associated with difference of 2 mmol/l in plasma cholesterol concentration, by age at death and interval of follow up*

	Cause of death		
	Coronary heart disease	Other	All causes
Age at death (years):			
50-54	1·78	1·43	1·55
55-59	1·75	1·07	1·36
60-64	1·47	0·95	1·14
65-69	1·31	0·93	1·06
70-74	1·34	0·83	1·00
75-79	1·46	0·72	0·91
p value for trend	0·032	0·015	<0·001
Interval of follow up (years):			
0-4	1·33	0·76	1·04
5-9	1·48	1·02	1·19
10-14	1·64	1·00	1·20
≥15	1·60	1·12	1·29
p value for trend	0·064	0·11	0·032

*Relative risks by age at death are adjusted for interval of follow up, and vice versa.

years but a positive association for plasma cholesterol measured over 10 years before—that is, a 17% increase in risk of dying for a 2 mmol/l increase in cholesterol (p=0·003).

Discussion

As the number of elderly people is increasing it is important to know if plasma cholesterol concentration continues to predict coronary heart disease in elderly people. Our data suggest that it does, at least up to the age of 80. This agrees with recent data from the Honolulu heart study.[2]

Does the power of plasma cholesterol concentration to predict coronary heart disease fall with age? This question should be specified in two parts: age at which cholesterol concentration was measured and age at which death occurs.

Throughout the age range that we studied, 40-69, a single measurement of plasma cholesterol concentration predicted subsequent death from coronary heart disease occurring up to 20 years after the measurement. Measured as a proportional increase in risk, relative risk, the strength of the association fell with age at screening (fig 2), suggesting that the aetiological importance of raised plasma cholesterol concentration may be less in older people. It would, however, be unwise to extrapolate to cholesterol concentrations measured in people aged under 40 and further studies are needed to explore the relation of cholesterol concentrations in infancy, childhood, and young adult life to later risk of coronary heart disease. Because of the steep age gradient for mortality from coronary heart disease the absolute number of deaths attributable to raised plasma cholesterol concentrations was much greater at older ages.

Plasma cholesterol concentration, therefore, is an important predictor if measured up to the age of 69. We cannot say from these data whether this holds for cholesterol measured in people aged over 70. Extrapolating, one might expect its importance to continue to diminish with advancing age at which it was measured. What our data do suggest is that the best way to use plasma cholesterol concentration as a predictor of coronary heart disease in elderly people is to measure it at a younger age. For a given age at death, the longer the gap between measurement and death, the more predictive the cholesterol measurement. Apart from its great practical significance, this provides support for the validity of data from longitudinal studies that sample people at one point and follow them for years.

The increasing importance of the time elapsing between measurement and death may result from the long incubation period of coronary heart disease,[7] or because raised cholesterol concentration is more biologically meaningful the younger the age at which it becomes manifest. One might speculate that risk factors are predictors of premature death, the less premature the death, the less predictive the risk factor. Again, we must distinguish between age at measurement and at death. A single measurement of cholesterol concentration at age 60 predicts death from coronary heart disease even more strongly at age 75 than it does at age 65. This risk factor loses its predictive power only if measured at older ages. We know of no suitable data that would determine if the relation is similar in women.

Measurements of cholesterol concentration in middle aged people are better able to identify those who will develop coronary heart disease, and it may also be more feasible to modify cholesterol concentrations in middle aged people than older ones.

Analysis of deaths from causes other than coronary heart disease confirm the well known phenomenon that a low cholesterol concentration is associated with an increased risk of non-cardiac death, especially cancer, in the next few years. One possible explanation for this observation is that chronic non-cardiac disease lowers plasma cholesterol concentration.[8,9] The inverse association between cholesterol concentration and mortality from non-cardiac causes in people aged over 70 was evident even if cholesterol was measured over 15 years previously. This cancelled out the positive association with deaths from coronary heart disease found in this age group so that total mortality at ages 70-79 was not associated with plasma cholesterol concentration. We are preparing a paper examining the relation between cholesterol and mortality from non-cardiac causes in greater detail.

The total mortality showed a positive relation with plasma cholesterol concentration for age at death 60-69 provided that cholesterol was measured at least five years earlier. This reinforces the importance of measuring cholesterol concentration when people are in their 40s and 50s as it is a valuable marker of coronary heart disease and risk of death over a decade later.

Of course showing that plasma cholesterol concentration predicts death from coronary heart disease in elderly people does not necessarily mean that lowering it will confer benefit. Controversy continues over whether the trials of drugs or diets to lower cholesterol concentrations have shown an impact on total mortality, but there seems little doubt that lowering cholesterol concentrations lowers the risk of coronary heart disease. Trials have studied mainly middle aged men and it could be argued that no clinical trial ever lasts long enough to answer the questions posed by this paper. In the absence of trial data on elderly people it might be safer to lower plasma cholesterol concentrations at a younger age to prevent disease in elderly people.

We thank Professor Geoffrey Rose for his advice.

1 Anderson KM, Castelli WP, Levy D. Cholesterol and mortality: 30 years of follow-up from the Framingham study. *JAMA* 1987;**257**:2176-80.
2 Benfante R, Reed D. Is elevated serum cholesterol level a risk factor for coronary heart disease in the elderly? *JAMA* 1990;**263**:393-6.
3 Reid DD, Brett GZ, Hamilton PJS, Jarrett RJ, Keen H, Rose G. Cardiorespiratory disease and diabetes among middle-aged male civil servants. *Lancet* 1974;i:469-73.
4 Block WD, Jarrett KJ, Levine JB. An improved automated determination of serum total cholesterol with single color reagent. *Clin Chem* 1966;**10**:681-9.
5 Cox DR. Regression models and life-tables. *Journal of the Royal Statistical Society* [B] 1972;**34**:187-220.
6 Marmot MG, McDowall ME. Mortality decline and widening social inequalities. *Lancet* 1986;i:274-6.
7 Rose G. Incubation period of coronary heart disease. *BMJ* 1982;**284**:1600-1.
8 Rose G, Shipley MJ. Plasma lipids and mortality: a source of error. *Lancet* 1980;i:523-6.
9 International Collaborative Group. Circulating cholesterol level and risk of death from cancer in men aged 40 to 69 years: experience of an international collaborative group. *JAMA* 1982;**248**:2853-9.

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