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Outcome age-based prediction of successful cognitive aging by total cholesterol

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Abstract

INTRODUCTION—Some associations of high total cholesterol with dementia risk diminish as the outcome age—age at cognitive assessment—increases.

METHODS—The Framingham Heart Study provided 1897 participants with intact cognition at entry. Cox regression analysis for incident marked cognitive decline included “time-dependent” coefficients, with associations between total cholesterol and covariates changing by outcome age. Decline within age categories of 75–84 and 85–94 was also examined.

RESULTS—Significant associations of rising total cholesterol linear slope, low entry age, low education, and statin non-use with risk diminished significantly by outcome age. At 85–94, falling linear slope was significant.

DISCUSSION—The protected survival model posits a minority subpopulation with protection against mortality and cognitive decline associated with total cholesterol risk factors. It predicts the observed diminished or reversed cholesterol associations with increasing age. Protection is particularly likely for successful cognitive aging—intact cognition at very old age—despite increased risk from cholesterol.

Keywords

dementia; risk factors; protective factors; survival analysis; oldest-old; time-dependent coefficients; protected survivor

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1. INTRODUCTION

Total cholesterol levels tend to rise with age through midlife, and then decrease [1,2] (unless otherwise specified, “cholesterol” hereafter refers to total cholesterol). High cholesterol, especially when measured at midlife, has been associated with bad cognitive outcomes – cognitive decline, dementia, and Alzheimer’s disease (AD) [3,4]. Most of those studies had mean outcome age – age at follow up cognitive assessment – up to the mid-70s [5–9]. Longitudinal studies for older outcome ages were inconsistent [10–16], including reversed association – high cholesterol with lower AD risk [14]. Associations of a steeper decline in cholesterol levels with risk of concurrent [10,17–19] or subsequent [20] dementia have also been reported. When comparing studies of associations of cholesterol with risk of bad cognitive outcomes, attention has focused primarily on differences by mid- versus late-life cholesterol measurement [3,4], not by outcome age.

The original cohort of the longitudinal Framingham Heart Study provides extensive cholesterol measures and cognition information, enabling survival analyses that include changes in association by outcome age. In an earlier study of the original Framingham cohort, Tan et al. found no significant associations between cholesterol and AD [15]. The primary aim of this study was to determine whether specific cholesterol measures had different associations with marked cognitive decline at different outcome ages. It differed from the earlier study of this cohort in participant eligibility, cognitive outcome, cholesterol predictors, and the survival analysis model.

Rather than non-mortality, the present study defines “survival” as successful cognitive aging – having intact cognition while living to oldest-old age, 85 and above [21]. An unambiguous alternative is marked cognitive decline from intact cognition – a substantial reduction, or diagnosis of dementia. For increasing outcome age, we hypothesized diminished associations of cholesterol characteristics – measured while cognitively intact – with risk of subsequent marked cognitive decline. This hypothesis was evaluated in two ways: changing associations over a wide range of outcome ages, and contrasting associations in two ten-year age intervals with each other and with the broad age range associations.

2. METHODS

2.1 The Framingham Dataset: Cholesterol Assessment and Cognitive Status

The National Heart, Lung, and Blood Institute (NHLBI) provided de-identified datasets of 32 bi-annual longitudinal examinations from 1948-1953 through 2012-2014 for the original Framingham cohort [22]. Cholesterol was assessed at 22 scattered exams starting from exam 1 and self-reported statin use from exam 22 (years 1990-1994). At seven exams between 20 and 30, after a screening procedure, physicians performed a neurological and neuropsychological examination to diagnose dementia [15]. From exam 17, cognition was measured by the Mini Mental State Examination (MMSE; total score prorated based on administered items). The Institutional Review Boards of the Icahn School of Medicine at Mount Sinai and the James J. Peters Veterans Affairs Medical Center approved this retrospective study.

2.2 Definition of Intact Cognition and Marked Cognitive Decline

Intact cognition and marked cognitive decline were defined from dementia and cognition examination results. Their evaluation was nullified by a history or concurrent stroke, or after dementia diagnosis or MMSE ≥ 20 . Intact cognition was operationally defined as MMSE ≥ 25 . The “threshold age” was age at the last intact cognition. Marked cognitive decline was defined as deterioration from intact cognition at the threshold age to the first dementia diagnosis or MMSE ≥ 20 .

2.3 Participants

Inclusion requirements were intact cognition at some exam, reported years of education, and at least three cholesterol measurements up through the threshold age. Age at each exam and sex were complete.

2.4 Cholesterol Predictors

Two subsets of cholesterol predictors were used. The first consisted of the first cholesterol observation (obtained at midlife) and the late-life last observation up through the threshold age (called “last cholesterol”), each dichotomized between “normal” ($<200\text{mg/dL}$) and at least “borderline high cholesterol” ($\geq 200\text{mg/dL}$, called “high”). The second subset consisted of three predictors using all cholesterol measurements through the threshold age: mean, linear slope (i.e., the angle of the fitted line for cholesterol measurements), and the quadratic components of the cholesterol trajectory. Note that all, and the only, cholesterol measures used were those obtained when participants were cognitively intact. To reflect incremental contributions to prediction, variables were entered successively into the model within each subset, with the subsets also in succession.

2.5 Covariates

Outcome age, sex, and education are usual covariates in analyses of cognition in elderly samples. The survival analyses used outcome age as the “time” variable, not a separate covariate. Additional covariates were first cholesterol measurement age (called “entry age”) – on or near the age of Framingham study entry – and whether statins were ever used.

2.6 Statistical Analysis

To predict marked cognitive decline, hierarchical Cox regression survival analyses (SPSS version 22) added time-dependent coefficients [23] to the usual proportional hazard predictors. The latter assume the relative contribution of each predictor to the hazard function – the risk of failure as a function of age – does not vary with age. Time-dependent coefficients indicate how the contribution of each predictor changes with age at outcome, in contrast to proportional hazards. Each participant’s cholesterol predictors and covariates were constants (not varying with age), analyzed first assuming proportional hazards. Adding time-dependent coefficients, if significant, indicated a changing degree of association with age. To our knowledge, no previous survival analysis of cognitive outcomes has evaluated a time-dependent coefficient model.

Variables were entered in four blocks: the four covariates entered currently, (1) assuming proportional hazards, (2) their time dependent coefficients; for the five cholesterol predictors entered successively, (3) assuming proportional hazards, (4) their time-dependent coefficients. Each variable was tested by a chi-square on one degree of freedom. Results were considered “very significant” for $p < 0.0005$ and “significant” for $p < 0.05$. Results with $0.10 < p < 0.05$ “approached significance,” providing another category – in addition to “not significant” – for qualitative comparisons of strengths of associations in different samples. Results pertain to variables assuming proportional hazards unless time-dependent coefficients are specified.

To help interpret time-dependent coefficients, we compared survival analyses for the ten-year age intervals after {85,94} and before {75,84} age 85. In these analyses, risk of marked cognitive decline within the interval was assessed only for participants cognitively intact at the beginning of the interval. Threshold age and corresponding last cholesterol were recalculated limited to the years of an interval. Note that participants eligible for the {75,84} sample, who had not had incident marked cognitive impairment (MMSE ≥ 20) but no longer had intact cognition (MMSE ≥ 25) by age 85, were not eligible for the {85,94} sample. All subjects in the {85,94} analysis were considered to have successful cognitive aging, since – despite any subsequent outcome – they had intact cognition at age >85 . Participants in the {75,84} analysis had comparably intact cognition at age ≥ 75 , but were not oldest-old, and so were not considered to have successful cognitive aging.

3. RESULTS

3.1 Sample Description

Of 5079 participants with any data from the original Framingham cohort, 2838 had no MMSE observation available to demonstrate intact cognition. Of the remaining 2241, all MMSE observations were terminated by a stroke for 111, and dementia diagnosis other than stroke for 6. Of the remaining 2124 with MMSE evaluations, 160 never had intact cognition (MMSE ≥ 25), of whom 94 did not have MMSE ≥ 20 . Of the remaining 1964 participants with intact cognition, 59 had missing education (Framingham categories in Table 1, which were analyzed as an equal-interval scale). Of the remaining 1905 participants, only 8 lacked the required cholesterol measures by their threshold age, which was ≥ 62 . The remaining 1897 participants comprised the full sample for the primary survival analysis (mean entry age $\pm$ SD = 40.2 ± 6.8 years; 747 males, 1150 females). Of these, 316 eventually had marked cognitive decline: 114 with diagnosed dementia, and 202 with MMSE ≥ 20 .

Of the 3182 participants not included in full sample, 3125 (98%) did not have required cholesterol, 2838 (89%) were missing any MMSE assessments, all of whom were also among those missing cholesterol. Supplemental Table 1 compares demographic characteristics of the 1897 (37%) participants in the full sample, with the 2838 (56%) missing both MMSE and cholesterol, and the 344 (7%) other participants. Those missing both were older, more male, and less educated than the included sample.

Table 1 shows characteristics of the full sample and the {75,84} and {85,94} samples. Full-sample participants who did not demonstrate intact cognition during an interval were not

included in the interval analysis. Similarly, marked cognitive decline after the end of the interval was not a “failure” in the interval survival analysis. These restrictions explain the small sample sizes and lower rates of marked cognitive decline in the interval samples. Only five participants had marked cognitive decline before age 75, and only nine had threshold ages ≥ 95 , so there were too few participants to investigate earlier or later ten-year age intervals.

3.2 Survival Analyses

For the survival analyses of the full sample and the {75,84} and {85,94} samples, Tables 2 through 4 present the regression coefficient with its standard error, chi-square, significance, hazard ratio, and 95% confidence interval, for each covariate or cholesterol predictor, and for its time-dependent coefficient. In all these analyses, every significant time-dependent coefficient reduced the association of a significant predictor for marked cognitive decline as the outcome age increased. At the “crossover age” of the fitted model for a significant predictor of risk, the association of the predictor was reversed by the modulating time-dependent coefficient – approaching the crossover age, the risk associated with the predictor diminished to zero; beyond the crossover age, the protection associated with the predictor increased from zero.

In the full sample (Table 2), of the four covariates, all but sex were significant or very significant, with increased risk of marked cognitive decline associated with lower entry age, less education, and non-use of statins. Each of these significant proportional hazards results was modulated by a significant time-dependent coefficient (entry age and statin use very significant). Three of the five cholesterol predictors were significantly associated with increased risk: high last cholesterol, rising linear slope, and lower (i.e., negative rather than positive) quadratic slope. However, rising linear slope also had a significant negative time-dependent coefficient, indicating its association with risk diminished with increasing age.

Applying the model used on the full-sample to the two ten year age intervals provided more detail on the changes in associations. For the {75,84} analysis (N=1043; Table 3), no predictors or time-dependent coefficients were significant; marked cognitive decline associations with younger entry age and rising linear slope each approached significance – in the same direction as the full sample analysis. For the {85,94} analysis (N=391; Table 4), increased risk of marked cognitive decline was significantly associated with the younger entry age covariate, as was its time-dependent coefficient – both in the same direction as the full sample analysis, but weaker. Among the cholesterol predictors, rising linear slope was significantly associated with reduced risk of marked cognitive decline – the opposite association from the full sample analysis. High first cholesterol was also significantly associated with reduced risk; this was not associated in either direction in the full sample analysis. Lower (i.e., negative rather than near zero) quadratic slope approached significance; its association with marked cognitive decline was in the same direction as the full sample analysis.

Figure 1 shows marked cognitive decline hazard ratios for high first cholesterol and rising linear slope in the full sample and the two subsamples. This highlights how the {85,94}

sample differs from the other two samples, composed primarily or completely of younger participants.

4. DISCUSSION

4.1 Implications of Results

The present findings support the hypothesis that the association of cholesterol on marked cognitive decline diminish with increasing cognitive outcome age, particularly for rising linear slope of cholesterol measures from mid- to late-life in cognitive healthy participants. In the full sample, there was a significant association between a rising linear slope in cholesterol measures from midlife while cognitively intact and a subsequent marked cognitive decline. However, the significant time-dependent coefficient demonstrates diminishing strength of this association of risk for cognitive decline with rising linear slope as the outcome age increased. The survival model projects that the association reverses in direction at the crossover age. This reduction in the overall association was dramatically illustrated by reversal between the two age-limited samples. For {75,84}, the corresponding association of rising linear slope with risk of cognitive decline approached significance. In contrast, for {85,94}, rising linear slope was significantly associated with reduced risk.

To highlight the reversal in the two age-limited samples of the distinction between rising and falling linear slopes, post-hoc survival analyses dichotomized linear cholesterol slope at zero. For the {75,84} age interval, the 36.7% of the sample with a rising slope had significantly increased risk for marked cognitive decline ($\chi^2=4.196$, $df=1$, $p=0.041$) compared with those having a falling slope. In contrast, for the {85,94} age interval, the 23.3% of the sample with a rising slope had a significantly lower risk ($\chi^2=4.228$, $df=1$, $p=0.040$), compared with those having a falling slope. If cholesterol is specifically associated with AD risk its reduced impact with increasing age might reflect accumulation of other mechanisms for cognitive decline, but this explanation does not readily account for reversals of association.

For high first cholesterol, in comparison with studies of younger elderly, the present study also shows a reversal with outcome age for the {85,95} sample. In all three samples, the average interval between the age of midlife cholesterol (entry age) and threshold age was at least 40 years – ~48 for the {85,94} sample – prior to the identification of marked cognitive decline. In longitudinal studies evaluating midlife cholesterol before cognitive impairment, high midlife cholesterol has been associated with high relative risk for dementia [4], specifically for average outcome ages up to the mid-70s [5,6,8,9,24,25]. To our knowledge, the few studies that had both midlife cholesterol measures and samples with late outcome ages did not find a relationship [16,19]. Nor was there a relationship found with midlife cholesterol in the present study with the full sample, where the average age at outcome was 82.5. Moreover, in contrast to studies with earlier outcome ages, high first cholesterol was significantly associated with reduced risk in the {85,94} sample, with average outcome age 90.9.

Association of predictors varying with outcome age is further supported by the covariates in the full sample. Fewer years of education, non-statin use, and earlier entry age – all

significantly associated with marked cognitive decline – were also significantly weakened as outcome age increased. The crossover ages – all in the 90s – indicate when this weakening would reverse the direction of association. More generally, some null findings for risk factors in other studies that have a broad range of outcome ages may be explained by dilution or even cancellation due to opposite associations at different ages.

4.2 The Protected Survivor Model for Successful Cognitive Aging

Although the crossover age for cholesterol linear slope in the full sample was 98, the {85,94} age interval sample showed an earlier reversed relationship. The full sample included many participants without marked cognitive decline who were no longer cognitively intact by age 85, and thus not eligible for the {85,94} sample. In contrast, the {85,94} sample was comprised solely of participants with successful cognitive aging.

We described the “protected survivor” model in which the association of a risk factor with dementia is reduced or reversed with increasing outcome age [26,27]. This model posits a minority protected against a risk factor for dementia affecting most of the population. An individual’s underlying risk does not change with increased age, but rather there is greater attrition with aging for the initially large proportion of vulnerable individuals than the protected minority. Applied to the risk factor of cholesterol and survival defined as successful cognitive aging – rather than simply not dying – a minority is protected from cholesterol’s associations with mortality [28] and dementia [3]. As age increases, among unprotected individuals, those with risk factors constitute a decreasing proportion of survivors. In contrast, protected individuals – even those with the risk factor – constitute an increasing proportion of survivors. As the proportion of protected among survivors increases, the association of cholesterol with subsequent cognitive decline is diminished or even reversed. If this model applies, among oldest-old participants with successful cognitive aging, those with high risk would be relatively likely to have protective factors. Thus, factors associated with risk – while probably not directly conferring protection – are candidate markers for the presence of some protective factor in those with successful cognitive aging.

4.3 Other Longitudinal Studies of Cholesterol

As in the present study, two longitudinal studies had multiple cholesterol measurements into late-life that preceded dementia incidence. Tan et. al. found no significant associations between cholesterol measures and AD, in the earlier study of the original Framingham cohort [15]. Stewart et al., examined dementia-free participants with five prior cholesterol measurements over 26 years. The participants were assessed three years later for dementia, where the mean age of ascertainment of dementia was 84 years. Those with a subsequent dementia had a steeper falling linear slope [20]. This finding contrasts with rising linear slope associated with risk in the full sample, but was similar to falling linear slope associated with risk in the {85,94} sample (average age 91.3 at marked cognitive decline).

In four longitudinal studies of cholesterol, dementia was assessed concurrently with late-life cholesterol, obscuring the temporal order of cholesterol changes and dementia onset. Finnish men age 40-59 at first cholesterol who had mean cholesterol above 250 mg/dl had more AD than those with lower cholesterol. Those with AD showed a stronger cholesterol decline in

late-life [17]. Swedish women, with up to five observations of cholesterol and cognition over 32 years, had incident dementia associated with the extent of downward change in cholesterol between successive observations [19]. Similarly, another Finnish population-based study, with median age of 74 for dementia outcomes, found decline in cognitive functioning associated with moderate – but not extreme – decrease from midlife to late-life cholesterol, averaging 21 years apart [18]. In a small German birth cohort, those who developed AD or mild cognitive impairment by age 74 declined in three measures of cholesterol – over 14 years – that were stable in cognitively healthy individuals [25]. These results are not directly comparable with the results of the present study, in which cholesterol was measured only while cognitively intact, before dementia.

Collectively, the studies with multiple cholesterol measures from midlife to late-life show the relevance of considering cholesterol change, beyond individual midlife and late-life measures. Assessing cholesterol more – preferably far more, as in the present study – than twice permits extending a linear model to include quadratic slope (acceleration or deceleration of the slope). In the present study, the associations of quadratic slope with risk of marked cognitive decline were negative (significant in the full sample and approaching statistical significance in {85,94}). This is consistent with accelerating decline in cholesterol levels among those who eventually develop dementia [20].

4.4 Constraints and Limitations

Epidemiological studies of cholesterol and cognition, including the present one, used serum cholesterol for which there is no understanding of an association with cognitive decline, and which is not in equilibrium with brain cholesterol [29]. Also, we did not assess associations with LDL or HDL cholesterol, since most prior studies finding associations have been with total cholesterol [3,4], and these were less frequently measured in the Framingham cohort. The present study did not include other cardiovascular risk factors as additional covariates. It sought cholesterol measures as biomarkers for the presence of protective factors, not limited to candidate causal protective factors for successful cognitive aging. Including such covariates would have counterproductively nullified the association of cholesterol markers with protection mediated through other cardiovascular risk factors, which alternatively might be common causes. Similarly, more general measures of frailty such as weight or BMI, were not included as covariates.

A limitation of the present study was the absence of analysis for the {65,74} age interval that would have permitted comparisons with our other intervals and other studies of such outcome ages. Another limitation was that the statin use covariate was not relevant to cholesterol levels in the early years of the Framingham study. Subsidiary analyses (not shown) that excluded the relatively few statin users did not appreciably affect the major results. By requiring that a case for an interval analysis have intact cognition in addition to marked cognitive decline within the period, excluded many individuals with only marked cognitive decline. Requiring intact cognition within the age interval ensured that the {85,94} sample had successful cognitive aging.

A strength of the present study was identification of age-related relationships by time-dependent coefficients calculated in the full sample, in addition to comparison between outcome age intervals in the same cohort.

4.5 Conclusions

Our results demonstrate that some relationships of cholesterol and other risk factors with subsequent marked cognitive decline diminish, or even reverse, as outcome age increases. This suggests the importance of interpreting results in the context of outcome ages, as has already been recognized for age at risk factor assessment, sex, and education. According to the protected survival model, these results suggest that oldest-old individuals who are cognitively intact despite having high risk would be particularly informative for genetic and other studies seeking protective factors.

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Research in Context

The association of high total cholesterol with risk of marked cognitive decline differs according to the age when cholesterol is measured – typically significant in midlife but not in late life. This study examines whether cholesterol associations differ according to “outcome age” – the age at cognitive assessment.

We found several total cholesterol predictors and other risk factors that were associated with increased risk of a marked cognitive decline. However, as outcome age increased, some associations were reduced, or even reversed, the latter suggesting that those who survive to very old age with intact cognition tend to have higher risk factor levels.

These results are consistent with the protected survivor model – among individuals who survive to very old age with intact cognition; those with high risk factor levels are more likely to possess protective factors than those with lower risk factor levels. Long-lived individuals who are cognitively intact despite high risk should be targeted in searches for protective factors.

Highlights

- Total cholesterol and cognition associations differ in studies at different outcome ages.
- Some associations of cholesterol with cognition diminish as outcome age increases.
- In the oldest-old, some relationships reverse from younger elderly samples.
- Studies seeking protection should focus on good cognition despite high risk.

Figure 1. Hazard ratios (midline tick) for marked cognitive decline with 95% confidence intervals (bar ends) associated with two cholesterol predictors assuming proportional hazards – (a) high first cholesterol & (b) rising linear slope in the full – in the full, {75,84}, and {85,94} samples.

Table 1

Characteristics of the full sample and the {75,84} and {85,94} samples.

	Full Sample	Sample {75,84}	{85,94}
N	1897	1041	391
Female: N (%)	1150 (60.6)	660 (63.4)	261 (66.8)
Years of Education: N (%)			
8	388 (20.5)	194 (18.6)	77(19.7)
9-11	250 (13.2)	121 (11.6)	44 (11.3)
12	641 (33.8)	354 (34.0)	130 (33.2)
13-15	175 (9.2)	98 (9.4)	32 (8.2)
16	163 (8.6)	96 (9.2)	38 (9.7)
17	280 (14.8)	178 (17.1)	70 (17.9)
Statin Use – Ever: N (%)	168 (8.9)	128 (12.3)	65 (16.6)
Entry age: mean (SD)	40.2 (6.8)	39.6 (6.2)	42.0 (7.3)
First cholesterol (mg/dL): mean (SD)	215.6 (42.1)	213.4 (41.7)	215.4 (42.8)
High First cholesterol 200mg/dL: N (%)	1131 (59.6)	594 (57.1)	228 (58.3)
Age at last cholesterol: mean (SD)	76.8 (9.1)	80.5 (3.0)	88.2 (2.5)
Last cholesterol (mg/dL): mean (SD)	210.1 (44.5)	203.7 (41.4)	189.3 (37.5)
High last cholesterol 200mg/dL: N (%)	1102 (58.1)	563 (54.1)	135 (37.1)
From first cholesterol through threshold age:			
# cholesterol measures: mean (SD)	13.8 (3.4)	14.8 (2.9)	16.7 (3.4)
Mean cholesterol: mean (SD)	230.0 (34.6)	228.1 (33.2)	227.2 (32.5)
Linear cholesterol slope: mean (SD)	−0.215 (1.429)	−0.395 (1.076)	−0.834 (1.034)
Quadratic cholesterol slope: mean (SD)	−0.093 (0.349)	−0.081 (0.078)	−0.077 (0.065)
Threshold age: mean (SD)	81.2 (7.7)	81.9 (2.3)	89.9 (2.7)
MMSE at threshold age: mean (SD)	27.7 (1.6)	28.0 (1.6)	27.5 (1.6)
Age at marked cognitive decline or censorship: mean (SD)	82.5 (7.9)	82.2 (2.1)	90.9 (2.6)
Marked Cognitive Decline: N (%)	316 (16.7)	39 (3.7)	50 (12.8)
Years, threshold age to marked cognitive decline: mean (SD)	4.3 (2.6)	2.8 (1.3)	2.9 (1.5)

Table 2

Hierarchical Cox regression analysis of the full sample.

Block	Variables Entered	Full Sample N=1897 Coefficient (SE)	X ² (df=1)	p	HR (95% CI)	Crossover*
1	Covariates (concurrent entry)					
	Entry age	−0.040 (0.008)	24.305	<0.0005	0.961 (0.945, 0.976)	
	Sex	0.057 (0.127)	0.199	0.655	1.058 (0.825, 1.357)	
	Education	−0.123 (0.036)	11.776	0.001	0.884 (0.824, 0.949)	
	Statin Use	−0.973 (0.215)	20.547	<0.0005	0.378 (0.248, 0.576)	
2	Time-dependent Coefficients: Covariates (concurrent entry)					
	Entry age	0.006 (0.001)	19.130	<0.0005	1.006 (1.003, 1.009)	95
	Sex	−0.011 (0.021)	0.277	0.599	0.989 (0.949, 1.030)	
	Education	0.015 (0.006)	6.922	0.009	1.015 (1.004, 1.027)	96
	Statin Use	0.135 (0.040)	11.721	0.001	1.145 (1.060, 1.237)	96
3	Cholesterol Predictors (stepwise entry)					
	High First Cholesterol	−0.064 (0.123)	0.271	0.603	0.938 (0.738, 1.193)	
	High Last Cholesterol	0.563 (0.123)	21.475	<0.0005	1.756 (1.381, 2.233)	
	Mean Cholesterol	0.003 (0.342)	0.340	0.560	1.002 (0.996, 1.007)	
	Rising linear Slope	0.250 (0.053)	19.595	<0.0005	1.285 (1.157, 1.426)	
4	Quadratic Slope	−0.400 (0.156)	3.876	0.049	0.670 (0.494, 0.911)	
	Time-dependent Coefficients: Cholesterol (stepwise entry)					
	High First Cholesterol	−0.018 (0.020)	0.789	0.374	0.982 (0.945, 1.022)	
	High Last Cholesterol	−0.023 (0.020)	1.292	0.256	0.978 (0.940, 1.017)	
	Mean Cholesterol	0.0001 (0.0004)	0.085	0.771	1.000 (0.999, 1.001)	
	Rising linear Slope	−0.018 (0.009)	4.024	0.045	0.982 (0.966, 0.999)	98
	Quadratic Slope	−0.034 (0.032)	0.786	0.375	0.967 (0.908, 1.030)	

* Crossover ages are given only for significant time-dependent coefficients

Table 3

Hierarchical Cox regression analysis of the {75,84} sample.

Block	Variables Entered	{75,84} sample N=1041 Coefficient (SE)	X ² (df=1)	p	HR (95% CI)	Crossover*
1	Covariates (concurrent entry)					
	Entry age	-0.048 (0.028)	2.838	0.092	0.953 (0.902, 1.008)	
	Sex	-0.226 (0.327)	0.480	0.488	0.798 (0.421, 1.512)	
	Education	-0.069 (0.100)	0.476	0.490	0.933 (0.766, 1.136)	
	Statin Use	-0.989 (0.619)	2.554	0.110	0.372 (0.110, 1.251)	
2	Time-dependent Coefficients: Covariates (concurrent entry)					
	Entry age	0.029 (0.019)	2.429	0.119	1.029 (0.993, 1.067)	
	Sex	0.130 (0.194)	0.448	0.503	1.139 (0.778, 1.666)	
	Education	0.095 (0.064)	2.169	0.141	1.099 (0.969, 1.247)	
	Statin Use	0.446 (0.471)	0.897	0.344	1.562 (0.621, 3.928)	
3	Cholesterol Predictors (stepwise entry)					
	High First Cholesterol	-0.200 (0.339)	0.348	0.555	0.819 (0.421, 1.592)	
	High Last Cholesterol	0.157 (0.351)	0.201	0.654	1.170 (0.588, 2.329)	
	Mean Cholesterol	-0.004 (0.008)	0.331	0.565	0.996 (0.981, 1.011)	
	Rising linear Slope	0.426 (0.267)	3.611	0.057	1.531 (0.981, 2.391)	
4	Quadratic Slope	-4.127 (2.666)	2.296	0.130	0.016 (0.000, 2.999)	
	Time-dependent Coefficients: Cholesterol (stepwise entry)					
	High First Cholesterol	-0.113 (0.199)	0.322	0.570	0.893 (0.605, 1.319)	
	High Last Cholesterol	-0.087 (0.206)	0.177	0.674	0.917 (0.612, 1.374)	
	Mean Cholesterol	-0.003 (0.005)	0.509	0.476	0.988 (0.988, 1.006)	
	Rising linear Slope	-0.116 (0.134)	0.737	0.391	0.891 (0.686, 1.157)	
	Quadratic Slope	1.690 (1.683)	1.001	0.317	5.421 (0.200, 146.836)	

* Crossover ages are given only for significant time-dependent coefficients

Table 4

Hierarchical Cox regression analysis of the {85,94} sample.

Block	Variables Entered	{85,94} sample N=391 Coefficient (SE)	X ² (df=1)	p	HR (95% CI)	Crossover*
1	Covariates (concurrent entry)					
	Entry age	-0.059 (0.022)	6.948	0.008	0.943 (0.903, 0.985)	
	Sex	-0.123 (0.304)	0.165	0.685	0.884 (0.488, 1.603)	
	Education	-0.111 (0.089)	1.539	0.215	0.895 (0.751, 1.066)	
	Statin Use	-0.446 (0.443)	1.114	0.291	0.640 (0.280, 1.466)	
2	Time-dependent Coefficients: Covariates (concurrent entry)					
	Entry age	0.023 (0.011)	3.870	0.049	1.023 (1.000, 1.046)	93
	Sex	0.089 (0.140)	0.408	0.523	1.094 (0.831, 1.439)	
	Education	0.049 (0.044)	1.247	0.264	1.051 (0.963, 1.145)	
	Statin Use	0.240 (0.208)	1.329	0.249	1.271 (0.845, 1.911)	
3	Cholesterol Predictors (stepwise entry)					
	High First Cholesterol	-0.711 (0.318)	5.187	0.023	0.491 (0.263, 0.917)	
	High Last Cholesterol	0.170 (0.307)	0.303	0.583	1.185 (0.649, 2.164)	
	Mean Cholesterol	0.007 (0.007)	1.112	0.292	1.007 (0.994, 1.021)	
	Rising linear Slope	-0.582 (0.194)	8.765	0.003	0.559 (0.382, 0.817)	
4	Quadratic Slope	-4.056 (2.154)	3.008	0.083	0.017 (0.000, 1.180)	
	Time-dependent Coefficients: Cholesterol (stepwise entry)					
	High First Cholesterol	0.271 (0.175)	2.624	0.105	1.311 (0.929, 1.848)	
	High Last Cholesterol	-0.030 (0.151)	0.038	0.845	0.971 (0.722, 1.305)	
	Mean Cholesterol	0.0002 (0.003)	0.004	0.950	1.000 (0.994, 1.006)	
	Rising linear Slope	-0.002 (0.093)	0.001	0.979	0.998 (0.832, 1.197)	
	Quadratic Slope	0.529 (1.157)	0.205	0.651	1.697 (0.176, 16.400)	

* Crossover ages are given only for significant time-dependent coefficients