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Featured Article

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 years was also examined.
Results: Significant associations of rising total cholesterol linear slope, low entry age, low education, and statin nonuse with risk diminished significantly by outcome age. At 85–94 years, 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.
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Keywords: Dementia; Risk factors; Protective factors; Survival analysis; Oldest-old; Time-dependent coefficients; Protected survivor

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 midlife 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

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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 nonmortality, the present study defines "survival" as successful cognitive aging—having intact cognition while living to oldest-old age, 85 years 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 10-year age intervals with each other and with the broad age range associations.

2. Methods

2.1. The Framingham data set: Cholesterol assessment and cognitive status

The National Heart, Lung, and Blood Institute provided de-identified data sets of 32 biannual longitudinal examinations from 1948–1953 through 2012–2014 for the original Framingham cohort [22]. Cholesterol was assessed at 22 scattered examinations starting from examination 1 and self-reported statin use from examination 22 (years 1990–1994). At seven examinations between 20 and 30, after a screening procedure, physicians performed a neurological and neuropsychological examination to diagnose dementia [15]. From examination 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 $\leq$20. Intact cognition was operationally defined as MMSE $\geq$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 having MMSE $\leq$20.

2.3. Participants

Inclusion requirements were intact cognition at some examination, reported years of education, and at least three cholesterol measurements up through the threshold age. Age at each examination 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" ($<$200 mg/dL) and at least "borderline high cholesterol" ($\geq$200 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 that 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—for the four covariates entered concurrently: (1) assuming proportional hazards, (2) their time-dependent coefficients; for the five cholesterol predictors entered successively: (3) assuming proportional hazards, and (4) their time-dependent