The 32-year relationship between cholesterol and dementia from midlife to late life

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ABSTRACT

Background: Cellular and animal studies suggest that hypercholesterolemia contributes to Alzheimer disease (AD). However, the relationship between cholesterol and dementia at the population level is less clear and may vary over the lifespan.

Methods: The Prospective Population Study of Women, consisting of 1,462 women without dementia aged 38–60 years, was initiated in 1968–1969 in Gothenburg, Sweden. Follow-ups were conducted in 1974–1975, 1980–1981, 1992–1993, and 2000–2001. All-cause dementia was diagnosed according to *DSM-III-R* criteria and AD according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria. Cox proportional hazards regression examined baseline, time-dependent, and change in cholesterol levels in relation to incident dementia and AD among all participants. Analyses were repeated among participants who survived to the age of 70 years or older and participated in the 2000–2001 examination.

Results: Higher cholesterol level in 1968 was not associated with an increased risk of AD (highest vs lowest quartile: hazard ratio [HR] 2.82, 95% confidence interval [CI] 0.94–8.43) among those who survived to and participated in the 2000–2001 examination. While there was no association between cholesterol level and dementia when considering all participants over 32 years, a time-dependent decrease in cholesterol over the follow-up was associated with an increased risk of dementia (HR 2.35, 95% CI 1.22–4.58).

Conclusion: These data suggest that midlife cholesterol level is not associated with an increased risk of AD. However, there may be a slight risk among those surviving to an age at risk for dementia. Declining cholesterol levels from midlife to late life may better predict AD risk than levels obtained at one timepoint prior to dementia onset. Analytic strategies examining this and other risk factors across the lifespan may affect interpretation of results. ***Neurology*® 2010;75:1888–1895**

GLOSSARY

AD = Alzheimer disease; **BMI** = body mass index; **CI** = confidence interval; **DBP** = diastolic blood pressure; ***DSM-III-R*** = *Diagnostic and Statistical Manual of Mental Disorders,* 3rd edition, revised; **HR** = hazard ratio.

It is well-established in animal and cell culture studies that high cholesterol level is associated with amyloid-β deposition, one of the hallmark pathologies of Alzheimer disease (AD). Experimental studies have reported that cholesterol accelerates the production of amyloid-β by shifting amyloid precursor protein metabolism from α- to β-cleavage products, thus increasing the ratio of insoluble to soluble amyloid-β.[1,2] Indeed, both rabbits and transgenic mice fed

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high-cholesterol diets have greater amyloid pathology relative to controls,[3,4] and intake of cholesterol-lowering medications are associated with reduced pathology.[5] In humans, high cholesterol level has been reported to be associated with the presence of early amyloid deposition in subjects aged 40–55 years, but less so in older subjects,[6] suggesting the relationship changes with age.

Despite consistent associations at the cellular level and in animal models, the relationship between cholesterol level and dementia at the population level is less clear (see [7] for meta-analysis). When stratified by age at cholesterol measurement (midlife vs late life), however, patterns emerge. In support of the pathologic findings,[6] epidemiologic data suggest that high cholesterol levels in midlife may increase risk for subsequent dementia and AD[8-11]; however, in late life, low cholesterol levels have been predictive of subsequent dementia[12,13] or no association has been observed.[14,15] Nevertheless, results are conflicting as some studies have not found high midlife cholesterol level to predict later dementia.[16-18]

Epidemiologic studies examining the cholesterol–dementia relationship include those with midlife or late-life approaches, as well as continuous, longitudinal approaches, depending on the availability of data. Differences in study designs, lengths of observational periods, analytical strategies, and the natural history of the disorder in relation to the timing of the occurrence of high cholesterol may influence observations. Given the importance of the timing of high cholesterol to the onset of dementia suggested above, it is necessary to study the relationship between cholesterol level and dementia over the lifespan.[7,19] The present study examines the relationship between cholesterol level, measured from midlife to late life, and dementia in a population-based study of 5 birth cohorts of women followed for 32 years.

METHODS

Participants. The Prospective Population Study of Women was initiated in 1968–1969 in Gothenburg, Sweden. A representative sample of 1,622 women living in Gothenburg, and born on specific dates of the years 1908, 1914, 1918, 1922, and 1930 (aged 38–60 years), were randomly selected from the Revenue Office Register. Women living both in the community and in institutions were included. There were 1,462 women who participated in the initial physical and mental health examination, resulting in a participation rate of 90%.[20] Additional follow-ups were conducted in 1974–1975, 1980–1981, 1992–1993, and 2000–2001 (figure e-1 on the *Neurology*® Web site at www.neurology.org). Those who died or refused to take part were traced in records from hospitals and homes for the aged, inpatient and outpatient departments in psychiatric hospitals and clinics, municipal psychiatric outpatient departments in Gothenburg, the hospital-linkage system, and death certificates.[21]

Standard procedures and participant consents. All participants (or their nearest relatives) gave their informed consent to participate in the study. The study, conducted in accordance with the provisions of the Helsinki Declaration, was approved by the Ethics Committee for Medical Research at Gothenburg University.

Examinations. The detailed, longitudinal examinations of manifestations of aging and somatic and psychiatric disorders included a physical examination performed by a physician, electrocardiogram, chest X-ray, battery of blood tests, and neuropsychiatric examination. Participants were surveyed about a variety of potential risk factors for age-related diseases, such as smoking habits, alcohol intake, medication use, education, and medical history. Body weight was recorded to the nearest 0.1 kg, and body height was measured to the nearest centimeter. Body mass index (BMI) is a weight-per-height measurement and was calculated as kg/m^2. Casual blood pressure was measured in the right arm in the seated position after 5 minutes' rest using a mercury manometer. Systolic and diastolic blood pressures were registered to the nearest 2 mm Hg. Diastolic blood pressure (DBP) was defined as Korotkoff phase 5. Diagnosis of myocardial infarction, stroke, other vascular diseases, diabetes, and cancer were based on self-reports and clinical examinations (including echocardiogram), case records, the hospital discharge registry, the national cancer registry, and the national stroke registry (from 1995) over the 32-year follow-up.

Assessments of dementia. Neuropsychiatric examinations occurred over the entire 32 years of follow-up. More extensive neuropsychiatric examinations and close informant interviews to include dementia ascertainment began when participants were 70 years or older, and were performed by psychiatrists in 1992–1993 and experienced psychiatric nurses in 2000–2001.[22,23] Medical records were collected from hospitals and outpatient departments in Gothenburg, and dementia diagnoses were based on consensus conferences by geriatric psychiatrists. The Swedish Hospital Discharge Registry provided medical diagnostic information for individuals discharged from hospitals since 1978. Thus, information regarding a dementia diagnosis was obtained for all study participants, since virtually all people in Sweden receive their health care from the Swedish health care system and all participants have an equal chance of having a case record.

Dementia was diagnosed according to *DSM-III-R* criteria.[24] AD (probable and possible) was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria.[25] Year of dementia onset was estimated for each participant on the basis of neuropsychiatric status at examination, medical record review, and close informant interviews.

Serum cholesterol assessments. Blood samples were drawn in the fasting state. At the conclusion of each examination, all chemical analyses were run in batch at the Department of Clinical Chemistry at the Sahlgrenska University Hospital in Gothenburg. Laboratory analyses were comparable between the examination years. Serum cholesterol was measured in g/L prior to 1980, then subsequently converted to mmol/L. Starting at the 1980–1981 examination, serum cholesterol was directly mea-

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sured in mmol/L. At each examination, cholesterol levels beyond 3 standard deviations from the mean were excluded, thus 2 women were excluded in 1968–1969, 9 in 1974–1975, 17 in 1980–1981, 8 in 1992–1993, and 4 in 2000–2001.

Statistical analysis. *t* Tests and χ^2 tests, as appropriate, were used to assess differences in demographic and health-related characteristics at each examination by dementia diagnosis during the 32-year follow-up. No participants had dementia at baseline. Endpoints included all-cause dementia and AD without a history of stroke. Cox proportional hazards regression models were used to evaluate the relationship between cholesterol and dementia over the 32-year follow-up. Multiple models were run, including 1) considering different baseline cholesterol measurements defined by examination year and subsequent risk of dementia over 8–32 years; 2) examining baseline cholesterol in 1968–1969 and dementia only among those surviving to and participating in the 2000–2001 examination; 3) measuring cholesterol and covariates in a time-dependent manner at each examination in relationship to onset of dementia; and 4) examining time-dependent change in cholesterol levels between examinations and onset of dementia and AD. In the last analysis, we chose to examine time-dependent cholesterol change in relationship to dementia risk rather than change over 32 years, as only considering change in cholesterol between 1968 and 2000–2001 would restrict the sample to those surviving to 2001. Time at risk for these analyses was calculated to the end of the study period (i.e., 2000–2001 examination), diagnosis of dementia, or death. For all analyses, cholesterol was 1) considered as a continuous variable; 2) dichotomized at >6.5 mmol/L vs less, as other studies have done[8,9]; and 3) examined in quartiles (lowest quartile as reference). Cox proportional hazards models were also used to assess the association between baseline cholesterol in 1968–1969 and mortality over the 32-year follow-up.

Covariates were chosen based on those reported in the literature and factors that have been examined in other studies of cholesterol and dementia.[8,10,12] Covariates were entered into regression models using a single step approach. Birth cohort (an indicator of age) was adjusted as a stratification variable. Additional covariates included DBP, BMI, cigarette smoking, and education. DBP and BMI were examined as continuous variables. Cigarette smoking was defined as ever vs never use in each examination year. Levels of education (completing ≤6 years vs >6 years compulsory education; 7 years for those born in 1930) were based on responses to the 1968–1969 survey. Covariates and cholesterol measurements were concurrent; time-dependent covariates were included in the time-dependent cholesterol analyses. The a priori *p* value was set at $p < 0.05$. Analyses were conducted using STATA version 10.0 (StataCorp, College Station, TX).

Table 1 Characteristics of PPSW participants by dementia status over 32 years (n = 1,462)[a]

Characteristics	All-cause dementia[b] (n = 161)	No dementia[b] (n = 1,301)	*p* Value[c]
Participants by birth cohort			
1908 (age 60 y at baseline)	14	67	
1914 (age 54 y at baseline)	36	144	
1918 (age 50 y at baseline)	61	337	
1922 (age 46 y at baseline)	41	390	
1930 (age 38 y at baseline)	9	363	
Education			
Compulsory vs less[d]	42/161 (26.1%)	401/1,301 (30.8%)	0.21
History of CVD			
History vs no history	54/161 (33.5%)	441/1,301 (33.9%)	0.93
Cholesterol (mmol/L) in year:			
1968	7.2 (1.0)	6.8 (1.1)	<0.01
1974	7.2 (1.2)	6.9 (1.2)	<0.01
1980	7.3 (1.2)	7.0 (1.2)	<0.01
1992	6.4 (1.2)	6.3 (1.0)	0.62
2000	6.2 (1.3)	6.1 (1.0)	0.56
DBP (mm Hg) in year:			
1968	86.0 (9.4)	85.6 (11.3)	0.63
1974	88.6 (10.4)	87.2 (9.7)	0.10
1980	88.4 (10.6)	88.9 (10.5)	0.62
1992	81.1 (10.6)	82.9 (10.9)	0.14
2000	82.8 (16.2)	82.9 (12.0)	0.95
BMI (kg/m^2) in year:			
1968	24.4 (3.8)	24.1 (3.8)	0.29
1974	24.6 (4.3)	24.6 (4.0)	0.97
1980	24.8 (4.6)	25.1 (4.0)	0.41
1992	24.8 (4.2)	26.4 (4.3)	<0.01
2000	24.1 (4.2)	26.6 (4.4)	<0.01
Smoking status in year:			
1968	73/161 (45.3%)	631/1,300 (48.5%)	0.44
1974	59/139 (42.5%)	552/1,155 (47.8%)	0.23
1980	52/131 (39.7%)	463/1,018 (45.5%)	0.21
1992	38/95 (40.0%)	355/737 (48.2%)	0.13
2000	6/23 (26.1%)	210/482 (43.6%)	0.10

Abbreviations: BMI = body mass index; CVD = cardiovascular disease; DBP = diastolic blood pressure; PPSW = Prospective Population Study of Women.
[a] SI conversion factor: to convert cholesterol to mg/dL, multiply by 38.66976.
[b] Data are reported as mean (SD) or number/total (percentage).
[c] t Test for continuous data and χ^2 test for categorical data.
[d] Compulsory education was 6 years for the 1980–1922 birth cohorts, and 7 years for the 1930 birth cohort.

RESULTS **Participant characteristics.** Over the 32-year follow-up, 161 (11.0%) of the 1,462 women developed dementia, including 80 participants who developed AD without a history of stroke. Total risk time evaluated was 41,219 risk-years. Number of dementia cases by birth cohort and characteristics of women at each examination are shown in table 1. Across all cohorts, participants who developed dementia over the follow-up had higher mean cholesterol levels ($p < 0.01$) in 1968–1969, 1974–1975, and 1980–1981, but not 1992–1993 or 2000–2001 compared to participants who did not develop dementia by the 2000–2001 examination. Mean BMI levels were also lower in 1992–1993 and 2000–2001 in women who developed dementia ($p < 0.01$) compared to women who did not. Mean cholesterol levels varied by birth cohort and over time (figure 1). In 1968–1969 and 1974–1975, the 1908 and 1914

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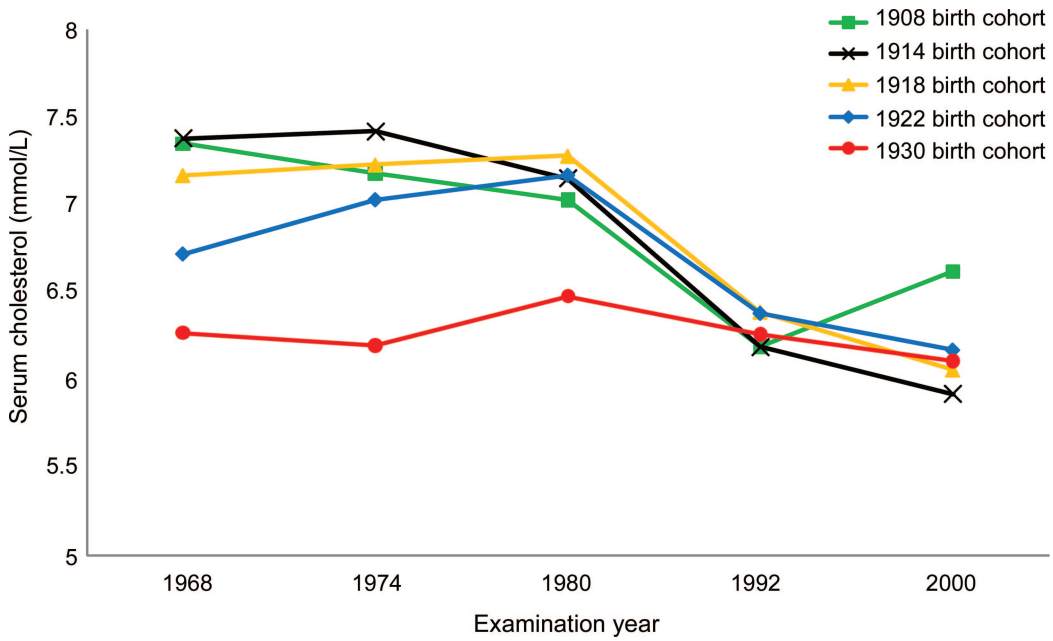
Figure 1 Mean cholesterol levels in the Prospective Population Study of Women by examination year and birth cohort



birth cohorts had higher mean cholesterol levels ($p <$ 0.05) compared to the 1930 birth cohort. There were no differences in mean cholesterol levels at other examinations, and mean levels decreased over the 32-year follow-up for all birth cohorts.

Serum cholesterol at each examination and risk of dementia (AD and all-cause dementia). Evaluation of the cholesterol–dementia relationship using age-adjusted Cox proportional hazards models showed no associations from midlife to late life (table 2). There was also no association between cholesterol and risk of dementia when analyzing cholesterol as a time-dependent variable over the 5 examinations (data not shown).

Serum cholesterol in 1968 and risk of dementia (AD and all-cause) among those who survived to the 2000 examination. Some epidemiologic studies examining midlife cholesterol have information on dementia diagnosis only for those who survived to the follow-up examination,[8,9,11] often decades after the midlife cholesterol measurement. In order to replicate these analyses and better determine the effects of survival on the results, the analysis was restricted to the 648 women who survived and participated in the 2000 examination (table 3). In univariate analyses, high cholesterol was associated with dementia such that the highest quartile, compared to the lowest, was associated with a fourfold increase in risk of all-cause dementia (hazard ratio [HR] = 4.13, 95% confidence interval [CI] 2.09–8.16) and almost a sixfold increase in risk of AD (HR = 5.98, 95% CI 2.17–16.47). However, the results were attenuated after age stratification and, while there was a trend for high cholesterol to increase risk, results were not significant at the $p < 0.05$ level.

Change in cholesterol and risk of dementia (AD and all-cause). Finally, change in cholesterol between visits was examined as a predictor of subsequent dementia using Cox proportional hazards regression (table 4). Cholesterol change was analyzed by quartiles as a time-dependent variable at each examination. While the intervals between examinations varied over the follow-ups, the range for each quartile was relatively consistent. The middle 2 quartiles (change of ~−0.50 to 0.75 mmol/L between examinations) was the reference group. The quartiles showing the greatest decline (reduction of cholesterol greater than 0.50 mmol/L) and the greatest increase (increase in cholesterol greater than 0.75 mmol/L) were examined in relationship to risk of dementia. Compared to the middle 2 quartiles, the quartile of greatest decrease in cholesterol was related to increased risk of dementia (multivariate adjusted HR = 2.37, 95% CI 1.22–4.58). While there was a similar trend for AD, results were not significant.

Serum cholesterol, lipid-lowering medications, and mortality. Over the 32-year follow-up, 515 (35.2%) women died. Using age- and multivariate-adjusted Cox proportional hazards models, total cholesterol in 1968–1969 was not associated with a higher risk of mortality (table e-1). Information on lipid-lowering medication use was available at each examination. However, only 8 (0.5%) of 836 women present at

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Table 2 Cholesterol level at each examination and risk of dementia (all-cause and Alzheimer disease) over 32 years

	All-cause dementia			Alzheimer disease		
Cholesterol by year	HR (95% CI) unadjusted	HR (95% CI) model 1[a]	HR (95% CI) model 2[b]	HR (95% CI) unadjusted	HR (95% CI) model 1[a]	HR (95% CI) model 2[b]
1968	Person-years = 41,219 (n = 161 cases)			Person-years = 38,545 (n = 80 cases)		
>6.5 mmol/L	2.03 (1.44–2.86)	1.28 (0.90–1.83)	1.27 (0.89–1.80)	1.79 (1.10–2.92)	1.08 (0.65–1.78)	1.11 (0.67–1.84)
Quartile 1 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quartile 2	1.26 (0.76–2.09)	0.91 (0.55–1.52)	0.90 (0.54–1.50)	1.37 (0.67–2.82)	1.00 (0.48–2.06)	1.00 (0.48–2.07)
Quartile 3	2.10 (1.31–3.38)	1.25 (0.77–2.03)	1.24 (0.76–2.02)	2.24 (1.14–4.43)	1.25 (0.62–2.52)	1.31 (0.65–2.64)
Quartile 4	2.61 (1.64–4.16)	1.22 (0.75–1.98)	1.18 (0.73–1.93)	2.32 (1.16–4.63)	1.01 (0.49–2.08)	1.04 (0.50–2.16)
1974	Person-years = 29,702 (n = 141 cases)			Person-years = 27,188 (n = 64 cases)		
>6.5 mmol/L	1.81 (1.25–2.64)	1.11 (0.75–1.62)	1.07 (0.72–1.58)	1.59 (0.94–2.69)	0.95 (0.55–1.64)	0.94 (0.54–1.63)
Quartile 1 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quartile 2	1.68 (0.99–2.85)	1.17 (0.69–2.00)	1.13 (0.65–1.94)	1.75 (0.84–3.64)	1.24 (0.59–2.60)	1.26 (0.59–2.68)
Quartile 3	1.61 (0.95–2.74)	0.97 (0.57–1.67)	0.93 (0.54–1.61)	1.59 (0.76–3.33)	0.97 (0.46–2.07)	0.98 (0.46–2.11)
Quartile 4	2.49 (1.51–4.11)	1.26 (0.76–2.12)	1.19 (0.71–2.01)	1.88 (0.90–3.93)	0.95 (0.44–2.03)	0.93 (0.43–2.01)
1980	Person-years = 20,429 (n = 129 cases)			Person-years = 18,537 (n = 60 cases)		
>6.5 mmol/L	1.72 (1.16–2.57)	1.27 (0.85–1.90)	1.22 (0.81–1.84)	1.53 (0.88–2.66)	1.15 (0.66–2.02)	1.11 (0.63–1.96)
Quartile 1 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quartile 2	0.99 (0.56–1.75)	0.83 (0.47–1.46)	0.81 (0.46–1.44)	0.76 (0.33–1.75)	0.62 (0.27–1.44)	0.62 (0.26–1.44)
Quartile 3	1.36 (0.82–2.28)	1.01 (0.60–1.70)	0.99 (0.59–1.67)	1.35 (0.66–2.74)	1.00 (0.49–2.05)	0.98 (0.47–2.02)
Quartile 4	2.08 (1.28–3.39)	1.34 (0.82–2.21)	1.30 (0.78–2.16)	1.93 (0.98–3.83)	1.28 (0.64–2.58)	1.26 (0.62–2.57)
1992	Person-years = 5,960 (n = 73 cases)			Person-years = 5,389 (n = 29 cases)		
>6.5 mmol/L	1.06 (0.66–1.72)	1.12 (0.69–1.83)	1.16 (0.69–1.94)	0.65 (0.29–1.42)	0.68 (0.31–1.49)	0.53 (0.22–1.27)
Quartile 1 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quartile 2	1.16 (0.60–2.26)	1.21 (0.61–2.37)	1.00 (0.48–2.07)	1.41 (0.53–3.69)	1.75 (0.66–4.61)	1.41 (0.51–3.84)
Quartile 3	0.92 (0.46–1.87)	0.95 (0.47–1.93)	0.91 (0.43–1.89)	0.84 (0.28–2.49)	0.88 (0.29–2.63)	0.83 (0.27–2.56)
Quartile 4	1.10 (0.56–2.15)	1.10 (0.56–2.16)	0.96 (0.47–1.95)	0.83 (0.28–2.47)	0.84 (0.28–2.50)	0.51 (0.15–1.78)

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a] Model 1 stratifies by age.
[b] Model 2 controls for education, diastolic blood pressure, body mass index, and smoking status at the examination concurrent with the cholesterol measurement, and stratified by age.

the 1992–1993 examination and 40 (2.7%) of 660 women at the 2000–2001 examination were taking lipid-lowering medications. Neither excluding participants on lipid-lowering medications at these examinations nor controlling for medication use altered any results.

DISCUSSION In this population-based study of 5 birth cohorts of women, age 38–60 at baseline and followed for up to 32 years, the relationship between cholesterol and dementia (all-cause and AD) was examined utilizing multiple statistical methodologies that have been previously published in the examination of this relationship. In summary: 1) high cholesterol at baseline in 1968–1969 was not associated with risk of all-cause dementia or AD once age was considered; 2) high cholesterol at baseline in 1968–1969 was more strongly associated (albeit not significant) with incident dementia (all-cause and AD) when only including those who survived to and participated in the 2000–2001 examination compared to the inclusion of all participants and their respective survival times; and 3) a decrease in cholesterol levels over the follow-up was associated with a modest increased risk of dementia.

There is increasing awareness that identification of risk factors for syndromes of late life, such as dementia, need to be considered using a life-course perspective. Throughout life, genetic and environmental (e.g., diet, physical activity, obesity) factors have interactive effects in predisposing a person to dementia. One impediment to the current lifespan approach evaluating the cholesterol–dementia relationship is that most longitudinal studies have only examined this relationship among people that survived to old age. In the present study, we used different methodologies to examine the cholesterol–dementia relationship. We ex-

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Table 3 Cox proportional hazards models relating cholesterol level in 1968 to incident dementia and Alzheimer disease among women surviving to and participating in the 2000 examination (n = 648)

	All-cause dementia			Alzheimer disease		
	HR (95% CI) unadjusted	HR (95% CI) model 1[a]	HR (95% CI) model 2[b]	HR (95% CI) unadjusted	HR (95% CI) model 1[a]	HR (95% CI) model 2[b]
Serum cholesterol level	Person-years = 20,420 (n = 85 cases)			Person-years = 19,016 (n = 46 cases)		
>6.5 mmol/L	2.34 (1.47–3.73)	1.39 (0.85–2.28)	1.33 (0.80–2.18)	2.50 (1.31–4.75)	1.50 (0.76–2.99)	1.48 (0.73–2.96)
Quartile 1 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quartile 2	2.02 (1.00–4.11)	1.41 (0.69–2.91)	1.45 (0.70–2.99)	2.62 (0.91–7.54)	1.99 (0.68–5.83)	2.05 (0.70–6.04)
Quartile 3	3.01 (1.51–5.99)	1.67 (0.81–3.43)	1.61 (0.78–3.32)	4.14 (1.49–1.50)	2.51 (0.87–7.26)	2.51 (0.87–7.30)
Quartile 4	4.13 (2.09–8.16)	1.82 (0.88–3.77)	1.68 (0.80–3.52)	5.98 (2.17–6.47)	2.88 (0.97–8.51)	2.82 (0.94–8.43)

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a] Model 1 stratifies by age.
[b] Model 2 controls for education, diastolic blood pressure, and body mass index in 1968, and stratifies by age.

amined the relationship continuously over the middle to late lifespan as well as only among those who survived to old age. A clear difference was demonstrated. When including all persons, there was no association between midlife cholesterol and risk of dementia or AD in multivariate models. In contrast, when only including those who survived to old age, there was a clear trend for high cholesterol to be associated with an increased risk of AD. This difference is likely due to a survival bias and competing mortality,[23] and demonstrates that thoughtful consideration of this bias is needed when examining relationships between midlife risk factors and late-life outcomes only among survivors. Including survivors only may lead to an overestimation of association. As loss to follow-up is negligible in this study sample, this consideration is underscored.

Perhaps more importantly, the present study found that decreasing cholesterol between visits was associated with an increased risk of dementia, but not AD, similar to results found in other studies.[9,17] Thus, unintended decreases in cholesterol levels (e.g., not via medications or cholesterol-lowering diet) greater than expected due to aging may be more indicative of dementia risk than midlife cholesterol levels and may reflect underlying dementia processes. This pattern is observed for other dementia risk factors, such as BMI[23] and blood pressure.[26] In these women, we observe declines in both BMI and blood cholesterol levels, yet these observations are statistically independent of each other indicating that decline in each parameter is important. Hypotheses related to observed declines may have to do with regions of the brain affected by amyloid deposition, such as the arcuate nucleus and in general, the hypothalamus, which are areas of homeostatic regulation.[27] In addition, consequences of the dementia prodrome such as apathy or reduced olfactory function[28,29] may lead to decreased energy intake, which may also affect blood cholesterol levels.

There are some limitations and methodologic factors that need to be addressed. First, it is often difficult to discriminate between AD and VAD. However, our criteria for AD are strict and we exclude all cases with stroke or infarcts on CT. Second, loss of participants due to death or refusal may have influenced the results, particularly in the oldest age groups. While we have information from examinations, close informants, case records, hospital registers, and death certificates, some of these secondary sources are known to underrate dementia. Thus, undiagnosed cases of dementia may be included in the no-dementia group, which would most likely diminish differences between the 2 groups, and

Table 4 Time-dependent cholesterol level change between examinations and risk of dementia and Alzheimer disease over 32 years

	All-Cause dementia		Alzheimer disease	
Serum cholesterol	HR (95% CI) unadjusted	HR (95% CI) adjusted[a]	HR (95% CI) unadjusted	HR (95% CI) adjusted[a]
Middle quartiles	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Declining quartile	2.49 (1.31–4.73)	2.37 (1.22–4.58)	1.66 (0.71–3.89)	1.73 (0.71–4.20)
Increasing quartile	1.16 (0.51–2.65)	1.13 (0.48–2.69)	1.06 (0.39–2.90)	1.03 (0.35–3.04)

Abbreviations: CI = confidence interval; HR = hazard ratio.
[a] Adjusted models control for birth cohort (age), education, time-dependent diastolic blood pressure, body mass index, and smoking status.

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lead to conservative estimates of effects. Third, *APOE* ϵ4 genotyping and low-density lipoprotein and high-density lipoprotein cholesterol were not available. However, a recent meta-analysis[7] reported no interaction between the *APOE* ϵ4 allele and total cholesterol in predicting dementia risk or an association between high-density lipoprotein and dementia. Finally, the study is composed of women in Sweden and the results may not be generalizable to men or other ethnicities.

Despite these limitations, the present study has several notable strengths. First, among the strengths of this study are the 32 years of follow-up with multiple cholesterol measurements and health information, which has allowed for the lifespan examination of the relationship and temporality between cholesterol and dementia. Second, there was no loss to follow-up because information regarding a dementia diagnosis was obtained for all study participants. Participants who died or refused to take part in the study were traced through several registries and records from hospital systems and homes for the aged. Although case records may underdiagnose the number of dementia cases, this methodologic aspect has a distinct advantage over other longitudinal studies because persons lost to follow-up are not representative of the population in that they are more likely to be ill and/or cognitively impaired. Finally, the study timeframe was 1968–2000; only during the last few years of the study were statins and other lipid-lowering drugs available. Thus, without potential confounding with medications, a true relationship between cholesterol and dementia is observed.

On neither an individual nor population level can we determine whether a person will develop dementia in late life based on a midlife cholesterol level. However, in accordance with heart healthy guidelines, we suggest that midlife cholesterol levels be monitored and treated via diet, exercise, and medication as recommended or required. In addition, we suggest that declines in metabolic parameters, such as blood cholesterol levels, BMI, and blood pressure, be monitored with aging, and that there may be precedent for stabilization of these parameters in relation to lowering dementia risk.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by H. Shao, Dr. Zandi, and Dr. Mielke.

DISCLOSURE

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