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Abstract—*Objective:* To examine the longitudinal association between plasma total cholesterol and triglyceride levels and incident dementia. *Methods:* Neuropsychiatric, anthropometric, laboratory, and other assessments were conducted for 392 participants of a 1901 to 1902 birth cohort first examined at age 70. Follow-up examinations were at ages 75, 79, 81, 83, 85, and 88. Information on those lost to follow-up was collected from case records, hospital linkage system, and death certificates. Cox proportional hazards regression examined lipid levels at ages 70, 75, and 79 and incident dementia between ages 70 and 88. *Results:* Increasing cholesterol levels (per mmol/L) at ages 70 (hazard ratio [HR] 0.77, 95% CI: 0.61 to 0.96, $p = 0.02$), 75 (HR 0.70, CI: 0.52 to 0.93, $p = 0.01$), and 79 (HR 0.73, CI: 0.55 to 0.98, $p = 0.04$) were associated with a reduced risk of dementia between ages 79 and 88. Examination of cholesterol levels in quartiles showed that the risk reduction was apparent only among the highest quartile at ages 70 (8.03 to 11.44 mmol/L [311 to 442 mg/dL]; HR 0.31, CI: 0.11 to 0.85, $p = 0.03$), 75 (7.03 to 9.29 mmol/L [272 to 359 mg/dL]; HR 0.20, CI: 0.05 to 0.75, $p = 0.02$), and 79 (6.82 to 9.10 mmol/L [264 to 352 mg/dL]; HR 0.45, CI: 0.17 to 1.23, $p = 0.12$). Triglyceride levels were not associated with dementia. *Conclusions:* High cholesterol in late life was associated with decreased dementia risk, which is in contrast to previous studies suggesting high cholesterol in mid-life is a risk factor for later dementia. The conflicting results may be explained by the timing of the cholesterol measurements in relationship to age and the clinical onset of dementia.

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Epidemiologic studies examining the association between cholesterol and dementia have reported conflicting results. Among longitudinal studies, high total cholesterol has been associated with both an increased[1,2] and decreased[3,4] risk of Alzheimer disease (AD) and/or vascular dementia (VaD), whereas other studies have found no association.[5-7] One potential explanation for the heterogeneous results is whether cholesterol was assessed in mid-life[1,2] or late life.[3,4] Multiple studies have suggested that high cholesterol in mid-life,[8,9] but not late life,[10-12] is associated with an increased risk of cardiovascular disease, and it is possible that a similar timing phenomenon exists for measures of cholesterol in relationship to risk of dementia. In addition, studies of cholesterol in old age have had short follow-ups, which leads to unclear conclusions regarding the direction of the cholesterol–dementia association. Furthermore, few studies have examined the relationship between dementia and other lipids, such as triglycerides. Thus, we examined the relationship between plasma total cholesterol and triglyceride levels and incident dementia in a birth cohort of 70 year old subjects from Göteborg, Sweden, who were followed for 18 years.

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Methods. In 1971 to 1972, the 70-year-old residents of Göteborg were systematically sampled from the population register by selecting those born on dates (days) ending with 2, 5, and 8.[13] The selected residents were asked to take part in a comprehensive examination of aging (H70). Of the 1,148 who were eligible, 973 (85%) agreed to participate. All participants were consecutively given a proband number of 1 to 5. Those with numbers 1 and 2 were further selected for a psychiatric examination. A total of 392 individuals, 166 men and 226 women, took part in this psychiatric examination.[14] The main sample and the subsample were representative of the population base in regards to sex; marital status; income; community rent allowance for those who could not afford housing; rate of inpatient and outpatient care in psychiatric hospitals, clinics, and municipal outpatient departments; and rates of registration with the Temperance Board (national registry for alcohol abuse). All participants were invited back for reexaminations at ages 75, 79, 81, 83, 85, and 88 years.[15,16] The Ethics Committee of Göteborg University approved the study. All subjects (or their nearest relatives) gave informed consent to participate in the study, which was conducted in accordance with the provisions of the Helsinki Declaration.

The detailed assessment at each visit included a physical examination performed by a geriatrician, an EKG, a chest x-ray, a battery of blood tests, and a neuropsychiatric examination performed by a psychiatrist.[13,15-17] The neuropsychiatric examination was semistructured and included tests of mental functioning and ratings of dementia symptoms.[17] The examinations at ages 85 and 88 also included a key informant interview and a CT scan. Those participants who died or, for any reason, were not able to participate in a second investigation 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 Göteborg, the hospital linkage system, and death certificates.[15,16] Thus, information regarding a dementia diagnosis was obtained for all study participants because almost all people in Sweden receive their health care from the community and all participants have an equal chance of having a case record.

The diagnosis of dementia at ages 70, 75, 79, 81, and 83 years required the presence of severe disorientation for time and place or a long-standing severe memory impairment as measured by rating scales and information from case records or relatives.[15,16] The diagnosis of dementia at ages 85 and 88 was based on *Diagnosis and Statistical Manual, Third Edition, Revised* (DSM-III-R) criteria, as described previously.[17] Diagnoses from collateral sources required information on symptoms of dementia in case records, death certificates, and the hospital linkage system. Although two diagnostic criteria were incorporated over the 18 years of follow-up (resulting from the publication of the DSM-III-R), at age 85, we were able to diagnose dementia according to both sets of criteria in an enriched sample of 494 85 year old subjects, which included participants in this analysis. Of 166 persons diagnosed with dementia using either criterion, the observed agreement for a dementia diagnosis was 93.3%, with an overall kappa of 0.842. Of those diagnosed with dementia using DSM-III-R and not earlier criteria (n = 14), there was an almost equal number of those with AD (n = 7) vs VaD (n = 6), and they tended to have milder forms of dementia (71%).

Dementia onset was defined as the point at which there was loss of cognitive abilities sufficient to produce obvious impairment in psychosocial functioning. The type of dementia was determined for subjects with dementia between ages 79 and 88. AD was diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria[18] and VaD according to National Institute of Neurologic Disorders and Stroke-Association Internationale pour la Recherche et L'Enseignement en Neurosciences.[19] VaD was diagnosed when an individual with dementia had one or more infarcts detected by CT scanning or a history of acute focal neurologic signs and symptoms (restricted to definite signs or symptoms, such as acute hemiparesis or acute motor aphasia). AD and VaD were not confirmed by autopsy. However, in other studies using the same diagnostic criteria and extensive clinical evaluation that we used the clinical diagnoses of AD and VaD were confirmed at autopsy in over 80% of cases.[20,21] Case records were consulted for participants lost to follow-up using compatible diagnostic criteria.

Risk factor assessment. At each assessment, the participants provided venous blood samples after an overnight fast. A detailed description of the blood component procedure has previously been reported.[22] Briefly, the samples were obtained with the subject in a sitting position and without tourniquet or muscle contraction. Blood was collected in heparin tubes for the determination of plasma lipid levels. Chemical analyses were done at the Department of Clinical Chemistry at the Sahlgrenska University Hospital in Göteborg using gas liquid chromatography for cholesterol and photometry for triglycerides.

At all examinations, participants were surveyed about a variety of potential risk factors for age-related diseases such as education, smoking status, socioeconomic status, alcohol intake, medication use, medical history, and current medical status. Casual blood pressure was taken with a mercury manometer from the right arm after 5 minutes rest with the participant in the seated position. Systolic blood pressure and diastolic blood pressure (DBP) were registered to the nearest 5 mm Hg. DBP was defined as Korotkoff phase 5.

Statistical analyses. Differences in mean lipid levels between those who developed dementia and those who never developed dementia over the 18-year follow-up period were assessed using two-sided t tests. Comparisons between those with and without dementia regarding other potential modifiers of the lipid-dementia relationship were made using χ^2 tests for categorical variables and Student t tests for continuous variables. Spearman's rank correlation coefficient was used to examine correlations between total cholesterol and triglycerides, and an extension of the Wilcoxon's rank sum test was used to inspect trends in lipid levels by age. Before examining correlations and mean lipid levels, outliers greater than or less than 3 SDs from the mean were excluded. Thus, three persons at age 70, three at 75, and four at 79 were excluded from the triglyceride analyses.

Cox proportional hazards regression analyses were used to examine the relationship between lipid levels and incident dementia. Lipid levels at age 70 were examined in relation to incident dementia between ages 70 and 88, at ages 70 and 75 for dementia onset between ages 75 and 88, and at ages 70, 75, and 79 years for incident dementia between ages 79 and 88 (figure). The dementia subtypes AD and VaD were only evaluated from age 79 to 88. In all AD and VaD analyses, persons with other dementia types were excluded. Univariate analyses were first used to examine the association between lipid levels and dementia. As DBP and body mass index (BMI) have already been reported as risk factors for dementia in this data set,[15,16] the analyses were repeated controlling for these factors as well as sex, education, and smoking. Additional variables were examined and not included in the multivariate models if they were not significantly ($p < 0.05$) associated with dementia and did not add to the model based on the log-likelihood ratio. These variables included systolic blood pressure, use of antihypertensive medication, cardiovascular disease, myocardial infarction, stroke or TIA, angina pectoris, diabetes,

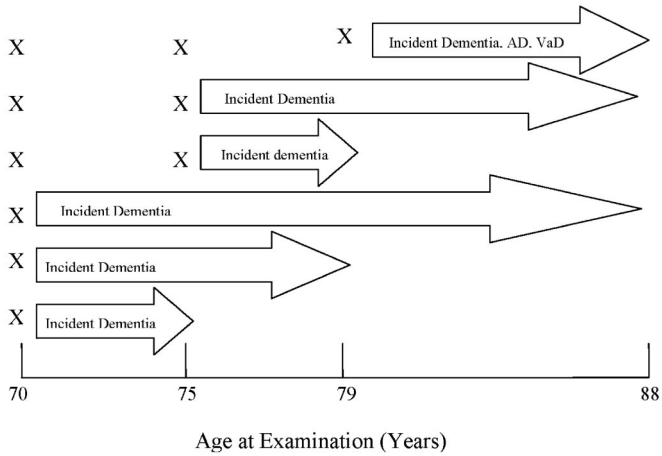

Figure. Age of cholesterol measurement (X) evaluated in relation to age interval of incident dementia. AD = Alzheimer disease; VaD = vascular dementia.

and alcohol intake. We logarithmically transformed the triglyceride variables at all ages before conducting regression analyses because the distributions were skewed to the right.

In further analyses, we examined the interaction between lipid levels and smoking and sex. We also evaluated change in lipid levels between ages 70 and 79 in relation to incident dementia between ages 79 and 88. Finally, to assess the effect of lipid-lowering drugs, analyses were performed with and without the inclusion of the few users of these drugs (four at age 70, seven at 75, and none at 79).

We also used Cox proportional hazards regression to examine the association between lipid levels at age 70 and all-cause mortality over the study duration. Multivariate models controlled for BMI, DBP, sex, ever smoking, myocardial infarction, stroke or TIA, and dementia, as these factors have been associated with an increased risk of mortality.

Cholesterol and triglyceride levels were examined as continuous variables (per mmol/L increase) and in quartiles (lowest quartile as the reference category). Quartile ranges were defined separately at each age for all lipid levels because of the different distributions of lipid values by age. BMI and DBP were modeled as continuous variables. Smoking (ever vs never) and education (<6 vs ≥ 6 years) were examined as dichotomous variables. In all analyses, concurrent (during one examination year) measures were included in individual models. Results of Cox regression analyses are presented as hazard ratios (HRs) with 95% CIs. Schoenfeld residuals were used to test the proportional hazards assumption.[23] Time at risk for dementia onset between ages 79 and 88 was calculated to age 88, death, or diagnosis of dementia. All analyses were conducted using the STATA statistical package, version 6 (StataCorp, 1999).

Results. Of the 392 participants in the study at age 70, 10 were identified at the first assessment with prevalent dementia and thus were excluded from the present analyses. The remaining 382 participants were followed for 4,091 person-years between the ages of 70 and 88. During this period, 93 participants developed incident dementia (19 cases between ages 70 and 75, 29 cases between 75 and 79, and 45 cases between 79 and 88). Characteristics at age 70 of those who developed dementia between ages 70 and 88 and those who did not were not significantly different except that those who developed dementia had a higher BMI at age 70. Dementia type was diagnosed between the ages of 79 and 88 years; the 45 dementia cases consisted of AD (19 cases), VaD (23 cases), and other dementia (three cases).

Mean total cholesterol levels at age 70 were lower in persons who developed dementia between ages 75 and 79 compared with those who did not (6.10 ± 1.06 vs 6.94 ± 1.42 mmol/L [236 ± 41 vs 268 ± 55 mg/dL], $p < 0.01$). Total cholesterol levels were also lower at ages 70 and 75 for participants with incident dementia between ages 79 and 88 years (see table E-1 on the *Neurology* Web site at www.neurology.org). Mean triglyceride levels at all ages did not differ by dementia diagnosis despite correlations between total cholesterol and triglycerides at ages 70 ($r = 0.26$, $p < 0.001$), 75 ($r = 0.25$, $p < 0.001$), and 79 ($r = 0.27$, $p < 0.01$).

We next examined the association between lipid levels (per mmol/L) and incident dementia using Cox proportional hazards models, controlling for BMI, DBP, sex, ever smoking, and education (table 1). In these analyses, higher total cholesterol levels at ages 70 and 75 were associated with a reduced risk of dementia between ages 75 and 79. Similarly, higher levels at ages 70, 75, and 79 were associated with a reduced risk between ages 79 and 88. The reduction in risk of dementia between ages 79 and 88 was similar for both AD and VaD, but the results did not attain conventional levels of significance ($p < 0.05$), likely due to small numbers (data not shown). There was no association between triglycerides at any age and incident dementia or dementia type. Stratifying by sex did not change the associations between cholesterol or triglyceride levels and incident dementia.

Quartiles of lipid levels (with the lowest quartile as the reference category) in relation to incident dementia between ages 79 and 88 were examined using multivariate survival analysis (table 2 for quartile ranges of lipid levels by age). At ages 70 and 75, and less so at age 79, there was a threshold effect for cholesterol such that only those within the highest quartile had a reduced risk of dementia between ages 79 and 88 (table 3). There was no association between quartiles of triglycerides and dementia. We could not examine dementia subtype and quartiles of lipid levels because the numbers were too small.

Examining mean cholesterol levels by smoking status at ages 70, 75, and 79 showed that cholesterol levels were significantly lower ($p < 0.02$) in those who had ever smoked. Therefore, we further examined the relationship between cholesterol and dementia after stratification by ever vs never smoking status. Increasing total cholesterol at ages 70, 75, and 79 was associated with a decreased risk of dementia between ages 79 and 88 among never smokers in multivariate analyses (table 4). In contrast, there was no association between cholesterol and dementia among ever smokers. There was no difference in the association

Table 1 *Lipid quartile ranges by age*

Lipids by age, y, mmol/L (mg/dL)	Quartile 1 (low)		Quartile 2		Quartile 3		Quartile 4 (high)	
	Range	n	Range	n	Range	n	Range	n
Cholesterol								
70	3.51–6.07 (136–234)	54	6.08–7.18 (235–277)	57	7.19–8.02 (278–310)	54	8.03–11.44 (311–442)	56
75	3.21–5.30 (124–204)	52	5.31–6.12 (205–236)	51	6.13–7.02 (237–271)	54	7.03–9.29 (272–359)	53
79	3.05–5.17 (118–199)	46	5.18–6.10 (200–235)	47	6.11–6.81 (236–263)	46	6.82–9.10 (264–352)	47
Triglycerides								
70	0.44–0.79 (39–70)	54	0.80–1.06 (71–93)	54	1.07–1.43 (94–126)	54	1.44–2.54 (127–225)	55
75	0.41–1.01 (36–89)	53	1.02–1.30 (90–115)	50	1.31–1.78 (116–157)	51	1.79–3.90 (158–345)	52
79	0.10–0.99 (9–88)	46	1.00–1.29 (89–114)	43	1.30–1.69 (115–149)	44	1.70–3.80 (150–336)	48

Table 2 *Hazard ratios for the multivariate association between lipid levels and incident dementia*

Lipids by age, y (mmol/L)	Dementia ages 70–75			Dementia ages 75–79			Dementia ages 79–88		
	HR (95% CI)	*p* Value	Cases/person-years	HR (95% CI)	*p* Value	Cases/person-years	HR (95% CI)	*p* Value	Cases/person-years
Cholesterol									
70	0.99 (0.70–1.41)	0.976	19/1692	0.62 (0.46–0.83)	0.001	29/1030	0.77 (0.61–0.96)	0.020	44/1334
75				0.71 (0.51–1.00)	0.051	25/952	0.70 (0.52–0.93)	0.014	40/1266
79							0.73 (0.55–0.98)	0.037	39/1141
Triglycerides									
70	2.11 (0.54–8.25)	0.282	16/1660	0.49 (0.18–1.29)	0.148	29/1014	0.55 (0.25–1.23)	0.146	43/1313
75				1.09 (0.43–2.79)	0.858	25/942	0.81 (0.39–1.67)	0.570	40/1255
79							0.87 (0.41–1.85)	0.723	38/1114

All analyses control for body mass index, diastolic blood pressure, sex, education, and smoking in year of examination.

HR = hazard ratio.

between triglycerides and dementia when stratifying by smoking status.

There was a linear trend of decreasing mean cholesterol levels with age ($p < 0.01$) (see table E-1). However, we found no evidence that changes in the individual levels of cholesterol or triglycerides were associated with incident dementia or dementia type (data not shown). Furthermore, excluding the few participants who used lipid-lowering medications did not alter any of the observed inverse associations between cholesterol and dementia (data not shown).

To consider the effects of mortality bias after the age of 70, we examined lipid levels at age 70 and mortality between ages 70 and 88. Increasing total cholesterol levels at age 70 (HR 0.87, 95% CI: 0.79 to 0.97), but not triglyceride levels (HR 1.21, 95% CI: 0.84 to 1.74), were associated with a reduced risk of mortality over the study period, controlling for BMI, DBP, sex, ever smoking, myocardial infarction, stroke or TIA, and dementia.

Discussion. In this 18-year longitudinal study of 70 year olds, we observed an association between higher total cholesterol and a decreased risk of dementia. Examination of cholesterol in quartiles showed that the reduction in risk was associated exclusively with the highest quartile. The exclusion of lipid-lowering medication users did not attenuate the association. Furthermore, the association was found only among nonsmokers. We did not find an association between triglyceride levels and dementia.

Our results are consistent with those of Romas et al.[3] who found a lower risk of AD among individuals aged 65 and older in the highest quartile of total cholesterol after a follow-up of more than 2 years. Additionally, a more recent study,[4] with approximately 5 years of follow-up, suggested a similar relationship such that high cholesterol in late life was again associated with a lower risk of AD. By contrast, two longitudinal studies[1,2] reported that high total cholesterol measured in mid-life was associated with an increased risk of dementia as long as 30 years later.

The conflicting results may be due to whether cholesterol is measured in mid- vs late life. Several studies have suggested a similar pattern with cardiovascular disease, in which high cholesterol in

Table 3 *Hazard ratios for the multivariate association between quartiles of lipids and incident dementia between ages 79 and 88*

Lipids by age, y (mmol/L)	Quartile 1 (low)		Quartile 2		Quartile 3		Quartile 4 (high)	
	HR	Cases/person-years	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Cholesterol								
70	1.00 (ref)	44/1334	1.05 (0.48–2.29)	0.899	0.97 (0.43–2.17)	0.942	0.31 (0.11–0.85)	0.029
75	1.00 (ref)	40/1266	0.95 (0.39–2.30)	0.915	1.26 (0.54–2.91)	0.594	0.20 (0.05–0.75)	0.017
79	1.00 (ref)	39/1141	0.82 (0.33–2.07)	0.682	0.83 (0.34–2.02)	0.684	0.45 (0.17–1.23)	0.120
Triglycerides								
70	1.00 (ref)	43/1313	0.47 (0.20–1.13)	0.093	0.76 (0.35–1.66)	0.496	0.45 (0.18–1.11)	0.084
75	1.00 (ref)	40/1255	1.15 (0.49–2.71)	0.742	0.71 (0.29–1.77)	0.467	0.91 (0.37–2.24)	0.839
79	1.00 (ref)	38/1114	0.60 (0.23–1.57)	0.297	1.09 (0.49–2.45)	0.831	0.77 (0.30–1.93)	0.571

All analyses control for body mass index, diastolic blood pressure, gender, education, and smoking in year of examination.

HR = hazard ratio.

Table 4 *Hazard ratios for the association between total cholesterol and incident dementia between ages 79 and 88, stratifying by smoking status*

Cholesterol by age, y (mmol/L)	Nonsmokers			Ever smokers		
	HR (95% CI)	*p* Value	Cases/person-years	HR (95% CI)	*p* Value	Cases/person-years
70	0.71 (0.54–0.92)	0.010	32/868	0.83 (0.53–1.32)	0.432	12/467
75	0.64 (0.46–0.89)	0.009	32/847	1.00 (0.52–1.96)	0.989	8/419
79	0.70 (0.50–0.98)	0.037	32/764	1.03 (0.52–2.05)	0.938	7/378

All analyses control for gender, education, body mass index, and diastolic blood pressure in the year of examination.

HR = hazard ratio.

mid-life,[8,9] but not late life,[10-12] is a risk factor. High cholesterol in late-life may be an indicator of better health status.[24,25] Those who survive to old age with high cholesterol may be a more robust and select population and therefore relatively invulnerable to the potential adverse effects of high cholesterol, including dementia. Interestingly, we found that high cholesterol was associated with a lower incidence of dementia in late life only among nonsmokers. It may be that smokers who live to age 70 are similarly robust and therefore less likely to develop dementia regardless of their cholesterol levels.

Alternatively, the conflicting results from studies on cholesterol and dementia may be due to whether cholesterol is measured early versus late in the course of the disease process. This has been suggested for blood pressure and BMI. In studies with more than 10 years of follow-up,[2,15,16,26] high blood pressure and BMI have been associated with an increased risk of AD. However, in studies with less than 10 years of follow-up,[27-30] the null or opposite relationship has been observed. The divergent findings appear to be due to the fact that several years before dementia onset blood pressure and BMI begin to decline, possibly as a result of the ongoing AD pathology.[15] The same may be true for cholesterol. Indeed, in their study Notkola et al.[1] found that high cholesterol was associated with a higher risk of dementia 30 years later, but before the onset of dementia cholesterol levels began to decline, and, as a result, low cholesterol was associated with dementia cross-sectionally. The authors noted that a decrease in cholesterol immediately before the dementia diagnosis was also predictive of dementia. In our study, we found that low cholesterol was associated with dementia as long as or longer than 9 years before the onset of clinical symptoms, suggesting that any decline in cholesterol may occur earlier in the course of the disease than for blood pressure or BMI. However, we did not find any evidence that a decrease in cholesterol over time was associated with the risk of dementia. Longer periods of follow-up may be necessary to observe this latter effect.

Another less likely explanation for the current findings is mortality bias. Participants with high cholesterol may have had an increased risk of mortality between the ages of 70 and 88 and therefore had less chance to develop dementia over the course of the study than participants with low cholesterol. However, it has been noted elsewhere[31] that low (not high) cholesterol is associated with mortality among the elderly, and this was true in our study as well.

Finally, it is possible that high cholesterol plays a role in protecting against dementia. Experimental studies suggest that high cholesterol accelerates the production of β-amyloid, the putative pathologic species in AD, by shifting amyloid precursor protein metabolism from alpha to beta cleavage products.[32-34] However, cholesterol is an essential molecule for many physiologic processes and may have several beneficial effects as well. Cholesterol is a precursor of steroid hormones (estrogens, androgens, vitamin D), provides structural integrity and modulates fluidity of cell membranes, and is essential for basic synaptic integrity and neurotransmission.[35,36] All these processes are compromised with aging and have been shown to be dysfunctional in patients with AD. In addition, in vitro studies have suggested that cholesterol acts as an antioxidant and therefore has a protective role in dementia pathogenesis,[37,38] possibly through intercepting pro-oxidants to create oxysterols, which are less toxic than free radicals.

The current study has limitations. First, the study followed a homogeneous population of white subjects in Scandinavia, and the results may not generalize to other populations or races. Second, we were not able to examine levels of high- or low-density lipoprotein cholesterol, which may be more strongly associated with dementia than total cholesterol. Third, some studies have reported an interaction between cholesterol levels and the *APOE* ϵ4 allele in AD.[1,39,40] In our study, *APOE* ϵ4 phenotyping was only available for a very small number of participants at age 85. Among those participants, there was no association between the *APOE* ϵ4 allele and cholesterol or triglycerides levels. Given the small numbers with available phenotypes, however, it is difficult to interpret these results. Fourth, there were too few cases of AD and VaD to adequately examine the association between lipid levels and dementia subtype. The reported nonsignificant associations between lipid levels and AD and VaD were most likely due to the small number of cases. Last, cholesterol levels were high in our study. The percentage of participants

with cholesterol levels greater than 6.2 mmol/L (240 mg/dL) were 71.5% at age 70, 48.6% at age 75, and 47.3% at age 79. However, other population-based studies from Scandinavia have also reported high cholesterol levels,[2] and the Framingham study reported that 61% of women aged 65 to 74 had total cholesterol levels greater than 6.2 mmol/L.[41] In 1971 to 1972, the year of our first assessment, very few effective cholesterol-lowering drugs were available and the thresholds for defining high cholesterol were higher than they are today. Therefore, our study may be a good indicator of cholesterol levels among the elderly in the absence of cholesterol-lowering drugs.

The present study also has strengths. It followed a 70-year-old birth cohort for over 18 years. Lipid measurements were available from seven assessments, allowing a closer examination of the temporal relationship between cholesterol and dementia. In addition, 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 or cognitively impaired.

The prevailing wisdom is that high cholesterol is a risk factor for dementia. However, the relationship between cholesterol and dementia may vary considerably depending on when cholesterol is measured over the life course or, alternatively, in relation to the underlying course of the disease. In the present study, we found that high cholesterol as long as and longer than 9 years before dementia onset is associated with a reduced risk of dementia among 70 year olds. Other studies have reported similar results, lending support to the conclusion that this association is real. It is important to determine the basis for this association, especially given the increasing interest in controlling cholesterol among the elderly.[42] If high cholesterol plays a protective role against dementia in the elderly, then the risk-benefit ratio of lowering cholesterol in this population may need to be reevaluated. Several observational studies have suggested that statins, which are effective in lowering cholesterol, may reduce the risk of dementia,[43,44] but the results of these studies are inconclusive. If, conversely, high cholesterol is merely a marker of robustness in the elderly, then this may also be important because it could help us to identify what makes these individuals invulnerable to developing dementia and other illnesses. Thus, more studies with long-term follow-up and serial assessments of cholesterol are needed to further clarify the causal relationship between cholesterol and dementia.

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