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Midlife Serum Cholesterol and Increased Risk of Alzheimer's and Vascular Dementia Three Decades Later

Alina Solomon[a, b] Miia Kivipelto[a, b] Benjamin Wolozin[c] Jufen Zhou[d] Rachel A. Whitmer[d]

[a]Department of Neurology, University of Kuopio, Kuopio, Finland; [b]Aging Research Center, Karolinska Institutet, Stockholm, Sweden; [c]Department of Pharmacology, Boston University School of Medicine, Boston, Mass., and [d]Division of Research, Kaiser Permanente, Oakland, Calif., USA

Key Words
Dementia · Epidemiology · Alzheimer's dementia · Cholesterol · Vascular dementia

Abstract
Aims: To investigate midlife cholesterol in relation to Alzheimer's disease (AD) and vascular dementia (VaD) in a large multiethnic cohort of women and men. ***Methods:*** The Kaiser Permanente Northern California Medical Group (healthcare delivery organization) formed the database for this study. The 9,844 participants underwent detailed health evaluations during 1964–1973 at ages 40–45 years; they were still members of the health plan in 1994. AD and VaD were ascertained by medical records between 1 January 1994 and 1 June 2007. Cox proportional hazards models – adjusted for age, education, race/ethnic group, sex, midlife diabetes, hypertension, BMI and late-life stroke – were conducted. ***Results:*** In total, 469 participants had AD and 127 had VaD. With desirable cholesterol levels (<200 mg/dl) as a reference, hazard ratios (HR) and 95% CI for AD were 1.23 (0.97–1.55) and 1.57 (1.23–2.01) for borderline (200–239 mg/dl) and high cholesterol (≥240 mg/dl), respectively. HR and 95% CI for VaD were 1.50 (1.01–2.23) for borderline and 1.26 (0.82–1.96) for high cholesterol. Further analyses for AD (cholesterol quartiles, 1st quartile reference) indicated that cholesterol levels >220 mg/dl were a significant risk factor: HR were 1.31 (1.01–1.71; 3rd quartile, 221–248 mg/dl) and 1.58 (1.22–2.06; 4th quartile, 249–500 mg/dl). ***Conclusion:*** Midlife serum total cholesterol was associated with an increased risk of AD and VaD. Even moderately elevated cholesterol increased dementia risk. Dementia risk factors need to be addressed as early as midlife, before underlying disease(s) or symptoms appear.
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Introduction

A fully manifest dementia syndrome represents the end stage of underlying disease(s), the most frequent of which are Alzheimer's disease (AD) and cerebrovascular disease. Thus, the best approach implies not only early diagnosis and treatment, but also emphasizes prevention. However, chronic diseases with a long preclinical phase (such as AD) pose inherent difficulties in the identification of their risk factors. Since disease onset cannot be pinpointed, the chances are that true risk relationships (factors increasing the probability of getting the disease) and reverse causality (the effects of the disease itself on various factors) get confused. In later life, any apparently normal population will be a mixture of individuals with-

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Alina Solomon
Department of Neurology, University of Kuopio
PO Box 1627
FI–70211 Kuopio (Finland)
Tel. +46 8 690 5822, Fax +46 8 690 5954, E-Mail alina.solomon@uku.fi

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out the disease and individuals who have the disease, although clinically silent and undiagnosed. Thus, midlife is more suitable as a starting point when looking for risk factors, since AD is not as likely to be present already.

The relationship between midlife serum total cholesterol and the risk of subsequent dementia has so far been investigated in only a few long-term epidemiological studies with relatively homogeneous populations [1]. In the Finnish cohort of the Seven Countries Study and the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study, high midlife cholesterol was associated with increased dementia/AD risk [2, 3], but no association was observed in the Honolulu Asia Aging Study (HAAS) or Framingham study [4, 5].

High midlife cholesterol has previously been shown to be a risk factor for dementia in the multiethnic cohort of women and men from the Kaiser Permanente Medical Care Program of Northern California [6]. The present study investigates further the cholesterol-dementia relationship by focusing on the 2 main dementia subtypes, AD and vascular dementia (VaD), in a larger Kaiser Permanente cohort with updated follow-up information. We also examined the full range of cholesterol values (not just high cholesterol, >240 mg/dl), to determine whether even moderate elevations may be associated with increased dementia risk.

Methods

Study Population

This is a retrospective cohort study of members of the Kaiser Permanente Medical Care Program of Northern California who participated in voluntary periodic multiphasic health checkups (MHC) in San Francisco and Oakland, Calif., USA, between 1964 and 1973 when they were 40–45 years old. If members attended more than one MHC during this interval, data from the first visit were considered. The present cohort includes only 9,844 persons who were still members of the health plan in 1994 when computerized outpatient diagnoses of dementia became available.

Kaiser Permanente of Northern California is a nonprofit group-practice integrated health delivery system that covers more than one fourth of the population in the geographic areas served. Kaiser Permanente members are representative of the sociodemographics of the local population [7].

Data Collection

At the MHC, participants were interviewed and information on demographics, lifestyle and medical history was collected, including questions on medical conditions and medication use [8]. Systolic and diastolic blood pressure, weight, and height were measured according to standard procedures [9] and body mass index (BMI) was calculated (kg/m^2). Blood was drawn for total serum cholesterol, and levels were measured with an auto-analyzer (Technicon Co., White Plains, N.Y., USA) from 1964 to 1968, with an autochemist (AGA, Stockholm, Sweden) from 1969 to 1972, and with an auto-analyzer (model SMA-12; Technicon Co., White Plains, N.Y., USA) in 1973 [8, 10]. The participants were considered to have hypertension if they had one of the following: self-reported physician-diagnosed hypertension, use of antihypertensive medication, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg. Diabetes was defined by self-report of physician-diagnosed diabetes, use of insulin or oral hypoglycemic agents, a fasting glucose level (last food eaten in ≥8 h) ≥140 mg/dl, or a nonfasting (last food eaten in ≤4 h) glucose level ≥200 mg/dl. If the participants did not mention hypertension or diabetes, were not taking medications for these diseases, and had no laboratory or hematological evidence of these diseases, it was assumed that the participants did not have these risk factors at midlife. Stroke was recorded from hospital discharge diagnoses (ICD-9 codes for ischemic stroke, 433–438, hemorrhagic stroke, 430–432) from 1985 through the end of the study in June 2007. The MHC study was approved by the Internal Review Board of Kaiser Permanente.

Dementia Diagnoses

Dementia diagnoses were ascertained through electronic medical records from a database that contains diagnoses from all outpatient encounters at Kaiser Permanente medical centers and clinics. The form is completed by the treating clinician. Diagnoses considered in this study included AD (ICD-9 CM code 331.0) and VaD (ICD-9 CM code 290.4) from visits to the Neurology Department. Diagnoses were ascertained from January 1994 to June 2007 when the MHC participants would have been 61–88 years of age. Mortality information was available on our cohort through the end of 2005 using the California Automated Mortality Linkage System, which has a sensitivity of 0.97 compared to the National Death Index [11]. From 1 January 2005 to 31 December 2006, mortality information was available using a weighted linkage system incorporating matches by social security number, name, date of birth and home address to Social Security Death Data. From 1 January 2007 to June 2007, mortality information was not yet available.

Statistical Analyses

All analyses were performed using SAS version 8.0 (SAS Institute, Cary, N.C., USA). Three groups were considered: control (no dementia), AD and VaD (9,844 persons in total); χ^2 tests and F tests were used to determine if demographic and clinical characteristics at the time of the MHC were significantly different by the presence of AD or VaD. We used Cox proportional hazards (age) as time scale models to investigate the relationship between midlife cholesterol and AD or VaD.

Participants were censored according to age at dementia diagnosis, age at date of death, age at date of end of Kaiser membership, or age at end of follow-up (1 June 2007).

Cholesterol levels were grouped into 3 categories, according to the 2002 Adult Treatment Panel (ATP) III guidelines: <200 mg/dl (desirable; used as a reference category), 200–239 mg/dl (borderline) and ≥240 mg/dl (high) [12]. For a more detailed evaluation of the relation between cholesterol and AD, analyses were also carried out using 4 cholesterol categories (quartiles, with first quartile as reference category).

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Table 1. Sociodemographic and clinical characteristics of the study population (n = 9,844)

	No dementia (n = 9,248)	AD (n = 469)	VaD (n = 127)	p values
Age at MHC exam	42.4 ± 1.7	42.8 ± 1.7	42.7 ± 1.5	<0.0001
Age in 1994, years	68.8 ± 2.8	69.9 ± 2.5	69.5 ± 2.5	<0.0001
Sex, male	4,281 (46.3)	188 (40.1)	58 (45.7)	0.03
Education				0.08
Grade school	1,261 (13.6)	81 (17.3)	22 (17.3)	
High school	3,159 (34.2)	160 (34.1)	55 (43.3)	
Trade school	651 (7.0)	29 (6.2)	4 (3.2)	
College 1–2 years	1,197 (12.9)	60 (12.8)	17 (13.4)	
College 3–4 years	1,297 (14.0)	62 (13.2)	10 (7.9)	
Postgraduate	1,683 (18.2)	77 (16.4)	19 (14.9)	
Race/ethnic group (self-reported)				<0.0001
Asian	598 (6.5)	17 (3.6)	5 (3.9)	
Black	1,387 (15)	109 (23.2)	35 (27.6)	
White	6,863 (74.2)	325 (69.3)	85 (66.9)	
Other	400 (4.3)	18 (3.8)	2 (1.6)	
Cholesterol[1], mg/dl	224.1 ± 41.4	228.5 ± 37.8	226.4 ± 38.4	0.06
Midlife BMI	24.9 ± 3.9	25.1 ± 3.9	26.1 ± 4.6	0.002
Midlife diabetes	1,025 (11.1)	59 (12.6)	25 (19.7)	0.03
Midlife hypertension	1,771 (19.2)	97 (20.7)	36 (28.4)	0.02
Late-life stroke	1,626 (17.6)	128 (27.3)	83 (65.4)	<0.0001

Values represent means ± SD or number of participants with percentages in parentheses.
[1] To convert cholesterol to millimoles per liter, multiply by 0.0259.

Models were adjusted for age (as time scale), sex, education (categorized as high school, trade school, college 1–2 years, college 3–4 years and postgraduate, with grade school as reference), race/ethnic group (self-reported, it was entered in analyses as black, Asian, or other, with Caucasian as referent group), midlife BMI (continuous variable), diabetes and hypertension (yes/no). For AD, the model was additionally controlled for late-life stroke (yes/no). To determine whether the association between midlife cholesterol and risk of AD or VaD varied by sex or race/ethnic group, we entered interaction terms to the fully adjusted models.

Results

Sociodemographic and clinical characteristics of the study population are shown in table 1. As expected, people with AD or VaD were significantly older than those without dementia. A lower percentage of patients with AD or VaD (compared to nondemented individuals) had formal education at the college level and above (p = 0.08). There were more women in the dementia groups than in the group without dementia (p = 0.03). Mean BMI (p = 0.002) and cholesterol level (p = 0.06) were higher in the AD and VaD groups. A medical history of hypertension, diabetes or stroke was also significantly more common among patients with AD or VaD. Table 2 presents the percentages of persons with AD, VaD and no dementia in each cholesterol category.

Cox proportional hazards models of ATP III cholesterol categories for AD and VaD are shown in table 3. In the fully adjusted model, high midlife cholesterol (≥240 mg/dl) was associated with an increased risk of developing AD 3 decades later; the HR was 1.57 (95% CI: 1.23–2.01). Borderline cholesterol levels tended to increase AD risk as well, but the results were not statistically significant; the HR was 1.23 (95% CI: 0.97–1.55). However, borderline cholesterol levels represented a significant risk factor for VaD; HR in the fully adjusted model was 1.50 (95% CI: 1.01–2.23). High midlife cholesterol tended to increase the risk for VaD, but without reaching statistical significance; HR was 1.26 (95% CI: 0.82–1.96).

In order to investigate the association between different cholesterol levels and AD risk in more detail, additional analyses were performed using 4 cholesterol categories (quartiles): <198 mg/dl (first quartile, reference), 198–220 mg/dl (second quartile), 221–248 mg/dl (third quartile) and 249–500 mg/dl (fourth quartile). As shown

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Table 2. Incidence of AD, VaD and no dementia in each cholesterol category

	No dementia (n = 9,248)	AD (n = 469)	VaD (n = 127)	All (n = 9,844)
Cholesterol categories				
Desirable (<200 mg/dl)	2,545 (94.93)	107 (3.99)	29 (1.08)	2,681 (100)
Borderline (200–239 mg/dl)	3,771 (93.9)	186 (4.63)	59 (1.47)	4,016 (100)
High (≥240 mg/dl)	2,932 (93.17)	176 (5.59)	39 (1.24)	3,147 (100)

Values represent the number of people with percentages in parentheses.

Table 3. Cox proportional hazards models of ATP III cholesterol categories for AD and VaD

	HR and 95% CI	
	AD	VaD
Model 1		
Desirable (<200 mg/dl)	reference	reference
Borderline (200–239 mg/dl)	1.25 (0.99–1.58)	1.52 (1.02–2.25)*
High (≥240 mg/dl)	1.66 (1.31–2.09)*	1.34 (0.87–2.07)
Model 2		
Desirable (<200 mg/dl)	reference	reference
Borderline (200–239 mg/dl)	1.23 (0.97–1.55)	1.50 (1.01–2.23)*
High (≥240 mg/dl)	1.57 (1.23–2.01)*	1.26 (0.82–1.96)

Model 1 is unadjusted. Model 2 is adjusted for age (as time scale), sex, education, race/ethnic group, midlife BMI, diabetes and hypertension; for AD, the model is additionally adjusted for late-life stroke. * $p \leq 0.05$.

Table 4. Cox proportional hazards models of cholesterol quartiles for AD

	HR and 95% CI
Model 1	
<198 mg/dl	reference
198–220 mg/dl	1.26 (0.97–1.63)
221–248 mg/dl	1.43 (1.11–1.85)*
249–500 mg/dl	1.64 (1.27–2.12)*
Model 2	
<198 mg/dl	reference
198–220 mg/dl	1.25 (0.96–1.63)
221–248 mg/dl	1.31 (1.01–1.71)*
249–500 mg/dl	1.58 (1.22–2.06)*

Model 1 is unadjusted. Model 2 is adjusted for age (as time scale), sex, education, race/ethnic group, midlife BMI, diabetes, hypertension and late-life stroke. * $p \leq 0.05$.

in table 4, cholesterol levels >220 mg/dl represented a significant risk factor for AD; HR in the fully adjusted model were 1.31 (95% CI: 1.01–1.71) for the third quartile and 1.58 (95% CI: 1.22–2.06) for the fourth quartile.

No statistically significant interactions were observed between sex and cholesterol or between race/ethnic group and cholesterol in relation to the risk of AD or VaD (results not shown).

Discussion

This is the first study to specifically investigate the relationship between midlife serum total cholesterol levels and the risk of AD and VaD 3 decades later in a large and very diverse cohort of both women and men. After controlling for a wide range of confounders, midlife cholesterol was associated with both AD and VaD in late life. Testing of interaction terms by race/ethnic group and sex showed that effects were not statistically different for men and women or by race/ethnic group.

High cholesterol levels as defined by the 2002 ATP III guidelines (≥240 mg/dl) [12] represented a significant risk factor for AD as well, besides the well-known connection to cardiovascular disease risk. Cholesterol values >250 mg/dl have been previously linked to an increased risk of dementia/AD in the Finnish population (CAIDE study, Finnish cohorts of the Seven Countries Study) [2, 3]. The results of the present study point to an even lower threshold, as additional analyses with cholesterol levels categorized into quartiles indicated that midlife cholesterol values >220 mg/dl increase the risk of developing AD 3 decades later. Therefore, even moderately elevated cholesterol in midlife was associated with an increased risk of AD.

No relationship between midlife serum total cholesterol and the risk of AD was found in the HAAS study, although clustering of cardiovascular metabolic risk fac-

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tors (including total cholesterol) at midlife increased the risk of dementia in general [4]. The differences in findings could be due to differences in study population characteristics, since HAAS included Japanese-American men only, while our results are based on a multi-ethnic population of women and men. In the Framingham study, long-term (30 years) average serum total cholesterol was not related to AD development [5]. This approach does not reflect the influence of cholesterol at midlife as a risk factor for subsequent AD. Since the exact onset of AD (long before it shows itself as Alzheimer's dementia) cannot be diagnosed with current methods and criteria, relating the average of multiple cholesterol measurements over 30 years to AD may mix the influence of cholesterol on AD with the influence of clinically-silent undiagnosed AD on cholesterol. As the CAIDE and HAAS studies have shown, the pattern of change in cholesterol levels after midlife is also important; a decline in serum total cholesterol after midlife may be associated with early stages in the development of dementia [13, 14].

Several mechanisms may lie behind the cholesterol-AD association. One hypothesis would indicate the vascular pathway, since high serum cholesterol is related to cardiovascular and cerebrovascular conditions, which have been linked to AD. However, the relation between high midlife serum total cholesterol and AD was significant in our study even after controlling for several vascular factors and conditions, suggesting that there might be other mechanisms as well. A key component for brain function, cholesterol turnover has also been associated with neurodegenerative diseases [15]. Due to the blood-brain barrier, serum and brain cholesterol are 2 separate pools, but they do interact, for example through 24- and 27-hydroxycholesterol [15].

Borderline cholesterol levels as defined by the 2002 ATP III guidelines (200–239 mg/dl) [12] significantly increased the risk of developing VaD 3 decades later. High cholesterol levels (≥240 mg/dl) tended to increase VaD risk as well, but the association did not reach statistical significance. One reason for this could be the small sample size of VaD (127 persons in total, 39 with high cholesterol).

VaD represents a markedly heterogeneous group of disorders [16]. Despite its strong link with coronary artery disease, elevated serum cholesterol has a less straightforward relation with stroke, since stroke subtypes are not accounted for in many studies [17]. Moreover, persons with stroke do not always get dementia, and VaD may also be the result of small and clinically silent infarcts. Risk factor profiles may be slightly different for different types of lesions contributing to VaD: atherosclerosis in larger brain vessels is thought to be related primarily to blood pressure and secondarily to blood lipids; atherosclerosis in smaller vessels is thought to be related to blood pressure alone and not affected by blood lipids [18]. Since our cohort included fewer VaD cases, and since current diagnostic criteria (including ICD-9 CM) are not able to differentiate the main VaD subtypes (such as multi-infarct dementia, strategic infarct dementia, or subcortical ischemic VaD) [16], more refined conclusions on cholesterol and VaD are difficult to formulate.

Strengths and Limitations of the Study

To date, this is the largest longitudinal study to investigate the link between midlife serum total cholesterol, AD and VaD. It has comprehensive health examinations at midlife, a long follow-up period, and a multiethnic representative sample including both men and women with equal access to medical care. Also, because cholesterol was measured in people aged 40–45 years, it is highly unlikely that subclinical dementia was present at baseline; thus, the temporality of the associations is clear.

About 60–70% of the total serum cholesterol is typically represented by LDL cholesterol, the major atherogenic lipoprotein [12]. However, the role of LDL as a risk factor for AD or VaD could not be investigated in this study because data on LDL levels in 1964–1973 were not available.

Since AD and VaD diagnoses were obtained electronically from chart diagnoses, which may be insensitive, a portion of our sample may have had undiagnosed dementia. It is also likely that some AD or VaD cases were missed in participants who died prior to 1994, the onset of the ascertainment. However, this would tend to bias the results toward an underestimation of the true effect of midlife cholesterol on AD or VaD. Information on lipid-lowering treatments, which have been suggested to decrease dementia risk [19], was not available for this study. Due to the study design, it was only possible to assess AD/VaD status in those who were still Kaiser members at the time of the ascertainment. Post hoc analyses revealed no significant differences in any of the midlife cardiovascular risk factors by health plan membership status in 1994.

Neuropathological data regarding the diagnoses of AD and VaD in our cohort was not available. Diagnostic criteria used in current clinical practice are known to have a bias towards AD due to the emphasis on memory impairment in dementia diagnosis [20]. As a result, some VaD cases may have been labeled as AD. Also, current

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diagnostic criteria define AD and VaD as entirely separated from one another, at the cost of mixed dementia etiologies [20]. Although our cohort does not include persons with mixed dementia as recognized by ICD-9 CM, the concomitant presence of neurodegenerative and vascular pathologies in a portion of the sample cannot be excluded.

Clinical Significance and Conclusions

Physicians tend to confine AD and VaD to geriatric age borders, and address symptoms as they occur. Our study, along with others [21], points out the importance of addressing risk factors as early as midlife, before the underlying disease(s) or the symptoms appear. Elevated midlife serum total cholesterol increases the risk of both AD and VaD, a finding that adds to the existing body of evidence on a degree of overlap between the two dementia types in terms of risk factors, symptoms and neuropathology [22]. Moreover, dementia and cardiovascular disease are common major health problems, share several risk factors and often occur simultaneously, interacting with one another. Effective management of such disorders thus warrants a transdisciplinary approach.

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