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Research paper

Cholesterol in midlife increases the risk of Alzheimer's disease during an up to 43-year follow-up

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AD, Alzheimer' disease
BP, Blood pressure
BMI, Body mass index
CI, Confidence interval
TC, Total cholesterol
RCT, Randomized controlled trial

ABSTRACT

Purpose: Vascular risk factors in midlife may play a role in the development of cognitive decline, dementia and Alzheimer' disease (AD). The role of serum total cholesterol has yielded inconsistent results in diverse cohorts.
Objective: To analyze the relationship between the midlife cholesterol level and AD in late life in a homogenous cohort of Caucasian men.
Methods: The Helsinki Businessmen Study is a cohort of male business executives who have been followed-up since 1964. Midlife cholesterol level was available in 3293 men, of whom 205 developed a register-verified AD. Cognitively intact men in 2007 (n = 844) served as controls, and logistic regression adjusted for age and cardiovascular risk factors was used to investigate the association between cholesterol and AD.
Results: At baseline, the men with subsequent AD diagnosis had 0.4 mmol/L higher total cholesterol level than controls (6.7 vs 6.3 mmol/L). In adjusted analyses 1 mmol/L rise in total cholesterol was associated with a 22% increased risk of AD (odds ratio [OR] 1.22, 95% confidence interval 1.06 to 1.40, P = 0.005). Risk of AD (OR with 95% CI) also increased in a stepwise manner from the lowest to highest quartile of midlife cholesterol from 1.0 (referent) to 1.6 (1.01–2.6), 1.9 (1.2–3.0), and 2.0 (1.2–3.3), respectively.
Conclusion: In this longitudinal study with up to 43 years of follow-up, higher serum total cholesterol in early midlife was clearly associated with a higher risk of AD in late life.

1. Introduction

Cardiovascular risk factors are increasingly recognized to contribute to Alzheimer's disease (AD) [1].

A few long-term epidemiological studies have investigated the relationship between serum total cholesterol (TC) in midlife and the risk of subsequent dementia in old age [2–6]. In a sample of men aged 70–89 years with AD, TC was elevated already 15–25 years before the diagnosis of AD [2]. In a prospective population-based study of 1449 participants and 26-year follow-up, high serum TC (> 6.5 mmol/L) in midlife was associated with an increased risk of AD in late life [4]. In a large multiethnic cohort recruited between 1964–1973 at ages 40 to 44, the number of vascular risk factors was associated with dementia in a dose-dependent manner and midlife TC was associated with an increased risk of dementia [6].

On the other hand, in a cohort of Japanese–American men there was no association between midlife TC and incident AD as such, but clustering of cardiovascular risk factors at midlife increased the risk of dementia in general [3]. Also in a Swedish cohort of 2268 men followed from age 50 years there was no general association

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between vascular risk factors and AD, but high systolic blood pressure, or the combination of APOE epsilon 4 allele with vascular risk factors were associated with all-type dementia [7]. Midlife TC increased the risk of both AD and vascular dementia in a population-based study [8]. Several other epidemiological studies haven't found the association between TC and AD [9,10].

Because these conflicting results may be due to difficulties in adjustments and finding a cognitively intact control group in old age, we investigated the relationship between TC and AD in the Helsinki Businessmen Study, a socioeconomically homogenous group of men followed-up from early midlife to old age, up to 43 years.

2. Methods

The Helsinki Businessmen Study is a cohort of Finnish business executives born between 1919–1934. The participants had the initial assessments between 1964–1973, at the mean age of 40 (range 30–45) years at baseline, whereupon various cardiovascular risk factors (blood pressure, TC and triglycerides, one-hour post-load glucose, smoking, body mass index (BMI) were measured [11]. Thereafter the cohort has been followed-up with clinical studies, mailed questionnaires (in 2000, 2002/2003, 2005, and 2007) and using national registers through December 31, 2007. The Ethics Committee of the Helsinki University Central Hospital, Department of Medicine has approved the follow-up investigations, the most recent application by the code HUS 429/13/03/01/09.

The present cohort includes all 3293 men without clinical vascular diseases and of whom serum cholesterol measurement was available in early midlife between 1964–1973. In the 1960s and until 1974 serum cholesterol concentration was determined using the method by Huang et al. [12], which gives 8.3% greater values than the current enzymatic methods [13]. To ease comparisons, we have in the present analyses used the corrected values. The baseline serum total cholesterol was divided into quartiles as follows: < 5.8 mmol/L (224.3 mg/dL), 5.8–6.5 mmol/L (224.3–251.3 mg/dL), 6.6–7.3 mmol/L (255.2–282.3 mg/dL) and > 7.3 mmol/L (282.3 mg/dL).

Total mortality of the study cohort was retrieved from the Central Population Register, and the cause of death from the countrywide computerized Cause-of-Death Register of Statistics Finland. The diagnosis of AD during follow-up was based either on:

- AD cited in the death certificate;
- medication for AD reimbursed by the Finnish Social Security Office (KELA), which keeps statistics of prescribed medications in Finland.

Reimbursement for AD medication requires the fulfillment of strict diagnostic criteria including brain imaging, and practically all diagnosed AD cases in Finland have received this reimbursement. Incident cases of dementia (not necessarily AD) during follow-up were also identified from the repeated questionnaire surveys in 2000–2007. As a cognitively intact control group, we used those men who in the 2007 survey reported zero points (sum of boxes) in the Clinical Dementia Rating (CDR) embedded in the questionnaire.

2.1. Statistical methods

Statistical analyses were performed with NCSS 2007 (NSCC, Kaysville, UT). We used descriptive statistics, stratification, and logistic regression to compare the association between midlife cholesterol and AD or incident dementia in late life. As covariates we used age and all risk factors measured in over 3000 men at baseline. We analyzed separately the association between midlife cholesterol and register-verified AD, and the combination of AD and questionnaire-identified dementia cases. Odds-ratios (OR) with their 95% confidence intervals (CI) were calculated. Significance was defined as two-sided $P < .05$.

3. Results

The follow-up period was up to 43 years, but the mean due to mortality 33.1 years (range 0 to 43 years). According to the principles described in Methods, by the year 2007 we could identify 844 cognitively intact controls, 205 men with register-verified AD, and a further 45 men with other dementia identified from questionnaire surveys during follow-up. In addition, 1469 men had died of causes other than AD, 196 men had CDR > 0 (but no clinical diagnosis of AD or report of dementia) in 2007, and 534 did not respond in 2007 (but were not identified to have AD in registers). Consequently, we could classify 83.8% of the 3293 men with cholesterol measurement in early midlife. Although the focus of the present analysis is on the difference between AD and normal cognition, we present the baseline characteristics of all the groups in Table 1 for comparisons.

Table 1
Comparison of baseline vascular risk factors in various groups.

	Status 2007						
Variable at baseline[a]	CDR= 0, $n=844$	CDR > 0, no AD, $n=196$	AD diagnosis in registers, $n=205$	Reported dementia in questionnaires, $n=45$	Alive, no response, but no AD, $n=536$	Dead, no AD, $n=1469$	P value between groups
Age	40.2 (0.2)	41.8 (0.3)	43.0 (0.3)	41.7 (0.7)	41.1 (0.2)	42.7 (0.2)	< 0.001
Ever smokers, n = 3300, n (%)	394 (53.4)	123 (62.8)	118 (57.6)	26 (57.8)	292 (54.5)	944 (64.1)	< 0.001
BMI, n = 3217	25.4 (0.1)	25.8 (0.2).	25.6 (0.2)	26.3 (0.4)	25.6 (0.1)	26.3 (0.08)	< 0.001
Blood pressure, mm Hg, n = 3253							
Systolic	133.9 (0.5)	133.0 (1.1)	133.8 (1.1)	131.9 (2.4)	133.6 (0.7)	139.0 (0.4)	< 0.001
Diastolic	84.9 (0.4)	85.4 (0.8)	84.6 (0.7)	85.5 (1.6)	85.0 (0.5)	88.1 (0.3)	< 0.001
Cholesterol, mmol/L, n = 3265	6.4 (0.04)	6.5 (0.08)	6.7 (0.03)	6.3 (0.2)	6.6 (0.05)	6.7 (0.03)	< 0.001
One-hour glucose, mmol/L, n = 2749	6.1 (0.07)	6.0 (0.2)	6.2 (0.1)	6.2 (0.3)	6.2 (0.09)	6.6 (0.05)	< 0.001 (log)
Triglycerides, mmol/L, n = 1408	1.46 (0.04)	1.61 (0.05)	1.49 (0.1)	1.58 (0.2)	1.53 (0.08)	1.62 (0.03)	0.09 (log)

Values are mean (SE) unless otherwise indicated. CDR = 0, CDR > 0, but no AD, AD register diagnosis, reported dementia, alive without AD and dead without AD according to the status in 2007.

[a] Age-adjusted.