Apolipoproteins and HDL cholesterol do not associate with the risk of future dementia and Alzheimer's disease: the National Finnish population study (FINRISK)

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Abstract Data on associations of apolipoproteins A-I and B (apo A-I, apo B) and HDL cholesterol (HDL-C) with dementia and Alzheimer's disease (AD) are conflicting. Our aim was to examine, whether apo B, apoA-I, their ratio, or HDL-C are significant, independent predictors of incident dementia and AD in the general population free of dementia at baseline. We analyzed the results from two Finnish prospective population-based cohort studies in a total of 13,275 subjects aged 25 to 74 years with mainly Caucasian ethnicity. The follow-up time for both cohorts was 10 years. We used Cox proportional hazards regression to evaluate hazard ratios

(HR) for incident dementia (including AD) ($n = 220$) and for AD ($n = 154$). Cumulative incidence function (CIF) analysis was also performed to adjust the results for competing risks of death. Adjusted for multiple dementia and AD risk factors, log-transformed apo A-I, log HDL-C, log apo B, and log apo B/A-I ratio were not associated with incident dementia or AD. HDL-C was inversely associated with AD risk when adjusted for competing risks but no other statistically significant associations were observed in the CIF analyses. Apo A-I, HDL-C, apo B, or apo B/A-I ratio were not associated with future dementia or AD. HDL-C was inversely

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associated with incident AD risk when adjusted for competing risks of death, but the finding is unlikely to be of clinical relevance. Our study does not support the use of these risk markers to predict incident dementia or AD.

Keywords Apolipoprotein A-I · Apolipoprotein B · HDL-C · Dementia · Alzheimer's disease · Prospective · ApoE genotype

Introduction

Dementia and Alzheimer's disease (AD) comprise a heavy health and economic burden in western countries (Mura et al. 2010; Hurd et al. 2013). Cardiovascular risk factors are known to predict the risk of dementia (Kivipelto et al. 2006; Kaffashian et al. 2013). Higher total serum cholesterol (TC) in midlife is associated with higher risk of AD (Kivipelto et al. 2001; Li et al. 2005; Solomon et al. 2007) but the association of TC and dementia risk is reversed in later life (Mielke et al. 2005). Low levels of high density lipoprotein cholesterol (HDL-C) also associate with adverse cerebral white matter changes (Gouw et al. 2008; Crisby et al. 2010), but no clear association of HDL with the risk of dementia or AD has been found in prospective studies (Li et al. 2005; Reitz et al. 2005; Reitz et al. 2010; Arntzen et al. 2011). Apolipoprotein A-I (apo A-I) is the major surface protein of HDL-C, which is associated with lower risk for cardiovascular diseases (CVD). Apolipoprotein B (apo B), specific to all other lipid particles, is considered to be proatherogenic. The ratio of apo B and apo A-I has some stratification value over TC and HDL in predicting CVD (Emerging Risk Factors Collaboration et al. 2012). The aggregation of amyloid-beta peptide is recognized to be a hallmark of pathogenesis of AD, and apo A-I has neuroprotective effect by forming a complex with the amyloid-beta peptide, altering its aggregation and neurodegenerative abilities (Paula-Lima et al. 2009).

Previous studies have shown that patients with AD have lower levels of circulating apo A-I compared with healthy controls (Merched et al. 2000). A genetic polymorphism of apo A-I is related to cognitive impairment (Helbecque et al. 2008) and AD (Vollbach et al. 2005). However, opposite results have also been published (Smach et al. 2011; Shibata et al. 2013). Although apo A-I levels have been associated with increased white

matter lesions (Yin et al. 2014), the results of prospective studies are inconclusive regarding the possible association between apo A-I and risk of dementia (Saczynski et al. 2007; Reynolds et al. 2010). Apo B level seems to be lower among patients with AD compared with healthy controls (Caramelli et al. 1999) and apo B associated with cognitive decline in a twin study with longitudinal design (Reynolds et al. 2010). To our knowledge, no other prospective studies have been reported on apo B and risk of dementia or AD.

The purpose of our study was to examine whether apo A-I, HDL-C, apo B, or apo B/A-I ratio can be used as risk markers for incident dementia or AD after adjustment for multiple established dementia or AD risk markers based on a previously established dementia risk score (Kivipelto et al. 2006).

Materials and methods

Subjects

Two independent cross-sectional, population-based health examination surveys (the National FINRISK Study) were carried out in six areas in Finland in 1997 and 2002 (Vartiainen et al. 2010). The original random sample was stratified by area, sex, and 10-year age group according to the World Health Organization (WHO) MONICA (Monitoring trends and determinants of Cardiovascular disease) protocol (Pajak et al. 1988), and the sample was mainly comprised of subjects with Caucasian ethnicity. The participation rates were 72 and 70 % in years 1997 and 2002, respectively (Vartiainen et al. 2010). The total number of participants with sufficient data from these two surveys was 13,275 (of whom 48.3 % were men) after excluding participants with prevalent dementia ($n = 14$). These surveys were conducted in accordance with the Declaration of Helsinki. For both surveys, ethics approval was obtained from the Ethics Committee of the National Public Health Institute (1997) or from the Coordinating Ethics Committee of Helsinki and Uusimaa Hospital District (2002). Following the law on medical surveys in Finland (1999), participants gave a written informed consent in 2002 survey.

Baseline measurements

A self-administered questionnaire included questions on medical history and socioeconomic factors (Vartiainen

et al. 2010). In health examination, specially trained research nurses measured participants' height and weight following the standardized WHO MONICA protocol (Pajak et al. 1988). The measurement of height was done to the accuracy of 0.1 cm and weight to the nearest 100 g (Pajak et al. 1988). BMI was calculated as weight (kg)/height (m²). Blood pressure was measured in each survey from the right arm after 5 min of sitting using a mercury sphygmomanometer. After blood pressure measurement, a venous blood specimen was taken. Blood samples in both studies were analyzed in the same central laboratory (National Public Health Institute, Helsinki). Blood sampling, sample handling, methods, accuracy, and precision for total cholesterol and HDL cholesterol (HDL-C) measurements have been described previously (Sundvall et al. 2007; Leiviska et al. 2013).

The samples were stored at -80°C before the apo A-I and apo B analyses. Measurements for the plasma samples of the 1997 survey were performed in 2006 and the serum samples of the 2002 survey in 2008. Apo A-I and apo B were measured immunoturbidimetrically by Abbott Architect reagents (Abbott Laboratories, Abbott Park, IL, USA). For standardizing apo A-I and apo B measurements, the central laboratory has taken part in the External Quality Assessment Scheme organized by Labquality, Helsinki, Finland. The inter-assay coefficient of variation (CV %) (mean $\pm$ SD) in the control samples was 1.7 ± 0.1 % for apo A-I and 3.2 ± 0.8 % for apo B in 2006 and 1.8 ± 0.3 % for apo A-I and 2.5 ± 0.6 % for apo B in 2008, respectively.

The samples were genotyped on a number of different genome-wide genotyping arrays and subsequently imputed using Shapelt2 and IMPUTE2 following standard protocols using the 1000 Genomes project (1000G) phase1 haplotypes or a combination of 1000G phase 3 haplotype set augmented with a custom Finnish haplotype panel as a reference. We compared the accuracy of this method using an independent Finnish dataset ($N = 2067$) where rs429358 and rs7412 were additionally genotyped on the Sequenom iPLEX platform and observed an overall concordance of 96.6 % between the two methods, with relatively little variation in the genotype-specific concordances.

Follow-up

The follow-up was performed using data from the Finnish Hospital Discharge Register (HDR) and the Causes of Death Register (CDR). These registers cover all

hospitalizations and deaths in Finland. National Social Insurance Institution's Drug Reimbursement Register was also used for identifying drug reimbursements and anticholinesterase inhibitor (AChRi) or memantine drug purchases. During the study period, a special reimbursement was granted for donepezil, galantamine, rivastigmine, or memantine only if the patient was diagnosed with Alzheimer's disease (AD) and for rivastigmine if the patient had Parkinson's disease related dementia as described previously (Tynkkynen et al. 2015). The study subjects were identified and followed from the national registers using an individual ID code, unique to every permanent resident of Finland. The follow-up time was restricted to 10 years for both cohorts. The follow-up continued for each individual until the date of dementia diagnosis, death, or for 10 years. Thanks to the national health care registers, the coverage of the follow-up was 100 % for participants living in Finland. Only 0.5 % of participants, who had permanently moved abroad (by Dec. 31, 2010), were lost to follow-up.

End-point descriptions

Participants entitled to a special reimbursement for AChRis or memantine and those who had purchased AChRis or memantine more than three times during the follow-up were considered to have incident dementia (including AD) as well as participants with a hospitalization or death with ICD-10 codes of F00, F01, F02, F03, or G30. ICD-8, ICD-9, and ICD-10 codes were used depending on the date of diagnosis. Participants were considered to have an incident AD if the drug reimbursement was entitled only with the ICD-10 code of G30 (AD but not for Parkinson's disease). According to a previous validation study, AD cases detected by this methodology are correctly diagnosed during our study period (97 % positive predictive value) (Solomon et al. 2013). Sensitivity of an incident AD was 63.5 %. Dementia detection by this methodology had PPV of 96.3–100 % and approximately 50 % sensitivity during our study period. Since the validation study referred previously did not consider drug purchases, the sensitivity of our methodology is likely to be higher. In the analyses of AD, participants with any incident dementia detected by HDR or CDR but not by Drug Reimbursement register were excluded from the analysis in Cox regression model since these participants could have been wrongly subcategorized ($n = 62$), also subjects with granted drug

reimbursement with the ICD-10 code G20 (Parkinson disease) were excluded ($n = 4$).

Statistical analysis

All variables not distributed normally in density plots were log-transformed for multivariable models (body mass index, total serum cholesterol, systolic blood pressure, HDL-C, apo A-I, apo B, apo B/A-I ratio). For missing values, five imputed data sets were generated to perform the multivariable Cox regression modeling. Since we had two cohorts, we performed the imputation and analyses for both cohorts separately and combined the results using inverse variance weighted meta-analysis. Missing data was imputed using predictive mean matching for numeric data, logistic regression imputation for binary data with two levels, polytomous regression imputation for unordered and proportional odds model for ordered categorical data. We used an imputation method where the data always depended on the most recently generated imputations (Buuren and Groothuis-Oudshoorn 2011). The number of missing data for each variable is presented in Table 1.

We used Cox regression model to calculate the hazard ratios (HR) and 95 % confidence intervals (CI) for incident dementia and AD. For global model fit

assessment, we used cohort and model specific plotted Cox-Snell residuals. Since we decided to use the variables based on Cardiovascular Risk Factors, Aging, and Dementia study (CAIDE) score (Kivipelto et al. 2006) in both cohorts, some deviation from slope 1 optimum fit was accepted and age was categorized into quantiles (1st <34.9, 2nd >34.9–44.2, 3rd >44.2–53.1, 4th >53.1–61.1, 5th >61.1) to achieve better model fit. Proportional hazard (PH) assumption was tested for each variable with the Schoenfeld's global test independently in both cohorts and in all models, and was found to be valid. According to Martingale residual plots, all the effects were linear. Covariates based on the CAIDE dementia score used in multivariable models were age, sex, total serum cholesterol (mmol/l) (TC), mean systolic blood pressure (mmHg) (SPB), body mass index (BMI), years of education, and number of apo E ϵ 4 alleles (Kivipelto et al. 2006). Tested variables were apo A-I (g/l), HDL-C (mmol/l), apo B (g/l), and apo B/A-I ratio and they were all log-transformed. Apo A-I and HDL-C were tested separately due to their strong correlation (Pearson correlation = 0.85), and apo B and TC were not included in the same model (Pearson correlation = 0.87). Our study had an 80 % power ($\alpha = 0.05$) to detect a hazard ratio of 1.21. The average causal mediation effect (ACME) was calculated using 500 rounds of quasi-

Table 1 Pooled baseline characteristics of FINRISK 1997 and 2002 cohorts. Combined a total of 13,275 subjects, and one-way ANOVA statistics for the differences in apo A-I, HDL-C, apo B, and apo B/A ratio between the groups with 0, 1, or 2 apoE ϵ 4 alleles

Characteristic	Mean (SD) or n (%)			Number of subjects with missing data
Males, n (%)	6429 (48.4)			0
Age (years)	48.4 (13.3)			0
Total cholesterol (mmol/l)	5.57 (1.08)			2
Systolic blood pressure (mmHg)	135.7 (20.0)			9
Body mass index (kg/m^2)	26.8 (4.6)			95
Education (years)	11.7 (4.0)			198
ApoE subjects with 0/1/2 ϵ 4 risk alleles (%)	8814/3998/463 (66.4/30.1/3.5)			0
	Number of ApoE ϵ 4 alleles			
	0	1	2	
Apolipoprotein A-I, mean (SD) (g/l) ^a	1.59 (0.30)	1.57 (0.30)	1.53 (0.29)	432
HDL cholesterol, mean (SD) (mmol/l) ^a	1.45 (0.39)	1.43 (0.40)	1.39 (0.39)	2
Apolipoprotein B, mean (SD) (g/l) ^a	0.98 (0.25)	1.04 (0.25)	1.08 (0.26)	431
Apolipoprotein B/A, mean (SD) ^a	0.64 (0.22)	0.68 (0.22)	0.73 (0.24)	432

^a p value < 0.001 between groups of 0, 1, or 2 ApoE ϵ 4 alleles (one-side ANOVA)

apo A-I apolipoprotein A-I, *HDL-C* high density lipoprotein cholesterol, *apo B* apolipoprotein B, *apo B/A ratio* ratio between apo B and apo A-I

Bayesian Monte Carlo simulations in whole data. P level <0.05 was considered statistically significant. The results for continuous variables in Cox regression models are presented as corresponding to a 1SD increase in the respective risk factor unless stated otherwise. Cumulative incidence function (CIF) analysis was made using Gray's method to compare incident rates between groups of interest (Gray 1988). All the analyses were performed using “survival”, “meta”, “mediate”, “etm”, “cmprsk,” and “mice” packages of R vers. 3.2.3 software (Buuren and Groothuis-Oudshoorn 2011; Allignol et al. 2011; Team 2013; Therneau 2014; Tingley et al. 2014; Gray 2014; Schwarzer 2015).

Results

Median follow-up time of the study population was 9.61 (IQR 0.17) years. During 10 years of follow-up, altogether, 220 new dementia cases, including 154 cases of Alzheimer's disease (AD), were detected in addition to the 850 deaths of any cause (6.4 %). Of these deaths, 787 were among subjects without incident dementia and 32 were among subjects under 40 years of age. There were no cases of incident dementia among subjects under the age of 43 years. Baseline characteristics are presented in Table 1. The mean age of subjects with incident dementia at baseline was 66.8 years (1SD 5.4) and the mean detection age of dementia was 74.3 years (Table 1).

In multivariable models adjusted for dementia and AD risk factors, log apo A-I, log HDL-C, log apo B, or log apo B/A-I ratio were not associated with incident dementia (Table 2) or AD (Table 3). Log apo A-I was inversely associated and log apo B/A ratio directly associated with AD if models were not adjusted for apo E genotype (HR 0.77, 95 % CI 0.65–0.92, $p = 0.005$, and HR 1.22, 95 % CI 1.01–1.48, $p = 0.040$, respectively). There was no evidence for gender differences, so genders were pooled for all the analyses. Apo A-I, HDL-C, and apo B mean levels were significantly different in groups with 0, 1, or 2 apo E ϵ 4 alleles (Table 1). The effect size of apo E genotype decreased only modestly from HR 3.24 (95 % CI 2.57–4.09, $p < 0.001$) to HR 3.17 (95 % CI 2.51–4.01, $p < 0.001$) if apo A-I was included in the model regarding AD. The average causal mediation effect of apo A-I was further tested between groups of 0, 1, and 2 apo E risk alleles and no statistically significant effect was detected (2.1 %, $p = 0.05$; 1.7 %, $p = 0.09$; 1.7 %,

$p = 0.08$ between groups of 0 and 2; 1 and 2; 0 and 1 apo E risk alleles, respectively).

Since most of the deaths occurred in subjects without incident dementia or AD, we also analyzed if there was a difference between groups over and under median level of apo A-I, HDL-C, apo B, or apo B/A-I in cumulative incidence functions (CIF) of dementia, AD, and death. In this analysis among subjects over 40 years of age ($n = 9263$), cumulative incidence of death was lower in the group exceeding the median level of apo A-I ($p < 0.001$, 6.3 versus 10.6 % at 10 years), and HDL-C ($p < 0.001$, 6.6 versus 9.7 % at 10 years), and higher in the group exceeding the median level of apo B/A ratio ($p < 0.001$, 9.8 versus 6.5 % at 10 years). No difference was seen regarding apo B level ($p = 0.091$, 8.6 versus 7.7 % at 10 years).

No differences were observed between groups of over and under median level of apo B or apo B/A ratio and cumulative incidence of dementia or AD. The group exceeding median level of HDL-C had lower cumulative incidence of dementia but this association was not statistically significant if HDL-C was categorized in apo E specifically ($p = 0.087$, 2.1 versus 2.6 % at 10 years). Higher apo E specific HDL-C associated with lower cumulative incidence of AD ($p = 0.024$, 1.4 % versus 2.0 % at 10 years) but no difference was found between apo E specific apo A-I groups ($p = 0.200$, 1.5 vs 1.9 % at 10 years; over and under the median level, respectively), and apo A-I was not associated with dementia in CIF analysis ($p = 0.173$, 2.1 versus 2.6 % at 10 years; over and under the median level, respectively). Competing risk for dementia was death, and for AD, death and other than AD dementias.

Of the adjusting variables, log BMI was inversely associated with incident dementia and AD (HR 0.72, 95% CI 0.62–0.84, $p < 0.001$ and HR 0.70, 95% CI 0.59–0.85, $p < 0.001$, respectively) (Tables 2 and 3). Higher BMI increases the cumulative incidence of deaths ($p < 0.001$), but there was no difference between cumulative incidence of dementia ($p = 0.738$, 2.2 versus 2.6 % at 10 years; over and under the median level, respectively) or AD ($p = 0.145$, 1.5 versus 1.9 % at 10 years; over and under the median level, respectively) indicating the inverse association of BMI with incident dementia and AD is caused by the increased rate of deaths among higher BMI group. The results remained the same after the BMI was categorized to four groups (<21 , 21–27, 27–32, >32 kg/m²) or when BMI was categorized to two groups, over and under 27 kg/m².

Table 2 Multivariate Cox regression modeling of incident dementia ($n = 220$). Hazard ratios (HR) and p values of random effects meta-analyses of FINRISK 1997 and 2002 cohorts are presented

	Variable	HR (95% CI), random	p
Multivariate model without Apo A-I, HDL-C, or Apo B or apo B/A ratio in the model	Sex (for female gender)	1.14 (0.87–1.50)	0.331
	Age (per quantile step)	7.61 (5.56–10.42)	<0.001
	log—Total cholesterol (per 1SD)	0.89 (0.78–1.03)	0.112
	log—Systolic blood pressure (per 1SD)	0.99 (0.86–1.13)	0.838
	log Body mass index (per 1SD)	0.72 (0.62–0.84)	<0.001
	Education (per year)	0.94 (0.88–1.01)	0.072
	ApoE (number of risk $\epsilon 4$ alleles)	2.78 (2.29–3.39)	<0.001
Analyzed separately of each other and adjusted for all variables above	log Apolipoprotein A-I (per 1SD)	0.90 (0.66–1.22)	0.507
	log—HDL cholesterol (per 1SD)	0.94 (0.65–1.37)	0.762
	log Apolipoprotein B (per 1SD) ^a	0.90 (0.53–1.51)	0.683
	log Apolipoprotein B/A (per 1SD) ^a	1.06 (0.72–1.55)	0.778
Analyzed separately of each other and adjusted for all variables above except for apo E genotype	log Apolipoprotein A-I (per 1SD)	0.85 (0.64–1.12)	0.253
	log—HDL cholesterol (per 1SD)	0.89 (0.61–1.31)	0.557
	log Apolipoprotein B (per 1SD) ^a	1.07 (0.61–1.85)	0.8181
	log Apolipoprotein B/A (per 1SD) ^a	1.16 (0.79–1.71)	0.434

Total cholesterol, HDL cholesterol, systolic blood pressure, body mass index, apolipoprotein A-I, apolipoprotein B, and apolipoprotein B/A ratio were log-transformed before multivariate analysis

^aModel is not adjusted for total cholesterol

apo A-I apolipoprotein A-I, *HDL-C* high density lipoprotein cholesterol, *apo B* apolipoprotein B, *apo B/A ratio* ratio between apo B and apo A-I

Discussion

Our results show that baseline apo A, HDL-C, apo B, or apo B/A-I levels do not predict the risk of dementia or AD in a prospective setting beyond multiple dementia and AD risk factors. In previous studies, lower apo A-I levels have been seen among patients with Alzheimer's disease (AD) compared with healthy controls (Merched et al. 2000). The data from prospective studies are more controversial (Saczynski et al. 2007; Reynolds et al. 2010). In the Honolulu aging study, apo A-I was found to associate with incident dementia (Saczynski et al. 2007). The physiological mechanism by which higher levels of apo A-I could protect from dementia and especially AD is that apo A-I seems to have a neuroprotective effect by forming a complex with amyloid-beta peptide altering its aggregation and neurodegenerative abilities (Paula-Lima et al. 2009). Nevertheless, this association was not seen in our ten-year follow-up. Since apo A-I levels were associated with cumulative incidence of death, this association might also have an effect on the results of Cox regression model, yet no association between apo A-I and dementia or AD was

seen in cumulative incidence function (CIF) analysis. The Honolulu aging study was conducted among men with Japanese-American ethnicity and since our study comprised of subjects with Caucasian background, the difference in the results might be explained by these genetic factors. There was no evidence for gender differences in our study. Reynolds et al. reported corresponding results to ours regarding apo A-I in Swedish twin study, and the genetic background in Swedish twin study is more comparable to ours than in the Honolulu aging study. In the Honolulu aging study, Swedish twin study and in ours, the mean sample collection age was 67.5, 63.8, and 48.4 years, respectively. Based on previous studies, lipid-related markers like total serum cholesterol has a changing effect on dementia risk by age so differences in results regarding lipids can be explained by this in some measure. Yet it should be noticed that Reynolds et al. reported the association of lipids and lipoproteins with cognitive functions to be most prominent before the age of 65.

Based on previous studies, HDL-C does not seem to associate with dementia or AD (Li et al. 2005; Reitz et al. 2010; Arntzen et al. 2011) albeit the association is

Table 3 Multivariate Cox regression modeling of incident Alzheimer's disease ($n = 158$). Hazard ratios (HR) and p values of random effects meta-analyses of FINRISK 1997 and 2002 cohorts are presented

	Variable	HR (95% CI), random	p^*
Multivariate model without Apo A-I, HDL-C, or Apo B in the model	Sex (for female gender)	1.16 (0.84–1.61)	0.370
	Age (per quantile step)	9.72 (6.37–14.84)	<0.001
	log—Total cholesterol (per 1SD)	0.90 (0.76–1.07)	0.233
	log—Systolic blood pressure (per 1SD)	0.91 (0.77–1.08)	0.282
	log Body mass index (per 1SD)	0.70 (0.59–0.85)	<0.001
	Education (per year)	0.95 (0.86–1.04)	0.243
	ApoE (number of risk $\epsilon 4$ alleles)	3.24 (2.57–4.09)	<0.001
Analyzed separately of each other and adjusted for all variables above	log Apolipoprotein A-I (per 1SD)	0.83 (0.69–1.01)	0.057
	log—HDL cholesterol (per 1SD)	0.84 (0.66–1.07)	0.166
	log Apolipoprotein B (per 1SD) ^a	0.93 (0.77–1.11)	0.418
	log Apolipoprotein B/A (per 1SD) ^a	1.08 (0.89–1.31)	0.430
Analyzed separately of each other and adjusted for all variables above except for apo E genotype	log Apolipoprotein A-I (per 1SD)	0.77 (0.65–0.92)	0.005
	log—HDL cholesterol (per 1SD)	0.79 (0.61–1.03)	0.087
	log Apolipoprotein B (per 1SD) ^a	1.05 (0.88–1.27)	0.584
	log Apolipoprotein B/A (per 1SD) ^a	1.22 (1.01–1.48)	0.040

Total cholesterol, HDL cholesterol, systolic blood pressure, body mass index, apolipoprotein A-I, apolipoprotein B, and apolipoprotein B/A ratio were log-transformed before multivariate analysis

^a In the model without total cholesterol

apo A-I apolipoprotein A-I, *HDL-C* high density lipoprotein cholesterol, *apo B* apolipoprotein B, *apo B/A ratio* ratio between apolipoprotein B and apolipoprotein A-I

seen in cross-sectional studies (Merched et al. 2000). These findings are in line with our results where death is considered as a competing risk for dementia and AD, and statistically significant association is seen in CIF but not in Cox regression model between HDL-C and AD. This indicates that lower HDL-C is a risk factor for dementia for those who will not die a premature death for other reasons, and lower levels of HDL-C are seen among survivors with AD compared with survivors without AD. The literature regarding the association of apo B or apo B/A ratio with dementia or AD is scant, and our results do not support any association. Since the apo E genotype is associated with apo A-I level, we tested if a part of the association of apo E genotype with AD might be mediated through apo A-I levels but no statistically significant support for the mediation effect was seen. Apo B/A-I ratio associated with AD without adjustment for apo E genotype, but this association might only be mediated by apo A-I since apo B was not independently associated with dementia or AD.

Of the adjusting variables, body mass index (BMI) associates inversely with incident dementia and AD in Cox regression model. In CIF analysis, this association

was not seen and higher BMI associated with higher incidence of death. It seems that higher BMI's protective effect on dementia is caused by premature deaths in the higher BMI group, and BMI's protective effect is also noted in another large population study (Qizilbash et al. 2015). In the study of Whitmer et al., higher BMI was associated with increased risk for dementia and AD but the follow-up time in this study was longer (Whitmer et al. 2007) and also the higher cardiovascular death rate in Finland (Rosolova and Nussbaumerova 2011) compared with the European average level might have had an impact on these results.

Limitations of our study are the lack of specific clinical evaluation of cognitive status at baseline and during the follow-up. The exclusion criteria at baseline and incident dementia during the follow-up are based on register data. These registers used in our study have full coverage of Finnish hospitalizations and drug purchases, reimbursements, and deaths in Finland and the validity of these registers has been generally good (Pajunen et al. 2005). According to a previous validation study, diagnoses detected by this method have high specificity but approximately 50 % of dementia and

36 % Alzheimer's disease cases are missed most likely due to delays in registration (Solomon et al. 2013). However, the drug purchases and drug reimbursements were not included in this validation study and the diagnostic procedures and registration have developed since then, most likely giving higher detection rate of incident dementia and AD in our recent study. These results may not be universally applicable due to restricted ethnicity of the study group as pointed out above. The strength of our study is the large sample size with no restrictions of gender or underlying diseases as well as the prospective study design and almost complete follow-up.

Our study had 80 % power (α 0.05) to detect HR over 1.21 and, accordingly, we can conclude that there are no strong or clinically significant associations of apo A-I, HDL-C, apo B, or apo B/A-I ratio with incident dementia or AD, independent of previously known dementia and AD risk factors. HDL-C's association to incident AD risk in CIF analysis has little clinical significance since death as a competing risk only emphasizes the importance of good cardiovascular health and measures to maintain it. Based on our results, there is no indication to use apo A-I, HDL-C, apo B, or apo B/A ratio as risk markers for future dementia or AD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interests.

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