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Adverse lipid profile elevates risk for subarachnoid hemorrhage: A prospective population-based cohort study

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ABSTRACT

Background and aims: Studies report that both high and low total cholesterol (TC) elevates SAH risk. There are few prospective studies on high-density lipoproteins (HDL-C) and low-density lipoproteins (LDL-C), and apparently none concerns apolipoproteins A and B. We aimed to clarify the association between lipid profile and SAH risk.

Methods: The National FINRISK study provided risk-factor data recorded at enrolment between 1972 and 2007. During 1.52 million person-years of follow-up until 2014, 543 individuals suffered from incident hospitalized SAH or outside-hospital-fatal SAH. Cox proportional hazards model was used to calculate the hazard ratios and multiple imputation predicted ApoA1, ApoB, and LDL-C values for cohorts from a time before apolipoprotein-measurement methods were available.

Results: One SD elevation (1.28 mmol/l) in TC elevated SAH risk in men (hazard ratio (HR) 1.15 (95% CIs 1.00–1.32)). Low HDL-C levels increased SAH risk, as each SD decrease (0.37 mmol/l) in HDL-C raised the risk in women (HR 1.29 (95% CIs 1.07–1.55)) and men (HR 1.20 (95% CIs 1.14–1.27)). Each SD increase (0.29 g/l) in ApoA1 decreased SAH risk in women (HR 0.85 (95% CIs 0.74–0.97)) and men (HR 0.88 (95% CIs 0.76–1.02)). LDL-C (SD 1.07 mmol/l) and ApoB (SD 0.28 g/l) elevated SAH risk in men with HR 1.15 (95% CIs 1.01–1.31) and HR 1.26 (95% CIs 1.10–1.44) per one SD increase. Age did not change these findings.

Conclusions: An adverse lipid profile seems to elevate SAH risk similar to its effect in other cardiovascular diseases, especially in men. Whether SAH incidence diminishes with increasing statin use remains to be studied.

1. Introduction

According to prospective studies also including sudden-death subarachnoid hemorrhages (SAHs), elevated risk for SAH associates with hypertension, smoking, increasing age, and possibly with female sex [1–4]. Studies on lipid profile and risk for SAH are limited, and their results are controversial [5]. A recent systematic review [5] found only two [2,6] low-risk-of-bias prospective studies on the effect of total cholesterol (TC) on risk for SAH, both suggesting that high TC elevates the risk. However, several high-risk-of-bias studies found an inverse or no association between TC and SAH. In addition, few prospective studies have focused on the association between HDL-C and SAH, and no prospective studies exist on the association between SAH and LDL-C or apolipoproteins [5].

Due to the high prevalence of the adverse lipid profile, its population-attributable fraction (PAF) in SAH can reach up to 35% in Europe in men and up to 32% in the USA in men [5]. Since statin use is nowadays frequent and may have pleiotropic protective effects [7], the role of adverse lipid profile in SAH can be best studied by

Abbreviations: SAH, aneurysmal subarachnoid hemorrhage; TC, total cholesterol; HDL-C, high-density lipoprotein (calculated); LDL-C, low-density lipoprotein (calculated); ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; TG, triglycerides; CPD, cigarettes per day; SBP, systolic blood pressure; SES, socioeconomic status; BMI, body mass index; HR, hazard ratio; CIs, confidence intervals; SD, standard deviation; PAF, population attributable fraction; MAR, missing at random assumption.

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utilizing prospective cohorts gathered before the widespread statin introduction. Moreover, to obtain a comprehensive understanding of lipid profile and SAH, irrespective of patients' access to a health care facility, our prospective cohort also included sudden-death SAH individuals who died outside of the hospitals. This is important because these individuals represent 25% of all SAHs and their exclusion may lead to limited ability to detect SAH risk factors [8]. We aimed to study associations between SAH and lipid-profile in the pre- and post-statin era by analyzing also LDL-C, HDL-C, and apolipoprotein levels, which may be more accurate predictors of cardiovascular diseases than TC [9–13].

2. Materials and methods

2.1. Ethics statement

Ethical approval came from the corresponding ethics committee according to the commonly required research procedures and Finnish legislation for each survey, and the study was conducted according to the World Medical Association's Declaration of Helsinki on ethical principles for medical research. From 1997 onwards, written informed consent has been provided by each participant [14]. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement [15] guided the reporting.

2.2. Study cohort and data collection

The study cohort and data collection methods have been described in detail [2,16]. Briefly, the ongoing National FINRISK study, done every five years using independent, random, and representative population samples from different geographical areas of Finland, provided the risk-factor data recorded at enrolment between 1972 and 2007 [17]. For variables studied, experienced and specially trained nurses measured blood pressure, height, and weight, and acquired semi-fasting blood samples for cholesterol and lipoprotein measurement after at least 4-h fasting. The Supplementary Data describes lipid-profile measurement methods in detail. A structured questionnaire provided data on smoking habits, alcohol consumption, socioeconomic status (SES) measured as years of education, and use of lipid-lowering and antihypertensive drugs. All factors studied were measured at enrolment for each cohort. The study cohort comprised 65,521 individuals, enrolled between 1972 and 2007.

2.3. Follow-up

The follow-up protocol has been described [2,16]. Briefly, follow-up started at enrolment and ended at first-ever SAH, at emigration, death, or on 31 December, 2014, whichever came first. The nationwide Hospital Discharge Register and Causes of Death Register identified all fatal (including out-of-hospital deaths) and non-fatal SAHs with high accuracy [18]. Sudden-death SAHs were defined as deaths occurring away from hospitals, on the way to a hospital, or in an emergency room. Sudden deaths from SAH were confirmed at autopsy, and, when necessary, a specifically trained nosologist checked and corrected the underlying cause of death. The follow-up was complete regarding deaths and hospitalizations for persons who continued to live in Finland; emigration was rare during follow-up [16].

2.4. Statistical analyses

Basic descriptives were generated by standard methods. Correlations between variables were tested by Spearman's rank correlation coefficients. We used the Cox proportional hazard model to calculate hazard ratios (HRs) and 95% confidence interval (CI) in adjusted models. Because of long follow-up, we also ran competing risks models [19] to show the associations when other causes of death were taken into account and divided TC and HDL-C into tertiles. Based on other prospective and population-based studies [2,3,20], our final model included age, sex, smoking, SBP, and TC (or one of the following: HDL-C, LDL-C, ApoA1, or ApoB). BMI, study year, and study area were also included in the model as possible confounders. The preliminary models examined also the role of self-reported cholesterol-lowering drug use, alcohol consumption, and SES. Because associations between risk factors and outcomes may not be linear, we sought non-linear associations between our variables and SAH with multivariable fractional polynomial models [21] and with cubic splines. We found that the inverse of HDL-C (HDL-C^{-1}) had a stronger association with SAH than HDL-C had, and therefore our final analysis model for HDL-C included HDL-C^{-1}. According to Schoenfeld residuals and log-log inspection, our models met the proportional assumption criteria. We tested multiplicative interactions with the likelihood ratio test. PAFs were computed to provide estimates of the fraction of cases preventable by elimination or minimization of a risk factor. To avoid over-estimation of PAFs, these were calculated by the average attributable fraction method, which restricts overall PAFs to 100% [22]. The cut-off value for TC (=5 mmol/l) was adopted from the 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice and the 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias [12,13]. We also conducted sensitivity analyses using pre-statin era cohorts and pre- and post-menopausal women. All statistical analyses were done with Stata Corp version 12.1, College Station, TX, USA, and with R 3.3.0.

2.5. Imputation model

Because study year alone explained missing values of ApoA1, ApoB, HDL-C, and LDL-C, we used the missing at random (MAR) assumption [23]. The percentages of missing values were for smoking status 1.1%, SBP 1.6%, TC 1.9%, HDL-C 36.1%, TG 41.1%, LDL-C 58.8%, ApoB 65.5%, and for Apoa1 65.8% (Fig. 1A and B and Supplementary Table I). We used multiple imputation to supplement missing variables. Our imputation model included continuous variables of ApoA1, ApoB, BMI, HDL-C, LDL-C, SBP, and TC and additionally quartiles of alcohol consumption, eight categories of smoking, three categories of SES, and use of cholesterol-lowering drug (self-reported) as binary variable. We used linear regression to impute continuous, ordered logistic regression to impute ordinal, and logistic regression to impute binary variables. Because smoking has a stronger association with SAH risk among women than among men [4], we added an interaction term between smoking and sex in the imputation model. In addition, our imputation allowed for interaction between each lipoprotein variable and sex, hypertension, or smoking. We used the imputation model based on substantive-model compatible fully conditional specification, which may be a better approach in nonlinear and interaction models than is the ordinary fully conditional model [24]. Depending on convergence, we used 50 to 150 iterations to draw the missing values and up to 80 imputations to reduce simulation error. Convergence analyses [25] showed that our iterations were sufficient and reached statistical reproducibility except for TG.

3. Results

3.1. SAH

Follow-up of 1.52 million person-years provided 543 first-ever

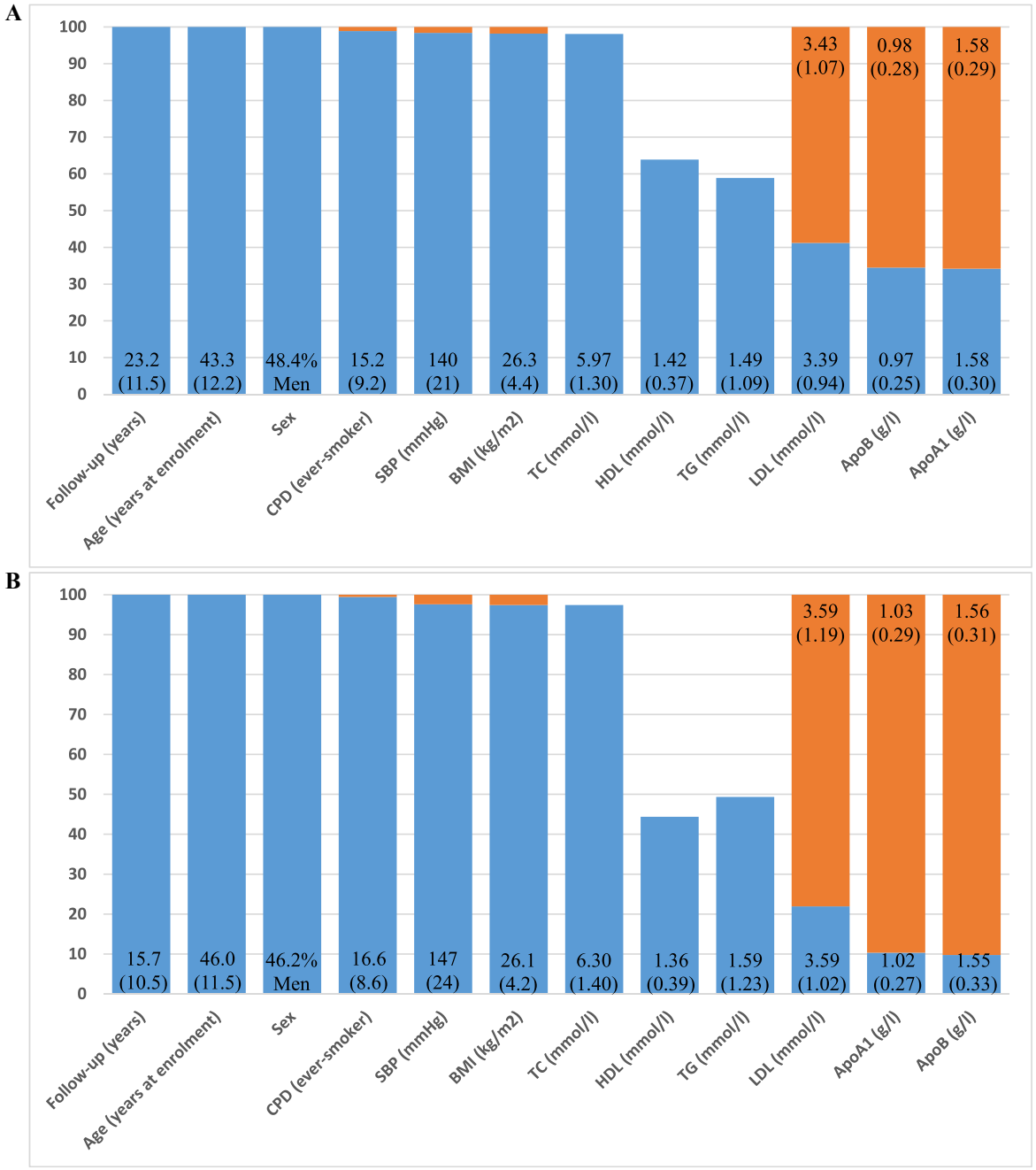

Fig. 1. Percentage of measured (blue) and imputed (orange) values in the whole cohort and SAH cases.
(A) Cohort, (B) SAHs. Numbers in blue columns describe mean and standard deviation values of measured variables whereas numbers in orange describe corresponding values after imputation. No imputation was used in analysis of HDL-C and total cholesterol (TC), while imputation of trigycerides (TG) did not converge. CPD, cigarettes smoked per day. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

SAHs. SAH patients had more missing lipid values when compared to the whole cohort (Fig. 1A and B and Supplementary Table I), because LDL, ApoA1, and ApoB measurements were available only for more recent cohorts and the majority of SAHs stemmed from older cohorts. All the results presented are from multivariable adjusted models.

3.2. TC

The model including both sexes showed no association between TC and SAH. When analyzed by sex, moderate evidence emerged that each 1-SD increase in TC values elevated SAH risk in men (HR = 1.15 95%CIs = (1.00–1.32) but not in women. (Fig. 2 and Supplementary Table II).

3.3. HDL-C

Our models showed evidence that each 1-SD decrease in HDL-C elevated risk for SAH (1.20 (1.14–1.26)) and this effect was seen both in women (1.29 (1.07–1.55)) and in men (1.20 (1.14–1.27)) (Fig. 2 and Supplementary Table II).

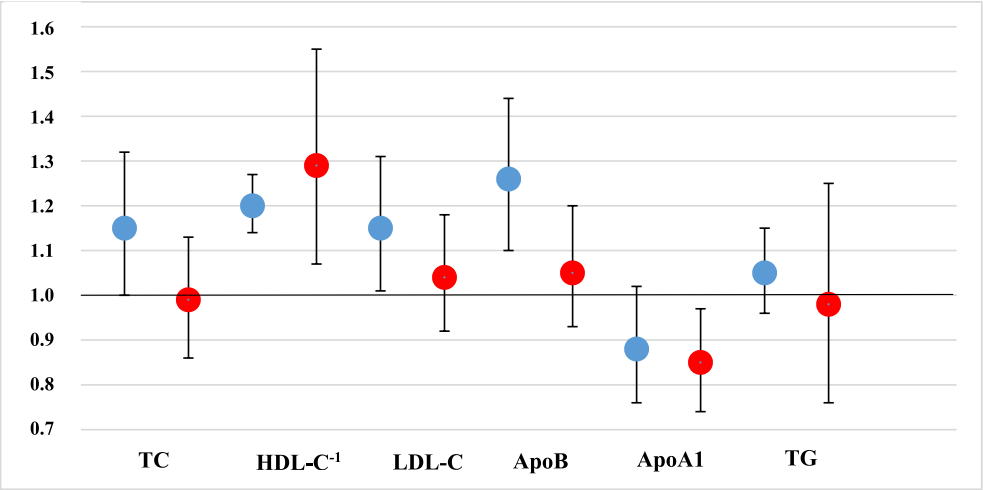

Fig. 2. Hazard ratios and 95% confidence intervals per standard deviation increase for each lipid variable from multivariate models.
Blue, men; red, women; the y-axis shows the hazard ratio scale. TC, total cholesterol; TG, triglycerides. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.4. LDL-C

The complete case model showed no associations between LDL-C and SAH. The model including imputations and both sexes showed moderate evidence that each 1-SD elevation in LDL-C elevated SAH risk 1.09 (1.00–1.19), and the association seemed stronger in men (1.15 (1.01–1.31)). (Fig. 2 and Supplementary Table II), but no interaction emerged.

3.5. TG

No association between TG and SAH emerged in any analysis model (Fig. 2 and Supplementary Table II).

3.6. ApoA1 and ApoB

The complete case analysis had too few SAHs to reliably investigate associations between ApoA1 or ApoB and SAH. Analysis with imputations suggested that each 1-SD increase in ApoA1 reduced SAH risk (0.86 (0.78–0.95)) in the model including both sexes. Model including imputed data and both sexes also suggested that each 1-SD elevation in ApoB elevates SAH risk (1.14 (1.04–1.25)). Similar to LDL-C, this association was present only in men (1.26 (1.10–1.26)) (Fig. 2 and Supplementary Table II).

3.7. Competing risk models

In line with multivariate Cox models, multivariate competing risk models showed that in men high TC elevates SAH risk, whereas no evidence in women emerged. However, high HDL-C decreased SAH risk in women and men (Fig. 3A and B). Competing risks analysis also suggested a steeper rise in SAH incidence in women after age 65 when compared to men.

3.8. Interactions and sensitivity analysis

No strong evidence emerged of interactions between sex, hypertension, or smoking and any lipid variable. When the analysis was performed separately on women aged over 55 (presumably post-menopausal women), the results remained essentially the same. When all our analyses included only pre-statin era cohorts, (time-line restricted between 1972 and 1995) the results remained essentially the same.

3.9. Population-attributable fraction (PAFs)

We estimated PAFs by sex from a multivariable-adjusted model including binary variables of SBP (normotensives vs hypertensives), TC (5 mmol/l as cut-off) and smoking (never-smokers *vs.* smoker). In men, smoking, hypertension, and TC elevated SAH risk with very similar PAFs of 34%, 34%, and 33%, respectively. In women, smoking and hypertension elevated SAH risk with PAFs of 22% and 49% (Fig. 4), indicating a relatively greater population-attributable role for hypertension than smoking in women compared to men.

4. Discussion

Our results suggest that elevated SAH risk is associated with an adverse lipid profile. Low HDL-C and ApoA1 elevated SAH risk in both sexes, whereas high TC, high LDL-C, and high ApoB elevated the risk only in men. The competing risks models were in line with TC and HDL-C results and also suggested slightly steeper rise in SAH incidence in women after age 65. No strong evidence of interactions emerged in our analyses between lipid variables and sex, or SBP, or smoking, or study year. Recent publications [2,5] suggest that high TC may elevate SAH and our results provide stronger evidence of this association. Because of the high prevalence of high TC, its PAF in men is as high as PAFs of smoking and hypertension indicating that, at population level, adverse lipid profile plays a major role in SAH. Our results challenge the reliability of hospital-based studies reporting low TC as an SAH risk factor [26–29]. Overall, up to one-fourth of those suffering from SAH die outside hospitals or in emergency rooms [30] and are therefore missing from hospital-based studies. In hospital-based studies selection of controls may lead to bias and measurement of lipid variables after SAH may lead to reverse causality [5]. We used premorbid semi-fasting blood samples, which provide estimates as reliable as fasting samples [31] and included also those SAH patients dying outside of the hospital, on the way to the hospital, or in emergency rooms.

On biological bases, adverse lipid profile may promote inflammation in aneurysm walls, which can induce cell death in vascular smooth muscle cells [32]. This hypothesis seems plausible especially because smooth muscle cells are the key regulators of the balance between degrading and repairing processes in aneurysm

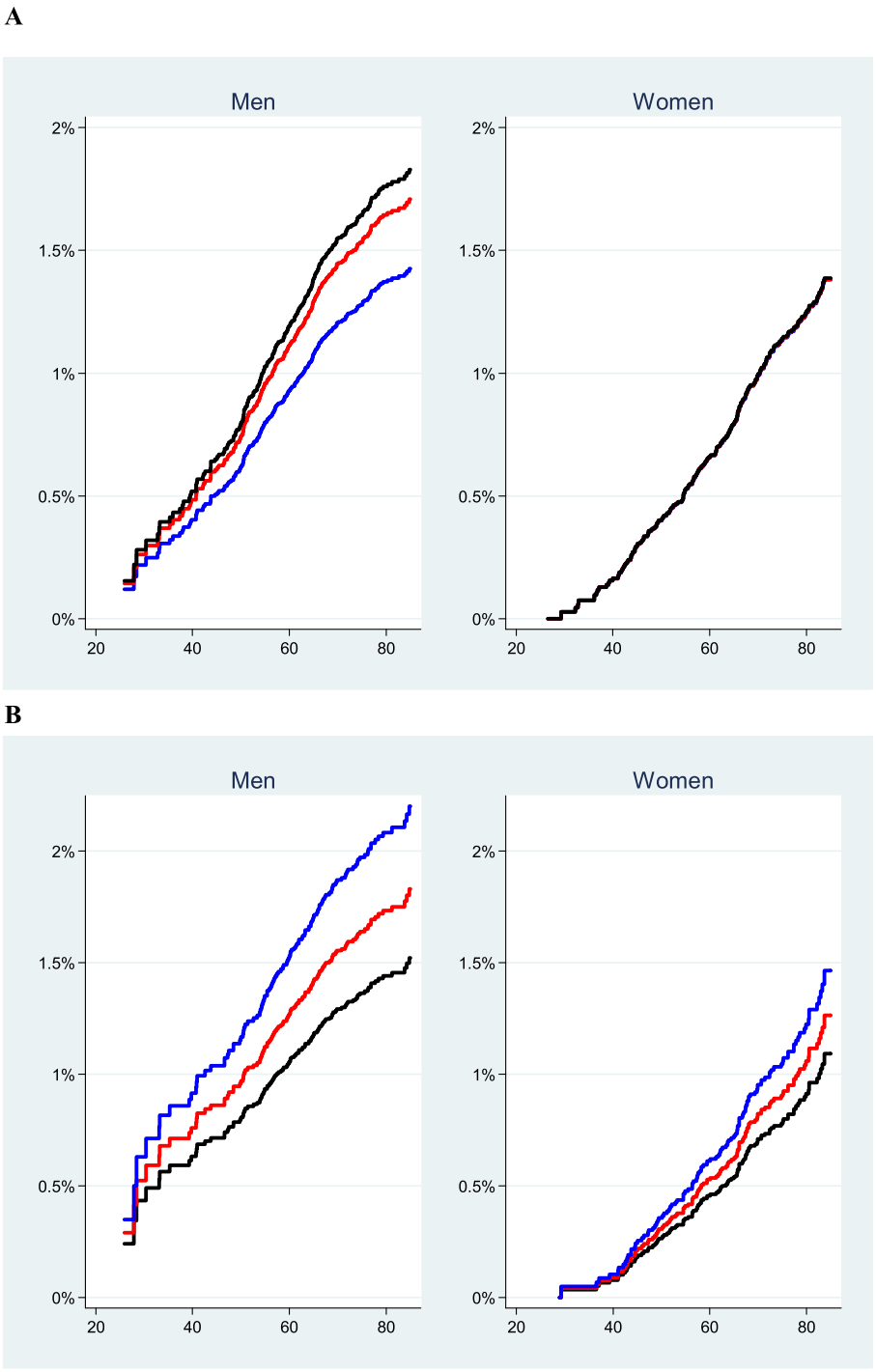

Fig. 3. Cumulative incidence of SAH from competing risks model.
(A) Tertiles of total cholesterol and (B) tertiles of HDL-C. For total cholesterol in women, the lines are on top of each other.
X-axis, age in years; Y-axis, cumulative SAH risk. The blue line represents the lowest first total cholesterol or HDL-C tertile, red second, and black third, the highest tertile. The limits in mmol/l for tertiles are for total cholesterol in men: (1) <5.43, (2) ≤5.43–6.46<, (3) 6.46, and in women: (1) <5.26, (2) ≤5.26–6.34<, (3) 6.34≤. The corresponding tertiles for HDL-C stem from a model including HDL-C^{-1} and are: in men (1) <1.12, (2) ≤1.12–1.37<, (3) 1.37 ≤, and in women (1) <1.37, (2) ≤1.37–1.67<, (3) 1.67≤. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

walls [33,34]. Interactions between other SAH risk factors (smoking and hypertension) and adverse lipid profile may exist to some extent [33,34]. Moreover, the effect of an adverse lipid profile may differ between age-groups and differing time-points. Our results suggest, however, that these interactions are not strong, and even larger sample sizes would be needed to detect them.

Our results are similar to findings in prospective studies on abdominal aortic aneurysms (AAA), myocardial infarction, and stroke [35–38]. Although pathophysiology of these diseases is different from SAH, our results suggest that SAH belongs to atherosclerotic diseases family. In fact, apart from diabetes [39,40] and obesity, SAH shares the major risk factors that are age, smoking,

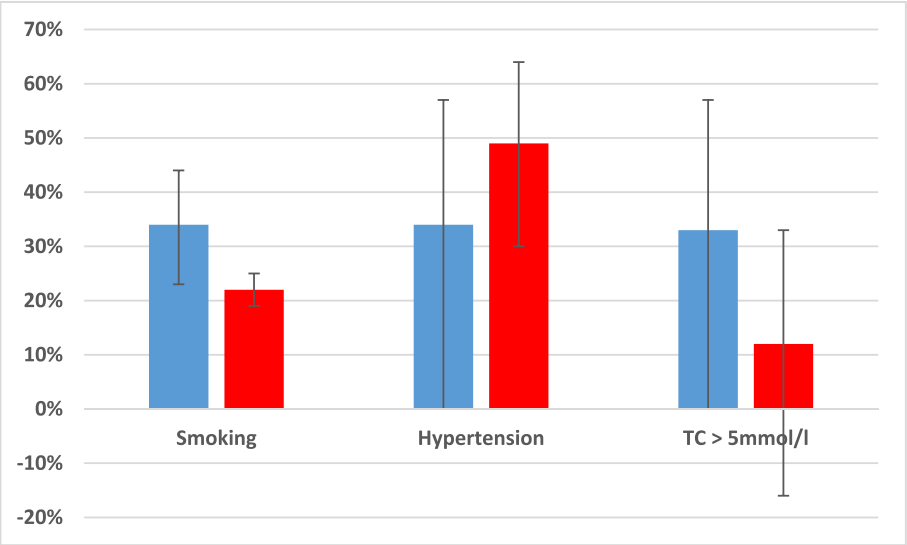

Fig. 4. Population attributable fraction estimates and 95% confidence intervals of the major SAH risk factors by sex.
Blue, men; red, women. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

hypertension and adverse lipid profile, with atherosclerotic diseases. The result of TC in men is comparable to Systematic Coronary Risk Estimation risk charts presented in the 2016 European Guidelines on cardiovascular disease prevention in clinical practise [13]. In addition, a large prospective AMORIS study [38] implied that high HDL-C protects women against hemorrhagic stroke (intracranial hemorrhage (ICH) and SAH combined), but unfortunately the study lacked data on smoking and, as the authors reported, probably included unreliable hypertension estimates. Our associations may be stronger because we analyzed SAH separately from ICH.

Because of long follow-up, the measured lipid values may have changed especially after introduction of statins in 1995. However, lipid variables did not violate proportionality in any of our model, indicating that the association between lipids and SAH remained the same during follow-up and that the effect of statins in this study population is small. This could have resulted from a large proportion of pre-statin era participants.

Even though no interaction between lipid variables and sex was present, TC, LDL-C, and ApoB had higher HR in men. The lack of interaction could have resulted from the limited number of SAH. The weaker association in women may also relate to later development of adverse lipid profile because LDL-C starts to rise in menopause and peaks in women at 60 years of age [41]. This was somewhat supported by our competing risks model on HDL-C, which suggested steeper SAH incidence rise in women after age 65. Potential protecting or adverse effects of widely used hormone replacement therapy [41–43] may confound association between CVDs and women. However, we did not find differences in lipid-variable HRs between pre- and postmenopausal women possibly due to limited number of SAHs in pre-menopausal women.

Missing values are, in many studies, a common problem, and they can reduce power and can bias the results of complete case analysis [23]. If the imputation model is correctly built, and if the pattern of missingness is known, multiple imputation can overcome some of the shortcomings of complete case analysis. The missingness of apolipoprotein and LDL-C values in our study was only explained by study year justifying the MAR assumption [23]. HDL-C measurements were unavailable for cohorts from the 1970s, LDL-C could not be calculated before 1992, and measurement methods for apolipoproteins were unavailable before 1992. Our imputation results on apolipoproteins and LDL-C tend towards a slightly more adverse lipid profile when compared to the values measured. This was expected, because the values were imputed to older cohorts and is also in line with the rapid decrease in cholesterol values in Finland since 1972 [44]. If a data set includes many variables and observations, and if the variables correlate well with these variables with missing values, imputations can provide accurate results even when the proportion of missing values is relatively high [45,46]. Our imputation results did not differ much from measured data, indicating that they are plausible. However, because of a large number of missing values for ApoA1, ApoB, and LDL-C, the results for these variables should be interpreted with caution.

The strengths of our study include: 1) long follow-up, 2) high number of incident SAHs, 3) prospective set-up reducing risk for information bias and reverse causality, 4) population-based cohort reducing risk for selection bias, 5) detailed data and accurate measurements allowing reliable subgroup analyses, 6) accurate diagnosis of SAH [47], 7) inclusion of out-of-hospital SAH deaths, and 8) a cohort including individuals in the period before widespread statin use, 9) inclusion of SES in adjusted models.

Our study has several limitations, as well. First, we imputed a high proportion of apolipoprotein and LDL-C values, which may have biased results for these variables. However, HRs based on imputations were similar to HRs based on measured values suggesting that our results are plausible. Second, even though our accuracy in aneurysmal SAH diagnosis was high with positive predictive value of 87% [18], our study may include few traumatic SAH cases, due to indexing errors. Such errors, if existent, however, were more likely to weaken the associations. Third, our results are based on one nationality, and thus may not be generalizable globally. However, contrary to the common belief, the incidence of SAH in Finland is similar to that in other countries [30,48], suggesting that SAH has no exceptional risk factors in Finland. Fourth, we could not reliably study the confounding effect of statin medication on SAH incidence. However, despite the fact that the effect of TC on risk for SAH remained the same in the pre-statin era, we cannot exclude the possibility that the risk-increasing effect of adverse lipid profile would be even stronger if adjusted for statin use.

4.1. Conclusion

An atherogenic lipid profile predicts an elevated risk for SAH in men and plays a major role at population level, whereas low HDL-C level is associated with elevated risk in women. Given that effects of lipid profiles on risk for SAH are challenging to study nowadays, when statin use is common, these results with pre-statin era analysis may perhaps be the best available evidence on the topic. Whether the rupture risk of unruptured intracranial aneurysms could be reduced by statin use, or whether SAH incidence diminishes with increasing statin use, remains to be studied.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

JVL, JK, and MK, planned the study, and JVL and JK did the data-analysis. All authors participated in interpreting the results and writing the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.05.011.

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