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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