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ORIGINAL CONTRIBUTION

Obesity Does Not Protect From Subarachnoid Hemorrhage: Pooled Analyses of 3 Large Prospective Nordic Cohorts

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BACKGROUND AND PURPOSE: Several population-based cohort studies have related higher body mass index (BMI) to a decreased risk of subarachnoid hemorrhage (SAH). The main objective of our study was to investigate whether the previously reported inverse association can be explained by modifying effects of the most important risk factors of SAH—smoking and hypertension.

METHODS: We conducted a collaborative study of three prospective population-based Nordic cohorts by combining comprehensive baseline data from 211 972 adult participants collected between 1972 and 2012, with follow-up until the end of 2018. Primarily, we compared the risk of SAH between three BMI categories: (1) low (BMI<22.5), (2) moderate (BMI: 22.5–29.9), and (3) high (BMI≥30) BMI and evaluated the modifying effects of smoking and hypertension on the associations.

RESULTS: We identified 831 SAH events (mean age 62 years, 55% women) during the total follow-up of 4.7 million person-years. Compared with the moderate BMI category, persons with low BMI had an elevated risk for SAH (adjusted hazard ratio [HR], 1.30 [1.09–1.55]), whereas no significant risk difference was found in high BMI category (HR, 0.91 [0.73–1.13]). However, we only found the increased risk of low BMI in smokers (HR, 1.49 [1.19–1.88]) and in hypertensive men (HR, 1.72 [1.18–2.50]), but not in nonsmokers (HR, 1.02 [0.76–1.37]) or in men with normal blood pressure values (HR, 0.98 [0.63–1.54]; interaction HRs, 1.68 [1.18–2.41], P=0.004 between low BMI and smoking and 1.76 [0.98–3.13], P=0.06 between low BMI and hypertension in men).

CONCLUSIONS: Smoking and hypertension appear to explain, at least partly, the previously reported inverse association between BMI and the risk of SAH. Therefore, the independent role of BMI in the risk of SAH is likely modest.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: blood pressure ■ body mass index ■ hypertension ■ smoking ■ subarachnoid hemorrhage

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Although obesity increases the risk of various cardiovascular diseases,[1] several large population-based cohort studies[2–7] have reported that higher body mass index (BMI) may be associated with a decreased risk of subarachnoid hemorrhage (SAH). As the number of obese people is rapidly increasing while the incidence of SAH is decreasing,[8] the role of excess weight in the risk of SAH is gaining more interest.

Addressing the independent role of BMI in the risk of SAH is challenging as the most important risk

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Nonstandard Abbreviations And Acronyms

BMI	body mass index
HR	hazard ratio
SAH	subarachnoid hemorrhage
WHO	World Health Organization

factors for SAH, namely smoking and hypertension,[9,10] are associated with body fatness and excess weight—for which BMI is a commonly used proxy. Specifically, because smoking is strongly associated with lower[11] and hypertension with higher[12] body fatness and BMI, they may induce an indirect negative (smoking) or positive (hypertension) effect on the association between BMI and the risk of SAH. Moreover, as the number of lean people in high-income countries is relatively low, difficulties in collecting large enough cohorts have hindered incisive analyses of these complex relationships. Therefore, we decided to combine 3 large, long-term population-based cohorts from Norway and Finland and evaluate the impact of BMI on the risk of SAH. Contrary to previous studies,[2–7] the large sample size and detailed risk factor data enabled us to focus on the possible indirect effects related to the 2 most important risk factors for SAH—smoking and hypertension. Thus, the aim of the present study was to assess the modifying effects of smoking and hypertension on the relationship between BMI and the risk of SAH.

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METHODS

Data Availability Statement

More information about detailed study protocol and statistical analysis plan can be obtained from the corresponding author. Due to the European Union and Norwegian data privacy laws, the data of the FINRISK, HUNT (The Trøndelag Health Study), and the Tromsø studies cannot be shared for a public use along with the publication. However, the data can be requested from the Finnish Health and Social Data Permit Authority (https://www.findata.fi/en/) for the FINRISK cohort, from the HUNT Research Center of the Norwegian University of Science and Technology (https://www.ntnu.edu/hunt/data) for the HUNT cohort, and from the Arctic University of Norway (https://uit.no/research/tromsostudy) for the Tromsø cohort. Detailed requirements for data applications are found in the aforementioned web pages.

Study Cohorts

We combined data from three large, prospective population-based cohorts. Two were from Norway (the HUNT study[13] and the Tromsø study[14]), and one was from Finland (the FINRISK study[15]). The combined analysis cohort included 211 972 adults (aged 18–103 years) who were enrolled between 1972 and 2012 and had no previous history of SAH. Details of the Norwegian and Finnish cohorts and their data collection methods have been described in previous publications.[13–15] A brief summary is given below and in the Supplemental Material.

Data Collection and Obesity Assessment

At enrollment, we collected data on age, sex, smoking (never/former/current), systolic and diastolic blood pressures, and BMI. If a person had been diagnosed with hypertension, used antihypertensive medication, or their systolic blood pressure exceeded 140 or diastolic blood pressure exceeded 90 mm Hg at baseline, we classified the person as hypertensive (category). In line with previous studies,[2–4,6] we assessed BMI as a continuous variable (per SD increase) and as a categorical variable based on the World Health Organization (WHO) classification[16] with slight modifications. Briefly, to preserve sufficient sample size in the groups of weight extremes (ie, the leanest and the most obese persons), we created three BMI categories by dichotomizing the WHO-classified normal weight category as follows: (1) low BMI (BMI<22.5; combination of underweight and the lower half of the normal weight category), (2) moderate BMI (BMI 22.5–29.9; combination of overweight and the upper half of the normal weight category), and (3) high BMI (BMI≥30; combination of all obese categories). The moderate BMI category served as a reference group in all categorical assessments. To examine quadratic (nonlinear) effects of BMI on the risk of SAH, we also computed the centered (difference to the mean value of BMI) and squared centered BMI values. Finally, we calculated the risk of SAH for each BMI unit value between 21 and 35 by calculating 3-unit moving averages (eg, BMI values 24.0–26.9 represented BMI unit 25, and BMI values 25.0–27.9 represented BMI unit 26) to obtain a smoother and more robust risk estimate based on a sufficient sample size for each BMI unit (please see Supplemental Material).

Follow-Up and SAH Identification

The follow-up started at enrollment and ended at death, emigration, first-ever SAH, or at the end of each cohort's follow-up (December 31, 2014, for the HUNT study; December 31, 2016, for the Tromsø study; and December 31, 2018, for the FINRISK study), whichever came first. Data about nonfatal SAHs were extracted from the national (FINRISK study) and local (HUNT and Tromsø studies) validated Hospital Discharge Registers. Data about SAH deaths (also including deaths without hospitalization) were extracted with high accuracy from the nationwide Cause of Death Registers (please see Supplemental Material for details).

Statistical Analyses

In addition to crude incidence rates of SAH, we calculated European age-standardized (European standard population 1976) incidence rates for the whole study cohort. We used the Cox proportional hazard model to calculate hazard ratios (HRs) with 95% CIs, first for each cohort separately and then with estimates from the pooled cohorts, which was done by using the meta-analysis of the weighted random-effects model. In addition, we used the I^2 test to evaluate the cohort heterogeneity. The Schoenfeld residuals and log-log plots examined proportionality assumptions of the Cox model. We also performed a competing risk analysis (Fine and Gray model) to calculate the cumulative incidence of SAH by BMI categories in the presence of a

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competing risk by other causes of death. Based on the previous prospective population-based studies[7,10] that included outside hospital deaths, we considered the well-established risk factors for SAH (age, sex, smoking, and systolic blood pressure) as possible confounders and included them in our adjusted multivariable model. In addition, we included study cohort and year of enrollment in the final model in attempt to control a possible cohort effect. To investigate whether smoking or hypertension rates are associated with BMI, we used a logistic regression model to calculate any changes (an average estimate as a percentage with 95% CIs) in the proportion of current smokers and hypertensive persons (separately for all study participants and SAH cases) per each SD increase of BMI. We also graphically illustrated these proportions by the three-unit moving averages of BMI. To evaluate the possible modifying effect of smoking and hypertension on the association between BMI and risk of SAH, we calculated interaction terms (HRs with 95% CIs) in stratified analyses of BMI within categories of smoking (nonsmokers [never or former] versus current smokers) and hypertension (normotensive versus hypertensive persons). Lastly, as post hoc subgroup analyses, we calculated the HRs separately for men and women, as well as by age for younger (<50 years of age) and older (≥50 years of age) persons. All statistical analyses were performed by Stata version 16.1 (Stata Corp, College Station, TX).

Ethical Considerations

Norwegian cohorts received ethical approvals from the Norwegian Data Protection Authority, the Norwegian Board of Health Supervision, and the Regional Committee for Medical and Health Research Ethics. Depending on the ethical rules of the study year, the Finnish cohort (FINRISK study) received the ethical approval from the ethical committee of the National Public Health Institute (currently Finnish Institute for Health and Welfare) or from the Coordinating Ethical Committee of Helsinki and Uusimaa Hospital District. All participants gave either oral or written informed consent, and each study followed the principles of the Declaration of Helsinki. In addition, the manuscript followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline (please see Supplemental Material for details).

RESULTS

General Characteristics

During the follow-up of 4.7 million person-years, we identified 831 first-ever SAHs. The crude incidence of SAH was 17.9 (16.7–19.1) per 100 000 person-years, whereas the European age-standardized incidence rate was 13.7 as weighted by age groups represented in our cohort (age range, 18–103) and 9.7 as weighted by all age groups (only <1% of SAHs occur before the age of 18 years[17]). The mean (median) age at SAH was 61.5 (61.8) years, and over half of the cases were women (Table). Persons with SAH were more often women, hypertensive and current smokers, and had low BMI values (BMI<22.5) at baseline (Table). By study cohorts, Finnish participants were more commonly hypertensive and had high BMI values (BMI≥30), whereas the proportion of current smokers was higher in Norwegian cohorts (Table I in the Supplemental Material).

BMI and the Risk of SAH

In the adjusted Cox regression model, every SD (=4.2 unit) increase in BMI was associated with an 11% (adjusted HR, 0.89 [0.83–0.97]) decrease in the risk of SAH (Figure 1A). Compared with moderate BMI, being in the low BMI category was associated with an increased risk of SAH (adjusted HR, 1.30 [1.09–1.55]), whereas no risk difference was detected between moderate and high BMI categories (adjusted HR, 0.91 [0.73–1.13]; Figure 1B). The same associations were found in both men and women, with no significant cohort heterogeneity (I^2 test=0.0% for all associations; Figures I–III in the Supplemental Material). In the competing risk of death analysis, the low BMI category was still associated with a higher risk of SAH (adjusted HR, 1.27 [1.06–1.51]), compared to the moderate BMI category (Figure 1C). There were no significant quadratic effects on the association between BMI and SAH, which indicates that the relationship between BMI and SAH is rather linear than curvilinear and that the Cox model was appropriate.

BMI and the Risk of SAH by Hypertension Status

Per each SD (=4.2 unit) increase of BMI, the prevalence of hypertension increased by 94.3% (92.3%–96.3%) in all study participants and 92.2% (61.6%–128.5%) among SAH cases (Figure 2A). An inverse association between BMI and the risk of SAH was, however, slightly more evident among hypertensive (HR, 0.90 [0.82–0.99] per each SD increase of BMI) than normotensive persons (HR, 0.96 [0.83–1.10]; interaction HR, 0.94 [0.80–1.11], P=0.48 for effect change of continuously increasing BMI by hypertension). In our post hoc analyses by sex, we found that this result originated mainly from the risk difference between normotensive and hypertensive men with low BMI (interaction HR, 1.76 [0.98–3.14], P=0.06 for effect change of low BMI by hypertension; Figure 2B). In addition, hypertension appeared to be associated with the increased risk of SAH mostly in men with low BMI (Figure 2C). In women, the association between low BMI and the risk of SAH did not differ by hypertension status (Figure 2B) and the risk increase of hypertension occurred similarly in each BMI category (Figure 2C).

BMI and the Risk of SAH by Smoking Status

The overall proportion of current smokers was on average 24.7% lower (23.9%–25.5%) per each SD (=4.2 units) increase of BMI. In comparison to all study participants, this decreasing trend was more pronounced among future SAH cases (37.4% [26.7%–46.6%] per each SD increase; Figure 3A). Similar to hypertension, the inverse association

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Table. General Characteristics at Baseline of the Future SAH Cases and Other Participants

	No SAH	SAH	Age-adjusted HR (95% CI) for SAH
No. of participants (% of total)			NA
Total	211 141 (100.0)	831 (100.0)	
FINRISK study	70 373 (33.3)	534 (64.3)	
HUNT study	106 183 (50.3)	211 (25.4)	
Tromsø study	34 585 (16.4)	86 (10.4)	
Age at baseline			NA
Mean (SD)	44.6 (15.9)	46.0 (12.5)	
Median (IQR)	42.0 (31.0–56.0)	46.0 (36.0–56.0)	
Sex, n (%)			
Male	101 985 (48.3)	352 (42.4)	(Reference)
Female	109 156 (51.7)	479 (57.6)	1.19 (1.04–1.37)
SBP			NA
Mean (SD)	136.1 (21.8)	144.3 (23.4)	
Median (IQR)	132.0 (121.0–148.0)	140.0 (128.0–156.0)	
Missing, n (%)	6166 (2.9)	15 (1.8)	
DBP			NA
Mean (SD)	81.5 (12.8)	87.8 (12.7)	
Median (IQR)	81.0 (72.0–90.0)	88.0 (79.0–95.5)	
Missing, n (%)	6195 (2.9)	15 (1.8)	
Smoking, n (%)			
Never	88 999 (42.2)	282 (33.9)	(Reference)
Former	40 717 (19.3)	112 (13.5)	0.90 (0.72–1.12)
Current	60 535 (28.7)	381 (45.9)	2.24 (1.91–2.62)
Missing	20 890 (9.9)	56 (6.7)	
Hypertension, n (%)			
No	117 179 (55.5)	337 (40.6)	(Reference)
Yes	91 349 (43.3)	494 (59.5)	1.68 (1.45–1.94)
Missing	2613 (1.2)	0 (0.0)	
BMI			NA
Mean (SD)	25.5 (4.2)	25.5 (4.2)	
Median (IQR)	24.9 (22.6–27.8)	24.8 (22.5–27.8)	
Missing, n (%)	6823 (3.2)	16 (1.9)	
BMI by categories, n (%)			
Low (BMI<22.5)	48 155 (22.8)	205 (24.7)	1.24 (1.05–1.46)
Moderate (BMI 22.5–29.9)	129 017 (61.1)	497 (59.8)	(Reference)
High (BMI≥30)	27 146 (12.9)	113 (13.6)	1.14 (0.93–1.40)
Missing	6823 (3.2)	16 (1.9)	

BMI indicates body mass index; DBP, diastolic blood pressure; HR, hazard ratio; HUNT, The Trøndelag Health Study; IQR, interquartile range; NA, not applicable; SAH, subarachnoid hemorrhage; and SBP, systolic blood pressure.

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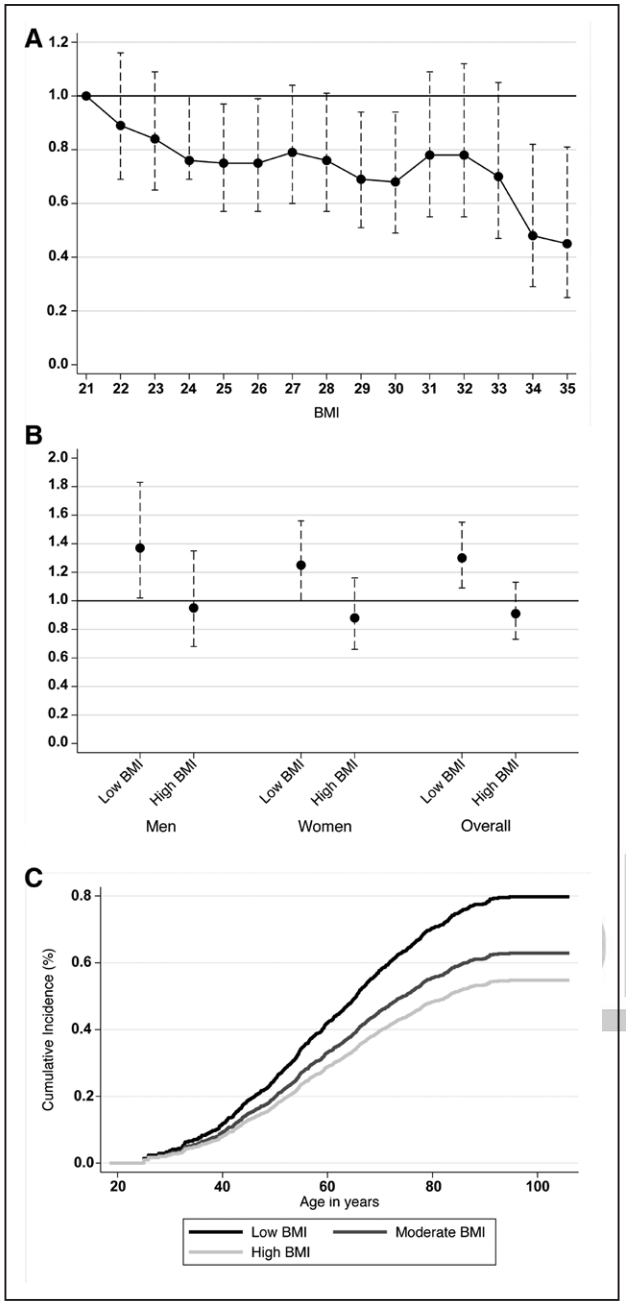
between an increasing BMI and the risk of SAH was stronger among current smokers (HR, 0.82 [95% CI, 0.72–0.93] per each SD increase of BMI) but weaker in nonsmokers (HR, 0.93 [95% CI, 0.83–1.04]; interaction HR, 0.88 [0.76–1.02], P=0.10 for the effect change per SD increase of BMI by smoking). In the categorical assessment, low BMI was associated with the increased risk of SAH among current smokers (HR, 1.49 [95% CI, 1.19–1.88]), whereas in nonsmoking men and women the association was practically negligible (HR, 1.02 [95% CI, 0.76–1.37]; interaction HR, 1.68 [95% CI, 1.18–2.41], P=0.004 for the effect change of low BMI by smoking; Figure 3B). In addition, current smoking increased the risk of SAH in all BMI categories, but the point estimate was the highest in persons with low BMI (no overlap with the 95% CIs of comparison groups, and a significant interaction between low BMI and smoking as described above)—especially in low BMI women (Figure 3C).



Figures 1. Body mass index (BMI) and the risk of subarachnoid hemorrhage (SAH).
All models were adjusted for age, sex, smoking, systolic blood pressure, study cohort, and study year. **A**, Adjusted hazard ratios (HRs; dots) and 95% CIs (whiskers) for SAH by BMI units. The BMI range 18–21 was used as a reference group. **B**, Adjusted HRs (dots) and 95% CIs (whiskers) for SAH by the low and high BMI categories. The moderate category was used as the reference group. **C**, The cumulative incidence of SAH by the BMI categories in the presence of competing risk by other causes of death.

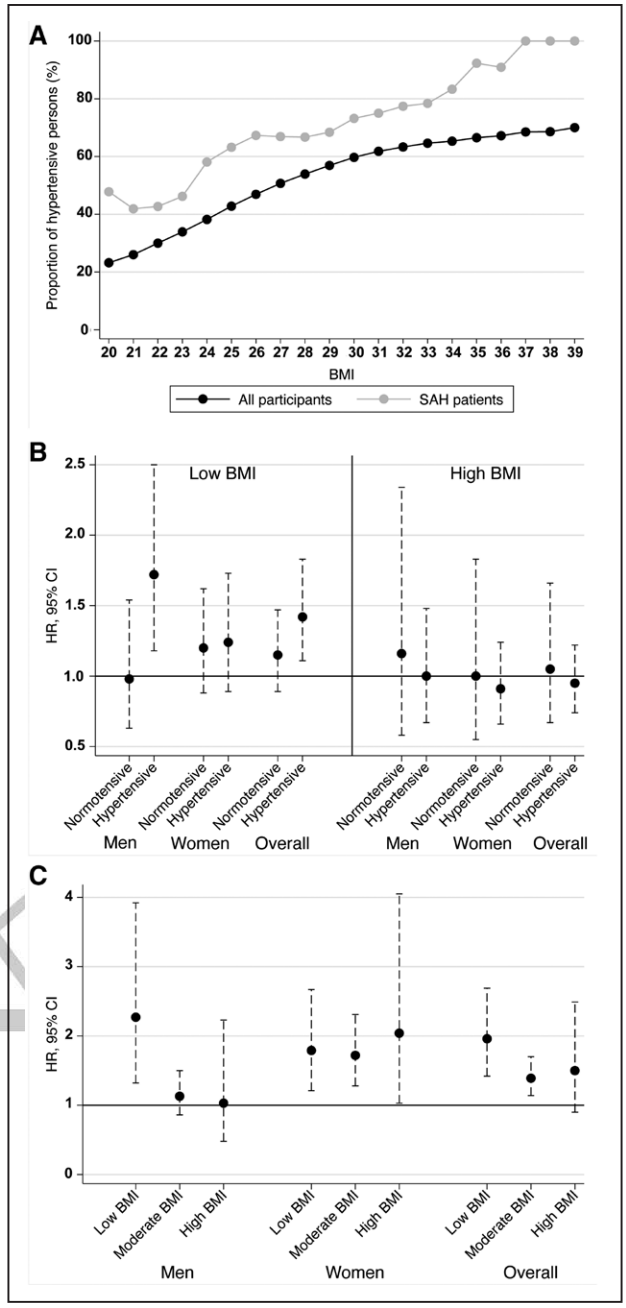


Figure 2. Body mass index (BMI) and the risk of subarachnoid hemorrhage (SAH) by hypertension subgroups.
A, Hypertension rates by BMI in the entire cohort (black connected line) and in the SAH cases (gray connected line). These relationships were similar in all 3 study cohorts, in both men and women, and were not dependent on age. **B**, Adjusted hazard ratios (HRs; dots) and 95% CIs (whiskers) for SAH in men and women with low BMI. Moderate BMI category serves as a reference group. The estimates are presented by sex and hypertension status at baseline. Models are adjusted for age, sex, smoking, study cohort, and study year. **C**, Adjusted HRs (dots) and 95% CIs (whiskers) for SAH in hypertensive participants by BMI categories. Normotensive participants represent the reference category. Adjusted models included variables of age, sex, smoking, study cohort, and study year.

DISCUSSION

In this pooled analysis of 3 large, prospective population-based cohorts from Norway and Finland, we found that BMI was negatively associated with risk of SAH, which is in line with previous population-based cohort studies.[2–7] However, the risk seemed to differ according to smoking and hypertension; the association between low BMI and the risk of SAH was low or nonexistent in nonsmokers

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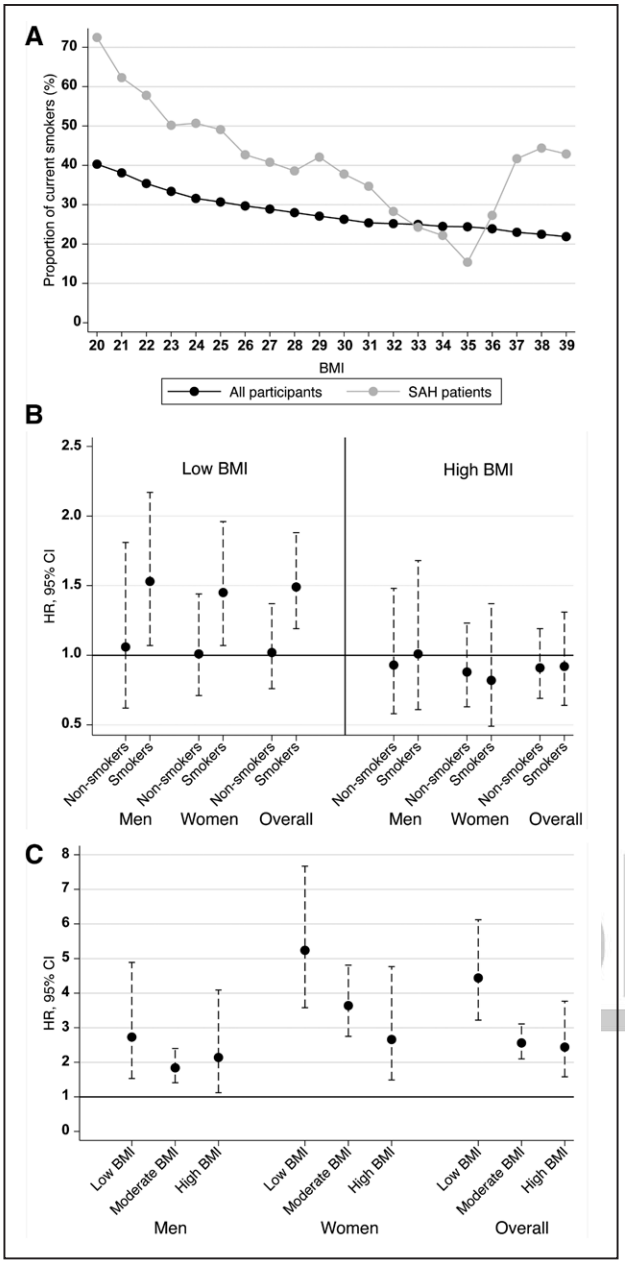

Figure 3. Body mass index (BMI) and the risk of subarachnoid hemorrhage (SAH) by smoking subgroups. **A**, Smoking rates by BMI in the entire cohort (black connected line) and in the SAH cases (gray connected line). These relationships were seen in all three study cohorts, in both men and women, and were not dependent on age. **B**, Adjusted hazard ratios (HRs; dots) and 95% CIs (whiskers) for SAH in men and women with low and high BMI. The moderate BMI category was used as a reference group. The estimates are presented by sex and by smoking status at baseline. The models were adjusted for age, sex, systolic blood pressure, study cohort, and study year. **C**, Adjusted HRs (dots) and 95% CIs (whiskers) for SAH in current smokers by BMI categories in men and women. Never/former smokers represent the reference category. The models were adjusted for age, sex, systolic blood pressure, study cohort, and study year.

and in normotensive participants. In addition, the risk of SAH associated with hypertension and smoking seemed to be stronger among participants with low BMI, at least in hypertensive men. For example, when considering the absolute risk estimates, the crude incidence of SAH was higher in smokers with low BMI (31.4 per 100 000 person-years) than in smokers with moderate BMI (25.9 per 100 000 person-years), whereas in nonsmokers, the figures were vice versa (9.6 in nonsmokers with low BMI and 14.0 in nonsmokers with moderate BMI). Similar results were also found between normotensive (10.9 in men with low BMI and 11.2 in men with moderate BMI) and hypertensive men (33.0 in men with low BMI and 20.0 in men with moderate BMI; Table II in the Supplemental Material). Thus, our results suggest that the established risk factors of smoking and hypertension may not only confound the obesity-SAH relationship but also mediate and modify it. It is possible that residual confounding of smoking in both sexes, and perhaps hypertension in men, may increase or induce an inverse association between BMI and SAH. Taken together, our findings suggest that neither low nor high BMI seem to be strong independent risk factors for SAH, contrary to the previous population-based studies.[2–7]

In general, smokers are leaner than people who have never smoked. This is believed to be related to appetite suppression and increased thermogenesis induced by nicotine and other compounds in tobacco.[18] Correspondingly, weight gain is common after smoking cessation,[18] and fear of gaining weight may prevent people from quitting or even initiate smoking.[19] In our study, we could not assess the smoking habits in detail, but the proportion of current smokers was higher in the low BMI category (40%) compared to the moderate (31%) or high BMI (26%) categories. Because being overweight/obese is known to increase blood pressure values,[12] weight loss is often recommended following the diagnosis of hypertension. Hence, the association between blood pressure and obesity is also potentially bidirectional. In our study, the prevalence of hypertension was almost 3× higher in the high BMI category than in the low BMI category (68% versus 24%), but hypertension increased the risk of SAH more in the men with low BMI. One possible explanation could be that hypertension is diagnosed and treated sooner in overweight and obese persons than in lean persons. If true, hypertension could cause a stronger cumulative effect in persons with low BMI compared with those with high BMI. Moreover, as several physiological mechanisms inducing hypertension have been related to obesity,[12] the pathophysiology and impact of hypertension may differ between persons with high and low BMI. Why we only observed the interaction between BMI and hypertension on the risk of SAH in men but not in women, remains however to be studied. In short, smoking and hypertension may not only confound the obesity-SAH relationship but also mediate and modify it. Thus, large sample sizes, detailed risk factor data, as well as proper interaction and risk factor-stratified analyses are useful to evaluate the true relationship between BMI and the risk of SAH.

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In addition to smoking and high blood pressure, adverse lipid profiles (high level of total cholesterol and low-density lipoproteins and low levels of high-density lipoproteins) have been associated with both high BMI[20] and the increased risk of SAH, especially in men.[21] Unfortunately, lipids were not measured in all of the earliest cohorts, and thus we decided to exclude these variables from the analyses. However, when we adjusted the analyses to the total cholesterol (and excluded 15% of the participants with missing values), our study findings did not change (results not shown). Another potential bias relates to the fact that people with a higher BMI have an increased risk of all-cause mortality,[22] and are, therefore, more likely to die from other causes than SAH. However, in our competing risk analyses, low BMI was associated with the increased risk of SAH, and high BMI with the decreased risk of SAH, regardless of the competing risk caused by other causes of death.

To our knowledge, this is the first study setup capable of considering the indirect effect of BMI on the risk of SAH via the most important risk factors for SAH—smoking and hypertension. In a recent study of 1.3 million women, Kroll et al[4] found that the lean participants (BMI<22.5) had a higher risk of SAH, but the authors did not investigate whether smoking and hypertension contributed to this association. In 2019, Sundström et al.[3] reported that every SD increase of BMI associated with a 14% reduction in risk of SAH in women, and that this association was weaker among nonsmokers than among smokers. However, the study,[3] which was based on 21 pooled population-based Swedish cohorts of nearly 950 000 individuals did not assess the indirect effects of smoking by proper interaction analyses for low and high BMI subgroups. In fact, both studies[3,4] concluded that a higher BMI may associate with a lower risk of SAH.

Our study has limitations. First, as the data were pooled from 3 different cohort studies and 2 different countries, heterogeneity in data collection and identification methods of SAHs may have caused unknown bias. For example, autopsy rates in Finland are higher than in Norway,[23] and thus sudden-death SAHs without hospitalization are more likely included in the Finnish cohort. However, the exclusion of sudden-death SAHs had no substantial impact on the reported associations between BMI and SAH (results not shown). Fortunately, the data about the most important variables (eg, BMI, blood pressure, and smoking status) were collected similarly for all three cohorts, and according to our meta-analysis, there was no significant heterogeneity between the results of each cohort. Therefore, it is unlikely that the cohort differences would have distorted the reported associations. Second, our dataset may include a few nonaneurysmal SAHs, especially in the Finnish cohort where the patient-level data was not available. However, a recent publication that performed similar case identification from the very same Finnish registers (the nationwide Hospital Discharge Register and Cause of Death Register) reported that the accuracy of aneurysmal SAH events in the described register-based search was 99.8%.[24] However, for the Norwegian cohorts, we only included aneurysmal SAH events that were diagnosed by angiography, surgery or autopsy, and fatal SAH events with highly suggestive aneurysmal origin (typical clinical presentation, massive SAH detected on a computed tomography scan, and death occurring within four weeks after the onset of symptoms).[25] Therefore, it is difficult to envision how a low number of misdiagnosed cases could strengthen the reported associations, especially when results stratified by cohorts do not differ. Third, data about the risk factors were collected at enrollment, and our dataset included follow-up measurements only for a minority of the participants. As most people tend to gain weight until late life sarcopenia or severe illnesses that occur commonly in elderly (after the mean age of SAH),[26] our study may overestimate the proportion of lean persons and therefore underestimate the increased risk of SAH among persons with a lower BMI. Regarding hypertension, because blood pressure values often increase as people age,[27] our analysis may have underestimated the proportion of hypertensive participants and thus, the adverse effects of hypertension. How this would affect the performed interaction analyses is more difficult to speculate based on the available data. Because successful smoking cessation[28] happens relatively rarely, and very few start smoking in the middle or later adulthood,[29] it is unlikely that changes in participants' smoking habits (especially from never to current smokers or vice versa) could distort the conclusions. Nevertheless, because we cannot fully exclude that the changes of risk factors could have an impact on our interaction analyses, the findings should be interpreted with some caution. To overcome this typical limitation of large and long-term observational studies, future investigations could perhaps utilize repeated risk factor measurements or combine clinical and genetic risk factor variables, for example, by using Mendelian randomization approaches. Fourth, despite the large sample size, the number of the WHO-classified underweight individuals (BMI<18.5) was still small (1.2%; only 9 SAH cases) and thus, in our categorical assessment, we dichotomized the WHO-classified normal weight category to create a low BMI category with sufficient sample size. This was done in line with the previous study by Kroll et al.[4] Moreover, as the WHO classification is based on the BMI units, the obesity categories were not balanced between the study cohorts. For example, the high BMI category was slightly overrepresented and the low BMI category slightly underrepresented by Finnish participants (from the FINRISK cohort; Table III in the Supplemental Material). However, when we generated balanced BMI categories by first dividing each cohort into BMI quartiles, and then pooling the lowest, 2 middle, and highest quartiles to create 3 BMI categories, the category characteristics were very similar to the categories based on the WHO classification (Table

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III in the Supplemental Material). Thus, the results based on these balanced categories were also similar to those presented here (results not shown). Fifth, because other obesity measurements such as waist circumference and waist-to-hip ratio were not collected in almost 40% of the participants, we based our obesity assessments entirely on the BMI. However, both of these variables correlated significantly with BMI (ρ=0.67, P<0.001 for BMI and waist circumference, and ρ=0.43, P<0.001 for BMI and waist-to-hip ratio). When studying the SAH risk in the subgroup that included waist circumference and waist-to-hip ratio measurements, continuously increasing values associated similarly with the decreased risk of SAH, but this relationship was not detected independently from smoking (results not shown).

CONCLUSIONS

The most important risk factors for SAH—smoking and hypertension—appear to explain, at least partly, the previously reported inverse association between BMI and the risk of SAH. Therefore, the independent role of BMI in the risk of SAH is modest, and although the obesity epidemic is increasing in many countries, the impact of BMI on the decreasing incidence rates of SAH is likely to be minor at most.

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Disclosures

Dr Salomaa has received honoraria from Novo Nordisk and Sanofi for consulting and also has an ongoing research collaboration with Bayer Ltd (all unrelated to the present study). The other authors report no conflicts.

Supplemental Materials

Expanded Materials and Methods
Supplemental Figures I–III
Supplemental Tables I–III

REFERENCES

1. Kivimäki M, Kuosma E, Ferrie JE, Luukkonen R, Nyberg ST, Alfredsson L, Batty GD, Brunner EJ, Fransson E, Goldberg M, et al. Overweight, obesity, and risk of cardiometabolic multimorbidity: pooled analysis of individual-level data for 120 813 adults from 16 cohort studies from the USA and Europe. *Lancet Public Health*. 2017;2:e277–e285. doi: 10.1016/S2468-2667(17)30074-9
2. Sandvei MS, Lindekleiv H, Romundstad PR, Müller TB, Vatten LJ, Ingebrigtsen T, Njølstad I, Mathiesen EB, Vik A. Risk factors for aneurysmal subarachnoid hemorrhage - BMI and serum lipids: 11-year follow-up of the HUNT and the Tromsø Study in Norway. *Acta Neurol Scand*. 2012;125:382–388. doi: 10.1111/j.1600-0404.2011.01578.x
3. Sundström J, Söderholm M, Söderberg S, Alfredsson L, Andersson M, Bellocco R, Björck M, Broberg P, Eriksson M, Eriksson M, et al. Risk factors for subarachnoid haemorrhage: a nationwide cohort of 950 000 adults. *Int J Epidemiol*. 2019;48:2018–2025. doi: 10.1093/ije/dyz163
4. Kroll ME, Green J, Beral V, Sudlow CL, Brown A, Kirichek O, Price A, Yang TO, Reeves GK; Million Women Study Collaborators. Adiposity and ischemic and hemorrhagic stroke: prospective study in women and meta-analysis. *Neurology*. 2016;87:1473–1481. doi: 10.1212/WNL.0000000000003171
5. Knekt P, Reunanen A, Aho K, Heliövaara M, Rissanen A, Aromaa A, Impivaara O. Risk factors for subarachnoid hemorrhage in a longitudinal population study. *J Clin Epidemiol*. 1991;44:933–939. doi: 10.1016/0895-4356(91)90056-f
6. Lindbohm JV, Kaprio J, Jousilahti P, Salomaa V, Korja M. Risk factors of sudden death from subarachnoid hemorrhage. *Stroke*. 2017;48:2399–2404. doi: 10.1161/STROKEAHA.117.018118
7. Sandvei MS, Romundstad PR, Müller TB, Vatten L, Vik A. Risk factors for aneurysmal subarachnoid hemorrhage in a prospective population study: the HUNT study in Norway. *Stroke*. 2009;40:1958–1962. doi: 10.1161/STROKEAHA.108.539544
8. Etminan N, Chang HS, Hackenberg K, de Rooij NK, Vergouwen MDI, Rinkel GJE, Algra A. Worldwide incidence of aneurysmal subarachnoid hemorrhage according to region, time period, blood pressure, and smoking prevalence in the population: a systematic review and meta-analysis. *JAMA Neurol*. 2019;76:588–597. doi: 10.1001/jamaneurol.2019.0006
9. Korja M, Silventoinen K, Laatikainen T, Jousilahti P, Salomaa V, Hernesniemi J, Kaprio J. Risk factors and their combined effects on the incidence rate of subarachnoid hemorrhage–a population-based cohort study. *PLoS One*. 2013;8:e73760. doi: 10.1371/journal.pone.0073760
10. Lindbohm JV, Kaprio J, Jousilahti P, Salomaa V, Korja M. Sex, smoking, and risk for subarachnoid hemorrhage. *Stroke*. 2016;47:1975–1981. doi: 10.1161/STROKEAHA.116.012957
11. Dare S, Mackay DF, Pell JP. Relationship between smoking and obesity: a cross-sectional study of 499,504 middle-aged adults in the UK general population. *PLoS One*. 2015;10:e0123579. doi: 10.1371/journal.pone.0123579
12. Jiang SZ, Lu W, Zong XF, Ruan HY, Liu Y. Obesity and hypertension. *Exp Ther Med*. 2016;12:2395–2399. doi: 10.3892/etm.2016.3667
13. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, Bratberg G, Heggland J, Holmen J. Cohort profile: the HUNT Study, Norway. *Int J Epidemiol*. 2013;42:968–977. doi: 10.1093/ije/dys095
14. Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njølstad I. Cohort profile: the Tromso Study. *Int J Epidemiol*. 2012;41:961–967. doi: 10.1093/ije/dyr049
15. Borodulin K, Tolonen H, Jousilahti P, Jula A, Juolevi A, Koskinen S, Kuulasmaa K, Laatikainen T, Männistö S, Peltonen M, et al. Cohort profile: The National FINRISK Study. *Int J Epidemiol*. 2018;47:696–696i. doi: 10.1093/ije/dyx239
16. WHO Consultation on Obesity (1999: Geneva, Switzerland) & World Health Organization. Obesity: preventing and managing the global epidemic. Report of a who consultation. *World Health Organ Tech Rep Ser*. 2000;894:i-xii, 1-253
17. Westra DL, Colohan ART. Pediatric subarachnoid haemorrhage. In: Kırış T, Zhang JH (eds). Cerebral Vasospasm. *Acta Neurochirurgica Supplement*, vol 104. 2008. Vienna: Springer. https://doi.org/10.1007/978-3-211-75718-5_84

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18. Piirtola M, Jelenkovic A, Latvala A, Sund R, Honda C, Inui F, Watanabe M, Tomizawa R, Iwatani Y, Ordoñana JR, et al. Association of current and former smoking with body mass index: a study of smoking discordant twin pairs from 21 twin cohorts. *PLoS One*. 2018;13:e0200140. doi: 10.1371/journal.pone.0200140
19. Luostarinen M, Tuovinen EL, Saarni SE, Kinnunen T, Hukkinen M, Haukkala A, Patja K, Kaprio J, Korhonen T. Weight concerns among Finnish ever-smokers: a population-based study. *Nicotine Tob Res*. 2013;15:1696–1704. doi: 10.1093/ntr/ntt043
20. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, Marks JS. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA*. 2003;289:76–79. doi: 10.1001/jama.289.1.76
21. Lindbohm J, Korja M, Jousilahti P, Salomaa V, Kaprio J. Adverse lipid profile elevates risk for subarachnoid hemorrhage: a prospective population-based cohort study. *Atherosclerosis*. 2018;274:112–119. doi: 10.1016/j.atherosclerosis.2018.05.011
22. Global BMI Mortality Collaboration; Di Angelantonio E, Bhupathiraju ShN, Wormser D, Gao P, Kaptoge S, Berrington de Gonzalez A, Cairns BJ, Huxley R, Jackson ChL, Joshy G, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet*. 2016;388:776–786. doi: 10.1016/S0140-6736(16)30175-1
23. Korja M, Kaprio J. Controversies in epidemiology of intracranial aneurysms and SAH. *Nat Rev Neurol*. 2016;12:50–55. doi: 10.1038/nrneurol.2015.228
24. Rautalin I, Lindbohm JV, Kaprio J, Korja M. Substantial within-country variation in the incidence of subarachnoid hemorrhage: A Nationwide Finnish Study. *Neurology*. 2021;97:e52–e60. doi: 10.1212/WNL.0000000000012129
25. Sandvei MS, Mathiesen EB, Vatten LJ, Müller TB, Lindekleiv H, Ingebrigtsen T, Njølstad I, Wilsgaard T, Løchen ML, Vik A, et al. Incidence and mortality of aneurysmal subarachnoid hemorrhage in two Norwegian cohorts, 1984-2007. *Neurology*. 2011;77:1833–1839. doi: 10.1212/WNL.0b013e3182377de3
26. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384:766–781. doi: 10.1016/S0140-6736(14)60460-8
27. Whelton PK, He J, Muntner P. Prevalence, awareness, treatment and control of hypertension in North America, North Africa and Asia. *J Hum Hypertens*. 2004;18:545–551. doi: 10.1038/sj.jhh.1001701
28. Borland R, Partos TR, Yong HH, Cummings KM, Hyland A. How much unsuccessful quitting activity is going on among adult smokers? Data from the International Tobacco Control Four Country cohort survey. *Addiction*. 2012;107:673–682. doi: 10.1111/j.1360-0443.2011.03685.x
29. Edwards R, Carter K, Peace J, Blakely T. An examination of smoking initiation rates by age: results from a large longitudinal study in New Zealand. *Aust N Z J Public Health*. 2013;37:516–519. doi: 10.1111/1753-6405.12105

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