

1 **Risk Factors for Unruptured Intracranial Aneurysms and Subarachnoid**
2 **Hemorrhage in a Prospective Population-Based Study**

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1 **Background and purpose**

2 We wanted to evaluate potential risk factors for unruptured intracranial aneurysms
3 (UIA) and aneurysmal subarachnoid hemorrhage (aSAH) in a large, prospective study
4 of the general population with risk factors collected before the detection of UIA or
5 aSAH.

6 **Methods**

7 All residents ≥ 20 years were invited to the The Nord-Trøndelag Health Study
8 (HUNT). In this study, 89,951 participants were included. The study included
9 standardized measurements of blood pressure and self-administered questionnaires.
10 Cases of UIA and aSAH from 1999 to 2014 were identified using hospital records and
11 the Norwegian Cause of Death Register. Hazard ratios (HR) with confidence intervals
12 (CIs) were estimated using Cox regression analysis.

13 **Results**

14 The detection rate of UIA was 8.2 per 100,000 person-years (97 patients). Current
15 smoking (HR 4.1, 95% CI 2.4-7.1) and female sex (HR 2.8, 95% CI 1.7-4.5) were
16 associated with markedly increased risk of UIA, but we found no association with
17 systolic blood pressure (p for trend 0.62). The incidence of aSAH was 9.9 per 100,000
18 person years (117 patients). The most important risk factors for aSAH were current
19 smoking, female sex and increasing blood pressure (p for trend 0.006 for systolic
20 blood pressure).

21 **Conclusions**

22 In contrast to previous studies on risk factors of UIA, we found no association with
23 systolic blood pressure. However, there was a strong association between systolic

- 1 blood pressure and aSAH in the same population. Current smoking and female sex
- 2 were associated with both diseases.

1 Unruptured intracranial aneurysms (UIAs) have an estimated prevalence of 2-3 %, ^{1,2}
2 and more UIAs are being detected due to increased availability of brain imaging.
3 Most previous studies of risk factors for UIA have either collected these after the
4 diagnosis, ^{3,4} or assessed risk of de novo aneurysms in patients with previous
5 aneurysmal subarachnoid hemorrhage (aSAH), ⁵⁻⁷ which have questionable relevance
6 for a population without aSAH. Only one study had information on potential risk
7 factors before the diagnosis of UIA in an unselected population. ⁸

8 We therefore examined risk factors for later detection of UIA in a large,
9 prospective study of the general population. We also included aSAH patients to
10 uncover possible differences in risk factors.

11 **Materials and methods**

12 Because of the sensitive nature of the data collected for this study, requests to access
13 the dataset from qualified researchers trained in human subject confidentiality
14 protocols, and with permission from the regional committee for medical and health
15 care research and the Central Norway Regional Health Authority, may be sent to
16 HUNT (hunt@medisin.ntnu.no), and the corresponding author.

17 All residents ≥ 20 years in Nord-Trøndelag county were invited to the The
18 Nord-Trøndelag Health Study (HUNT), described in detail previously. ^{9,10} We used
19 the first three waves of the study (HUNT 1 (1984-1986), 2 (1995-1997), and 3 (2006
20 to 2008)), including 89,951 participants. The HUNT Study is a collaboration between
21 the Faculty of Medicine and Health Sciences at the Norwegian University of Science
22 and Technology, the Norwegian Institute of Public Health, and Nord-Trøndelag
23 County Council.

24

1 Case finding and ascertainment

2 Using hospital records, we identified all patients with UIA or SAH at St Olav's
3 Hospital, Trondheim University Hospital (the only hospital with a neurosurgical
4 department that serves the HUNT population), Levanger Hospital and Namsos
5 Hospital (the local hospitals) from January 1, 1999 to December 31, 2014, as
6 described previously.^{11,12} In addition, the HUNT study was linked to the Norwegian
7 Cause of Death Register. In a HUNT 3 sub-study, 1005 participants aged 50-65 years
8 underwent magnetic resonance imaging (MRI) including angiography.^{1,13}

9 The patients' medical records were reviewed by author MSS. Patients with an
10 aneurysm at angiography (MRI, computed tomography (CT), and/or digital
11 subtraction angiography) were included as UIA cases (n=97). Patients were included
12 as aSAH cases if they had subarachnoid hemorrhage on a CT scan and an aneurysm
13 found at angiography (n=96), during operation (n=3), or at autopsy (n=2). Sixteen
14 cases of SAH were also included, despite lack of angiography or autopsy, because the
15 medical history was highly suggestive of fatal aSAH, as described previously.¹²

16 Follow up

17 Patients who died or emigrated from Nord-Trøndelag were identified through the
18 Population Register of Norway. Most participants were followed from January 1,
19 1999, as CT scanners were in common use from about this time. Participants who
20 only participated in HUNT 3, or had attended the HUNT MRI sub-study, were
21 followed from date of attendance (2006-2008). Participants were followed until date
22 of detection of UIA or aSAH, date of emigration or death, or December 31, 2014.

1 **Ethic approval**

2 The Regional Committee for Ethics in Medical Research approved this study and the
3 HUNT studies. In HUNT 2 and 3, all participants gave their informed, written consent
4 to participate.

5 **Statistics**

6 We used Poission regression to estimate trends in detection rates of UIA over time,
7 and Cox regression to estimate hazard ratios (HRs) with 95% confidence intervals
8 (CIs), using attained age as time scale. We adjusted for sex and smoking. Participants
9 with missing data were excluded from the respective analyses. Inspection of log-log
10 plots and Schoenfeld residuals revealed proportionality between hazards. Statistical
11 analyses were conducted in Stata (Version 15.1).

12

13 **Results**

14 **UIA**

15 The detection rate of UIA was 8.2 per 100,000 person-years (97 patients), and
16 increased by 10% per year (HR 1.10, 95% CI 1.04-1.15) when excluding the HUNT
17 MRI patients (Figure 1).

18 Applying the prevalence of UIA in the HUNT MRI population
19 ($19/1005=0.0189$) to the whole population ($89,951*0.0189$), we estimated the number
20 of participants with UIA in the HUNT population to be 1700. Of these, only 6%
21 ($97/1700$) had been detected.

22 Current smoking and female sex were associated with increased risk of UIA
23 (Table 1). However, we found no association between systolic blood pressure and risk
24 of UIA.

1 In analyses including only HUNT MRI participants (19 patients), the results
2 were essentially identical (data not shown).

3 **aSAH**

4 The incidence rate of aSAH was 9.9 per 100,000 person-years (117 patients).

5 Current smoking and female sex were associated with increased risk of aSAH
6 (Table 1). However, in contrast to the UIA results, there was a strong positive
7 association between systolic and diastolic blood pressure and risk of aSAH (Figure 2).

8

9 **Discussion**

10 In this large, prospective population-based study, we found, as expected, that current
11 smoking and female sex were strongly associated with risk of both UIA and aSAH.
12 However, systolic blood pressure was not associated with risk of UIA, only aSAH.
13 Previous studies, most collecting risk factors at the time of aneurysm detection, found
14 hypertension to be associated with UIA.^{3,4,8} Regarding aSAH, our results agree with
15 previous studies.^{11,14}

16 In contrast to most previous studies of risk factors for UIA among persons
17 with no previously known aneurysm, the potential risk factors were collected before
18 the detection of the UIA. This makes reverse causation unlikely. Other strengths
19 include the population-based design and the size. Nonetheless, since UIA and aSAH
20 are uncommon diseases, the number of cases was relatively small. The most
21 important limitation is that only about 6% of all participants with UIA have been
22 detected, possibly introducing selection bias, as both women, smokers and persons
23 with hypertension may use health care services more than others.¹⁵

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1 **Summary**

2 Current smoking was the strongest risk factor for UIA and aSAH, and female sex was
3 also associated with both diseases. Surprisingly, we found no association with systolic
4 blood pressure and risk of UIA, only with risk of aSAH. Our results suggest that
5 systolic blood pressure may be associated with rupture, but not formation of
6 intracranial aneurysms.

7 **Disclosures**

8 None

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1 References

- 2 1. Muller TB, Sandvei MS, Kvistad KA, Rydland J, Haberg A, Vik A, et al.
3 Unruptured intracranial aneurysms in the Norwegian Nord-Trondelag Health
4 Study (HUNT): risk of rupture calculated from data in a population-based
5 cohort study. *Neurosurgery*. 2013;73:256-261.
- 6 2. Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, et
7 al. Incidental findings on brain MRI in the general population. *N Engl J Med*.
8 2007;357:1821-1828.
- 9 3. Kang HG, Kim BJ, Lee J, Kim MJ, Kang DW, Kim JS, et al. Risk Factors
10 Associated With the Presence of Unruptured Intracranial Aneurysms. *Stroke*.
11 2015;46:3093-3098.
- 12 4. Vlak MH, Rinkel GJ, Greebe P, Algra A. Independent risk factors for
13 intracranial aneurysms and their joint effect: a case-control study. *Stroke*.
14 2013;44:984-987.
- 15 5. Juvela S, Poussa K, Porras M. Factors affecting formation and growth of
16 intracranial aneurysms: a long-term follow-up study. *Stroke*. 2001;32:485-491.
- 17 6. Wermer MJ, van der Schaaf IC, Velthuis BK, Algra A, Buskens E, Rinkel GJ.
18 Follow-up screening after subarachnoid haemorrhage: frequency and
19 determinants of new aneurysms and enlargement of existing aneurysms.
20 *Brain*. 2005;128:2421-2429.
- 21 7. Wang JY, Smith R, Ye X, Yang W, Caplan JM, Radvany MG, et al. Serial
22 Imaging Surveillance for Patients With a History of Intracranial Aneurysm:
23 Risk of De Novo Aneurysm Formation. *Neurosurgery*. 2015;77:32-42.

- 1 8. Kim T, Lee H, Ahn S, Kwon OK, Bang JS, Hwang G, et al. Incidence and risk
2 factors of intracranial aneurysm: A national cohort study in Korea. *Int J*
3 *Stroke*. 2016;11:917-927.
- 4 9. Holmen J, Midthjell K, Krüger Ø, Langhammer A, Holmen TL, Bratberg GH,
5 et al. The Nord-Trøndelag Health Study 1995-97 (HUNT 2): Objectives,
6 contents, methods and participation. *Norwegian Journal of Epidemiology*.
7 2003;13:19-32.
- 8 10. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, et
9 al. Cohort Profile: the HUNT Study, Norway. *Int J Epidemiol*. 2013;42:968-
10 977.
- 11 11. Sandvei MS, Romundstad PR, Muller TB, Vatten L, Vik A. Risk factors for
12 aneurysmal subarachnoid hemorrhage in a prospective population study: the
13 HUNT study in Norway. *Stroke*. 2009;40:1958-1962.
- 14 12. Sandvei MS, Mathiesen EB, Vatten LJ, Muller TB, Lindekleiv H, Ingebrigtsen
15 T, et al. Incidence and mortality of aneurysmal subarachnoid hemorrhage in
16 two Norwegian cohorts, 1984-2007. *Neurology*. 2011;77:1833-1839.
- 17 13. Haberg AK, Hammer TA, Kvistad KA, Rydland J, Muller TB, Eikenes L, et
18 al. Incidental Intracranial Findings and Their Clinical Impact; The HUNT
19 MRI Study in a General Population of 1006 Participants between 50-66 Years.
20 *PLoS One*. 2016;11:e0151080.
- 21 14. Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, et al.
22 Risk factors for subarachnoid hemorrhage: an updated systematic review of
23 epidemiological studies. *Stroke*. 2005;36:2773-2780.

- 1 15. Jorgensen JT, Andersen JS, Tjonneland A, Andersen ZJ. Determinants related
2 to gender differences in general practice utilization: Danish Diet, Cancer and
3 Health Cohort. *Scand. J. Prim. Health Care*. 2016;34:240-249.

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1 **Table 1** Risk factors for unruptured intracranial aneurysms and aneurysmal
 2 subarachnoid hemorrhage in the HUNT population

	Unruptured intracranial aneurysms		Subarachnoid hemorrhage	
	No cases/No participants *	HR (95% CI) adjusted†	No cases/No participants *	HR (95% CI) adjusted†
Sex				
Male	23/39,402	1	36/39,402	1
Female	69/44,308	2.8 (1.7-4.5)	75/44,308	1.8 (1.2-2.7)
Smoking				
Never	17/36,423	1	27/36,423	1
Former	19/21,574	1.7 (0.9-3.3)	17/21,574	1.0 (0.5-1.9)
Current	56/25,713	4.1 (2.4-7.1)	67/26,713	3.4 (2.2-5.4)
P for trend		<0.001		<0.001
Systolic blood pressure, mmHg				
<120	23/19,796	1	18/19,796	1
120-129	20/17,646	1.0 (0.6-1.9)	20/17,646	1.3 (0.7-2.5)
130-139	13/16,449	0.8 (0.4-1.5)	23/16,449	1.8 (0.9-3.3)
140-159	25/18,497	1.3 (0.7-2.4)	34/18,497	2.4 (1.3-4.4)
≥160	11/11,061	1.1 (0.5-2.5)	16/11,061	2.1 (1.0-4.4)

P for trend		0.62		0.006
Diastolic blood pressure, mmHg				
<70	13/18,689	1	15/18,689	1
70-79	29/26,333	1.2 (0.6-2.3)	22/26,333	0.8 (0.4-1.6)
80-89	27/22,339	1.3 (0.6-2.5)	40/22,339	1.8 (1.0-3.3)
90-99	14/11,006	1.4 (0.6-3.1)	23/11,006	2.2 (1.1-4.5)
≥100	9/5,080	2.2 (0.9-5.4)	11/5,080	2.5 (1.1-5.7)
P for trend		0.11		<0.001

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2 Abbreviations: CI=confidence interval; HR=hazard ratio

3 *Participants with non-missing on included covariates †Adjusted for attained age, sex

4 and smoking

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1 **Figure legends**

2 **Figure 1**

3 Numbers of detected UIAs per year

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7 **Figure 2**

8 Risk of UIA and aSAH according to systolic blood pressure