Supplementary file

The impact of risk factor trends on intracerebral hemorrhage incidence over the last two decades. The Tromsø Study.

Supplemental methods

Risk factors

Blood pressure was measured using an automatic device with three recordings separated by a 1-minute interval, after a 2-minute seated rest. The mean value of the two last recordings was used in the present study. Weight was measured with light clothing and no footwear, and height was measured in standing position. BMI was calculated as weight divided by the square of height (kg/m^2) . Diabetes mellitus was self-reported in questionnaires by answering the question: Do you have, or have you had diabetes mellitus?

Smoking was defined as daily current smoker (cigarettes and/or pipe and/or cigarillos/cigars). Alcohol consumption was categorised as teetotalism, moderate alcohol consumption (1-7 glasses per week in women, 1-14 glasses per week in men) and high alcohol consumption (>7 glasses per week in women, >14 glasses per week in men). However, questions concerning the amount of alcohol intake differed between the surveys. Because of this, analyses of the association between the amount of alcohol intake and risk of ICH were based on answers from questionnaires in the surveys performed in 1994-95 and in 2001, whereas analysis of trends in alcohol intake was limited to teetotalism yes/no.

Physical activity was defined as strenuous leisure physical activity (i.e. become sweaty and out of breath) for at least 1 hour per week. It was self-reported in the questionnaires; in 1994-95 and in 2001 by answering the following questions: "How has your physical activity in leisure time been during this last year? Think of your weekly average for the year. Time spent going to work count as leisure time." "Light activity (not sweating or out of breath): and "Hard physical activity (sweating/out of breath)". For both questions, response categories were: Hours per week: 1) None, 2) < 1 hour, 3) 1-2 hours, 4) 3 or more hours per week. In 2007-08 the questions were: "How often do you exercise (e.g. walking, skiing, swimming or work out/do sports?", response categories: 1) Never; 2) Less than once a week; 3) Once a week; 4) 2-3 times a week 5) almost daily "If you exercise – how hard do you exercise in average?", response categories: 1) Easy – you do not become out of breath or sweaty; 2) You become out of breath or sweaty; 3) Hard - you become exhausted, "For how long time do you exercise in average?", response categories: 1) Less than 15 minutes; 2) 15-29 minutes; 3) 30-60 minutes; 4) More than 1 hour. Use of blood pressure-lowering drugs at attendance was self-reported in questionnaires by answering the following question: Do you use blood pressure-lowering drugs? Response categories: 1) Now, 2) Previously, but not now, 3) Never. Use of lipid-lowering drugs was self-reported in questionnaires by answering the following question: Have you during the last 14 days used lipid lowering drugs? Response categories: 1) Yes 2) No. In 1994-95 this question was limited to individuals aged <70 years, and information from additional lists of the brand names of medication used on a regular basis was available only for participants aged 55-74 years and selected 5-10% samples of participants aged 25-54 and 75-85 years. A comparison of self-reported use of LLD in Tromsø 6 against data from the prescription database 6 months prior to the survey showed a kappa value of 0.94 (95% CI 0.93-0.95), a sensitivity of 98% and a specificity of 99% (Anne Elise Eggen, personal communication).

Anticoagulants were defined as use of vitamin-K antagonists, novel oral anticoagulants, treatment with high dose heparin or high dose low molecular weighted heparin, or thrombolytic treatment of indications other than IS.

Identification of ICH events and location of ICH

Cases were retrieved by searching for International Classification of Disease (ICD) versions 8 and 9 diagnosis codes 430-438 and ICD 10 diagnosis codes I60-I69. In addition, systematic text searches were made for the words "stroke", "ischemic stroke" and "intracerebral hemorrhage" in the medical records of all participants with ICD 8-10 diagnosis codes 410-414 and I20-I25, 798/R96, R98 and 799/R99.

All CT and MRI scans were assessed by a senior consultant in neurology (MC). In cases where radiologic examinations were not available (n=35), location was assessed by radiology reports and/or autopsy reports. In uncertain cases, the scans were additionally validated by a neuroradiologist (LHJ) at the University Hospital of Northern Norway, and consensus made in cooperation with a senior consultant in neurology (EBM). Location of ICH was categorised as lobar, non-lobar (deep/infratentorial), uncertain and other location (intraventricular or located to the corpus callosum). Uncertain ICH was further categorised as probably lobar, probably deep, and holohemispheric. In analyses stratified on location, probable lobar and probable deep ICHs were included in the analyses as lobar and non-lobar ICH, respectively. Cases with multiple ICHs affecting solely lobar (n=7) or nonlobar (n=3) regions were categorised according to location. Multiple ICHs affecting both regions (n=1), ICH located to the corpus callosum (n=2), intraventricular ICH (n=3), holohemispheric ICH (n=13) and ICH with missing location (the radiologic examination and radiologic report were not available at the time of the retrospective assessment) (n=1) were included in analyses of ICH overall, but excluded from analyses stratified on location. All ratings were performed blinded for risk factors.

 $Table\ I.\ Age\ span\ and\ attendance\ rates\ of\ eligible\ participants, and\ age-\ and\ sex\ distribution\ of\ attendees\ and\ non-attendees,$ by year of survey. The Tromsø Study 1994-2008.

		Men			Women				
		Attendees		Non-att	endees	Attendees		Non-att	endees
	Age group	n*	Mean age	n*	Mean age	n*	Mean age	n*	Mean age
	(Years)	$(\%)^{\dagger}$	(Years)		(Years)	$(\%)^{\dagger}$	(Years)		(Years)
Tromsø 4 (1994-95)	25-97	12,865 (69.6)	46.6	5615	40.9	14,293 (74.9)	47.2	4785	44.1
Tromsø 5 (2001)	30-89	3511 (75.7)	59.9	1125	46.0	4619 (80.8)	59.4	1098	50.8
Tromsø 6 (2007-08)	30-87	6054 (62.9)	57.5	3571	54.4	6930 (68.4)	57.5	3207	58.1

^{*}Number of subjects.

†Attendance rate

Table IIa. Crude baseline characteristics of participants with and without incident intracerebral hemorrhage (ICH) stratified by sex. The Tromsø Study.

	No ICH		ICH	
	Men N=13,250	Women N=14,698	Men N=123	Women N=96
Age, years	48.2 (13.0)	48.7 (14.1)	61.5 (11.4)	66.5 (12.0)
Systolic blood pressure, mm Hg	136.7 (17.8)	131.5 (23.1)	154.0 (22.8)	157.4 (26.6)
Diastolic blood pressure, mm Hg	80.6 (11.4)	76.6 (12.5)	91.1 (12.8)	86.3 (17.6)
Hypertension [†]	40.6 (5386)	31.6 (4640)	80.5 (99)	80.2 (77)
Total cholesterol, mmol/L	6.1 (1.2)	6.0 (1.4)	6.3 (1.1)	6.9 (1.3)
Triglycerides, mmol/L	1.79 (1.2)	1.36 (0.9)	1.69 (1.1)	1.64 (0.8)
HDL-cholesterol, mmol/L	1.34 (0.4)	1.63 (0.4)	1.40 (0.3)	1.64 (0.4)
Body mass index kg/m ²	25.9 (3.5)	25.1 (4.4)	26.6 (3.9)	25.8 (4.1)
Diabetes mellitus	2.1 (274)	2.1 (301)	3.3 (4)	2.1 (2)
Daily smoking	35.4 (4688)	34.4 (5059)	29.3 (36)	29.2 (28)
Teetotalism	8.5 (1125)	16.2 (2385)	11.4 (14)	35.4 (34)
Physical activity [‡]	35.9 (4753)	24.8 (3648)	30.9 (38)	10.4 (10)
Use of blood pressure-lowering drugs	7.0 (933)	7.0 (1024)	16.3 (20)	16.7 (16)
Use of lipid-lowering drugs	1.9 (248)	1.2 (174)	2.4 (3)	2.1 (2)

^{*}Continuous variables are presented as mean (SD), categorical variables are presented as % (n)

[†]Systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or use of blood pressure-lowering drugs

[‡]Strenuous leisure physical activity >1 hour/week

Table IIb. Crude baseline characteristics of participants with and without incident intracerebral hemorrhage (ICH) stratified by age. The Tromsø Study.

	No ICH		ICH	
	<75 years N= 26,457	≥75 years N=1491	<75 years N=179	≥75 years N=40
Age, years	46.8 (11.7)	79.4 (3.9)	60.3 (10.3)	79.0 (3.2)
Male sex	48.0 (12,696)	37.2 (554)	61.5 (110)	32.5 (13)
Systolic blood pressure, mm Hg	132.4 (19.6)	160.9 (25.1)	152.5 (23.2)	168.7 (26.1)
Diastolic blood pressure, mm Hg	78.1 (11.8)	85.4 (15.4)	88.7 (14.4)	90.5 (18.7)
Hypertension [†]	33.2 (8788)	83.0 (1238)	76.5 (137)	97.5 (39)
Total cholesterol, mmol/L	6.0 (1.3)	6.7 (1.4)	6.7 (1.3)	6.6 (1.2)
Triglycerides, mmol/L	1.55 (1.04)	1.74 (1.06)	1.69 (1.02)	1.58 (0.69)
HDL-cholesterol, mmol/L	1.49 (0.41)	1.53 (0.45)	1.49 (0.37)	1.58 (0.52)
Body mass index kg/m ²	26.1 (4.3)	25.5 (4.0)	26.5 (4.1)	26.2 (3.9)
Diabetes mellitus	1.7 (446)	8.7 (129)	2.2 (4)	5.0(2)
Daily smoking	36.0 (9522)	15.1 (225)	34.1 (61)	7.5 (3)
Teetotalism	10.8 (2861)	45.5 (649)	16.2 (29)	47.5 (19)
Physical activity [‡]	31.4 (8319)	5.5 (82)	25.1 (45)	7.5 (3)
Use of blood pressure-lowering drugs	6.2 (1638)	21.4 (319)	12.8 (23)	32.5 (13)
Use of lipid-lowering drugs	1.5 (403)	1.3 (19)	2.8 (5)	0.0(0)

^{*}Continuous variables are presented as mean (SD), categorical variables are presented as % (n)

[†]Systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or use of blood pressure-lowering drugs

[‡]Strenuous leisure physical activity >1 hour/week

Table III. Hazard ratios $(HR)^*$ for incident intracerebral hemorrhage according to location, by risk factors[†]. The Tromsø Study.

	Lobar (n=88)		Non-lobar (n=111)		
	HR (95% CI) Model 1 [‡]	HR (95% CI) Model 2 [‡]	HR (95% CI) Model 1 [‡]	HR (95% CI) Model 2 [‡]	
Age	2.59 (2.09-3.22)	2.22 (1.71-2.89)	2.49 (2.06-3.01)	1.80 (1.42-2.29)	
Male sex	1.37 (0.90-2.09)	1.37 (0.86-2.18)	2.06 (1.40-3.02)	2.42 (1.57-3.73)	
Systolic blood pressure	1.28 (1.04-1.57)	1.29 (1.05-1.59)	1.82 (1.53-2.16)	1.82 (1.52-2.17)	
Diastolic blood pressure	1.22 (1.01-1.47)	1.22 (1.01-1.48)	1.85 (1.61-2.13)	1.89 (1.64-2.19)	
Hypertension§	1.89 (1.12-3.18)	1.91 (1.12-3.25)	4.71 (2.71-8.19)	5.08 (2.86-9.01)	
Total cholesterol	1.17 (0.95-1.44)	1.18 (0.95-1.45)	1.26 (1.04-1.51)	1.14 (0.94-1.39)	
HDL-cholesterol	0.91 (0.73-1.14)	0.86 (0.68-1.09)	1.21 (0.93-1.36)	1.07 (0.88-1.31)	
Triglycerides	1.08 (0.89-1.30)	1.04 (0.84-1.29)	1.03 (0.86-1.24)	0.96 (0.78-1.18)	
Body mass index	0.92 (0.74-1.15)	0.84 (0.66-1.07)	1.02 (0.84-1.24)	0.90 (0.72-1.12)	
Diabetes mellitus	0.81 (0.25-2.57)	0.82 (0.26-2.63)	0.44 (0.11-1.80)	0.46 (0.11-1.87)	
Daily smoking	1.15 (0.72-1.84)	1.06 (0.65-1.74)	1.05 (0.69-1.60)	1.10 (0.71-1.71)	
Teetotalism	1.16 (0.69-1.96)	1.11 (0.65-1.90)	1.16 (0.72-1.88)	1.13 (0.69-1.85)	
Physical activity	0.85 (0.50-1.46)	0.89 (0.52-1.53)	1.08 (0.69-1.68)	1.11 (0.71-1.75)	

^{*}Hazard ratios are expressed per SD increase in continuous variables

[†]Updated at the date of attendance in the subsequent survey(s) in individuals who were still free of ICH

[‡]Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, SBP (except for hypertension and DBP) total cholesterol, high-density lipoprotein cholesterol (HDL-cholesterol) (except for triglycerides), body mass index (BMI), diabetes mellitus (DM), daily smoking, teetotalism and physical activity

[§]Systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg and/or use of blood pressure-lowering drugs

Strenuous leisure physical activity >1 hour/week

Table IVa. Cardiovascular risk factor levels in men by survey year. The Tromsø Study.

	1994-1995	2001	2007-2008	Relative change from	P-value*
	n=11,235	N=3457	N=6034	1994 to 2008 (%)	
Age	46.9 (46.7-47.2)	54.0 (53.6-54.5)	58.8 (58.3-59.2)		
Systolic blood pressure, mm Hg	140.5 (140.1-140.8)	136.0 (135.1-136.9)	136.1 (135.2-136.9)	-3	< 0.001
Diastolic blood pressure, mm Hg	82.0 (81.8-82.2)	80.0 (79.5-80.6)	80.0 (79.5-80.5)	-2	< 0.001
Hypertension [†]	49.1 (48.1-49.8)	43.5 (40.7-46.3)	47.1 (44.4-49.7)	-4	< 0.001
Total cholesterol, mmol/L	6.23 (6.21-6.25)	5.90 (5.84-5.96)	5.41 (5.36-5.47)	-13	< 0.001
HDL-cholesterol, mmol/L	1.37 (1.36-1.38)	1.30 (1.29-1.32)	1.33 (1.32-1.35)	-3	< 0.001
Triglycerides, mmol/L	1.77 (1.75-1.79)	1.72 (1.66-1.78)	1.71(1.65-1.76)	-4	< 0.001
BMI, kg/m ²	25.8 (25.7-25.8)	26.6 (26.5-26.7)	27.1 (26.9-27.2)	5	< 0.001
Diabetes mellitus	1.9 (1.6-2.2)	2.6 (2.0-3.5)	4.2 (3.2-5.5)	123	< 0.001
Daily smoking	36.0 (35.1-37.0)	31.2 (29.0-33.5)	21.6 (20.0-23.4)	-40	< 0.001
Teetotalism	9.6 (9.0-10.1)	6.8 (5.8-7.9)	6.5 (5.6-7.5)	-32	< 0.001
Physical activity [‡]	31.5 (30.6-32.4)	44.8 (41.7-47.8)	46.9 (44.1-49.8)	49	< 0.001
Use of blood pressure lowering drugs	6.2 (5.8-6.7)	11.1 (9.5-13.0)	15.6 (13.5-17.9)	150	< 0.001
Use of lipid lowering drugs	1.1 (0.9-1.3)	7.6 (5.4-10.5)	11.4 (8.4-15.5)	970	< 0.001
Use of antithrombotic drugs ^{§,}	3.8 (3.3-4.3)	6.6 (5.2-8.4)	9.2 (7.3-11.5)	144	< 0.001
Use of antiplatelets	3.3 (2.9-3.8)	6.1 (4.7-7.9)	8.0 (6.2-10.2)	139	< 0.001
Use of anticoagulants	0.8 (0.6-1.0)	1.0 (0.6-1.7)	1.5 (0.9-0.2.7)	102	< 0.001

Continuous variables are age- adjusted means with 95% CI. Categorical variables are age-adjusted prevalence (%) with 95% CI

^{*}Test for linear trend

[†]Systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg and/or use of blood pressure-lowering drugs

[‡] Strenuous leisure physical activity ≥1 hour per week

[§] Use of antiplatelets and/or anticoagulants

Calculated in the attendees of the second visit of the survey in 1994-1995 (n=3 331), and in all attendees of the surveys in 2001 and 2007-2008

Table IVb. Cardiovascular risk factor levels in women by survey year. The Tromsø Study.

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	1994-1995	2001	2007-2008	Relative change from	P-value*
	N=12,348	N=4559	N=6910	1994 to 2008 (%)	
Age	47.8 (47.5-48.0)	54.6 (54.1-55.1)	58.8 (58.3-59.3)		
Systolic blood pressure, mm Hg	138.2 (137.7-138.5)	131.8 (131.0-132.7)	131.0 (130.2-131.8)	-5	< 0.001
Diastolic blood pressure, mm Hg	78.8 (78.6-79-0)	77.3 (76.8-77.8)	73.8 (73.3-74.3)	-6	< 0.001
Hypertension [†]	39.5 (38.4-40.6)	33.3 (30.8-35.8)	36.2 (33.7-38.7)	-9	< 0.001
Total cholesterol, mmol/L	6.36 (6.34-6.38)	6.02 (5.97-6.07)	5.52 (5.47-5.57)	-13	< 0.001
HDL-cholesterol, mmol/L	1.65 (1.64-1.66)	1.54 (1.52-1.55)	1.63 (1.61-1.65)	-1	< 0.001
Triglycerides, mmol/L	1.43 (1.42-1.45)	1.38 (1.34-1.42)	1.36 (1.32-1.40)	-5	< 0.001
BMI, kg/m^2	25.3 (25.2-25.4)	26.1 (25.9-26.2)	26.2 (26.0-26.3)	3	< 0.001
Diabetes mellitus	1.8 (1.5-2.0)	2.2 (1.6-2.9)	3.2 (2.4-4.2)	80	< 0.001
Daily smoking	33.2 (32.3-34.1)	30.8 (28.9-32.7)	23.7 (22.1-25.4)	-29	< 0.001
Teetotalism	18.2 (17.5-18.9)	11.1 (10.0-12.4)	10.3 (9.3-11.4)	-43	< 0.001
Physical activity [‡]	16.9 (16.2-17.6)	30.5 (27.7-33.5)	42.1 (39.2-45.2)	149	< 0.001
Use of blood pressure lowering drugs	5.6 (5.2-6.0)	10.1 (8.7-11.8)	15.0 (13.1-17.1)	170	< 0.001
Use of lipid lowering drugs	0.6 (0.5-0.8)	4.8 (3.3-7.1)	7.9 (5.4-11.3)	1134	< 0.001
Use of antithrombotic drugs ^{§,}	1.5 (1.2-1.8)	2.9 (2.1-4.1)	4.2 (3.0-5.9)	184	< 0.001
Use of antiplatelets	1.3 (1.1-1.6)	2.7 (1.8-3.9)	3.7 (2.6-5.4)	188	< 0.001
Use of anticoagulants	0.3 (0.2-0.4)	0.4 (0.2-0.8)	0.5 (0.2-1.2)	105	< 0.001

Continuous variables are age-adjusted means with 95% CI. Categorical variables are age-adjusted prevalence (%) with 95% CI

^{*}Test for linear trend

[†]Systolic BP \geq 140 mm Hg and/or diastolic BP \geq 90 mm Hg and/or use of blood pressure-lowering drugs ‡ Strenuous leisure physical activity \geq 1 hour per week

[§] Use of antiplatelets and/or anticoagulants

Calculated in the attendees of the second visit of the survey in 1994-1995 (n=3 442), and in all attendees of the surveys in 2001 and 2007-2008

Table Va. Odds ratios (OR) for use of antithrombotic drugs at time of first-ever intracerebral hemorrhage by time period. The Tromsø Study.

	1994-2013	1994-2001	2002-2007	2008-2013	P for trend*
	n=219	n=59	n=72	n=88	
Antithrombotic drugs ^{†‡}	110 (50)	23 (39)	37 (51)	50 (57)	
OR (95% CI) §		1	1.53 (0.73-3.22)	1.84 (0.90-3.76)	0.10
Antiplatelets [†]	61 (28)	12 (20)	19 (26)	30 (34)	
OR (95% CI) §		1	1.29 (0.55-2.98)	1.80 (0.82-3.96)	0.13
Anticoagulants [†]	55 (25)	11 (19)	18 (25)	26 (30)	
OR (95% CI) §		1	1.34 (0.57-3.17)	1.65 (0.73-3.76)	0.23

^{*}P-value for linear trend

[†]Numbers are n (%)

[‡]Antiplatelets and/or anticoagulants

[§]Adjusted for age and sex

Table Vb. Odds ratios (OR) for use of antithrombotic drugs in men and women at time of intracerebral hemorrhage (ICH) by time period. The Tromsø Study.

	1994-2013	1994-2001	2002-2007	2008-2013	P for trend*
Men	n=123	n=30	n=39	n=54	
Antithrombotic drugs ^{†‡}	72 (59)	15 (50)	23 (59)	34 (63)	
OR (95% CI)§		1	1.13 (0.41-3.13)	1.60 (0.60-4.23)	0.32
Antiplatelets [†]	41 (33)	9 (30)	12 (31)	20 (37)	
OR (95% CI)§		1	0.92 (0.32-2.62)	1.24 (0.47-3.28)	0.66
Anticoagulants [†]	35 (28)	6 (20)	11 (28)	18 (33)	
OR (95% CI)§		1	1.44 (0.46-4.51)	1.83 (0.63-5.32)	0.26
Women	n=96	n=29	n=33	n=34	
Antithrombotic drugs ^{†‡}	38 (40)	8 (28)	14 (42)	16 (47)	
OR (95% CI)§		1	2.12 (0.70-6.39)	2.24 (0.76-6.60)	0.16
Antiplatelets [†]	20 (21)	3 (10)	7 (21)	10 (29)	
OR (95% CI)§		1	2.47 (0.55-11.0)	3.51 (0.83-14.8)	0.09
Anticoagulants [†]	20 (21)	5 (17)	7 (21)	8 (24)	
OR (95% CI)§		1	1.34 (0.37-4.84)	1.42 (0.41-4.94)	0.60

^{*}P-value for linear trend

[†]Numbers are n (%) ‡Antiplatelets and/or anticoagulants §Adjusted for age

Table VI. Incidence rates (IR) and incidence rate ratios (IRR) of incident intracerebral hemorrhage in 1995-2013. The Tromsø study.

	Crude IR (95% CI)	Adjusted IR* (95% CI)	IRR (95% CI) [†]
All	0.55 (0.48-0.63)	0.60 (0.52-0.68)	0.81 (0.52-1.27)
Men	0.66 (0.55-0.79)	0.80 (0.64-0.96)	1.27 (0.69-2.31)
Women	0.45 (0.37-0.56)	0.46 (0.36-0.55)	0.46 (0.23-0.90)
<75 years	0.31 (0.25-0.37)	0.30 (0.24-0.36)	0.89 (0.48-1.66)
≥75 years	2.45 (2.04-2.96)	2.50 (2.02-2.98)	0.78 (0.41-1.48)
Lobar ICH	0.22 (0.18-0.27)	0.24 (0.19-0.29)	1.36 (0.67-2.79)
Men	0.24 (0.18-0.33)	0.30 (0.21-0.40)	1.58 (0.58-4.29)
Women	0.20 (0.15-0.28)	0.20 (0.14-0.26)	1.17 (0.42-3.26)
Non-lobar ICH	0.28 (0.23-0.34)	0.31 (0.25-0.36)	0.71 (0.38-1.33)
Men	0.36 (0.28-0.46)	0.44 (0.32-0.56)	1.34 (0.60-3.02)
Women	0.20 (0.15-0.28)	0.21 (0.15-0.27)	0.26 (0.09-0.71)

^{*}Adjusted to age and sex by the direct method using the European standard population of 2013 as reference †Incidence rates in 2013 compared with 1995, adjusted for age and sex