Declining Incidence of Ischemic Stroke

What Is the Impact of Changing Risk Factors? The Tromsø Study 1995 to 2012

Anne M. Vangen-Lønne, MD; Tom Wilsgaard, PhD; Stein Harald Johnsen, MD, PhD; Maja-Lisa Løchen, MD, PhD; Inger Njølstad, MD, PhD; Ellisiv B. Mathiesen, MD, PhD

Background and Purpose—It is proposed that 20% to 40% of the decline in first-ever stroke incidence is attributed to the improvement of risk factor control. We estimated the impact of modifiable cardiovascular risk factors on the changing incidence of ischemic stroke (IS) between 1995 and 2012, using individual person data from repeated surveys in a general population.

Methods—The proportion of the IS incidence decline explained by change in each risk factor over time was estimated from 1995 to 2012 by Poisson regression among 26 329 participants who attended the fourth Tromsø survey in 1994 to 1995. Hazard ratios for IS were estimated with Cox proportional hazards regression among 27 936 participants who attended at least 1 of the Tromsø surveys in 1994 to 1995, 2001, or 2007 to 2008. Age- and sex-adjusted means or prevalences of risk factors over time were estimated by generalized estimating equations.

Results—There were 1226 first-ever IS during 367 636 person-years of follow-up. Changes in cardiovascular risk factors accounted for 57% of the decrease in IS incidence from 1995 to 2012. The most important contributors were decreasing mean systolic blood pressure and smoking prevalence, accounting for 26% and 17% of the observed decline, respectively. Conversely, increasing diabetes mellitus prevalence contributed negatively to the declining IS incidence.

Conclusions—Changes in cardiovascular risk factors explained 57% of the decrease in IS incidence from 1995 to 2012. Reduction in systolic blood pressure and prevalence of smoking were the most important contributors. **(*Stroke*. 2017;48:544-550. DOI: 10.1161/STROKEAHA.116.014377.)**

Key Words: cohort study ■ epidemiology ■ ischemic stroke ■ risk factors ■ time trends

The age-standardized stroke mortality rates have declined worldwide during the last decades, though the absolute number of stroke survivors and number of new strokes each year are increasing.[1] The decline in stroke mortality is a result of declining stroke incidence, as well as reduced case fatality. Although changes in case fatality reflect the severity of stroke, as well as treatment, changes in stroke incidence mirror the changes in risk factors for stroke over time and the implementation of primary prevention.[2,3]

Identification of modifiable lifestyle and risk factors remains critical for stroke prevention. It is proposed that 20% to 40% of the decrease in first-ever stroke incidence is attributed to the improvement of risk factor control.[3] Nevertheless, at population level, a combined risk score of trends in systolic blood pressure (BP), daily cigarette smoking, serum cholesterol, and body mass index (BMI) explained only a small proportion of stroke incidence decrease between 1982 and 1995.[4] Several studies have estimated population-attributable risks (PARs) for the association of ischemic stroke (IS) with cardiovascular risk factors.[5–7] Most studies on the relationship between the changes in risk factors over time and alterations of stroke incidence based their estimates on ecological data or mathematical modeling of aggregated data.[4,8,9] Fewer studies used individual person data from repeated surveys to assess how the changing trends in IS incidence are associated with changes in modifiable cardiovascular risk factors.[10–12] Some of these studies were limited to subgroups of age[11] or did not study out-of-hospital strokes.[12]

In the present study, we estimate the impact of modifiable risk factors on the changing incidence of IS between 1995 and 2012, using individual person data from repeated surveys in a general population.

Methods

Study Population

In the Tromsø Study, 6 surveys have been conducted between 1974 and 2008, referred to as Tromsø 1–6.[13] The municipality of Tromsø

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From the Departments of Clinical Medicine (A.M.V.-L., S.H.J., E.B.M.) and Community Medicine (T.W., M.-L.L., I.N.), The Arctic University of Norway, Tromsø; Department of Neurology, Innlandet Hospital Trust, Norway (A.M.V.-L.); and Department of Neurology, University Hospital of North Norway, Tromsø (S.H.J., E.B.M.).

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Correspondence to Anne M. Vangen-Lønne, MD, Department of Clinical Medicine, The Arctic University of Norway, Tromsø, Norway. E-mail am.vanglon@gmail.no

is located in the northern part of Norway, and the vast majority of the population is white. The fourth, fifth, and sixth Tromsø surveys were conducted in 1994 to 1995, 2001, and 2007 to 2008 with attendance rates of 72%, 79%, and 66%, respectively. The age and sex distribution of attendees and nonattendees are presented in Table I in the online-only Data Supplement. Participation was voluntary, and each participant gave written, informed consent to medical research. The Data Inspectorate of Norway and the Regional Committee for Medical Research Ethics approved the study.

Eligible for this study were men and women registered as inhabitants in Tromsø at the date of participation in ≥1 of the Tromsø 4, 5, or 6 surveys and aged ≥30 years at baseline or during follow-up (n=28 216). We excluded participants with prevalent confirmed IS (n=217) or unclassifiable stroke (n=57) at baseline. Participants with intracerebral or subarachnoid hemorrhage were not excluded. We further excluded those who during follow-up had an incident IS preceded by an incident unclassifiable stroke (n=6), leaving 27 936 persons for inclusion in the study (14 697 women and 13 239 men).

Cardiovascular Risk Factors

Each survey applied a standardized, almost identical protocol with physical examination, blood samples, and self-administered questionnaires.[13] Hypertension was defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or use of BP-lowering medication. BMI was calculated as weight divided by the square of height (kg/m^2). Overweight was defined as BMI ≥25 to <30 kg/m^2 and obesity as BMI ≥30 kg/m^2. Hyperlipidemia was defined as total cholesterol/high-density lipoprotein (HDL) ratio >5. Attendees were defined as physically active if they reported performance of strenuous physical activity (ie, became breathless and sweaty) at least 1 hour/week. Smoking status, diabetes mellitus, and use of BP-lowering or lipid-lowering drugs were collected from questionnaires (see Methods in the online-only Data Supplement for details).

Ascertainment of Incident Cases of Ischemic Stroke

We identified possible hospitalized and out-of-hospital stroke events through linkage of the national unique 11-digit identification number to The National Causes of Death Registry, the Population Registry of Norway, and the discharge diagnosis registry (outpatient diagnoses included) at the University Hospital of North Norway, which is the only hospital in the Tromsø area. Medical charts, death certificates, autopsy reports, and information from additional sources, such as records from nursing homes, general practitioners, and ambulance services, were used for validation.

IS was defined as rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting ≥24 hours or leading to death with no apparent cause other than vascular origin, when computed tomography, magnetic resonance imaging, or autopsy had ruled out intracerebral or subarachnoid hemorrhage.[14] Follow-up was assigned from the first date of entry to Tromsø 4, Tromsø 5, or Tromsø 6 to the date of first ever IS, emigration from Tromsø, death, or through December 31, 2012, whichever came first.

Statistical Analysis

We analyzed the data with the statistical software STATA, version 13 (Stata Corp LP TX) and SAS 9.4 (SAS Institute, Cary, NC). We applied generalized estimating equations to estimate age- and sex-adjusted means or prevalence of risk factors over time, accounting for dependencies between repeated observations. The identity link function was used for continuous variables and the logit link function for categorical variables. The estimates were calculated for participants aged 40 to 79 years, including the mean values for age and sex (56.8 years and 46.8% male) in the regression models. Supplemental generalized estimating equation analyses were performed for the whole cohort aged ≥30 years (n=27 936) and for the predefined age strata 30 to 49 years and ≥50 years. Additional generalized estimating equation analyses were done to estimate the prevalence of BP-lowering and lipid-lowering drug users over time.

Hazard ratios of IS were estimated for the different cardiovascular risk factors with Cox proportional hazards regression. For attendees who participated in >1 survey and who were still free of IS, cardiovascular risk factors were updated at the date of subsequent examinations.[15] Hazard ratios were adjusted for age and sex (model 1) and were additionally adjusted for systolic BP, cholesterol, HDL, daily smoking, BMI, diabetes mellitus, and physical activity (model 2). The proportional hazard assumption was verified by Schoenfeld residuals and log–log survival plots.

Incidence analyses were based on the participants of Tromsø 4 in 1994 to 1995 (n=26 329). The split function in STATA was used to make a new record for each year of follow-up for each person, and age was updated every year the attendees were under follow-up. We estimated crude incidence rates as the number of events per 100 000 person-years. Time trends in incidence were standardized by age and sex using the Tromsø population in 2007 as the standard population. A symmetrical moving average with a span of 5 was applied. By this, we calculated the average of the first 2 lagged values, the current value, and the 2 forward values, before moving ahead 1 year. Each term in the average was given an equal weight of 1. Linear time trends were estimated by Poisson regression.

The proportion of the IS incidence decline explained by the change in each risk factor over time could be estimated among those who attended Tromsø 4 in 1994 to 1995 without missing values of risk factors, by the expression $(\beta_0-\beta_1)/\beta_0$. The β's are time trend coefficients from Poisson regression models, where β_0 is adjusted for age and sex and the β_1 is additionally adjusted for risk factors added to the model as time-dependent covariates. End of follow-up was defined to 2001 for those who did not attend the 2001 survey and to 2007 for those who did not attend the 2007 to 2008 survey. Individuals who had an IS event were censored from the analyses at the time of their event. One thousand bootstrapped samples were selected to estimate 95% confidence interval (CI) for the explained decline. We performed supplemental Poisson regression analyses stratified by sex and by age group (<60 years and ≥60 years at baseline; this cut-off was chosen to get sufficient power in both groups). A 2-sided level of $P<0.05$ was considered statistically significant.

Results

There were 1226 first-ever IS (45% in women) during 367 636 person-years of follow-up. Mean observation time was 12.8 years (SD 6.0). Participants with incident IS had significantly higher systolic and diastolic BP at baseline, higher BMI and total cholesterol, and lower HDL cholesterol and were more often daily smokers. Women with IS had significantly higher prevalence of diabetes mellitus, were more often obese, and reported less vigorous physical activity than women without IS (Table 1).

In Cox proportional hazards regression analysis, hypertension was the strongest risk factor, with 92% increased hazard for IS (multiadjusted) in hypertensive participants (Table 2). Diabetes mellitus was associated with 80% higher risk, while the corresponding number for daily smoking was 71%. Hyperlipidemia was associated with 28% increased hazard, while obese attendees had 28% higher hazard for IS compared with those normal weighted. HDL was protective for IS, with a 22% reduced hazard ratios per 1 mmol/L increase in mean HDL. Associations that were significant in the age- and sex-adjusted model (model 1) remained significant in the multivariable adjusted model (model 2), except for overweight and physical activity.

Several cardiovascular risk factors changed favorably across the 3 surveys (Table 3; Tables II–IV in the online-only Data Supplement). Systolic and diastolic BP, total cholesterol, proportions of hypertension, hyperlipidemia, and daily smoking declined, and the proportion of participants who reported ≥1

Table 1. Age-Adjusted Baseline Characteristics* of Study Participants With and Without Incident Ischemic Stroke During Follow-Up. The Tromsø Study

	Women (n=14 697)			Men (n=13 239)		
	No Ischemic Stroke (n=14 144)	Ischemic Stroke (n=553)	*P* Value†	No Ischemic Stroke (n=12 566)	Ischemic Stroke (n=673)	*P* Value†
Age, y	48.1 (13.7)	66.7 (11.3)		47.5 (12.6)	61.7 (12.0)	
Hypertension‡	25.8 (4230)	39.0 (421)	<0.001	39.8 (4917)	54.7 (475)	<0.001
Systolic blood pressure, mm Hg	130.9 (130.6–131.2)	140.5 (138.9–142.0)	<0.001	136.5 (136.3–136.8)	142.7 (141.4–144.0)	<0.001
Diastolic blood pressure, mm Hg	76.3 (76.1–76.5)	80.7 (79.7–81.7)	0.001	80.6 (80.4–80.8)	83.7 (82.8–84.5)	<0.001
Hyperlipidemia§	15.6 (2362)	18.8 (185)	0.022	39.0 (4861)	44.8 (314)	0.003
Total cholesterol, mmol/L	6.02 (6.00–6.03)	6.12 (6.02–6.22)	0.044	6.06 (6.04–6.08)	6.22 (6.13–6.31)	0.001
HDL cholesterol, mmol/L	1.63 (1.63–1.64)	1.57 (1.54–1.61)	0.001	1.35 (1.34–1.35)	1.31 (1.28–1.33)	0.006
Daily smoking	34.7 (4886)	42.9 (178)	<0.001	35.7 (4438)	40.5 (247)	0.015
Overweight‖	30.7 (4341)	31.4 (219)	0.701	46.4 (5790)	49.2 (350)	0.158
Obesity¶	12.1 (1774)	15.2 (129)	0.013	11.5 (1444)	13.0 (90)	0.257
BMI, kg/m^2	25.1 (25.0–25.2)	25.7 (25.3–26.1)	0.001	25.9 (25.9–26.0)	26.2 (26.0–26.5)	0.021
Diabetes mellitus#	1.3 (249)	2.3 (42)	0.001	1.5 (232)	2.0 (31)	0.190
Physical activity**	24.0 (3664)	17.9 (52)	0.014	35.7 (4633)	35.5 (181)	0.917
Use of blood pressure–lowering drugs	4.2 (875)	6.8 (130)	<0.001	4.9 (796)	6.1 (108)	0.051
Use of lipid-lowering drugs	0.9 (168)	0.4 (6)	0.029	1.6 (222)	1.6 (19)	0.929

BMI indicates body mass index; CI, confidence interval; and HDL, high-density lipoprotein.

*Categorical variables are presented as % (n), continuous variables as mean (95% CI).

†*P* values for differences between participants with and without incident ischemic stroke estimated by linear and logistic regression for continuous and categorical variables, respectively.

‡Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or use of blood pressure–lowering drugs.

§Ratio of total cholesterol to HDL cholesterol >5.

‖BMI ≥25 and <30 kg/m^2.

¶BMI ≥30 kg/m^2.

#Self-reported.

**Strenuous physical activity ≥1 h/week.

hour strenuous physical activity per week enlarged. However, the prevalence of obesity and diabetes mellitus increased substantially. From Tromsø 4 (1994–95) to Tromsø 6 (2007–08), the prevalence of overweight and obesity combined increased from 51% to 61% among participants aged ≥30 years, a relative change of 20% (Table II in the online-only Data Supplement). The increase in use of BP-lowering and lipid-lowering drug users is shown in Table V in the online-only Data Supplement.

The proportions of decrease attributable to changes in risk factors are presented in Table 4. The reduction in systolic BP was the largest single contributor, accounting for 26% of the observed decline. The decreasing prevalence of daily smoking accounted for 17% and changes in HDL for 2%. Reduction of total cholesterol and increase in physical activity were associated with 12% and 5% of the declining IS incidence (not significant). In contrast, the increasing diabetes mellitus prevalence contributed negatively with 4% increase in risk, as did the change in BMI over time, which was associated with 5% increasing risk, though not significant. In the fully adjusted model, all risk factors together explained 57% of the decline in incidence of IS from 1995 to 2012. The sex-stratified analyses revealed that the reduction in systolic BP and decreasing prevalence of daily smoking contributed most to the declining IS incidence in both women and men (Tables VI and VII in the online-only Data Supplement). Age-stratified analyses (baseline age <60 years and ≥60 years) showed no differences in risk factor contribution to the IS incidence reduction (*P*=0.58) and, hence, no significant interaction by age in the fully adjusted model (Tables VIII and IX in the online-only Data Supplement). For the youngest age group (baseline age <60 years), all risk factors together explained 47% (95% CI, 17%–100%) of the decline in incidence of IS from 1995 to 2012, while the corresponding estimate for the eldest age group (baseline age ≥60 years) was 50% (95% CI, 13%–100%).

The incidence rate of IS among persons aged ≥30 years decreased from 363 per 100 000 person-years in 1995 (95% CI, 267–459) to 306 per 100 000 person-years in 2012 (95% CI, 234–379; Figure). By applying Poisson regression models, we found an average annual decline of IS incidence rate of 1.7% (95% CI, 0.6–2.8; *P* for linear trend 0.0022).

Discussion

In this study, changes in cardiovascular risk factors accounted for 57% of the decrease in incidence of IS from 1995 to 2012. The decline in systolic BP was the most important contributor to the incidence reduction.

Table 2. Hazard Ratios (HR) for First-Ever Ischemic Stroke by Updated Risk Factors. The Tromsø Study 1995 to 2012

	HR (95% CI) Model 1*	*P* Value†	HR (95% CI) Model 2‡	*P* Value†
Age (5 y)	1.56 (1.52–1.59)	<0.001	1.47 (1.43–1.51)	<0.001
Male sex	1.72 (1.54–1.93)	<0.001	1.83 (1.60–2.10)	<0.001
Hypertension§	2.00 (1.73–2.31)	<0.001	1.92 (1.63–2.25)	<0.001
Systolic blood pressure (15 mm Hg)	1.26 (1.21–1.30)	<0.001	1.26 (1.21–1.31)	<0.001
Diastolic blood pressure (15 mm Hg)	1.43 (1.35–1.52)	<0.001	1.20 (1.09–1.32)	<0.001
Hyperlipidemia‖	1.44 (1.28–1.62)	<0.001	1.28 (1.12–1.46)	0.001
Total cholesterol (1 mmol/L)	1.12 (1.07–1.18)	<0.001	1.11 (1.06–1.17)	<0.001
HDL cholesterol (1 mmol/L)	0.72 (0.62–0.83)	<0.001	0.78 (0.66–0.92)	0.003
Overweight¶	1.26 (1.11–1.44)	<0.001	1.13 (0.98–1.30)	0.105
Obesity#	1.51 (1.29–1.76)	<0.001	1.28 (1.07–1.54)	0.008
Body mass index (4 kg/m^2)	1.14 (1.08–1.20)	<0.001	1.08 (1.01–1.15)	0.018
Daily smoking	1.59 (1.41–1.80)	<0.001	1.71 (1.49–1.97)	<0.001
Diabetes mellitus**	1.78 (1.44–2.21)	<0.001	1.80 (1.42–2.29)	<0.001
Physical activity††	0.79 (0.68–0.92)	<0.003	0.87 (0.74–1.02)	0.078

BMI indicates body mass index; CI, confidence interval; and HDL, high-density lipoprotein.

*Model 1: adjusted for age and sex only.

†Model 2: adjusted for age, sex, systolic blood pressure (except for hypertension), total cholesterol and HDL cholesterol (except for hyperlipidemia), daily smoking, body mass index (except for overweight and obesity), diabetes mellitus, and physical activity.

‡*P* value for estimated β-coefficient.

§Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or use of blood pressure–lowering drugs.

‖Ratio of total cholesterol to HDL cholesterol >5.

¶BMI ≥25 to <30 kg/m^2.

#BMI ≥30 kg/m^2.

**Self-reported.

††Strenuous physical activity ≥1 h/week.

The concept of explained decline used in our analysis reflects both the proportion of the decline in risk for IS that can be attributed to specific risk factors (the PAR) and the change of each particular risk factor in this cohort during the time period of interest. We were not able to find other studies estimating the impact of risk factor contribution to changing stroke incidence by similar methodology as in our study. However, several studies have estimated PARs for the association of IS with established as well as potential risk factors.[5–7,16] A large case–control study from 22 countries found that hypertension, current smoking, abdominal obesity, diet, and physical activity accounted for 82% of the global risk of IS (PAR, 81.8%; 95% CI, 72.5–86.9).[6] In contrast to these high values of combined PAR, the population-based Rotterdam Study reported a total PAR of 55% (95% CI, 41–68) for the combined risk factors hypertension, smoking, diabetes mellitus, atrial fibrillation, coronary disease, overweight/obesity, and total cholesterol/HDL.[5] The differences in the combined PAR estimates may partly be explained by differences in selection of risk factors in the populations under study and in study design. Moreover, PARs are prone to overestimation in case–control studies because of reversed causality.

Impact of Change in Risk Factors on IS Incidence

Decline in systolic BP contributed most to the decreasing stroke incidence in our study. Hypertension is the single most important treatable risk factor for IS, with estimated PAR between 26% and 33%.[5,6,16] Globally, BP levels have decreased in the last decades, with the most pronounced decline in Western countries and in high-income groups.[17]

The decreasing prevalence of daily smoking contributed second most to the observed decline of IS, explaining 17% of the decline. Cigarette smoking is an independent risk factor for IS, associated with approximately a doubling of risk.[18] The estimated multiadjusted PARs of daily smoking for IS vary from 12% to 21%.[6,16,19] The prevalence of daily smoking among participants aged ≥30 years decreased by 34% between 1994 and 2008 (Table II in the online-only Data Supplement).

Our results showed a significant negative contribution of diabetes mellitus prevalence on the declining incidence of IS, with an explained decline of –4%. The prevalence of diabetes mellitus has increased steadily the last decades, both in developed countries and globally.[20,21] We found that the prevalence of diabetes mellitus among participants aged 40 to 79 years nearly doubled from 1994 to 1995 to 2007 to 2008. We observed a substantial increase in BMI in the same period. The increase in diabetes mellitus might also have been influenced by changing criteria for diabetes mellitus in the time period.[22]

The estimated contribution of the change in BMI on the declining incidence of IS was negative, reflecting the increasing BMI in our cohort, however, statistically nonsignificant with explained decline –5.3%. Both elevated BP, cholesterol, and glucose mediate the effects of elevated BMI, as shown in a meta-analysis of pooled data from 97 prospective cohort studies.[23]

Table 3. Cardiovascular Risk Factor Levels in Participants Aged 40 to 79 Years, by Survey Year. The Tromsø Study

Risk Factor	1994–1995 (n=16 062)	2001 (n=6896)	2007–2008 (n=11 723)	Relative Change 1994–2008, %	*P* Value*
Age, y, mean (SD)	54.5 (10.8)	61.5 (11.2)	57.2 (11.1)		<0.001
Male sex, % (n)	48.2 (7746)	43.1 (2971)	46.9 (5499)		0.008
Hypertension†	50.9 (50.1–51.8)	44.5 (43.4–45.7)	48.0 (47.0–48.9)	–6	<0.001
Systolic blood pressure, mm Hg	141.1 (140.8–141.4)	135.6 (135.2–136.0)	135.4 (135.0–135.7)	–6	<0.001
Diastolic blood pressure, mm Hg	81.9 (81.7–82.1)	80.0 (79.8–80.3)	77.9 (77.7–78.1)	–5	<0.001
Hyperlipidemia‡	31.6 (30.9–32.4)	30.4 (29.4–31.4)	17.8 (17.1–18.5)	–44	<0.001
Total cholesterol, mmol/L	6.51 (6.49–6.53)	6.11(6.08–6.13)	5.62 (5.60–5.64)	–14	<0.001
HDL cholesterol, mmol/L	1.54 (1.53–1.54)	1.44 (1.43–1.45)	1.51 (1.50–1.52)	–2	<0.001
Overweight§	41.3 (40.4–42.1)	42.9 (41.8–44.0)	43.5 (42.7–44.4)	5	<0.001
Obesity‖	13.2 (12.7–13.7)	18.3 (17.5–19.1)	18.9 (19.3–20.7)	43	<0.001
Daily smoking	34.4 (33.6–35.1)	30.9 (30.0–31.8)	22.4 (21.8–23.1)	–35	<0.001
Diabetes mellitus	2.2 (2.0–2.4)	2.6 (2.3–3.0)	4.2 (3.8–4.6)	91	<0.001
Physical activity¶	22.1 (21.4–22.8)	36.3 (35.0–37.6)	42.6 (41.6–43.6)	93	<0.001

The risk factor values (apart from age and sex) are age- and sex-adjusted means (95% confidence interval) or prevalence (%) estimated by generalized estimating equations (GEE) to account for dependencies between repeated observations. The identity link function was used for continuous variables and the logit link function for categorical variables. BMI indicates body mass index; and HDL, high-density lipoprotein.

*Test for linear trend.

†Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or use of blood pressure–lowering drugs.

‡Total cholesterol/HDL cholesterol ratio >5.

§BMI ≥25 to <30 kg/m^2.

‖BMI ≥30 kg/m^2.

¶Strenuous physical activity ≥1 h/week.

Although baseline cholesterol levels were associated with increased risk of IS in our cohort, changes in total cholesterol level did not contribute significantly to the decline in incidence of IS, despite decreasing total cholesterol during the observation period. The associations between lipids and stroke incidence are complex. Several large, observational studies have found total cholesterol to be a significant risk factor for IS.[24,25] In contrast, other studies have shown only a weak association between total cholesterol and risk of IS or no association.[26,27] Some of the explanation for this discrepancy may be because of the different associations between cholesterol level and the IS subtypes and different distributions of these subtypes in the cohorts studied.[28] In our study, we had regretfully no information regarding the distribution of IS subtypes.

This study is important because it estimates the actual contribution of risk factors changes for the decreasing incidence of IS in the population. Hence, it extends results of previous studies that found declining incidence of stroke across time, attributed to improvement of lifestyle and metabolic risk factors.[10–12]

Comparison With Previous Studies

Our results are in line with other studies from high-income countries. In a cohort based on 9152 persons aged ≥55 years from the Framingham (original and offspring) study, the age-adjusted incidence of first-ever stroke declined significantly across the time periods 1950 to 1977, 1978 to 1989, and 1990 to 2004 (30% in men, *P*=0.02; 18% in women, *P*=0.01).[11] Concurrently, the prevalence of risk factors in the study population (examined at age 65 years) improved overall, despite some divergent trends, as systolic BP, total cholesterol, prevalence of hypertension, and daily smoking declined, whereas mean BMI and diabetes mellitus prevalence (in women) worsened significantly over time. In the OxVASC study (Oxford Vascular Study), the age-standardized incidence of first-ever IS fell by 27% (*P*=0.0002) from 1981 to 2004; simultaneously, there were significant reductions in the premorbid levels of systolic BP, cholesterol, and proportions of smokers.[10] The Atherosclerosis Risk in Communities Study found a significant decrease in stroke incidence from 1987 to 2011, with an age-adjusted decrease in stroke risk by 24% (95% CI 13%–34%) per 10 years. However, the results were not consistent for participants aged <65 years. Concomitantly, the age-adjusted rates of diabetes mellitus increased, as did the rate of hypertension, while the prevalence of current smoking declined, resulting in a relatively small effect on the IS risk estimates when adjusting for time-varying risk factors and demographic variables.[29]

Implications for Primary Prevention

The adverse contribution of increasing diabetes mellitus prevalence to IS risk decline and the negative but not significant association between the BMI trend and decreasing IS risk underscore the need for expanded public-health initiatives, especially targeting these connected risk factors. By initiatives at national level, aimed to increase physical activity and optimizing nutrition, stagnation in the obesity and diabetes mellitus epidemic may be within reach, as well as beneficial effects on other components of the metabolic syndrome.

Table 4. The Decline in Risk of First Ischemic Stroke Event and Percentage of Risk Decline Accounted for by Risk Factors. The Tromsø Study 1995 to 2012

	Calendar Time β-Coefficient, per Year	Decline in Risk per Year, % (95% CI)	Decline in Risk 1995–2012,* % (95% CI)	Explained Decline by Risk Factors,† % (95% CI)‡
Model 1, age+sex adjusted	–0.0259	2.6 (1.1–4.0)	37.2 (18.7–51.6)	Ref.
Model 1, +systolic blood pressure, mm Hg	–0.0191	1.9 (0.5–3.3)	29.1 (8.1–45.4)	26.2 (15.4–56.4)
Model 1, +total cholesterol mmol/L	–0.0228	2.3 (0.8–3.7)	33.7 (12.8–49.5)	12.0 (–6.8 to 45.0)
Model 1, +HDL cholesterol, mmol/L	–0.0254	2.5 (1.1–3.9)	36.7 (17.8–51.2)	2.1 (0.3–6.5)
Model 1, +daily smoking	–0.0216	2.1 (0.7–3.6)	32.3 (12.0–47.9)	16.5 (8.2–40.7)
Model 1, +BMI, kg/m^2	–0.0273	2.7 (1.3–4.1)	38.8 (20.5–52.9)	–5.3 (–15.0 to 0.3)
Model 1, +diabetes mellitus	–0.0269	2.7 (1.2–4.0)	38.3 (20.0–52.4)	–3.6 (–10.2 to –0.9)
Model 1, +physical activity§	–0.0245	2.4 (1.0–3.8)	35.7 (16.4–50.5)	5.4 (–2.8–16.3)
Model 1, +all risk factors	–0.0112	1.1 (–0.4 to 2.6)	18.3 (–8.1 to 38.2)	56.8 (27.8–100.0)

BMI indicates body mass index; CI, confidence interval; and HDL, high-density lipoprotein.

*Decline in risk from 1995 to 2012, that is, during 18 years=100%×[1−$e^{(\beta\times 18)}$].

†Percentage of the observed decline in risk explained by the risk factors =100%×(β_0−β_1)/β_0, where β_0 is the coefficient for calendar time in the model with adjustment for age and sex only (model 1), and β_1 is the coefficient for calendar time in the model with additional adjustment for the risk factor(s).

‡95% CI is estimated using 1000 boot-strapped samples.

§Strenuous physical activity ≥1 h/week.

Our findings emphasize the need for directed public-health programs and continuous clinical intervention on acknowledged etiologic factors to further decrease IS incidence. Moreover, our results demonstrate the significant proportion of the decline in IS incidence not attributable to this measured change in established risk factors, which encourages future research of less well recognized risk factors.

Strengths and Limitations

The strengths of this study are the population-based design, the large sample of repeated individual data, standardized diagnostic criteria and survey methods, rigorous validation of cases, and high attendance rate. The loss to follow-up is negligible because of usage of the unique personal identity number to search official health registries. However, case identification was retrospective, not hot pursuit, which is a limitation. We may have failed to identify some nonhospitalized, nonfatal cases. Increased hospitalization rates for stroke and increased use of imaging with time may have resulted in relatively higher detection rates in the latest compared with the earliest years, resulting in an underestimation of IS incidence rates in the earliest part of the study period. Furthermore, the associations between trends in IS incidence and risk factors were based on participants with updated risk factors, which could have introduced response and survival bias. Diabetes mellitus, smoking, and physical activity was self-reported. Hence, the prevalence of diabetes mellitus is most likely underestimated. Smoking may be under-reported, and the degree of physical activity may be misclassified by the respondent.[30,31] Furthermore, the analysis is based on the assumption that the effects of changes in risk factors on the IS incidence became evident within the observation period. We did not perform competing risk analyses, meaning that the occurrence of the event of interest (IS) could have been impeded by competing events.

Selection bias may have affected the estimates, because nonattendees were younger, a higher proportion was single, and the proportion of men was higher compared with the proportion of attendees.[13] Attendance rates were also lower in the elderly, who are at higher risk of stroke. Legal restrictions have precluded analyses of mortality or morbidity in nonattendees. Moreover, the lack of ethnic diversity may also limit the external validity of the obtained results.

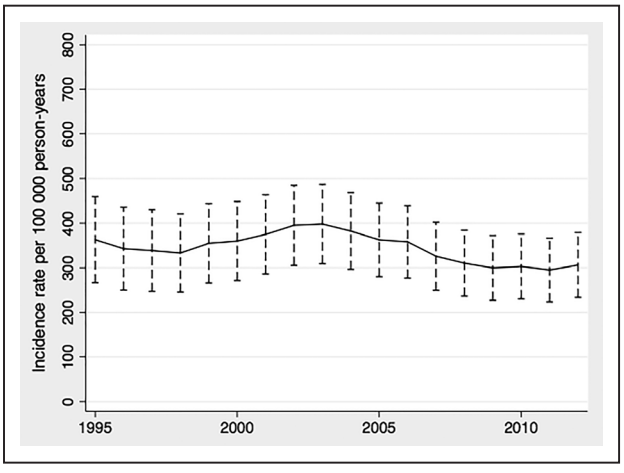

Figure. Trends in annual incidence rates of ischemic stroke in participants aged ≥30 years. The Tromsø Study 1995 to 2012. The incidence rates are fitted as 5-years moving mean. The separate bars represents 95% confidence intervals. Rates are directly age- and sex-standardized to the Tromsø population in 2007.

Conclusions

Our study showed that changes in vascular risk factors accounted for 57% of the decrease in incidence of IS from 1995 to 2012. The most important contributors were the concurrent decline in mean systolic BP and prevalence of smoking, while the increasing diabetes mellitus prevalence contributed adversely to the decreasing IS incidence. Our findings emphasize the need for continued targeted public-health initiatives

to further reduce modifiable risk factors and encourage future research of less well-recognized risk factors.

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Disclosures

None.

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Declining Incidence of Ischemic Stroke: What Is the Impact of Changing Risk Factors? The Tromsø Study 1995 to 2012

Anne M. Vangen-Lønne, Tom Wilsgaard, Stein Harald Johnsen, Maja-Lisa Løchen, Inger Njølstad and Ellisiv B. Mathiesen

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ONLINE SUPPLEMENT

Declining incidence of ischemic stroke: What is the impact of changing risk factors? The Tromsø Study 1995-2012.

Supplemental Methods

Cardiovascular risk factors

Blood pressure (BP) was measured with an automatic device by trained personnel (Dinamap Vital Signs Monitor 1846 in Tromsø 4 and Tromsø 5, and Dinamap Procare 300 monitor, GE Healthcare, Oslo; Norway in Tromsø 6). After 2 minutes rest in sitting position, 3 readings were taken from the right upper arm separated by 1-minutes intervals. The mean of the two last recordings were used in the analyses. Height (cm) was measured in a standing position, to the closest cm in Tromsø 4, and to the nearest 0.1 cm in Tromsø 5 and 6. Weight (kg) was measured to the closest 500 g in Tromsø 4 and to the nearest 100 g in Tromsø 5 and 6, with participants wearing light clothing and no shoes.

Non-fasting blood samples were analyzed by standard methods at the University Hospital of Northern Norway. Non-fasting serum total cholesterol was analyzed within 10 h by enzymatic colorimetric methods (CHOD-PAP, Boehringer-Mannheim). Serum high-density lipoprotein cholesterol (HDL) was measured after the precipitation of lower-density lipoprotein with heparin and manganese chloride.

Information on diabetes and physical activity was collected from questionnaires. Diabetes was defined as self-reported diabetes, by answering the question "Do you have, or have you had diabetes?" The question regarding "hard" physical activity used in the 1994-95 and 2001 surveys has been used in several large population studies. [1-3] A validation study concluded that this physical activity question appeared to be a reasonably valid measure of vigorous activity, as reflected in moderate correlations with several other objective measures such as VO2max and time spent at over six METs. [4]

In the 1994-95 and 2001 survey, the participants were asked about "hard physical activity" (sweating or out of breath) with the wording: "How has your physical activity in leisure time been the last year? Think of your weekly average throughout the year (hours per week). Time spent going to work count as leisure time." Response categories: 1) None; 2) < 1 hours; 3) 1-2 hours; 4) 3 or more hours per week. A separate question with similar categories regarding "light" physical activity (you do not become short-winded or sweaty) was also present. In this paper physically active participants in 1994-95 and 2001 was defined as subjects who reported that they participated in hard physical activity one hour or more per week (response

In the 2007-08 survey physical activity was measured by three questions covering exercise level, frequency and duration. Exercise level: “If you exercise - how hard do you exercise?” Response categories: 1) Easy – you do not become short-winded or sweaty; 2) You become short-winded or sweaty; 3) Hard - you become exhausted. Exercise frequency: “How often do you exercise?” (i.e walking, skiing, swimming, training - /sports). Response categories: 1) Never; 2) Less than once a week; 3) Once a week; 4) 2-3 times a week; 5) Approximately every day. Exercise duration: “For how long time do you exercise?” Response categories: 1) Less than 15 minutes; 2) 15-29 minutes; 3) 30-60 minutes; 4) More than 1 hour. Physically active participants in 2007-08 was defined as subjects who reported response categories 2 or 3 for exercise level, AND either: 1) response category 3 in exercise frequency and response category 4 in exercise duration, or 2) response category 4 in exercise frequency and response categories 3 or 4 in exercise duration, or 3) response category 5 in exercise frequency regardless of exercise duration.

Table I. Attendance rates and age span of eligible participants, and age and sex distribution of attendees and non-attendees, by survey number (year). The Tromsø Study.

		Women				Men			
		Attendees		Non-attendees		Attendees		Non-attendees	
	Age group, Years *	n† (%)‡	Mean age, years (SD)	n†	Mean age, years (SD)	n† (%)‡	Mean age, years (SD)	n†	Mean age, years (SD)
Tromsø 4 (1994–95)	25-97	14,293 (74.9)	47.2 (15.6)	4,785	44.1 (19.9)	12,865 (69.6)	46.6 (14.5)	5,615	40.9 (15.4)
Tromsø 5 (2001)	30-89	4,619 (80.8)	59.4 (14.1)	1,098	50.8 (18.4)	3,511 (75.7)	59.9 (14.1)	1,125	46.0 (16.7)
Tromsø 6 (2007–08)	30-87	6,930 (68.4)	57.5 (13.0)	3,207	58.1 (16.5)	6,054 (62.9)	57.5 (12.3)	3,571	54.5 (14.8)

* Age groups included in the different surveys. † Number of participants. ‡ Attendance rate.

Table II. Cardiovascular risk factor levels in participants aged ≥30 years, by survey year. The Tromsø Study.

Risk factor	1994-95 n=23,380	2001 n=7,830	2007-08 n=12,722	Relative change 1994 -2008, %	p value *
Age in years, mean (SD)	49.5 (13.9)	59.4 (14.1)	57.3 (12.6)		<0.001
Male gender, % (n)	47.6 (11,120)	42.8 (3,350)	46.3 (5,891)		0.001
Hypertension †	44.0 (43.2-44.8)	37.9 (36.8-39.0)	41.1 (40.2-42.1)	–7	<0.001
Systolic blood pressure, mmHg	139.0 (138.8-139.3)	133.5 (133.2-133.9)	133.1 (132.8-133.5)	–5	<0.001
Diastolic blood pressure, mmHg	80.2 (80.1-80.4)	78.6 (78.4-78.8)	76.6 (76.4-76.8)	–4	<0.001
Hyperlipidemia ‡	28.7 (28.1-29.4)	28.2 (27.3-29.2)	16.4 (15.8-17.0)	–43	<0.001
Total cholesterol, mmol/l	6.30 (6.28-6.31)	5.96 (5.94-5.99)	5.47 (5.45-5.49)	–13	<0.001
HDL cholesterol, mmol/l	1.52 (1.52-1.53)	1.43 (1.42-1.43)	1.49 (1.49-1.50)	–2	<0.001
Overweight §	38.7 (38.1-39.4)	41.1 (40.1-42.2)	41.9 (41.0-42.7)	8	<0.001
Obesity ‖	11.8 (11.4-12.2)	17.2 (16.7-17.9)	18.9 (18.3-19.6)	60	<0.001
Daily smoking	34.6 (33.9-35.2)	31.1 (30.2-31.9)	22.9 (22.2-23.7)	–34	<0.001
Diabetes mellitus	1.7 (1.6-1.9)	2.2 (2.0-2.5)	3.4 (3.2-3.8)	100	<0.001
Physical activity **	23.7 (23.1-24.3)	37.5 (36.2-38.7)	44.9 (43.9-45.9)	90	<0.001

HDL, high-density lipoprotein; BMI, body mass index.

The risk factor values (apart from age and sex) are age- and sex-adjusted means (95% confidence interval) or prevalence (%) estimated by generalized estimating equations (GEE) to account for dependencies between repeated observations. The identity link function was used for continuous variables and the logit link function for categorical variables. *Test for linear trend. †Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or use of blood pressure-lowering drugs. ‡Total cholesterol /HDL cholesterol ratio >5. §BMI ≥25 to <30 kg/m^2. ‖BMI ≥30 kg/m^2. **Strenuous physical activity ≥1 hour/week.

Table III. Cardiovascular risk factor levels in participants aged 30–49 years, by survey year. The Tromsø Study.

Risk factor	1994-95 n=13,361	2001-02 n=2,037	2007-08 n=4,067	Relative change 1994 -2008, %	p value *
Age in years, mean (SD)	39.4 (5.7)	38.9 (6.0)	42.3 (4.0)		<0.001
Male gender, % (n)	48.2 (6,436)	43.0 (877)	45.9 (1,868)		0.002
Hypertension †	19.6 (18.9-20.3)	14.6 (13.2-16.0)	16.8 (15.7-17.9)	–14	<0.001
Systolic blood pressure, mmHg	127.8 (127.5 -128.0)	122.9 (122.4-123.4)	121.6 (121.2-122.0)	–5	<0.001
Diastolic blood pressure, mmHg	75.8 (75.6-76.0)	75.1 (74.7-75.5)	74.5 (74.2-74.8)	–2	<0.001
Hyperlipidemia ‡	20.9 (20.2-21.7)	25.5 (23.7-27.3)	17.7 (16.5-18.9)	–15	0.001
Total cholesterol mmol/l	5.78 (5.76-5.80)	5.64 (5.60-5.68)	5.21 (5.17-5.24)	–10	<0.001
HDL cholesterol mmol/l	1.49 (1.48-1.49)	1.38 (1.37-1.40)	1.40 (1.39-1.41)	–6	<0.001
Overweight §	33.5 (32.6-34.3)	39.4 (37.4-41.6)	38.6 (37.1-40.1)	15	<0.001
Obesity ‖	8.3 (7.8-8.8)	13.5 (12.2-14.9)	18.1 (16.9-19.3)	118	<0.001
Daily smoking	40.9 (40.0-41.7)	35.3 (33.6-37.0)	23.7 (22.5-25.0)	–42	<0.001
Diabetes mellitus	0.7 (0.5-0.8)	1.0 (0.7-1.5)	1.9 (1.5-2.4)	171	<0.001
Physical activity **	34.7 (33.9-35.6)	44.1 (41.9-46.3)	59.0 (57.3-60.8)	70	<0.001

HDL, high-density lipoprotein; BMI, body mass index.

The risk factor values (apart from age and sex) are age- and sex-adjusted means (95% confidence interval) or prevalence (%) estimated by generalized estimating equations (GEE) to account for dependencies between repeated observations. The identity link function was used for continuous variables and the logit link function for categorical variables. *Test for linear trend. †Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or use of blood pressure-lowering drugs. ‡Total cholesterol /HDL cholesterol ratio >5. §BMI ≥25 to <30 kg/m^2. ‖BMI ≥30 kg/m^2. **Strenuous physical activity ≥1 hour/week.

Table IV. Cardiovascular risk factor levels in participants aged ≥50 years, by survey year. The Tromsø Study.

Risk factor	1994-95 n=10,019	2001-02 n=5,793	2007-08 n=8,655	Relative change 1994 -2008, %	p-value *
Age in years, mean (SD)	62.9 (9.6)	66.6 (7.4)	64.3 (8.5)		<0.001
Male gender, % (n)	46.8 (4,684)	42.7 (2,473)	46.5 (4,023)		0.520
Hypertension †	65.5 (64.5-66.5)	60.5 (59.3-61.7)	63.8 (62.8-64.8)	–3	<0.062
Systolic blood pressure, mmHg	147.8 (147.4 -148.2)	141.9 (141.4-142.4)	142.0 (141.6-142.5)	–4	<0.001
Diastolic blood pressure, mmHg	84.1 (83.8-84.3)	82.0 (81.7-82.3)	79.0 (78.7-79.2)	–6	<0.001
Hyperlipidemia ‡	35.3 (34.3-36.3)	32.7 (31.5-33.8)	17.2 (16.4-18.0)	–51	<0.001
Total cholesterol, mmol/l	6.75 (6.73-6.78)	6.36 (6.33-6.38)	5.77 (5.75-5.80)	–15	<0.001
HDL cholesterol, mmol/l	1.55 (1.54-1.56)	1.47 (1.46-1.48)	1.56(1.55-1.56)	–1	0.270
Overweight §	43.3 (42.3-44.3)	44.7 (43.5-45.9)	45.2 (44.1-46.2)	4	<0.005
Obesity ‖	15.1 (14.4-15.8)	20.8 (19.9-21.7)	21.4 (20.6-22.2)	42	<0.001
Daily smoking	29.1 (28.2-30.0)	27.5 (26.5-28.5)	20.7 (19.9-21.5)	–29	<0.001
Diabetes mellitus	3.4 (3.1-3.8)	4.1 (3.7-4.6)	6.0 (5.5-6.5)	76	<0.001
Physical activity **	16.1 (15.3-16.9)	31.2 (29.8-32.5)	34.2 (33.1-35.4)	112	<0.001

HDL, high-density lipoprotein; BMI, body mass index.

The risk factor values (apart from age and sex) are age- and sex-adjusted means (95% confidence interval) or prevalence (%) estimated by generalized estimating equations (GEE) to account for dependencies between repeated observations. The identity link function was used for continuous variables and the logit link function for categorical variables. *Test for linear trend. †Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or use of blood pressure-lowering drugs. ‡Total cholesterol /HDL cholesterol ratio >5. §BMI ≥25 to <30 kg/m^2. ‖BMI ≥30 kg/m^2.

**Strenuous physical activity ≥1 hour/week.

Table V. Prevalence of blood-pressure and lipid lowering drug users by age-group and survey year. The Tromsø Study.

Age-group	1994-95	2001	2007-08	Relative change 1994 -2008, %	p-value *
40–79 years					
Blood pressure-lowering drugs	7.8 (7.4-8.2)	12.4 (11.7-13.1)	18.0 (17.3-18.7)	130	<0.001
Lipid-lowering drugs	1.2 (1.0-1.4)	6.9 (6.4-7.5)	10.9 (10.4-11.5)	808	<0.001
≥30 years					
Blood pressure lowering drugs	5.7 (5.3-6.0)	9.9 (9.4-10.5)	14.6 (14.0-15.3)	156	<0.001
Lipid lowering drugs	0.8 (0.7-1.0)	5.6 (5.2-6.1)	8.9 (8.4-9.4)	1013	<0.001
30–49 years					
Blood pressure lowering drugs	1.4 (1.2-1.6)	2.1 (1.6-2.8)	3.5 (3.0-4.1)	150	<0.001
Lipid lowering drugs	0.2 (0.2-0.3)	1.0 (0.6-1.4)	1.1 (0.8-1.5)	450	<0.001
≥50 years					
Blood pressure lowering drugs	12.6 (11.9-13.2)	21.2 (20.2-22.2)	29.1 (28.1-30.1)	131	<0.001
Lipid lowering drugs	1.7 (1.4-1.9)	11.7 (10.9-12.5)	18.2 (17.4-19.0)	971	<0.001

Blood pressure lowering and lipid lowering drug values are age- and sex adjusted prevalence (% (95% confidence interval)) estimated by generalized estimating equations (GEE) with the logit link function to account for dependencies between repeated observations.
*Test for linear trend.

Table VI. Decline in the risk of first ischemic stroke event in women, and percentage of risk declines accounted for by risk factors. The Tromsø Study 1995-2012.

	Calendar time β-coefficient, per year	Decline in risk per year, % (95% CI)	Decline in risk 1995-2012* % (95% CI)	Explained decline by risk factors† % (95% CI)‡
Model 1, age adjusted	–0.0316	3.1 (0.9, 5.3)	43.3 (14.5, 62.5)	Ref.
Model 1, + systolic blood pressure, mmHg	–0.0215	2.1 (–0.1, 4.3)	32.1 (–2.3, 54.9)	31.8 (16.8, 95.0)
Model 1, + total cholesterol mmol/l	–0.0340	3.3 (1.0, 5.6)	45.8 (16.5, 64.8)	–7.7 (–52.3, 21.6)
Model 1, + HDL cholesterol, mmol/l	–0.0309	3.0 (0.8, 5.2)	42.7 (13.4, 62.0)	2.0 (–0.0, 9.5)
Model 1, + Daily smoking	–0.0296	2.9 (0.7, 5.1)	41.3 (11.2, 61.2)	6.3 (1.9, 23.3)
Model 1, + BMI, kg/m^2	–0.0318	3.1 (0.9, 5.3)	43.6 (14.8, 62.7)	–0.8 (–6.2, 3.5)
Model 1, + diabetes mellitus	–0.0327	3.2 (1.0, 5.4)	44.5 (16.3, 63.2)	–3.7 (–13.1, 0.2)
Model 1, + physical activity§	–0.0285	2.8 (0.5, 5.1)	40.2 (9.1, 60.6)	9.5 (–6.3, 36.4)
Model 1, + all risk factors	–0.0208	2.1 (–0.4, 4.4)	31.2 (–6.6, 55.6)	34.2 (3.9, 100.0)

HDL, high-density lipoprotein; BMI, body mass index. *Decline in risk from 1995 throughout 2012, i.e. over 18 years =100% x [1-$e^{(\beta \times 18)}$]
†Percentage of the observed decline in risk explained by the risk factors =100% x (β0-β1)/β0, where β0 is the coefficient for calendar time in the model with adjustment for age and sex only (model 1), and β1 is the coefficient for calendar time in the model with additional adjustment for the risk factor(s). ‡95%CI is estimated using 1000 boot-strapped samples. §Strenuous physical activity ≥1 hour/week.

Table VII. Decline in the risk of first ischemic stroke event in men, and percentage of risk declines accounted for by risk factors. The Tromsø Study1995-2012.

	Calendar time β-coefficient, per year	Decline in risk per year, % (95% CI)	Decline in risk 1995-2012* % (95% CI)	Explained decline by risk factors† % (95% CI)‡
Model 1, age+ sex adjusted	–0.0219	2.2 (0.3, 4.0)	32.6 (5.6, 51.8)	Ref.
Model 1, + systolic blood pressure, mmHg	–0.0176	1.7 (–0.1, 3.6)	27.2 (–2.0, 48.0)	19.5 (7.5, 79.0)
Model 1, + total cholesterol mmol/l	–0.0150	1.5 (–0.5, 3.4)	23.7 (–8.6, 46.4)	31.3 (–0.9, 100.0)
Model 1, + HDL cholesterol, mmol/l	–0.0215	2.1 (0.3, 3.9)	32.1 (4.9, 51.5)	1.8 (–1.7, 10.3)
Model 1, + Daily smoking	–0.0162	1.6 (–0.3, 3.5)	25.2 (–5.1, 46.8)	26.2 (9.0, 100.0)
Model 1, + BMI, kg/m^2	–0.0251	2.5 (0.6, 4.3)	36.3 (10.5, 54.8)	–14.7 (–72.5, 1.9)
Model 1, + diabetes mellitus	–0.0227	2.2 (0.4, 4.1)	33.5 (6.9, 52.5)	–3.6 (–19.4, 0.7)
Model 1, + physical activity§	–0.0211	2.1 (0.2, 3.9)	31.6 (4.0, 51.2)	3.7 (–10.1, 25.4)
Model 1, + all risk factors	–0.0053	0.5 (–1.5, 2.5)	9.1 (–31.0, 37.0)	75.7 (26.1, 100.0)

HDL, high-density lipoprotein; BMI, body mass index. *Decline in risk from 1995 throughout 2012, i.e. over 18 years =100% x $[1\text{-}e^{(\beta \times 18)}]$
†Percentage of the observed decline in risk explained by the risk factors =100% x (β0-β1)/β0, where β0 is the coefficient for calendar time in the model with adjustment for age and sex only (model 1), and β1 is the coefficient for calendar time in the model with additional adjustment for the risk factor(s). ‡95%CI is estimated using 1000 boot-strapped samples. §Strenuous physical activity ≥1 hour/week.

Table VIII. Decline in the risk of first ischemic stroke event in participants aged <60 years at baseline, and percentage of risk declines accounted for by risk factors. The Tromsø Study 1995-2012.

	Calendar time β-coefficient, per year	Decline in risk per year, %	Decline in risk 1995-2012* % (95% CI)	Explained decline by risk factors† % (95% CI)‡
Model 1, age+ sex adjusted	–0.0314	3.1 (–0.1, 6.2)	43.2 (–2.1, 68.4)	Ref.
Model 1, + systolic blood pressure, mmHg	–0.0266	2.6 (–0.6, 5.8)	38.1 (–11.0, 65.6)	15.3 (3.5, 97,8)
Model 1, + total cholesterol mmol/l	–0.0307	3.0 (–0.3, 6.3)	42.5 (–5.7, 68.7)	2.2 (–75.3, 81.3)
Model 1, + HDL cholesterol, mmol/l	–0.0338	3.3 (0.1, 6.4)	45.6 (2.0, 70.0)	–7.5 (–53.2, –0.6)
Model 1, + Daily smoking	–0.0199	2.0 (–1.3, 5.2)	30.1 (–26.0, 61.4)	36.6 (6.9, 100.0)
Model 1, + BMI, kg/m^2	–0.0315	3.1 (–0.1, 6.2)	43.3 (–2.0, 68.5)	–0.3 (–19.9, 16.7)
Model 1, + diabetes mellitus	–0.0324	3.2 (–0.2, 6.3)	44.2 (–0.4, 69.0)	–3.1 (–24.5, 4.9)
Model 1, + physical activity§	–0.0291	2.9 (–0.4, 6.0)	40.8 (–6.6, 67.1)	7.4 (–3.5, 48.3)
Model 1, + all risk factors	–0.0166	1.6 (–1.8, 5.0)	25.8 (–38.0, 60.1)	47.3 (–17.0, 100.0)

HDL, high-density lipoprotein; BMI, body mass index. *Decline in risk from 1995 throughout 2012, i.e. over 18 years =100% x [1-e $^{(\beta \times 18)}$]
†Percentage of the observed decline in risk explained by the risk factors =100% x (β0-β1)/β0, where β0 is the coefficient for calendar time in the model with adjustment for age and sex only (model 1), and β1 is the coefficient for calendar time in the model with additional adjustment for the risk factor(s). ‡95%CI is estimated using 1000 boot-strapped samples. §Strenuous physical activity ≥1 hour/week.

Table IX. Decline in the risk of first ischemic stroke event in participants aged ≥60 years at baseline, and percentage of risk declines accounted for by risk factors. The Tromsø Study1995-2012.

	Calendar time β-coefficient, per year	Decline in risk per year, % (95% CI)	Decline in risk 1995-2012* % (95% CI)	Explained decline by risk factors† % (95% CI)‡
Model 1, age+ sex adjusted	–0.0239	2.4 (0.4, 4.3)	34.9 (6.8, 54.6)	Ref.
Model 1, + systolic blood pressure, mmHg	–0.0176	1.7 (–0.2, 3.7)	27.1 (–4.4, 49.1)	26.5 (11.6, 100.0)
Model 1, + total cholesterol mmol/l	–0.0209	2.1 (0, 4.1)	31.3 (0.1, 52.8)	12.5 (–18.4, 78.6)
Model 1, + HDL cholesterol, mmol/l	–0.0232	2.3 (0.3, 4.2)	34.1 (5.6, 54.1)	2.8 (–0.3, 14.1)
Model 1, + Daily smoking	–0.0221	2.2 (0.2, 4.1)	32.8 (3.7, 53.2)	7.4 (1.1, 42.2)
Model 1, + BMI, kg/m^2	–0.0251	2.5 (0.5, 4.4)	36.4 (8.8, 55.7)	–5.3 (–22.0, 1.9)
Model 1, + diabetes mellitus	–0.0241	2.4 (0.4, 4.3)	35.1 (7.1, 54.7)	–0.7 (–10.8, 7.9)
Model 1, + physical activity§	–0.0236	2.3 (0.3, 4.3)	34.7 (6.0, 54.6)	1.0 (–19.8, 21.8)
Model 1, + all risk factors	–0.0121	1.2 (–0.9, 3.4)	19.5 (–18.0, 45.1)	49.5 (12.9, 100.0)

HDL, high-density lipoprotein; BMI, body mass index. *Decline in risk from 1995 throughout 2012, i.e. over 18 years =100% x [1-e $^{(\beta \times 18)}$]
†Percentage of the observed decline in risk explained by the risk factors =100% x (β0-β1)/β0, where β0 is the coefficient for calendar time in the model with adjustment for age and sex only (model 1), and β1 is the coefficient for calendar time in the model with additional adjustment for the risk factor(s). ‡95%CI is estimated using 1000 boot-strapped samples. §Strenuous physical activity ≥1 hour/week.

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