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Determinants of social inequalities in stroke incidence across Europe: a collaborative analysis of 126 635 individuals from 48 cohort studies

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Background. Knowledge on the origins of the social gradient in stroke incidence in different populations is limited. This study aims to estimate the burden of educational class inequalities in stroke incidence and to assess the contribution of risk factors in determining these inequalities across Europe.

Methods. The MORGAM Study comprises 48 cohorts recruited mostly in the 1980s and 1990s in 4 European regions using standardized procedures for baseline risk factor assessment and fatal and non-fatal stroke ascertainment and adjudication during follow-up. Among the 126 635 middle-aged participants, initially free of cardiovascular diseases, generating 3788 first stroke events during a median follow-up of 10 years, we estimated differences in stroke rates and hazard ratios for the least vs. the most educated individuals.

Results. Compared to their most educated counterparts, the overall age-adjusted excess hazard for stroke was 1.54 (95%CI: 1.25-1.91) and 1.41 (1.16-1.71) in least educated men and women, respectively, with little heterogeneity across populations. Educational class inequalities accounted for 86-413 and 78-156 additional stroke events per 100,000 person-years in the least compared to most educated men and women, respectively. The additional events were equivalent to 47%-130% and to 40%-89% of the average incidence rates. Inequalities in risk factors accounted for 45%-70% of the social gap in incidence in the Nordic Countries, the UK and Lithuania-Kaunas (men); but for no more than 17% in Central and South Europe. The major contributors were cigarette smoking, alcohol intake and body mass index.

Conclusions. Social inequalities in stroke incidence contribute substantially to the disease rates in Europe. Healthier life-styles in the most disadvantaged individuals should have a prominent impact in reducing both inequalities and the stroke burden.

What is already known on this subject

- Two recent reviews and one meta-analysis highlighted the increased risk of stroke among lower socio-economic classes.

- However, current knowledge on the origins of social inequalities in stroke across Europe hinder the possibility to prioritize interventions that might help close the social gap in different populations

What this study adds

- Our collaborative analysis of 126,635 middle-aged individuals from 48 cohort studies in 4 European regions confirmed that educational class inequalities contribute substantially (40%-130% of the average event rate) to stroke incidence in both gender groups

- Clinical and behavioural risk factors accounted for 45%-70% of the social gap in stroke incidence in the Nordic Countries, the UK and Lithuania; but for no more than 17% in Central and South Europe. Major contributors were cigarette smoking, alcohol intake and body mass index

- Tailored interventions affecting the social determinants of behavioural risk factors in lower socio-economic strata may effectively reduce the stroke burden in most European regions. Further research is needed to expose the underlying determinants of inequalities in Central and South Europe

Introduction

Stroke accounts for 9% and 14% of all deaths in European men and women, respectively [1], and was ranked as the third most common cause of disability-adjusted life-years lost in developed countries [2]. The INTERSTROKE study showed that ten modifiable risk factors may account for up to 90% of stroke events [3], although there were important variations in the relative importance of individual risk factors across geographic regions and population subgroups. They concluded that targeted population-specific programs for stroke prevention are required [3].

Two reviews [4,5] and one meta-analysis [6] recently highlighted the increased risk of stroke incidence among lower socio-economic classes. At the same time, these overviews uncovered some important limitations in our knowledge concerning the origin of these inequalities. First, a narrow geographic coverage, with most data coming from the US, the UK and the Nordic Countries [4-9]. Second, the documented heterogeneity across studies [6] arising from differences in the measure of socio-economic status, the characteristics of the underlying populations in terms of age range and gender groups, as well as in the endpoint definition reduces the comparability and limits the interpretation of the results. Finally, there is a lack of information on which clinical, biological and behavioural risk factors are the most critical in determining social inequalities in disease, as the set of risk factors and their measurement methods varies from study to study [6]. Thus current literature offers us only incomplete insights on how individual risk factors affect social inequalities in stroke and limits the potential to prioritize interventions that might help close the social gap in different populations and gender groups.

The MORGAM (MOnica Risk, Genetics, Archiving and Monograph) Project Cohort Component [10] is a multinational collaborative study of prospective cohorts with follow-up data on major cardiovascular disease, including stroke. Risk factors measurements at baseline and endpoint ascertainment and definition during follow-up are well harmonized and underwent carefully data quality assessments. Our investigation includes 48 population-based cohorts from 12 countries representative of the main European regions (Nordic Countries, the UK, Central and South Europe; East Europe and Russia) and it is aimed to: *i)* assess the burden of educational class inequalities in stroke incidence; and *ii)* to estimate the extent to which inequalities in stroke incidence can be accounted for by the social gradient in risk factors, across Europe.

Methods

Study population

The present analysis includes 126 635 middle-aged men and women, initially free of cardiovascular disease, participants of 48 MORGAM cohorts from Sweden, Finland, Norway, Denmark, Northern Ireland (men only), Scotland, France (men only), Germany, Italy, Lithuania, Poland and Russia. All study cohorts were population-based, with the only exception being cohorts in France and Northern Ireland. Baseline recruitment was mostly between the early 1980s and the early 1990s, although more recent cohorts are available for some populations (see Table I in the online only Material). Detailed descriptions of MORGAM cohorts and quality assessments of risk factor measurements at baseline and of follow-up procedures are publicly available http://www.thl.fi/publications/morgam. Key methodological aspects are summarized below.

Definition of educational classes

Information on the number of years of schooling was collected at baseline (“How many years have you spent at school or in full time study?”). Comparability across populations was high, and the prevalence of missing data was generally low [11]. We derived three categories of education (high, intermediate and low) from population-, sex- and birth cohort-specific tertiles of the distribution of years of schooling [12].

Baseline cardiovascular disease risk factors assessment

As most of MORGAM cohorts were investigated at baseline as population surveys of the WHO-MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) Project, baseline assessment of risk factors followed either the WHO-MONICA protocol or MONICA-like procedures. Blood pressure was measured after 2-5 minutes rest while sitting, using a standard or random zero sphygmomanometer or an automated oscillometric device. Except in France and Belfast (one measure only), two consecutive measurements were available, and the average was used as the study variable for systolic blood pressure. Total cholesterol and HDL-cholesterol were determined on sera except in France and Belfast (plasma). Body Mass Index (BMI) was computed from measured height and weight; individuals were classified as normal weight (BMI<25); overweight (BMI between 25 and 29.9) and obese (BMI ≥30 kg/m^2). Daily cigarette smoking, alcohol intake and history of diabetes were derived from interviews or self-reported questionnaires; we combined former and never smokers as non-smokers. Daily alcohol intake (in grams) was converted to average drinks per day, considering 12.5 grams of alcohol as a standard drink [13]. We further categorized alcohol intake as abstainers (less than 0.5 drinks per day), 1-2, 3-4, 5 or more drinks per day. History of cardiovascular disease, including myocardial infarction, unstable angina and stroke was obtained from clinical records or self-reports at the initial recruitment visit.

Follow-up procedures and endpoints definition

Participants in each MORGAM cohort were followed-up for non-fatal and fatal strokes and death from other causes. Deaths were identified through record linkage with national or regional health information systems. Non-fatal strokes were identified by linkage to population registers, hospital discharge data, or direct contact with the participant. There was an upper age limit of 65 years for follow-up of non-fatal events in Kaunas and Warsaw; this was also applied to fatal events in the current analyses. Most centres adjudicated the events using MONICA diagnostic criteria [14].

We looked at inequalities in death from incident stroke and in stroke incidence, including fatal and non-fatal events. Poland-Tarnobrzeg (no follow-up for non-fatal events) and Russia (short follow-up and elevated fatal:non-fatal event ratio) contributed to the mortality analysis only. To reduce differences in follow-up length across MORGAM populations, the follow-up was truncated at 20 years.

Statistical analysis

Of the available 129747 men and women aged 35-74 years and free of previous cardiovascular diseases at baseline, we excluded 3112 (2.4%) due to missing data on years of schooling, leaving a final sample size of 126635 individuals. All the analyses were stratified by sex and, unless otherwise indicated, by population; study cohort was included in the models using dummy variables. Since the distribution of educational classes may vary across populations, we used regression-based measures of inequality [15-17], according to which if a, b and c are the proportions of people in the low, intermediate and high educational class, then the mean rank a/2, a+b/2 and a+b+c/2 is attributed to all subjects within that category, separately by population and gender group. The rank variable is then used in regression models to estimate the difference in health outcome among person at rank 0 (the least educated) and rank 1 (the most educated).

As a measure of absolute inequalities, we estimated the Slope Index of Inequality (SII) in stroke rates from Poisson regression models adjusting for attained age during follow-up to mitigate the effect on rate estimates of different lengths of follow-up across populations. We used the formula proposed by Mackenbach et al. [16], while 95% confidence intervals were obtained through bootstrapping (n=2000 samples, bias corrected method; http://support.sas.com/kb/24/addl/fusion_24982_1_jackboot.sas.txt). The SII estimates the age-adjusted difference in stroke rates between the least and the most educated subjects and it is interpretable as the additional number of events per 100000 person years attributable to educational inequalities.

As a relative measure of inequalities in stroke incidence, we estimated the Relative Index of Inequality (RII) from Cox regression models with attained age during follow-up as the time scale. The RII is interpretable as the hazard ratio for the least compared to the most educated subjects. We first estimated the age-adjusted RIIs in each population, and provided a pooled estimate using a meta-analysis approach and a random effects model, reporting the Cochrane Q test and the I^2 statistic as measures of heterogeneity across populations [18]. Then, to identify which risk factor(s) played a major role in determining inequalities in stroke incidence, we considered the following models: age; age, smoking, body mass index and alcohol intake; age, non-HDL and HDL-cholesterol, systolic blood pressure, diabetes; all the mentioned risk factors. The % change in the age-adjusted RII for education due to risk factors was computed as: $(\ln RII[RFadj] - \ln RII[age]) / \ln RII[age]$)×100 comparing any of multivariable-adjusted models to the age-adjusted model. Multivariate analyses were restricted to individuals with available follow-up on non-fatal stroke events and valid data on alcohol intake (n=108184), which led to the exclusion of Poland-Warsaw due to the high prevalence of missing information on alcohol consumption. We used standard multiple imputation techniques ([19]; 10 imputed datasets) whenever one or more of the other risk factors was missing (n=4826, 4.5% of subjects). Since there was little evidence of heterogeneity in the age-adjusted associations, the risk factor-adjusted analyses were carried out by pooling populations into geographic regions to reduce variation in the % change estimates. We used the "metafor" package in R [18] for the random effect pooled estimates and Figure 1, and SAS 9.4 for all the remaining analyses.

Results

During a median follow-up of 10.4 years (IQR: 6.7-16.3), 727 fatal and 3061 non-fatal incident stroke events occurred among participants. Age-adjusted stroke death rates in men (2nd column of Table 1) were the highest in East Europe and Russia, intermediate in Scotland and the Nordic Countries, and the lowest in Central and South European populations. Incidence rates (6th column of Table 1) showed a different ranking, with higher rates in Denmark and other Nordic Countries, intermediate in Augsburg (Germany), Warsaw (Poland) and Scotland, and lower in France and Italy. In women, higher stroke death rates were detected in Scotland and Russia (Table 2, 2th column), and the ranking of stroke incidence rates was more similar to the one previously described for men (Table 2, 6th column).

Absolute inequalities in stroke rates

The least educated men had higher rates of death from incident stroke (i.e. SII>0) than their most educated counterparts in 12 out of the 15 investigated populations, significantly so in Finland and Poland-Warsaw (Table 1). Among women, a positive, statistically significant SII was estimated in the Italy-Latina population only. When considering absolute inequalities in stroke incidence rates, statistically significant SIIs emerged in 8 (Finland, Denmark, Scotland, France, Germany-Augsburg, Italy-Brianza, Italy-Latina and Poland-Warsaw; Table 1) out of 13, and 5 (Finland, Norway-Tromsø, Denmark-Glostrup, Scotland and Italy-Latina; Table 2) out of 11 populations in men and women, respectively. For none of the populations that showed a negative SII (with higher rates in least educated) was this pattern significant (either for men or women). In those populations where the SIIs were statistically significant, the ratio between the SII and the average incidence rate ranged between 47% (Finland) and 130% (Warsaw) in men, and between 40% (Finland) to 89% (Italy-Latina) in women.

Relative inequalities in stroke incidence and the role of risk factors

The forest plot for the age-adjusted hazard excess of stroke incidence for the least vs. the most educated individuals (Relative Index of Inequality, RII) by populations is displayed in Figure 1, in men (left panel) and women (right panel); while event rates and hazard ratios in each educational class are shown as online only material (Table II). The least educated men had a significant excess hazard for stroke in Finland, Denmark, Scotland, France, Germany, Italy (Brianza and Latina) and Poland-Warsaw, confirming the absolute inequalities analysis. The pooled RII estimate was 1.54 (95% CI: 1.25-1.91), with little evidence of heterogeneity across populations (I^2 = 31%, Q test statistic = 17.5, p-value = 0.13). The least educated women had a significant excess hazard for stroke in Finland, Denmark and Italy-Latina; the pooled RII estimate was 1.41 (95% CI: 1.16-1.71), with no evidence of heterogeneity across populations (I^2 = 0%, Q test statistic = 8.7, p-value = 0.56).

Inequalities in the distribution of risk factors have already been documented in these populations [17]; a summary by geographic regions is reported in Table III (online only). Most of RIIs were reduced after adjustment for smoking, alcohol intake, body mass index, non-HDL and HDL-cholesterol, systolic blood pressure and diabetes, with the notable exception of Central and South European populations (Table 3, last three columns on the right). The pooled RII estimate reduced by 30% and remained statistically significant in men (1.33; 95% 1.09-1.62), but not in women (1.17; 0.96-1.43). Inequalities in risk factors largely accounted for the social gradient in Lithuania-Kaunas, in both men and women. In the Nordic

Countries and the UK, the proportion of the social gradient accounted for by all the risk factors was almost half (44.5% and 49.5%) in men and more than half (66.3% and 58.4%) in women. When separating the contributions of behavioural-related (cigarette smoking, BMI and alcohol intake) from clinical-biological (non-HDL- and HDL-cholesterol, systolic blood pressure and diabetes) risk factors, the former apparently account for more than the latter in all these hazard ratios. In Central and South Europe, the proportion accounted for by the considered risk factors was less pronounced (14% in men and 16.7% in women), and in women entirely attributable to inequalities in systolic blood pressure, lipids and diabetes.

Discussion

Previous multi-national comparative analyses have focused on social inequalities in stroke mortality [16, 20, 21]. Time trend studies have shown that absolute inequalities in cerebrovascular disease mortality are declining in many European countries, with reductions in death rates reported to be larger among the less than among more educated individuals [20]. Gallo and colleagues estimated that the least educated European men and women had a 42% and 41% overall excess risk of age-adjusted stroke death, respectively [21]. In our analysis of middle-aged European adults initially free of cardiovascular disease, inequalities between the least and most educated were more commonly observed for stroke incidence than for stroke death rates, being statistically significant in 8 out of the 13 investigated populations in men, and in 5 out of 11 in women. Across the investigated populations, we estimated a 54% and 41% increase in the age-adjusted hazard of stroke incidence for the least educated men and women, respectively. These estimates were slightly lower than the gender-pooled 67% risk excess in stroke incidence derived from the meta-analysis of Kerr [6]. In contrast to the current paper, the studies included in the meta-analysis were highly heterogeneous in terms of study design (cohort vs. cross-sectional), definition of social class (education, occupation and income), stroke diagnosis (self-reporting vs. hospital discharge/death certificate codes) and endpoint (fatal only vs. fatal and non-fatal strokes). This heterogeneity makes comparisons very difficult, but on the other hand it elucidates the need for well-harmonized collaborative prospective studies to provide comparable estimates of social inequalities in stroke incidence across populations.

We contend that educational class inequalities in stroke incidence rates, either measured by differences in absolute inequalities (SII) or by relative hazard ratios (RII), can overwhelmingly better characterize the social gap than the corresponding inequalities in stroke death rates in our European populations, with higher rates in less educated men and women. This is mainly because of the higher statistical power due to the larger number of events when using incidence rates, but our results support the notion that the indexes of social inequalities are of the same direction in most populations when considering death or incidence rates. In our populations, the estimated number of additional first stroke events per 100000 person-years in the least educated individuals corresponded to 47%-130% and to 40%-89% of the average incidence rates, respectively. As low education is associated with increased post-stroke disability [22], the social gradient may contribute greatly to stroke costs and disability-adjusted life-years lost.

In the meta-analysis of socioeconomic differences in stroke incidence [6], the adjustment for known risk-factors (not the same for all the studies) led to a reduction of the pooled hazard ratio of 47% (range across studies: 28% to 145%; one study showing no attenuation). In the present analysis inequalities in risk factors accounted for between 45% and 70% of the social gap in stroke incidence in the Nordic Countries, the UK and Lithuania-Kaunas (men), while in Central and South Europe, the estimates of the risk explained was not more than 17% of the social gradient.

We have added two important pieces of information to previous literature. First, in most regions and gender groups the major contributors to educational inequalities in stroke incidence were behavioural risk factors, i.e. cigarette smoking, alcohol intake and body mass index. From the paper by Gallo et al. [21], it is possible to infer that the same behavioural risk factors, in addition to levels of physical activity and vegetable and fruit consumption, explain up to 39.7% and 18.4% of the risk in men and women respectively. The presence of a synergistic effect of smoking with low education on the risk of stroke [8] and cardiovascular diseases [23] would suggest that targeting the most disadvantaged individuals might be worthwhile in order to reduce both inequalities and disease rates at a population level. Now this reasoning may be extended to other behavioural risk factors as well.

Second, the investigated risk factors largely accounted for inequalities in stroke incidence in the Nordic Countries, the UK and Lithuania-Kaunas, but not in Central and South Europe. In the latter region, less educated women were less likely to smoke and more likely to have a moderate alcohol intake than their most educated counterparts (Table III, supplementary material), thus explaining the lack of attenuation attributable to these factors. These advantages were still present in the most recently recruited cohort (i.e. the Moli-Sani Study, with recruitment period 2005-2010), and may be due to cultural and social factors.

Educational differences of other risk factors, like HDL-cholesterol, higher blood pressure and diabetes prevalence, were similar to other populations, and these produced an attenuation of the risk due to clinical risk factor adjustments. In men from the Central and South Europe region, low education was associated with higher levels of HDL-cholesterol and with higher prevalence of moderate alcohol intake (Table III). Since these two have a stronger protective effect on coronary heart disease than on stroke, we may speculate that inequalities in these two major cardiovascular events may act in a competing risk fashion in these populations. As previously reported, the magnitude of social inequalities was smaller for the coronary heart disease than for the stroke [17, 24]. In part, this may have contributed to less attenuation of the relative hazards after adjustment for the investigated risk factors in these populations.

Strengths and limitations

We acknowledge several study limitations. The France and Belfast cohorts were partly drawn from working populations and we may have underestimated absolute inequalities in those populations, due to the healthy worker effect. Risk factors were measured only once at baseline, leading to potential residual confounding when estimating the effect of smoking (more educated subjects more likely to quit), or systolic blood pressure and non-HDL cholesterol (better control among the most educated subjects) on stroke inequalities. Alcohol intake was based on average daily consumption and the pattern of drinking, i.e., binge vs non-binge was not known. In some centre, the number of events was too small to get stable centre-specific estimates of the magnitude of inequalities and of the contribution of risk factors. For the same reason, the study endpoint included all incident strokes. The proportion of ischemic strokes in those centres with available stroke subtype information (11 out of 13) consistently ranged between 75% and 82% of all the incident events. A sensitivity analysis (Table IV, supplementary material) restricted to ischemic strokes only, substantially confirmed the main results. In one population the proportion of fatal events was 48% (range: 10%-28% in the remaining ones), perhaps suggesting loss of non-fatal events during the follow-up. Participation rates were below 60% in two populations and ranged between 65% and 77% in the remaining centres, potentially introducing some selection bias based on educational class. We do not have data on the overall caloric intake or on the usual diets of the individuals in these cohorts, or their leisure time physical active levels, or stress related factors, so the contribution of behavioural risk factors may be underestimated.

Among the study strengths, we provided both absolute and relative measures of educational class inequalities in stroke incidence in several European populations using prospective cohort studies with widely standardized measurement of risk factors and thorough end-point assessment. By deriving three educational classes based on age and birth cohort specific tertiles of years of schooling, we mitigated the effects of differences in educational systems across countries and time periods; while the use of regression-based measures of inequality attenuated the impact of differences in the educational class distributions across populations. Thus we avoided most of the artefactual heterogeneity when estimating health inequalities [25]. Heterogeneity across populations as measured by standard meta-analysis indicators was lower than previously reported [6]. Compared to other measures of socioeconomic position, education is easier to investigate, it represents - at least to some extent - a person's cognitive functioning and it may influence the individual susceptibility to preventive advice [25]. This aspect is particularly relevant for our paper, which looks at the impact of risk factors on the social gap in stroke. Moreover, it has been recently demonstrated that education itself carries a causal relationship with cardiovascular risk as they share some genetic determinants [26]. To conclude, comparative studies on stroke mortality do not fully capture the global burden of social inequalities in stroke across European populations. Interventions targeting risk factor distributions [27] and their social determinants [28] are expected to have a large impact in reducing the stroke burden, especially in the Nordic Countries, the UK and East European populations. An approach to reduce the social gap in cardiovascular diseases is to include education or other socio-economic indices in cardiovascular risk prediction equations, to adequately estimate risk in low social classes and to improve social equity in primary prevention [29]. Since a significant proportion of the variance in stroke incidence attributable to social disadvantage is not explained by traditional risk factors, particularly in Central and

South European populations, further research is needed to expose the underlying determinants of these differentials.

Contributors

MMF and GV conceived the research and drafted the manuscript, with the contribution of FK, LEC, KK, TJ and HTP. GV conducted the statistical analyses. KK directs the MORGAM Project and is the overall guarantor of the MORGAM data. AP, AD, MB, GC, WD, JF, SG, LI, NY, AP, AP, VS, SS, AT, TW actively contributed to the interpretation of the results and made critical revision of the manuscript drafts for important intellectual content. MMF, FK, TJ, PA, DA, GC, WD, JF, SG, LI, NY, AP, AP, VS, SS, AT, TW, HTP are responsible for data collection.

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Competing interests

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Table 1: Number of events, event rates and difference (SII*) in the event rate between the least and the most educated men, for death from incident stroke (left) and stroke incidence (right). Men, 35-74 years old, free of CVD at baseline

Population	Death from incident stroke			Stroke incidence (fatal or non-fatal)		
	N	Rate†	SII* (95% CI)	N	Rate†	SII* (95% CI)
Nordic Countries	205	46.9	33.6 (12.4; 53.4)	1567	383.0	121.1 (53.5; 186.6)
Northern Sweden	29	36.2	12.3 (-24.6; 62.9)	213	348.0	-35.8 (-199.5; 133.1)
Finland (East/West)	108	54.5	53.0 (20.6; 84.5)	774	398.6	188.2 (92.7; 282.6)
Norway (Tromsø)	35	36.1	2.5 (-38.3; 42.7)	356	356.2	29.1 (-97; 161.5)
Denmark (Glostrup)	33	42.4	39.2 (-3.3; 89.1)	224	412.6	229.3 (43; 398.4)
The UK	45	43.4	-7.8 (-48.2; 33.8)	241	234.6	119.7 (20.8; 214.4)
Northern Ireland (Belfast)	13	33.7	-15.8 (-62.4; 36.4)	102	226.5	22.8 (-130.2; 168.3)
Scotland (SHHEC Study)	32	60.5	-16.5 (-80.4; 55.3)	139	272.5	206.8 (48.4; 341.4)
Central and South Europe	104	24.6	4.5 (-11.9; 23.6)	396	144.0	92.1 (43.6; 139.7)
France	9	11.4	12.3 (-6.9; 31.3)	89	122.0	86.0 (1.3; 155.8)
Germany (Augsburg)	23	42.2	-21.9 (-100.1; 31.6)	92	315.7	279.4 (67.1; 481.1)
Northern Italy (Brianza)	22	35.0	0.1 (-47.5; 47.5)	96	200.8	160.5 (23.8; 300.5)
Central Italy (Latina)	43	66.5	57.9 (-14.9; 141)	86	154.1	128.1 (5.2; 248)
Southern Italy (Moli-Sani)	7	10.8	4.5 (-11.8; 42.2)	33	63.1	-16.8 (-79.4; 62.2)
East Europe and Russia	64	93.3	102.4 (33.2; 164.5)	90	208.0	112.7 (-43.3; 246.1)
Lithuania (Kaunas) ‡	12	36.4	38.2 (-24.3; 94.1)	65	199.6	29.8 (-138.5; 191.8)
Poland (Tarnobrzeg/Voivodship)§	22	85.6	57.7 (-53.5; 146.7)	-	-	- -
Poland (Warsaw)‡	10	121.5	195.7 (28.3; 425.1)	25	316.6	412.5 (51; 760)
Russia (Novosibirsk)§	20	189.8	233.3 (-57.7; 435.6)	-	-	- -

*: SII, Slope Index of Inequality; a SII >0 indicates higher event rates among the least educated men. †: Rate at the attained age of 60 years during the follow-up, per 100000 p-y. ‡: upper age limit at 65 years for non-fatal events. §: these centers contributed to the analyses of fatal events only (see methods).
Rates and SIIs estimated from Poisson regression models (see methods). 95% confidence interval for SII from n=2000 bootstrapped samples. SHHEC: Scottish Heart Health Extended Cohort.

Table 2: Number of events, event rates and difference (SII*) in the event rate between the least and the most educated women, for death from incident stroke (left) and stroke incidence (right). Women, 35-74 years old, free of CVD at baseline

Population	Death from incident stroke			Stroke incidence (fatal or non-fatal)		
	N	Rate†	SII* (95% CI)	N	Rate†	SII* (95% CI)
Nordic Countries	169	33.5	24.4 (7.7; 41.2)	1094	234.5	92.3 (45.6; 140.2)
Northern Sweden	28	22.9	12.7 (-16.4; 51)	176	265.9	-13.0 (-134.4; 124.9)
Finland (East/West)	86	33.3	22.3 (-0.9; 45.4)	567	227.3	93.0 (29.8; 158.4)
Norway (Tromsø)	31	36.4	25.7 (-15.4; 62.6)	174	207.9	141.3 (30.5; 237.3)
Denmark (Glostrup)	24	37.3	37.3 (-8.9; 83.1)	177	277.4	155.5 (16.1; 293.5)
The UK						
Scotland (SHHEC Study)	35	62.4	45.3 (-25.2; 108)	102	186.9	143.8 (9.7; 248.1)
Central and South Europe	76	16.6	5.6 (-8.1; 20.9)	235	92.3	30.4 (-17.7; 73.8)
Germany (Augsburg)	14	32.1	-13.5 (-75; 32.8)	67	222.8	123.2 (-58.7; 307.1)
Northern Italy (Brianza)	13	20.8	-17.8 (-52.8; 18.6)	50	77.4	-48.0 (-121.7; 32.9)
Central Italy (Latina)	43	23.1	27.0 (9; 68.8)	92	87.1	77.9 (20.7; 150.4)
Southern Italy (Moli-Sani)	6	5.7	-8.8 (-31.6; 0.7)	26	54.4	-1.9 (-67.6; 70)
East Europe and Russia	29	38.0	-5.3 (-47.7; 40.3)	63	152.3	-0.6 (-125.2; 118)
Lithuania (Kaunas)‡	7	22.8	10.3 (-7.3; 40.5)	52	166.7	18.4 (-126.8; 173.7)
Poland (Tarnobrzeg/Voivodship)§	8	31.8	-27.5 (-81.9; 36.7)	-	-	- -
Poland (Warsaw)‡	4	38.6	-31.1 (-139.5; 62.7)	11	160.8	-81.6 (-292.3; 176.1)
Russia (Novosibirsk)§	10	82.7	6.1 (-130.2; 169.5)	-	-	- -

*: SII, Slope Index of Inequality; a SII >0 indicates higher event rates among the least educated women. †: Rate at the attained age of 60 years during the follow-up, per 100000 p-y. ‡: upper age limit at 65 years for non-fatal events. §: these centers contributed to the analyses of fatal events only (see methods).
Rates and SIIs estimated from Poisson regression models (see methods). 95% confidence interval for SII from n=2000 bootstrapped samples. SHHEC: Scottish Heart Health Extended Cohort

Table 3: Age- and risk-factor-adjusted hazard ratio (RII*) of stroke incidence for the least compared to the most educated individuals by region, and % change in the index due to traditional and behavioural risk factors. Men (above) and women (below), 35-74 years old and free of CVD at baseline

	Age-adjusted			Age, smoking, BMI, alcohol intake				Age, non-HDL&HDL-cholesterol, SBP, diabetes				All risk factors			
	RII*	95% CI		RII*	95% CI		% Change†	RII*	95% CI		% Change†	RII*	95% CI		% Change†
Men															
Nordic Countries	1.32	1.09	1.59	1.20	0.99	1.45	-34.0	1.24	1.02	1.50	-22.5	1.16	0.96	1.41	-44.5
The UK	1.67	1.04	2.70	1.36	0.84	2.22	-39.4	1.54	0.96	2.50	-15.2	1.30	0.80	2.11	-49.4
Central and South Europe	2.09	1.43	3.06	1.92	1.31	2.81	-12.0	2.03	1.39	2.98	-4.1	1.89	1.28	2.78	-13.9
East Europe (Lithuania-Kaunas) ‡	1.34	0.55	3.26	1.21	0.48	3.03	-34.2	1.25	0.50	3.12	-23.2	1.09	0.43	2.79	-69.7
Women															
Nordic Countries	1.35	1.07	1.69	1.16	0.92	1.47	-48.9	1.20	0.96	1.51	-38.4	1.11	0.88	1.39	-66.3
The UK (Scotland)	1.82	0.82	4.03	1.31	0.58	2.95	-54.6	1.72	0.77	3.83	-9.2	1.28	0.57	2.90	-58.4
Central and South Europe§	1.52	0.94	2.47	1.59	0.97	2.59	10.3	1.29	0.79	2.11	-39.1	1.42	0.86	2.33	-16.7
East Europe (Lithuania-Kaunas) ‡	1.33	0.49	3.63	0.96	0.34	2.71	-112.8	1.10	0.39	3.09	-65.3	0.89	0.31	2.56	-139.3

*: RII, Relative Index of Inequality, as the ratio of the hazards of stroke incidence for the least educated and the most educated subjects.
†: % of change in log(RII) between the age and the RF-factors adjusted modes, computed as (ln(RII(adj)) - ln(RII(age)))/ln(RII(age))
Models are additionally adjusted by center and by cohort.
‡: upper age limit at 65 years for non-fatal events. §: German and Italian cohorts. French cohorts are men only.
Poland-Warsaw excluded due to the high prevalence of missing data on alcohol intake. Abbreviations: BMI = Body Mass Index, SBP=Systolic Blood Pressure

Figure 1. Age-adjusted hazard ratio (Relative Index of Inequality, RII*) of stroke incidence for the least compared to the most educated individuals with 95% confidence intervals by population, and pooled estimate from random effect model. Men (panel a.) and women (panel b.), 35-74 years old and free of CVD at baseline

*: RII, Relative Index of Inequality, as the ratio of the hazards of stroke incidence for the least educated and the most educated subjects
UK-Bel and France: cohorts of men only.

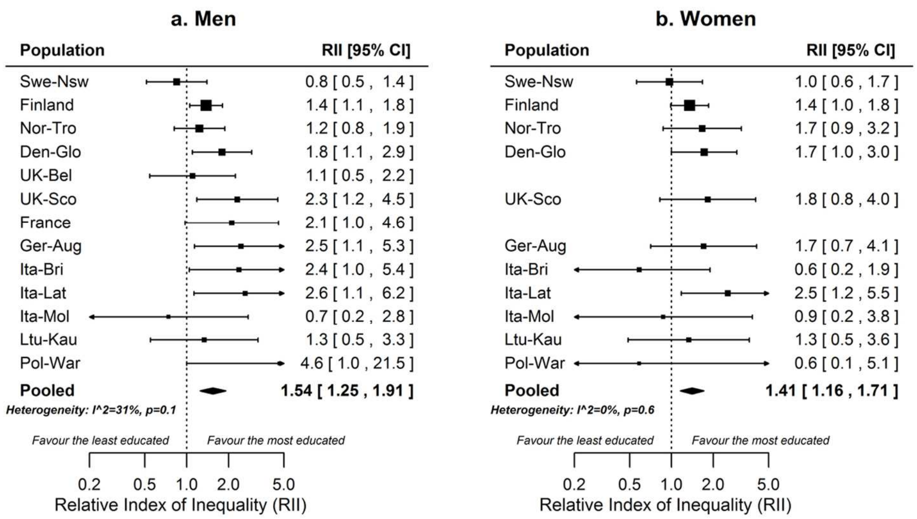

Figure 1. Age-adjusted hazard ratio (Relative Index of Inequality, RII*) of stroke incidence for the least compared to the most educated individuals with 95% confidence intervals by population, and pooled estimate from random effect model. Men (panel a.) and women (panel b.), 35-74 years old and free of CVD at baseline.

*: RII, Relative Index of Inequality, as the ratio of the hazards of stroke incidence for the least educated and the most educated subjects
UK-Bel and France: cohorts of men only.

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ONLINE SUPPLEMENT

Paper: "Determinants of social inequalities in stroke incidence across Europe: a collaborative analysis of 126 635 individuals from 48 cohort studies".

Supplemental Tables

Table I: Characteristics of the surveyed populations.

	Population	No. of cohorts	Baseline visit	No. of subjects		Age Range	Particip rates	Length of follow-up and stroke no.		
				M	**W**			**Years°°**	**F**	**F+NF**
Nordic Countries	Northern Sweden (Västerbotten\Norrbotten Counties)	5	1986-04	3078	3269	35-74	76%	14.0	57	389
Nordic Countries	East Finland (North Karelia\Kuopio\Oulu\Lapland)	5	1982-02	7689	8519	35-74	77%	13.9	120	883
Nordic Countries	West Finland (Helsinki\Turku\Loimaa)	5	1982-02	4716	5151	35-74	75%	13.9	74	458
Nordic Countries	Norway-Tromsø	1	1986-95	6878	6719	35-70	72%	15.8	66	530
Nordic Countries	Denmark-Glostrup[§]	3	1982-92	2522	2484	40, 50, 60	77%	20.0	57	401
The UK	Northern Ireland-Belfast[#]	1	1991-94	2537	-	49-60	52%	18.0	13	102
The UK	Scotland (SHHEC Study)^	6	1984-95	6685	6840	35-74	70%	10.0	67	241
Central and South Europe	France[°, #]	3	1991-93	7566	-	49-60	‡	10.0	9	89
Central and South Europe	Germany-Augsburg	1	1994-95	1740	1737	35-74	74%	13.9	37	159
Central and South Europe	Northern Italy-Brianza[§§]	4	1986-94	2552	2649	35-74	67%	14.6	35	146
Central and South Europe	Central Italy-Latina	2	1984-87	1567	2052	35-71	56%	17.9	86	178
Central and South Europe	Southern Italy-Moli-Sani	1	2005-10	10308	11580	35-74	70%	4.3	13	59
East Europe and Russia	Lithuania-Kaunas	3[†]	1983-93	2053	2131	35-64	65%	13.9	19	117
East Europe and Russia	Poland-Tarnobrzeg/Voivodship	3	1983-93	2103	2450	35-64	77%	11.4	30	-
East Europe and Russia	Poland-Warsaw	3	1983-93	2354	2332	35-64	75%	6.3	14	36
East Europe and Russia	Russia-Novosibirsk	2	1988-95	2205	2229	35-64	72%	4.5	30	-
	All populations	**48**	**-**	**66553**	**60082**	**-**	**-**	**10.0**	**727**	**3788**

§: Birth-cohorts of individuals 40, 50 and 60 years old at baseline. ^: SHHEC: Scottish Heart Health Extended Cohort. °: PRIME Lille, Strasbourg and Toulouse. ‡: participation rates: na Lille, 80% Strasbourg, 68% Toulouse. §§: MONICA-Brianza and PAMELA Study. #: these studies enrolled only men. °°: Median length of follow-up (years). †: in one cohort educational classes were defined based on the educational attainment, using the relationship between educational attainment and years of schooling observed in the remaining two cohorts.

Table II: Number of incident stroke events (fatal and non-fatal), age-adjusted event rates and age-adjusted hazard ratios (95% CI) for low, intermediate and high education, by population. Men (left) and women (right), 35-74 years old, free of CVD at baseline

		Men							Women						
Population	**Educ**	**N**	**# Ev**	**Event Rates^**	**HR°**	**95%CI**		**p-val°°**	**N**	**# Ev**	**Event Rates^**	**HR°**	**95%CI**		**p-val°°**
Northern Sweden	Low	1226	93	333.1	0.9	0.7	1.2		1165	70	247.9	1.0	0.7	1.4	
	Interm	757	50	363.2	1.0	0.7	1.4	0.8	962	51	302.4	1.2	0.8	1.7	0.6
	High	1095	70	353.7	ref	-	-		1142	55	253.3	ref	-	-	
Finland (East/West)	Low	4138	299	464.0	1.2	1.0	1.5		4327	212	258.2	1.2	1.0	1.5	
	Interm	3747	226	397.4	1.1	0.9	1.3	0.07	4177	174	231.9	1.1	0.9	1.4	0.2
	High	4250	249	339.0	ref	-	-		5136	181	196.8	ref	-	-	
Norway (Tromsø)	Low	2127	132	381.3	1.1	0.9	1.5		2231	85	284.5	1.4	0.9	2.0	
	Interm	2169	94	327.4	0.9	0.7	1.2	0.3	2107	36	147.7	0.7	0.4	1.1	0.02
	High	2582	130	360.0	ref	-	-		2381	53	188.2	ref	-	-	
Denmark (Glostrup)	Low	696	65	469.3	1.4	1.0	2.0		789	69	335.2	1.4	1.0	2.0	
	Interm	780	84	476.4	1.4	1.1	2.0	0.04	707	47	279.9	1.2	0.8	1.8	0.1
	High	1046	75	329.8	ref	-	-		988	61	231.7	ref	-	-	
Northern Ireland (Belfast)	Low	722	28	221.2	1.0	0.6	1.7								
	Interm	847	36	249.2	1.2	0.8	1.9	0.7			Men only				
	High	968	38	211.2	ref	-	-								
Scotland (SHHEC)	Low	3182	78	315.6	1.9	1.2	3.0		3632	62	216.3	1.6	0.9	2.7	
	Interm	1592	38	315.8	1.8	1.1	3.1	0.02	1303	22	202.7	1.7	0.9	3.2	0.2
	High	1911	23	167.1	ref	-	-		1905	18	120.5	ref	-	-	

Table II (cont.)

Population	Educ class	Men N	Men # Ev	Men Event Rates^	Men HR°	Men 95%CI	Men p-value°°	Women N	Women # Ev	Women Event Rates^	Women HR°	Women 95%CI	Women p-value°°
France	Low	2067	27	137.2	1.6	0.9 2.9							
	Interm	2513	38	154.5	1.8	1.1 3.1	0.06	Men only					
	High	2986	24	84.7	ref	- -							
Germany (Augsburg)	Low	619	40	419.1	1.8	1.1 3.0		618	30	284.2	1.4	0.8 2.4	
	Interm	500	27	305.3	1.3	0.8 2.3	0.06	451	13	177.1	0.9	0.5 1.8	0.4
	High	621	25	228.0	ref	- -		668	24	200.9	ref	- -	
Northern Italy (Brianza)	Low	1155	60	251.5	1.6	1.0 2.6		1113	16	70.8	0.8	0.4 1.5	
	Interm	489	13	160.9	1.0	0.5 2.0	0.09	615	13	54.0	0.5	0.2 1.0	0.1
	High	908	23	157.1	ref	- -		921	21	101.4	ref	- -	
Central Italy (Latina)	Low	565	35	204.4	1.8	1.0 3.3		623	39	124.9	1.8	1.1 3.0	
	Interm	593	34	132.5	1.1	0.6 1.9	0.04	648	26	75.0	1.2	0.7 2.0	0.04
	High	409	17	117.0	ref	- -		781	27	67.3	ref	- -	
Southern Italy (Moli-Sani)	Low	3605	11	54.6	0.8	0.4 1.9		4102	10	55.4	0.9	0.4 2.3	
	Interm	2122	9	71.8	1.2	0.5 2.8	0.7	2718	6	49.6	0.9	0.3 2.6	1.0
	High	4581	13	65.2	ref	- -		4760	10	56.4	ref	- -	
Lithuania (Kaunas)	Low	654	23	217.3	1.2	0.7 2.2		715	17	164.3	1.2	0.6 2.5	
	Interm	745	21	186.4	0.9	0.5 1.7	0.7	770	21	182.6	1.3	0.7 2.7	0.7
	High	654	21	196.6	ref	- -		646	14	150.2	ref	- -	

Table II (cont.)

Population	Educ class	Men N	Men # Ev	Men Event Rates^	Men HR°	Men 95%CI	Men p-value°°	Women N	Women # Ev	Women Event Rates^	Women HR°	Women 95%CI	Women p-value°°
Poland (Warsaw)	Low	731	12	499.0	2.8	1.0 7.9		742	2	83.0	0.6	0.1 3.1	
	Interm	776	8	302.9	1.7	0.5 5.1	0.1	700	5	262.2	1.8	0.5 6.7	0.4
	High	847	5	176.7	ref	- -		890	4	144.5	ref	- -	

^: Stroke incidence rate at the attained age of 60 years during the follow-up, per 100,000 person-years.
°: Hazard Ratio of first stroke event during follow-up for low and intermediate educations, as compared to subjects in the high educational class group (reference).
°°: 2 df test p-value for the null hypothesis of no association between education and stroke incidence. Belfast, France: men only.
Abbreviations: Educ = educational, Interm = Intermediate, Ev = event, HR = Hazard Ratio, CI = confidence Interval, SHHEC: Scottish Heart Health Extended Cohort.

Table III: Inequality in the distribution of major risk factors, by region. Men and women, 35-74 years old, free of CVD at baseline.

Population	Non HDL-C° (mmol/L)	HDL-C°° (mmol/L)	Systolic BP° (mmHg)	BMI° (Kg/m^2)	Smoke^	DM^	Alcohol intake (drinks/day)^		
							0	**1-2**	**3+**
Men									
Nordic Countries	**0.31**	0.01	**2.1**	**0.97**	**2.7**	1.2	ref	**0.5**	**0.4**
The UK	-0.05	-0.02	**3.6**	**0.75**	**3.5**	1.0	ref	**0.5**	1.2
Central and South Europe	-0.02	**0.04**	**2.3**	**1.42**	**1.7**	**1.5**	ref	**1.6**	**0.7**
East Europe (Lithuania-Kaunas)	**-0.20**	**0.09**	**3.7**	0.16	**3.7**	1.8	ref	0.9	**5.4**
Women									
Nordic Countries	**0.47**	**-0.10**	**4.8**	**1.99**	**3.3**	**1.5**	ref	**0.3**	**0.3**
The UK (Scotland)	**0.31**	**-0.17**	**5.1**	**1.81**	**4.5**	1.0	ref	**0.4**	**0.4**
*Central and South Europe**	-0.01	**-0.08**	**4.9**	**3.50**	**0.7**	**2.2**	ref	**1.6**	1.1
East Europe (Lithuania-Kaunas)	-0.16	**-0.09**	**5.9**	**3.06**	1.2	**5.0**	ref	**0.6**	na

°: Slope Index of Inequality, as the mean difference between the least and the most educated subjects. If SII > 0, the mean value is higher (= less favorable risk factor distribution) among the least educated than in the most educated subjects.
°°: Slope Index of Inequality, as the mean difference between the least and the most educated subjects. If SII > 0, the mean value is higher (= more favorable risk factor distribution) among the least educated than in the most educated subjects
^: Relative Index of Inequality, as the risk factor prevalence ratio between the most and the least educated subjects. If RII > 1, the risk factor prevalence is higher among the least educated subjects
In bold: rejection of the null hypothesis of no difference among educational classes at 5% significance level.
The SII (RII) were estimated from linear (logistic) regression models adjusting for baseline age and cohort. For alcohol intake we used a generalized logistic model.
*: German and Italian cohorts. French cohorts are men only.

Table IV: Age- and risk-factor-adjusted hazard ratio (RII*) of ischemic stroke incidence for the least compared to the most educated individuals by region, and % change in the index due to traditional and behavioral risk factors. Men (above) and women (below), 35-74 years old and free of CVD at baseline

	Age-adjusted			Age, smoking, BMI, alcohol intake				Age, non-HDL&HDL-cholesterol, SBP, diabetes				All risk factors			
	RII*	95% CI		RII*	95% CI		% Change†	RII*	95% CI		% Change†	RII*	95% CI		% Change†
Men															
Nordic Countries	1.36	1.10	1.69	1.22	0.99	1.52	-34.5	1.28	1.03	1.58	-20.5	1.19	0.96	1.48	-42.9
The UK	2.04	1.19	3.51	1.74	1.01	3.02	-22.2	1.89	1.10	3.25	-11.0	1.66	0.96	2.87	-29.3
Central and South Europe	2.68	1.72	4.17	2.41	1.54	3.77	-10.5	2.62	1.68	4.09	-2.2	2.40	1.53	3.76	-11.0
Women															
Nordic Countries	1.34	1.03	1.74	1.14	0.87	1.48	-55.7	1.19	0.92	1.54	-41.1	1.08	0.83	1.41	-73.2
The UK (Scotland)	1.81	0.74	4.44	1.28	0.51	3.21	-58.1	1.68	0.68	4.15	-12.7	1.24	0.49	3.12	-63.6
Central and South Europe§	1.70	0.94	3.07	1.74	0.96	3.17	4.7	1.47	0.80	2.67	-27.7	1.58	0.86	2.89	-13.8

*: RII, Relative Index of Inequality, as the ratio of the hazards of stroke incidence for the least educated and the most educated subjects.
†: % of change in log(RII) between the age and the RF-factors adjusted modes, computed as (ln(RII(adj)) - ln(RII(age)))/ln(RII(age))
Models are additionally adjusted by center and by cohort.
‡: upper age limit at 65 years for non-fatal events. §: German and Italian cohorts. French cohorts are men only.
Poland-Warsaw excluded due to the high prevalence of missing data on alcohol intake. Lithuania-Kaunas excluded due to the low number of ischemic stroke events.
Abbreviations: BMI = Body Mass Index, SBP=Systolic Blood Pressure