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

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ABSTRACT

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.

Materials and methods The MORGAM (MOnica Risk, Genetics, Archiving and Monograph) Study comprises 48 cohorts recruited mostly in the 1980s and 1990s in four European regions using standardised 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 HRs for the least versus the most educated individuals.

Results Compared with their most educated counterparts, the overall age-adjusted excess hazard for stroke was 1.54 (95% CI 1.25 to 1.91) and 1.41 (95% CI 1.16 to 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 with most educated men and women, respectively. The additional events were equivalent to 47%–130% and 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 lifestyles in the most disadvantaged individuals should have a prominent impact in reducing both inequalities and the stroke burden.

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 10 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 programmes 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 socioeconomic 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 USA, the UK and the Nordic Countries.[4–9] Second, the documented heterogeneity across studies[6] arising from differences in the measure of socioeconomic 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 prioritise 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 harmonised and underwent 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 (1) assess the burden of educational class inequalities in stroke incidence and (2) estimate the extent to which inequalities in stroke incidence can be accounted for by the social gradient in risk factors, across Europe.

MATERIALS AND METHODS

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 (see online supplementary table I). 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 summarised 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-specific, sex-specific 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 min of 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 high-density lipoprotein (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) or 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 g of alcohol as a standard drink.[13] We further categorised alcohol intake as abstainers (less than 0.5 drinks per day), 1–2, 3–4 and ≥5 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 129 747 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 126 635 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% CIs 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 100 000 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 HR for the least compared with 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-effect 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, BMI 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: $(\mathrm{In}\ RII[RFadj] - \mathrm{In}\ RII[age]/\mathrm{In}\ RII[age]) \times 100$ 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=108 184), which led to the exclusion of Poland-Warsaw due to the high prevalence of missing information on alcohol consumption. We used standard multiple imputation

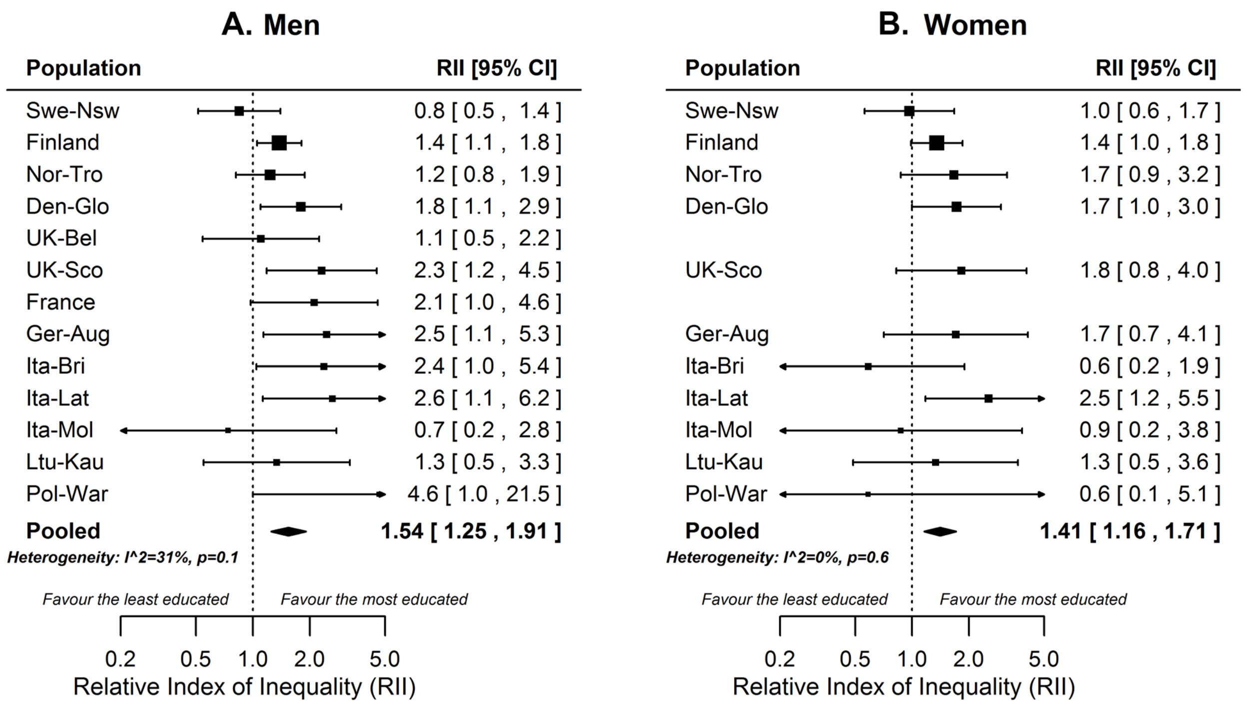

Figure 1 Age-adjusted HR (RII) of stroke incidence for the least compared with the most educated individuals with 95% CIs by population and pooled estimate from random-effect model. Men (A) and women (B), 35–74 years old and free of cardiovascular disease at baseline. RII, as the ratio of the hazards of stroke incidence for the least educated and the most educated subjects. UK-Bel and France: cohorts of men only.

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 (figure 1) and SAS V.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 (table 1, second column) 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 (table 1, sixth column) 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, second column), and the ranking of stroke incidence rates was more similar to the one previously described for men (table 2, sixth column).

Absolute inequalities in stroke rates

The least educated men had higher rates of death from incident stroke (ie, 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. We estimated no statistically significant negative SIIs (higher rates in least educated), both for men and women. In those populations with a statistically significant positive SII, the ratio between the SII and the average incidence rate ranged between 47% (Finland) and 130% (Warsaw) in men and between 40% (Finland) and 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 versus the most educated individuals (RII) by populations is displayed in figure 1, in men (left panel) and women (right panel), while event rates and HRs in each educational class are shown as online-only material (online supplementary table II in supplementary file). 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 to 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 to 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 online supplementary table III in supplementary file. Most of RIIs were reduced after adjustment for smoking, alcohol intake, BMI, 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

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 cardiovascular disease at baseline

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

*An SII >0 indicates higher event rates among the least educated men.
†Rate at the attained age of 60 years during the follow-up, per 100 000 person-years.
‡Upper age limit at 65 years for non-fatal events.
§These centres contributed to the analyses of fatal events only (see the Materials and methods section).
SHHEC, Scottish Heart Health Extended Cohort Study; SII, Slope Index of Inequality.

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 cardiovascular disease at baseline

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

*An SII >0 indicates higher event rates among the least educated women.
†Rate at the attained age of 60 years during the follow-up, per 100 000 person-years.
‡Upper age limit at 65 years for non-fatal events.
§These centres contributed to the analyses of fatal events only (see the Materials and methods section).
SHHEC, Scottish Heart Health Extended Cohort Study; SII, Slope Index of Inequality.

Table 3 Age-adjusted and risk factor-adjusted HR (RII*) of stroke incidence for the least compared with 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 cardiovascular disease at baseline

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

Models are additionally adjusted by centre and by cohort. Poland-Warsaw was excluded due to the high prevalence of missing data on alcohol intake.
*RII 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)).
‡Upper age limit at 65 years for non-fatal events.
§German and Italian cohorts. French cohorts are men only.
BMI, body mass index; SBP, systolic blood pressure; RII, Relative Index of Inequality.

by 30% and remained statistically significant in men (1.33; 95% CI 1.09 to 1.62), but not in women (1.17; 95% CI 0.96 to1.43). 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 accounted for more than the latter in all these HRs. 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 multinational 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, and reported larger reductions in death rates among the less educated individuals.[20] Gallo and colleagues[21] estimated that the least educated European men and women had a 42% and 41% overall excess risk of age-adjusted stroke death, respectively. 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 *et al*.[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-harmonised 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 as absolute (SII) or relative (RII) inequalities, can overwhelmingly better characterise the social gap than the corresponding inequalities in stroke death rates in our European populations. 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 100 000 person-years in the least educated individuals corresponded to 47%–130% and 40%–89% of the average incidence rates, respectively. As low education is associated with increased poststroke 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 HR of 47% (range across studies: 28%–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 estimate 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, that is, cigarette smoking, alcohol intake and BMI. From the paper by Gallo *et al*,[21] it is possible to infer that the same behavioural risk factors, in addition to the 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 (online supplementary table III), thus explaining the lack of attenuation attributable to these factors. These advantages were still present in the most recently recruited cohort (ie, the Moli-Sani Study, with recruitment period 2005–2010) and may be due to cultural and social factors. Educational differences of other risk factors, such as 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 (online supplementary table III in supplementary file). 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; that is, binge versus non-binge was not known. In some centres, 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 ischaemic 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 (online supplementary table IV) restricted to ischaemic 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 standardised measurement of risk factors and thorough endpoint assessment. By deriving three educational classes based on age-specific 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 with 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.

What is already known on this subject

- ► Two recent reviews and one meta-analysis highlighted the increased risk of stroke among lower socioeconomic classes.
- ► However, current knowledge on the origins of social inequalities in stroke across Europe hinders the possibility to prioritise interventions that might help close the social gap in different populations.

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