

## **Incidence of ischemic stroke according to income level among older people: the 3C study**

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### **Abstract**

#### **Background**

Stroke has been shown to follow a social gradient with incidence rising as socioeconomic status decreases.

#### **Objective**

To examine the relationship between socioeconomic status and ischemic stroke risk amongst older people.

#### **Setting**

The Cities of Bordeaux, Dijon and Montpellier in France.

#### **Subjects and methods**

9294 non institutionalised persons aged 65 years or more followed for 6 years.

## **Results**

The distribution of cardiovascular risks factors was consistent with the classical finding of more favourable risk profiles among the advantaged socioeconomic groups. 136 individuals developed a first ever ischemic stroke (incidence rate: 3.2 per 1000 py, 95% CI 2.7-3.8). The age and sex adjusted incidence of ischemic stroke increased with increasing level of income (from 2.4 to 4.1 per 1000 py,  $p=0.04$ ). In the multivariable analysis adjusting for cardiovascular risk factors, the higher income group displayed a 80% increased risk of ischemic stroke compared with less wealthy participants (hazards ratio 1.77, 95% CI 1.20-2.61).

## **Conclusions**

In this community-based sample of older individuals, a higher level of household income was associated with a higher risk of ischemic stroke, a reversal of the social gradient usually reported in younger age groups. Selective survival is one of the potential explanations for this unexpected finding.

## **Key words**

aged, elderly, social class, stroke

## Introduction

Stroke carries a high human, family and societal burden which is unfairly distributed [1;2]. Like most other diseases, stroke has been shown to follow a social gradient with higher levels of morbidity and mortality associated with lower socioeconomic status (SES) [3;4]. This pattern held during the 1990s in European countries, whether cerebrovascular disease mortality [5] or stroke prevalence [6] were analysed in relation to education level. Although overall socioeconomic disparities in mortality have been shown to decrease in older age [7], less is known about what happens at the level of specific causes of morbidity and mortality in this age group. In the face of population ageing, the question of health inequalities in older age is critical [8]. Studying stroke in this respect seems particularly pertinent since registries from England, Germany and France have shown that 3 out of 4 strokes occur over 65 [9]. In Europe, analysis of stroke mortality according to educational level showed that the intensity of the social gradient decreases with age [10]. Using wealth and income as a socioeconomic indicator, cohort studies from the USA showed a decrease of the social gradient over 65 years in one case [11], and a reversal over 74 years in the other case [12]. Reasons for this phenomenon are not clear and may include a combination of causes and artefacts. It should be noted that former studies did not analyse risk by type of stroke, which might be of interest since ischemic and hemorrhagic strokes display differing patterns of risk factors and pathological mechanisms. The impact of high blood pressure is significantly more important on hemorrhagic compared to ischemic strokes [13], whereas there is evidence that *APOE* genotype is associated with hemorrhagic but not with ischemic stroke [14]. This study therefore explores the association between socioeconomic status and ischemic stroke risk using data from the Three-City (3C) study, a cohort of French residents aged 65 years or more established in 1999.

## Methods

The Three-City (3C) study is an ongoing longitudinal study that aims to evaluate the relation between vascular risk factors and risk of dementia. A detailed account of the study design is available elsewhere [15]. Briefly, between 1999 and 2001, 9294 non-institutionalized persons aged 65 years and over were enrolled in three French cities (Bordeaux, Dijon and Montpellier). Administrative districts were selected in the first stage of the sampling procedure. Eligible inhabitants identified by the electoral rolls were invited to participate. Among all persons contacted the acceptance rate was 37%. Baseline data, including household income, alcohol and tobacco consumptions, self-rated health, medical history and medication use were collected during face to face interviews. Measurements of height, weight, systolic and diastolic blood pressure, and ECG recording were performed during clinical examinations. History of stroke prior to study inclusion was defined as self-report of hospital admission for stroke. At each follow-up examination (2, 4 and 6 years after enrolment), information was collected concerning suspicion of stroke occurrence. An endpoint adjudication committee reviewed source documentation for all individuals with a suspected stroke or for those who died during follow-up. Outcomes were coded according to the tenth revision of the International Classification of Diseases. A stroke was classified as non-fatal if the patient was alive 28 days after stroke onset. One laboratory (University Hospital of Dijon) analysed all blood specimens (consented by 95% of participants) for the determination of parameters such as glycaemia and lipids levels.

Participants were asked to indicate their monthly [current](#) household income in one of four categories (<750€, 750 to 1500€, 1500 to 2200€, >2200€). Participants also indicated whether they lived alone, with their partner, or with other relatives. In the latter instance, no further information regarding household composition was sought thus precluding estimation of

household income per consumption unit. Instead we repeated analyses on the sub-sample of participants living with a partner (60% of all participants). Education level was categorised as no education (no diploma), intermediate (secondary school) or high (above secondary school). We used standard criteria to define hypertension (SBP>160 mmHg, or DBP>95 mmHg, according to definition used at study onset), diabetes (glycaemia > 7mmol/l, or treatment) and hypercholesterolaemia (serum cholesterol  $\geq$  6mmol/l or treatment). Smoking behaviour was classified as non smoker, former smoker or current smoker. Alcohol consumption was classified in 5 categories (abstinent, 1 to 9, 10 to 19, 20 to 29 and 30 or more gr/day). We dichotomised the five points self rated health scale as very good and good versus average, bad or very bad.

We first calculated and tested trend in prevalence of risk factors according to income level. We then calculated standardised incidence rates - per 1000 person-years (py) - by levels of income, education and for participants living with their partner or not, excluding those with a prior stroke at inclusion. We used the logrank test to identify a trend in ischemic stroke incidence according to income level. In the multivariable analysis, we dichotomised the income variable defining high income as reporting 2200€ or more per month. We used Cox proportional hazards modelling to estimate the association between income and ischemic stroke risk, and to examine whether this association was affected by other social, behavioural and biological risk factors. Since results did not differ by sex in the multivariable analysis, we combined men and women so as to increase the precision of the estimates. All analyses were performed with Stata v 10.2 (StataCorp LP, Texas, USA).

## Results

Of the 9 294 participants, 8 676 (93 %) provided information on household income. As income levels increased, participants were more often male, younger, better educated and more often living with a partner (table 1). Those not living with a partner were either living alone (49% in the low income group, versus 13% in the high income group) or sharing accommodation with a relative (5% versus 2%,  $p < 10^{-3}$ ). There were significant differences between higher and lower income participants regarding biological cardiovascular risk factors. The prevalence of high blood pressure and diabetes decreased as income increased. Given the presence of hypertension, receiving antihypertensive treatment was more frequent in the low income group. Lower income participants were more likely to be overweight, but alcohol consumption and smoking were more frequent among the more wealthy participants. There was a moderate but statistically significant downward trend in history of coronary event as income increased, but none for history of stroke.

After exclusion of 270 individuals (3%) who declared a history of stroke at baseline and of a further 337 subjects (4%) who had missing follow up data, 8 644 participants were involved in the longitudinal, prospective analysis. During the 6-year follow-up period, 180 subjects had a first ever stroke (incidence rate: 4.3 per 1000 py, 95%CI:3.7 to 5). 136 of which (76%) were ischemic strokes (incidence rate: 3.2 per 1000 py, 95%CI:2.7 to 3.8). Ischemic stroke incidence in women was nearly half the level in men (age adjusted rate ratio: 0.57, 95% CI 0.40 to 0.80). There was a statistically significant trend of increasing incidence as level of income increased [from 2.42 to 4.11 per 1000 py](#) (logrank test for trend:  $p=0.04$ ), although incidence did not gradually increased from the second to the third income groups (table 2). No association was observed between ischemic stroke incidence and either education level or

living in a couple. There were 8 fatal ischemic strokes and the case fatality was 5% (3/58) in the highest income group compared with 7% (5/68) in all other participants ( $p=0.72$ ).

Table 3 summarises the results of the multivariable analysis investigating the potential effects of known risk factors on the association between ischemic stroke incidence and income level dichotomised as high (> 2 200€ per month) versus low. As mentioned above, we performed multivariable analysis on the total population (panel on the left of the table) and on the restricted sample of participants living with a partner (right hand side panel) as a further validation step. The results suggest a statistically significant 70% increased risk of ischemic stroke with higher income. Adjustment for risk factors only marginally modified this association.

## Discussion

In this prospective study on a sample of French non institutionalised older people we found a substantial increase (~70%) of ischemic stroke incidence among participants with the highest income compared to the rest of the sample. Among the strengths of this study was the ability to consider ischemic, as opposed to all strokes and to adjust for cardiovascular risk factors. The results are compatible with the existence of an increasing trend of ischemic stroke incidence with increasing level of income. The high level of follow up and a thorough ascertainment of events contribute to the validity of this study.

This finding is the opposite to what is seen in younger populations [3;16] and raises a number of questions, some of which relate to specific features of the 3C study. Firstly, the 37% acceptance rate at inception of the cohort questions the ability of the sample to fairly represent

the general population. Compared with the 1999 population census, 3C participants were younger, more often born in France (94% versus 82%,  $p < 10^{-3}$ ) and had more often been to university (23% versus 16%,  $p < 10^{-3}$ ). This suggests an overrepresentation of individuals of high socioeconomic status in the sample. Healthy volunteering is likely to have been an important factor influencing acceptance and this could in part explain why stroke incidence among the 3C participants of Dijon is approximately 30% lower than that measured in 1995-1997 in the Dijon population-based stroke register [9]. What is critical for the interpretation of our findings however, is whether healthy volunteering affected acceptance differentially between income groups leading to, for example, the enrolment of a higher proportion of less healthy high income individuals.

Although we can not rule out that such a selection process has occurred, several arguments plead against it as a major or sole explanation to our findings. Firstly, low income participants displayed, as would be expected, a less favourable cardiovascular risk profile, including significantly higher frequencies of prior coronary events, higher prevalence of high blood pressure and diabetes (table 1). Secondly, their overall health level, as reflected by self rated health, was lower than that of higher income participants. Lastly, and more importantly, low income (<2200€) was associated with a significantly higher all causes mortality risk (age and sex adjusted hazards ratio: 1.22; 95%CI:1.05 to 1.43). Therefore, the benefit of a lower incidence of ischemic stroke did not translate into better survival.

This pattern of higher mortality among low income participants raises then the question of competing risks. This would arise if a significant proportion of individuals from the lower income group dropped out from the cohort by death due to a disease which has similar risk factors but earlier onset than ischemic stroke. Coronary heart diseases (CHD) and tobacco

linked cancers such as lung cancer are likely candidates. 97 CHD deaths were recorded during follow-up of the study population and, although the risk estimates suggested a lower CHD mortality among the higher income group, this difference did not reach statistical significance (age and sex adjusted hazards ratio: 0.77, 95% CI 0.49 to 1.22). There was no statistically significant difference in mortality from lung cancer between the two income groups either (n=44 deaths, age and sex adjusted hazards ratio: 0.93; 95% CI 0.49 to 1.76). Competing risks may therefore contribute, but in our opinion, are unlikely to account for all the association identified between ischemic stroke risk and higher household income.

Since identification of strokes relied on self-reporting our findings could result from a lower level of case ascertainment in the low income groups. However, low income (<2200€) participants did not declared significantly less symptoms than those in the high income group (respectively 4.2 and 4.8%, p=0.28), but their symptoms were less frequently confirmed as stroke case by the adjudication committee (34% versus 43%, p=0.04). The similar proportions of ischemic stroke cases admitted to hospital (79% and 77% respectively in low and high income groups), suggesting comparable level of severity, are not in favour of significant under-ascertainment among the low income group either.

An association between high stroke incidence and high socioeconomic status was also found in two USA studies [12;17]. Both of them suggest that stroke incidence in high and low socioeconomic groups crosses over around the age of 75. In France, higher stroke mortality in low socioeconomic status population has been shown under 65 years of age for the period 1970 to 1990 [16]. If this situation still held between 2000 and 2006, a cross over of ischemic stroke incidence in high and low income population might have occurred before [or around](#) age 65 [in our sample. Differences in methods, outcomes \(e.g. all strokes versus ischemic strokes\).](#)

as well as in ~~and in~~ background levels of risk factors prevalence (or earliness of exposures over lifetime) and stroke incidence may further explain this discrepancy.

Why would stroke incidence in old age be associated with high socioeconomic status remains a puzzling question. The contribution of cardiovascular risk factors, which, in younger age groups, have been shown to explain a large amount of socioeconomic status disparities [12;18], does not seem to be of similar importance in old age. Variation in detection and management of these risk factors, particularly of high blood pressure, could determine incidence disparities. Although there is evidence in the 3C sample that hypertensive high income participants were less often receiving treatments (-6%), this difference did not affect significantly the risk variations. A similar comment applies to atrial fibrillation: ~~which~~ although less frequent in the lowest income group (c.f. table 1), it was evenly distributed after adjustment for age and gender (2.2% in both groups of income). Known risk factors have been said to explain only 60% of attributable risk for stroke (compared with 90% for ischemic heart disease) [19]. Self declared household income at age 65, a marker of long-life earning, is an unlikely direct causal factor. Which individual factor(s) or interaction(s) of genetic, environmental, behavioural, social and psychosocial determinants acted, and when over the lifecourse, to determine the difference we observed is therefore open to question.

The selective survival hypothesis, as suggested by Avendano et al, may provide a potential explanation [12]. Selective survival refers to the phenomenon whereby above an age threshold of around 75 years old, mortality of advantaged population rises faster so as to crossover that of disadvantaged populations [20]. A plausible biological explanation for this phenomenon is that a genetic determinant of longevity initially homogeneously distributed across populations, ends up being more prevalent among the disadvantaged at old age, once

other factors have taken their toll [21]. Both materialist and psychosocial theories relating to health inequalities suggest that, due to lack of resources, poor people are exposed to less healthy living environments and less able to avoid health risks or to adopt more healthy behaviours, through direct or indirect pathways [22]. If these pressures intervened during early and working life, observing participants over 65 years in a prospective study would result in studying  $\sigma$ resistant poor $\sigma$ . The very low level of ischemic stroke incidence observed in our study suggests the presence of resistance factors among low income participants than susceptibility factors among the high income group, which is what would be expected under the selective survival hypothesis.

Most work on health inequalities rightly concentrates on premature morbidity and mortality. Bearing in mind the overall challenge of understanding and tackling social health inequalities [22], this study highlights the merits of examining social distribution of specific diseases in older age and the potential of such analysis to raise questions about etiological mechanisms. From a clinical point of view, the implication of this finding is that, despite their more favourable cardiovascular risk factor profile, specific attention should be paid towards ischemic stroke risk amongst affluent seniors.

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Table 1 : Sociodemographic characteristics and risk factors frequencies according to income level

Monthly household income	<750"	750-1500"	1500-2200"	>2200"	p (trend)
	n = 516	n = 2711	n = 2449	n = 3000	
<b>Sociodemographic characteristics</b>					
Male	14%	25%	43%	55%	< 10 <sup>-3</sup>
Age (mean)	75.3	74.9	73.8	73.5	< 10 <sup>-3</sup>
Living with partner	10%	34%	68%	86%	< 10 <sup>-3</sup>
High education	6%	6%	14%	38%	< 10 <sup>-3</sup>
<b>Behavioral risk factors</b>					
BMI >25 kg/m <sup>2</sup>	59%	54%	53%	50%	< 10 <sup>-3</sup>
Smoking (former or current)	24%	29%	42%	48%	< 10 <sup>-3</sup>
Alcohol consumption (> 20g/d)	11%	18%	27%	32%	< 10 <sup>-3</sup>
<b>Biological risk factors</b>					
High blood pressure	69%	65%	60%	58%	< 10 <sup>-3</sup>
Atrial fibrillation*	1.08%	2.49%	2.18%	2.76%	0.16
Diabetes	13%	11%	11%	9%	0.001
High blood cholesterol	55%	60%	57%	55%	0.002
Good or very good self rated health	44%	53%	61%	66%	< 10 <sup>-3</sup>
<b>Medical history</b>					
Coronary event	16%	12%	10%	12%	0.03
Stroke	3.3%	2.9%	2.6%	3.2%	0.84
<b>Medication use</b>					
Anti hypertensive	83%	83%	82%	77%	< 10 <sup>-3</sup>
Aspirine	21%	17%	18%	20%	0.05

All % exclude missing records

\* Information missing for 1414 participants

Table 2: Ischemic stroke incidence (per 1 000 person-years) by socio-economic status

	No.	Person-Years	Incidence Rate* (95%CI)	Hazard Ratio* (95%CI)
Monthly household income «				
<750"	5	2 179	2.42 (0.00 - 5.27)	1.00
750-1500"	35	12 299	2.89 (1.19 - 3.92)	1.33 (0.52 - 3.42)
1500-2200"	28	11 242	2.49 (1.57 - 3.42)	1.16 (0.44 - 3.04)
>2200"	58	13 784	4.11 (2.97 - 5.25)	1.89 (0.74 - 4.82)
Education level				
No education	14	3 959	3.36 (1.57 - 5.15)	1.00
Intermediate	92	29 793	3.14 (2.50 - 3.79)	0.92 (0.52-1.62)
High education	30	8 187	3.32 (2.07 - 4.57)	1.00 (0.52-1.89)
Living with partner				
No	48	16 675	3.25 (2.12 - 4.37)	1.00
Yes	88	25 326	3.59 (2.76 - 4.42)	1.22 (0.82-1.81)

\* *adjusted for age and sex*

Ä *Total number of events amounts to 126 because of missing household income data*

Table 3 : Association between income level and ischemic stroke risk

	All participants		Participants living with partner	
	Low income*	High income	Low income*	High income
No.	5 285	2 802	2 436	2 414
No. of strokes	68	58	30	51
Hazard ratio (95%CI)				
Adjusted for age, sex and educational level	1	1.68 (1.15-2.47)	1	1.67 (1.04-2.67)
Adjusted for biological risk factors«	1	1.72 (1.17-2.53)	1	1.72 (1.08-2.76)
Adjusted for behavioral risk factorsr	1	1.75 (1.19-2.58)	1	1.69 (1.05-2.73)
Adjusted for medication§	1	1.69 (1.15-2.49)	1	1.65 (1.03-2.64)
Fully adjusted	1	1.77 (1.20-2.61)	1	1.71 (1.06-2.74)

*Note: all hazard ratios are adjusted for age, sex and education level*

*\* baseline category*

*« include high blood pressure, atrial fibrillation, diabetes and hypercholesterolaemia*

*r include smoking, alcohol consumption and overweight*

*§ include antihypertensive and aspirin*

*include all risk factors and medication use*