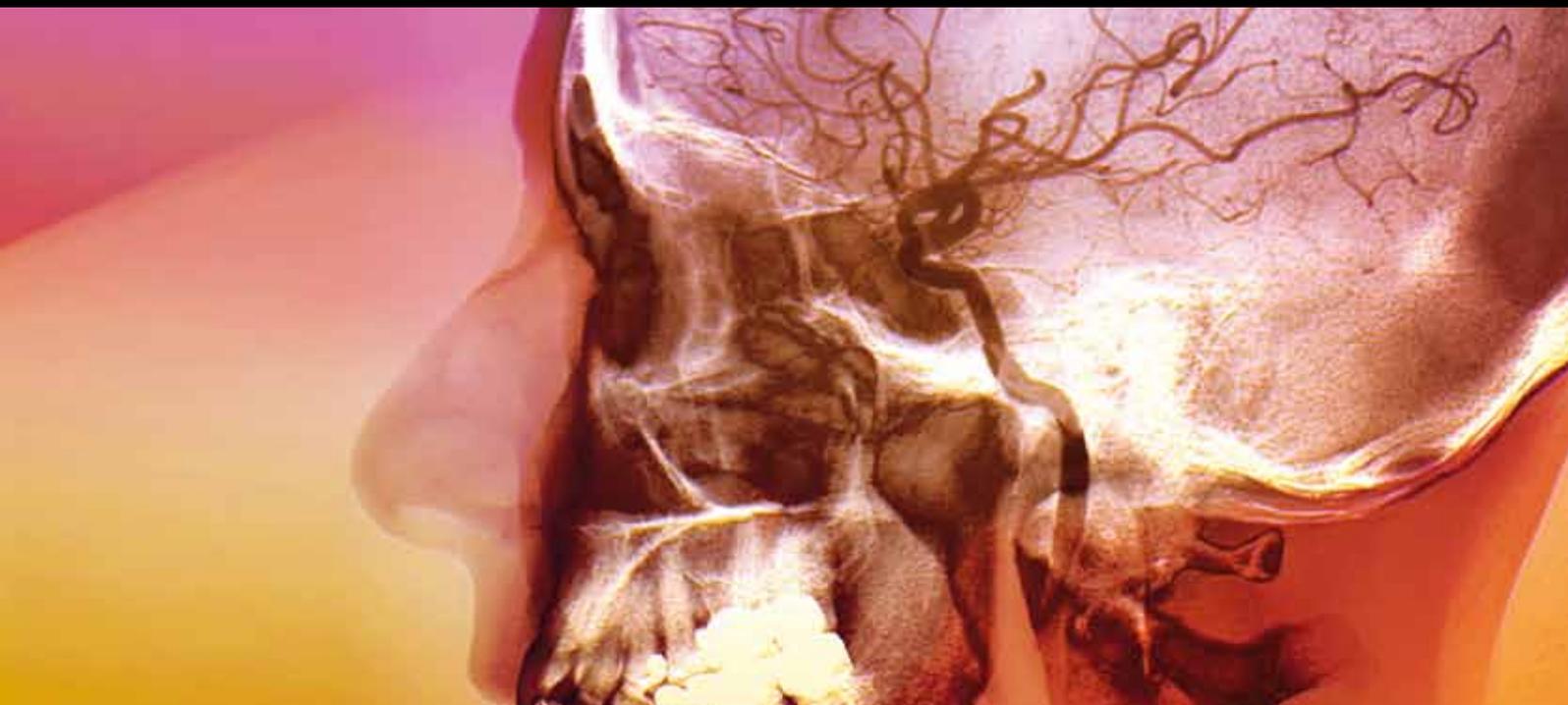


Stroke in the Young 2012

Guest Editors: Halvor Naess, Turgut Tatlisumak, and Janika Kõrv





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Stroke Research and Treatment

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Editorial

Stroke in the Young 2012

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This is the second special issue on stroke in the young. In recent years there has been an increasing research activity concerning stroke in young adults and children. Important data has been published as to long-term outcome in young adults with cerebral infarction. Long-term mortality is high compared to controls without stroke and more is known about risk factors both regarding mortality and recurrence of stroke or other vascular events. This knowledge helps physicians to target secondary preventive medication. Most prognostic studies have been performed among young patients with cerebral infarction. Less is known about prognosis after cerebral hemorrhage. This is at least partly due to lower frequency of cerebral hemorrhage than cerebral infarction. We hope that more research will be performed among young patients with cerebral hemorrhage in the future. In addition, more studies from developing countries and from nonwhite populations are needed in all aspects of ischemic and hemorrhagic stroke in the young and in children.

The range of causes underlying stroke is wider in children and young adults than in old stroke patients. This makes diagnosis and choice of treatment particularly challenging in young patients. The present issue includes 6 papers which offer a small contribution to the knowledge that may help physicians reach better decisions as to providing better care for young stroke patients.

This special issue includes 6 articles ranging from perinatal stroke to long-term survival after stroke in young adults. One paper reports factors associated with social, thought, and attention problems in children with perinatal stroke. These factors included male gender, neonatal seizures, and uteroplacental insufficiency. A study from China compares

the distribution of risk factors in young stroke patients with old stroke patients. Hypertension and diabetes mellitus were equally frequent among young and old stroke patients, whereas smoking and heavy drinking were much more frequent among young stroke patients. Heart disease was more common among old stroke patients. A study from Canada shows that ischemic stroke is associated with acute exposure to ambient sulfur dioxide. A comparison of provision of stroke care in younger and older patients in London shows that younger patients had equal or greater access to evidence-based care than older patients. A study from Sweden including more than 10,000 stroke patients, 40–59 years old, shows that low income was associated with higher long-term mortality. A study from Estonia compares long-term survival of young stroke patients included in two time periods (1991–1993 and 2001–2003). Patients with intracerebral hemorrhage had the lowest survival. Five-year survival rate for patients with ischemic stroke 15 to 44 years was 75%. There was no difference in overall long-term survival for the two time periods.

We hope this special issue presents information that may be of help in caring for children and young adults with stroke and that it will unleash ideas for future research.

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Research Article

Age- and Gender-Specific Prevalence of Risk Factors in Patients with First-Ever Ischemic Stroke in China

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Background. Evidences are accumulating that age and gender have great impact on the distribution of stroke risk factors. Such data are lacking in Chinese population. **Methods.** 1027 patients with first-ever ischemic stroke (IS) were recruited and divided into young adult (<50 years), middle-aged (50~80 years), and very old (>80 years) groups according to stroke onset ages. Vascular risk factors were collected and compared among groups. **Results.** Female patients were globally older than male patients at stroke onset and having higher prevalence of diabetes mellitus (DM), heart diseases, and atrial fibrillation (AF). However, females were less likely to drink heavily or smoke than males. Young patients had a much higher proportion of smoking and drinking than middle-aged and very old patients and the highest family history of hypertension, while very old patients had the highest prevalence of heart diseases and AF but lowest proportion of positive family history of vascular diseases. Hypertension and DM were equally frequent among three groups. **Conclusion.** Our study showed that vascular risk factors had a specific age and gender distribution pattern in Chinese IS patients. Secondary prevention strategy should emphasize on the control of different risk factors based on patient's age and gender.

1. Introduction

Cerebrovascular disease ranks as the first leading cause of death in China according to the recent report of the global relative burden of stroke [1] and the major cause of disability in adolescent [2], with up to half of all patients who survive a stroke failing to regain independence and needing long-term health care [3]. Stroke can affect individuals of any age, although the incidence and prevalence of this disease increase sharply with age [4]. Prior data from both western countries and China disclose a higher incidence of ischemic stroke in men than in women in patients under 80, however, most very old patients with stroke (aged >80 years) are women [5, 6]. In addition, disparities exist in risk factors, clinical presentation, and outcomes of stroke among patients with different ages and genders [6–11].

Most ischemic stroke patients have multiple vascular risk factors and it is ultimately important in the primary and secondary preventive strategies to recognize and control them. There are quite a few studies from developed countries

concerning the age and gender effect on the profile of vascular risk factors in ischemic stroke patients and the results are inconsistent [5, 12–14]. Studies of a cohort of over 2600 ischemic stroke patients from a single Chinese center also revealed a relatively distinguished pattern of risk factors between male and female patients and between patients over 80 and under 80 [6, 11], but such studies are scarce in Chinese population and whether the distribution pattern is different from that of developed countries remains to be elucidated. Thereby, we investigated the age- and gender-specific prevalence of vascular risk factors in patients with first-ever ischemic stroke in Shanghai, a metropolitan urban area in China.

2. Methods

From January 2004 to December 2009, patients admitted to the Department of Neurology of Shanghai Renji Hospital, with first-ever acute ischemic stroke confirmed by cranial

CT or MRI within 14 days after onset were, retrospectively, reviewed. Renji Hospital is a teaching hospital affiliated to Shanghai Jiaotong University School of Medicine and its stroke center is one of the largest centers in Shanghai with around 800 to 1000 patients visiting stroke clinic and around 100–150 stroke patients sending to emergency room every week.

Data on the following risk factors were collected: (1) smoking history (including both current and exsmoking); (2) heavy alcohol consumption (≥ 2 standard alcohol consumption per day); (3) hypertension (including documented history of hypertension or undertaking antihypertensive drugs); (4) diabetes mellitus (documented medical record of diabetes mellitus or taking oral antidiabetic agents/insulin before the stroke); (5) heart diseases (including coronary heart diseases, arrhythmia and chronic heart failure); (6) atrial fibrillation; (7) family history of cerebrovascular and/or cardiovascular diseases. Systematic investigations were performed during the admission time, including brain CT and/or MRI, carotid ultrasound, 12 lead ECG, as well as standard blood and urine tests that including fasting serum glucose, cholesterol, and triglyceride.

All patients were divided into three age groups according their ages at onset: (1) young adult group (<50 years); (2) middle-aged group (50~80 years); (3) very old group (>80 years).

Categorical variables were summarized as counts (percentage) and continuous variables as means (standard deviation (SD)) or medians (interquartile ranges (IQR)), if not distributed normally. We performed univariate analyses of continuous variables using Mann-Whitney test and categorical variables using the chi-square test. The Cochran-Mantel-Haenszel test was used to carry out adjustment for age groups when testing the association between gender and risk factors. A two-tailed probability value <0.05 was considered significant. Data analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, III, USA).

3. Results

3.1. General Features. One thousand and twenty-seven patients with first-ever ischemic stroke were included in our study. Their demographic characteristics and vascular risk factors were summarized in Table 1. Overall, 60.5% of these patients were male. The median age (IQR) was 67.5 (57.6–74.7) years.

3.2. The Comparison of Risk Factor Profiles between Male and Female Patients. Female patients were much older than male patients (71.1 versus 65.0 years, $P < 0.001$) when experiencing their first ischemic stroke attack and had a significantly higher prevalence of diabetes mellitus ($P = 0.004$), heart diseases ($P < 0.001$), and atrial fibrillation ($P = 0.009$). In contrast, male patients were more likely to be current or exsmokers ($P < 0.001$) and to drink heavily ($P < 0.001$) than female patients. Hypertension was equally frequent in both groups. With regard to family history, more male patients had positive family history of hypertension

than female patients ($P = 0.040$) while the family history of heart diseases and stroke showed no significant differences (Table 1).

3.3. The Comparison of Risk Factor Profiles in Three Age Groups. The median (IQR) ages of the young adult group, the middle-aged group, and the very old group were 47.3 (43.7–48.8), 67.0 (59.5–73.2), and 83.0 (81.5–85.6) years, respectively, range 25.1–49.9, 50.1–79.9, and 80.0–102.5, years, respectively. The results of the comparison among the three age groups were displayed in Table 2.

The incidence of ischemic stroke in patients <80 years of age was higher in men than in women. Most patients in the very old group, however, are women. Young adult patients had a much higher proportion of smoking and drinking than the other two groups, while very old patients had a much lower proportion of smoking and drinking than the other two group patients. So an increasing prevalence of smoking and heavy drinking with the lowering of age at stroke onset was observed.

Hypertension and diabetes were equally prevalent in three age groups, which suggested these two risk factors were common and consistent in ischemic stroke patients with all age ranges, while heart diseases were more frequent in very old patients.

Family history of hypertension was more frequent in young adults than in middle-aged and very old patients, whereas very old patients were less likely to have positive family history of hypertension, heart diseases, or stroke. It suggested a genetic component in the pathogenesis of ischemic stroke in young patients. In other words, patients with positive family history of hypertension, heart diseases, or stroke tended to have stroke attack at an earlier age.

3.4. The Comparison of Risk Factor Profiles between Male and Female Patients in Different Age Groups. In the young adult group, discrepancies of the distribution of risk factors were presented between male and female patients (Table 3). Male patients were predominantly more likely to be current or past smokers and heavy drinkers than female patients, whereas more females had heart diseases ($P = 0.015$). No difference could be observed in the family history of hypertension, heart diseases, or stroke between males and females.

In the middle-aged group, smoking and drinking history were still more prevalent in male than in female patients, but female patients were more likely to have diabetes, heart diseases, and atrial fibrillation ($P = 0.004$, 0.001, and 0.039, resp.).

In the very old group, we could not find any difference between two genders in the distributed pattern of vascular risk factors except that males had a higher frequency of smoking and drinking.

4. Discussion

A few large-scale studies carried out in western countries revealed that there were complex interactions among age,

TABLE 1: The comparison of demographic characteristics and vascular risk factors between female and male patients.

	Total (<i>n</i> = 1027)	Male (<i>n</i> = 621)	Female (<i>n</i> = 406)
Age (years)	67.5 (57.6–74.7)	65.0 (11.5)	71.1 (60.7–76.8)*
Smoking	38.0%	59.9%	4.4%*
Heavy alcohol consumption	19.5%	31.6%	1.0%*
Hypertension	66.2%	64.3%	69.2%
Diabetes mellitus	22.2%	19.2%	26.8%*
Heart diseases	23.0%	19.2%	28.8%*
Atrial fibrillation	5.4%	3.9%	7.6%*
Family history			
Hypertension	45.6%	48.1%	41.6%*
Heart diseases	13.1%	12.7%	13.8%
Stroke	24.8%	25.8%	23.4%

**P* < 0.05.

TABLE 2: The comparison of vascular risk factors in three age groups.

	Total (<i>n</i> = 1027)	Young adult group (<i>n</i> = 98)	Middle-aged group (<i>n</i> = 801)	Very old group (<i>n</i> = 128)
Male	60.5%	69.4%	61.5%	46.9% ^{#†}
Smoking	38.0%	55.1%*	38.5%	21.9% ^{#†}
Heavy alcohol consumption	19.5%	32.7%*	20.0%	6.3% ^{#†}
Hypertension	66.2%	70.4%	65.5%	67.2%
Diabetes mellitus	22.2%	15.3%	23.1%	21.9%
Heart diseases	23.0%	7.1%*	23.2%	33.6% ^{#†}
Atrial fibrillation	5.4%	1.0%	5.2%	9.4% [†]
Family history				
Hypertension	45.6%	63.3%*	46.9%	23.4% ^{#†}
Heart diseases	13.1%	18.4%	14.1%	3.1% ^{#†}
Stroke	24.8%	33.7%	25.6%	13.3% ^{#†}

**P* < 0.05 versus middle-aged group; [#]*P* < 0.05 versus middle-aged group; [†]*P* < 0.05 versus young adult group.

gender, and prevalence of stroke risk factors [8, 9, 12]. These results are not completely consistent and differ between countries and ethnics. Thus, it becomes increasingly important to find out the age- and gender-specific stroke risk factors in Chinese population in order to develop better stroke prevention strategies.

In this group of 1027 Chinese first-ever ischemic stroke patients, women were globally older than men at the stroke onset; had less unhealthy lifestyles such as smoking and heavy drinking, however, were more likely to have diabetes, heart diseases, and atrial fibrillation than men. Hypertension, the most important risk factor for ischemic stroke, was equally common in both genders. As for the age effect, younger patients were more frequent to have an unhealthy lifestyles and positive family history of cardiovascular or cerebrovascular diseases, while older patients had higher prevalence of classic vascular risk factors such as ischemic heart diseases, chronic heart failure, and atrial fibrillation.

Currently, the wide accepted risk factors for ischemic stroke include old age, male sex, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking, heavy

drinking, et al. The INTERSTROKE study, a standardized case-control study carried out in 22 countries worldwide, showed that 12 risk factors including hypertension (OR = 2.37), current smoking (OR = 2.32), waist-to-hip ratio (OR = 1.65), unhealthy diet (OR = 1.29), regular physical activity (OR = 0.68), diabetes mellitus (OR = 1.60), alcohol intake (OR = 1.41), psychosocial stress (OR = 1.30), depression (OR = 1.47), cardiac causes (OR = 2.74), and ratio of apolipoproteins B to A1 (OR = 1.30) collectively accounted for 89.7% of the population-attributable risks for ischemic stroke [15]. The present study found that men were generally younger than women at their first attack of ischemic stroke and there is a higher percentage of male among all ischemic stroke patients. The results were consistent with prior data from consecutive inception cohorts from China [10, 11], which also revealed a relatively younger onset age in male ischemic stroke patients and a nearly 60:40 split of male and female in all recruited patients. However, our data and previous studies [5, 11] all showed that women predominate in the very old group of ischemic stroke patients. With the proportion of elderly individuals increasing rapidly, ischemic

TABLE 3: The comparison of vascular risk factors between male and female patients in each age group.

	<50 years		50–80 years		>80 years	
	Male (<i>n</i> = 68)	Female (<i>n</i> = 30)	Male (<i>n</i> = 493)	Female (<i>n</i> = 308)	Male (<i>n</i> = 60)	Female (<i>n</i> = 68)
Smoking history	77.9%	3.3%*	60.0%	3.9%*	38.3%	7.4%*
Heavy alcohol consumption	44.1%	6.7%*	32.0%	0.6%*	13.3%	0%*
Hypertension	67.6%	76.7%	62.5%	70.5%	75.0%	60.3%
Diabetes mellitus	14.7%	16.7%	19.7%	28.6%*	20.0%	23.5%
Heart diseases	2.9%	16.7%*	19.5%	29.2%*	35.0%	32.4%
Atrial fibrillation	1.5%	0%	3.9%	7.5%*	6.7%	11.8%
Family history						
Hypertension	60.3%	70.0%	49.3%	43.2%	25.0%	22.1%
Heart diseases	13.2%	30.0%	13.8%	14.6%	3.3%	2.9%
Stroke	32.4%	36.7%	26.2%	24.7%	15.0%	11.8%

* $P < 0.05$.

stroke will represent a massive epidemic in the forthcoming years, especially in women. So this female subgroup is becoming a specific healthcare issue for society.

Previous studies had consistently reported that there was a significantly higher proportion of smokers and heavy drinkers in male than in female patients [16, 17]. We found such a phenomenon in all age groups in the present cohort, furthermore, the younger the age, the higher the proportion of smokers and drinkers in male patients. These findings suggest that the change of unhealthy lifestyles is of great importance to prevent ischemic stroke in men, especially in young men, which also brings public health education an urgent issue.

In the present study, hypertension is the most common risk factor for ischemic stroke. Its prevalence showed no significant difference between two gender groups or in all age groups. A meta-analysis including 45 studies and representing a total of 673,935 ischemic stroke patients showed that women had more hypertension than men (OR = 1.17, 95% CI: 1.03–1.34, $P = 0.017$) [18]. However, there are also studies showed that hypertension became increasingly (although slightly) common in women after the age of 65 whereas the prevalence of it decreased in men after that age [12, 19]. The discord between different studies may be resulted from the different racial and environmental factors in the pathogenesis of hypertension.

We noted that female patients were more frequently to have diabetes mellitus, mainly in patients aged 50 to 80, which is similar to the results of other studies carried out in Chinese and African American [10, 11, 20], but obviously opposite to most studies in European and White American [13, 16, 17]. The real reason for this discrepancy is unknown and probably owing to genetic liability and different life styles.

In agreement with other study results [13, 16, 17], we observed a higher incidence of atrial fibrillation in female patients than in male; moreover, atrial fibrillation was far more common in patients over 80 than under the age of 50. As reported by Framingham Heart Study and other related studies, women are more susceptible to atrial fibrillation [18, 21], thus taking higher risk for cardiogenic embolism [22]. To be more specified, Roquer et al. figured out through their work that the risk of cardiogenic embolism in women

was twice as much as that in men [14]. The progressive loss of conduction tissue cells and pacemaker function accounts for the increased incidence of atrial fibrillation in the elderly [23]. There is a high prevalence of atrial fibrillation and heart diseases (including coronary heart diseases, arrhythmia and chronic heart failure) in elderly patients, which makes cardiogenic embolism a more frequent cause of ischemic stroke [24]. Some studies suggested that atrial fibrillation might supercede hypertension to be the primary risk factor for ischemic stroke in patients aged over 80 or 85 years [25]. Therefore, early recognition and intensive control of heart diseases, especially using warfarin, are of critical importance in reducing the incidence of ischemic stroke in the elderly.

With regards to the analysis of the family history in first-ever ischemic stroke patients, we found that young patients aged under 50 were more likely to have positive family history of hypertension, heart diseases, or stroke. Family history was reported as the second most common risk factor (18.4%) by De Silva et al. in young stroke patients in Sri Lanka [26]. Also, Rasura et al. found a positive family history of vascular events in 63% of young stroke patients [27]. A significant genetic component underlying the occurrence of young stroke was demonstrated in prior studies and meta-analysis of all published twin studies on stroke [28, 29]. These findings have important value in stroke prevention because it is presumed that those who have positive family history of vascular events will impressively perceive the harm of stroke early in their lives and realize the importance of early prophylaxis. Thus, they might be easier to be educated to change their unhealthy lifestyles and have a good compliance. In another way, they are supposed to be the main target population for primary stroke prevention.

The present study has inevitable limitations. Firstly, it was carried out in a single stroke center (although one of the largest) in Shanghai and thus could not stand for the whole population of ischemic stroke patients. Secondly, patients with minor symptoms or fatal events (especially in very old patients) might not be able to be admitted to our hospital, which could cause selection bias. Finally, the analysis of risk factor profiles was incomplete in this study for not collecting other possible stroke risk factors such as the body mass index, serum homocysteine, peripheral vascular diseases, psychogenic factors, and severity of atherosclerosis (such as the

intima-media thickness of carotid arteries and the stenosis of intra- and extracranial arteries).

Despite these limitations, however, the present study still provided some valuable information on the distribution of risk factors in first-ever ischemic stroke patients with different genders and ages. The identification of risk factor profiles in different groups of ischemic stroke patients is essential before the draft of etiologic preventive strategies. According to the findings in present study, the priority in stroke prevention for men and young (especially young men) should be the change of lifestyles such as giving up smoking and alcohol drinking. As for women and the elderly, it is much more important to treat traditional vascular risk factors such as hypertension and diabetes mellitus. The recognition and control of atrial fibrillation should also be taken seriously in elderly population. Additionally, young adults with a positive family history of vascular events should be educated early to control risk factors effectively.

5. Conclusions

Overall, the present study was one of the very few studies to demonstrate the age and gender specific distribution of risk factors in ischemic stroke patients in Chinese population and found out that female and male, young and old patients had very different stroke risk factor profiles. Population based epidemiological studies are warranted to a better understanding of this distribution pattern.

References

- [1] A. S. Kim and S. C. Johnston, "Global variation in the relative burden of stroke and ischemic heart disease," *Circulation*, vol. 124, no. 3, pp. 314–323, 2011.
- [2] C. J. L. Murray and A. D. Lopez, "Global mortality, disability, and the contribution of risk factors: global burden of disease study," *The Lancet*, vol. 349, no. 9063, pp. 1436–1442, 1997.
- [3] J. W. Sturm, G. A. Donnan, H. M. Dewey et al., "Quality of life after stroke: the North East Melbourne stroke incidence study (NEMESIS)," *Stroke*, vol. 35, no. 10, pp. 2340–2345, 2004.
- [4] C. Marini, L. Triggiani, N. Cimini et al., "Proportion of older people in the community as a predictor of increasing stroke incidence," *Neuroepidemiology*, vol. 20, no. 2, pp. 91–95, 2001.
- [5] J. I. Rojas, M. C. Zurrú, M. Romano, L. Patrucco, and E. Cristiano, "Acute ischemic stroke and transient ischemic attack in the very old-risk factor profile and stroke subtype between patients older than 80 years and patients aged less than 80 years," *European Journal of Neurology*, vol. 14, no. 8, pp. 895–899, 2007.
- [6] D. Wang, Z. Hao, W. Tao et al., "Acute ischemic stroke in the very elderly Chinese: risk factors, hospital management and one-year outcome," *Clinical Neurology and Neurosurgery*, vol. 113, no. 6, pp. 442–446, 2011.
- [7] S. Olindo, P. Cabre, R. Deschamps et al., "Acute stroke in the very elderly: epidemiological features, stroke subtypes, management, and outcome in Martinique, French West Indies," *Stroke*, vol. 34, no. 7, pp. 1593–1597, 2003.
- [8] M. Niewada, A. Kobayashi, P. A. Sandercock, B. Kamiński, and A. Członkowska, "International stroke trial collaborative group. Influence of gender on baseline features and clinical outcomes among 17,370 patients with confirmed ischemic stroke in the international stroke trial," *Neuroepidemiology*, vol. 24, no. 3, pp. 123–128, 2005.
- [9] C. Ayala, J. B. Croft, K. J. Greenlund et al., "Sex differences in US mortality rates for stroke and stroke subtypes by race/ethnicity and age, 1995–1998," *Stroke*, vol. 33, no. 5, pp. 1197–1201, 2002.
- [10] Y. Huang, J. G. Wang, J. W. Wei et al., "Age and gender variations in the management of ischaemic stroke in China," *International Journal of Stroke*, vol. 5, no. 5, pp. 351–359, 2010.
- [11] F. Y. Kong, W. D. Tao, Z. L. Hao, and M. Liu, "Predictors of one-year disability and death in Chinese hospitalized women after ischemic stroke," *Cerebrovascular Diseases*, vol. 29, no. 3, pp. 255–262, 2010.
- [12] K. K. Andersen, Z. J. Andersen, and T. S. Olsen, "Age- and gender-specific prevalence of cardiovascular risk factors in 40 102 patients with first-ever ischemic stroke: a Nationwide Danish Study," *Stroke*, vol. 41, no. 12, pp. 2768–2774, 2010.
- [13] D. Giralt, S. Domingues-Montanari, M. Mendioroz et al., "The gender gap in stroke: a meta-analysis," *Acta Neurologica Scandinavica*, vol. 125, no. 2, pp. 83–90, 2012.
- [14] J. Roquer, A. Rodríguez Campello, and M. Gomis, "Sex differences in first-ever acute stroke," *Stroke*, vol. 34, no. 7, pp. 1581–1585, 2003.
- [15] M. J. O'Donnell, X. Denis, L. Liu et al., "Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study," *The Lancet*, vol. 376, no. 9735, pp. 112–123, 2010.
- [16] M. J. Reeves, C. D. Bushnell, G. Howard et al., "Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes," *The Lancet Neurology*, vol. 7, no. 10, pp. 915–926, 2008.
- [17] M. J. Reeves, G. C. Fonarow, X. Zhao, E. E. Smith, and L. H. Schwamm, "Quality of care in women with ischemic stroke in the GWTG program," *Stroke*, vol. 40, no. 4, pp. 1127–1133, 2009.
- [18] J. P. Broderick, S. J. Phillips, W. M. O'Fallon, R. L. Frye, and J. P. Whisnant, "Relationship of cardiac disease to stroke occurrence, recurrence, and mortality," *Stroke*, vol. 23, no. 9, pp. 1250–1256, 1992.
- [19] National Centre for Health Statistics, *Health, United States, 2009: With Special Feature on Medical Technology*, National Centre for Health Statistics, Hyattsville, Md, USA, 2010.
- [20] M. Eriksson, E. L. Glader, B. Norrving, A. Terént, and B. Stegmayr, "Sex differences in stroke care and outcome in the swedish national quality register for stroke care," *Stroke*, vol. 40, no. 3, pp. 909–914, 2009.
- [21] J. M. Holroyd-Leduc, M. K. Kapral, P. C. Austin, and J. V. Tu, "Sex differences and similarities in the management and outcome of stroke patients," *Stroke*, vol. 31, no. 8, pp. 1833–1837, 2000.
- [22] H. S. Cabin, K. S. Clubb, C. Hall, R. A. Perlmutter, and A. R. Feinstein, "Risk for systemic embolization of atrial fibrillation without mitral stenosis," *American Journal of Cardiology*, vol. 65, no. 16, pp. 1112–1116, 1990.
- [23] A. Shuaib and V. C. Hachinski, "Mechanisms and management of stroke in the elderly," *Canadian Medical Association Journal*, vol. 145, no. 5, pp. 433–443, 1991.
- [24] A. Arboix, M. Miguel, E. Císcar, L. García-Eroles, J. Massons, and M. Balcells, "Cardiovascular risk factors in patients aged 85 or older with ischemic stroke," *Clinical Neurology and Neurosurgery*, vol. 108, no. 7, pp. 638–643, 2006.
- [25] E. Auriel, A. Y. Gur, O. Urale et al., "Characteristics of first ever ischemic stroke in the very elderly: profile of vascular risk

- factors and clinical outcome,” *Clinical Neurology and Neurosurgery*, vol. 113, no. 8, pp. 654–657, 2011.
- [26] R. De Silva, R. Gamage, C. Wewelwala et al., “Young strokes in Sri Lanka: an unsolved problem,” *Journal of Stroke and Cerebrovascular Diseases*, vol. 18, no. 4, pp. 304–308, 2009.
- [27] M. Rasura, A. Spalloni, M. Ferrari et al., “A case series of young stroke in Rome,” *European Journal of Neurology*, vol. 13, no. 2, pp. 146–152, 2006.
- [28] E. Floßmann, U. G. R. Schulz, and P. M. Rothwell, “Systematic review of methods and results of studies of the genetic epidemiology of ischemic stroke,” *Stroke*, vol. 35, no. 1, pp. 212–227, 2004.
- [29] L. M. Brass, J. L. Isaacsohn, K. R. Merikangas, and C. D. Robinette, “A study of twins and stroke,” *Stroke*, vol. 23, no. 2, pp. 221–223, 1992.

Research Article

Perinatal Risk Factors and Later Social, Thought, and Attention Problems after Perinatal Stroke

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Objective. Survivors of perinatal stroke may be at risk for behavioral problems. Perinatal risk factors that might increase the likelihood of later behavior problems have not been identified. The goal of this study was to explore whether perinatal factors might contribute to behavior problems after perinatal stroke. **Methods.** 79 children with unilateral perinatal stroke were studied. Perinatal factors included gender, gestational age, neonatal seizures, instrumented delivery, fetal distress, acute birth problems, birth weight, and time of diagnosis. Subjects with evidence of hypoxic ischemic encephalopathy were excluded. Parents completed the Achenbach Child Behavior Checklist (CBCL) (Achenbach 1985). The CBCL yields T-scores in several symptom scales. We focused on Social, Thought, and Attention Problems scales. **Results.** Gestational age and the presence of uteroplacental insufficiency were associated with significant differences on the Thought Problems scale; Attention Problems scores approached significance for these variables. Fetal distress, neonatal seizures, or neonatal diagnosis was associated with 25–30% incidence of clinically significant T-scores on Social, Thought, and Attention Problems scales. **Conclusions.** Several perinatal factors were associated with a high incidence of social, thought, and behavior problems in children with perinatal stroke. These findings may be useful in anticipatory guidance to parents and physicians caring for these children.

1. Introduction

Perinatal stroke is surprisingly common, affecting 1 in 2300 to 4000 children per year. The incidence of stroke in neonates is second only to that of the elderly [1]. Perinatal stroke is the primary cause of hemiplegic cerebral palsy. In addition to motor impairment, children with perinatal stroke are at risk for other problems such as epilepsy, learning disorders, cognitive impairment, language delay, and behavioral problems [2, 3]. A number of studies have reported a higher incidence of behavioral problems, particularly social and attention problems, in children with early focal brain injury [2, 4].

Early studies reported that children with hemiparesis or unilateral abnormalities on neurological exam (although without radiological confirmation of a unilateral brain lesion) were found to have more social difficulties than children without hemiparesis [5–7]. Lee et al. found that of 36 children with perinatal stroke, 22% were later diagnosed with behavioral problems [2]. This study was a retrospective review of stroke cases in the Kaiser Health System and utilized medical records reports to identify the presence of behavioral problems. Almost 1/4 of the patients (8 of 36) were said to have behavior problems that included hyperactivity and poor attention. Both unilateral and bilateral stroke cases were included in this report. A cohort study of

children with hemiplegic CP found that half had behavioral or psychiatric problems, including hyperactivity, conduct disorders, and oppositional behavior [8, 9]. The mode of ascertainment in this study (presence of cerebral palsy rather than documentation of a unilateral infarct of perinatal onset) may have led to a heterogeneous subject group, and thus it is difficult to determine how relevant those studies were to the perinatal stroke population. Max et al. investigated attention in children with childhood stroke with onset at different ages [10]. They found that attention was significantly poorer than matched controls and that the younger the age at lesion acquisition, the poorer the attentional ability. Other studies using a very homogeneous group of children with radiographically and historically documented evidence of unilateral perinatal stroke found a surprisingly low incidence of later behavioral problems in that population [11, 12]. A small percentage were found to have social, thought, and attention problems compared with controls, but the majority of children did not demonstrate such behavioral issues. Talib et al. studied a small group of twin children with perinatal stroke and compared them to their unaffected twin. There was no clear pattern of attentional impairment in the twin with stroke [13].

Although these earlier studies suggest the possibility that children with perinatal stroke have attention and social difficulties, it is not clear from previous studies whether there are specific risk factors within the perinatal stroke population that may predispose to later behavioral difficulties. The goal of the present study was to examine the occurrence of specific perinatal risk factors and their potential association with later social, thought, and attention problems as identified by a parent report, the Child Behavior Checklist.

2. Methods

In a large prospective cohort study, 79 children with a diagnosis of perinatal or presumed perinatal stroke were identified. Recruitment for subjects in this cohort was approved by the Institutional Review Board at the University of California San Diego. Subjects were recruited from 1983 to 2006 via referrals from a large catchment area in southern California and also from the New York metropolitan area. Perinatal stroke subjects presented in the neonatal period with seizures and/or encephalopathy. Subjects with presumed perinatal stroke presented after the neonatal period, typically with hemiparesis or epilepsy. All subjects had evidence of a focal unilateral infarct on neuroimaging (either CT or MRI).

Birth information and hospital data from the inpatient stay as a newborn (if available) were obtained for each subject. Variables considered included the presence of neonatal seizures, gestational age, uteroplacental insufficiency (defined by poor maternal weight gain, small-for-gestational-age infant, maternal hypertension and/or preeclampsia, maternal chronic disease, maternal smoking, maternal infection, placental event such as thrombus or abruption, or twin-twin transfusion syndrome), presence of fetal distress (defined as nonreassuring fetal heart tracings, need for emergency C-section, need for instrumentation at

delivery, presence of meconium, or diagnosis of chorioamnionitis), and use of instrumentation at delivery (assistance via forceps or vacuum). Exclusionary criteria included a history of intrauterine drug exposure, evidence of neonatal hypoxic-ischemic encephalopathy, neonatal meningitis, or bilateral or multifocal lesions on neuroimaging studies. Imaging variables collected included lesion side and lesion severity. Lesion severity was graded on a 1–5 scale in which 1 = focal ventricular dilation/atrophy seen on <3 cuts on CT or MRI; 2 = focal ventricular dilation/atrophy seen on >3 cuts on CT or MRI; 3 = focal porencephaly involving one lobe and observed in <3 cuts on CT or MRI; 4 = focal porencephaly involving one lobe and observed on >3 cuts on CT or MRI; 5 = porencephaly or atrophy involving multiple lobes.

For each subject, a parent completed the Achenbach Child Behavior Checklist (CBCL), which is a 113-item checklist validated for use in children 4–18 years of age [14]. The parent responses are based on their observations of behaviors in the two months prior to the questionnaire. Each item is scored on a 0–2 scale, in which 0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true. Nine Behavior Problem Scales, as well as Internalizing and Externalizing scores and a Total Problem score are derived. T-scores above 70 are considered clinically significant, while scores between 67 and 70 are in the “borderline clinical” range. Based on our previous study indicating that children with perinatal stroke differed from controls only on Social, Thought, and Attention Problems scales [12], we focused our analyses on these problem scales only.

Statistical analyses were performed using IBM SPSS Version 15.0 for Windows (2006 IBM Corporation.) The Pearson correlation was employed for comparisons using categorical variables, and the ANOVA test was used for continuous variables. *P* values of $\leq .05$ were considered to be statistically significant.

3. Results

Seventy-nine cases with focal infarct had parent-completed CBCL evaluations. The mean age of the child at the time of CBCL evaluation was 9.4 years; subjects ranged from 4 to 19 years of age. Fifty of the subjects (63%) were male. Fourteen subjects were born preterm (<37 weeks gestation), 52 were term, 9 were postterm (>42 weeks), and 4 had unknown gestational age. Eleven infants were delivered with instrumentation (forceps or vacuum-assisted delivery). Twenty-five subjects (32%) had a history of fetal distress, and 19 (24%) had evidence of uteroplacental insufficiency. Twenty-seven of 79 subjects (34%) presented in the newborn period, and 52 of 79 presented after the newborn period (66%). Twenty-four subjects (34%) presented with neonatal seizures. On neuroimaging, 50 subjects (63%) had left-sided lesions. Fifty-two patients (66%) had hemiparesis.

Gestational age and the presence of uteroplacental insufficiency were associated with significant differences on the Thought Problems scale, and Attention Problems scores approached significance for these variables. Fetal distress was associated with higher Attention Scale T-scores approaching

TABLE 1: *P* values reflecting perinatal risk factors and elevated CBCL scores.*

	Total score	Social problem score	Thought problem score	Attention problem score
Gender	0.18	0.74	0.52	0.99
Neonatal seizures	0.36	0.70	0.49	0.06
Gestational age	0.20	0.43	0.04	0.07
Uteroplacental insufficiency	0.13	0.93	0.05	0.08
Fetal distress	0.55	0.97	0.22	0.06
Instrumentation	0.24	0.76	0.88	0.53
Lesion side	0.23	0.33	0.31	0.49
Lesion severity	0.98	0.54	0.43	0.23
Hemiparesis	0.86	0.18	0.19	0.48
Presentation in neonatal period	0.47	0.84	0.91	0.08
Age at testing	0.70	0.48	0.25	0.49

**P* values obtained using one-way ANOVA.

traditional levels of statistical significance (-4.56 , 95% CI 2.41, $P = 0.06$), and the presence of neonatal seizures was similarly associated with higher Attention Scale scores (-4.47 , 95% CI 2.36, $P = 0.06$). Subjects diagnosed in the neonatal period had higher Attention Scale scores than subjects presenting after the newborn period, and results approached traditional levels of statistical significance (4.07, 95% CI 2.26, $P = 0.08$.)

Table 1 displays all relationships between CBCL T-score subsets, perinatal variables, and nonperinatal variables. Some elevated CBCL subscores were correlated with nonperinatal variables. The side of the lesion was not associated with abnormal T-scores. The presence of hemiparesis was not associated with elevated total score or subscores. Age at the time of CBCL testing was also not associated with any elevation in scores.

Although there were no statistically significant differences found between perinatal risk factors and the behavioral measures examined, we qualitatively reviewed all T-scores of 70 or above (clinically significant range of behavior) within each category. Figure 1 shows a pattern in which clinically significant T-score elevations for Social Problems are present in approximately 1/3 of all perinatal stroke infants with fetal distress, neonatal seizures, or a diagnosis in the neonatal period; these children also had a higher percentage of $T > 70$ than children without fetal distress or neonatal seizures or whose diagnosis was not made until several months after birth. Similarly, children with a history of fetal distress, neonatal seizures, or neonatal diagnosis had a higher percentage of T-scores > 70 on Thought and Attention scales than did those children without such a history.

4. Discussion

Children with perinatal stroke may be at higher risk for developmental, cognitive, motor, and behavioral problems compared with the general pediatric population. Previous studies have had mixed results, with some finding major behavioral/psychiatric disorders [8, 9, 15] while others found little evidence of behavioral dysfunction [11, 12]. Many of the previous studies are limited by either small sample size

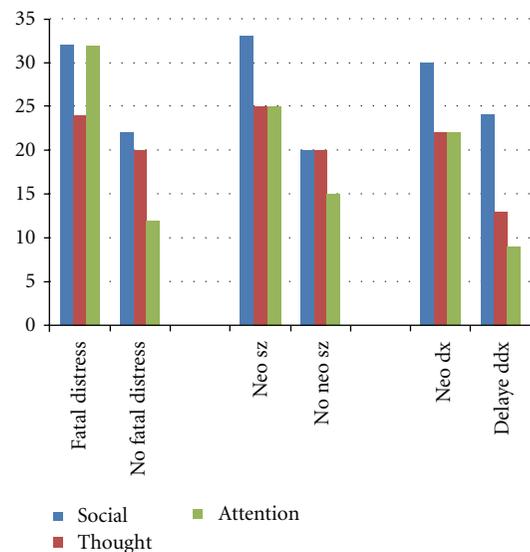


FIGURE 1: Percent of cases with T-scores ≥ 70 on Social, Thought, or Attention Problems scales of the CBCL, related to the presence or absence of fetal distress, neonatal seizures, or time of diagnosis.

or utilizing a heterogeneous group of children (hemiplegic without radiological confirmation of lesion, bilateral lesions, mixed etiologies, and/or timing of lesion onset). The current study used a homogeneous group of children with unilateral perinatal stroke and set out to determine whether specific perinatal problems (other than HIE) might place the child at higher risk for later behavior problems. Our results failed to show a significant relationship between perinatal factors and later social, thought, or attention problems as measured by the Child Behavior Checklist. Three specific risk factors, the presence of fetal distress, neonatal seizures, and diagnosis of stroke in the neonatal period, did, however, correspond to higher mean T-scores on the Attention Problems scale, and the results approached statistical significance. Furthermore, a qualitative analysis of the data using a clinically significant T-score of ≥ 70 found that more than 30% of children with these risk factors had clinically elevated T-scores on Social

Problems, and 22–32% of children with the same risk factors had T-scores ≥ 70 on the Thought and Attention Problems scales. These percentages are markedly higher than would be expected in a typical pediatric population [12] and indicate that certain perinatal factors may place a child at higher risk for later social and attention problems.

Although a number of studies have looked at perinatal factors that might predict later behavior or social difficulties, we found surprisingly little research on the influence of fetal distress or neonatal seizures on psychosocial function in childhood. Most studies have focused on the influence of birth weight, gestational age, and infant feeding on later psychosocial difficulties [16, 17]. Jacobs and colleagues have conducted several studies of early brain injury of diverse causes and ages and have found that social problems are more likely to be present if the brain injury occurred prior to 2 years of age [18]. We found no evidence for an association between gestational age and later attention or social difficulties in our subject population. The role of other specific perinatal factors, including fetal distress and neonatal seizures, has not been previously examined in detail. One study of long-term outcome after neonatal seizures in “normal” survivors found that over half of the children studied had social adjustment difficulties in their teenage years [19]. In contrast, a study from Canada found no significant group differences on behavioral measures in various groups of “high-risk” children, including those who had neonatal seizures [20]. The risk of neonatal seizures and fetal distress in the perinatal stroke population has not been previously reported, to our knowledge. Though fetal distress and encephalopathy are clinically more likely to be associated with global hypoxic injury in the newborn period, both can be presenting features of perinatal stroke. A significant percentage of neonates presenting with presumed hypoxic encephalopathy are actually later found on imaging to have a focal ischemic stroke [21].

Our study thus provides needed information about the role of specific perinatal factors that may increase the likelihood that a child with perinatal stroke will exhibit social, thought, and/or attention problems during childhood. These children may derive great benefit from early intervention for behavioral problems, such as implementation of individualized education plans, social skills training, individual counseling, and pharmacotherapy.

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References

- [1] J. K. Lynch and K. B. Nelson, “Epidemiology of perinatal stroke,” *Current Opinion in Pediatrics*, vol. 13, no. 6, pp. 499–505, 2001.
- [2] J. Lee, L. A. Croen, C. Lindan et al., “Predictors of outcome in perinatal arterial stroke: a population-based study,” *Annals of Neurology*, vol. 58, no. 2, pp. 303–308, 2005.
- [3] D. A. Trauner, C. Chase, P. Walker, and B. Wulfeck, “Neurologic profiles of infants and children after perinatal stroke,” *Pediatric Neurology*, vol. 9, no. 5, pp. 383–386, 1993.
- [4] J. E. Max, “Effect of side of lesion on neuropsychological performance in childhood stroke,” *Journal of the International Neuropsychological Society*, vol. 10, no. 5, pp. 698–708, 2004.
- [5] M. B. Denckla, “The neuropsychology of social-emotional learning disabilities,” *Archives of Neurology*, vol. 40, no. 8, pp. 461–462, 1983.
- [6] D. Tranel, L. E. Hall, S. Olson, and N. N. Tranel, “Evidence for a right-hemisphere developmental learning disability,” *Developmental Neuropsychology*, vol. 3, pp. 114–127, 1987.
- [7] S. Weintraub and M. Marsel Mesulam, “Developmental learning disabilities of the right hemisphere. Emotional, interpersonal, and cognitive components,” *Archives of Neurology*, vol. 40, no. 8, pp. 463–468, 1983.
- [8] R. Goodman and P. Graham, “Psychiatric problems in children with hemiplegia: cross sectional epidemiological survey,” *British Medical Journal*, vol. 312, no. 7038, pp. 1065–1069, 1996.
- [9] R. Goodman and C. Yude, “Do unilateral lesions of the developing brain have side-specific psychiatric consequences in childhood?” *Laterality*, vol. 2, no. 2, pp. 103–115, 1997.
- [10] J. E. Max, D. A. Robin, H. G. Taylor et al., “Attention function after childhood stroke,” *Journal of the International Neuropsychological Society*, vol. 10, no. 7, pp. 976–986, 2004.
- [11] D. A. Trauner, J. L. Panyard-Davis, and A. O. Ballantyne, “Behavioral differences in school age children after perinatal stroke,” *Assessment*, vol. 3, no. 3, pp. 265–276, 1996.
- [12] D. A. Trauner, R. Nass, and A. Ballantyne, “Behavioural profiles of children and adolescents after pre- or perinatal unilateral brain damage,” *Brain*, vol. 124, no. 5, pp. 995–1002, 2001.
- [13] T. L. Talib, S. J. Pongonis, L. S. Williams et al., “Neuropsychologic outcomes in a case series of twins discordant for perinatal stroke,” *Pediatric Neurology*, vol. 38, no. 2, pp. 118–125, 2008.
- [14] T. M. Achenbach, *Assessment and Taxonomy of Child and Adolescent Psychopathology*, Sage, Thousand Oaks, Calif, USA, 1985.
- [15] R. Goodman, “The longitudinal stability of psychiatric problems in children with hemiplegia,” *Journal of Child Psychology and Psychiatry and Allied Disciplines*, vol. 39, no. 3, pp. 347–354, 1998.
- [16] W. H. Oddy, M. Robinson, G. E. Kendall, J. Li, S. R. Zubrick, and F. J. Stanley, “Breastfeeding and early child development: a prospective cohort study,” *Acta Paediatrica*, vol. 100, no. 7, pp. 992–999, 2011.
- [17] C. Galéra, S. M. Côté, M. P. Bouvard et al., “Early risk factors for hyperactivity-impulsivity and inattention trajectories from age 17 months to 8 years,” *Archives of General Psychiatry*, vol. 68, no. 12, pp. 1267–1275, 2011.
- [18] R. Jacobs, A. S. Harvey, and V. Anderson, “Executive function following focal frontal lobe lesions: impact of timing of lesion on outcome,” *Cortex*, vol. 43, no. 6, pp. 792–805, 2007.
- [19] C. M. Temple, J. Dennis, R. Carney, and J. Sharich, “Neonatal seizures: long-term outcome and cognitive development among “normal” survivors,” *Developmental Medicine and Child Neurology*, vol. 37, no. 2, pp. 109–118, 1995.

- [20] A. K. F. Li, R. S. Sauve, and D. E. Creighton, "Early indicators of learning problems in high-risk children," *Journal of Developmental and Behavioral Pediatrics*, vol. 11, no. 1, pp. 1–6, 1990.
- [21] J. K. Lynch, D. G. Hirtz, G. DeVeber, and K. B. Nelson, "Report of the National Institute of neurological disorders and stroke workshop on perinatal and childhood stroke," *Pediatrics*, vol. 109, no. 1, pp. 116–123, 2002.

Research Article

Comparison of Provision of Stroke Care in Younger and Older Patients: Findings from the South London Stroke Register

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Background. Evidence-based stroke care should be available to all patients. However, evidence exists of inequalities according to age. This study compared access to care for younger adults to that for over 65s. **Methods.** Using population-based data from 4229 patients with first-ever stroke between 1995 and 2010, associations between age and 21 care indicators were investigated using multivariable logistic regression. **Results.** Age was not associated with stroke unit admission for ischaemic stroke ($P = 0.666$). Younger PICH patients were least likely to be admitted to stroke units ($P = 0.001$), instead treated on neurosurgical or ICU wards. Younger age was also associated with admission to neurosurgery or ICU after SAH ($P = 0.006$), increased occupational or physiotherapy at 1 year ($P = 0.043$), and contact with a GP 3 months after stroke ($P < 0.001$). **Conclusion.** Younger patients have equal or greater access to evidence-based care. However, there is a need to ensure that services meet the needs of this group.

1. Introduction

Stroke incidence increases with age but a significant proportion of strokes occur in younger people: around 30% of people recruited to the multiethnic South London Stroke Register are under 65 years of age [1]. A range of social consequences affect younger people with stroke, including an inability to return to work [2, 3]. A recent study estimated the loss of earnings attributable to stroke in the UK, for those younger than 65, to be approximately £1.5 billion or 15% of the total cost of stroke to the UK economy [4].

Evidence-based stroke care is associated with improved patient outcomes [5]. The National Clinical Guideline for Stroke (England and Wales) recommends that all patients receive access to evidence-based care appropriate to their condition and regardless of age [5]. However, there is evidence of inequalities in the provision of care and secondary prevention management according to age [1, 6–13]. Studies have found younger stroke patients more likely to

be admitted to hospital [1, 10] and receive brain imaging [1, 10–13] but less likely to have physiotherapy [1, 10], access to organised stroke care [6], and appropriate secondary prevention medication [8]. Contrastingly, other studies have found improved secondary prevention [9] and access to outpatient physiotherapy or occupational therapy [1] to be associated with younger age.

While admission to a stroke unit improves outcome across all age groups [5], the relative increase in survival rates and decrease in levels of dependency associated with stroke unit admission has been found to be the greatest among the 18–64-year age group [6, 14]. It is therefore particularly important to ensure this age group are admitted to stroke units to ensure they benefit from the associated improvements in outcome.

Existing studies vary in their definition of younger age and have not looked specifically at provision of care for those under 65 years. Therefore, this study focuses on the role of age as a predictor of access to evidence-based care, including

risk factor management, acute care, and rehabilitation therapies, in an unbiased sample of younger and older patients with stroke from a multiethnic population-based cohort in south London.

2. Methods

2.1. Study Population. The South London Stroke Register (SLSR) is an ongoing population-based register, established in January 1995, which records all first-ever strokes in patients of all ages within a defined area of south London. The source population was 271 817 with 63% white, 15% black African, 9% black Caribbean, 4% black other, and 9% of other ethnic groups (source: Census 2001 [15]).

2.2. Data Collection. Methods used in data collection have been previously described [16] and are summarised below. To maximise case ascertainment and reduce bias in studies, the SLSR uses multiple overlapping sources of notification [17, 18]. Completeness of case ascertainment has been estimated to be between 75 and 84% [17]. Stroke was defined using WHO criteria [19] and classified as ischaemic stroke, primary intracerebral haemorrhage (PICH), or subarachnoid haemorrhage (SAH) based on brain imaging (computed tomography (CT) or magnetic resonance imaging (MRI)) within 30 days of stroke onset, necropsy examination, or cerebrospinal examination (SAH only). Where there was no known pathological confirmation of stroke subtype patients were classified as undefined. Initial data were collected within 48 hours of notification to the SLSR where possible. Data were collected at onset and at 3 months, 12 months and annually after stroke by a study nurse or specially trained field worker. Sociodemographic data collected at the initial assessment included age, ethnicity (categorised as white, black, or other), socioeconomic status (classified as manual or nonmanual according to the Registrar General's occupational codes [20]), and employment status prior to stroke, categorised as full time employed (more than 30 hrs per week), part time employed (less than 30 hrs per week), unemployed and looking for work, unable to work due to disability or ill health, carer (for home, family, or dependents), retired, or unknown. Incontinence, motor deficits, and Glasgow Coma Score (categorised as 3–8, 9–12, 13–15) [21] were also collected in the acute phase following stroke onset and used as a proxy for stroke severity.

We defined patients as being of younger if aged 18–64 years at the time of stroke, based on the default retirement age in the UK. Younger patients were further categorised into two age groups, 18–54 years and 55–64 years.

2.3. Indicators of Care. A range of indicators, suggested to be useful proxies for overall quality of care [1, 5], were derived. Four indicators of short-term care were included: admission to hospital, admission to an appropriate specialist unit, more than 50% of hospital stay spent on an appropriate specialist unit, and brain imaging (using CT or MRI). The National Clinical Guideline for Stroke (England and Wales) [5] recommends that all patients with stroke be treated on

a specialist stroke unit. However, for patients with an SAH admission to an intensive care unit (ICU) or neurosurgical ward would be appropriate. Therefore, where patients had a SAH, an appropriate specialist ward was defined as a neurosurgical ward or ICU. For all other patients admission to an appropriate unit was defined as stroke unit admission. Receipt of thrombolysis was not included in this study due to low numbers of patients receiving the therapy within each age group.

There were 11 indicators relating to the appropriate management of risk factors. Information on the prior to stroke diagnosis and management of risk factors, including hypertension (>140 mm Hg systolic or >90 mm Hg diastolic), atrial fibrillation, and diabetes mellitus, was obtained using general practice records and hospital records at baseline. At 3- and 12-month follow-up information was collected using patient self-report. Appropriate medication use in patients with a diagnosis of hypertension or diabetes mellitus was recorded prior to stroke and at 3 and 12 months after stroke. In ischaemic stroke patients, the use of antiplatelets was recorded at 3 and 12 months after stroke. Anticoagulation in patients with atrial fibrillation was recorded in all patients prior to stroke and in ischaemic stroke patients at 3 and 12 months after stroke.

In eligible patients, provision of physiotherapy, occupational therapy (PT/OT), and speech and language therapy (SALT) in the month prior to the 3- and 12-month follow-ups was recorded. Eligibility for PT/OT was defined as recorded motor or sensory deficits in the arm, hand, or leg while. For SALT, patients with dysarthria, dysphasia, or a failed swallow test were considered eligible. Contact with a general practitioner (GP) was also recorded at 3 and 12 months after stroke.

2.4. Statistical Methods. Univariable analyses examined differences between sociodemographic factors, case mix factors, and indicators of care across the three age groups using χ^2 tests or Fisher's exact test as appropriate. Multivariable logistic regression models were used to analyse associations between age and the indicators of care, while adjusting for time trends in the receipt of care and controlling for possible sociodemographic (ethnicity, gender, and socioeconomic status) and case mix (Glasgow coma score, stroke subtype, motor and swallow deficits, and urinary incontinence) differences. Interaction terms between age and year of stroke were added to multivariable models to examine whether any disparities between age groups had varied across the 16 years of the study.

Models of indicators of acute care were analysed firstly across all patients and then in those with ischaemic stroke, PICH, and SAH separately. Analyses on admission to appropriate specialist units were restricted to those admitted to hospital and analyses of rates of patients spending at least 50% of stay on appropriate units were carried out firstly among all admitted patients and then only those admitted to an appropriate ward at some point during their hospital stay. Multivariate models for admission to hospital and receipt of brain imaging in patients with PICH or SAH were not

included due to the low number of younger patients not admitted or not receiving a scan ($n < 10$).

Sensitivity analyses were also conducted for the indicators of acute care. Only patients surviving at least 24 hours were included in the analyses of hospital admissions to account for differing rates of early deaths across age groups. For the other indicators only those in hospital for at least 3 days were included to remove patients who died very soon after admission and may not have had time to be admitted to an appropriate ward, or those with very mild strokes who are discharged home quickly.

Changes in access to care were controlled for in the analyses. However, the organisation of stroke services has changed considerably over the period of the study, therefore, further analyses of acute care indicators examined trends in rates of appropriate care prior to and from 2005 onwards.

Due to a change in the format of variables relating to the provision of therapies, in 2000 for the 3-month follow-up and 1999 for the one-year follow-up, data collected before and after these cut-off points were not comparable. Models for PT/OT and SALT at 3 months after stroke were therefore restricted to patients with first-ever stroke between 2001 and 2010 and at 12 months to patients with first-ever stroke between 1999 and 2010.

The use of anticoagulation therapy was not considered in multivariable analyses due to the very low number of surviving patients in the 18–54-year age group with a diagnosis of atrial fibrillation ($N = 17$ at time of stroke).

Analyses were restricted to patients without missing values. All tests were two-tailed with P values < 0.05 considered to be statistically significant. Statistical analyses were performed using Stata 11MP statistical software package.

2.5. Ethics. Informed written consent for participation in the study was obtained from all patients or their relatives. The study was approved by the St. Thomas' Hospital Research Ethics Committee (06/Q0702/147).

3. Results

Between January 1995 and December 2010 4338 patients were registered with first-ever strokes. Nine patients under 18 years of age at stroke onset were excluded leaving a total sample size of 4229. By 3 months after stroke 1102 (26.1%) patients had died and 1069 (25.3%) were lost to follow up. By 12 months after stroke 1409 (33.3%) had died, 738 (17.5%) were lost to follow up, and a further 164 (3.8%) had not yet reached the one-year follow-up point. Patient characteristics, broken down by age group, are reported in Table 1. The distribution of sociodemographic factors (gender, ethnicity, socioeconomic status, employment status) differed across age groups (all $P < 0.001$) with the largest proportion of females in the over 65-year olds and the largest proportion of blacks observed in the 18–54-year olds.

The associations between age and indicators of acute care, for all patients, and broken down by stroke subtype, are presented in Table 2. In univariable analyses, younger patients were more likely to be admitted to hospital ($P =$

0.007) and to have brain imaging ($P < 0.001$). They were also more likely to be admitted to a stroke unit, neurosurgical ward, or ICU, as appropriate, with 65.5% of 18–54-year olds compared to 57.8% of 55–64-year olds and 55.6% of over 65s who were admitted to hospital spending at least some of their stay on an appropriate unit. After controlling for sociodemographic and case mix differences, the odds of being admitted to an appropriate unit across all patients did not significantly differ with age ($P = 0.914$). However, older patients with PICH were 3 times more likely to be admitted to a stroke unit than those aged 18–54 years ($P = 0.001$). Conversely, in patients with SAH, the odds of admission to ICU or neurosurgical ward decreased with age ($P = 0.006$) with 86.6% of 18–54-year olds, 85.7% of 55–64-year olds and 58.1% of over 65s admitted to one of these wards. For patients with ischaemic stroke, although a higher proportion of young patients were admitted to a stroke unit (66.5% of 18–54-year olds, 59.3% of 55–64-year olds, and 57.5% of over 65s) after adjusting for sociodemographic and case mix factors, the difference in odds of admission was not significant ($P = 0.666$).

In sensitivity analyses, where models were restricted to those with a length of stay in hospital of at least 3 days, the significance and size of these associations remained unchanged (data not shown).

Analyses of patients admitted prior to 2005 showed similar trends and significance levels to those reported above, with overall admission rates slightly lower than average. Similarly, while the overall proportion of patients accessing appropriate care was higher than average from 2005 onwards, differences across age groups remained. During this time period, the 55–64-year age group were found to have the highest rates of admission to appropriate wards. Across all patients, 85% of 55–64-year olds were admitted to a stroke unit, ICU, or neurosurgical ward compared to 78% of 18–54 year olds and 81% of over 65s ($P = 0.0168$). In patients with ischaemic stroke the rates were 82% for 18–54 years, 90% for 55–64 years, and 83% for over-65-year olds ($P = 0.089$). The corresponding figures for PICH patients were 61%, 80%, and 73% ($P = 0.227$) and 82%, 100%, and 45% for SAH ($P = 0.016$).

The location of care for patients with PICH is summarised in Table 3. A higher proportion of younger patients with PICH were admitted to a neurosurgical ward or ICU with 55.5% of all patients of 18–54 years admitted to one of these wards at some point, compared to 27.5% of 55–64 years and 14.4% of over 65s. Among those not admitted to a stroke unit, 75% of 18–54-year olds were treated in ICU or on a neurosurgical ward.

Table 4 reports the association between age and risk factor control prior to and at 3 and 12 months after stroke. A significantly lower proportion of younger patients were on treatment for hypertension prior to stroke (53.8% of 18–54-year olds, 61.4% of 55–64-year olds, and 61.7% of over 65s) and the difference remained significant in multivariable analyses ($P = 0.029$). However, by 3 months after stroke, the lowest rate of treatment was in the over-65-year age group and no significant trend was observed in any multivariable analyses at 3 or 12 months.

TABLE 1: Patient characteristics by age group.

Patient characteristics, n()	Total (n = 4229)	18–54 years (n = 648)	55–64 years (n = 671)	65≥ years (n = 2910)	P value
Gender					
Male	2125 (50.2)	379 (58.5)	455 (67.8)	1291 (44.4)	<0.001
Female	2104 (49.8)	269 (41.5)	216 (32.2)	1619 (55.6)	
Ethnic group					
White	3021 (73.3)	320 (51.4)	434 (66.2)	2267 (79.7)	<0.001
Black	861 (20.9)	245 (39.3)	163 (24.9)	453 (15.9)	
Other	241 (5.9)	58 (9.3)	59 (9.0)	124 (4.4)	
Socioeconomic status					
Manual	1996 (47.2)	243 (37.5)	352 (52.5)	1401 (48.1)	<0.001
Nonmanual	929 (22.0)	179 (27.6)	137 (20.4)	613 (21.1)	
Unknown	1304 (30.8)	226 (34.9)	182 (27.1)	896 (30.8)	
Employment status prior to stroke					
Full time employed	541 (12.8)	293 (45.2)	187 (27.9)	61 (2.1)	<0.001
Part time employed	100 (2.4)	32 (4.9)	25 (3.7)	43 (1.5)	
Unemployed and looking for work	132 (3.1)	85 (13.1)	44 (6.6)	3 (0.1)	
Unable to work due to ill health	217 (5.1)	90 (13.9)	103 (15.4)	24 (0.8)	
Carer for family/dependents	87 (2.1)	37 (5.7)	22 (3.3)	28 (1.0)	
Retired	2905 (68.7)	22 (3.4)	215 (32.0)	2668 (91.7)	
Unknown	244 (5.8)	89 (13.3)	75 (11.2)	83 (2.9)	
Stroke subtype					
Infarction	3145 (74.4)	365 (56.3)	515 (76.8)	2265 (77.8)	<0.001
PICH	540 (12.8)	128 (19.8)	84 (12.5)	328 (11.3)	
SAH	212 (5.0)	122 (18.8)	34 (5.1)	56 (1.9)	
Undefined	332 (7.9)	33 (5.1)	38 (5.7)	261 (9.0)	
Glasgow comma score					
≤8	671 (16.5)	115 (18.5)	93 (14.6)	463 (16.5)	<0.001
9–12	480 (11.8)	60 (9.7)	50 (7.9)	370 (13.2)	
13–15	2909 (71.7)	447 (71.9)	494 (77.6)	1968 (70.3)	

There was no difference in the odds of patients in different age groups receiving physiotherapy or occupational therapy 3 months after stroke ($P = 0.461$) (Table 5). However, by 1 year after stroke those aged 18–54 were significantly more likely to still be having therapy compared to those of an older age ($P = 0.043$). Younger patients were also more likely to have had contact with their GP at 3 months after stroke ($P < 0.001$).

None of the interactions between age and stroke year were significant for any indicator of care, suggesting that differences across age groups occurred consistently throughout the study.

4. Discussion

This study compared patterns of care across stroke patients aged 18–54, 55–64, and over 65 years, by investigating management of risk factors prior to stroke, access to acute care, and provision of therapies and risk factor management over a 1-year period following stroke, using predefined

indicators of care based on clinical guidelines [1, 5, 10]. There were no significant differences in the rates of admission to stroke units among ischaemic stroke patients. However, the likelihood of admission to a stroke unit in patients with PICH increased with age, with younger patients more likely to be treated on a neurosurgical ward or in ICU. In patients with an SAH, increasing age was also associated with lower likelihood of admission to neurosurgery or ICU. The proportion of patients with hypertension on anti-hypertensive medication prior to stroke was the lowest among 18–54-year olds but there was no association between risk factor control and age found at 3 and 12 months after stroke. Younger age was also found to be associated with increased GP contact at 3 months and greater likelihood of ongoing physiotherapy or occupational therapy at 1 year after stroke.

The National Clinical Guidelines for Stroke [5] recommends that “all patients with suspected stroke should be admitted directly to a specialist acute stroke unit following initial assessment either from the community or from the A&E

TABLE 2: Association between age and indicators of acute care.

	Univariable, N(%)				P value	Multivariable, OR (95% CI)			P value
	18–54 years	55–64 years	≥65 years			18–54 years	55–64 years	≥65 years	
All patients									
Admission to hospital	590 (91.1)	573 (85.4)	2557 (87.9)	0.007	1	0.58 (0.37–0.93)	0.61 (0.40–0.93)	0.071	
Admission to SU/NS/ICU	368 (65.5)	321 (57.8)	1391 (55.6)	<0.001	1	1.01 (0.72–1.42)	1.01 (0.76–1.36)	0.914	
50% time on SU/NS/ICU	280 (55.5)	242 (48.4)	1017 (45.2)	<0.001	1	0.84 (0.59–0.56)	0.77 (0.56–1.04)	0.092	
50% time on SU/NS/ICU*	280 (84.0)	242 (85.2)	1017 (83.9)	0.855	1	0.54 (0.31–0.97)	0.52 (0.31–0.86)	0.017	
Brain imaging	600 (96.3)	617 (95.4)	2557 (91.5)	<0.001	1	0.92 (0.31–2.70)	0.63 (0.27–1.54)	0.189	
Ischaemic stroke									
Admission to hospital	327 (89.6)	431 (83.7)	1991 (87.9)	0.013	1	0.60 (0.37–0.99)	0.67 (0.42–1.03)	0.183	
Admission to SU	214 (66.5)	252 (59.3)	1127 (57.5)	0.010	1	0.90 (0.59–1.37)	0.91 (0.63–1.30)	0.666	
50% time on SU	171 (58.7)	197 (50.8)	844 (47.0)	0.001	1	1.07 (0.68–1.68)	0.87 (0.59–1.28)	0.266	
50% time on SU*	171 (90.4)	197 (88.3)	844 (85.4)	0.126	1	0.75 (0.33–1.68)	0.63 (0.32–1.24)	0.148	
Brain imaging	359 (99.2)	502 (98.2)	2173 (96.9)	0.019	1	0.71 (0.14–3.61)	0.44 (0.10–1.91)	0.129	
PICH									
Admission to hospital	123 (96.1)	81 (96.4)	311 (94.8)	0.744					
Admission to SU	53 (43.1)	33 (40.7)	166 (53.4)	0.043	1	2.23 (1.01–5.10)	3.07 (1.55–6.09)	0.001	
50% time on SU	35 (33.3)	21 (31.8)	101 (39.5)	0.364	1	0.96 (0.36–2.54)	0.99 (0.46–2.17)	0.999	
50% time on SU*	35 (76.1)	21 (80.7)	101 (73.2)	0.697	1	0.42 (0.08–2.23)	0.31 (0.09–1.14)	0.072	
Brain imaging	125 (98.4)	80 (96.4)	305 (95.0)	0.245					
SAH									
Admission to hospital	113 (92.6)	32 (94.1)	49 (87.5)	0.438					
Admission to NS/ICU	84 (86.6)	24 (85.7)	25 (58.1)	<0.001	1	0.84 (0.13–5.43)	0.12 (0.02–0.56)	0.006	
50% time on NS/ICU	60 (68.2)	13 (52.0)	15 (45.5)	0.049	1	0.30 (0.09–1.06)	0.12 (0.03–0.47)	<0.001	
50% time on NS/ICU*	59 (73.8)	13 (56.5)	13 (59.1)	0.182	1	0.23 (0.06–0.92)	0.12 (0.02–0.61)	0.002	
Brain imaging	109 (90.1)	31 (93.9)	44 (81.5)	0.145					

* Excluding patients admitted to hospital but not SU/NS/ICU.
 SU: stroke unit, NS: neurosurgical ward, and ICU: Intensive care unit.

TABLE 3: Location of care of patients with PICH.

	18–54 years, N(%)	55–64 years, N(%)	≥65 years, N(%)	P value
Admitted at any point during hospital stay				
Stroke unit	53 (43.1)	33 (40.7)	166 (53.4)	0.043
Neurosurgery	32 (31.7)	7 (10.1)	11 (4.1)	<0.001
ICU	38 (37.6)	14 (20.3)	33 (12.2)	<0.001
Neurosurgery or ICU	56 (55.5)	19 (27.5)	39 (14.4)	<0.001
Location of care of patients not admitted to a stroke unit				
Neurosurgery	20 (36.4)	6 (15.0)	4 (3.5)	<0.001
ICU	33 (60.0)	13 (32.5)	20 (17.2)	<0.001
Neurosurgery or ICU	42 (76.4)	17 (42.5)	21 (18.1)	<0.001

TABLE 4: Association between age and indicators relating to the management of risk factors.

	Univariable, N(%)				18–54 years	Multivariable, OR(95% CI)		
	18–54 years	55–64 years	≥65 years	P value		55–64 years	≥65 years	P value
Hypertension treatment								
Prior to stroke	143 (53.8)	261 (61.4)	1156 (61.7)	0.046	1	1.88 (1.29–2.76)	1.68 (1.21–2.36)	0.029
3 months	108 (68.8)	197 (73.8)	649 (64.1)	0.010	1	1.28 (0.75–2.19)	0.81 (0.50–1.29)	0.058
1 year	116 (71.2)	183 (71.8)	558 (66.0)	0.143	1	0.97 (0.56–1.70)	0.80 (0.49–1.31)	0.247
Diabetes								
Prior to stroke	61 (77.2)	107 (80.5)	424 (77.5)	0.752	1	0.94 (0.40–2.22)	1.21 (0.57–2.56)	0.436
3 months	31 (67.4)	61 (75.3)	190 (74.1)	0.581	1	1.90 (0.67–5.51)	1.56 (0.61–3.99)	0.607
1 year	29 (61.7)	56 (76.7)	173 (72.4)	0.194	1	1.86 (0.68–5.11)	1.70 (0.72–4.01)	0.357
Atrial Fibrillation								
Prior to stroke	6 (35.3)	16 (26.7)	85 (15.1)	0.008				
3 months	4 (40.0)	5 (31.3)	36 (37.9)	0.863				
1 year	3 (30.0)	8 (33.3)	41 (36.0)	0.912				
Antiplatelet therapy (IS)								
3 months	146 (71.6)	228 (78.1)	910 (77.8)	0.131	1	1.24 (0.78–1.99)	1.44 (0.96–2.15)	0.071
1 year	165 (79.0)	254 (81.2)	825 (77.3)	0.327	1	0.95 (0.57–1.60)	0.83 (0.53–1.30)	0.309

TABLE 5: Associations between age and continuing therapy and GP contact after stroke.

	Univariable, N(%)				18–54 years	Multivariable, OR (95% CI)		
	18–54 years	55–64 years	≥65 years	P value		55–64 years	≥65 years	P value
PT/OT								
3 months	67 (46.9)	61 (45.9)	247 (46.2)	0.985	1	1.11 (0.60–2.03)	0.88 (0.53–1.45)	0.461
1 year	43 (31.4)	32 (19.4)	100 (19.6)	0.009	1	0.61 (0.34–1.13)	0.56 (0.34–0.94)	0.043
SALT								
3 months	30 (30.3)	22 (21.6)	91 (31.2)	0.144	1	0.78 (0.34–1.82)	0.72 (0.36–1.42)	0.360
1 year	13 (12.4)	9 (8.2)	29 (7.4)	0.262	1	0.62 (0.19–1.95)	0.83 (0.33–2.07)	0.896
Seen by GP								
3 months	198 (77.0)	237 (82.9)	760 (68.8)	<0.001	1	1.54 (0.93–2.53)	0.67 (0.45–1.00)	<0.001
1 year	163 (86.2)	164 (84.1)	505 (79.0)	0.045	1	1.06 (0.52–2.16)	0.72 (0.39–1.32)	0.167

department.” However, it also states that younger adults with stroke should be managed within settings that “*recognise and manage the particular physical, psychological and social needs of younger patients with stroke*” and that this should be “*provided in an environment suited to their specific social needs.*” Results from this study suggest that the majority of younger stroke patients are receiving care on a specialist unit. While young patients with PICH are less likely to be treated on a stroke unit at any time during their stay, the majority are admitted to a neurosurgical ward or ICU instead. It has been suggested that the increased survival rates and lower levels of dependency associated with stroke unit admission are the greatest among the 18–64-year age group [14]. Although ICU may be deemed more appropriate for a younger patient, it is also important to ensure that they are not missing out on improved outcomes associated with stroke unit admission, afforded by specialist multidisciplinary stroke care.

A qualitative study of hospital and community stroke service providers looked at stroke unit admissions and selection procedures [22]. Service providers report that, even when policy states that all stroke patients be admitted, selection was occasionally required due to limited bed availability. In these cases providers commonly based selection on rehabilitation potential. Patients with mild strokes, likely to recover quickly, and those with very severe strokes, deemed unlikely to recover, may be less likely to be admitted. Younger stroke patients may be deemed more likely to recover, potentially accounting in part for the higher rates of appropriate acute care observed. The greater perceived recovery potential of younger patients may also lead to longer contact with rehabilitation services as suggested by the higher rates of physiotherapy or occupational therapy 1 year after stroke in the 18–54-year age group. A qualitative study looking at stroke professional’s attitudes to rehabilitation found elderly and unmotivated patients may be treated differently by some professionals, with greater encouragement to continue therapy potentially given to younger patients [23]. Younger patients themselves may also be more likely to push for ongoing rehabilitation therapies.

Although this study has not demonstrated any large differences in access to care according to age, with the exception of stroke unit admission for those with PICH, younger patients are more likely to report larger number of unmet needs and greater dissatisfaction with stroke services [24]. It is therefore important to ensure that existing services are meeting the needs of young people.

A study from the US found stroke survivors under 65 years of age were less likely to be seen by a general practitioner and less likely to be able to afford medications [8]. However, increasing age was associated with decreasing likelihood of being prescribed secondary prevention in the [9]. However, only stroke survivors aged 50 and over were included. In this study, there was no evidence of any differences in rates of secondary prevention and those under 65 were most likely to be seen by a GP.

A higher likelihood of having a brain scan in younger patients has previously been observed in other studies [10–13]. No significant trend between age and odds of having a

scan were found in this study although slightly higher overall rates were observed among younger patients. However, rates of brain imaging in this population were high; over 90% of all patients were scanned and this neared 100% towards the end of the study. Further, previous studies have focused on older stroke patients, categorising age differently.

A 2005 study using data from the SLSR, for the period 1995 to 2000, investigated patterns of care using similar indicators and reported that overall quality of care was suboptimal [1]. Another 2011 study looked at acute care services in the same area from 1995 to 2011 [10]. Significant improvements in care were found over the 15-year period but inequalities still exist. This study focused on the younger patients, further dividing the under-65-year age group in two, to identify any further differences between younger people, more likely to be working, and those who may already be retired or have other comorbidities, while controlling for changes in uptake of services over time.

The main strengths of this study lie in its design. Data were obtained from a large multiethnic population-based register, estimated to be 75–84% complete [17], spanning a period of 16 years. While there is a number of population-based studies that examine outcomes of stroke among working age or younger adults [25–27], to the best of our knowledge this is the first population-based study examining access to and provision of evidence-based stroke care for this age group.

The study is limited by the proportion of eligible patients completing the 3- and 12-month follow-up interview, 65.1% and 72.2%, respectively. These rates are similar to those reported in other urban population-based studies [28, 29]. This study also relied on the self-report of the receipt of rehabilitation therapies and diagnosis of new risk factors at 3 and 12 months after stroke. This could be subject to recall bias as certain subgroups of patients may be less able to accurately recall new diagnoses or having received therapy.

Current SLSR data collection allowed us to compare access to evidence-based care that should be provided regardless of age. However, clinical guidelines also suggest that working age adults may have other needs not met by these services, which need to be identified and appropriate provision made available. Data on access to other services, such as vocational rehabilitation, was not available as part of this study. Further investigation of longer-term needs and outcomes of younger stroke survivors is needed to ensure current service provision reflects their priorities.

5. Conclusions

The majority of younger stroke patients have equal, or greater, access to evidence-based care when compared to older patients. However, the UK Department of Health’s National Stroke strategy calls for the development of services to meet the particular needs of people who have a stroke in working age [29]. There is a need to ensure that evidence-based stroke services, such as stroke unit care, are meeting the needs of this group.

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References

- [1] C. McKeivitt, C. Coshall, K. Tilling, and C. Wolfe, "Are there inequalities in the provision of stroke care? Analysis of an inner-city stroke register," *Stroke*, vol. 36, no. 2, pp. 315–320, 2005.
- [2] M. A. Busch, C. Coshall, P. U. Heuschmann, C. McKeivitt, and C. D. A. Wolfe, "Sociodemographic differences in return to work after stroke: the South London Stroke Register (SLSR)," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 80, no. 8, pp. 888–893, 2009.
- [3] K. Daniel, C. D. A. Wolfe, M. A. Busch, and C. McKeivitt, "What are the social consequences of stroke for working-aged adults? A systematic review," *Stroke*, vol. 40, no. 6, pp. e431–e440, 2009.
- [4] O. Saka, A. Mcguire, and C. Wolfe, "Cost of stroke in the United Kingdom," *Age and Ageing*, vol. 38, no. 1, pp. 27–32, 2009.
- [5] Royal College of Physicians Intercollegiate Stroke Working, *National Clinical Guidelines for Stroke*, Royal College of Physicians, London, UK, 2008.
- [6] A. Bhalla, R. Grieve, K. Tilling, A. G. Rudd, and C. D. A. Wolfe, "Older stroke patients in Europe: stroke care and determinants of outcome," *Age and Ageing*, vol. 33, no. 6, pp. 618–624, 2004.
- [7] C. A. Di, M. Lamassa, G. Pracucci et al., "Stroke in the very old: clinical presentation and determinants of 3-month functional outcome: a European perspective. European BIOMED Study of Stroke Care Group," *Stroke*, vol. 30, no. 11, pp. 2313–2319, 1999.
- [8] D. A. Levine, C. I. Kiefe, T. K. Houston, J. J. Allison, E. P. McCarthy, and J. Z. Ayanian, "Younger stroke survivors have reduced access to physician care and medications: National Health Interview Survey from years 1998 to 2002," *Archives of Neurology*, vol. 64, no. 1, pp. 37–42, 2007.
- [9] R. Raine, W. Wong, G. Ambler et al., "Sociodemographic variations in the contribution of secondary drug prevention to stroke survival at middle and older ages: cohort study," *British Medical Journal*, vol. 338, Article ID b1279, 2009.
- [10] J. Addo, A. Bhalla, S. Crichton, A. G. Rudd, C. McKeivitt, and C. D. Wolfe, "Provision of acute stroke care and associated factors in a multiethnic population: prospective study with the South London Stroke Register," *British Medical Journal*, vol. 342, article d744, 2011.
- [11] A. I. Lazzarino, W. Palmer, A. Bottle, and P. Aylin, "Inequalities in stroke patients' management in english public hospitals: a survey on 200,000 patients," *PLoS One*, vol. 6, no. 3, Article ID e17219, 2011.
- [12] J. Heidrich, P. U. Heuschmann, P. Kolominsky-Rabas, A. G. Rudd, and C. D. A. Wolfe, "Variations in the use of diagnostic procedures after acute stroke in Europe: results from the BIOMED II study of stroke care," *European Journal of Neurology*, vol. 14, no. 3, pp. 255–261, 2007.
- [13] A. G. Rudd, A. Hoffman, C. Down, M. Pearson, and D. Lowe, "Access to stroke care in England, Wales and Northern Ireland: the effect of age, gender and weekend admission," *Age and Ageing*, vol. 36, no. 3, pp. 247–255, 2007.
- [14] A. Terent, K. Asplund, B. Farahmand et al., "Stroke unit care revisited: Who benefits the most? A cohort study of 105 043 patients in Riks-Stroke, the Swedish Stroke Register," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 80, no. 8, pp. 881–887, 2009.
- [15] Office for National Statistics, "2001 Census: Standard Area Statistics (England and Wales)," [computer file]. ESRC/JISC Census Programme, Census Dissemination Unit, Mimas (University of Manchester), 2003.
- [16] J. A. Stewart, R. Dundas, R. S. Howard, A. G. Rudd, and C. D. A. Wolfe, "Ethnic differences in incidence of stroke: prospective study with stroke register," *British Medical Journal*, vol. 318, no. 7189, pp. 967–971, 1999.
- [17] P. U. Heuschmann, A. P. Grieve, A. M. Toschke, A. G. Rudd, and C. D. A. Wolfe, "Ethnic group disparities in 10-year trends in stroke incidence and vascular risk factors: the South London Stroke Register (SLSR)," *Stroke*, vol. 39, no. 8, pp. 2204–2210, 2008.
- [18] C. L. M. Sudlow and C. P. Warlow, "Comparing stroke incidence worldwide what makes studies comparable?" *Stroke*, vol. 27, no. 3, pp. 550–558, 1996.
- [19] S. Hatano, "Experience from a multicentre stroke register: a preliminary report," *Bulletin of the World Health Organization*, vol. 54, no. 5, pp. 541–553, 1976.
- [20] C. D. A. Wolfe, A. G. Rudd, R. Howard et al., "Incidence and case fatality rates of stroke subtypes in a multiethnic population: the South London stroke register," *Journal of Neurology Neurosurgery and Psychiatry*, vol. 72, no. 2, pp. 211–216, 2002.
- [21] J. Pal, R. Brown, and D. Fleiszer, "The value of the Glasgow Coma Scale and injury severity score: predicting outcome in multiple trauma patients with head injury," *Journal of Trauma*, vol. 29, no. 6, pp. 746–748, 1989.
- [22] F. Mold, C. Wolfe, and C. McKeivitt, "Falling through the net of stroke care," *Health and Social Care in the Community*, vol. 14, no. 4, pp. 349–356, 2006.
- [23] N. Maclean, P. Pound, C. Wolfe, and A. Rudd, "The concept of patient motivation: a qualitative of stroke professionals' attitudes," *Stroke*, vol. 33, no. 2, pp. 444–448, 2002.
- [24] R. Morris, "The psychology of stroke in young adults: the roles of service provision and return to work," *Stroke Research and Treatment*, vol. 2011, Article ID 534812, 2011.
- [25] N. Glozier, M. L. Hackett, V. Parag, and C. S. Anderson, "The influence of psychiatric morbidity on return to paid work after

- stroke in younger adults: the auckland regional community stroke (ARCOS) study, 2002 to 2003,” *Stroke*, vol. 39, no. 5, pp. 1526–1532, 2008.
- [26] L. J. Kappelle, H. P. Adams, M. L. Heffner, J. C. Torner, F. Gomez, and J. Biller, “Prognosis of young adults with ischemic stroke: a long-term follow-up study assessing recurrent vascular events and functional outcome in the Iowa Registry of Stroke in Young Adults,” *Stroke*, vol. 25, no. 7, pp. 1360–1365, 1994.
- [27] H. Naess, H. I. Nyland, L. Thomassen, J. Aarseth, and K. M. Myhr, “Long-term outcome of cerebral infarction in young adults,” *Acta Neurologica Scandinavica*, vol. 110, no. 2, pp. 107–112, 2004.
- [28] H. M. Dewey, J. Sturm, G. A. Donnan, R. A. L. Macdonell, J. J. McNeil, and A. G. Thrift, “Incidence and outcome of subtypes of ischaemic stroke: initial results from the North East Melbourne Stroke Incidence Study (NEMESIS),” *Cerebrovascular Diseases*, vol. 15, no. 1-2, pp. 133–139, 2003.
- [29] M. L. Niemi, R. Laaksonen, M. Kotila, and O. Waltimo, “Quality of life 4 years after stroke,” *Stroke*, vol. 19, no. 9, pp. 1101–1107, 1988.
- [30] Department of Health, *National Stroke Strategy*, Department of Health, 2007.

Research Article

Income and Education as Predictors of Stroke Mortality after the Survival of a First Stroke

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Background. It is well known that socioeconomic indicators, such as income and education, predict both stroke incidence and stroke mortality. This means that persons in lower socioeconomic positions are less likely to survive their stroke, and there will be a selective survival in the group discharged from hospital after their first stroke. **Question.** Does socioeconomic position continue to predict mortality, stroke specific, or from other causes, among patients surviving their first stroke in spite of this selective survival? **Methods.** All persons in Sweden aged 40–59 years who were discharged after a first hospitalization for stroke in 1996–2000 were included ($n = 10,487$), then followed up until the end of the fourth calendar year after discharge. Data were analysed with Cox regressions controlling for age, sex, and stroke type. **Results.** Persons with high socioeconomic position, measured by education and income, have lower mortality than those of low position. Education was not significant when adjusted for income, however. The risk of dying was similar for stroke-specific mortality and all-cause mortality, for those with cerebral infarction as well as for all patients. **Conclusions.** Socioeconomic position predicted stroke-specific mortality also in the selective group of persons who survived their first stroke.

1. Introduction

Many studies show that persons in lower socioeconomic positions, such as low-income groups or persons with a short education, have higher risk of dying from stroke [1–3]. This also means that persons in lower socioeconomic positions will survive a stroke to a lesser degree than persons in higher positions. Thus, among people discharged from hospital after their first stroke a selective survival will have occurred. It is moreover reasonable to assume that people who come under health care supervision may fare better, for example, due to medication and physiotherapy. In other words, it seems likely that the general access to a universal health care system and/or selective survival may have modified the association with socioeconomic position.

Our question is whether socioeconomic position predicts stroke-specific mortality also among the selective group of patients surviving their first stroke. When death was measured as all-cause mortality, socioeconomic position did continue to play a role as persons in low socioeconomic position

that survived a first stroke remained at higher risk of early mortality [4]. However, it is unclear whether the socioeconomic gradient for stroke-specific mortality is similar to that for all-cause mortality. Some studies indicate that socioeconomic position continues to predict stroke-specific mortality [5–8], but to our knowledge this specific issue has not been addressed before.

Object of This Study. To what extent does income and education predict stroke-specific mortality and mortality due to other causes after the discharge from a first hospitalization for stroke?

2. Methods

2.1. Study Population. This study was carried out in Sweden, where approximately 30 000 persons are afflicted by stroke each year [9]. Stroke is a disease of the elderly but about 20 percent of stroke sufferers in Sweden are of working age, that is, under 65. Most hospitals are public and the few

TABLE 1: Descriptive statistics ($n = 10,487$).

	Income (quartiles)				Education			
	1 (lowest)	2	3	4	Compulsory	Upper secondary	University	All
Died during the followup (%)								
No	83.0	90.8	94.4	94.9	90.0	90.9	93.3	91.0
Yes, from stroke	5.2	2.5	2.0	1.1	3.3	2.5	1.6	2.6
Yes, other cause	11.8	6.7	3.6	4.0	6.7	6.6	5.1	6.4
Age (%)								
40–44	6.7	9.6	8.7	7.2	5.7	9.4	9.9	8.1
45–49	14.3	17.9	19.2	16.9	14.8	18.3	19.2	17.1
50–54	28.6	29.9	33.2	34.2	30.4	32.8	30.9	31.5
55–59	50.5	42.7	38.9	41.8	49.1	39.6	40.0	43.3
Sex (%)								
Men	59.4	51.2	56.6	82.1	64.0	61.8	60.7	62.4
Women	40.6	48.8	43.4	17.9	36.0	38.2	39.3	37.6
Stroke category (%)								
Cerebral infarction	71.4	65.7	66.8	68.7	69.8	68.1	64.7	68.1
Subarachnoid haemorrhage	8.7	15.0	15.4	12.8	11.6	13.4	15.4	13.1
Intracerebral haemorrhage	12.1	12.7	12.3	13.2	11.7	12.6	14.5	12.6
Stroke, not specified (I64)	7.7	6.6	5.5	5.3	6.8	6.0	5.4	6.2
Income 1999 (100 SEK)								
Min	0	59	1627	2361	0	0	0	0
Max	57	1621	2358	16089	5335	8020	16089	16089
Median	0	956	2022	2909	1305	1621	2394	1680
Days of inpatient care								
Median	11	10	9	8	10	10	9	9
No. of observations	2,458	2,605	2,725	2,699	4,035	4,501	1,951	10,487

private ones have contracts with the county council. A wide range of rehabilitation measures are available to stroke survivors, from acute hospital care with special stroke teams to rehabilitation clinics for both in- and outpatient care.

2.2. Inclusion Criteria. All persons in Sweden aged 40–59 who were hospitalized for the first time for stroke in 1996–2000 ($n = 11,687$) were identified from the national register of inpatient care. Among the population there are approximately 2.5 million persons in this age group. The stroke types cerebral infarction, subarachnoid haemorrhage, intracerebral haemorrhage, and “stroke, not specified” (ICD 10 = I60, I61, I63, and I64) were included (both principal and secondary diagnoses). Persons with a previous ischemic heart disease (ICD 10 = I20–I25) were excluded to avoid comorbidity as well as TIA (ICD 10 = G45.8 and G45.9) due to less reliable data. Other data were then added, such as income and education, from a Statistics Sweden population-based data register. While 1200 stroke patients died during their hospitalization, 10,487 were later discharged (see Table 1 for descriptives). The study group consists of these cases.

Both stroke-specific mortality and mortality from other causes were analysed from the first day after discharge until the end of the fourth calendar year after the stroke. We also modelled data with 30-day case fatality from hospital admission, but the results were very similar compared to data from

discharge (not shown). During the followup $n = 946$ died and of those $n = 277$ died from stroke. Information about cause and exact date of death is from the Swedish Cause of Death Register (ICD 10 I60–I69).

Education is measured as elementary, upper secondary, and university. Income was grouped into four equally sized quartiles. The income and education data concerned the calendar year prior to the stroke.

We used Cox regressions to analyse mortality after discharge. Results are presented as relative risks. Analyses are controlled for sex, age, age square, stroke category, days of inpatient care, and days square. Days of inpatient care was used as a proxy of stroke severity. This adjustment did not affect estimates for education and income.

The study was approved by the Regional Ethical Committee in Stockholm (2006/5 : 1).

3. Results

Table 1 gives an overview of the studied group, showing the distribution of sex, age groups, proportion that died, stroke category, and days of inpatient care, by income quartiles and education.

Table 2 shows the mortality risk after surviving any stroke subtype, Table 3 after the main stroke category cerebral infarction. The first three columns with results in Table 2 show the risk stroke-specific mortality and the last three columns

TABLE 2: Relative risk of dying after a stroke ($n = 10,487$).

	Stroke-specific mortality			Other causes of death than stroke		
	Model 1	2 RR (<i>P</i> value)	3	1	2 RR (<i>P</i> value)	3
<i>Education</i>	<i>P</i> = 0.006		<i>P</i> = 0.392	<i>P</i> = 0.070		<i>P</i> = 0.313
Compulsory	1 (ref)		1 (ref)	1 (ref)		1 (ref)
Upper secondary	0.81 (0.098)		0.89 (0.384)	1.04 (0.651)		1.14 (0.129)
University	0.54 (0.002)		0.77 (0.203)	0.80 (0.055)		1.06 (0.652)
<i>Income (quartiles)</i>		<i>P</i> < 0.001	<i>P</i> < 0.001		<i>P</i> < 0.001	<i>P</i> < 0.001
1 (lowest)		1 (ref)	1 (ref)		1 (ref)	1 (ref)
2		0.53 (<0.001)	0.53 (<0.001)		0.58 (<0.001)	0.60 (<0.001)
3		0.42 (<0.001)	0.43 (<0.001)		0.31 (<0.001)	0.30 (<0.001)
4		0.21 (<0.001)	0.22 (<0.001)		0.32 (<0.001)	0.31 (<0.001)
<i>Stroke category</i>	<i>P</i> = 0.033	<i>P</i> = 0.105	<i>P</i> = 0.108	<i>P</i> < 0.001	<i>P</i> = 0.005	<i>P</i> = 0.005
Cerebral infarction	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Subarachnoid haemorrhage	0.53 (0.008)	0.60 (0.031)	0.60 (0.033)	0.56 (<0.001)	0.63 (0.003)	0.63 (0.003)
Intracerebral haemorrhage	1.07 (0.699)	1.11 (0.534)	1.11 (0.517)	1.15 (0.209)	1.18 (0.145)	1.18 (0.143)
Stroke, not specified (I64)	1.24 (0.385)	1.17 (0.518)	1.17 (0.530)	1.10 (0.523)	1.03 (0.853)	1.03 (0.843)

Controlling for sex, age, age square, stroke category, days of inpatient care, and days square. “Ref” is the reference category. The *P* value to the right of the variable name shows whether the variables have made a significant contribution to the model. Results in bold have $P < 0.05$.

RR: relative risk. RR > 1.0 means higher likelihood of dying.

the similar results for other causes of death than stroke. The analyses show that persons with low education and low income had higher risk for stroke-specific mortality when analysed separately (Table 2). The risk of dying was lower for persons with university education than for those with elementary education (Model 1) and was lower for persons with higher-income than for persons with lower-income (Model 2). Including both variables measuring socioeconomic position, that is, controlling for each other, only income continued to be significant (Model 3).

The relative risk of stroke-specific mortality in the highest income quartile was only about one fifth compared to the lowest quartile (RR 0.22) when adjusted for education. The table presents income quartiles in average over educational groups, although a detailed analysis suggests that the relative difference in risk was greater in the group with the shortest education.

The analyses of the risk for other causes of death than stroke showed similar pattern as stroke-specific mortality, except that education was only significant on the 10-percent level and that the mortality differences between income quartiles was slightly smaller. The highest income quartile had a mortality risk that was about a third of the lowest income quartile.

Among persons discharged from hospital the risk of dying from stroke was about half among those with subarachnoid haemorrhage as compared to the other stroke subcategories.

Table 3 displays the mortality pattern for the main stroke category cerebral infarction separately. This pattern was similar to that of all stroke subtypes except that association between education and mortality was significant for both stroke-specific mortality and mortality from other causes of death.

4. Discussion

Socioeconomic position, that is, income and education, predicted stroke-specific mortality—as well as mortality due to other causes—also after the selective survival of a first stroke. While education was not significant when income was included in the model, the risk of dying from stroke in the highest income quartile was one-fifth of that in the lowest income quartile.

This might indicate that economic resources are more decisive than educational ones (e.g., how well-informed someone is). However, since education generally precedes income as it is completed early in life, and income is partly

TABLE 3: Relative risk of dying after a cerebral infarction ($n = 7, 143$).

	Stroke-specific mortality			Other causes of death than stroke		
	Model 1	2 RR (<i>P</i> value)	3	1	2 RR (<i>P</i> value)	3
<i>Education</i>	<i>P</i> = 0.007		<i>P</i> = 0.198	<i>P</i> = 0.006		<i>P</i> = 0.102
Compulsory	1 (ref)		1 (ref)	1 (ref)		1 (ref)
Upper secondary	0.78 (0.109)		0.86 (0.345)	1.08 (0.448)		1.18 (0.101)
University	0.45 (0.002)		0.63 (0.083)	0.67 (0.009)		0.90 (0.486)
<i>Income (quartiles)</i>		<i>P</i> < 0.001	<i>P</i> < 0.001		<i>P</i> < 0.001	<i>P</i> < 0.001
1 (lowest)		1 (ref)	1 (ref)		1 (ref)	1 (ref)
2		0.43 (<0.001)	0.44 (<0.001)		0.57 (<0.001)	0.56 (<0.001)
3		0.35 (<0.001)	0.36 (<0.001)		0.27 (<0.001)	0.27 (<0.001)
4		0.20 (<0.001)	0.22 (<0.001)		0.30 (<0.001)	0.31 (<0.001)

Controlling for sex, age, age square, days of inpatient care, and days square. “Ref” is the reference category. The *P* value to the right of the variable name shows whether the variables have made a significant contribution to the model. Results in bold have $P < 0.05$.

RR: relative risk. RR > 1.0 means higher likelihood of dying.

the result of educational achievements, education may be conceptualized as a factor underlying the later association between income and mortality.

While none of the previous studies specifically examines income and education as predictors of stroke mortality after the selective survival from a first stroke, some studies have had followup periods that partly overlap with ours [5–8], and although some of them have other indicators of socioeconomic position, for example, occupation [6] or looking at stroke incidence rather than mortality [10], their results point in the same direction as ours, that is, that socioeconomic position continues to be a strong predictor also after the selective survival of a first stroke. If anything, the socioeconomic gradient indicated in our results was even steeper than for stroke mortality in general [3].

That socioeconomic position predicts stroke mortality also after the selective survival from a first stroke may indicate the importance of buffering socioeconomic inequalities with secondary prevention. The utilization of health care differs by socioeconomic position also in countries with universal health coverage. In Sweden, for example, higher income groups utilize physicians to a greater extent than lower income groups [11]. Studies have also found a socioeconomic gradient for waiting time for carotid surgery [5], use of magnetic resonance imaging (MRI) [5, 12], and for receiving optimal acute care [13]. Even so, the latter study also indicates that the socioeconomic differences in stroke outcome cannot be explained by differences in acute care [13].

There are many factors besides health care utilization and medication that affect mortality risk. Disabled individuals also run an increased risk of dying from stroke [14] that may be related to income differences in disability [12, 15], compliance, and coping ability [16].

Health behaviour is important for both primary and secondary prevention and lower-income groups are in greater need of health behaviour counselling, for example, concerning smoking habits [17]. In one study, the socioeconomic gradient for the incidence of stroke among middle-aged persons could largely be explained by health behaviour, that is, smoking and alcohol consumption [9]. On the other hand, in a population-based Swedish study on elderly patients with cerebral infarction [18], the socioeconomic gradient persisted with adjustments for health behaviour.

In our results, the socioeconomic gradient was just slightly larger for stroke-specific mortality than for mortality due to other causes. This indicates that determinants of socioeconomic differences may be shared between stroke and other morbidity. It also indicates that in spite of the fact that we have focused on socioeconomic differences in mortality late in the disease process, that is, after surviving and being discharged from hospital after a first stroke, it is the effects of determinants further upstream that are captured.

Our results indicate the need to allocate more resources to low-income groups than to high-income groups, targeting them as a high-risk population. But it remains unclear whether the increased risk is of relatively recent origin, or whether it reflects disadvantages accumulated over a life-span, with respect to health care and health behaviour as well as to other factors.

It is worth noting that a review of the most effective evidence-based strategies for reducing health inequalities suggests interventions focused on early life and general living conditions, that is, a good start in life, that all young people should be able to maximize their capabilities and have control over their lives, fair employment, good work, and healthy standards of living for all, and healthy and sustainable

communities, besides the role and impact of ill-health prevention [19].

Otherwise, it has been recognized that people's working conditions, such as work stress and control, are closely correlated with income differences [20–22]. Other factors may interact with socioeconomic position so that the joint exposure of such factors as health behaviour and received health care play a role for stroke mortality.

This study did not examine the effect of socioeconomic position on the risk of a first stroke or the selectivity in the survival of it. Thus, it was not able to compare risks before and after a first stroke. This might be interesting for future research.

The registers used are considered to be of high quality, but there are limitations. There are no records of stroke severity, or such traditional risk factors as smoking, obesity, and hypertension. In a recent study we described how persons of working age belonging to higher-income groups were more likely to return to paid work after a stroke [23]. This interest in the possibility to return to paid work also lays behind the age limits applied in this study.

Another limitation was the lack of information on ethnicity or comorbidity. It would also have been interesting to examine the pathway separately for men and for women, as the pattern may differ both due to different environmental influences and to different susceptibility for the disease. A separate analysis by gender was not viable because of the small number of women who died from stroke ($n = 81$). Any closer analysis of the determinants was similarly restricted due to the rather small number of deaths, and there is a possibility of bias due to omitted variables.

A complication that obscures comparability between studies is the choice of reference group, which will tend to differ along the pathway of the disease. In studies of stroke incidence the natural choice is the general population, but in studies of poststroke mortality the nonfatal cases of the disease are the obvious choice. It is unclear how the socioeconomic gradient, as well as the influence of other factors, are affected by the choice of reference group. This is an issue that deserves to be recognized and more closely studied in the future.

This study recognizes that the influence of a factor might differ depending on the stage in the pathway of the disease. An important implication of our study is that there is a need to separate the influence of different factors along the pathway from disease to death.

There is no exact boundary between when mortality risk from the first stroke ends and when the mortality risk from a second stroke should be conceived to begin. This boundary was also alternatively operationalized using 30 days from hospital admission with similar results, but there is a certain face validity in using hospital discharge as an indication of survival from the first stroke.

Conclusion. There are major socioeconomic differences in stroke mortality, also after the selective survival from a first stroke.

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References

- [1] A. M. Cox, C. McKeivitt, A. G. Rudd, and C. D. A. Wolfe, "Socioeconomic status and stroke," *Lancet Neurology*, vol. 5, no. 2, pp. 181–188, 2006.
- [2] A. E. Kunst, M. Del Rios, F. Groenhof, and J. P. Mackenbach, "Socioeconomic inequalities in stroke mortality among middle-aged men. An international overview," *Stroke*, vol. 29, no. 11, pp. 2285–2291, 1998.
- [3] S. Toivanen, "Income differences in stroke mortality: a 12-year follow-up study of the Swedish working population," *Scandinavian Journal of Public Health*, vol. 39, no. 8, pp. 797–804, 2011.
- [4] J. Arrich, W. Lalouschek, and M. Müllner, "Influence of socioeconomic status on mortality after stroke: retrospective cohort study," *Stroke*, vol. 36, no. 2, pp. 310–314, 2005.
- [5] M. K. Kapral, H. Wang, M. Mamdani, and J. V. Tu, "Effect of socioeconomic status on treatment and mortality after stroke," *Stroke*, vol. 33, no. 1, pp. 268–273, 2002.
- [6] C. Li, B. Hedblad, M. Rosvall, F. Buchwald, F. A. Khan, and G. Engström, "Stroke incidence, recurrence, and case-fatality in relation to socioeconomic position: a population-based study of middle-aged Swedish men and women," *Stroke*, vol. 39, no. 8, pp. 2191–2196, 2008.
- [7] G. Cesaroni, N. Agabiti, F. Forastiere, and C. A. Perucci, "Socioeconomic differences in stroke incidence and prognosis under a universal healthcare system," *Stroke*, vol. 40, no. 8, pp. 2812–2819, 2009.
- [8] G. Zhou, X. Liu, G. Xu, X. Liu, R. Zhang, and W. Zhu, "The effect of socioeconomic status on three-year mortality after first-ever ischemic stroke in Nanjing, China," *BMC Public Health*, vol. 6, p. 227, 2006.
- [9] National Board of Health and Welfare, "Folkhälsorapport 2009," Popular Health Report 2009, National Board of Health and Welfare, Stockholm, Sweden, 2009.
- [10] H. Kuper, H. O. Adami, T. Theorell, and E. Weiderpass, "The socioeconomic gradient in the incidence of stroke: a prospective study in middle-aged women in Sweden," *Stroke*, vol. 38, no. 1, pp. 27–33, 2007.
- [11] E. van Doorslaer, C. Masseria, and X. Koolman, "Inequalities in access to medical care by income in developed countries," *Canadian Medical Association Journal*, vol. 174, no. 2, pp. 177–183, 2006.
- [12] D. Jakovljević, C. Sarti, J. Sivenius et al., "Socioeconomic status and ischemic stroke: the FINMONICA stroke register," *Stroke*, vol. 32, no. 7, pp. 1492–1498, 2001.
- [13] V. Langagergaard, K. H. Palnum, F. Mehnert et al., "Socioeconomic differences in quality of care and clinical outcome after stroke: a nationwide population-based study," *Stroke*, vol. 42, no. 10, pp. 2896–2902, 2011.
- [14] G. A. M. van den Bos, J. P. J. M. Smits, G. P. Westert, and A. Van Straten, "Socioeconomic variations in the course of stroke: unequal health outcomes, equal care?" *Journal of Epidemiology and Community Health*, vol. 56, no. 12, pp. 943–948, 2002.

- [15] N. U. Weir, A. Gunkel, M. McDowall, and M. S. Dennis, "Study of the relationship between social deprivation and outcome after stroke," *Stroke*, vol. 36, no. 4, pp. 815–819, 2005.
- [16] Q. Liu, M. Wang, J. Guo, J. Li, C. Li, and M. Qian, "Effect of socioeconomic status on secondary prevention of stroke," *International Journal for Quality in Health Care*, vol. 23, no. 4, pp. 405–412, 2011.
- [17] K. Ahacic, P. Allebeck, and K. D. Thakker, "Being questioned and receiving advice about alcohol and smoking in health care: associations with patients' characteristics, health behavior, and reported stage of change," *Substance Abuse Treatment, Prevention, and Policy*, vol. 5, no. 1, p. 30, 2010.
- [18] U. Löfmark and A. Hammarström, "Evidence for age-dependent education-related differences in men and women with first-ever stroke: results from a community-based incidence study in northern Sweden," *Neuroepidemiology*, vol. 28, no. 3, pp. 135–141, 2007.
- [19] M. Marmot, "Fair society, healthy lives," Tech. Rep., The Marmot Review, London, UK, 2010, <http://www.instituteofhealth-equity.org/projects/fair-society-healthy-lives-the-marmot-review/fair-society-healthy-lives-executive-summary.pdf>.
- [20] S. Toivanen, "Exploring the interplay between work stress and socioeconomic position in relation to common health complaints: the role of interaction," *American Journal of Industrial Medicine*, vol. 54, no. 10, pp. 780–790, 2011.
- [21] R. A. Karasek and T. Theorell, *Healthy Work: Stress, Productivity and Reconstruction of Working Life*, Basic Books, New York, NY, USA, 1990.
- [22] R. Wilkinson and M. Marmot, Eds., *Social Determinants of Health: The Solid Facts*, World Health Organization The Regional Office for Europe, Copenhagen, Denmark, 2nd edition, 2003.
- [23] S. Trygged, K. Ahacic, and I. Kåreholt, "Income and education as predictors of return to working life among younger stroke patients," *BMC Public Health*, vol. 11, p. 742, 2011.

Clinical Study

Long-Term Survival of Young Stroke Patients: A Population-Based Study of Two Stroke Registries from Tartu, Estonia

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The aim of this paper was to evaluate the long-term survival of young stroke patients in Estonia, analyse time trends of survival, and compare the results with other studies. We have used 2 population-based first-ever stroke registry data (1991–1993 and 2001–2003) to analyse the 1-, 5-, and 7-year outcome of young stroke patients by the Kaplan-Meier method of analysis. From the group of 1206 patients, 129 (11%) were aged under 55 years. The overall survival rate at 1, 5, and 7 years was 0.70 (95% CI 0.62–0.78), 0.63 (95% CI 0.55–0.72), and 0.61 (95% CI 0.53–0.70), respectively. The survival was significantly worse for patients with intracerebral haemorrhage ($P < 0.01$) and for those aged from 45 to 54 years compared to the younger age group from 0 to 44 years ($P = 0.03$). For patients with ischemic stroke, aged from 15 to 44 years, the 1-, 5-, and 7-year survival rate was 0.89 (95% CI 0.79–1.00), 0.75 (95% CI 0.61–0.93), and 0.75 (0.61–0.93), respectively. There was no difference in overall survival between the two studied periods. We report a low long-term survival rate among young stroke patients in Estonia. Increasing age and hemorrhagic stroke subtype were associated with lower survival. We have previously shown a worse outcome for 1-year survival compared to other studies and currently this trend continues for 5- and 7-year survival rates. In fact, these are the lowest survival rates for the combined and separate stroke subtypes reported so far.

1. Introduction

A young patient with a stroke is always a challenge, even for a stroke physician. Although the outcome of a stroke in the young is believed to be better, it still has a significant impact on the person's quality of life and moreover can be fatal. Data about long-term survival of young stroke patients are scarce and are usually collected retrospectively or are hospital-based [1–20]. Most of these studies have included ischemic strokes and have reported a rather good prognosis but some of the studies were performed years ago when the diagnostic criteria for stroke differed considerably.

Stroke incidence is known to be higher in developing countries, and also in Eastern Europe, compared to the Western countries. In Estonia, the total first-ever stroke incidence is comparable to that of other European countries, but is higher for the younger age groups [21]. The incidence declined by 2001–2003, but it was still 13 per 100 000 for the subjects aged 0 to 44 and 118 per 100 000 for subjects aged

45 to 54 years in Tartu, Estonia [22]. In addition, the 1-year outcome of stroke in terms of functional deficit and survival has also been worse compared to the data from several other study centres [23].

The aim of this paper was to evaluate long-term survival of young stroke patients in Estonia, analyse changes in survival between 1991 to 2003, and compare the results with other studies.

2. Methods

Data from the two population-based stroke registries [21, 25] from Tartu, Estonia, were used. The first registry included all first-ever in a lifetime strokes from 1991 to 1993 (3 years) and the other registry included patients from 2001 to 2003 (2 years). These registries included both hospitalised and nonhospitalised cases and prospective “hot pursuit” case-finding methods were used to assure the inclusion of all stroke patients in the area. The more detailed description

TABLE 1: Median survival rates by age group, stroke subtype, and gender.

Time	Survival	95% CI	Survival	95% CI	Survival	95% CI	P value
	All		Men		Women		
1 year	0.70	0.62–0.78	0.73	0.63–0.83	0.65	0.53–0.80	0.45
5 years	0.63	0.55–0.72	0.61	0.52–0.73	0.65	0.53–0.80	
7 years	0.61	0.53–0.70	0.59	0.49–0.71	0.65	0.53–0.80	
			0–44 years (<i>n</i> = 41)		45–54 years (<i>n</i> = 88)		
1 year			0.85	0.75–0.97	0.63	0.53–0.74	0.03
5 years			0.73	0.61–0.89	0.58	0.49–0.69	
7 years			0.73	0.61–0.89	0.56	0.46–0.67	
	BI (<i>n</i> = 91)		ICH (<i>n</i> = 26)		UND (<i>n</i> = 12)		
1 year	0.79	0.71–0.88	0.39	0.24–0.63	0.67	0.45–0.99	<0.001
5 years	0.71	0.63–0.81	0.31	0.17–0.55	0.67	0.45–0.99	
7 years	0.69	0.60–0.79	0.31	0.17–0.55	0.67	0.45–0.99	
			BI 0–44 years (<i>n</i> = 30)		BI 45–54 years (<i>n</i> = 61)		
1 year			0.90	0.80–1.00	0.74	0.64–0.86	0.15
5 years			0.77	0.63–0.93	0.69	0.58–0.82	
7 years			0.77	0.63–0.93	0.66	0.55–0.79	

of methods used for data collection, definitions, and other criteria for these registries have been published earlier [21, 22, 25].

In this current study, patients aged <55 years at stroke onset were included in the analysis. The Estonian Population Register was used for obtaining survival data. The cut-off point for survival data was February 2001 for the first and January 2011 for the second registry for the evaluation of the 7-year outcome.

The study was approved by the Ethics Review Committee on Human Research of the University of Tartu.

2.1. Statistical Methods. Survival rate was estimated by the Kaplan-Meier method (1-, 5-, and 7-year survival rate). Survival distributions were compared using the log-rank test. *P* values less than 0.05 were considered significant. The analysis was carried out by the statistical software package R.

3. Results

A total of 1280 patients, (501 men and 779 women) with first-ever stroke, were registered during the 5-year study period, with 829 patients from 1991 to 1993 and 451 patients from 2001 to 2003. Patients with subarachnoid haemorrhage (64 patients) were excluded from this current analysis and additionally 10 patients were lost for the long-term followup. From the group of 1206 patients, 129 (11%) were <55 years of age (38% women and 62% men), and these were included in the survival analysis. The mean age of patients was 46.1 (± 9.6) years (range 1 to 55 years). Of them, 91 (71%) had a brain infarction (BI), 26 (20%) an intracerebral haemorrhage (ICH), and 12 (9%) had an undefined type of stroke (UND). Only 3 patients were <15 years of age (2 of them with BI and one with ICH). Perinatal strokes were not included.

Sixty-four of 129 patients (50%) had hypertension, 4 (3%) atrial fibrillation, 17 (13%) diabetes mellitus, 20 (16%) ischemic heart disease, and 7 (5%) had had a previous transient ischemic attack. In 48 patients (38%), no cardiovascular risk factors were identified at stroke onset. The survival rates by age, gender, and stroke subtypes are shown in Table 1. For comparison with previous studies we also calculated the survival rates for patients with ischemic stroke aged 15 to 44 years. The 1-, 5-, and 7-year survival rates were 0.89 (95% CI 0.79–1.00), 0.75 (95% CI 0.61–0.93), and 0.75 (0.61–0.93), respectively.

As expected, the survival rate was worse for patients with ICH and for the older age group. There was no significant difference in overall survival rates between the two studied periods (*P* = 0.8) nor in young ischemic stroke survival between the two study periods (*P* = 0.6).

4. Discussion

The main finding of our study is the low long-term survival rate among young first-ever stroke patients. At the same time most previous reports agree that although the survival of young stroke patients is lower than in the general population, it is still comparatively high [17, 26]. Our previous study [23] has shown a worse outcome for 1-year survival compared to other studies and currently this trend continues for 5- and 7-year survival rates. In fact, these are the lowest survival rates for combined and separate stroke subtypes reported so far. In our study increasing age (0–44 years versus 45–54 years) and hemorrhagic stroke subtype were associated with lower long-term survival. Earlier studies have also found an association between the male gender and higher mortality in young stroke patients [2, 4]. Although this trend can also be seen in our study, it did not reach statistical significance. The more recent study by Putaala et al. [16] could also not

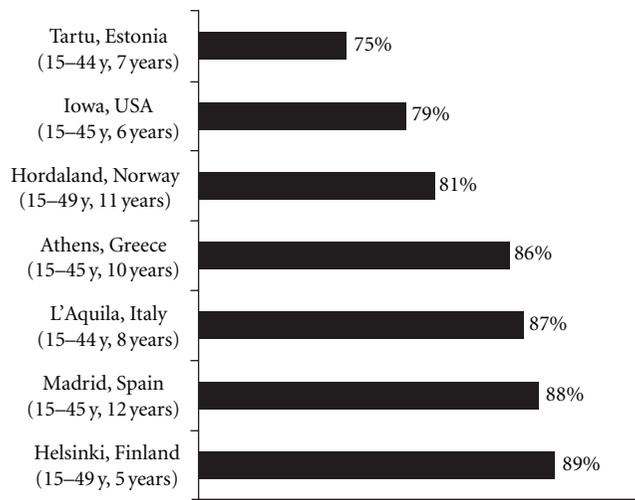


FIGURE 1: Survival of young patients with ischaemic stroke in different studies [1, 2, 4, 16, 18, 24].

identify this association. Quite surprisingly, the survival rate for women remained unchanged after 1 year.

The survival rates for young ischaemic stroke patients from several studies are summarized in Figure 1. The general annual survival rate follows the pattern of earlier studies being clearly lowest in the first year and significantly increases thereafter, but is constantly lower than other studies. The differences in survival rates across the studies could be associated with several aspects. The study type, inclusion criteria, follow-up period, and type of data analysis differ across studies. All, with the exception of three [2, 17, 18], have been hospital based and do not represent a defined population. Although the follow-up periods in these studies are variable, the trend of outcome is still obvious. The results of our study come from two prospective population-based registries. However, a limitation of our study is the small sample size.

The main factor for low survival may be severe stroke, and although there are no comparative data, we speculate that stroke cases are more severe in Estonia. This may be related to a higher prevalence of risk factors leading to a worse outcome. However, in 38% of cases no cardiovascular risk factors were identified despite extensive diagnostic tests. This points to the fact that there may be also other possible causes for higher stroke incidence and lower survival among young subjects in Estonia, for example, genetics, lifestyle, or environmental factors. However, these hypotheses are difficult to prove. And finally, the life expectancy in Estonia was 75.8 years in 2010, 70.6 years for men and 80.8 years for women. Although this rate has constantly grown during the past decade, it is still 3 to 4 years less for women and 5 to 7 years less for men, compared to that of most other European countries [27]. Still, there was no significant difference in stroke survival between the two study periods.

Unfortunately, we were not able to identify the causes of death of young stroke patients because of the strict Estonian data protection legislation. The causes of death

are confidential and coded linking between registries is not allowed. As the cardiovascular mortality and deaths, due to accidents and excess alcohol intake, are high in the young Estonian population (especially in men), a number of our young stroke patients might die due to other causes rather than from stroke.

5. Conclusion

Long-term survival rates of young stroke patients differ significantly across the world. The causes of high stroke incidence and low survival rates in Eastern Europe can be explained in some terms, but the proportion of stroke patients with no identifiable risk factors is high. Future studies and everyday clinical practice should focus on thorough detection of the etiology of stroke, promoting a healthy lifestyle, optimizing primary and secondary prevention strategies thus decreasing the incidence of stroke and achieving a better outcome for young stroke patients.

Acknowledgment

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References

- [1] L. J. Kappelle, H. P. Adams, M. L. Heffner, J. C. Torner, F. Gomez, and J. Biller, "Prognosis of young adults with ischemic stroke: a long-term follow-up study assessing recurrent vascular events and functional outcome in the Iowa Registry of Stroke in Young Adults," *Stroke*, vol. 25, no. 7, pp. 1360–1365, 1994.
- [2] C. Marini, R. Totaro, and A. Carolei, "Long-term prognosis of cerebral ischemia in young adults," *Stroke*, vol. 30, no. 11, pp. 2320–2325, 1999.
- [3] D. Leys, L. Bandu, H. Hénon et al., "Clinical outcome in 287 consecutive young adults (15 to 45 years) with ischemic stroke," *Neurology*, vol. 59, no. 1, pp. 26–33, 2002.
- [4] J. F. Varona, F. Bermejo, J. M. Guerra, and J. A. Molina, "Long-term prognosis of ischemic stroke in young adults: study of 272 cases," *Journal of Neurology*, vol. 251, no. 12, pp. 1507–1514, 2004.
- [5] B. Hindfelt and O. Nilsson, "The prognosis of ischemic stroke in young adults," *Acta Neurologica Scandinavica*, vol. 55, no. 2, pp. 123–130, 1977.
- [6] J. M. Ferro and M. Crespo, "Prognosis after transient ischemic attack and ischemic stroke in young adults," *Stroke*, vol. 25, no. 8, pp. 1611–1616, 1994.
- [7] J. Bogousslavsky and F. Regli, "Ischemic stroke in adults younger than 30 years of age. Cause and prognosis," *Archives of Neurology*, vol. 44, no. 5, pp. 479–482, 1987.
- [8] G. Lanzino, A. Andreoli, G. di Pasquale et al., "Etiopathogenesis and prognosis of cerebral ischemia in young adults. A survey of 155 treated patients," *Acta Neurologica Scandinavica*, vol. 84, no. 4, pp. 321–325, 1991.
- [9] M. Camerlingo, L. Casto, B. Corsori et al., "Recurrence after first cerebral infarction in young adults," *Acta Neurologica Scandinavica*, vol. 102, no. 2, pp. 87–93, 2000.

- [10] J. Matias-Guiu, J. Alvarez-Sabin, and R. Falip, "Prognosis of ischaemic stroke in young adults," in *Proceedings of the ECST Collaborators Meeting*, Edinburgh, UK, September 1991.
- [11] A. B. Grindal, R. J. Cohen, R. F. Saul, and J. R. Taylor, "Cerebral infarction in young adults," *Stroke*, vol. 9, no. 1, pp. 39–42, 1978.
- [12] B. D. Snyder and M. Ramirez Lassepas, "Cerebral infarction in young adults. Long term prognosis," *Stroke*, vol. 11, no. 2, pp. 149–153, 1980.
- [13] K. Srinivasan, "Ischemic cerebrovascular disease in the young. Two common causes in India," *Stroke*, vol. 15, no. 4, pp. 733–735, 1984.
- [14] A. M. Chancellor, G. L. Glasgow, P. A. Ockelford, A. Johns, and J. Smith, "Etiology, prognosis, and hemostatic function after cerebral infarction in young adults," *Stroke*, vol. 20, no. 4, pp. 477–482, 1989.
- [15] R. Musolino, P. La Spina, A. Granata et al., "Ischaemic stroke in young people: a prospective and long-term follow-up study," *Cerebrovascular Diseases*, vol. 15, no. 1-2, pp. 121–128, 2003.
- [16] J. Putaala, S. Curtze, S. Hiltunen, H. Tolppanen, M. Kaste, and T. Tatlisumak, "Causes of death and predictors of 5-year mortality in young adults after first-ever ischemic stroke: the Helsinki young stroke registry," *Stroke*, vol. 40, no. 8, pp. 2698–2703, 2009.
- [17] K. Nedeltchev, T. A. der Maur, D. Georgiadis et al., "Ischaemic stroke in young adults: predictors of outcome and recurrence," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 76, no. 2, pp. 191–195, 2005.
- [18] H. Naess, H. I. Nyland, L. Thomassen, J. Aarseth, and K. M. Myhr, "Long-term outcome of cerebral infarction in young adults," *Acta Neurologica Scandinavica*, vol. 110, no. 2, pp. 107–112, 2004.
- [19] U. Waje-Andreassen, H. Naess, L. Thomassen, G. E. Eide, and C. A. Vedeler, "Long-term mortality among young ischemic stroke patients in Western Norway," *Acta Neurologica Scandinavica*, vol. 116, no. 3, pp. 150–156, 2007.
- [20] J. L. Ruiz-Sandoval, C. Cantu, and F. Barinagarrementeria, "Intracerebral hemorrhage in young people: analysis of risk factors, location, causes, and prognosis," *Stroke*, vol. 30, no. 3, pp. 537–541, 1999.
- [21] R. Vibo, J. Kõrv, and M. Roose, "The third stroke registry in Tartu, Estonia, from 2001 to 2003," *Acta Neurologica Scandinavica*, vol. 116, no. 1, pp. 31–36, 2007.
- [22] R. Vibo, J. Kõrv, and M. Roose, "The third stroke registry in Tartu, Estonia: decline of stroke incidence and 28-day case-fatality rate since 1991," *Stroke*, vol. 36, no. 12, pp. 2544–2548, 2005.
- [23] R. Vibo, J. Kõrv, and M. Roose, "One-year outcome after first-ever stroke according to stroke subtype, severity, risk factors and pre-stroke treatment. A population-based study from Tartu, Estonia," *European Journal of Neurology*, vol. 14, no. 4, pp. 435–439, 2007.
- [24] K. Spengos and K. Vemmos, "Risk factors, etiology, and outcome of first-ever ischemic stroke in young adults aged 15 to 45—the Athens young stroke registry," *European Journal of Neurology*, vol. 17, no. 11, pp. 1358–1364, 2010.
- [25] J. Kõrv, M. Roose, and A. E. Kaasik, "Stroke registry of Tartu, Estonia, from 1991 through 1993," *Cerebrovascular Diseases*, vol. 7, no. 3, pp. 154–162, 1997.
- [26] J. F. Varona, "Long-term prognosis of ischemic stroke in young adults," *Stroke Research and Treatment*, vol. 2011, Article ID 879817, 2011.
- [27] Selection of EU statistics, "Life expectancy at birth," Statistics Estonia, 2011, <http://www.stat.ee/29928>.

Research Article

Sulfur Dioxide and Emergency Department Visits for Stroke and Seizure

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The purpose of this study was to assess an association between ambient sulfur dioxide and the number of emergency department (ED) visits for ischemic stroke and seizure. The study used data collected in a Vancouver (Canada) hospital in the years 1999–2003. Daily ED visits diagnosed as ministroke, stroke, or seizure were investigated using the case-crossover technique. Conditional logistic regression models were applied to estimate the odds ratios (ORs) and their respective 95% confidence intervals (CIs). The models included temperature and relative humidity in the form of natural splines. The results were reported for an increase in interquartile range ((IQR), IQR = 1.9 ppb for SO₂). Positive and statistically significant associations were obtained for SO₂ and ischemic stroke for all patients (OR = 1.12; CI 1.02, 1.23; lag 3) and for female patients (OR = 1.17; CI 1.01, 1.33; lag 0). In the case of ED visits for seizure, for female patients the results were also statistically significant (OR = 1.15; CI 1.02, 1.28; lag 1 and OR = 1.18; CI 1.05, 1.32; lag 2). These findings suggest that cases of ischemic cerebrovascular accidents are associated with acute exposure to ambient sulfur dioxide.

1. Introduction

The toxic, oxidative, and irritating properties of gaseous air pollutants are recognized health hazards [1, 2]. Ambient sulfur dioxide (SO₂) is considered a risk factor for ischemic stroke and seizure, yet the mechanism of its effects on the brain is not currently readily understood. The gas when breathed in dissolves in the mucus lining of the upper respiratory tracts and thus affects their mechanical function, which may result in bronchoconstriction [3–5]. Connections between this syndrome and short-term exposure to SO₂ have been reported [6]. Clinical assays suggested a synergism between this action of SO₂ and a prior exposure to ozone [7]. But SO₂ exposure arguably exacerbates the states of cardiopulmonary and cardiovascular diseases and increases the risk of premature death from circulatory system causes, including ischemic stroke [8–13]. The involvement of SO₂ may be challenged on the basis that it tends to be correlated with toxic combustion particles [14], yet pathophysiologic images of animal stroke model after inhalation of SO₂ show brain injuries similar to those caused by cerebral ischemia [15].

Understanding how exposure to SO₂ causes the onset of brain ischemia would be helpful in preventing devastating health effects. Air pollution may affect the brain through multiple pathways, which are better understood in the case of photochemical pollutants causing neurodegeneration [2, 16], yet the pathway may include depression and symptoms of depression, which are risk factors for cerebral ischemia and stroke [17–24]. The ischemic injury caused by pollutants and the onset of stroke in patients affected by depression may involve the same pathophysiologic mechanism of action [25]. However, studies have found no associations between the presence of depressive symptoms and the risk of stroke in women, while SO₂ associations are only found for women [26].

The present study contributes to the observations of the impact of four gaseous pollutants and two types of particulate matter on ED presentations of ischemic stroke and seizure. A seizure is often caused by conditions that reduce the supply of oxygen to brain cells, so this diagnosis is also included in the analysis [27]. This study mainly focused

on sulfur dioxide exposure and ED visits for stroke or seizure. While the impact of the pollutants on the central nervous system is convoluted, a general pattern appears: sulfur dioxide contributes significantly to the occurrences or symptoms of cerebrovascular ischemia and seizure.

2. Materials and Methods

2.1. Study Population. The study population includes all patients serviced in the period from January 1999 to February 2003 by St. Paul's Hospital located in downtown Vancouver, BC. During that time the hospital was providing emergency health services for approximately 53,000 patients per year, with an admission rate of 15%. A total of 194,443 visits with subsequent diagnoses were registered. The emergency physicians recorded the discharge diagnoses in ED charts using standardized medical vocabulary. The cases were identified using the corresponding standardized strings. The presentations of mini-stroke and stroke were recorded as transient ischemic attack ($n = 307$) and cerebrovascular accident-ischemic ($n = 695$), respectively. These two diagnosed health conditions were combined and summarized to 1002 (females = 449) cases. ED visits with the diagnosis of seizure were retrieved and totaled 2120 (females = 597) cases.

2.2. Meteorological Data. Environment Canada supplied hourly data for temperature, relative humidity, and atmospheric pressure for the city of Vancouver. We used the daily means of two weather parameters: temperature (dry bulb) and relative humidity. Each of these was calculated as an average of 24 hourly measurements.

2.3. Air Pollution Data. Hourly data for gaseous pollutants (concentrations of CO, NO₂, SO₂, and O₃) and particulate matter (PM, PM₁₀, and PM_{2.5}-PMs of less than 10 and 2.5 μm in aerodynamic diameter, resp.) supplied by Environment Canada were obtained from a number of fixed continuous monitoring stations in the greater Vancouver area. During the study period (4 years and 2 months), the number of monitoring stations that reported air pollution data ranged from 4 to 11. The distances of stations from the hospital varied from 3 to 43 kilometers. The measurements of the common daily exposure were obtained by first averaging the 24 hourly readings in each functioning station and next averaging across the stations.

2.4. Statistical Methods. Case-crossover methods are suitable for the estimation of odds of acute health effects triggered by acute and transient exposures [28]. The design is an adaptation of the case-control approach where the case serves as his/her own control. For each presented case of ischemia or seizure, the patient's exposure to pollutants on the case day (the day of admission or an earlier day when considering a lagged effect) was compared to the exposure on referent days when the patient has not been affected. The referent days were selected in a way to match year, month, and day of week of the case day, so that each case had 3 or 4 controls.

TABLE 1

	Mean value	SD	IQR
CO (in ppm)	0.6	0.2	0.2
NO ₂ (in ppb)	16.8	4.6	6.2
SO ₂ (in ppb)	2.5	1.5	1.9
O ₃ (in ppb)	14.2	7.4	10.9

TABLE 2

	Mean value	SD	IQR
PM ₁₀ (in $\mu\text{m}/\text{m}^3$)	25.8	14.2	6.9
PM _{2.5} (in $\mu\text{m}/\text{m}^3$)	8.6	6.7	5.1

Conditional logistic regression analysis was used to estimate the odds ratios (ORs) with 95% confidence intervals (CIs) associated with an increase by conventional unit in the concentrations of pollutants. In order to compensate for possible nonlinear effects of the weather conditions (temperature, relative humidity), natural splines of the weather parameters, with 3 degrees of freedom, were incorporated into the regression models. Potential links between a pollutant and a health outcome were evaluated with single-pollutant models in order to assess the stability of the method and the causal nature of the association. The analysis was performed for all realistic combinations of the gaseous pollutants and PMs, individually lagged with different 0- to 7-day lags. The calculations were performed using the PHREG procedure in SAS.

In addition, we constructed the sequence of the age groups as follows: (0, 29), (1, 30), and so on up to (56, 85). Thus, each age group spans 30 years. It was chosen arbitrarily and was driven by number of ED visits. For larger number of cases the groups may have shorter span. The first age group (0, 29) contains the patients not older than 30 years. The next (1, 30) has patients older than 1 year of age and younger than 31, and so on. For each age group the calculations were performed separately for the health outcomes considered here, that is, stroke and seizure. This analysis was performed only for females and the same-day exposure (lag 0) to sulfur dioxide. The results were compared with similar calculations done for female ED visits for depression and anxiety.

3. Results and Discussion

The mean value of temperature during the study period was 7.7°C, with a standard deviation (SD) of 11.4. Relative humidity had a mean value of 70.7%, with SD = 12.5. These values reflect the generally tepid and humid weather in the city of Vancouver and its surroundings. For the gaseous pollutants, the point statistics are as shown in Table 1.

In the case of particulate matter, the corresponding statistics are as shown in Table 2.

The average pollution levels in Vancouver are comparable to those in other large urban regions in Canada, but Vancouver's ozone level is among the lowest in Canada [29, 30]. Mostly suburban areas had higher ozone levels and

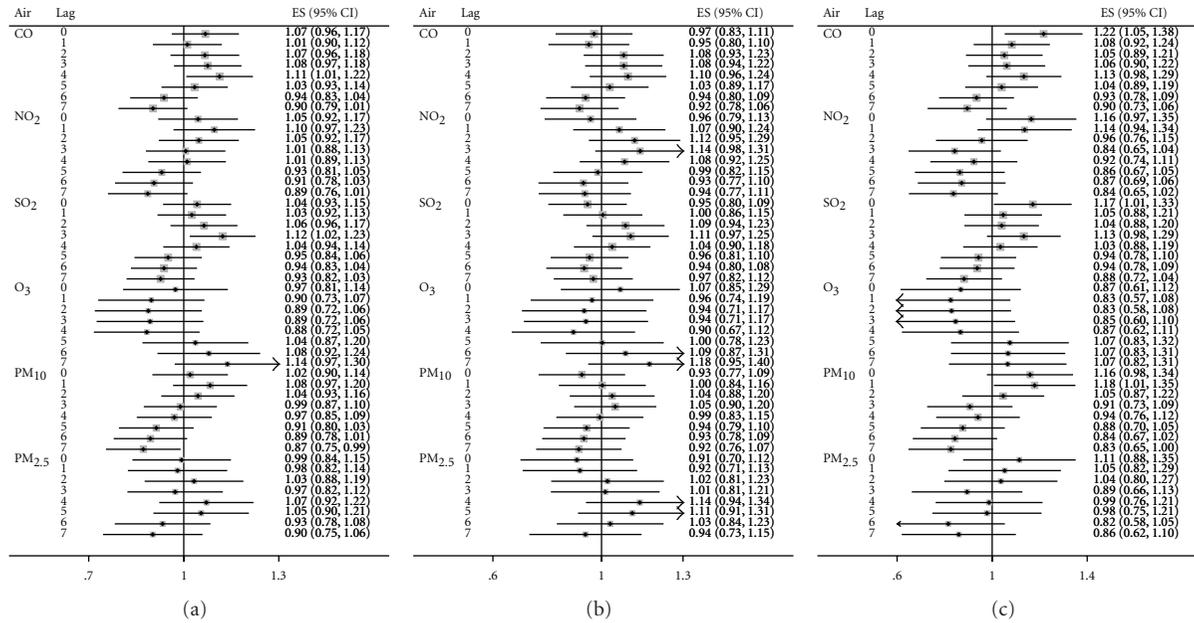


FIGURE 1: Odds ratios for ED visits for stroke associated with exposure to air pollutants.

were showing larger-range variation than that for downtown Vancouver, where the St. Paul’s Hospital is located.

The results for ED visits for stroke are reported in Figure 1. The figure has three parts (in a horizontal direction) and shows the estimated ORs and their corresponding 95% CIs for six considered air pollutants (lagged by 0–7 days) for all (a), male (b), and female (c) patients, respectively. The results are shown numerically and are also represented graphically as barlines. The results were positive and significant for all patients for exposure to CO (lag 4) and SO₂ (lag 3), and none was significant in the case of male patients. For female patients the results were statistically significant ($P < 0.05$) for CO (lag 0), PM₁₀ (lag 1), and SO₂ (lag 0). Table 3 presents the results from multipollutant models. In these models different combinations of lagged exposure were used. For example in the two-pollutant model SO₂ (lag 3) + O₃ (lag 6), early exposure to ozone (6 days before the event) increases effect of sulfur dioxide, and in this case OR = 1.16 (95% CI: 1.05, 1.29). In this case weather parameters were used with lag 0.

Figure 2 is constructed in a similar manner as Figure 1 and represents the results for ED visits for seizure. As in all cases, the results are reported for an increase in concentration of the air pollutant represented by its one IQR. The results are positive and significant for all patients and for male patients and exposure to PM₁₀ (lag 1, lag 4). For female patients, the association was significant for SO₂ (lag 1 and 2) and ozone (lag 7).

Figure 3 represents the results for ED visits for stroke, seizure, depression, and anxiety for age groups of length 30 years. The results are shown for SO₂ exposure on the same day as the health event. The pattern of responses (OR values and their respective 95% CIs) is very similar for seizure and depression. For anxiety, the pattern is weak but slightly similar for both mentioned health conditions [13].

Figure 4 illustrates levels of the gaseous air pollutants (CO, NO₂, SO₂, and O₃) and daily number of ED visits for stroke (a) and for seizure (b). The figure indicates periodicity of carbon monoxide, nitrogen dioxide, and ozone. It also suggests that levels of ambient sulfur dioxide are decreasing.

The acute and often severe nature of symptoms of stroke and seizure results in the affected individuals first seeking help in the ED rather than in a doctor’s office. This allows the frequency of ED visits for these disorders to be considered an adequate measure of the actual occurrences of the disorders in the examined population [31]. The presented results show that ambient sulfur dioxide constitutes a cerebrovascular health hazard, particularly for the female population. The findings in this study corroborate those in other studies on sulfur dioxide neurophysiologic effects [32]. They suggest that inhalation of SO₂, rather than O₃, may initiate a cerebral ischemic accident, causing specific pathophysiological effects on the brain. The mechanism has no analogy to the way bronchoconstriction occurs in vulnerable subjects exposed to SO₂, where rather acidic compounds derived from CO and SO₂ appear as agents of toxicity [33–38]. This suggests that SO₂ may follow its own biochemical pathway of breaking through or penetrating the brain’s protective barrier. The consequences appear to be stronger in the female population than in the male population. This calls for more clinical inquiry into the sulfur dioxide mediation mechanism in developing abnormal brain neural activity or brain ischemia.

The results of the current study should be considered in the context of its limitations. Regional estimates of exposure may not have correlated with patient-level exposures prior to visits to the ED, which would bias the risk estimates towards the null. Possible correlation between health outcome severity and patient age and sex was not captured due to the limited number of observations. Some patients may have repeat visits to the emergency department for follow-up, and

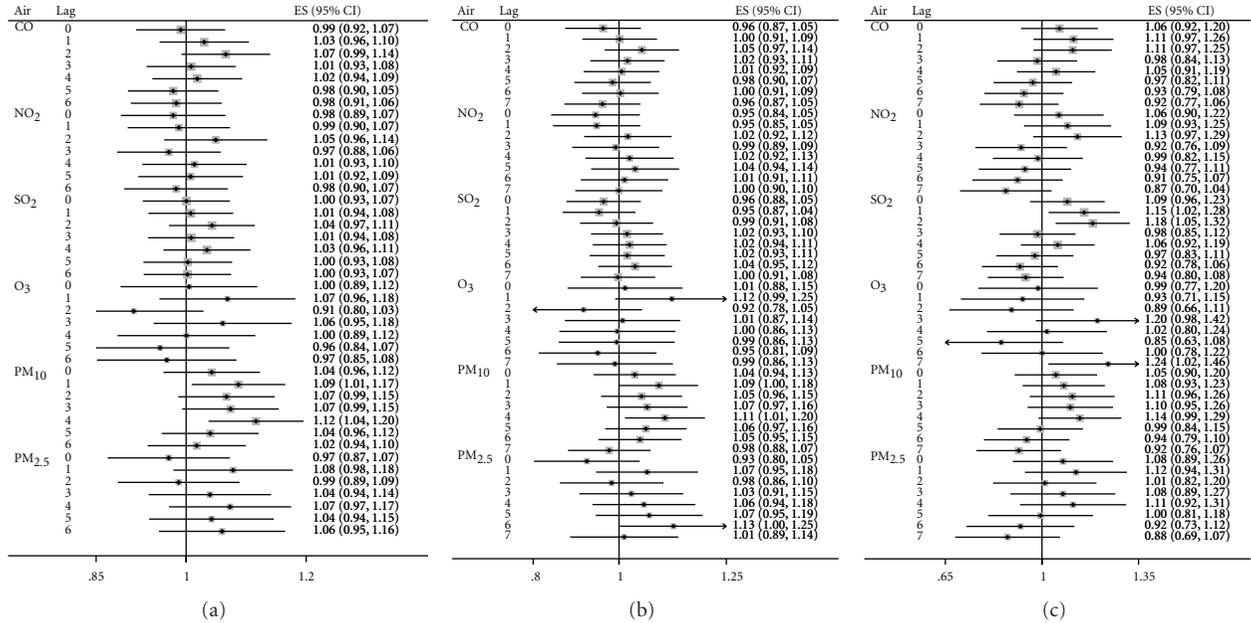


FIGURE 2: Odds ratios for ED visits for seizure associated with exposure to air pollutants.

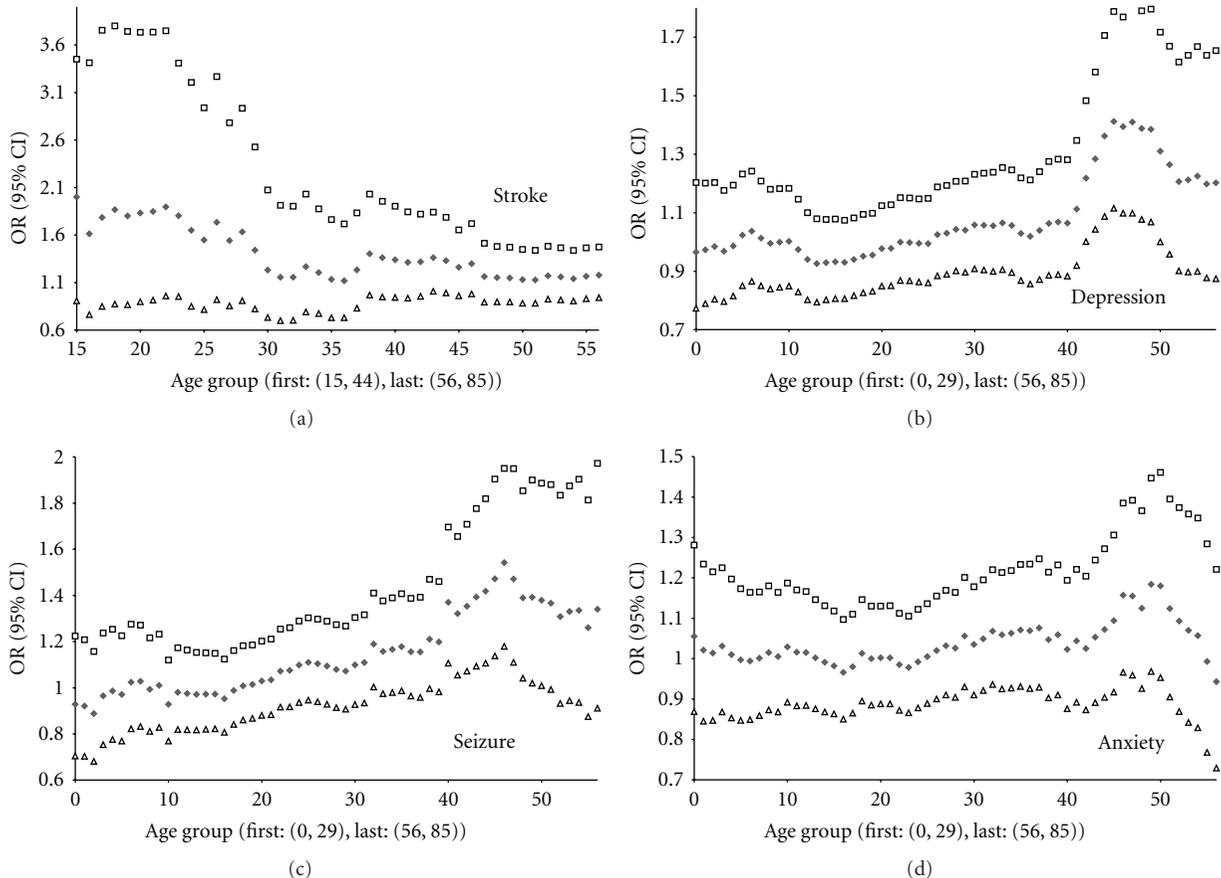


FIGURE 3: Odds ratios for female ED visits for stroke, seizure, depression and anxiety associated with exposure to SO₂— by age group.

TABLE 3: Odds ratios and their 95% confidence intervals for ED visits for ischemic stroke.

Model	Predictors					
	Lag	SO ₂	Lag	CO	Lag	O ₃
SO ₂	2	1.11 (1.00, 1.23)				
	3	1.15 (1.04, 1.27)*				
CO			3	1.10 (1.00, 1.21)*		
			4	1.12 (1.02, 1.23)*		
O ₃					5	1.02 (0.89, 1.18)
					6	1.10 (0.96, 1.27)
SO ₂ + O ₃	2	1.11 (1.00, 1.23)			5	1.04 (0.90, 1.20)
	3	1.16 (1.05, 1.29)*			6	1.13 (0.98, 1.30)
CO + O ₃			3	1.12 (1.01, 1.23)*	5	1.07 (0.92, 1.24)
			4	1.15 (1.05, 1.27)*	6	1.17 (1.01, 1.35)*
SO ₂ + CO	2	1.07 (0.96, 1.20)	3	1.07 (0.97, 1.19)		
	3	1.11 (1.00, 1.24)*	4	1.07 (0.97, 1.19)		
SO ₂ + CO + O ₃	2	1.07 (0.95, 1.20)	3	1.09 (0.98, 1.21)	5	1.07 (0.92, 1.24)
	3	1.11 (1.00, 1.24)*	4	1.11 (1.00, 1.24)*	6	1.17 (1.01, 1.35)*

*P value <0.05.

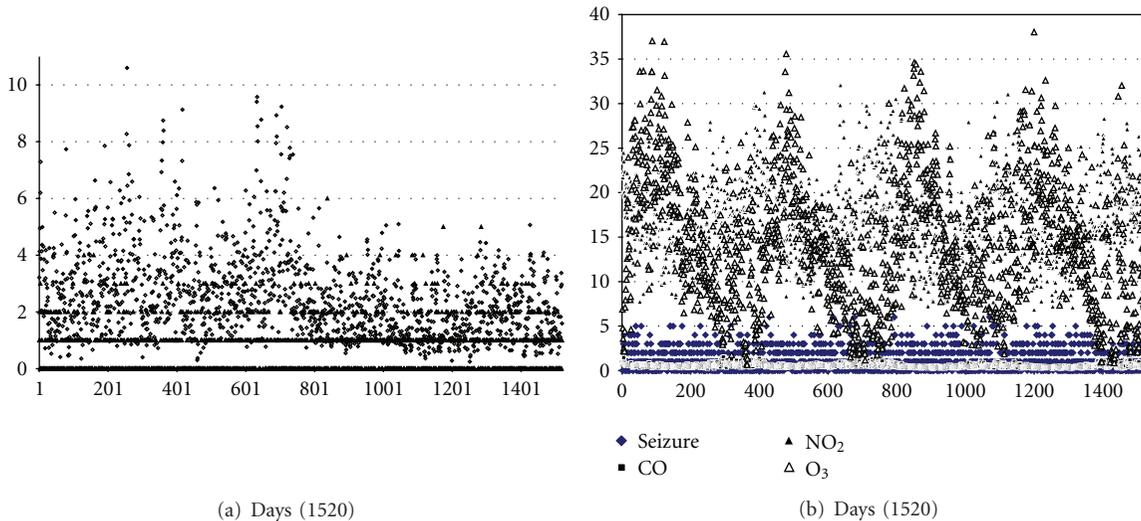


FIGURE 4: Air pollutants and daily counts of ED visits for stroke and seizure.

those visits would not be correlated to concentrations of air pollutants. While time-stable confounders (e.g., genetics and chronic diseases) are controlled for by the case-crossover study design, confounders that fluctuate in time may not have been controlled. Weather parameters (i.e., temperature and humidity) were adjusted in the analysis; however, measurements of acid aerosol concentrations were not available. Thus, future studies will be needed to replicate our findings and confirm that the increased risks of cerebral ischemia manifestations as stroke and seizures were due to the specific combinations of exposures.

This study suggests novel modifiable risk factors for ischemic stroke and seizure. Increases in concentrations of ambient sulfur dioxide were associated with increased probability of emergency department visit for ischemic cerebral accidents or transient ischemia. If these findings are confirmed, prevention of some cases of stroke or seizure may be

achieved by improving air quality, or by better regulating the allowable levels of exposures to ambient gases in the workplaces.

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References

[1] B. Brunekreef and S. T. Holgate, "Air pollution and health," *The Lancet*, vol. 360, no. 9341, pp. 1233–1242, 2002.
 [2] M. L. Block and L. Calderón-Garcidueñas, "Air pollution: mechanisms of neuroinflammation and CNS disease," *Trends in Neurosciences*, vol. 32, no. 9, pp. 506–516, 2009.

- [3] D. Sheppard, W. S. Wong, and C. F. Uehara, "Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide," *American Review of Respiratory Disease*, vol. 122, no. 6, pp. 873–878, 1980.
- [4] R. A. Bethel, J. Epstein, and D. Sheppard, "Sulfur dioxide-induced bronchoconstriction in freely breathing, exercising, asthmatic subjects," *American Review of Respiratory Disease*, vol. 128, no. 6, pp. 987–990, 1983.
- [5] M. A. Bauer, M. J. Utell, and P. E. Morrow, "Inhalation of 0.30 ppm nitrogen dioxide potentiates exercise-induced bronchospasm in asthmatics," *American Review of Respiratory Disease*, vol. 134, no. 6, pp. 1203–1208, 1986.
- [6] C. Y. Yang and C. J. Chen, "Air pollution and hospital admissions for chronic obstructive pulmonary disease in a subtropical city: Taipei, Taiwan," *Journal of Toxicology and Environmental Health A*, vol. 70, no. 14, pp. 1214–1219, 2007.
- [7] J. Q. Koenig, D. S. Covert, and W. E. Pierson, "Effects of inhalation of acidic compounds on pulmonary function in allergic adolescent subjects," *Environmental Health Perspectives*, vol. 79, pp. 173–178, 1989.
- [8] J. T. Lee and J. Schwartz, "Reanalysis of the effects of air pollution on daily mortality in Seoul, Korea: a case-crossover design," *Environmental Health Perspectives*, vol. 107, no. 8, pp. 633–636, 1999.
- [9] T. F. Mar, G. A. Norris, J. Q. Koenig, and T. V. Larson, "Associations between air pollution and mortality in Phoenix, 1995–1997," *Environmental Health Perspectives*, vol. 108, no. 4, pp. 347–353, 2000.
- [10] Y. C. Hong, J. T. Lee, H. Kim, and H. J. Kwon, "Air pollution: a new risk factor in ischemic stroke mortality," *Stroke*, vol. 33, no. 9, pp. 2165–2169, 2002.
- [11] S. S. Tsai, W. B. Goggins, H. F. Chiu, and C. Y. Yang, "Evidence for an association between air pollution and daily stroke admissions in kaohsiung, Taiwan," *Stroke*, vol. 34, no. 11, pp. 2612–2616, 2003.
- [12] G. Chen, G. Song, L. Jiang et al., "Short-term effects of ambient gaseous pollutants and particulate matter on daily mortality in Shanghai, China," *Journal of Occupational Health*, vol. 50, no. 1, pp. 41–47, 2008.
- [13] M. Szyszkowicz, "Ambient air pollution and daily emergency department visits for ischemic stroke in Edmonton, Canada," *International Journal of Occupational Medicine and Environmental Health*, vol. 21, no. 4, pp. 295–300, 2008.
- [14] J. Schwartz, "Daily deaths are associated with combustion particles rather than SO₂ in Philadelphia," *Occupational and Environmental Medicine*, vol. 57, no. 10, pp. 692–697, 2000.
- [15] N. Sang, Y. Yun, H. Li, L. Hou, M. Han, and G. Li, "SO₂ Inhalation contributes to the development and progression of ischemic stroke in the brain," *Toxicological Sciences*, vol. 114, no. 2, pp. 226–236, 2010.
- [16] D. Gruol, T. Nelson, J. Sabeti et al., "CNS Actions of Inflammatory Factors," The Scripps Research Institute: Molecular and Integrative Neurosciences, <http://www.scripps.edu/news/sr/sr2008/mind08gruol.html>.
- [17] K. J. Salaycik, M. Kelly-Hayes, A. Beiser et al., "Depressive symptoms and risk of stroke: the Framingham study," *Stroke*, vol. 38, no. 1, pp. 16–21, 2007.
- [18] P. G. Surtees, N. W. Wainwright, R. N. Luben, N. J. Wareham, S. A. Bingham, and K. T. Khaw, "Psychological distress, major depressive disorder, and risk of stroke," *Neurology*, vol. 70, no. 10, pp. 788–794, 2008.
- [19] S. A. Everson, R. E. Roberts, D. E. Goldberg, and G. A. Kaplan, "Depressive symptoms and increased risk of stroke mortality over a 29-year period," *Archives of Internal Medicine*, vol. 158, no. 10, pp. 1133–1138, 1998.
- [20] B. S. Jonas and M. E. Mussolino, "Symptoms of depression as a prospective risk factor for stroke," *Psychosomatic Medicine*, vol. 62, no. 4, pp. 463–471, 2000.
- [21] S. L. Larson, P. L. Owens, D. Ford, and W. Eaton, "Depressive disorder, dysthymia, and risk of stroke: thirteen-year follow-up from the Baltimore Epidemiologic Catchment Area Study," *Stroke*, vol. 32, no. 9, pp. 1979–1983, 2001.
- [22] T. Ohira, S. Satoh, T. Sankai et al., "Prospective study of depressive symptoms and risk of stroke among Japanese," *Stroke*, vol. 32, no. 4, pp. 903–907, 2001.
- [23] L. A. Simons, J. McCallum, Y. Friedlander, and J. Simons, "Risk factors for ischemic stroke: dubbo study of the elderly," *Stroke*, vol. 29, no. 7, pp. 1341–1346, 1998.
- [24] M. May, P. McCarron, S. Stansfeld et al., "Does psychological distress predict the risk of ischemic stroke and transient ischemic attack? The Caerphilly study," *Stroke*, vol. 33, no. 1, pp. 7–12, 2002.
- [25] M. J. Bos, T. Lindén, P. J. Koudstaal et al., "Depressive symptoms and risk of stroke: the Rotterdam Study," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 79, no. 9, pp. 997–1001, 2008.
- [26] M. Szyszkowicz, B. Rowe, and I. Colman, "Air pollution and daily emergency department visits for depression," *International Journal of Occupational Medicine and Environmental Health*, vol. 22, no. 4, pp. 355–362, 2009.
- [27] S. Cakmak, R. E. Dales, and C. B. Vidal, "Air pollution and hospitalization for epilepsy in Chile," *Environment International*, vol. 36, no. 6, pp. 501–505, 2010.
- [28] H. Janes, L. Sheppard, and T. Lumley, "Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias," *Epidemiology*, vol. 16, no. 6, pp. 717–726, 2005.
- [29] S. C. Pryor, I. G. McKendry, and D. G. Steyn, "Synoptic-scale meteorological variability and surface ozone concentrations in Vancouver, British Columbia," *Journal of Applied Meteorology*, vol. 34, no. 8, pp. 1824–1833, 1995.
- [30] CCME (Canadian Council of Ministers of the Environment) Ground-level ozone and its precursors, 1980–1993, 1997.
- [31] I. Mosley, M. Nicol, G. Donnan, I. Patrick, and H. Dewey, "Stroke symptoms and the decision to call for an ambulance," *Stroke*, vol. 38, no. 2, pp. 361–366, 2007.
- [32] J. Joubert, T. B. Cumming, and A. J. McLean, "Diversity of risk factors for stroke: the putative roles and mechanisms of depression and air pollution," *Journal of the Neurological Sciences*, vol. 262, no. 1–2, pp. 71–76, 2007.
- [33] R. W. Atkinson, H. R. Anderson, D. P. Strachan, J. M. Bland, S. A. Bremner, and A. Ponce De Leon, "Short-term associations between outdoor air pollution and visits to accident and emergency departments in London for respiratory complaints," *European Respiratory Journal*, vol. 13, no. 2, pp. 257–265, 1999.
- [34] O. V. J. Rossi, V. L. Kinnula, J. Tienari, and E. Huhti, "Association of severe asthma attacks with weather, pollen, and air pollutants," *Thorax*, vol. 48, no. 3, pp. 244–248, 1993.
- [35] G. D. Thurston, K. Ito, M. Lippmann, and C. Hayes, "Reexamination of London, England, mortality in relation to exposure to acidic aerosols during 1963–1972 winters," *Environmental Health Perspectives*, vol. 79, pp. 73–82, 1989.
- [36] D. V. Bates and R. Sizto, "Air pollution and hospital admissions in Southern Ontario: the acid summer haze effect," *Environmental Research*, vol. 43, no. 2, pp. 317–331, 1987.

- [37] J. H. Ware, B. G. Ferris, and D. W. Dockery, "Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children," *American Review of Respiratory Disease*, vol. 133, no. 5, pp. 834–842, 1986.
- [38] J. Sunyer, F. Ballester, A. Le Tertre et al., "The association of daily sulfur dioxide air pollution levels with hospital admissions for cardiovascular diseases in Europe (the Aphea-II study)," *European Heart Journal*, vol. 24, no. 8, pp. 752–760, 2003.