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RESEARCH

The stroke offspring study: is parental stroke history of value in targeted risk factor screening?

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Aim: This study aimed to compare the prevalence of stroke risk factors among people with a parental history of stroke to those in a control group of individuals, of similar age, gender and social class, with no parental stroke history. **Background:** Parental stroke increases an individual's risk of stroke, but little is known of the potential value of using this information in targeted screening for primary prevention in general practice. **Method:** We sent questionnaires to 300 randomly selected individuals aged 40–65 years, in each of 11 different general practices in Northern Ireland. Among 1061 responses received within six weeks, 332 reported a parental history of stroke (31.3%). We matched respondents with (cases) and without (controls) a parental history of stroke on characteristics of age, gender and socioeconomic status. Matched pairs were invited to attend a consultation at which their diet and exercise habits were assessed using validated questionnaires and height, weight, blood pressure and serum lipids and glucose were measured. **Findings:** Matched data were available for 199 case–control pairs (398 individuals). Mean systolic and diastolic blood pressures were significantly higher in cases than in paired controls (systolic 146.3 versus 140.6 mmHg ($P < 0.01$); diastolic 87.7 versus 85.0 mmHg ($P = 0.014$)). Cases consumed more alcohol than their paired controls (13.8 versus 10.1 U/week ($P < 0.01$)), but their measures of body mass index, lipids, diabetes, diet and exercise did not differ significantly. The results of this study suggest that screening offspring of patients with stroke in respect of blood pressure has potential value in identifying people likely to benefit from primary prevention, but do not support the adoption of a targeted screening strategy for other commonly cited stroke risk factors.

Key words: blood pressure; cardiovascular risk factors; family history; general practice; screening; stroke

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Introduction

Stroke is the leading cause of death and disability worldwide (Lopez *et al*., 2006) despite the knowledge that its risk can be reduced by the appropriate management of modifiable cardiovascular risk factors (Goldstein *et al*., 2006).

Studies show that parental stroke is an independent risk factor for stroke (Jousilahti *et al*., 1997; Polychronopoulos *et al*., 2002) and, in those who have suffered a primary cerebrovascular event, there is evidence of an association between family history of stroke and modifiable risk (Flossmann and Rothwell, 2005; Lindgren *et al*., 2005). Lindgren

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found that first-degree relatives of people who had suffered a stroke reported a higher prevalence of hypertension than did relatives of controls who had not suffered a stroke (Lindgren *et al*., 2005), but this finding was not linked to any validated measurements.

There is evidence to suggest that individuals with a parental history of cardiovascular disease do not pursue self-initiated, sustained change in modifiable risk factors (Kip *et al*., 2002). Thus, opportunities may exist for improving primary prevention of stroke through targeted screening of individuals with a relevant parental history, for risk identification and reduction. However, there is a lack of evidence of the relative prevalence of modifiable risk factors between those with and without a parental history of stroke or of the potential value of adopting such a strategy in general practice.

This study therefore aimed to compare, in the general population, the prevalence of stroke risk factors, among people with a parental history of stroke, to those in a control group of individuals, of similar age, gender and social class, with no parental stroke history.

Methods

Design

We carried out a case–control study of individuals from 11 selected general practices in Northern Ireland (NI) between August 2004 and July 2005. These practices were chosen to represent the general population of NI and included a range of geographical location, practice list size, deprivation scores and population density. Three hundred individuals from the total population in each practice falling between the ages of 40 and 65 years (the 'invitees') were selected using random number assignment (Urbaniak and Plous, 2005). A questionnaire was sent relating to a history of parental stroke, sociodemographic information and consent for contact by the researcher. A pre-paid pre-addressed envelope was included for return. Replies received within six weeks of posting (the 'responders') were considered for recruitment to the study; those received later were excluded.

Recruitment

Within each practice those with a parental history of stroke were matched to individuals with no parental stroke history. Matching was performed on gender, age ($\pm$5 years) and socioeconomic status ($\pm$10) using a commonly used regional index of multiple deprivation (IMD; Noble *et al*., 2001) (scored from 0 to 100) derived from the postal code of the place of residence. Potential participants were telephoned on at least three occasions, at a variety of times including evening, before attempted contact was abandoned. Those contacted were invited to attend their own general practice surgery (the 'attendees') to meet with the researcher for an interview and medical examination.

Data collection

At interview, following written consent, biographical and sociodemographic data were collected by the researcher. Data were gathered about the symptoms observed at the time of the stroke of their parent in order to provide some validation of the diagnosis. Participants were asked about their own relevant past medical history, current medications and smoking and alcohol consumption. Height was measured (to nearest 0.1 cm) using a stadiometer (Seca 214 Portable Stadiometer, Hamburg, Germany) and weight (to nearest 1 kg) using mechanical clinical scales (Seca 761 Medical Scales, Hamburg, Germany). Waist circumference (widest point of abdomen below bottom of rib cage and above iliac crest) and hip circumference (maximum width over greater trochanters of the pelvic girdle) were measured using a tape measure to the nearest 1 cm. Body mass index (BMI) (kg/m^2) and waist–hip ratio (WHR) were each derived. Resting non-invasive brachial arterial blood pressure was measured (Williams *et al*., 2004) twice, with a 3-min gap between the first and second measurements, using an approved validated automated oscillometric device (Omron HEM-705CP, Omron, Schaumburg, IL, USA) (O'Brien *et al*., 1996; The British Hypertension Society, 2006); the second measurement was used for analysis. Participants with a blood pressure above 140/90 mmHg (Williams *et al*., 2004) were asked to return to their own general practitioner for further checks. Results of blood tests were returned to each practice with abnormal results highlighted for attention.

Participants completed one validated questionnaire for dietary habit (Dietary Instrument for Nutrition Education questionnaire (Roe *et al*., 1994;

Little and Margetts, 1996)) and another for exercise habit (Baecke Physical Activity Questionnaire; Baecke *et al*., 1982).

Data analysis

A number of dichotomous variables were derived for analysis. 'Raised blood pressure' was defined as a history of hypertension, currently taking anti-hypertensive medication, systolic blood pressure (SBP) above 140 mmHg or diastolic blood pressure (DBP) above 90 mmHg (Williams *et al*., 2004). 'Raised cholesterol' included participants with TChol/high-density lipoprotein (HDL) ratio above 5.0. An individual was deemed to have diabetes if they reported a history of diabetes, were currently taking diabetic medication or their fasting blood glucose was above 6.9 mmol/L (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). Alcohol intake was categorised using recommeded limits for weekly consumption (21 U for men; 14 U for women; Mulvihill *et al*., 2005). Using a conversion of 8 g alcohol per unit (Miller *et al*., 1991), units consumed per week were converted into grams of alcohol per day and recoded into another categorical variable (greater or less than 60 g of alcohol per day), based on a meta-analysis detailing alcohol levels that were clinically significant (Reynolds *et al*., 2003). 'Metabolic syndrome' was defined by the presence of central obesity (abdominal circumference $\geqslant$94 cm for men and $\geqslant$80 cm for women) plus two of the following: raised triglycerides (>1.7 mmol/L), reduced HDL cholesterol (<1.03 mmol/L for males and 1.29 mmol/L for females), raised blood pressure (SBP $\geqslant$ 130 mmHg or DBP $\geqslant$ 85 mmHg)) and raised fasting blood glucose ($\geqslant$5.6 mmol/L; Alberti *et al*., 2005).

SPSS (Statistics Computer Programme 15.0.1 – Release November 2006) was used for data entry and analysis. Descriptive statistics were used to summarise data. Continuous variables were compared for case–control pairs using a *t*-test for paired samples. Categorical variables were analysed using McNemar's test for non-parametric data. For variables with missing data, case–control data pairs were removed from the analysis. Multiple regression analysis was used to adjust paired comparisons of blood pressure between cases and controls for confounding variables.

Sample size was based on an assumption of risk factor prevalence (eg, current cigarette smoking or hypertension) of 30% in the control group. A 50% difference between the groups (ie, 30% versus 45%) in risk factor prevalence would be detected at the 5% significance level and power greater than 80% with independent samples of 200 cases and 200 controls.

Ethics approval

Ethics approval to conduct the study was sought and granted by the Queen's University Belfast Research Ethics Committee.

Results

The total population of the 11 practices from which the study sample was drawn was 104 207, which represents 6.2% of the NI population. Of the 3300 questionnaires sent, 1061 (32%) were returned within six weeks of posting. Completed data were obtained for 199 case–control pairs (398 individuals; Figure 1). Comparing the study attendees to invitees, attendees were slightly older (mean age 53 years (SD 6.7) versus 51.2 years (SD 7.0; $P < 0.001$)), had lower levels of deprivation (IMD 16.7 (SD 16.4) versus 23.2 (SD 20.8; $P < 0.001$)) and had a greater representation of females (54.5% versus 51.4%; Table 1). Comparison of cases and controls in respect of mean age (53.1 (SD 6.7) years versus 53.0 (SD 6.7) years) and mean deprivation status (IMD 16.8 (SD 16.7) versus 16.6 (SD 16.2)) confirmed successful matching on those characteristics.

Mean diastolic BP (DBP) was 2.7 mmHg higher and mean systolic BP (SBP) 5.7 mmHg higher in cases than in controls (Table 2). More cases than controls had 'raised blood pressure', but the difference was not statistically significant ($P = 0.07$). Cases were more likely than controls to have a prior diagnosis of hypertension and to be on anti-hypertensive medication.

A greater proportion of cases than controls declared a history of hypercholesterolaemia, diabetes mellitus, previous stroke, previous myocardial infarction, atrial fibrillation and ischaemic heart disease, but these differences were not statistically significant (Table 3).

Similar proportions of cases and controls were both current smokers and considered to have a 'smoking-associated risk' (current smoker

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or exsmoker of <10 years). Cases consumed a mean of 3.7 U of alcohol more per week than their paired controls. In addition, significantly more cases than controls consumed above the recommended limits. No significant differences were found between cases and controls for measures of lipids, glucose, diabetes, BMI, WHR, dietary habit or physical activity. However, it was noted that differences in fasting blood glucose and triglycerides between groups approached statistical significance.

A regression analysis was carried out to adjust the blood pressure comparisons for BMI, smoking, alcohol consumption, fasting blood glucose and diabetic mellitus history (Table 4). After adjustment, the difference between cases and controls remained statistically significant for SBP, but for DBP the difference between cases and controls failed to reach significance.

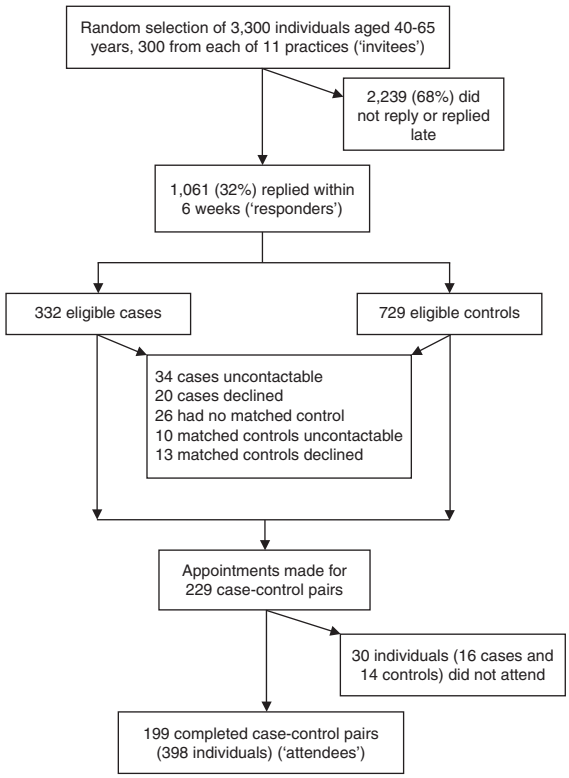

Figure 1 Flow diagram of recruitment process

Discussion

This study shows that screening individuals with a parental history of stroke for stroke risk factors returns significantly higher mean systolic and DBP and higher alcohol consumption compared with those with no parental history of stroke. Furthermore, the relative prevalence of hypertension and of alcohol consumption above recommended limits are higher among those with a parental history of stroke.

After regression analysis, with adjustment for other risk factors, a relationship between higher mean SBP and positive parental history of stroke remains. The mean difference between age- and gender-matched pairs in systolic BP is 5.7 mmHg, with a mean BP of 146/88 mmHg for those with a parental history of stroke. Stroke risk has been shown to have a direct and linear relationship with blood pressure down to at least 115/75 mmHg (Lewington *et al*., 2002), and a meta-analysis has shown that a reduction of 10 mmHg of systolic BP in those under 60 years was associated with a 40% to 50% reduction in stroke risk (Lawes *et al*., 2004).

The findings of our study add to the evidence from previous work of the relevance of self-reported hypertension in those with a family history of stroke (Flossmann and Rothwell, 2005; Lindgren *et al*., 2005). In keeping with the relative importance of blood pressure for all stroke risk it may be that blood pressure is the most important element in the manifestation of that heritability. Either way the findings lend weight to the argument for targeting the offspring of patients with a history

Table 1 Summary characteristics of 'invitees', 'responders' and 'attendees'

	Invitees ($n = 3300$)	Responders ($n = 1061$)	Attendees ($n = 398$)
Age (mean years (SD))	51.2 (7.0)	51.5 (6.9)	53.0 (6.7)
Index of multiple deprivation (mean units (SD))	23.2 (20.8)	20.1 (19.6)	16.7 (16.4)
Males (n(%))	1602 (48.6)	490 (46.2)	180 (45.2)

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Table 2 Summary of characteristics of 199 case–control pairs (continuous data)

	Number of pairs	Case	Control	Paired difference	*P*-value
		Mean (SD)	Mean (SD)	(95% CI)	
Diastolic blood pressure (mmHg)	199	87.7 (11.4)	85.0 (11.5)	2.7 (0.6, 4.8)	0.014
Systolic blood pressure (mmHg)	199	146.3 (19.7)	140.6 (19.8)	5.7 (2.0, 9.3)	0.003
Total cholesterol (mmol/L)	197	5.20 (0.93)	5.21 (0.87)	0.00 (−0.18, 0.18)	0.987
HDL cholesterol (mmol/L)	196	1.54 (0.45)	1.54 (0.44)	0.00 (−0.08, 0.08)	0.966
Total cholesterol/HDL ratio	196	3.6 (1.2)	3.6 (1.1)	0.0 (−0.2, 0.3)	0.679
Triglycerides (mmol/L)	197	1.55 (1.11)	1.38 (0.80)	0.18 (−0.01, 0.37)	0.07
Fasting glucose (mmol/L)	197	5.3 (1.5)	5.1 (1.1)	0.2 (0.0, 0.5)	0.096
Units of alcohol per week (units)	199	13.8 (18.2)	10.1 (12.4)	3.7 (1.1, 6.4)	0.006
BMI (kg/m^2)	199	27.9 (5.2)	27.3 (4.9)	0.6 (−0.4, 1.6)	0.22
Waist-hip ratio	199	0.89 (0.08)	0.88 (0.08)	0.01 (−0.01, 0.02)	0.316
DINE dietary fibre index	195	35.0 (14.3)	35.5 (11.4)	−0.6 (−3.0, 1.9)	0.647
DINE total fat index	194	30.3 (12.1)	32.1 (11.0)	−1.8 (−4.0, 0.4)	0.113
DINE unsaturated fat index	156	10.5 (2.7)	10.2 (2.4)	0.3 (−0.3, 0.9)	0.262
Baecke leisure physical activity index (0–5)	165	2.8 (0.6)	2.8 (0.6)	0.0 (−0.1, 0.1)	0.919
Baecke sports physical activity index (0–5)	157	2.3 (0.7)	2.4 (0.8)	−0.1 (−0.2, 0.1)	0.419
Baecke work physical activity index (0–5)	84	2.8 (0.7)	2.8 (0.8)	0.1 (−0.1, 0.3)	0.518

BMI = body mass index; DINE = Dietary Instrument for Nutrition Education.

Table 3 Summary of characteristics of 199 case–control pairs (categorical data)

	Number of pairs	Case	Control	Paired difference	*P*-value
		n (%)	*n* (%)	(95% CI)	
History of hypertension	199	66 (33)	40 (20)	13 (5, 21)	0.002
History of hypercholesterolaemia	199	40 (20)	26 (13)	7 (0, 14)	0.08
History of diabetes mellitus	199	16 (8)	9 (5)	3 (−1, 8)	0.23
History of stroke	199	2 (1)	1 (1)	–[a]	1.00
History of myocardial infarction	199	4 (2)	4 (2)	–[a]	1.00
History of ischaemic heart disease	199	17 (9)	10(5)	4 (−2, 9)	0.25
History of atrial fibrillation	199	2 (1)	0 (0)	–[a]	0.50
On medication for hypertension	199	61 (31)	40 (20)	11 (2, 19)	0.01
Raised blood pressure ('history of hypertension', on anti-hypertensive medication or BP>140/90)	199	133 (67)	115 (58)	9 (−1, 19)	0.07
Current smoker	199	46 (23)	40 (20)	3 (−5, 11)	0.53
Smoking associated risk (current smoker or ex-smoker of <10 years)	199	70 (35)	66 (33)	2 (−8, 12)	0.75
Total cholesterol/HDL ratio >5.0	196	21 (11)	20 (10)	1 (−6, 7)	0.87
Diabetes mellitus (history of diabetes or fasting glucose >6.9 mmol/L)	197	22 (11)	12 (6)	5 (−1, 11)	0.12
Alcohol above recommended limits (males:21 units, females:14 units/week)	199	57 (29)	40 (20)	9 (0, 17)	0.04
Alcohol consumption >60 g daily	199	7 (4)	1 (1)	3 (0, 6)	0.07
Metabolic syndrome	199	83 (42)	72 (36)	6 (−4, 15)	0.27

[a] Insufficient numbers to permit formal testing.

of stroke for blood pressure screening and monitoring in routine clinical practice.

The higher mean weekly alcohol consumption among cases compared with controls (14 versus 10 U/week; $P < 0.01$) and greater proportion drinking above recommended limits (29% versus 20%; $P < 0.05$) were unexpected findings. These patterns of alcohol consumption may reflect other family-influenced lifestyle behaviours. However, their clinical significance is unclear given the lack of

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Table 4 Multiple regression analysis of mean differences between cases and controls in paired measures of blood pressure

Adjustment	Diastolic blood pressure		Systolic blood pressure	
	Mean difference (95% CI)	*P*-value	Mean difference (95% CI)	*P*-value
Unadjusted	2.7 (0.6, 4.8)	0.01	5.7 (2.0, 9.3)	0.003
Adjusted for BMI	2.5 (0.4, 4.6)	0.02	5.4 (1.8, 9.1)	0.004
Adjusted for smoking	2.7 (0.5, 4.8)	0.02	5.7 (2.0, 9.4)	0.002
Adjusted for alcohol (units/week)[a]	2.2 (0.1, 4.4)	0.04	5.2 (1.5, 8.9)	0.006
Adjusted for fasting glucose[a]	2.4 (0.2, 4.6)	0.03	5.1 (1.4, 8.8)	0.007
History of diabetes	2.2 (0.0, 4.4)	0.02	4.9 (1.2, 8.7)	0.002
Adjusted for BMI, smoking, alcohol (units/week)[a], fasting glucose[a], diabetes	2.0 (−0.1, 4.2)	0.07	4.9 (1.2, 8.7)	0.009

BMI = body mass index.
[a] log10 scale (after addition of 1 unit/week for alcohol).

consensus about the role that light-to-moderate alcohol consumption plays in stroke risk (Mukamal *et al*., 2005). A greater consensus exists around the role that alcohol consumed in large quantities plays in stroke risk, with a relative risk of 1.69 for total stroke for those consuming more than 60 g of alcohol per day compared with abstainers (Reynolds *et al*., 2003). Although not statistically significant, we observed a trend towards a higher proportion of people with a parental history of stroke consuming more than 60 g alcohol per day. The lack of statistical significance may have been due to an inadequate sample size given that the prevalence of this level of alcohol consumption was small (4%, 1%) in both groups.

Strengths

This study was based in general practice, the setting in which application of its results is likely to be most relevant. The method used an introductory letter from the practice where the study was to take place. It was considered that this added credibility to the researcher's letter of invitation and contributed to the willingness of those contacted to participate, thus optimising the potential to obtain a representative sample.

A single researcher carried out all the assessments, thus providing standardisation of measurements and consistency of approach. Conversely, the potential for bias in measurement from an observer who was not blind to the group status of participants should also be acknowledged. These criticisms are at least partially addressed in that the study used, where possible, validated research tools such as the diet and exercise questionnaires and an automatic oscillometric sphygmomanometer, which were not observer-dependent. Biochemical analysis of blood samples was done blind to group status.

Limitations

Although we observed differences in measured BP, we also found that more of those with than without a parental history of stroke reported a history of hypertension (33% versus 20%; $P < 0.01$) and were on anti-hypertensive treatment. Possible explanations for this are that those with a positive family history were aware of blood pressure as a stroke risk factor and pro-actively sought BP measurement or that physicians' awareness of parental history of stroke prompted BP screening. The observation prompts speculation as to whether treatment may have masked a greater true mean difference in blood pressure between cases and controls.

Within the study protocol there was no reliable way of confirming the parental history of stroke or stroke subtype as in many cases the parent was dead and their medical notes would not be accessible. However, only those who were able to recall signs and symptoms in keeping with the FAS test (Nor *et al*., 2004) (facial, arm or leg weakness or a disorder of speech) that suggested their parent had suffered a stroke were included in the study. Reassuringly, from work done in the Family Heart Study population, the κ-statistics for agreement between proband-reported family history and the self-reported personal history of stroke in members of the proband's family were 0.77 for a proband-reported father's history

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versus father's self-reported history of stroke and 0.76 for a proband-reported mother's history versus mother's self-reported history (Kornegay *et al*., 1997). Although the method adopted is unvalidated and lacks diagnostic rigour, it represents real-world clinical practice in which practitioners often do not have access to the notes of their patients' parents.

There may have been an attendance bias within the study as attendees were slighty older, more likely to be female and less socioeconomically deprived than invitees and responders. It may be that those attending were more health-conscious than non-responders and non-attendees. This may explain the failure to observe any difference in smoking prevalence between cases and controls: both may already have been following good advice in respect of stroke prevention and healthy lifestyles. However, the overall reported prevalence of smoking among the study population (22%) is similar to recent estimates for smoking habits in Great Britain (General Household Survey, 2004), suggesting that the population studied is representative of the wider population in respect of smoking habits.

Generalisability of the findings

Within each general practice a random sample was drawn to avoid selection bias. However, a non-response bias, with consequent over-representation within our sample of those who were more health conscious, slightly older and of higher socioeconomic status, may remain a possibility as acknowledged above.

Conclusion

The results of this study suggest that targeting the offspring of patients with stroke as part of a screening strategy in respect of blood pressure may be worthwhile in identifying those for whom primary prevention would be a worthwhile step towards reducing the stroke burden. Given the assertion that individuals with a parental history of cardiovascular disease do not pursue self-initiated, sustained change in modifiable risk factors (Kip *et al*., 2002) and the relative importance of blood pressure reduction for the primary prevention of stroke, such a strategy could be justified (Goldstein *et al*., 2006).

However, with the exception of alcohol consumption, the results do not support the adoption of a strategy to screen these individuals for all other commonly cited stroke risk factors. Further work would be required for a full understanding of the implications of the findings in respect of consumption of alcohol.

The introduction of a screening strategy to assess these risk factors in the offspring of all patients with a history of stroke would have implications for service provision. To avoid redundancy of effort, to ensure the appropriate use of limited resources and to provide a definitive answer of likely benefit, the adoption of a targeted screening strategy for blood pressure among the offspring of stroke patients would need to be measured against population strategies currently in use (NHS Confederation (Great Britain), 2003; British Cardiac Society *et al*., 2005; Goldstein *et al*., 2006; Jessani *et al*., 2006).

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