Can the cardiovascular family history reported by our patients be trusted? The Norwegian Stroke in the Young Study

H. Øygarden[a], A. Fromm[a,b], K. M. Sand[a], G. E. Eide[c,d], L. Thomassen[a,b], H. Naess[a,b] and U. Waje-Andreassen[b]

[a]Institute of Clinical Medicine, University of Bergen, Bergen; [b]Department of Neurology, Haukeland University Hospital, Bergen; [c]Centre for Clinical Research, Haukeland University Hospital, Bergen; and [d]Lifestyle Epidemiology Research Group, Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway

Background and purpose: Family history (FH) is used as a marker for inherited risk. Using FH for this purpose requires the FH to reflect true disease in the family. The aim was to analyse the concordance between young and middle-aged ischaemic stroke patients' reported FH of cardiovascular disease (CVD) with their parents' own reports.

Methods: Ischaemic stroke patients aged 15–60 years and their eligible parents were interviewed using a standardized questionnaire. Information of own CVD and FH of CVD was registered. Concordance between patients and parents was tested by kappa statistics, sensitivity, specificity, predictive values and likelihood ratios. Regression analyses were performed to identify patient characteristics associated with non-concordance of replies.

Results: There was no difference in response rate between fathers and mothers ($P = 0.355$). Both parents responded in 57 cases. Concordance between patient and parent reports was good, with kappa values ranging from 0.57 to 0.7. The patient-reported FH yielded positive predictive values of 75% or above and negative predictive values of 90% or higher. The positive likelihood ratios (LR+) were 10 or higher and negative likelihood ratios (LR−) were generally 0.5 or lower. Interpretation regarding peripheral arterial disease was limited due to low parental prevalence. Higher age was associated with impaired concordance between patient and parent reports (odds ratio 1.05; 95% confidence interval 1.01–1.09; $P = 0.020$).

Conclusions: The FH provided by young and middle-aged stroke patients is in good concordance with parental reports. FH is an adequate proxy to assess inherited risk of CVD in young stroke patients.

Introduction

A positive family history (FH) of cardiovascular disease (CVD) in first-degree relatives confers an increased risk of stroke and coronary artery disease (CAD) [1–7]. FH is used as a marker for inherited risk of disease both for cancer and CVD [8,9]. FH can serve as a tool in identifying individuals with high risk of developing CVD, and may aid in risk stratification and disease prevention [9–12]. FH is usually self-reported and the accuracy or validity of such self-reporting has been tested in various ways, e.g. by confirmation from medical records and by reports from patient relatives, with varying accuracy [10,13–16]. Higher age reduces accuracy, and female sex seems associated with increased accuracy of FH reporting [15]. Studies have found that under-reporting a FH of cancer is common and may be a problem when assessing FH as a risk factor [17,18]. Misreporting of FH could introduce bias and lead to misclassification of patients with inherited risk, and thereby hamper the use of FH as a tool to study the heredity of CVD [15]. The accuracy of FH has predominantly

Correspondence: H. Øygarden, Department of Neurology, Haukeland University Hospital, N-5021 Bergen, Norway (tel.: +47-55975040; fax: +47-55975164; e-mail: havy@helse-bergen.no).

been tested in healthy cohorts, with a few exceptions assessing the accuracy of FH in patients with CAD [19,20]. The Norwegian Stroke in the Young Study (NOR-SYS), a prospective population-based study conducted in a well-defined region of western Norway, enrols young and middle-aged ischaemic stroke patients up to 60 years of age. The patients are interviewed regarding FH of stroke, CAD and peripheral arterial disease (PAD) [21]. NOR-SYS is designed to evaluate family patterns in the development of vascular disease using reported events, clinical examinations (e.g. by ultrasound) and genetic analyses. As this cohort consists of patients with documented cerebral infarction, a need to evaluate the accuracy of the patient-provided FH of CVD became apparent. With standardized questionnaires sent to all eligible patient parents providing self-reported disease history, the aim was to analyse the concordance between patient- and parent-reported FH.

Subjects and methods

Patients aged 15–60 years admitted to the Stroke Unit, Department of Neurology at Haukeland University Hospital, with acute ischaemic stroke since September 2010 were prospectively included in NOR-SYS. Acute cerebral infarction was confirmed by computed tomography or magnetic resonance imaging.

Patients were interviewed regarding FH of CVD using a standardized questionnaire, most within 3 days after acute ischaemic stroke was diagnosed (see Data S1). Only events recalled and reported by the patient were registered by the interviewing doctor. The interview was done face-to-face and contact with family members by mobile phone or in any other way was avoided. Only patients able to answer without assistance were included. To increase similarity and ensure reproducibility, all new interviewers participated as a bystander in at least five interviews, thereby minimizing differences amongst interviewers. The questionnaire contained detailed questions regarding the FH of stroke, CAD and PAD in mothers, fathers, siblings and all four grandparents separately. Confirmative answers prompted follow-up questions to further classify the disease. Patients were assigned to the educational categories basic school, high school and college/university education.

Patients were asked if their parents were alive and able to fill out a similar questionnaire. Based on the patient's consent a similar questionnaire was sent to the parent/parents along with a stamped return envelope. The standardized parent questionnaire recorded the parent's own clinical events of CVD, risk factors and medication, in addition to their parental FH of CVD (see Data S2).
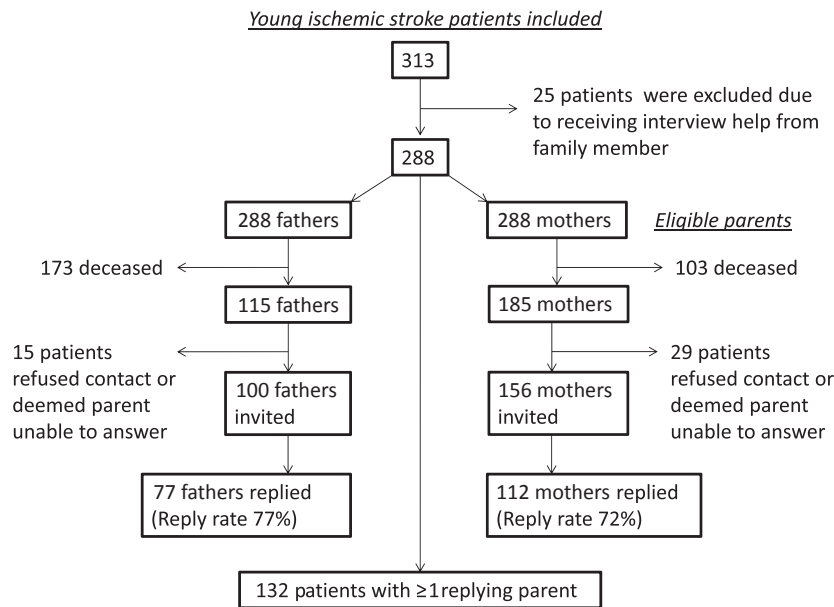
Statistics

STATA 13.1 (StataCorp, College Station, TX, USA) was used for analyses. The chi-squared test, Wilcoxon rank-sum test or Student's t test was used to compare differences in patient and parent demographics, as appropriate. Spearman's correlation was used to test for correlation. Concordance was tested using kappa statistics. In addition, specificity, sensitivity, predictive values and likelihood ratios were calculated by a STATA module named 'diagt', with patient answers as the diagnostic test and parent reports as the gold standard [22]. Kappa values of 0.41–0.60 were interpreted as moderate, 0.61–0.80 as substantial and 0.81–0.99 as near perfect concordance [23]. Regression analyses were performed to examine if patient characteristics influenced concordance. The level of significance was set at $P < 0.05$.

Ethics

All participating patients and patients' parents gave informed written consent. The NOR-SYS protocol is approved by the Regional Ethics Committee of western Norway, and is conducted in accordance with the Declaration of Helsinki. The NOR-SYS protocol is registered at http://www.clinicaltrials.gov with the unique identifier NCT01597453.

Results

From September 2010 to August 2014, 313 acute ischaemic stroke patients were included in NOR-SYS. A flowchart for patient and parent eligibility and inclusion is presented in Fig. 1. A common reason for patients refusing the invitation of parents was parent dementia. However, causes for refusal were not asked for systematically. No differences in reply rates were seen between fathers and mothers ($P = 0.355$). The mean age of patients with both parents alive compared with one or more deceased parents was 41.55 and 53.77 years, respectively (SD 10.50 and 6.16, $P < 0.001$). The rate of parental reply was similar between patient sexes with 87 (44.67%) male and 45 (49.5%) female patients having one or more parents replying ($P = 0.402$). Spearman's correlation revealed a negative correlation between patient age and the number of parent replies ($r = -0.506$, $P < 0.001$), also present when the number of deceased parents was adjusted for in a linear regression analysis ($P < 0.001$). Both parents were alive and responded in 57

Young ischemic stroke patients included

313

25 patients were excluded due to receiving interview help from family member

288

| 288 fathers | 288 mothers | *Eligible parents* |

173 deceased ←

→ 103 deceased

| 115 fathers | 185 mothers |

15 patients refused contact or deemed parent unable to answer ←

→ 29 patients refused contact or deemed parent unable to answer

| 100 fathers invited | 156 mothers invited |

| 77 fathers replied (Reply rate 77%) | 112 mothers replied (Reply rate 72%) |

132 patients with ≥1 replying parent

Figure 1 Flowchart of patient and parent eligibility and study inclusion.

(19.8%) cases. Table 1 shows the demographic data and presence of risk factors in the 132 patients with one or more parents replying.

Table 1 Demographic data and presence of risk factors for cardiovascular disease in 132 patients included in the Norwegian Stroke in the Young Study (NOR-SYS)

	Patients N = 132
Mean age (SD)	44.5 (11.2)
Higher education (%)	65 (49.2)
Living situation	
Alone	26 (19.7)
Partner/family member	106 (80.3)
Institution	1 (0.8)
Employment status	
Full-time job[a]	103 (78.0)
Part-time job	13 (9.8)
Stay at home parent	1 (0.8)
Unemployed	4 (3.0)
Welfare benefits[b]	11 (8.3)
Hypertension (%)	41 (31.1)
Diabetes mellitus (%)	5 (3.8)
Overweight (%)	88 (66.7)
Active smoker (%)	49 (37.1)
Alcohol units/week	
≤3 or never	83 (62.9)
4–6	29 (22.0)
7–12	11 (8.3)
≥13	9 (6.8)

Higher education, defined as completed college or university education; hypertension, defined as current treatment for hypertension; diabetes mellitus, defined as treatment for diabetes mellitus, including both medical and non-medical treatment; overweight, defined as body mass index >25 kg/m^{2}.[a]Also includes self-employed, full-time students and pupils; [b]including full welfare benefit recipients and partial benefit recipients if no work was registered. Six cases reporting both partial welfare benefits and part-time job were registered as part-time job.

Patient answers were in moderate to substantial concordance with parental reports, with kappa values ranging from 0.54 to 0.69 regarding stroke and CAD (Table 2). The rate of concordance was similar between parent sexes. The number of incorrect answers was lowest with regard to parental PAD and highest for parental CAD. Patient under-reporting of FH was twice as frequent as false positive FH reports. Positive predictive values were generally above 70% and negative predictive values were generally above 90%, except with regard to PAD where prevalence amongst parents was low (Table 3). Positive likelihood ratios (LR+) were around 10 or higher and negative likelihood ratios (LR−) were generally 0.5 or less. Regression analyses revealed that increasing patient age was associated with non-concordance between patient and parent reports with an odds ratio of 1.05 per year (95% confidence interval 1.01–1.09; P = 0.020; Table 4). However, neither patient sex, level of education, employment status, living status, alcohol consumption nor smoking significantly influenced concordance between patient and parent reports (Table 4).

Discussion

A high proportion of deceased parents, especially deceased fathers, was observed, probably due to longer life expectancy in females and earlier debut of CVD in males [24,25]. Stroke, CAD and PAD were reported in 53 (18%), 42 (14%) and 10 (3%) mothers, and 51 (18%), 93 (32%) and 18 (6%) fathers, respectively (data not shown). The patients had a high

Table 2 Patient versus parental answers regarding cardiovascular disease history from 132 patients and 189 parents included in the Norwegian Stroke in the Young Study (NOR-SYS)

	Patients' answers			
	No	Yes	Non-concordance (%)	Kappa (SD)
Mothers' answers				
Stroke (n = 110)				
No	92	3	9 (8.18)	0.62[a] (0.09)
Yes	6	9		
CAD (n = 107)				
No	89	2	10 (9.35)	0.57[a] (0.09)
Yes	8	8		
PAD (n = 106)				
No	100	2	6 (5.66)	−0.03 (0.09)
Yes	4	0		
Fathers' answers				
Stroke (n = 75)				
No	61	2	6 (8.00)	0.68[a] (0.11)
Yes	4	8		
CAD (n = 77)				
No	49	4	9 (12.99)	0.69[a] (0.11)
Yes	6	18		
PAD (n = 75)				
No	71	1	3 (4.00)	0.38[a] (0.11)
Yes	2	1		

CAD, coronary artery disease, defined as either myocardial infarction or angina pectoris; PAD, peripheral arterial disease, defined as intermittent claudication or initiated treatment for peripheral arterial disease. Some patients' parents did not provide answers to all disease categories as indicated by the varying number of parent replies.
[a]$P < 0.001$.

Table 4 Logistic regression analysis displaying factors associated with non-concordance between patient-reported family history of CVD and parents' own reports, from 132 patients and 189 parents included in the Norwegian Stroke in the Young Study (NOR-SYS)

	OR	95% CI	P value
Age (years)	1.05	1.01–1.09	0.020
Gender (female)	1.72	0.63–4.72	0.291
Education	0.77	0.42–1.38	0.378
Full-time job (reference)			
Part-time job	1.09	0.28–4.37	0.895
Unemployed	0.94	0.09–10.39	0.960
Living with partner (reference)			
Living with family member	1.63	0.39–6.77	0.505
Living alone	1.07	0.37–3.07	0.898
Smoking	0.75	0.44–1.26	0.272
Alcohol consumption	0.89	0.57–1.40	0.632

OR, odds ratio; CI, confidence interval; CVD, cardiovascular disease. Full-time job also included full-time student, pupil and self-employed; part-time job included one stay at home parent; unemployed also included welfare recipients. Education, three categories: basic school, gymnasium and college/university. Living with family member, other than partner, e.g. child or parent.

burden of traditional vascular risk factors, as shown in young stroke populations in several European regions [26]. Concordance between patient and parent reports was good, especially with regard to stroke and CAD. The LR+ of 19 with regard to stroke in mothers tells us that a patient report of maternal stroke is 19 times more likely to concur with maternal reports

than to be a false positive report. Correspondingly the high negative predictive values and the low LR− show that a negative patient-reported FH truly reflects no disease event amongst first-degree family members. Concordance was mostly acceptable also regarding PAD. However, interpretation was limited by the low prevalence of parental PAD. The present study shows no difference between males and females regarding non-concordance, indicating that the previously reported higher frequency of positive FH in females is not a result of more accurate FH reporting by females [27]. This supports the previous studies showing no difference in accuracy of FH reporting between males and females [15,28].

Previous studies evaluating the FH of cancer show substantial under-reporting. In probands with verified

Table 3 Accuracy of 132 patient reports of cardiovascular parental disease compared with answers from 189 parents included in the Norwegian Stroke in the Young Study (NOR-SYS)

Parent	Condition	Prevalence	PPV (95% CI)	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR− (95% CI)
Mother	Stroke	13.6% (15/110)	74.9 (48–91)	93.9 (89–97)	60.0 (32–84)	96.8 (91–99)	19.0 (6–62)	0.41 (0.2–0.8)
	CAD	14.8% (16/107)	79.8 (48–94)	91.8 (97–94)	50.0 (25–75)	97.8 (92–100)	22.8 (5–97)	0.51 (0.3–0.8)
	PAD	3.8% (4/106)	NA	96.1 (96–96)	NA (0–60)	98.0 (93–100)	NA	1.02 (1.0–1.1)
Father	Stroke	16.0% (12/75)	80.0 (49–94)	93.8 (87–97)	66.7 (35–90)	96.8 (89–100)	21.0 (5–87)	0.34 (0.2–0.8)
	CAD	31.2% (24/77)	81.8 (63–92)	89.1 (79–94)	75.0 (53–90)	92.5 (82–98)	9.9 (4–26)	0.27 (0.1–0.5)
	PAD	4.0% (3/75)	50.0 (7–93)	97.3 (94–99)	33.3 (1–91)	98.6 (92–100)	24.0 (2–298)	0.68 (0.3–1.5)

CAD, coronary artery disease, defined as either myocardial infarction or angina pectoris; CI, confidence interval; LR+, positive likelihood ratio is the quotient of sensitivity/(1 − specificity); LR−, negative likelihood ratio is the quotient of (1 − sensitivity)/specificity; NA, not applicable; NPV, negative predictive value is the number of true negatives/number of negative calls; PAD, peripheral arterial disease, defined as diagnosed or treated PAD; PPV, positive predictive value is the number of true positives/number of positive calls.

colorectal cancer 25% of siblings reported a negative FH of cancer [17]. Another study reported interviewee sensitivities of 50%–60% regarding cancer in first-degree relatives [18]. The present study with low rates of non-concordance shows that under-reporting is around twice as frequent as over-reporting also regarding a FH of CVD, meaning that a patient reports a false negative FH more often than a false positive. However, the under-reporting of FH of CVD varies; the NHLBI-FHS compared proband and parent reports and showed 85% sensitivity for parental CAD and substantial agreement with a kappa value of 0.76 [15]. A MONICA sub-study verifying proband reports with medical records showed sensitivities regarding myocardial infarction in first-degree relatives of around 68% with kappa values above 0.65 in both cases and controls [20]. A study on healthy undergraduates reported sensitivities of 84.2% with regard to heart attack and 100% with regard to stroke in parents. However, due to the low proband age the numbers of diseased parents was low with only one reported stroke [29]. The Framingham study reported sensitivities of 74% for heart attack <55 years and 42% for stroke <65 years [14]. The differences in methodology, with some applying age limits on parental disease and some using medical records to confirm parental events, probably cause the prevalence discrepancy and impair direct comparison with the present results. Different methods for obtaining FH and different patient characteristics probably explain the variations in accuracy. Sending questionnaires by mail [15] permits obtainment of FH information from family members or other sources, thereby increasing accuracy and concordance between patient and family reports. The previously reported association between young age and high accuracy of reporting [14] is supported by the present study. Higher patient age was associated with an incorrect FH report with an odds ratio of 1.05 per year ($P = 0.020$). CVD events at young age tend to be a more dramatic event to the family involved. These events may therefore be more vividly remembered and thereby lead to better cross-generational knowledge of FH. Lastly our cohort consists of patients with verified ischaemic stroke, which it was feared would reduce the accuracy of reporting compared to healthy individuals [2,14,15]. However, the sensitivities and kappa values in the present study are comparable with previous results, with 75% sensitivity and a kappa value of 0.69 regarding CAD in fathers.

The study is strengthened by the questionnaire-based patient interview enabling control questions and thereby increasing the accuracy of FH reports. Additional strengths are the well-defined group of young and middle-aged patients and the mandatory verification of ischaemic stroke. Our study has some limitations. Parent information was used as the gold standard for disease status. However, the contact between patients and parents after the patient's interview was not limited and therefore the possibility of joint recall bias cannot be excluded. The numbers of eligible patients and parents were modest, in part limited by the high numbers of deceased parents. The study site of one hospital and the geographical catchment area with predominantly Caucasian inhabitants limits direct generalizability beyond this population.

This study shows that a detailed FH of CVD is mostly correct when young ischaemic stroke patients are interviewed in a standardized way by trained medical professionals. Increasing age was the only demographic factor associated with reduced concordance. FH is an inexpensive and widely available tool for evaluating inherited risk; verifying it with parental reports strengthens its validity [8]. The patient FH can be used as a proxy for inherited risk of CVD in young ischaemic stroke patients.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. NOR-SYS patient questionnaire regarding family history.
Data S2. NOR-SYS parent questionnaire regarding own disease- and family history.

References

1. Sesso HD, Lee IM, Gaziano JM, Rexrode KM, Glynn RJ, Buring JE. Maternal and paternal history of myocardial infarction and risk of cardiovascular disease in men and women. *Circulation* 2001; **104:** 393–398.
2. Lloyd-Jones DM, Nam BH, D'Agostino RB Sr, *et al.* Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective

study of parents and offspring. *JAMA* 2004; **291:** 2204–2211.

3. Pandey AK, Pandey S, Blaha MJ, *et al.* Family history of coronary heart disease and markers of subclinical cardiovascular disease: where do we stand? *Atherosclerosis* 2013; **228:** 285–294.

4. Flossmann E, Schulz UG, Rothwell PM. Systematic review of methods and results of studies of the genetic epidemiology of ischemic stroke. *Stroke* 2004; **35:** 212–227.

5. Jood K, Ladenvall C, Rosengren A, Blomstrand C, Jern C. Family history in ischemic stroke before 70 years of age: the Sahlgrenska Academy Study on Ischemic Stroke. *Stroke* 2005; **36:** 1383–1387.

6. Jousilahti P, Rastenyte D, Tuomilehto J, Sarti C, Vartiainen E. Parental history of cardiovascular disease and risk of stroke: a prospective follow-up of 14 371 middle-aged men and women in Finland. *Stroke* 1997; **28:** 1361–1366.

7. Seshadri S, Beiser A, Pikula A, *et al.* Parental occurrence of stroke and risk of stroke in their children: the Framingham Study. *Circulation* 2010; **121:** 1304–1312.

8. Guttmacher AE, Collins FS, Carmona RH. The family history – more important than ever. *N Engl J Med* 2004; **351:** 2333–2336.

9. Yoon PW. Can family history be used as a tool for public health and preventive medicine? 2002.

10. Murff HJ, Spigel DR, Syngal S. Does this patient have a family history of cancer?: an evidence-based analysis of the accuracy of family cancer history. *JAMA* 2004; **292:** 1480–1489.

11. Hunt SC, Gwinn M, Adams TD. Family history assessment: strategies for prevention of cardiovascular disease. *Am J Prev Med* 2003; **24:** 136–142.

12. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; **97:** 1837–1847.

13. Greenlund KJ, Valdez R, Bao W, Wattigney WA, Srinivasan SR, Berenson GS. Verification of parental history of coronary artery disease and associations with adult offspring risk factors in a community sample: the Bogalusa Heart Study. *Am J Med Sci* 1997; **313:** 220–227.

14. Murabito JM, Nam BH, D'Agostino RB Sr, Lloyd-Jones DM, O'Donnell CJ, Wilson PW. Accuracy of offspring reports of parental cardiovascular disease history: the Framingham Offspring Study. *Ann Intern Med* 2004; **140:** 434–440.

15. Bensen JT, Liese AD, Rushing JT, *et al.* Accuracy of proband reported family history: the NHLBI Family Heart Study (FHS). *Genet Epidemiol* 1999; **17:** 141–150.

16. Watt G, McConnachie A, Upton M, Emslie C, Hunt K. How accurately do adult sons and daughters report and

perceive parental deaths from coronary disease? *J Epidemiol Community Health* 2000; **54:** 859–863.

17. Mitchell RJ, Brewster D, Campbell H, *et al.* Accuracy of reporting of family history of colorectal cancer. *Gut* 2004; **53:** 291–295.

18. Glanz K, Grove J, Le Marchand L, Gotay C. Underreporting of family history of colon cancer: correlates and implications. *Cancer Epidemiol Biomarkers Prev* 1999; **8:** 635–639.

19. Silberberg JS, Wlodarczyk J, Fryer J, Ray CD, Hensley MJ. Correction for biases in a population-based study of family history and coronary heart disease. The Newcastle Family History Study I. *Am J Epidemiol* 1998; **147:** 1123–1132.

20. Kee F, Tiret L, Robo JY, *et al.* Reliability of reported family history of myocardial infarction. *BMJ* 1993; **307:** 1528–1530.

21. Fromm A, Thomassen L, Naess H, *et al.* The Norwegian Stroke in the Young Study (NOR-SYS): rationale and design. *BMC Neurol* 2013; **13:** 89.

22. Seed P. *DIAGT: stata module to report summary statistics for diagnostic tests compared to true disease status.* Statistical Software Components. S423401, Boston College Department of Economics, 2001. revised 19 Feb, 2010.

23. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; **33:** 159–174.

24. Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology a systematic review. *Stroke* 2009; **40:** 1082–1090.

25. Schmidt M, Jacobsen JB, Lash TL, Bøtker HE, Sørensen HT. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. *BMJ* 2012; **344:** e356.

26. Putaala J, Yesilot N, Waje-Andreassen U, *et al.* Demographic and geographic vascular risk factor differences in European young adults with ischemic stroke: the 15 Cities Young Stroke Study. *Stroke* 2012; **43:** 2624–2630.

27. Øygarden H, Fromm A, Sand KM, *et al.* Stroke patients' knowledge about cardiovascular family history – the Norwegian Stroke in the Young Study (NOR-SYS). *BMC Neurol* 2015; **15:** 30.

28. Herrmann N. Retrospective information from questionnaires. I. Comparability of primary respondents and their next-of-kin. *Am J Epidemiol* 1985; **121:** 937–947.

29. Hastrup JL, Hotchkiss AP, Johnson CA. Accuracy of knowledge of family history of cardiovascular disorders. *Health Psychol* 1985; **4:** 291–306.