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Family history differs between young women with myocardial infarction and ischaemic stroke

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Abstract

Introduction The phrases 'cardiovascular disease' and 'arterial thrombosis' might suggest that myocardial infarction (MI) and ischaemic stroke (IS) share a common aetiology and risk factors. This would imply that the family history of one disease would be predictive of occurrence of the other. A positive family history may help in risk stratification, especially in the young. This study assesses the specific predictive value of a positive family history of MI and stroke (of all types) for specific outcomes.

Methods The RATIO study is a population-based case-control study including women with MI (N=248), IS (N=203) and 925 healthy controls, frequency-matched on age, year of event and area of residence. Odds ratios (OR) and 95% confidence intervals (CI) were calculated as measures of rate ratios for a positive family history of MI or stroke (affected first-degree relative <60 years) with logistic regression analyses.

Results The risk of MI was almost fourfold increased in women with a family history positive for myocardial infarction (OR 3.70, 95%CI 2.68-5.10), whereas the risk of IS was, if anything, only slightly elevated (1.25, 0.83-1.87). A family history of stroke was associated with a twofold increased MI risk (2.00, 1.29-3.12), whereas the IS risk was again not clearly associated (1.37, 0.79-2.40).

Discussion In young women, a positive family history of cardiovascular disease is a predictor for MI but not for IS. The differences between the associations of family history of myocardial infarction and stroke might be caused by the heterogeneous nature of stroke. These findings support the notion that MI and IS have different risk factor profiles and therefore different aetiologies.

Introduction

The term 'arterial thrombosis' is used to denote disorders resulting from obstructive arterial thrombi. The reduction in blood flow can result in acute ischaemia and may present clinically as myocardial infarction or ischaemic stroke. The more common term 'cardiovascular disease' is used even more broadly and can include, but is not restricted to, myocardial infarction, angina, stroke, peripheral arterial disease but also venous thrombosis and even hypertension and diabetes .[1–4] The use of one term for all forms of cardiovascular disease is common, but can be misleading in aetiologic studies since these diseases could have, despite several common risk factors, different causal mechanisms.[4–6]

Risk stratification is used to identify those at high risk of developing a disease, and consequently to consider preventive measures. Family history can be used as such a tool: it can determine whether disease clusters in families and acts as a proxy for both genetic and environmental risk factors. The advantages of such an aggregate measure in a clinical setting is that family history is obtained easily and likely to be reported accurately.[7,8] However, the predictive value of a positive family history as a risk factor for cardiovascular diseases may differ per disease and patient group.

Previous research in different patient populations has shown that a positive family history of myocardial infarction is associated with an approximate doubling of the risk of myocardial infarction.[4,8] The risk of ischaemic stroke associated with a positive family of ischaemic stroke has also been studied extensively; a systematic review of 53 heterogeneous studies indicated that a positive family history of stroke is associated with a small increase in stroke risk whereas these associations are likely to differ for the several subtypes of stroke.[9–13] The addition of family history to a predictive model improved the prognostic value of some models, but not all.[14–16] This is not surprising since improvements of prediction models can only be achieved by including variables with a strong association.[17] One of the factors that could determine the value of family history is the age of the patient group. Since the incidence of cardiovascular disease rises sharply with increasing age, mainly due to the accumulation of traditional risk factors and a shift in the distribution of ischaemic stroke subtypes, an association between a positive family history and MI or IS is therefore likely to be stronger when studies are focused on early onset of disease and potentially more useful in risk stratification in these age categories.[15]

As both environmental and genetic risk factors for MI and IS might differ in their effects, the versus one of IS may differ too. Such differences would have direct consequences for the use of family history in risk stratification. In this study we first aim to determine the association of a family history of arterial thrombosis defined as a history of myocardial infarction or stroke (of all types) and the risk of MI and IS. Additionally, we impact of a family history of MI will also determine whether a positive family history of one of these diseases is equally prevalent in patients suffering from the other disease.

Table 1. Characteristics of participants

	Myocardial infarction N=248		Ischaemic stroke N=203		Control N=925	
Age (mean, SD)	42.9	(6.1)	39.4	(8.4)	38.1	(8.3)
Caucasian ethnicity	234	(94%)	188	(93%)	864	(93%)
History of *						
Hypertension	59	(24%)	48	(24%)	55	(6%)
Diabetes	15	(6%)	11	(5%)	13	(1%)
Hypercholesterolaemia	28	(11%)	10	(5%)	24	(3%)
Oral contraceptives use *	99	(40%)	100	(49%)	340	(37%)
Smoking *	208	(84%)	126	(62%)	395	(43%)
Family members affected by myocardial infarction before the age of 60 years						
Father	73	(29%)	40	(20%)	138	(15%)
Mother	39	(16%)	9	(4%)	40	(4%)
Brother	38	(15%)	12	(6%)	41	(4%)
Sister	16	(6%)	5	(2%)	12	(1%)
Family members affected by stroke before the age of 60 years						
Father	14	(6%)	14	(7%)	36	(4%)
Mother	18	(7%)	10	(5%)	37	(4%)
Brother	7	(3%)	2	(1%)	10	(1%)
Sister	9	(4%)	4	(2%)	7	(1%)

** in the year prior to event (cases) or index year(controls).*
SD = standard deviation, percentages might not add due to rounding.

Methods

Study design & participants The RATIO (Risk of Arterial thrombosis in relation to oral contraceptives) study is a nationwide multicenter case-control study designed to search for risk factors for myocardial infarction , ischaemic stroke and peripheral arterial disease in young women as has been described earlier.[18–20] The current study focuses on the two acute forms, myocardial infarction and ischaemic stroke. In short, women between the ages 18 and 50 who were diagnosed with a form of arterial thrombosis in the 16 participating hospitals were asked to participate. Diagnosis of myocardial infarction was based on the presence of symptoms, elevated cardiac-enzyme levels, and electrocardiographic changes (N=248), whereas ischaemic stroke was diagnosed on the basis of medical history, neurological examination, and CT or MRI scan by experienced neurologists in the participating centres. (N=203) The control group comprised women not suffering from myocardial infarction, ischaemic stroke or peripheral arterial disease who agreed to participate after they were approached by random digit dialling (N=925). The control group was frequency-matched with the case groups on age (in five year categories), year of event and area of residence. Al participants were asked to fill in a standardised questionnaire on several topics such as demographic characteristics, medical history among which family history and oral contraceptive use in index year. The study protocol was approved by the ethics committees of all participating hospitals and oral informed consent was obtained from all participants.

Definitions A positive first degree relative family history of arterial thrombosis was defined as having a first degree relative (parent, sibling) with either a 'myocardial infarction' or a 'stroke' before the age of 60. We use the more generic term 'stroke' instead of ischaemic stroke deliberately because we cannot distinguish haemorrhagic from ischaemic stroke with the questions used in the questionnaire. For clarity and emphasis, we will not use abbreviations to refer to the family history. We also determined the risks associated with a family history positive for myocardial infarction or stroke separately. Additionally, a positive parental history was defined in a similar manner, but restricted to affected parents. To account for a variation in the number of siblings and to investigate a graded dose-dependent association we defined the percentage of affected first degree relative and categorised these as 0% (no affected sibling) >0-20%, 20-40% and 40% and up. Graded associations in parental family history were determined by investigating the number of affected parents.

Table 2. Risk of myocardial infarction and ischaemic stroke due to a family history of arterial thrombosis

History of arterial thrombosis in first degree relatives	control	Myocardial infarction			Ischaemic stroke		
	N (%)	N (%)	OR*	95%CI	N (%)	OR*	95%CI
Negative family history of AT	655(74%)	98 (43%)	1	[ref]	119 (66%)	1	[ref]
Positive family history of AT	229(26%)	130 (57%)	3.45	(2.51-4.75)	62 (34%)	1.35	0.91-1.99
Parental history of arterial thrombosis							
No parent affected	693(78%)	132 (54%)	1	[ref]	131 (70%)	1	[ref]
Any parent affected	201(22%(	114 (56%)	2.87	2.09-3.94	56 (30%)	1.27	0.85-1.89
One parent affected	180(20%)	95 (39%)	2.62	1.88-3.65	49 (26%)	1.29	0.85-1.96
Both parents affected	21(2%)	19 (8%)	5.38	2.64-11.0	7 (4%)	1.14	0.40-3.27
AT in father	155(17%)	80 (33%)	2.24	1.59-3.14	47 (25%)	1.32	0.86-2.03
AT in mother	67(7%)	53 (22%)	3.42	2.24-5.22	16 (9%)	1.03	0.54-1.97

AT = Arterial Thrombosis, OR = Odds Ratio, CI = Confidence Intervals. Percentages might not add due to rounding.
**Odds ratios are calculated with the control group as reference and adjusted for stratification factors (i.e. area of residence, year of event and age (continuous.)). A family history of AT is defined as myocardial infarction or stroke before the age of 60 in a first degree relative*

Statistical analyses We calculated odds ratios and corresponding 95% confidence intervals (OR, 95%CI) from logistic models as measures of rate ratios. All models included age, index year and area of residence to account for the matching strategy.

Results

Traditional risk factors were more present in both case groups than in the control group (see table 1). Data on family history were missing in some participants resulting in 884 control women, 228 MI cases and 181 IS cases available for the analyses. Data from missing individuals (20 MI cases, 22 IS cases and 41 controls) were considered as missing at random.

Family history of arterial thrombosis A positive history of arterial thrombosis in a first degree relative was more prevalent in patients with MI and to a lesser extent in IS patients than in controls (table 2). The risk of MI was increased in women with a positive family history of arterial thrombosis (OR 3.45, 95%CI 2.51 - 4.75), whereas the risk of IS was not substantially affected (OR 1.35, 95%CI 0.91 - 1.99). A similar pattern was observed when the analyses were restricted to parental history of arterial thrombosis.

Family history of myocardial infarction A positive family history of myocardial infarction increased the risk of MI almost 4-fold (OR 3.70, 95%CI 2.68 - 5.10), whereas the risk of IS remained unchanged (OR 1.25, 95%CI 0.83 -1.87) (table 3). The risk of IS was only increased when >40% of first degree relatives had been affected with myocardial infarction. A similar pattern was observed for the analyses restricted to parental history of myocardial infarction: the risk of MI increased 3-fold (OR 3.00, 95%CI 2.17 - 4.15), and the risk of IS remained unaffected (OR 1.21, 95%CI 0.80 - 1.85).

Family history of stroke A positive family history of stroke (both ischaemic and haemorrhagic) was associated with a doubling of MI risk (OR 2.00, 95%CI 1.29 - 3.12), whereas the risk of IS was only marginally increased (OR 1.37, 95% CI 0.79 - 2.40) (table 3). With more than 40% of their first degree relatives affected by stroke the risks were highest (MI OR 8.44, 95%CI 1.74 - 41; IS OR 6.78, 95%CI 1.15 - 40).

Discussion

A positive family history of arterial thrombosis is associated with an increased risk of MI and not clearly associated with IS risk. Furthermore, we found that a positive family history

of myocardial infarction was more frequent in cases who suffered from MI than in IS cases. A positive family history of stroke was associated with a moderate increase in risk of both MI and IS and the difference between MI and IS was less clear in these analyses. This was especially so in the analyses of parental family history, where most associations were less pronounced. So, our results show that a family history of neither myocardial infarction nor stroke are strong predictors of IS, whereas both are associated with MI indicating that the use of a combined family history as a predictor of disease is limited.

Our results are in line with a recent study on family clustering of coronary and cerebral events; myocardial infarction tends to cluster more in families compared with ischaemic stroke.[21] This is perhaps a demonstration of the heterogeneous nature of ischaemic stroke, as is hypothesised by the auhors: myocardial infarction may be primarily caused by atherosclerotic plaque instability and subsequent rupture, where thromboembolisms and small vessel disease also determines ischaemic stroke risk. The OXVASC study also investigated the relation between the two diseases and showed there was sex-specific familial clustering across different vascular beds.[22] The RATIO study only included women and therefore lacks the data to confirm this sex-differential heritability.

Our study has some limitations. The information on family history was self-reported and was not validated. However, previous studies indicated that questionnaires are highly accurate on family history, especially among women and the young.[7] Women who had missing data regarding their family history were excluded from our analyses. Upon closer examination of these data (not shown) the women with incomplete data were slightly more likely to rapport classical risk factors, although groups were too small to perform formal statistics. This means that, if anything, our point estimates are an underestimation of the true effects. Our questionnaire can also be a source of misclassification bias: the questions did not differentiate between ischaemic or haemorrhagic stroke. This could have affected our results if only a family history of ischaemic stroke affects risk in family members. However, ischaemic stroke makes up the bulk of all strokes, especially in stroke under 60 years of age, minimising the effect of this non-differential misclassification.[4]

Myocardial infarction is thought to manifest at an earlier age than ischaemic stroke.[4,23] This could mean that the affected parents of an ischaemic stroke patient are older than parents of a patient suffering from a myocardial infarction which could result in a differential chance of being ‘exposed’ for the two case groups introducing bias. However, since our

study is an age-matched case-control study with subjects under 50 years of age, and a positive family history defined as a event before the age of 60, this effect is minimised. Nonetheless, our restriction to young patients results in a lower prevalence of a positive family history resulting in a lower power for our analyses.

Conclusion Our results indicate that a family history of the cardiovascular diseases myocardial infarction and stroke is a predictor of MI but not for IS, limiting the potential use of a these family histories for risk stratification. Additionally the difference in associations of these aggregate measures between the MI and IS analyses raises the question whether these two diseases are different diseases and should preferably be treated as such in aetiologic research.

Table 2. Risk of myocardial infarction and ischaemic stroke due to a family history of myocardial infarction and ischaemic stroke

	Control	Myocardial infarction			Ischaemic stroke		
	N (%)	N (%)	OR	95%CI	N (%)	OR	95%CI
History of MI in first degree relatives							
FDR MI -	702(78%)	114 (49%)	1	[ref]	131 (71%)	1	[ref]
FDR MI +	194(22%)	121 (51%)	3.70	2.68-5.10	54 (29%)	1.25	0.83-1.87
FDR MI >0-20%	86(10%)	47 (20%)	3.04	1.97-4.68	22 (12%)	1.15	0.69-2.06
FDR MI >20-40%	89(10%)	52 (22%)	3.81	2.49-5.83	23 (12%)	1.19	0.70-2.12
FDR MI >40%	19(2%)	22 (9%)	6.28	3.11-13	9 (5%)	1.93	0.72-4.73
Parental history of MI							
No parent affected	734(81%)	146 (59%)	1	[ref]	143 (75%)	1	[ref]
Any parent affected	169(19%)	100 (41%)	3.00	2.17-4.15	48 (25%)	1.21	0.80-1.85
One parent affected	160(18%)	88 (36%)	2.79	1.99-3.90	47 (25%)	1.27	0.83-1.94
Both parents affected	9(1%)	12 (5%)	7.36	2.78-19.5	1 (1%)	0.36	0.03-3.82
MI in father	138(15%)	73 (30%)	2.30	1.62-3.28	40 (21%)	1.26	0.80-1.97
MI in mother	40(4%)	39 (16%)	4.34	2.62-7.17	9 (5%)	0.82	0.35-1.92
History of stroke in first degree relatives							
FDR stroke -	814(91%)	189 (83%)	1	[ref]	166 (87%)	1	[ref]
FDR stroke +	76(9%)	40 (17%)	2.00	1.29-3.12	24 (13%)	1.37	0.79-2.40
FDR stroke >0-20%	41(5%)	11 (6%)	1.97	1.12-3.45	11 (6%)	1.14	0.53-2.44
FDR stroke >20-40%	32(4%)	10 (5%)	1.53	0.72-3.21	10 (5%)	1.30	0.55-3.07
FDR stroke >40%	3(0.5%)	5 (2%)	8.44	1.74-41	3 (2%)	6.78	1.15-40
Parental history of stroke							
No parent affected	834(92%)	217 (88%)	1	[ref]	174 (89%)	1	[ref]
Any parent affected	58(8%)	29 (12%)	1.52	0.93-2.49	22 (11%)	1.35	0.75-2.41
One parent affected	63(7%)	26 (11%)	1.45	0.87-2.42	20 (10%)	1.36	0.74-2.48
Both parents affected	5(1%)	3 (1%)	2.67	0.54-13.2	2 (1%)	1.22	0.17-9.04
Stroke in father	36(4%)	14 (6%)	1.35	0.68-2.69	14 (7%)	1.53	0.72-3.25
Stroke in mother	37(4%)	18 (7%)	1.77	0.97-3.28	10 (5%)	1.13	0.50-2.51

FDR = first degree relative, OR = Odds Ratio, CI = Confidence Intervals. Percentages might not add due to rounding. Odds ratios are calculated with the control group as reference and adjusted for stratification factors (i.e. area of residence, year of event and age (continuous.)) A family history of MI is defined as myocardial infarction before the age of 60 in a first degree relative or parent, a family history of stroke is defined as a stroke before the age of 60 in a first degree relative or parent.

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