Different Types of Family History of Stroke and Stroke Risk: Results Based on 655,552 Individuals

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Background: Many studies concentrated on the relationships between different types of family history and stroke, but they have not arrived at an unified conclusion. We conducted a comprehensive systematic review to further evaluate the associations. *Methods:* Different databases were searched for related studies published from 1990 to August 2017. The relative risk was considered as the common measure of association across different studies. Heterogeneity of effects across studies was quantified by I^2. *Results:* Sixteen published studies (total participants: 655,552) were eligible in this study. The pooled multifactorial adjusted relative risk (RR) (95% confidence interval [CI]) was 1.40 (1.18, 1.67) for individuals with paternal history, 1.36 (1.20, 1.53) for those with maternal history, and 1.44 (1.17, 1.77) for those with sibling history. Based on cohort studies, the pooled adjusted RRs (95%CIs) for paternal, maternal, and sibling history were 1.33 (1.11-1.59), 1.28 (1.14-1.45), and 1.24 (1.01-1.51), respectively, all of which were smaller than those based on case-control and cross-sectional studies. In studies with large sample size, the respective adjusted RR (95%CI) of stroke for paternal, maternal, and sibling history was 1.30 (1.09, 1.56), 1.30 (1.18, 1.44), and 1.26 (1.02, 1.56), which was lower than that in studies with small sample size. *Conclusions:* Each type of family history of stroke was associated with an increased stroke risk. We could not find significant differences among stroke risks relating to different types of family history of stroke. Thus, paternal, maternal, and sibling history require our equal attention in the stroke prevention and control work.

Key Words: Family history—Stroke—Cohort studies—Case-control studies—Cross-sectional studies

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Introduction

Stroke remains a leading cause of death and adult disability worldwide.[1] Among various risk factors of stroke, family history of stroke (FHS) was regarded as a very important one for the development of stroke. Obtaining information of family history could be useful in identifying people who might have high risk of stroke (Class IIa; Level of Evidence A), which was recommended by the 2014 American Heart Association/American Stroke Association guidelines for primary prevention of stroke.[2] To date, many studies have explored the relationship between FHS and stroke risk, and a meta-analysis published in 2004 revealed that positive FHS could increase the risk of stroke by nearly 30%.[3] In addition, the associations of different types of FHS (maternal history, paternal history, and sibling history) with stroke risk have been studied by many researches.[4-10] However, results on the relationships between different types of FHS and stroke risk remained controversial. Based on data from the China Kadoorie Biobank which is a large cohort study involving 0.5 million Chinese adults, we have recently revealed that there was no significant difference on stroke risk between individuals with sibling and parental history of stroke.[5] Similar to our recently published study,[5] certain studies also could not identify the difference,[6] nevertheless, other studies found that sibling history of stroke was more strongly related to the development of stroke than parental history.[7] Besides, some studies revealed that paternal history of stroke conferred a higher stroke risk in their offspring than maternal history,[8,9] although the difference was not always observed,[5,6] and even a higher risk to maternal history was found by some other studies.[10]

To further evaluate the relationships of different types of FHS to stroke risk, we carried out a systematic review to quantitatively combine the results from all published case-control, cross-sectional, and cohort studies.

Methods

Our study was conducted and reported on the basis of the preferred reporting items for systematic reviews and meta-analyses [11] and the meta-analysis of observational studies in epidemiology guidelines.[12] And our meta-analysis was registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/) under number CRD42016026486. Based on the Newcastle-Ottawa quality assessment scales (NOS), we evaluated the methodological quality of each selected study.[13]

Search Strategy

We systematically searched PubMed and Embase databases using the key search terms "stroke," "cerebrovascular disease," "cerebrovascular attack," "cerebral ischemia," "brain ischemia," "intracranial hemorrhage," "transient ischemic attack" or "TIA," and using the terms related to family history, including "family history," "familial history," "familial aggregation," "parental history," "sibling history," "paternal history," or "maternal history." The search was restricted to case-control studies, cross-sectional studies, and cohort studies in humans published from 1990 to August 2017, with only English language limits. We also checked the reference lists of the included articles for other potentially eligible articles that had not been identified by the electronic search strategy.

Study Selection and Data Extraction

Studies were selected in the review if they fulfilled the following criteria:

(1) Observational studies focused on the relationship between FHS and stroke risk (any type of stroke); and (2) The family histories of stroke studied included sibling, paternal, or maternal history. Articles which provided insufficient data for the analyses were excluded. If data were published more than once, the most complete study was chosen. Two authors (Shumin Yu and Zhixia Su) searched the articles and extracted the data from the relevant studies independently. Discrepancies between the authors were discussed and resolved by consensus. From the selected studies the following information was extracted: first author's name, year of publication, country, study design, studied population, gender distribution, mean age or age range, sample size, number of stroke events, stroke types, definition of exposure, definition of outcome, and all reported risk estimates and their measures of precision (eg, confidence intervals or standard error).

Quality Assessment

Based on the NOS, we evaluated the methodological quality of each selected study.[13] Using the assessment scales, each study was judged on the criteria, categorized into 4 main groups: the selection of the study groups, the comparability of the groups, the ascertainment of the exposure, and the ascertainment of the outcome. We could achieve a summary score for each included study ranging from 0 to 9 points, and the higher scores might mean the lower risk of bias.

Statistical Analysis

The relative risk (RR) was considered as the common measure of association across different studies. In this study, hazard ratios (HRs) were directly regarded as RRs, because HRs were obviously equivalent to RRs[14,15]. It has been suggested that when the incidence of an outcome of interest in the study population is low (<5%), the odds ratios (ORs) are close to the RRs[16]. Thus, in our meta-analysis, the ORs could approximate to the RRs, and the ORs and other effect estimates (rate ratios and HR) were pooled for analyses. Besides, according to study design,

the ORs of case-control studies and cross-sectional studies were calculated, and the relative risks for cohort studies were analyzed separately as well. In order to identify potential effect of sex on the relationship between FHS and stroke risk, we performed stratified analyses by sex. The summary relative risks and ORs were calculated using the random-effects model of DerSimonian-Laird. Heterogeneity of effects across studies was assessed using χ^2 test statistics and quantified by I^2. I^2 was the proportion of observed variance due to real differences in effect sizes. Values of 25%, 50%, and 75% were regarded as low, moderate, and high heterogeneity. Different adjustments for potential confounders were performed across the selected studies. In this study, 2 models with different adjustment factors were used: model 1 with no adjustment (for age and gender, if available), and model 2 with adjustment for age, gender, and other relevant risk factors. The effect estimates were pooled first if the studies only provided results stratified for gender. Sensitivity analysis was performed to identify the effects of individual study on the pooled result by omitting one study in each turn. Besides, we conducted the subgroup analyses according to study design (cohort study or case-control study/cross-sectional study), gender (males or females), stroke type (ischemic stroke or hemorrhagic stroke), ethnicity (Asians or Caucasians), and individuals of sample size (<1000 or ≥1000 individuals), and we used a test for interaction to estimate differences between the subgroups.[17] Potential publication bias was assessed by funnel plots, Begg's test,[18] and Egger's test.[19] STATA version 11.0 (Stata Corporation, College Station, TX) was employed to conduct all data analysis.

Results

Study selection process and results from the literature search were showed in **Figure S1**. After systematic screening (**Fig S1**), 16 articles were included in the meta-analysis.[4,7-10,20-30] Two of the 16 studies were on the basis of data from the Framingham cohort,[4,22] however, one was based on original cohort[22], while the other one was based on offspring cohort.[4] Thus, the 2 studies were not excluded. Besides, among the 16 articles, 2 depended on the Japan Collaborative Cohort Study.[20,30] Because the 2 studies focused on different types of FHS, both 2 were included in this meta-analysis.

Table S1 showed the characteristics of the included studies. The study designs included case-control study (n = 7),[7,9,25-29] cohort study (n = 7),[4,10,20-24] and cross-sectional study (n = 2).[8,30] The published period of the included studies was 1993-2017, and the range of sample sizes was 537-473,849 (the total number of participants: 655,552). Three studies included only women, 1 study included only men, and 12 studies included both men and women. Five studies were conducted in Asia (1 in Korea, 3 in Japan, and 1 in China), 6 studies in the United States, and 5 studies in the Europe. A total of 14 articles reported the relationship between paternal history of stroke and stroke risk, 14 studies revealed the association of maternal history with stroke risk, and 11 articles explored the relationship of sibling history to stroke risk. Among the included studies, 14 reported the results with no adjustment or with adjustment for age or/and gender, and 12 reported the results adjusted for age, gender, and other stroke risk factors. Based on the quality assessment of NOS, all of the included studies were in moderate or high quality with scores ranging from 6 to 9 (**Table S2**).

After combining the results of all studies, the pooled age- and gender- adjusted RR (95%CI) of stroke for paternal history (1.47 [95%CI 1.26-1.72; I^2 67.8%]) was slightly lower than that for maternal history (1.58 [95%CI 1.37-1.82; I^2 58.7%]) (**Table 1**, **Fig 1A, Fig S2, and Fig S3**). **Figure 1A** and the sheer numbers indicated that sibling history (1.81 [95%CI 1.47-2.22; I^2 75.7%], **Fig S4**) was more strongly associated with stroke risk in comparison with paternal and maternal history. After adjustment for age, sex, and other stroke risk factors, a slight attenuation of the pooled RR for each type of FHS was identified: the pooled RR for

Table 1. *Relationship between each type of family history of stroke and stroke risk*

Adjusted models	Type of family history	Total participants ‡	RR (95%CI)	$P_{heterogeneity}$
Model 1*				
	Paternal history	558,350	**1.47 (1.26-1.72)**	<.001
	Maternal history	558,350	**1.58 (1.37-1.82)**	.004
	Sibling history	574,289	**1.81 (1.47-2.22)**	<.001
Model 2†				
	Paternal history	564,548	**1.40 (1.18-1.67)**	<.001
	Maternal history	564,548	**1.36 (1.20-1.53)**	.038
	Sibling history	491,280	**1.44 (1.17-1.77)**	.030

95%CI, 95% confidence intervals; RR, relative risk.
*Model 1: Unadjusted or adjusted for age and/or sex.
†Model 2: Adjusted for age, sex, and other stroke risk factors.
‡The total participants of related studies focusing on the relationship of each type of family history of stroke to stroke risk.

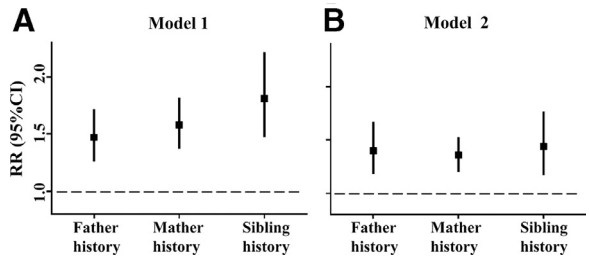

Figure 1. *Relationship between each type of family history of stroke and stroke risk. RRs and 95% CIs of model 1 are unadjusted or adjusted for age and/or sex; RRs and 95% CIs of model 2 are adjusted for age, sex, and other stroke risk factors. Squares represent the RRs and vertical lines represent the corresponding 95% CI.*

Abbreviations: CI, confidence interval; RR, relative risk.

paternal history (1.40 [95%CI 1.18-1.67; I^2 75.1%]) was similar to that for maternal history (1.36 [95%CI 1.20-1.53; I^2 47.8%]) (**Table 1**, **Fig 1B, Fig S2, and Fig S3**), and it appeared that there was a drop in the numerical difference of RRs between sibling history (1.44 [95%CI 1.17-1.77; I^2 51.2%]) and paternal history /maternal history (**Fig 1B, Fig S4**).

Based on case-control and cross-sectional studies, the combined age- and gender- adjusted ORs (95%CIs) for paternal history, maternal history, and sibling history were 1.49 (95%CI 1.11-1.99; I^2 29.6%), 1.91 (95%CI 1.50-2.44; I^2 10.1%), and 2.33 (95%CI 1.66-3.25; I^2 56.1%) (**Table 2**), respectively. As show in **Table 2**, after multivariable adjustment, the difference of ORs for stoke risk between paternal history (1.72 [95%CI 0.97-3.07, I^2 72.8%])/maternal history (1.73 [95%CI 1.27-2.37, I^2 27.9%]) and sibling history (1.96 [95%CI 1.36-2.83, I^2 20.9%]) seemed decline, and the OR for paternal history was almost identical for maternal history. On the basis of cohort studies, the pooled age- and gender- adjusted RRs (95%CIs) for paternal, maternal, and sibling history were 1.48 (95%CI 1.22-1.79; I^2 80.1%), 1.46 (95%CI 1.24-1.71; I^2 67.2%), and 1.41 (95%CI 1.14-1.75; I^2 60.8%), respectively, and the corresponding multifactorial-adjusted RRs (95%CIs) were 1.33 (95%CI 1.11-1.59; I^2 79.5%), 1.28 (95%CI 1.14-1.45; I^2 51.3%), and 1.24 (95%CI 1.01-1.51; I^2 65.8%).

Table 3 showed the different subgroup analyses of studies for each type of FHS. Among men, the multivariable-adjusted RR of stroke was 1.30 (95%CI = 1.10-1.55) for paternal history, and 1.32 (95%CI = 1.25-1.39) for maternal history. Among women, compared with paternal history (the multivariable-adjusted RR = 1.19; 95%CI = 0.92-1.53), maternal history was seemingly more strongly associated with stroke risk (the adjusted RR = 1.34; 95%CI = 1.28-1.41) (**Table 3**). In Asians, individuals with sibling history (multivariable-adjusted RR = 2.15; 95%CI = 0.99-4.65) were at higher risk of stroke versus those with paternal history (adjusted RR = 1.32; 95%CI = 1.06-1.66) and maternal history (adjusted RR = 1.37; 95%CI = 1.14-1.64). However, among Caucasians, the multivariable-adjusted RR (95%CI) was 1.49 (1.05, 2.11) for paternal history, 1.39 (1.13, 1.70) for maternal history, and 1.34 (1.02, 1.77) for sibling history. In studies with small sample size (<1000 individuals), the multivariable-adjusted RR (95%CI) of stroke was 2.23 (1.47, 3.37) for paternal history, 2.13 (1.15, 3.97) for maternal history, and 2.11 (1.47, 3.04) for sibling history. Nevertheless, the pooled multivariable-adjusted RR (95%CI) of stroke for each type of FHS was smaller in studies with large sample size (≥1000 individuals) than that in studies with small sample size. And the respective adjusted RR (95%CI) of stroke in studies with large sample size was 1.30 (1.09, 1.56) for paternal history, 1.30 (1.18, 1.44) for maternal history, and 1.26 (1.02, 1.56) for sibling history.

To explore potential source of heterogeneity across studies, we carried out several sensitivity analyses. As show in **Table S3**, based on multivariable-adjusted

Table 2. *Association of each type of family history of stroke with stroke risk according to study design*

Type of family history of stroke	Cohort studies				Case-control or cross-sectional studies			
	Study number	RR (95%CI)	Heterogeneity I^2	Heterogeneity P	Study number	OR (95%CI)	Heterogeneity I^2	Heterogeneity P
Paternal history								
Model 1*	6	**1.48 (1.22-1.79)**	80.1%	<.001	6	**1.49 (1.11-1.99)**	29.6%	.213
Model 2†	6	**1.33 (1.11-1.59)**	79.5%	<.001	5	1.72 (0.97-3.07)	72.8%	.005
Maternal history								
Model 1*	6	**1.46 (1.24-1.71)**	67.2%	.006	6	**1.91 (1.50-2.44)**	10.1%	.351
Model 2†	6	**1.28 (1.14-1.45)**	51.3%	.068	5	**1.73 (1.27-2.37)**	27.9%	.236
Sibling history								
Model 1*	4	**1.41 (1.14-1.75)**	60.8%	.037	6	**2.33 (1.66-3.25)**	56.1%	.044
Model 2†	3	**1.24 (1.01-1.51)**	65.8%	.054	6	**1.96 (1.36-2.83)**	20.9%	.270

95%CI, 95% confidence intervals; OR, odds ratio; RR, relative risk.
*Model 1: Unadjusted or adjusted for age and/or sex.
††Model 2: Adjusted for age, sex, and other stroke risk factors.

Table 3. *Stratified analysis of the relationship between each type of family history of stroke and stroke risk by gender, ethnicity, and sample size*

		Paternal history			Maternal history			Sibling history		
Studied factors	Adjusted models	Study number	RR (95%CI)	I^{2}‡	Study number	RR (95%CI)	I^{2}‡	Study number	RR (95%CI)	I^{2}‡
Gender										
Men	Model 1*	3	**1.45 (1.14-1.85)**	80.3%	3	**1.41 (1.24-1.59)**	36.6%	1	**1.51 (1.40-1.63)**	/
	Model 2†	4	**1.30 (1.10-1.55)**	59.2%	4	**1.32 (1.25-1.39)**	0%	1	**1.35 (1.25-1.45)**	/
Women	Model 1*	6	**1.36 (1.14-1.62)**	52.0%	6	**1.56 (1.36-1.80)**	31.7%	3	**2.30 (1.28-4.14)**	57.5%
	Model 2†	4	**1.19 (0.92-1.53)**	77.9%	4	**1.34 (1.28-1.41)**	0%	3	**1.51 (1.18-1.92)**	9.8%
Ethnicity										
Asians	Model 1*	4	**1.40 (1.13-1.73)**	79.2%	4	**1.49 (1.26-1.77)**	67.0%	4	**2.07 (1.52-2.82)**	84.2%
	Model 2†	4	**1.32 (1.06-1.66)**	80.2%	4	**1.37 (1.14-1.64)**	69.3%	3	2.15 (0.99-4.65)	71.3%
Caucasians	Model 1*	8	**1.58 (1.20-2.07)**	64.8%	8	**1.72 (1.31-2.24)**	59.8%	6	**1.67 (1.14-2.45)**	64.9%
	Model 2†	7	**1.49 (1.05-2.11)**	75.9%	7	**1.39 (1.13-1.70)**	35.5%	6	**1.34 (1.02-1.77)**	31.4%
Sample size										
<1000	Model 1*	4	**1.68 (1.25-2.26)**	0%	4	**2.41 (1.79-3.25)**	0%	4	**2.57 (1.84-3.59)**	0%
	Model 2†	3	**2.23 (1.47-3.37)**	0%	3	**2.13 (1.15-3.97)**	58.7%	4	**2.11 (1.47-3.04)**	0%
≥1000	Model 1*	8	**1.43 (1.19-1.72)**	80.1%	8	**1.42 (1.25-1.62)**	55.6%	6	**1.60 (1.27-2.01)**	83.3%
	Model 2†	8	**1.30 (1.09-1.56)**	78.7%	8	**1.30 (1.18-1.44)**	37.6%	5	**1.26 (1.02-1.56)**	58.7%

95%CI, 95% confidence intervals; RR, relative risk.
*Model 1: Unadjusted or adjusted for age and/or sex.
†Model 2: Adjusted for age, sex, and other stroke risk factors.
‡I^{2}: Quantifying heterogeneity of effects across studies.

models, sensitivity analyses did not show any significant difference of stroke risk in the subgroups for maternal history of stroke. The risk of paternal history-related stroke was significantly higher in the studies with small sample size compared with studies with large sample size ($P = .019$). The risk of sibling history-related stroke was significantly higher in the case-control studies compared with cohort studies ($P = .032$) and higher in the studies with small sample size compared with studies with large sample size ($P = .016$). To further confirm the robustness of the results, a series of the pooled results for each type of FHS were acquired after removing every single study. In this sensitivity test, no single study altered the overall RRs of total stroke risk substantially for each type of FHS either in age- and gender-adjusted models or in multivariable-adjusted models (data not shown).

No evidence of publication bias for the results of each type of FHS was suggested by visual inspection of funnel plots (data not shown). Besides, based on age- and gender-adjusted models, both Begg's test and Egger's test indicated no publication bias (Begg's test: $P = .951$ for paternal history, $P = .246$ for maternal history, and $P = 1.000$ for sibling history; Egger's test: $P = .798$ for paternal history, $P = .209$ for maternal history, and $P = .300$ for sibling history). Additionally, none of the 3 methods (funnel plots, Begg's test, and Egger's test) showed a significant publication bias on the basis of multivariable-adjusted models (data not shown).

Discussion

This study showed that each type of FHS was an independent risk factor for stroke after adjustment for various risk factors. The stroke risk related to sibling history of stroke was similar to paternal/maternal history. And we could not consider that there are significant differences for relevant stroke risk between maternal and paternal history of stroke.

The relationships of different types of FHS to stroke have been explored by many studies, however, the association between each type of FHS and stroke risk remained controversial. Take sibling history of stroke for example, MaClellan et al[27] and Kondo et al[30] found that sibling history was positively related to stroke risk, nevertheless, Liao et al[8] and many other researchers could not find the same result. Besides, there was the similar phenomenon when we estimated the associations of paternal/maternal history with stroke risk. In order to obtain more reliable and accurate information, we carried our meta-analysis on the basis of 655,552 individuals, and we identified that each type of FHS was an independent risk factor for stroke after adjustment for various risk factors. Therefore, regularly collecting information on each type of FHS could be useful in assessing heritability of stroke and promoting stroke prevention and control.

In our study, based on age- and gender-adjusted model, sibling history was numerically more strongly correlated with stroke risk than paternal and maternal history. Meschia et al showed that the severity of stroke was more strongly correlated with FHS in siblings than that in parents.[31] It has been reported that shared environmental effects on cardiovascular risk factors were stronger within sibling pairs in comparison with parent-offspring pairs.[32,33] It might suggest that, in addition to genetic effects involved, there is a greater sharing of environmental effects among siblings than between parents and offsprings. In present study, after the multivariable adjustment (including BMI, smoking, drinking, social class, and physical activity), the difference of RR values between sibling history-related stroke risk and paternal/maternal history-related stroke risk decreased, and the RR for sibling history was similar to paternal/maternal history. Additionally, after multivariable adjustment, we identified that the similar RR values between sibling history and paternal/maternal history also occurred in cohort studies (the results of cohort studies were more reliable than case-control or cross-sectional studies), and in studies with large sample size (statistical power was higher for studies with large sample size versus small sample size). Thus, the information mentioned above further revealed that after eliminating the interference of environmental factors, the stroke risk associated with sibling history might equate to that related to maternal/paternal history.

Some researches demonstrated that maternal history of stroke was much more important than paternal history.[34] And there might be several reasons or underlying mechanisms, such as genomic imprinting and maternally intrauterine environment.[35-37] Nevertheless, in 2015, Weijmans et al undertook a meta-analysis focusing on paternal/maternal history of cardiovascular disease (CVD) and CVD risk in offspring, and they reported that the conferred risk of CVD in offspring was not substantially different between positive paternal and maternal histories of CVD.[38] In addition, in line with the result of our previous published research,[10] our present meta-analysis involving 655,552 individuals also did not support the conclusion of certain researches mentioned above that maternal history of stroke was related to higher stroke risk than paternal history. Especially, based on studies with large sample size ($\geq$1000 individuals), the analysis result showed the multivariable-adjusted RR (95%CI) of stroke for maternal history was 1.30 (1.18, 1.44), which was equal to that for paternal history (1.30 [1.09, 1.56]). Therefore, both maternal and paternal history need our same concern in evaluating heritability of stroke, and no distinction had to be made in primary prevention and clinical practice whether the parent with stroke was the mother or the father.

Strengths and Limitations of This Meta-analysis

This meta-analysis was on a basis of all observational studies including prospective cohort, case-control, and cross-sectional studies from various populations. The estimates according on 2 kinds of adjustment models were conducted in this study. Our study was the most comprehensive analysis systematically evaluating the relationship of each type of FHS to stroke risk, and the combined sample size (more than 655,000 individuals) was large enough to achieve convincing results. However, there are several limitations to consider when interpreting results from our meta-analysis. First, none of the studies attempted to confirm the FHS through medical records to avoid the potential recall bias. However, previous studies showed that self-reported history for stroke was reliable.[39] Second, although 16 articles were included in our study totally, related studies were not enough to draw convincing conclusions in certain subgroup analyses, including different gender strata and stroke type strata (especially for hemorrhagic strata). Third, the included studies did not make adjustment for the identical factors, and some studies did not make adjustment for the important stroke risk factors, such as hypertension, diabetes, atrial fibrillation, and serum total cholesterol. In addition, 16 studies in this meta-analysis were relatively independent and the effect of heterogeneity on the pooled calculated estimate were inevitable, which is still an important limitation in our study. A multivariable adjusted model with same modified factors would be more suitable; however, factors for adjusting in each study were different. Based on the effect estimates adjusted for different factors for included studies in our meta-analysis, the pooled estimate, to some extent, might not reflect the real information.

Conclusions

Each type of FHS was associated with an increased stroke risk. Sibling history of stroke did not represent higher stroke risk than paternal/maternal history, and both paternal and maternal history were with similar stroke risk. Thus, sibling, paternal, and maternal history require our equal attention in the stroke prevention and control work.

Conflict of Interest Disclosure Statement

The authors report no disclosures.

Author Contributions

Shumin Yu: Document retrieval, analysis and interpretation, manuscript drafting.

Zhixia Su: Document retrieval, analysis and interpretation, manuscript drafting.

Junyan Miao: Acquisition of data, analysis, revision of the initial manuscript.

Yuhui Yu: Analysis and interpretation, critical revision of the manuscript for important intellectual content.

Shihan Zhang: Analysis and interpretation, critical revision of the manuscript for important intellectual content.

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Huiting Zheng: Acquisition of data, critical revision of the manuscript for important intellectual content.

Li Qiao: Critical revision of the manuscript for important intellectual content.

Shiyao Zhong: Critical revision of the manuscript for important intellectual content.

Huilin Li: Critical revision of the manuscript for important intellectual content.

Jie Liang: Study concept and design, critical revision of the manuscript for important intellectual content.

Minjie Chu: Directing the study implementation, critical revision of the manuscript for important intellectual content.

Tian Tian: Study concept and design, critical revision of the manuscript for important intellectual content, study supervision.

Supplementary Material

Supplementary data to this article can be found online at doi:10.1016/j.jstrokecerebrovasdis.2018.10.038.

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