

Risk factors of cerebral small vessel disease

A systematic review and meta-analysis

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Abstract

Background: Cerebral small vessel disease (CSVD) is a common neurological disease under the effect of multiple factors. Although some literature analyzes and summarizes the risk factors of CSVD, the conclusions are controversial. To determine the risk factors of CSVD, we conducted this meta-analysis.

Methods: Five authoritative databases of PubMed, Embase, Cochrane Library, CNKI, and Wan Fang were searched to find related studies published before November 30, 2020. The literature was screened according to the inclusion and exclusion criteria. We used RevMan 5.4 software to analyze the data after extraction.

Results: A total of 29 studies involving 16,587 participants were included. The meta-analysis showed that hypertension (odds ratio [OR] 3.16, 95% confidence interval [CI] 2.22-4.49), diabetes (OR 2.15, 95% CI 1.59-2.90), hyperlipidemia (OR 1.64, 95% CI 1.11-2.40), smoking (OR 1.47, 95% CI 1.15-1.89) were significantly related to the risk of lacune, while drinking (OR 1.03, 95% CI 0.87-1.23) was not. And hypertension (OR 3.31, 95% CI 2.65-4.14), diabetes (OR 1.66, 95% CI 2.65-1.84), hyperlipidemia (OR 1.88, 95% CI 1.08-3.25), smoking (OR 1.48, 95% CI 1.07-2.04) were significantly related to the risk of white matter hyperintensity, while drinking (OR 1.41, 95% CI 0.97-2.05) was not.

Conclusions: This study suggested that hypertension, diabetes, hyperlipidemia, and smoking are risk factors of CSVD, and we should take measures to control these risk factors for the purpose of preventing CSVD.

Abbreviations: CI = confidence interval, CSVD = cerebral small vessel disease, MRI = magnetic resonance imaging, NOS = Newcastle-Ottawa Scale, OR = odds ratio.

Keywords: cerebral small vessel diseases, lacune, meta-analysis, risk factors, white matter hyperintensity

1. Introduction

Cerebral small vessel disease (CSVD) refers to a series of clinical, imaging, and pathological syndromes resulting from various causes affecting the perforating arterioles, arterioles, capillaries, venules, and venules in the brain.^[1] CSVD, which causes about

All data generated or analyzed during this study are included in this published article.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

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25% of ischemic strokes and most hemorrhagic strokes, is the most common cause of vascular dementia. And it is usually associated with Alzheimer disease and exacerbates the resulting cognitive impairment, leading to about 50% of dementias worldwide.^[2] In China, lacunar infarction caused by cerebral microvascular disease accounts for 25% to 50% of ischemic stroke, which is higher than that in western countries.^[3] The prevalence of white matter hyperintensity (WMH) ranges from 50% to 95% between 45 and 80 years old. Cognitive impairment caused by CSVD can account for 36% to 67% of vascular dementia.^[4] It can be predicted that CSVD will be a major disease that will affect the quality of life of the elderly in the future.

In the early stage of CSVD, there can be no symptoms, only imaging changes,^[5] which makes the diagnosis and treatment not so timely. Magnetic resonance imaging (MRI) is the most common and accurate method to detect subtle changes in the brain of patients with CSVD. The imaging standards of CSVD were established in 2013 and widely recognized as WMH, lacune, recent subcortical small infarction, perivascular space, cerebral microbleed, and brain atrophy, with WMH and lacunar being the most common. WMH is manifested on MRI as extensive or fused abnormal signal, which is particularly evident in T2-weighted image and fluid-attenuated inversion recovery sequences, presenting as high signal. Lacune appears as round or ovoid subcortical fluid-filled (signal similar to cerebrospinal fluid) cavities on MRI and are most typical on fluid-attenuated inversion recovery sequences, appearing as a central low signal with a ring of high signal at the edges. This study will analyze from these 2 aspects. Although some progress has been made, it is clear that our understanding of CSVD is not enough. At present,

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the treatment is mainly to control hypertension, symptomatic treatment, and cognitive dysfunction treatment.^[6] But we all know that the best response should be to prevent CSVD from occurring, so it is important to identify the risk factors of CSVD. There are a number of studies on risk factors for CSVD, but they are often limited to a particular region or hospital, and the number of subjects included is not large enough, sometimes leading to opposite conclusions.^[7] Therefore, we conducted a review and meta-analysis of the existing literature aiming to more accurately identify risk factors for CSVD and provide evidence for the prevention of CSVD.

2. Methods

This study was designed and completed under the guidance of the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement. Since this is a meta-analysis of previous studies, no ethical approval is required.

2.1. Search strategy

We conducted a search of the following databases: PubMed, Cochrane library, Embase, CNKI, and Wan Fang. Databases were searched from the earliest data to 30 November 2020 with the search terms: "Cerebral Small Vessel Diseases", "Recent small subcortical infarct", "Lacune", "White matter hyperintensity", "Perivascular space", "Cerebral microbleed", "Brain atrophy", "Risk factor*", "Case control" and their entry term.

2.2. Selection criteria

Inclusion criteria:

- The study was a case-control study.
- The case group was patients with CSVD, and the control group was matched with healthy people or patients without brain disease.
- The imaging markers of patients with CSVD were measured by MRI.
- At least 3 of hypertension, diabetes mellitus, hyperlipidemia, smoking, and drinking were described.

Exclusion criteria:

- Patients in the control group had cerebrovascular disease, for example, the control group was stroke patients.
- Suffering from other serious diseases.
- Data is not perfect, or article data is not available.
- Duplicate published data.

2.3. Study selection

We import the documents retrieved from the 5 databases according to the search strategy into Endnote. First of all, use the software to remove the repeated literature, then browse the title and abstract, exclude the irrelevant literature, and finally read the full text, according to the inclusion and exclusion criteria to eliminate the literature that does not meet the requirements. The work above is done independently and blindly by the 2 researchers. If any disagreement arises, it will be resolved through mutual consultation. When consensus could not be reached, consult a third expert. The literature screening and data extraction protocol is shown in Figure 1

2.4. Data extraction and assessment of the risk of bias

From the included studies, the name of the first author, the year of publication, the total sample size, and the number of cases and controls were extracted. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included literature, which was divided into a total of 8 items, with the highest score of 2 given to the item of comparability and the highest score of 1 given to the others, for a total score of 9. A score of 0 to 3 was assigned to low-quality literature, 4 to 6 to moderate-quality literature, and 7 to 9 to high-quality literature. The evaluation of literature quality was performed by 2 researchers independently and blinded to each other. If 2 evaluators gave different scores, they need to discuss and negotiate the solution, and if necessary, they could consult a third party.

2.5. Statistical analysis

Extracted data were analyzed using RevMan 5.4 (https://training. cochrane.org/) for meta-analysis, and the count data were expressed using the odds ratio (OR) and their 95% confidence interval (CI). Heterogeneity of all included studies was assessed and quantified using the Cochrane Q statistic and the I^2 statistic, respectively. When $I^2 \ge 50$, the heterogeneity is significant, and the random effect model is used for analysis. The fixed effect model is used for analysis when $I^2 < 50\%$, which means the heterogeneity is not significant. Publication bias for the studies in the text was assessed using visual funnel plots. If the funnel chart is symmetrically distributed, there is no publication bias, if on the contrary, it indicates that there is publication bias. The sensitivity analysis was carried out by eliminating the study one by one, which was used to determine the stability and reliability of the conclusions.

3. Results

3.1. Literature retrieval results and basic characteristics

After the literature search process, 1652 potentially eligible articles were initially identified. After eliminating 187 duplicates, the titles and abstracts of the remaining 1465 studies were browsed, and 1352 irrelevant studies were removed. Finally, the full text was read, and the literatures that did not meet the requirements were excluded according to the inclusion and exclusion criteria, and 29 literatures that met the criteria were obtained. The screening process is shown in Figure 2. We divided the included literatures into lacune group, control group and WMH group, control group. There were 12 articles related to lacune, a total of 6944 people, and 17 articles related to WMH, a total of 9643 people. The basic characteristics of the included studies are shown in Table 1, and the research factors are divided into hypertension, diabetes, hyperlipidemia, smoking, drinking 5 aspects, with the number of events as the outcome index.

3.2. Quality assessment

The NOS scale is a commonly used scale for quality assessment of case-control studies, and its reliability and validity have been confirmed in long-term use. This meta-analysis also used the NOS scale for quality evaluation, and the green color in the figure indicates the score, and it can be seen that the included studies all scored above 5. The specific quality evaluation is shown in Figure 3.



Figure 1. The process of literature screening and data extraction.





Table 1

		Hypertension	Diabetes	Hyperlipidemia	Smoking	Drinkina	
First author, year	Group (number)	Yes/no	Yes/no	Yes/no	Yes/no	Yes/no	Mean age
Chen Liang 2018	Lacune (n $=$ 406)	258/148	131/275	122/284	129/277	52/354	N
	Control $(n = 452)$	196/256	52/400	119/333	114/338	45/407	
Christian Kukla 1998	Lacune $(n = 61)$	32/29	8/53	N	18/43	N	>65
	Control $(n = 57)$	15/42	7/50	N	11/46	N	
Feili 2019	Lacune $(n = 702)$	433/269	281/421	N	149/553	148/554	< 65
	Control $(n - 234)$	131/103	77/157	N	43/191	44/190	<00
Ki-Woong Nam 2018	Lacune $(n - 260)$	92/168	59/201	70/190	34/226	110/1/1	~65
REWOONS Nam 2010	Control $(n - 200)$	616/2260	277/2508	70/150	150/0422	1/06/1/70	<05
Vacilaina Arannina Ligutan 2017	L_{00} (n = 2000)	100/19	20/70	7 3 3/2 I J 2	452/2455	1400/1479 N	> 6 F
Vasileius-Aiseriius Liuulas 2017	Control $(n - 254)$	210/125	25/210	N	25/95	IN N	200
V Laira 2016	COTILIOI (11 = 304)	219/130	30/319	IN 06/06	30/319	IN 16/47	> CE
r. Lella 2016	Lacure $(1=62)$	33/29	10/47	20/30	20/34	13/47	<u>≥0</u> 5
V 11 1000	Control $(n = 60)$	20/40	6/54	11/49	11/49	6/52	. 05
Yoshitomo Notsu 1999	Lacune $(n = 147)$	108/39	16/131	N	57/90	N	≥65
	Control $(n = 214)$	52/162	22/192	Ν	73/141	Ν	
Xin Cui 2011	Lacune (n $=$ 50)	28/22	17/33	Ν	24/26	Ν	<65
	Control ($n = 42$)	10/32	4/38	Ν	16/26	Ν	
Zhijing Liang 2010	Lacune (n $=$ 65)	55/10	29/36	18/47	20/45	16/49	<65
	Control $(n = 60)$	38/22	16/44	7/53	9/51	11/49	
Hongjin Wang 2003	Lacune (n $=$ 52)	44/8	13/39	Ν	17/35	Ν	<65
	Control $(n = 30)$	8/22	6/24	Ν	4/26	Ν	
Huivun Yu 2012	Lacune $(n = 106)$	75/31	36/70	42/64	Ν	Ν	<65
	Control $(n = 100)$	52/48	20/80	23/77	N	N	
Ke Deng 2007	Lacune $(n = 105)$	76/29	12/93	N	44/61	20/83	< 65
to bong 2007	Control $(n - 322)$	110/203	19/303	N	120/103	81/2/1	<00
Haidiand lin 2020	WMH (n = 240)	77/163	13/303	63/177	/8/102	56/18/	~65
Tialqialiy Jili 2020	Control (n = 61)	0/61	0/61	0/50	40/192	10/104	<05
Oine Lie 0017	$\begin{array}{c} \text{COLLIOI} (11=01) \\ \text{COLLIOI} (11=0200) \end{array}$	0/01	0/01	9/32	12/49	13/40	-05
Qing Lin 2017	WIVIH $(I = 27.32)$	1505/1227	763/1969	IN	847/1885	211/2521	<0>
	Control $(n = 1951)$	607/1344	339/1612	N	398/1553	165/1786	
Xueying Yu 2018	WMH (n $= 379$)	245/134	39/340	Ν	90/289	Ν	<65
	Control (n $=$ 384)	162/222	30/354	Ν	108/276	Ν	
B. Censori 2007	WMH $(n=61)$	45/16	9/52	12/49	7/54	Ν	≥65
	Control (n $=$ 117)	52/65	13/104	21/96	29/88	Ν	
Dirk Sander 2000	WMH (n $=$ 82)	48/34	10/72	Ν	Ν	Ν	≥65
	Control (n = 145)	52/93	18/127	Ν	Ν	Ν	
Hongliang Feng 2017	WMH $(n = 193)$	155/38	43/150	Ν	13/180	Ν	<65
	Control $(n = 415)$	167/248	57/358	Ν	36/379	Ν	
Dinghua Zeng 2013	WMH $(n = 113)$	81/32	15/98	Ν	94/19	Ν	>65
5 5	Control $(n = 28)$	15/13	2/26	Ν	4/24	Ν	_
Xiuiun Mena 2011	WMH $(n = 50.9)$	377/132	142/367	N	213/296	150/359	>65
	Control $(n = 509)$	301/208	126/383	N	176/333	119/390	
Fand Du 2019	WMH $(n = 65)$	50/15	N	N	19/46	N	>65
rung bu zoro	Control $(n - 30)$	13/17	N	N	8/22	N	200
Vinona Chen 2015	WMH (n - 106)	7//32	12/0/	N	1//02	N	>65
Thinking offer 2013	Control $(n - 21)$	7/0/	2/22	N	5/26	N	<u>~00</u>
	$\frac{1}{1}$	1/24	3/20	IN 70/00	J/20	IN NI	
Hongli Yi 2008	(1 = 158)	89/69	43/115	/ 6/82	IN N	N	202
V:	Control (II = 158)	52/106	38/120	68/90	N 70/05	IN 10/00	. 05
Xinmin Huang 2005	WMH $(n = 144)$	113/31	53/91	86/58	79/65	48/96	≥65
	Control ($n = 102$)	22/80	15/87	14/88	26/76	9/93	
Qinghua Li 2002	WMH (n $=$ 69)	41/28	20/49	22/47	16/53	Ν	≥65
	Control (n $=$ 69)	25/44	13/56	17/52	14/55	Ν	
Ling Chen 2014	WMH (n $=$ 102)	71/31	50/52	58/44	40/62	34/68	≥65
	Control $(n=61)$	25/36	18/43	24/37	8/53	15/46	
Liwei Sun 2016	WMH (n=241)	130/111	50/191	119/122	41/200	35/206	<65
	Control $(n = 104)$	35/69	13/91	54/50	24/80	18/86	
Pan Tang 2014	WMH $(n = 36)$	27/9	11/25	N	25/11	23/13	>65
U	Control $(n = 36)$	14/22	13/23	Ν	14/22	16/20	
Fei Wang 2001	WMH $(n = 106)$	59/47	28/78	36/70	41/65	N	< 65
	Control $(n = 106)$	36/70	24/82	27/79	32/74	N	200
		00/10	L 1/ UL	L1/10		1.1	

 $N\!=\!not$ available, WMH $=\!white$ matter hyperintensity.



Figure 3. (A) Quality evaluation about risk factors of the lacune. (B) Quality evaluation about risk factors of the WMH.

3.3. Risk factors

Effectiveness indicators were expressed as combined ORs with 95% CI, and forest plots were used to visually depict each test and the combined results with weights.

3.3.1. Hypertension. The effect of hypertension on lacune was analyzed in 12 studies involving 2134 in the lacune group and 4810 in the control group. The pooled results of these studies indicated that people with hypertension are more likely to get CSVD (OR = 3.16; 95% CI 2.22-4.49; P < .00001; $I^2 = 84\%$). The effect of hypertension on WMH was analyzed in 17 studies involving 5336 in the WMH group and 4307 in the control group. The pooled results of these studies indicated that people with hypertension are more likely to get CSVD (OR = 3.31; 95% CI 2.65-4.14;

 $P < .00001; I^2 = 73\%$). The funnel plot is roughly symmetrical, suggesting that publication bias may be small (Fig. 4).

3.3.2. Diabetes. The effect of hypertension on lacune was analyzed in 12 studies involving 2134 in the lacune group and 4810 in the control group. The pooled results of these studies indicated that people with diabetes are more likely to get CSVD (OR=2.15; 95% CI 1.59-2.90; P < .00001; $I^2 = 67\%$). The effect of diabetes on WMH was analyzed in 16 studies involving 5271 in the WMH group and 4277 in the control group. The pooled results of these studies indicated that people with diabetes are more likely to get CSVD (OR=1.66; 95% CI 1.49-1.84; P < .00001; $I^2 = 33\%$). The funnel plot is roughly symmetrical, suggesting that publication bias may be small (Fig. 5).



Figure 4. (A) Forest plot showing the relationship between hypertension and lacune. (B) Forest plot showing the relationship between hypertension and WMH. (C) Funnel plot of hypertension on WMH. CI = confidence interval, WMH = white matter hyperintensity.

3.3.3. Hyperlipidemia. The effect of hyperlipidemia on lacune was analyzed in 5 studies involving 899 in the lacune group and 3557 in the control group. The pooled results of these studies indicated that people with hyperlipidemia are more likely to get CSVD (OR = 1.64; 95% CI 1.11-2.40; P=.01; I^2 =67%). The

effect of hyperlipidemia on WMH was analyzed in 7 studies involving 1060 in the WMH group and 661 in the control group. The pooled results of these studies indicated that people with hyperlipidemia are more likely to get CSVD (OR = 1.88; 95% CI 1.08-3.25; P = .03; $I^2 = 83\%$) (Fig. 6).





3.3.4. Smoking. The effect of smoking on lacune was analyzed in 11 studies involving 2028 in the lacune group and 4710 in the control group. The pooled results of these studies indicated that people who smoke are more likely to get CSVD (OR = 1.47; 95% CI 1.15-1.89; P = .002; $I^2 = 56\%$). The effect of smoking

on WMH was analyzed in 15 studies involving 5096 in the WMH group and 4004 in the control group. The pooled results of these studies indicated that people who smoke are more likely to get CSVD (OR=1.48; 95% CI 1.07-2.04; P=.02; $I^2=84\%$) (Fig. 7).



Figure 6. (A) Forest plot showing the relationship between hyperlipidemia and lacune. (B) Forest plot showing the relationship between hyperlipidemia and WMH. Cl = confidence interval, WMH = white matter hyperintensity.



Figure 7. (A) Forest plot showing the relationship between smoking and lacune. (B) Forest plot showing the relationship between smoking and WMH. CI = confidence interval, WMH = white matter hyperintensity.



Figure 8. (A) Forest plot showing the relationship between drinking and lacune. (B) Forest plot showing the relationship between drinking and WMH. CI = confidence interval, WMH = white matter hyperintensity.

3.3.5. Drinking. The effect of drinking on lacune was analyzed in 6 studies involving 1600 in the lacune group and 4013 in the control group. The pooled results of these studies indicated that people who drink are more likely to get CSVD (OR = 1.03; 95% CI 0.87-1.23; P=.70; $I^2=47\%$), but it is not statistically significant. The effect of drinking on WMH was analyzed in 7 studies involving 4004 in the WMH group and 2824 in the control group. The pooled results of these studies indicated that people who drink are more likely to get CSVD (OR = 1.41; 95% CI 0.97-2.05; P=.07; $I^2=76\%$) (Fig. 8), but it is not statistically significant.

3.4. Sensitivity analysis and publication bias evaluation

Excluding studies one by one for sensitivity analysis, and the conclusion is stable. When the number of studies included is greater than or equal to 15, the funnel chart is drawn (Figs. 4 and 5). The funnel chart is basically symmetrical, suggesting that the publication bias may be small.

3.5. Subgroup analysis

We performed a subgroup analysis based on the mean age of each study. The studies were divided by mean age into an elderly group (mean age of the included population ≥ 65) and a non-elderly group (mean age of the included population < 65). In the lacune-related subgroup analysis, the OR values of hypertension, diabetes, and smoking in the elderly group were higher than those in the non-elderly group (Fig. 9), in which hyperlipidemia and drinking were not included because of insufficient literature. The results showed that hypertension, diabetes, and smoking were more closely associated with lacune in the elderly group

compared to the non-elderly group, which implies that age is an important influencing factor for lacune. In the subgroup analysis of WMH, the OR values of hypertension, hyperlipidemia, smoking, and drinking in the elderly group were higher than those in the non-elderly group (Fig. 10A-D), while the OR value of diabetes in the elderly group was lower than that in the non-elderly group (Fig. 10E). The results showed that hypertension, hyperlipidemia, smoking, and drinking were more closely associated with WMH in the elderly group compared to the nonelderly group. This subgroup analysis proves that the older the age, the stronger the effect of each risk factor on CSVD, so we should take measures to control it at an early stage.

4. Discussion

CSVD is a kind of neurodegenerative disease, which refers to brain parenchymal damage related to pathological changes in the distal pia mater and cerebral blood vessels. Epidemiology shows that about a quarter of ischemic strokes are caused by cerebral small vessel disease, which accounts for 83.8% of all cerebrovascular diseases.^[8] CSVD is an important contributor to stroke, dyskinesia, cognitive, and affective disorders, but its onset is insidious, mostly in a resting state, and has not been paid attention to in clinical practice, with a poor prognosis.^[9] Previously, some studies have reported that CSVD is related to many risk factors, such as age, cardiovascular risk factors, inflammation, kidney disease, infection and so on,^[10-13] but the results are not entirely consistent. We chose 5 common factors from them and proved that hypertension, diabetes, hyperlipidemia, and smoking are the risk factors of lacune and WMH while drinking is not. At present, the pathogenesis of CSVD is still unclear, and there is a lack of unified and effective treatment plan.

	Study or Subgroup	Lacu Events	ne Total	Cont	Total	Weight	Odds Ratio M-H. Random, 95% C		Odds Ratio M-H, Random, 95% Cl
	1.6.1 Mean age ≥65 Christian Kukla 1998	32	61	15	57	8 3%	3 09 11 42 6 701		
	Vasileios-Arsenios Lioutas 2017	100	118	219	354	9.7%	3.42 [1.98, 5.91]		
	Y. Leira 2016	33	62	20	60	8.5%	2.28 [1.09, 4.74]		
	Yoshitomo Notsu 1999	108	147	52	214	10.1%	8.63 [5.33, 13.96]		
	Subtotal (95% CI)	079	388	200	685	36.6%	3.95 [2.12, 7.37]		
	Heterogeneity: $Tau^2 = 0.30$; $Chi^2 = Test$ for overall effect: $Z = 4.31$ (P	= 12.23, df < 0.0001)	= 3 (P	= 0.007);	² = 75	%			
	1.6.2 Mean age <65	1.22	1212	1	Visio	1 North 1			200
	Fei Li 2019	433	702	131	234	11.0%	1.27 [0.94, 1.71]		T
	KI-Woong Nam 2018 会据于 2012	92	106	616	2885	11.1%	2.02 [1.54, 2.64]		
	准欣 2011	28	50	10	42	7.5%	4.07 [1.65, 10.05]		
	王洪津 2003	44	52	8	30	6.4%	15.13 [5.01, 45.69]		
	聚志静 2010	55	65	38	60	7.8%	3.18 [1.36, 7.48]		
	邓可 2007	76	105	119	322	10.1%	4.47 [2.76, 7.25]		
	Subtotal (95% CI)	902	1340	074	36/3	03.4%	2.90 [1.85, 4.74]		
	Heterogeneity: $Tau^2 = 0.30$; $Chi^2 =$ Test for overall effect: $Z = 4.51$ (P	= 35.72, df < 0.00001	= 6 (P	< 0.0000	1); P =	83%			
	Total (95% CI)		1728		4358	100.0%	3.32 [2.20, 5.02]		•
	Total events	1076	12.112	1280					
A	Heterogeneity: Tau ² = 0.38; Chi ² = Test for overall effect: Z = 5.69 (P Test for suboroup differences: Chi	= 66.71, df < 0.00001 i ² = 0.53. c	= 10 (F l) ff = 1 (F	e < 0.000 e = 0.47).	01); i ² = i ² = 0%	= 85%		0.02	0.1 1 10 50 Favours Lacune Favours Control
		Lacu	ne	Cont	rol		Odds Ratio		Odds Ratio
	Study or Subgroup 1.7.1 Mean age ≥65	Events	Total	Events	Total	Weight	M-H, Random, 95% C		M-H. Random, 95% Cl
	Christian Kukla 1998	8	61	7	57	5.2%	1.08 [0.36, 3.19]		
	Vasileios-Arsenios Lioutas 2017	39	118	35	354	11.9%	4.50 [2.68, 7.56]		
	Y. Leira 2016	15	62	6	60	5.6%	2.87 [1.03, 8.00]		
	Yoshitomo Notsu 1999	16	147	22	214	9.3%	1.07 [0.54, 2.11]		
	Total events	78	300	70	003	32.170	2.03 [0.08, 4.03]		A CONTRACTOR OF A
	Heterogeneity: $Tau^2 = 0.53$; $Chi^2 = Test$ for overall effect: $Z = 1.68$ (P	= 13.35, df = 0.09)	= 3 (P	= 0.004);	² = 78	%			
	1.7.2 Mean age <65								
	Fei Li 2019	281	702	77	234	15.8%	1.36 [1.00, 1.86]		
	Ki-Woong Nam 2018	59	260	377	2885	15.8%	1.95 [1.43, 2.66]		
	余辉云 2012	36	106	20	100	10.0%	2.06 [1.09, 3.88]		
	王洪津 2003	13	52	6	30	5.1%	1.33 [0.45, 3.98]		
	梁志静 2010	29	65	16	60	8.4%	2.22 [1.04, 4.70]		
	邓可 2007	12	105	19	322	8.3%	2.06 [0.96, 4.40]		
	Subtotal (95% CI)		1340		3673	67.9%	1.79 [1.44, 2.23]		
	Total events Heterogeneity: $Tau^2 = 0.01$; $Chi^2 =$ Test for overall effect: Z = 5.25 (P	447 = 6.91, df = < 0.00001	= 6 (P = 1)	0.33); l ²	= 13%				
	Total (95% CI)		1728		4358	100.0%	1.99 [1.49, 2.66]		•
	Total events Heterogeneity: Tau ² = 0.11; Chi ² =	525 = 22.61, df	= 10 (F	589	² = 56	%		-	
в	Test for overall effect: Z = 4.66 (P Test for subaroup differences: Chi	< 0.0000 (1 ² = 0.08. c	l) # = 1 (F	9 = 0.77).	12 = 0%			0.05	0.2 1 5 20 Favours Lacune Favours Control
		Lacu	ne	Cont	lor		Odds Ratio		Odds Ratio
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C		M-H, Random, 95% Cl
	Christian Kukla 1998	18	61	11	57	7.3%	1.75 10.74. 4 131		
	Vasileios-Arsenios Lioutas 2017	25	118	35	354	11.1%	2.45 [1.40, 4.30]		
	Y. Leira 2016	28	62	11	60	7.7%	3.67 [1.61, 8.36]		
	Yoshitomo Notsu 1999	57	147	73	214	13.2%	1.22 [0.79, 1.89]		
	Total events	120	388	120	685	38.3%	1.96 [1.21, 3.23]		
	Heterogeneity: Tau ² = 0.14; Chi ² = Test for overall effect: Z = 2.73 (P	= 7.05, df = = 0.006)	= 3 (P =	0.07); 12	= 57%				
	1.8.2 Mean age <65								-
	Fei Li 2019	149	702	43	234	14.2%	1.20 [0.82, 1.74]		
	Ki-Woong Nam 2018	34	260	452	2885	14.3%	0.81 [0.56, 1.18]		
	催成 2011 工業第 2003	24	50	16	42	7.5%	1.50 [0.65, 3.45]		
	愛志静 2010	20	65	4	50	7.0%	2.52 [1.04, 6.09]		
	邓可 2007	44	105	129	322	13.0%	1.08 [0.69, 1.69]		
	Subtotal (95% CI)		1234		3573	60.7%	1.24 [0.90, 1.72]		-
	Total events	288	E /D	653	- 400				
	Test for overall effect: Z = 1.30 (P	= 0.19)	- 5 (P =	0.09); 1*	- 46%				
	Total (95% CI)	1973	1622	-	4258	100.0%	1.52 [1.13, 2.05]		•
	Heterogeneity: Tau ² = 0.13: Chi ² =	416 22.85 df	= 9 (P	= 0.007	12 = 61	%		-	1 1
~	Test for overall effect: Z = 2.77 (P	= 0.006)	- off	0.001),	01			0.05	0.2 1 5 20 Favours Lacune Favours Control

C Test for suboroup differences: Chi² = 2.43. df = 1 (P = 0.12). I^2 = 58.8%

Figure 9. (A) Forest plots showing the relationship between hypertension and lacune in different mean age groups. (B) Forest plot showing the relationship between diabetes and lacune in different mean age. (C) Forest plot showing the relationship between smoking and lacune in different mean age. CI=confidence interval.

Some studies reported that patients with moderate or severe WMH are highly likely to continue to progress, whereas patients with milder baseline CSVD showed slight progress in 9 years,^[14] which also shows from the side the importance of prevention. Regular examination and timely correction of the 4 risk factors of hypertension, diabetes, hyperlipidemia, and smoking in healthy people can prevent the occurrence of CSVD. Traditionally, the progress of CSVD is regarded as a continuous and gradual process, but recent studies have shown that the progress of CSVD is nonlinear, accelerated with the passage of time,^[15] and is a

study or subgroup	Europha	Tetal	Evente	Total	Malaht	M H Bandem OFW CI	NU Bandam 05% Cl
1 44 4 Maan ana > CI	Evenus	Iotal	Evenus	IOtal	weight	M-H, Kandom, 95% CI	M-H, Rangom, 95% Ci
1.11.1 Mean age = 03	,						· · · · · · · · · · · · · · · · · · ·
B. Censori 2007	45	61	52	117	5.3%	3.52 [1.79, 6.92]	
Dirk sander 2000	48	82	52	145	6.3%	2.52 [1.45, 4.40]	
并红阳 2008	89	158	52	158	7.2%	2.63 [1.66, 4.15]	
吉等 2014	27	36	14	36	3.3%	4.71 [1.72, 12.93]	
五秀君 2011	377	509	301	509	9.1%	1.97 [1.51, 2.57]	
習鼎华 2013	81	113	15	28	4.2%	2.19 [0.94, 5.12]	
李庆华 2002	41	69	25	69	5.2%	2.58 [1.30, 5.12]	
肚芳 2019	50	65	13	30	3.7%	4.36 [1.73, 10.99]	
乐奕农 2015	74	106	7	31	3.7%	7.93 [3.10, 20.27]	
东玲 2014	71	102	25	61	5.4%	3.30 [1.70, 6.39]	
黄新民 2005	113	144	22	102	5.8%	13.26 [7.15, 24.56]	
Subtotal (95% CI)		1445		1286	59.4%	3.56 [2.47, 5.13]	
Total events	1016		578				
Heterogeneity: Tau ² = 1	0.26; Chi ²	= 38.8	5, df = 10	(P<0	.0001); l ² :	= 74%	
Test for overall effect: 2	Z = 6.80 (I	P<0.0	0001)				
.11.2 Mean age < 65	5						
laigiang Jin 2020	77	240	0	61	0.6%	58.30 (3.56 955 08)	· · · · · · · · · · · · · · · · · · ·
Ding Lin 2017	1505	2732	607	1951	10 1%	2.72 [2.40 .3.07]	-
Kueving Yu 2018	245	370	162	384	8 8%	2 51 [1 87 3 36]	
从兩年 2016	120	241	35	104	7 0%	2 31 [1.07, 3.30]	
时间 7 2010	155	102	167	415	7 7%	6 06 M 04 0 001	
二十 2001	50	106	26	106	6 304	2 44 [1 40 4 25]	
Euptotal (95% CI)	38	3801	30	3021	40.6%	3 09 12 25 4 231	•
Fatal aveata	0474	5031	1007	5021	40.070	0.00 [2.20, 4.20]	
Test for overall effect: 2	Z = 6.98 (= 20.3	2, ar = 5 (0001)	P=0.0	JU1); I* = 7	5%	
Fotal (95% Ci)		5336		4307	100.0%	3.31 [2.65, 4.14]	•
Fotal (95% CI) Total events	3187	5336	1585	4307	100.0%	3.31 [2.65, 4.14]	•
Total (95% CI) Total events Heterogeneity: Tau ² = 1	3187 0.12; Chi ²	5336 = 59.2	1585 2, df = 16	4307 (P < 0	100.0% .00001); I ²	3.31 [2.65, 4.14] = 73%	◆ 0.05 0.2 1 5
Total (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2	3187 0.12; Chi ² Z = 10.52	5336 = 59.2 (P < 0.	1585 2, df = 16 00001)	4307 (P < 0	100.0% .00001); I ^s	3.31 [2.65, 4.14] = 73%	0.05 0.2 1 5 Favours WMH Favours Control
Fotal (95% CI) Fotal events Heterogeneity: Tau ² = (Fest for overall effect: 2 Fest for suborouo diffe	3187 0.12; Chi ² Z = 10.52 rences: C	5336 = 59.2 (P < 0. hi ² = 0.1	1585 2, df = 16 00001) 34. df = 1	4307 (P < 0 (P = 0	100.0% .00001); l ² .56). l ² = 0	3.31 [2.65, 4.14] = 73% %	0.05 0.2 1 5 Favours WMH Favours Control
Fotal (95% CI) Fotal events Heterogeneity: Tau ² = (Fest for overall effect: 2 Fest for suborouo diffe	3187 0.12; Chi ² Z = 10.52 rences: C	5336 = 59.2 (P < 0. hi ² = 0.1	1585 2, df = 16 00001) 34. df = 1 Contr	4307 (P < 0 (P = 0	100.0% .00001); l² .56). l² = 0	3.31 [2.65, 4.14] = 73% % Odds Ratio	0.05 0.2 1 5 Favours WMH Favours Control
Fotal (95% CI) Fotal events Heterogeneity: Tau ² = (Fest for overall effect: 2 Fest for subaroup diffe Study or Subaroup	3187 0.12; Chi ² Z = 10.52 rences: C WMI Events	5336 = 59.2 (P < 0.) hi ² = 0.3	1585 2, df = 16 00001) 34. df = 1 Contr Events	4307 (P < 0 (P = 0 rol Total	100.0% .00001); ² .56). ² = 0 Weight	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random, 95% Cl
Fotal (95% CI) Fotal events Heterogeneity: Tau ² = (Fest for overall effect: 2 Fest for suboroup differ Study or Subgroup	3187 0.12; Chi ² Z = 10.52 rences: C WMI- <u>Events</u>	5336 = 59.2 (P < 0.) hi ² = 0.3 I Total	1585 2, df = 16 00001) 34. df = 1 Contr Events	4307 (P < 0 (P = 0 rol Total	100.0% .00001); ² .56). ² = 0 <u>Weight</u>	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random. 95% Cl
Fotal (95% CI) Fotal events Heterogeneity: Tau ² = (Fest for overall effect: 2 Fest for suboroup differ Study or Subgroup I.13.1 Mean age ≥ 65	3187 0.12; Chi ² Z = 10.52 rences: C WMI- <u>Events</u> 5	5336 = 59.2 (P < 0.) hi ² = 0.3 1 Total	1585 2, df = 16 00001) 34. df = 1 Contr Events	4307 (P < 0 (P = 0 rol Total	100.0% .00001); I ² .56). I ² = 0 <u>Weight</u> 15.7%	3.31 [2.65, 4.14] = 73% % Odds Ratio <u>M-H. Random, 95% CI</u> 1 23 (0 79, 1 91)	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random. 95% Cl
Fotal (95% CI) Fotal events Heterogeneity: Tau ² = (Fest for overall effect: 2 Fest for suboroup diffe Study or Subgroup I.13.1 Mean age ≥ 65 并红酮 2008 苯定粉 2002	3187 0.12; Chi ² Z = 10.52 rences: C WMI- <u>Events</u> 5 76 22	5336 = 59.2 (P < 0.) hi ² = 0.1 I Total	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17	4307 (P < 0 (P = 0 rol <u>Total</u> 158 60	100.0% .00001); ² .56). ² = 0 <u>Weight</u> 15.7% 13.2%	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI 1.23 [0.79, 1.91] 1.43 [0.68, 3.02]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random. 95% Cl
Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 1 Fest for overall effect: 2 Fest for subgroup differ Study or Subgroup I.13.1 Mean age ≥ 65 尹红丽 2008 李庆华 2002 李庆华 2004	3187 0.12; Chi ² Z = 10.52 rences: C WMI- Events 5 76 22 59	5336 = 59.2 (P < 0. hi ² = 0. 1 Total 158 69 102	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24	4307 (P < 0 (P = 0 rol Total 158 69	100.0% .00001); ² .56). ² = 0 <u>Weight</u> 15.7% 13.2% 14.1%	3.31 [2.65, 4.14] = 73% % Odds Ratio <u>M-H. Random, 95% CI</u> 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.82]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random, 95% Cl
Fotal (95% CI) Fotal events Heterogeneity: Tau ² = I Fest for overall effect: 2 Fest for subgroup differ Study or Subgroup I.13.1 Mean age ≥ 65 并红酮 2008 李庆华 2002 陈玲 2014 黄新母 2005	3187 0.12; Chi ² Z = 10.52 rences: C WMI- <u>Events</u> 5 76 22 58 8	5336 = 59.2 (P < 0. hi ² = 0.3 1 Total 158 69 102 144	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24	4307 (P < 0 (P = 0 rol Total 158 69 61	100.0% .00001); ² .56). ² = 0 <u>Weight</u> 15.7% 13.2% 14.1%	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.88] 9 32 [4 84 17 64]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random. 95% Cl
Fotal (95% CI) Fotal events Heterogeneity: Tau ² = (Fest for overall effect: 2 Fest for subgroup differ Study or Subgroup I.13.1 Mean age ≥ 65 伊红丽 2008 李庆华 2002 陈玲 2014 黄新民 2005 Subtotal (95% CI)	3187 0.12; Chi ² Z = 10.52 rences: C WMH <u>Events</u> 5 76 22 58 86	5336 = 59.2 (P < 0.) hi ² = 0.3 1 Total 158 69 102 144 473	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24 14	4307 6 (P < 0 (P = 0 rol Total 158 69 61 102 390	100.0% .00001); ² .56). ² = 0 <u>Weight</u> 15.7% 13.2% 14.1% 14.0% 56 9 ⁴	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.88] 9.32 [4.84, 17.94] 2.38 [n.96 5.62]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random. 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Test for subgroup I.13.1 Mean age ≥ 65 伊红爾 2008 李庆华 2002 称玲 2014 質新長 2005 Subtotal (95% CI)	3187 0.12; Chi ² Z = 10.52 rences: C WMH <u>Events</u> 5 76 22 58 86	5336 = 59.2 (P < 0.) hi ² = 0.3 1 Total 158 69 102 144 473	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24 14	4307 6 (P < 0 (P = 0 rol Total 158 69 61 102 390	100.0% .00001); I ² .56). I ² = 0 <u>Weight</u> 15.7% 13.2% 14.1% 14.0% 56.9%	3.31 [2.65, 4.14] = 73% % Odds Ratio <u>M-H. Random, 95% CI</u> 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.88] 9.32 [4.84, 17.94] 2.38 [0.96, 5.92]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random. 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Test for subgroup 1.13.1 Mean age ≥ 65 伊红丽 2008 李庆华 2002 练玲 2014 黄新民 2005 Subtotal (95% CI) Total events	3187 0.12; Chi ² Z = 10.52 rences: C WMH Events 5 76 22 58 86 86 242 0.76; Chi ²	5336 = 59.2 (P < 0.) hi ² = 0.3 1 Total 158 69 102 144 473 - 26 7	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24 14 14	4307 (P < 0 (P = 0 rol 158 69 61 102 390	100.0% .00001); I ² .56). I ² = 0 <u>Weight</u> 15.7% 13.2% 14.1% 14.0% 56.9%	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.88] 9.32 [4.84, 17.94] 2.38 [0.96, 5.92]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random. 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Test for suboroup differ Study or Subgroup 1.13.1 Mean age ≥ 65 伊红丽 2008 李庆华 2002 陈玲 2014 黄新民 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2	3187 0.12; Chi ² Z = 10.52 rences: C WMH Events 5 76 22 58 86 242 242 0.76; Chi ² Z = 1.87 (l	5336 = 59.2 (P < 0.) hi ² = 0.3 1 Total 158 69 102 144 473 = 26.7 P = 0.0	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24 14 123 2, df = 3 (6)	4307 (P < 0 (P = 0 rol 158 69 102 390 (P < 0.0	100.0% .00001); ² .56). ² = 0 <u>Weight</u> 15.7% 13.2% 14.1% 14.0% 56.9%	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.88] 9.32 [4.84, 17.94] 2.38 [0.96, 5.92] = 89%	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random. 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 Test for subgroup 1.13.1 Mean age ≥ 65 伊红間 2008 李庆艳 2002 称玲 2014 黄新民 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2	3187 0.12; Chi ² Z = 10.52 rences: C WMH Events 5 76 22 58 86 242 0.76; Chi ² Z = 1.87 (I	5336 = 59.2 (P < 0.) hi ² = 0.3 I Total 158 69 102 144 473 = 26.7 P = 0.0	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24 14 123 2, df = 3 (6)	4307 (P < 0 (P = 0 Total 158 69 61 102 390 (P < 0.0	100.0% .00001); ² .56), ² = 0 <u>Weight</u> 15.7% 13.2% 14.1% 14.0% 56.9%	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.88] 9.32 [4.84, 17.94] 2.38 [0.96, 5.92] = 89%	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = 1 Fest for overall effect: 2 Fest for subgroup I.13.1 Mean age ≥ 65 #紅爾 2008 李庆华 2002 嫁玲 2014 黄新民 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Fest for overall effect: 2 I.13.2 Mean age < 65	3187 0.12; Chi ² Z = 10.52 rences: C WMH Events 5 76 22 58 86 242 0.76; Chi ² Z = 1.87 (I	5336 = 59.2 (P < 0. hi ² = 0.3 1 Total 158 69 102 144 473 = 26.7 P = 0.0	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24 14 123 2, df = 3 (6)	4307 (P < 0 (P = 0 rol 158 69 61 102 390 (P < 0.0	100.0% .00001); ² .56), ² = 0 <u>Weight</u> 15.7% 13.2% 14.1% 14.0% 56.9%	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.88] 9.32 [4.84, 17.94] 2.38 [0.96, 5.92] = 89%	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random. 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Fest for subgroup I.13.1 Mean age ≥ 65 伊紅爾 2008 李庆华 2002 弥玲 2014 黄新民 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 I.13.2 Mean age < 65 Haiqiang Jin 2020	3187 0.12; Chi ² Z = 10.52 rences: C WMH Events 5 76 22 58 86 242 2.76; Chi ² Z = 1.87 (1 5 63	5336 = 59.2 (P < 0. hi ² = 0.3 1 Total 158 69 102 144 473 = 26.7 P = 0.0 240	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24 14 123 2, df = 3 (6)	4307 (P < 0 (P = 0 rol 158 69 61 102 390 (P < 0.0	100.0% .00001); ² .56). ² = 0 <u>Weight</u> 15.7% 13.2% 14.1% 14.0% 56.9% 00001); ²	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.88] 9.32 [4.84, 17.94] 2.38 [0.96, 5.92] = 89% 2.06 [0.96, 4.41]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random. 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 Fest for subgroup I.13.1 Mean age ≥ 65 伊红爾 2008 李庆华 2002 称玲 2014 黄新長 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Fest for overall effect: 2 I.13.2 Mean age < 65 Haiqiang Jin 2020 孙丽伟 2016	3187 0.12; Chi ² Z = 10.52 rences: C WMH Events 5 76 22 58 86 242 0.76; Chi ² Z = 1.87 (1 5 63 119	5336 = 59.2 (P < 0.) hi ² = 0.3 1 Total 158 69 102 144 473 = 26.7 P = 0.0 240 241	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24 14 123 2, df = 3 6) 9 54	4307 (P < 0 (P = 0 rol 158 69 61 102 390 (P < 0.0 61 104	100.0% .00001); ² .56). ² = 0 <u>Weight</u> 15.7% 13.2% 14.1% 14.0% 56.9% 00001); ² 13.1% 15.5%	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.88] 9.32 [4.84, 17.94] 2.38 [0.96, 5.92] = 89% 2.06 [0.96, 4.41] 0.90 [0.57, 1.43]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random. 95% Cl
Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 1 Fest for overall effect: 2 Fest for subgroup 1.13.1 Mean age ≥ 65 ##11 Mean age ≥ 65 ##12 Mean age < 65	3187 0.12; Chi ² Z = 10.52 rences: C WMH Events 5 76 22 58 86 242 0.76; Chi ² Z = 1.87 (I 5 63 119 36	5336 = 59.2 (P < 0. hi ² = 0.3 1 158 69 102 144 473 = 26.7 P = 0.0 240 241 106	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24 14 123 2, df = 3 6) 9 54 27	4307 (P < 0 (P = 0 Total 158 69 61 102 390 (P < 0.0 61 104 104 106	100.0% .00001); ² .56). ² = 0 <u>Weight</u> 15.7% 13.2% 14.1% 14.0% 56.9% 00001); ² 13.1% 15.5% 14.5%	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.88] 9.32 [4.84, 17.94] 2.38 [0.96, 5.92] = 89% 2.06 [0.96, 4.41] 0.90 [0.57, 1.43] 1.50 [0.83, 2.72]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random. 95% Cl
Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 1 Fest for overall effect: 2 Fest for subgroup 1.13.1 Mean age ≥ 65 伊紅蘭 2008 李庆华 2002 蘇玲 2014 質新民 2005 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 1 Fest for overall effect: 2 1.13.2 Mean age < 65	3187 0.12; Chi ² Z = 10.52 rences: C WMH Events 5 76 22 58 86 242 0.76; Chi ² Z = 1.87 (I 5 63 119 36	5336 = 59.2 (P < 0. hi ² = 0.3 1 Total 158 69 102 144 473 = 26.7 P = 0.0 240 241 106 587	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24 14 123 2, df = 3 8) 9 54 27	4307 (P < 0 (P = 0 rol 158 69 61 102 390 (P < 0.0 61 104 106 271	100.0% .00001); ² .56). ² = 0 <u>Weight</u> 15.7% 13.2% 14.1% 14.0% 56.9% 00001); ² 13.1% 15.5% 14.5% 43.1%	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H, Random, 95% CI 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.88] 9.32 [4.84, 17.94] 2.38 [0.96, 5.92] = 89% 2.06 [0.96, 4.41] 0.90 [0.57, 1.43] 1.50 [0.83, 2.72] 1.31 [0.81, 2.12]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random, 95% Cl
Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 1 Fest for overall effect: 2 Fest for subgroup 1.13.1 Mean age ≥ 65 #### 2008 学庆华 2002 旅玲 2014 賞新民 2005 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 1 Fest for overall effect: 2 I.13.2 Mean age < 65	3187 0.12; Chi ² Z = 10.52 rences: C WMH Events 5 76 22 58 86 242 0.76; Chi ² Z = 1.87 (I 5 63 119 36 218	5336 = 59.2 (P < 0. hi ² = 0.3 1 158 69 102 144 473 = 26.7 P = 0.0 240 241 106 587	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24 14 123 2, df = 3 6) 9 54 27 90	4307 (P < 0 (P = 0 rol 158 69 61 102 390 (P < 0.0 (P < 0.0 (P < 0.0) 61 104 106 271	100.0% .00001); ² .56), ² = 0 <u>Weight</u> 15.7% 13.2% 14.1% 14.0% 56.9% 00001); ² 13.1% 15.5% 14.5% 43.1%	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.88] 9.32 [4.84, 17.94] 2.38 [0.96, 5.92] = 89% 2.06 [0.96, 4.41] 0.90 [0.57, 1.43] 1.50 [0.83, 2.72] 1.31 [0.81, 2.12]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random, 95% Cl
Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 1 Fest for overall effect: 2 Fest for subgroup 1.13.1 Mean age ≥ 65 #### 2008 学庆华 2002 旅玲 2014 賞新民 2005 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 1 1.13.2 Mean age < 65	3187 0.12; Chi ² Z = 10.52 rences: C WMH Events 5 76 22 58 86 242 0.76; Chi ² Z = 1.87 (I 63 119 36 218 0.09; Chi ² Z = 1.12 (I	5336 = 59.2 (P < 0. hi ² = 0.3 1 158 69 102 144 473 = 26.7 P = 0.0 240 241 106 587 = 3.92 P = 0.2	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24 14 123 2, df = 3 6 β) 9 54 27 90 , df = 2 (F δ)	4307 (P < 0 (P = 0 rol 158 69 61 102 390 (P < 0.0 (P < 0.0 61 104 104 271 P = 0.14	100.0% .00001); ² .56), ² = 0 <u>Weight</u> 15.7% 13.2% 14.1% 14.0% 56.9% 00001); ² 13.1% 15.5% 14.5% 14.5% 14.5%	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.88] 9.32 [4.84, 17.94] 2.38 [0.96, 5.92] = 89% 2.06 [0.96, 4.41] 0.90 [0.57, 1.43] 1.50 [0.83, 2.72] 1.31 [0.81, 2.12]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random, 95% Cl
Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 1 Fest for overall effect: 2 Fest for subgroup 1.13.1 Mean age ≥ 65 伊紅蘭 2008 学庆华 2002 旅玲 2014 貸新民 2005 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 65 Haiqiang Jin 2020 外雨特 2016 王菲 2001 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 1 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 1 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 1 Fest for overall effect: 2 Fotal events Heterogeneity: Tau ² = 1 Fest for overall effect: 2 Fotal (95% CI)	3187 0.12; Chi ² Z = 10.52 rences: C WMH Events 5 76 22 58 86 242 0.76; Chi ² Z = 1.87 (I 5 63 119 36 218 0.09; Chi ² Z = 1.12 (I	5336 = 59.2 (P < 0. hi ² = 0.3 1 Total 158 69 102 144 473 = 26.7 P = 0.0 240 241 106 587 = 3.92 P = 0.2 1060	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24 14 123 2, df = 3 (6) 9 54 27 90 , df = 2 (F 6)	4307 (P < 0 (P = 0 rol Total 158 69 61 102 390 (P < 0.0 61 104 106 271 P = 0.14 661	100.0% .00001); ² .56). ² = 0 <u>Weight</u> 15.7% 13.2% 14.1% 14.0% 56.9% 00001); ² 13.1% 15.5% 14.5% 43.1% 43.1%	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.88] 9.32 [4.84, 17.94] 2.38 [0.96, 5.92] = 89% 2.06 [0.96, 4.41] 0.90 [0.57, 1.43] 1.50 [0.83, 2.72] 1.31 [0.81, 2.12] 6	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random. 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = 1 Fest for overall effect: 2 Test for subgroup 1.13.1 Mean age ≥ 65 伊紅爾 2008 李庆埠 2002 陈玲 2014 質新民 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 1.13.2 Mean age < 65	3187 0.12; Chi ² Z = 10.52 rences: C WMH Events 5 76 22 58 86 242 0.76; Chi ² Z = 1.87 (I 5 63 119 36 218 0.09; Chi ² Z = 1.12 (I	5336 = 59.2 (P < 0. hi ² = 0.3 1 Total 158 69 102 144 473 = 26.7 P = 0.0 240 241 106 587 = 3.92 P = 0.2	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24 14 123 2, df = 3 6 8) 9 54 27 90 , df = 2 (F 8)	4307 (P < 0 (P = 0 rol 158 69 61 102 390 (P < 0.0 61 104 106 271 P = 0.14 661	100.0% .00001); ² .56), ² = 0 <u>Weight</u> 15.7% 13.2% 14.1% 14.0% 56.9% 00001); ² 13.1% 15.5% 14.5% 43.1% 43.1% 43.1%	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.88] 9.32 [4.84, 17.94] 2.38 [0.96, 5.92] = 89% 2.06 [0.96, 4.41] 0.90 [0.57, 1.43] 1.50 [0.83, 2.72] 1.31 [0.81, 2.12] 6 1.88 [1.08, 3.25]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = 1 Fest for overall effect: 2 Fest for subgroup 1.13.1 Mean age ≥ 65 伊紅蘭 2008 学庆华 2002 旅玲 2014 黄新民 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 1.13.2 Mean age < 65	3187 0.12; Chi ² Z = 10.52 rences: C WMH Events 5 76 22 58 86 242 0.76; Chi ² Z = 1.87 (I 63 119 36 218 0.09; Chi ² Z = 1.12 (I 460 0.45; Chi ²	5336 = 59.2 (P < 0. hi ² = 0.3 1 Total 158 69 102 144 473 = 26.7 P = 0.0 240 241 106 587 = 3.92 P = 0.2 1060 = 36.2	1585 2, df = 16 00001) 34. df = 1 Contr Events 68 17 24 14 123 2, df = 3 6 8) 9 54 27 90 , df = 2 (F 6) 213 9 df = 6	4307 (P < 0 (P = 0 rol 158 69 61 102 390 (P < 0.0 (P < 0.0 61 104 104 104 271 P = 0.14 661 (P < 0.0	100.0% .00001); ² .56), ² = 0 <u>Weight</u> 15.7% 13.2% 14.1% 14.0% 56.9% 14.0% 56.9% 14.5% 14.5% 43.1% 43.1% 43.1% 43.1%	3.31 [2.65, 4.14] = 73% % Odds Ratio M-H. Random, 95% CI 1.23 [0.79, 1.91] 1.43 [0.68, 3.02] 2.03 [1.07, 3.88] 9.32 [4.84, 17.94] 2.38 [0.96, 5.92] = 89% 2.06 [0.96, 4.41] 0.90 [0.57, 1.43] 1.50 [0.83, 2.72] 1.31 [0.81, 2.12] 6 1.88 [1.08, 3.25] = 83%	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random. 95% Cl

B Test for subaroup differences: $Chi^2 = 1.29$. df = 1 (P = 0.26). $l^2 = 22.3\%$

Figure 10. (A) Forest plots showing the relationship between hypertension and WMH in different mean age groups. (B) Forest plot showing the relationship between hyperlipidemia and WMH in different mean age. (C) Forest plots showing the relationship between smoking and WMH in different mean age groups. (D) Forest plot showing the relationship between drinking and WMH in different mean age. (E) Forest plots showing the relationship between diabetes and WMH in different mean age groups. CI = confidence interval, WMH = white matter hyperintensity.

highly dynamic procedure.^[16] Therefore, for patients with CSVD, we should control the risk factors at an early stage in time to slow down the development of CVSD. For now,

antihypertensive therapy is one of the most effective methods to alleviate CSVD,^[17] while anticoagulation, antiplatelet therapy, and lipid-regulating therapy are currently lacking sufficient

	WMH	1	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random. 95% Cl	M-H. Random, 95% Cl
1.14.1 Mean age ≥ 65	5	0.5	1.003	1000		11 - 12 - 12 - 12 - 12 - 12 - 12 - 12 -	10 C
B. Censori 2007	7	61	29	117	5.6%	0.39 [0.16, 0.96]	
唐搴 2014	25	36	14	36	5.1%	3.57 [1.35, 9.47]	
孟秀 君 2011	213	509	176	509	9.1%	1.36 [1.06, 1.75]	
曾鼎华 2013	94	113	4	28	4.3%	29.68 [9.23, 95.42]	
李庆华 2002	16	69	14	69	6.0%	1.19 [0.53, 2.67]	
杜芳 2019	19	65	8	30	5.2%	1.14 [0.43, 3.00]	
陈奕农 2015	14	106	5	31	4.5%	0.79 [0.26, 2.40]	
陈玲 2014	40	102	8	61	5.8%	4.27 [1.84, 9.93]	the second se
黄新民 2005 Subtotal (95% CI)	79	144	26	102	7.5%	3.55 [2.04, 6.18]	
Total events	507		284				
Heterogeneity: Tau ² = 0 Test for overall effect: 2	0.70; Chi² Z = 2.31 (I	= 53.29 P = 0.02	9, df = 8 (2)	(P < 0.0	00001); l² :	= 85%	
1.14.2 Mean age < 65	5						
Haigiang Jin 2020	48	240	12	61	6.6%	1.02 [0.50, 2.07]	
Qing Lin 2017	847	2732	398	1951	9.5%	1.75 [1.53, 2.01]	-
Xueving Yu 2018	90	379	108	384	8.8%	0.80 [0.58, 1.10]	+
孙丽伟 2016	41	241	24	104	7 5%	0.68 [0.39 1 20]	
封红亭 2017	13	193	36	415	6.9%	0.76 [0.39 1 47]	
王菲 2001	41	106	32	106	7 4%	1 46 [0 83 2 58]	+
Subtotal (95% CI)	41	3891	32	3021	46.8%	1.04 [0.68, 1.59]	•
Total events	1080		610			the fareat treat	
Heterogeneity: Tau ² = 0 Test for overall effect: 2	0.21; Chi ² Z = 0.18 (I	= 31.94 P = 0.86	4, df = 5 (3)	(P < 0.0	00001); l² :	= 84%	
Total (95% CI)		5096		4004	100.0%	1.48 [1.07, 2.04]	•
Total (95% CI) Total events	1587	5096	894	4004	100.0%	1.48 [1.07, 2.04]	•
Total (95% CI) Total events Heterogeneity: Tau ² = 0	1587 0.28: Chi ²	5096 = 86.84	894 4. df = 14	4004	100.0%	1.48 [1.07, 2.04]	· · ·
Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2	1587 0.28; Chi ² Z = 2.36 (l	5096 = 86.84 P = 0.02	894 4, df = 14 2)	4004 (P < 0	100.0% .00001); I ²	1.48 [1.07, 2.04] = 84%	0.05 0.2 1 5
Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Test for subgroup differ	1587 0.28; Chi ² Z = 2.36 (I rences: C	5096 = 86.84 P = 0.02 bl ² = 3.2	894 4, df = 14 2) 24. df = 1	4004 (P < 0. (P = 0.	100.0% .00001); l ² .07), l ² = 6	1.48 [1.07, 2.04] = 84% C 9.1%	0.05 0.2 1 5 Favours WMH Favours Control
Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Test for suboroup differ	1587 0.28; Chi² Z = 2.36 (I rences: C	5096 = 86.84 P = 0.02 hi ² = 3.2	894 4, df = 14 2) 24. df = 1	4004 (P < 0. (P = 0.	100.0% .00001); l ² .07). l ² = 6	1.48 [1.07, 2.04] = 84% 50 9.1%	0.05 0.2 1 5 Favours WMH Favours Control
Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Test for suboroup differ	1587 0.28; Chi ² Z = 2.36 (I rences: C WMH	5096 = 86.84 P = 0.02 hi ² = 3.2	894 4, df = 14 2) 24. df = 1 Contr	4004 (P < 0. (P = 0.	100.0% .00001); l ² .07). l ² = 6	1.48 [1.07, 2.04] = 84% 6 9.1% Odds Ratio	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio
Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Test for suboroup differ	1587 0.28; Chi ² Z = 2.36 (I rences: C WMI- <u>Events</u>	5096 = 86.84 P = 0.02 hi ² = 3.2 H Total	894 4, df = 14 2) 24. df = 1 Contr Events	4004 (P < 0. (P = 0. rol Total	100.0% .00001); i ² .07). i ² = 6 <u>Weight</u>	1.48 [1.07, 2.04] = 84% 6 9.1% Odds Ratio <u>M-H, Random, 95% Cl</u>	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: 2 Test for suboroup differ <u>Study or Subgroup</u> 1,15,1 Mean age ≥ 65	1587 0.28; Chi ² Z = 2.36 (I rences: C WMI- <u>Events</u> 5	5096 = 86.84 P = 0.02 hi ² = 3.2 1 Total	894 4, df = 14 2) 24. df = 1 Contr Events	4004 (P < 0. (P = 0. rol Total	100.0% .00001); I ² .07). I ² = 6 <u>Weight</u>	1.48 [1.07, 2.04] = 84% 6 9.1% Odds Ratio <u>M-H. Random, 95% Cl</u>	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Test for suboroup differ <u>Study or Subgroup</u> 1.15.1 Mean age ≥ 65 唐孝 2014	1587 0.28; Chi ² Z = 2.36 (I rences: C WMI <u>Events</u> 5 23	5096 = 86.84 P = 0.02 hi ² = 3.2 H Total 36	894 4, df = 14 2) 24. df = 1 Contr <u>Events</u> 16	4004 (P < 0) (P = 0) rol Total 38	100.0% .00001); l ² .07). l ² = 6 <u>Weight</u> 9.2%	1.48 [1.07, 2.04] = 84% 0 9.1% Odds Ratio <u>M-H. Random, 95% Cl</u> 2.21 [0.86, 5.69]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Test for suboroup differ <u>Study or Subgroup</u> 1.15.1 Mean age ≥ 65 唐孝 2014 孟秀君 2011	1587 0.28; Chi ² Z = 2.36 (I rences: C WMI- <u>Events</u> 5 23 150	5096 = 86.84 P = 0.02 hi ² = 3.2 1 <u>Total</u> 36 509	894 4, df = 14 2) 24. df = 1 Contr <u>Events</u> 16 119	4004 (P < 0) (P = 0) rol Total 36 509	100.0% .00001); l ² .07). l ² = 6 <u>Weight</u> 9.2% 19.7%	1.48 [1.07, 2.04] = 84% 9.1% Odds Ratio M-H. Random. 95% Cl 2.21 [0.86, 5.69] 1.37 [1.03, 1.81]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Test for subgroup differ <u>Study or Subgroup</u> 1.15.1 Mean age ≥ 65 唐攀 2014 孟秀君 2011 陈玲 2014	1587 0.28; Chi ² Z = 2.36 (I rences: C WMI- <u>Events</u> 5 23 150 34	5096 = 86.84 P = 0.02 hi ² = 3.2 1 Total 36 509 102	894 4, df = 14 2) 24. df = 1 Contr <u>Events</u> 16 119 15	4004 (P < 0. (P = 0. rol <u>Total</u> 36 509 61	100.0% .00001); l ² .07). l ² = 6 <u>Weight</u> 9.2% 19.7% 12.3%	1.48 [1.07, 2.04] = 84% 9.1% Odds Ratio M-H, Random, 95% Cl 2.21 [0.86, 5.69] 1.37 [1.03, 1.81] 1.53 [0.75, 3.13]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Test for subaroup differ <u>Study or Subgroup</u> 1.15.1 Mean age ≥ 65 唐攀 2014 孟秀君 2011 陈玲 2014 黄新民 2005	1587 0.28; Chi ² Z = 2.36 (I rences: C WMI- <u>Events</u> 5 23 150 34 48	5096 = 86.84 P = 0.02 hi ² = 3.2 fl Total 36 509 102 144	894 4, df = 14 2) 24. df = 1 Contr <u>Events</u> 16 119 15 9	4004 (P < 0. (P = 0. Total 36 509 61 102	100.0% .00001); l ² .07). l ² = 6 <u>Weight</u> 9.2% 19.7% 12.3% 11.5%	1.48 [1.07, 2.04] = 84% b 9.1% Odds Ratio M-H. Random. 95% CI 2.21 [0.86, 5.69] 1.37 [1.03, 1.81] 1.53 [0.75, 3.13] 5.17 [2.40, 11.12]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random. 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Test for subgroup 1.15.1 Mean age ≥ 65 唐孝 2014 孟秀君 2011 陈玲 2014 黄新民 2005 Subtotal (95% CI)	1587 0.28; Chi ² Z = 2.36 (I rences: C WMI- <u>Events</u> 5 23 150 34 48	5096 = 86.84 P = 0.02 hi ² = 3.2 1 Total 36 509 102 144 791	894 4, df = 14 2) 24. df = 1 Contr <u>Events</u> 16 119 15 9	4004 (P < 0. (P = 0. Total 36 509 61 102 708	100.0% .00001); l ² .07). l ² = 6 <u>Weight</u> 9.2% 19.7% 12.3% 11.5% 52.8%	1.48 [1.07, 2.04] = 84% 6 9.1% Odds Ratio M-H, Random, 95% Cl 2.21 [0.86, 5.69] 1.37 [1.03, 1.81] 1.53 [0.75, 3.13] 5.17 [2.40, 11.12] 2.09 [1.15, 3.81]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random, 95% Cl
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Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Test for suboroup differ <u>Study or Subgroup</u> 1.15.1 Mean age ≥ 65 唐攀 2014 黄莽見 2014 黄新見 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 1.15.2 Mean age < 65 Haiqiang Jin 2020 Qing Lin 2017 孙丽伟 2016 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Total events Heterogeneity: Tau ² = (Total sevents Heterogeneity: Tau ² = (Total (95% CI)	1587 0.28; Chi ² Z = 2.36 (I rences: C 23 150 34 48 255 0.26; Chi ² Z = 2.41 (I 5 5 5 6 211 35 302 0.00; Chi ² Z = 0.94 (I	5096 = 86.84 P = 0.02 hi ² = 3.2 1 Total 36 509 102 144 791 = 10.62 P = 0.02 240 2732 241 3213 = 0.500 P = 0.33 4004	894 4, df = 14 2) 24. df = 1 Contr Events 16 119 5 9 7, df = 3 (2) 13 165 18 196 df = 2 (F 5)	4004 (P < 0. (P = 0. rol Total 36 509 61 102 708 (P = 0.0 61 1951 104 2116 P = 0.78 2824	100.0% .00001); ² .07). ² = 6 .07). ² = 72 .12.8% .20.6% .13.8% .47.2% .3); ² = 0% .100.0%	1.48 [1.07, 2.04] = 84% 6 9.1% Odds Ratio M-H, Random, 95% CI 2.21 [0.86, 5.69] 1.37 [1.03, 1.81] 1.53 [0.75, 3.13] 5.17 [2.40, 11.12] 2.09 [1.15, 3.81] % 1.12 [0.57, 2.22] 0.91 [0.73, 1.12] 0.81 [0.44, 1.51] 0.91 [0.75, 1.11] 1.41 [0.97, 2.05]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Test for suboroup differ <u>Study or Subgroup</u> 1.15.1 Mean age ≥ 65 唐攀 2014 黄寿程 2011 陈玲 2014 黄新民 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 1.15.2 Mean age < 65 Haiqiang Jin 2020 Qing Lin 2017 孙弼伟 2016 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Total (95% CI) Total events	1587 0.28; Chi ² Z = 2.36 (I rences: C Events 5 23 150 34 48 255 0.26; Chi ² Z = 2.41 (I 5 5 56 211 35 302 0.00; Chi ² Z = 0.94 (I 557	5096 = 86.84 P = 0.02 hi ² = 3.2 1 Total 36 509 102 144 791 = 10.62 P = 0.02 240 2732 241 3213 = 0.50, P = 0.33	894 4, df = 14 24. df = 1 Contr Events 16 119 15 9 7, df = 3 (2) 13 165 18 196 df = 2 (F 5) 355	4004 (P < 0. (P = 0. Total 36 509 61 102 708 (P = 0.0 61 1951 104 2116 P = 0.78 2824	100.0% .00001); ² = 6 .07). ² = 6 .02% .03% .01); ² = 72 .02% .01); ² = 72 .02% .03% .01); ² = 72 .02% .03% .03% .04%	1.48 [1.07, 2.04] = 84% b 9.1% Odds Ratio M-H, Random, 95% CI 2.21 [0.86, 5.69] 1.37 [1.03, 1.81] 1.53 [0.75, 3.13] 5.17 [2.40, 11.12] 2.09 [1.15, 3.81] % 1.12 [0.57, 2.22] 0.91 [0.73, 1.12] 0.81 [0.44, 1.51] 0.91 [0.75, 1.11] 1.41 [0.97, 2.05]	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random, 95% Cl
Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Test for subgroup 1.15.1 Mean age ≥ 65 唐孝 2014 孟秀君 2011 陈玲 2014 黄新民 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 1.15.2 Mean age < 65 Haiqiang Jin 2020 Qing Lin 2017 孙丽伟 2016 Subtotal (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Total events Heterogeneity: Tau ² = (Test for overall effect: 2 Total (95% CI) Total events Heterogeneity: Tau ² = (Total (95% CI) Total events Heterogeneity: Tau ² = (Test for overall effect: 2	1587 0.28; Chi ² Z = 2.36 (I rences: C WMI Events 5 23 150 34 48 255 0.26; Chi ² Z = 2.41 (I 5 56 211 35 302 0.00; Chi ² Z = 0.94 (I 557 0.17; Chi ² Z = 1.78 (I	5096 = 86.84 P = 0.02 hi ² = 3.2 1 Total 36 509 102 144 791 = 10.62 P = 0.02 240 2732 241 3213 = 0.50, P = 0.33 4004 = 24.82 P = 0.02	894 4, df = 14 24. df = 1 Contr Events 16 119 15 9 7, df = 3 (2) 13 165 18 196 df = 2 (F 5) 3555 2, df = 6 (7)	4004 (P < 0. (P = 0. Total 36 509 61 102 708 (P = 0.0 61 1951 104 2116 P = 0.78 2824 (P = 0.0	100.0% .00001); ² .07). ² = 6 <u>Weight</u> 9.2% 19.7% 12.3% 11.5% 52.8% 01); ² = 72 12.8% 20.6% 13.8% 47.2% 8); ² = 0% 100.0%	1.48 [1.07, 2.04] = 84% b 9.1% Odds Ratio M-H, Random, 95% CI 2.21 [0.86, 5.69] 1.37 [1.03, 1.81] 1.53 [0.75, 3.13] 5.17 [2.40, 11.12] 2.09 [1.15, 3.81] % 1.12 [0.57, 2.22] 0.91 [0.73, 1.12] 0.81 [0.44, 1.51] 0.91 [0.75, 1.11] 1.41 [0.97, 2.05] 76% b	0.05 0.2 1 5 Favours WMH Favours Control Odds Ratio M-H. Random, 95% Cl

evidence to support them. Our results also support this view that there is a great correlation between hypertension and CSVD. Besides, in our study, hyperlipidemia is also a risk factor for CSVD, which provides evidence for lipid-modifying therapy.

Epidemiological investigations show that the older the age, the higher the incidence of CSVD.^[4] In the subgroup analysis stratified by mean age, the OR value of the elderly group is basically higher than that of the non-elderly group, indicating that the older people are more likely to suffer from CSVD under the same exposure



factors, which supports the above view. One exception to this is that in the meta-analysis related to WMH, the OR of diabetic patients in the elderly group was smaller than in the non-elderly group. For this result, we have 2 speculations: The insufficient number or quality of included studies. In one of the studies among the non-elderly group, no one in the control group had diabetes, which made its OR value much larger than any other study, thus pulling up the OR of the non-elderly group. There may be some unknown association between age, WMH, and diabetes. From an overall perspective, drinking cannot be considered as a risk factor for CSVD, because their *P* values are all greater than .05, which is not statistically significant. However, subgroup analysis showed that in the elderly group, drinking is a risk factor for WMH (OR = 2.09; 95% CI 1.15-3.81; P=.02). The pathways by which drinking leads to CSVD may be that ethanol directly stimulates the blood vessel wall, causing it to lose elasticity, making it inelastic, and the intermediate metabolite of ethanol in the body, acetaldehyde, has a strong lipid peroxidation reaction and toxicity, which can damage the vascular endothelial system.^[18] As alcohol consumption and drinking years increase, its destructive effect enhances, which may partly explain the results of the subgroup analysis. Therefore, further studies are needed to determine whether drinking is a risk factor for CSVD.

4.1. Advantages and limitations

Most studies on risk factors for CSVD use the method of casecontrol study to specifically assess the relationship between a

factor and CSVD through multifactorial regression analysis.^[19] For the first time, we choose the method of meta-analysis to analyze the risk factors of CSVD, which can synthesize the existing research and draw a more reasonable conclusion.^[20] Secondly, we included multiple studies with a total of 16,587 participants to illustrate the relationship between hypertension, diabetes, hyperlipidemia, smoking, alcohol consumption, and CSVD, which is impossible in a single-center study. Finally, in the course of our research, we discovered some new questions (such as what is the target blood pressure for antihypertensive treatment? Is diabetic retinopathy related to CSVD? Is drinking vears related to CSVD?), which pointed out the direction for further research. Yet, this meta-analysis also has some limitations. Clear definitions of smoking and drinking were not given in the respective studies, which may lead to inaccurate OR. Although we used a random effects model to try to avoid the effect of heterogeneity,^[21] there was still significant heterogeneity and no obvious source of heterogeneity was found. In addition, most of the included studies are in China, but the prevalence of CSVD in China is higher than average. A survey in 4 Chinese cities reported that lacune accounted for 42.3% of ischemic strokes, higher than the 25% to 30% reported in many international studies.^[22] Because of the large proportion of Chinese studies, the overall OR will be large and closer to the level of the Chinese population. The included studies are all retrospective studies, and causality cannot be determined, large prospective studies are needed to prove our conclusions.

5. Conclusion

Our study proves that hypertension, diabetes, hyperlipidemia, and smoking are risk factors for CSVD. We should pay attention to these factors and control them early, which has a positive effect on delaying the development of CSVD.

Author contributions

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