Systematic Review and Meta-Analysis

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Risk factors of cerebral small vessel disease

A systematic review and meta-analysis

Zheng Wang, BS, Qin Chen, MD, Jiajie Chen, MS, Ni Yang, MS, Kai Zheng, MD, PhD*

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

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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 $I^2 \geq 50$, 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.

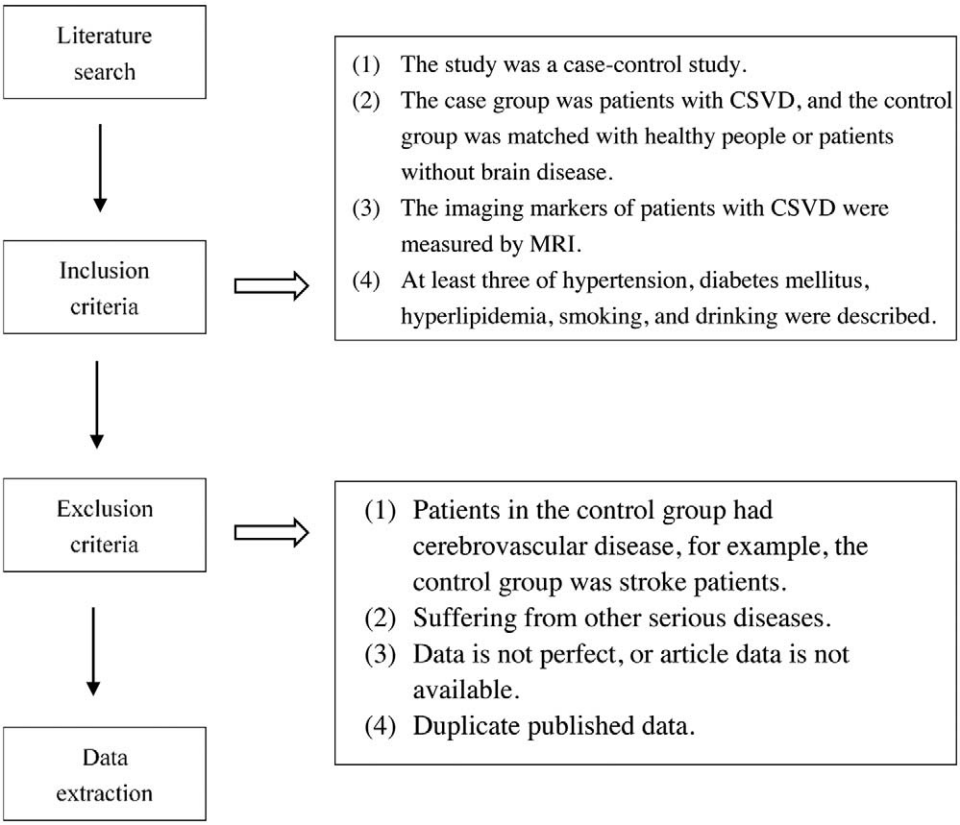

Figure 1. The process of literature screening and data extraction.

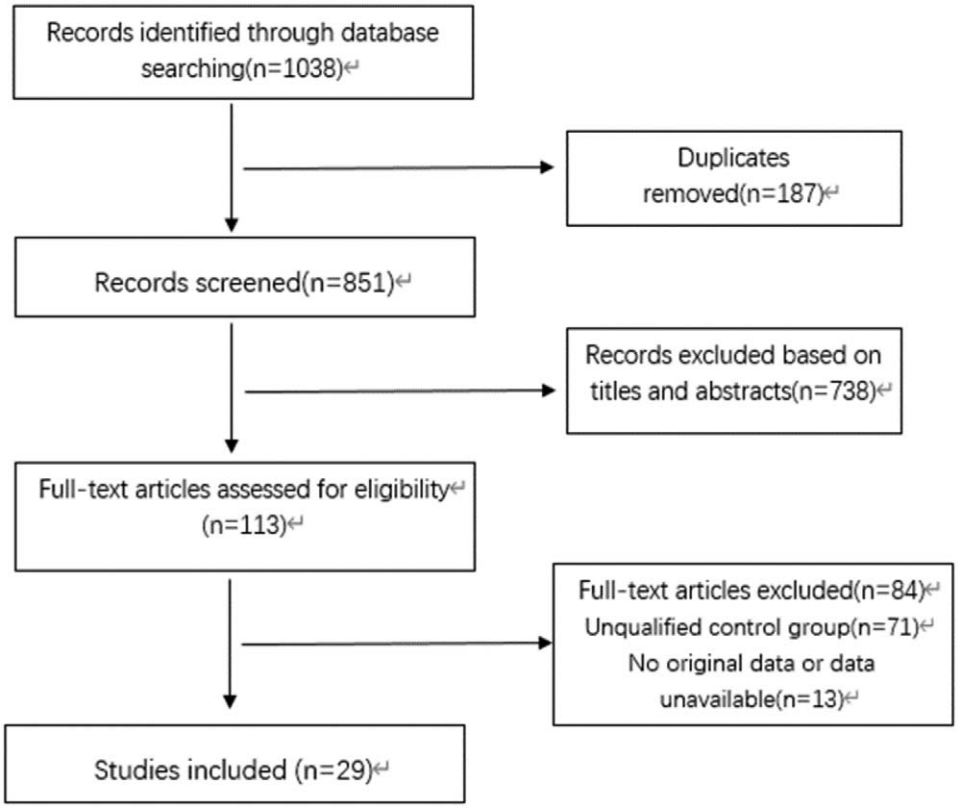

Figure 2. Flow chart of the systematic search process.

Table 1

Baseline characteristics of all included studies in our meta-analysis.

First author, year	Group (number)	Hypertension Yes/no	Diabetes Yes/no	Hyperlipidemia Yes/no	Smoking Yes/no	Drinking 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	
Fei Li 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	
Ki-Woong Nam 2018	Lacune (n = 260)	92/168	59/201	70/190	34/226	119/141	<65
	Control (n = 2885)	616/2269	377/2508	733/2152	452/2433	1406/1479	
Vasileios-Arsenios Lioutas 2017	Lacune (n = 118)	100/18	39/79	N	25/93	N	≥65
	Control (n = 354)	219/135	35/319	N	35/319	N	
Y. Leira 2016	Lacune (n = 62)	33/29	15/47	26/36	28/34	15/47	≥65
	Control (n = 60)	20/40	6/54	11/49	11/49	6/52	
Yoshitomo Notsu 1999	Lacune (n = 147)	108/39	16/131	N	57/90	N	≥65
	Control (n = 214)	52/162	22/192	N	73/141	N	
Xin Cui 2011	Lacune (n = 50)	28/22	17/33	N	24/26	N	<65
	Control (n = 42)	10/32	4/38	N	16/26	N	
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	N	17/35	N	<65
	Control (n = 30)	8/22	6/24	N	4/26	N	
Huiyun Yu 2012	Lacune (n = 106)	75/31	36/70	42/64	N	N	<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
	Control (n = 322)	119/203	19/303	N	129/193	81/241	
Haiqiang Jin 2020	WMH (n = 240)	77/163	13/227	63/177	48/192	56/184	<65
	Control (n = 61)	0/61	0/61	9/52	12/49	13/48	
Qing Lin 2017	WMH (n = 2732)	1505/1227	763/1969	N	847/1885	211/2521	<65
	Control (n = 1951)	607/1344	339/1612	N	398/1553	165/1786	
Xueying Yu 2018	WMH (n = 379)	245/134	39/340	N	90/289	N	<65
	Control (n = 384)	162/222	30/354	N	108/276	N	
B. Censori 2007	WMH (n = 61)	45/16	9/52	12/49	7/54	N	≥65
	Control (n = 117)	52/65	13/104	21/96	29/88	N	
Dirk Sander 2000	WMH (n = 82)	48/34	10/72	N	N	N	≥65
	Control (n = 145)	52/93	18/127	N	N	N	
Hongliang Feng 2017	WMH (n = 193)	155/38	43/150	N	13/180	N	<65
	Control (n = 415)	167/248	57/358	N	36/379	N	
Dinghua Zeng 2013	WMH (n = 113)	81/32	15/98	N	94/19	N	≥65
	Control (n = 28)	15/13	2/26	N	4/24	N	
Xiujun Meng 2011	WMH (n = 509)	377/132	142/367	N	213/296	150/359	≥65
	Control (n = 509)	301/208	126/383	N	176/333	119/390	
Fang Du 2019	WMH (n = 65)	50/15	N	N	19/46	N	≥65
	Control (n = 30)	13/17	N	N	8/22	N	
Yinong Chen 2015	WMH (n = 106)	74/32	12/94	N	14/92	N	≥65
	Control (n = 31)	7/24	3/28	N	5/26	N	
Hongli Yi 2008	WMH (n = 158)	89/69	43/115	76/82	N	N	≥65
	Control (n = 158)	52/106	38/120	68/90	N	N	
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	N	≥65
	Control (n = 69)	25/44	13/56	17/52	14/55	N	
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
	Control (n = 36)	14/22	13/23	N	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	

N = not available, WMH = white matter hyperintensity.

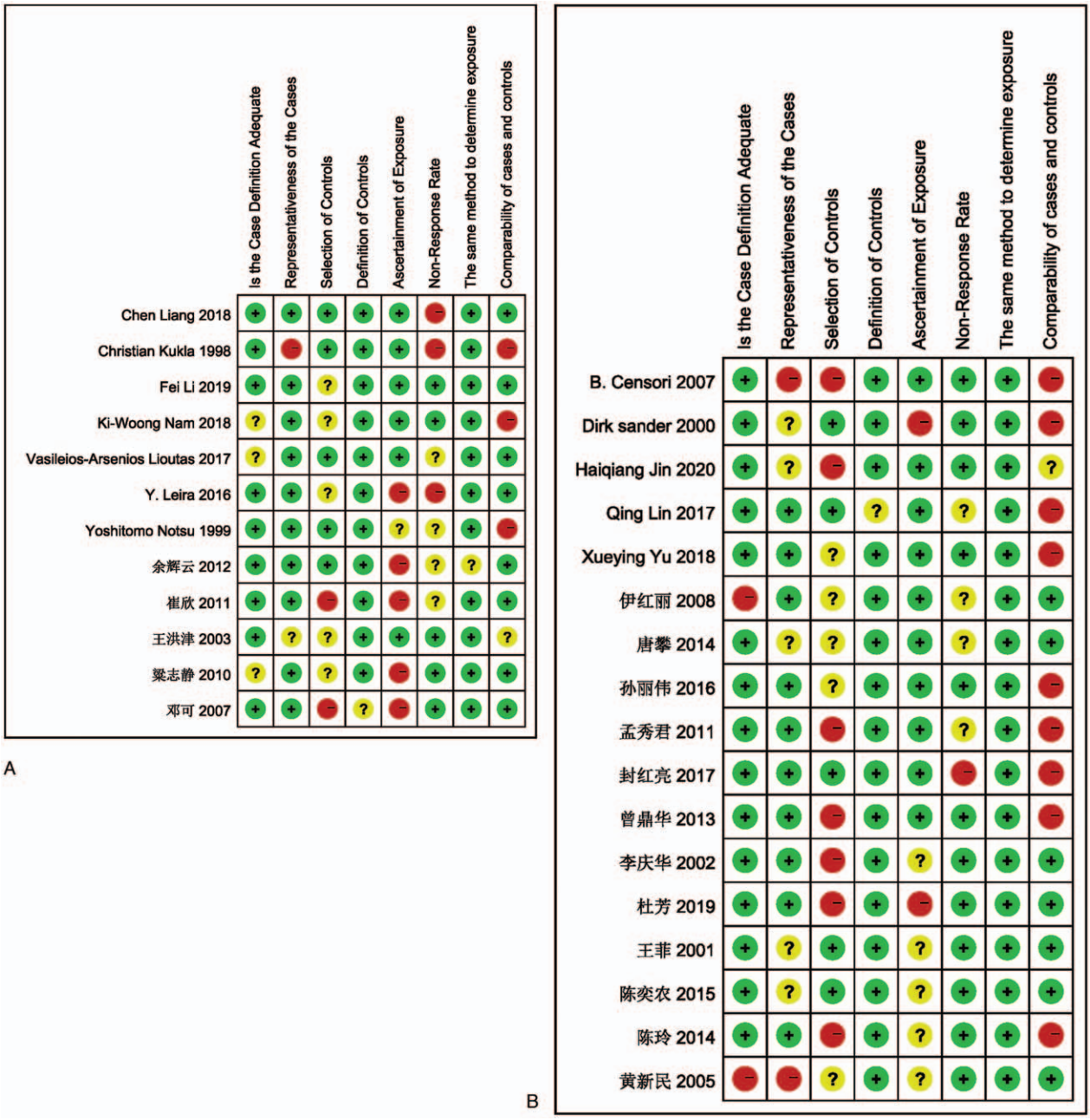

Figure 3. (A) Quality evaluation about risk factors of the lacune. (B) Quality evaluation about risk factors of the WMH.

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).

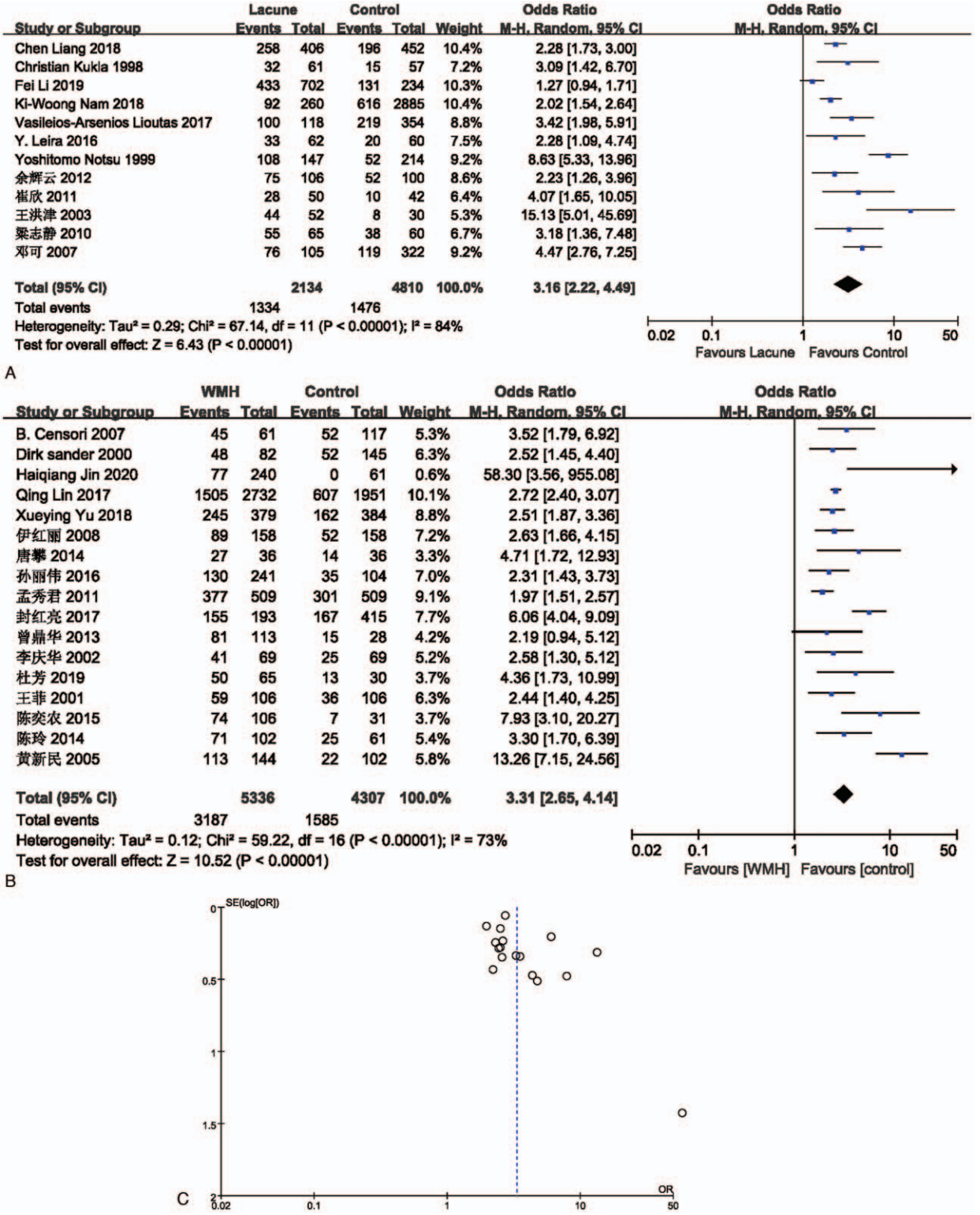

Figure 4. (A) Forest plot showing the relationship between hypertension and lacune. (B) Forest plot showing the relationship between hypertension and WMH. (C) Funnel plot of hypertension on WMH. CI = confidence interval, WMH = white matter hyperintensity.

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).

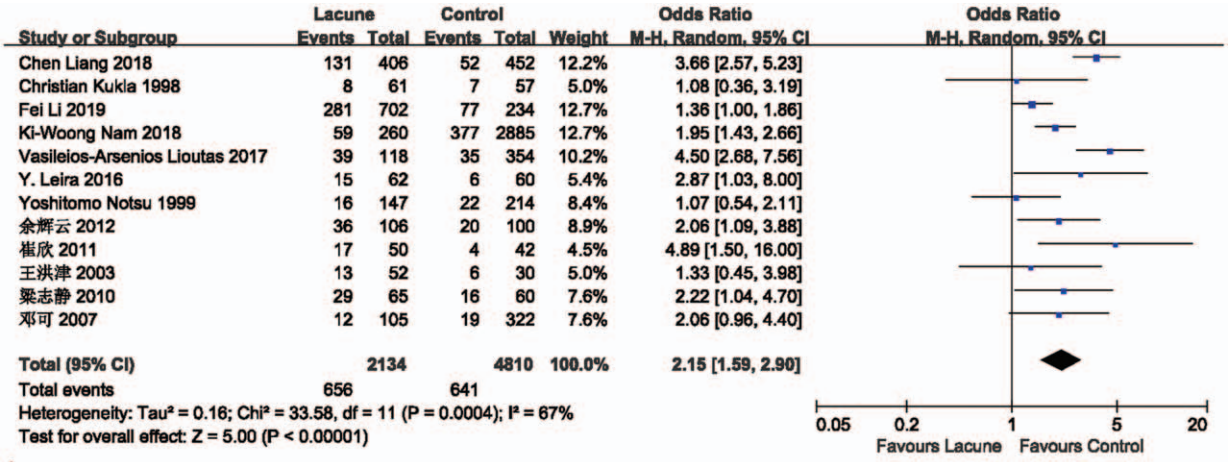

Figure 5. (A) Forest plot showing the relationship between diabetes and lacune. (B) Forest plot showing the relationship between diabetes and WMH. (C) Funnel plot of diabetes on WMH. CI = confidence interval, WMH = white matter hyperintensity.

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).

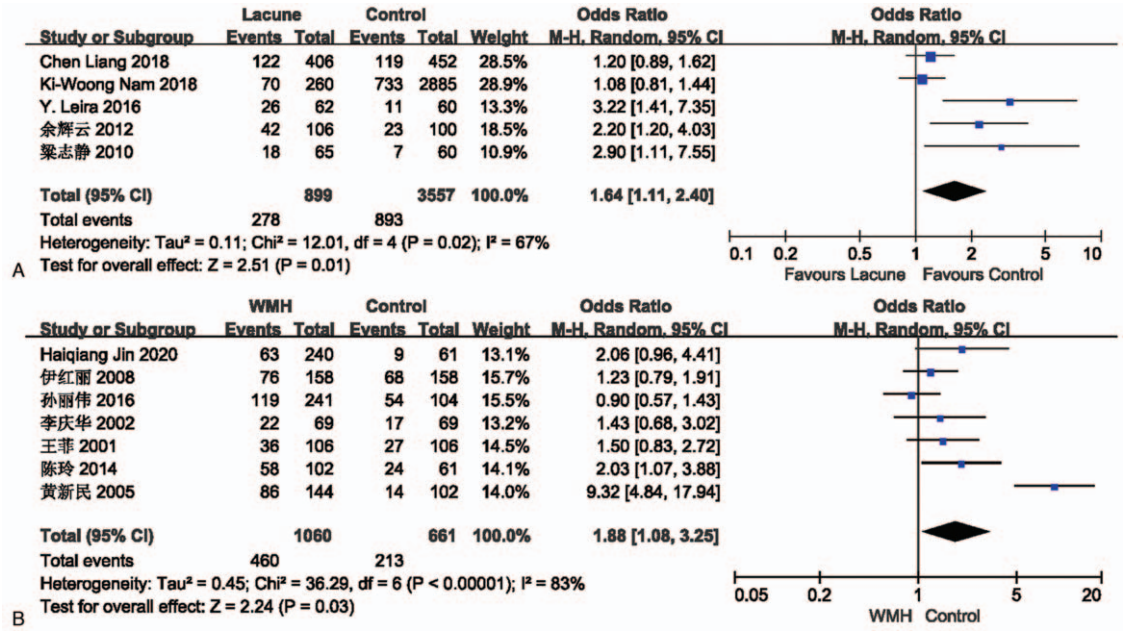

Figure 6. (A) Forest plot showing the relationship between hyperlipidemia and lacune. (B) Forest plot showing the relationship between hyperlipidemia and WMH. CI = confidence interval, WMH = white matter hyperintensity.

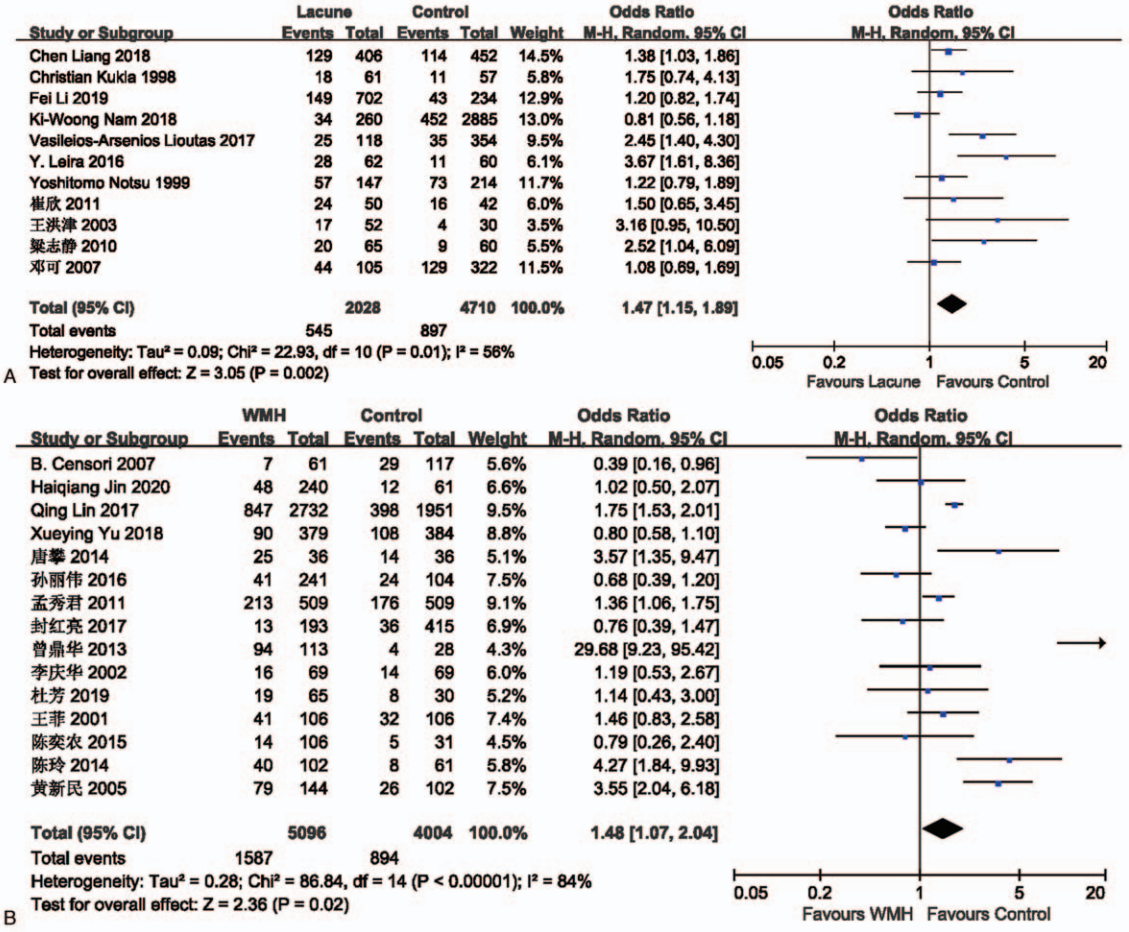

Figure 7. (A) Forest plot showing the relationship between smoking and lacune. (B) Forest plot showing the relationship between smoking and WMH. CI = confidence interval, WMH = white matter hyperintensity.

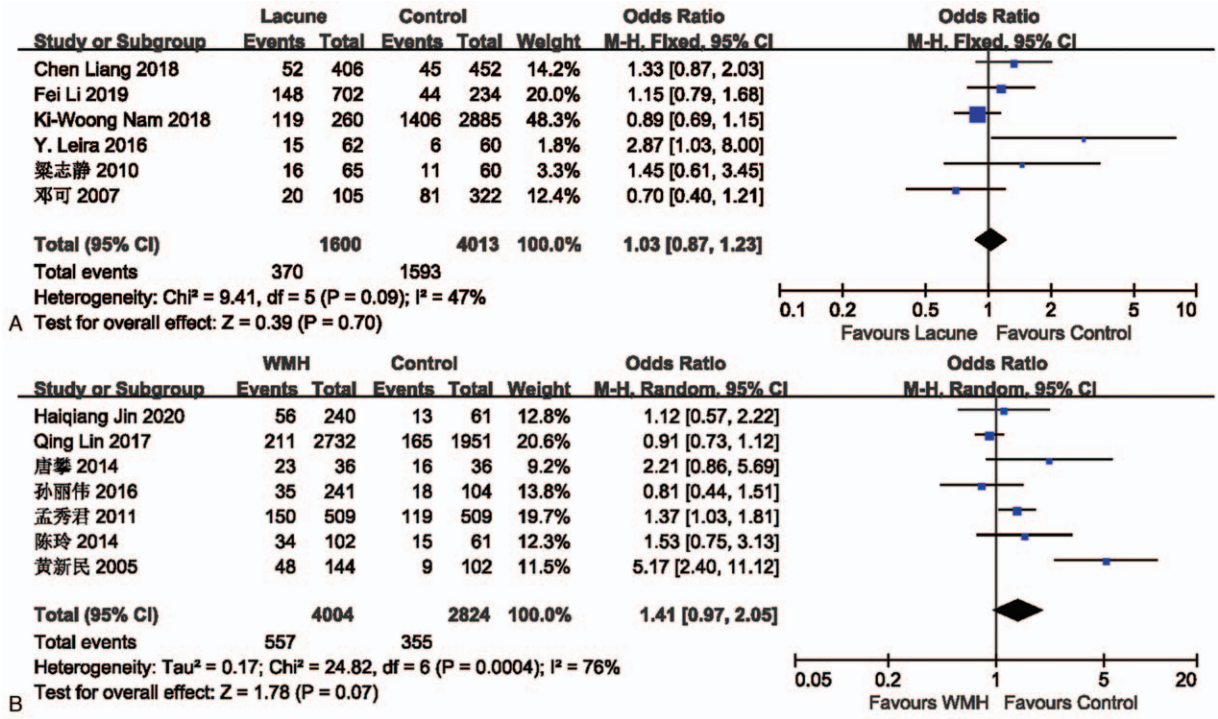

Figure 8. (A) Forest plot showing the relationship between drinking and lacune. (B) Forest plot showing the relationship between drinking and WMH. CI = confidence interval, WMH = white matter hyperintensity.

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 non-elderly 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.

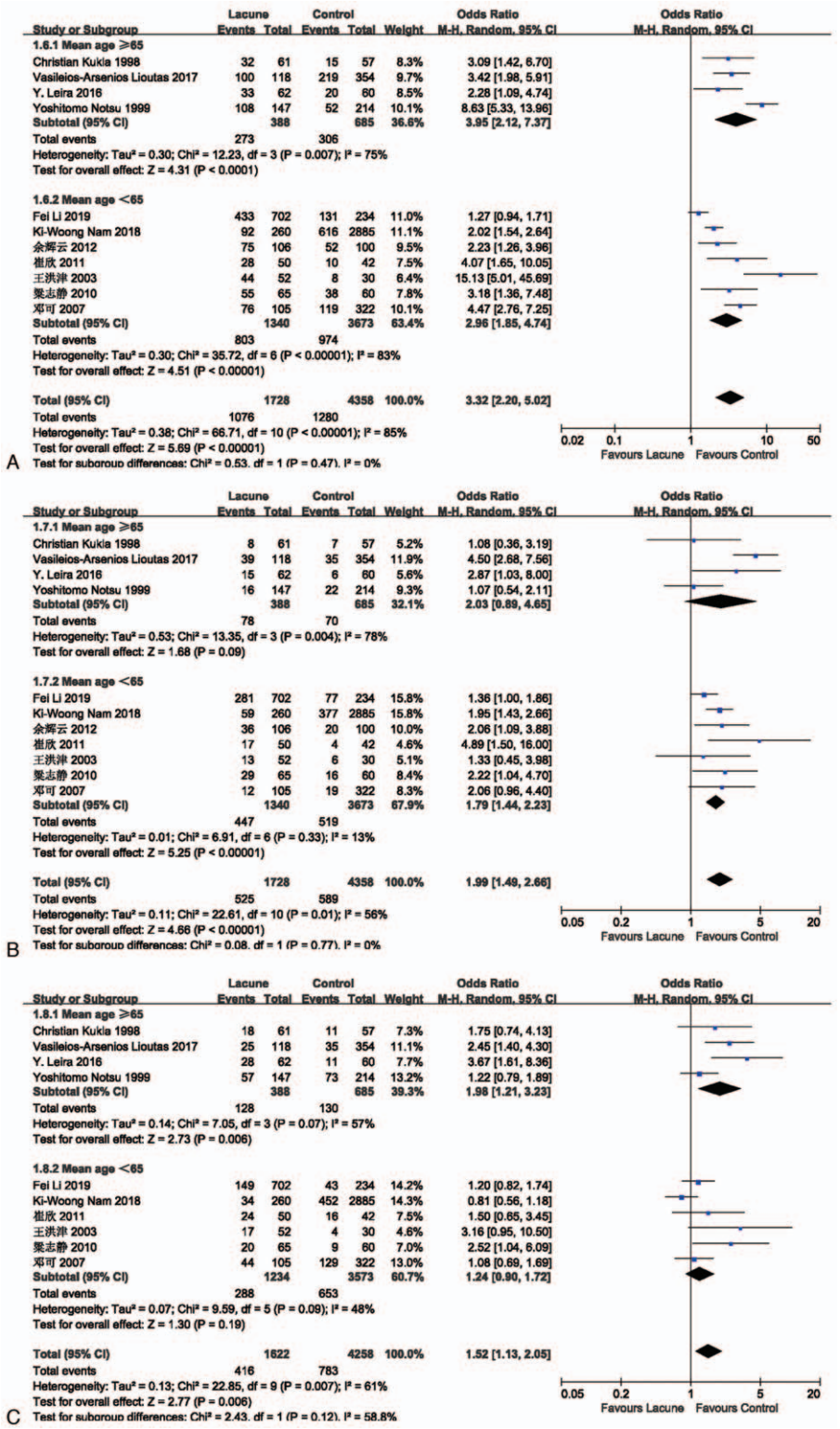

Figure 9. (A) Forest plots showing the relationship between hypertension and lacune in different mean age groups. (B) Forest plot showing the relationship between diabetes and lacune in different mean age. (C) Forest plot showing the relationship between smoking and lacune in different mean age. CI =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

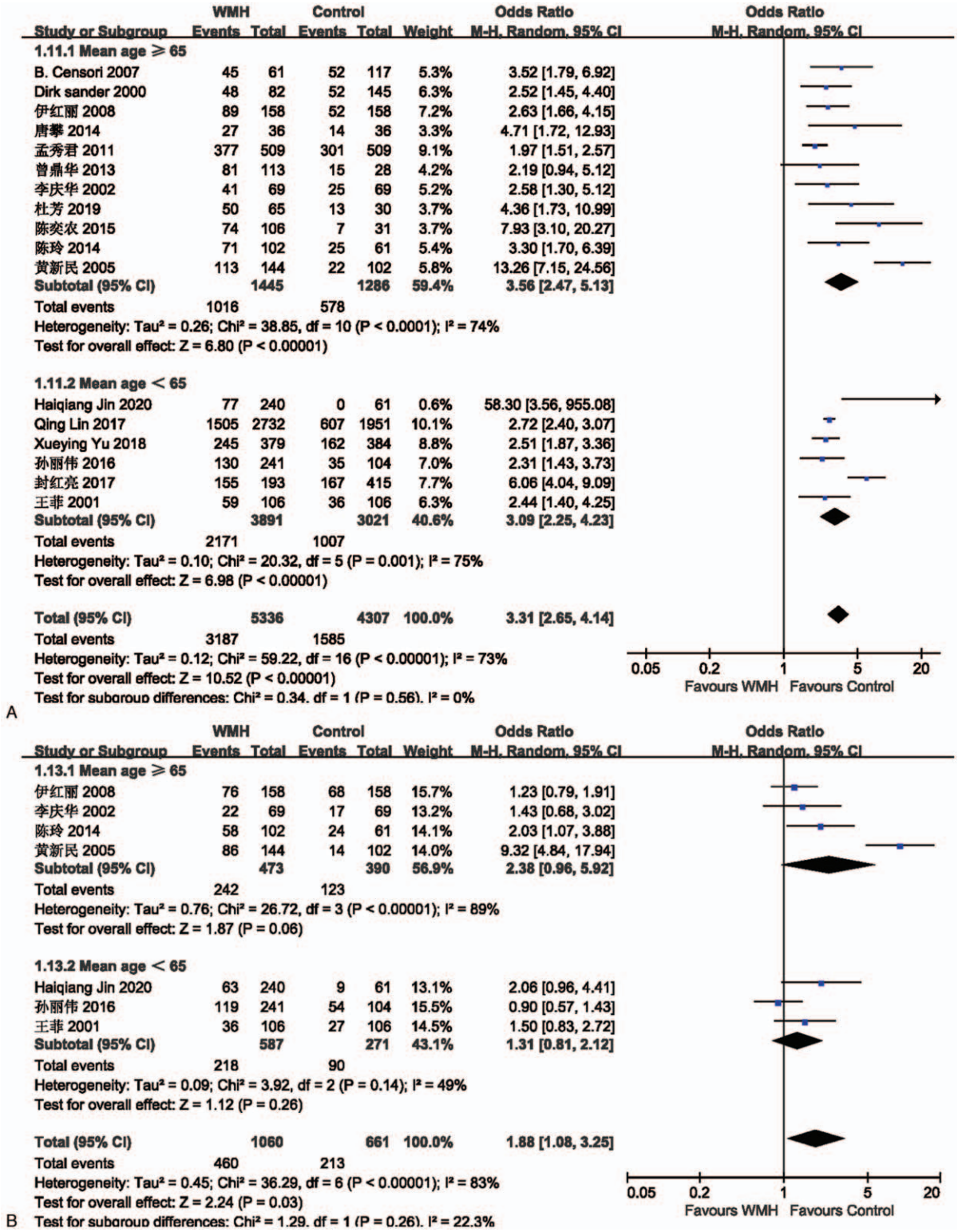

Figure 10. (A) Forest plots showing the relationship between hypertension and WMH in different mean age groups. (B) Forest plot showing the relationship between hyperlipidemia and WMH in different mean age. (C) Forest plots showing the relationship between smoking and WMH in different mean age groups. (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

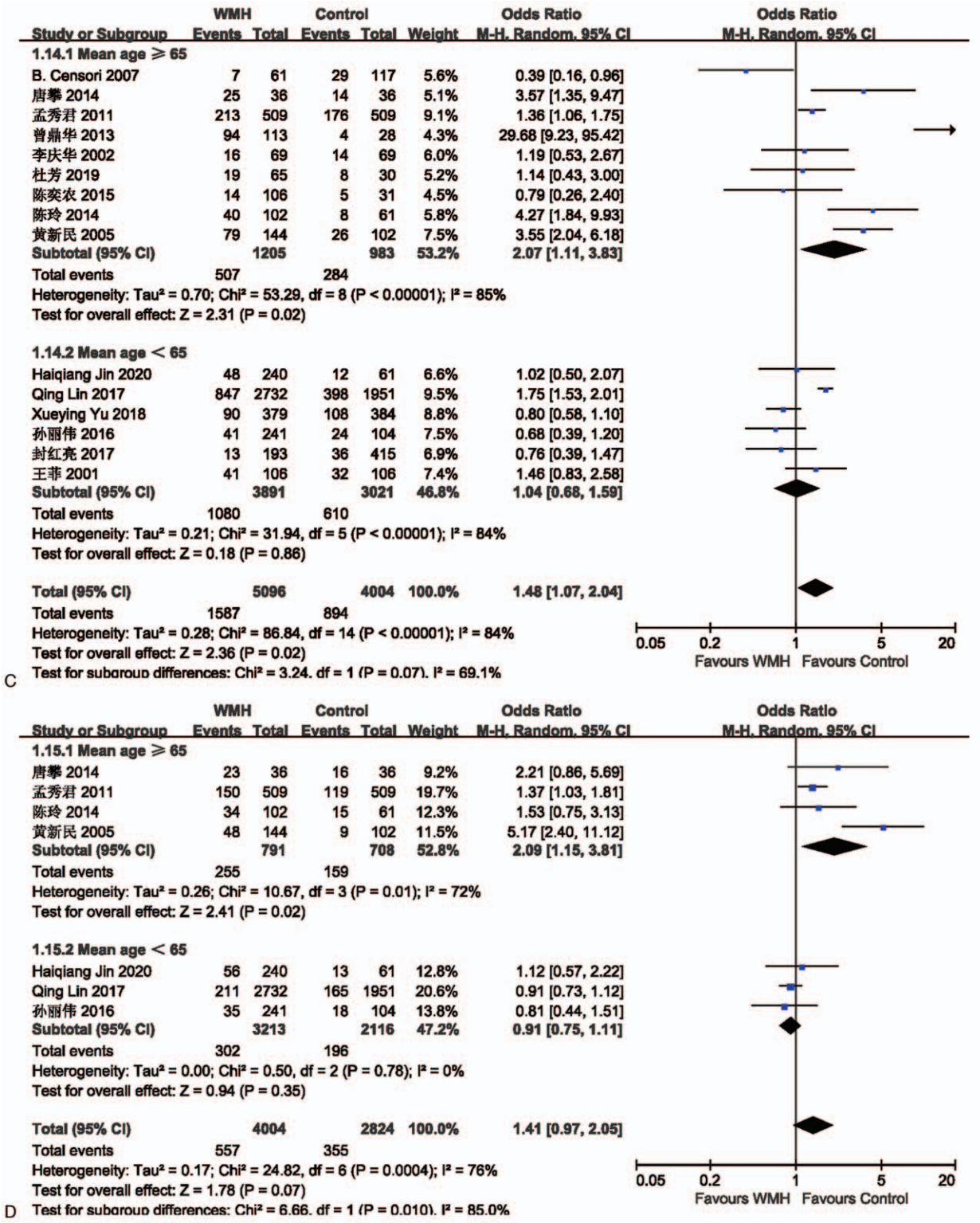

Figure 10. (Continued)

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

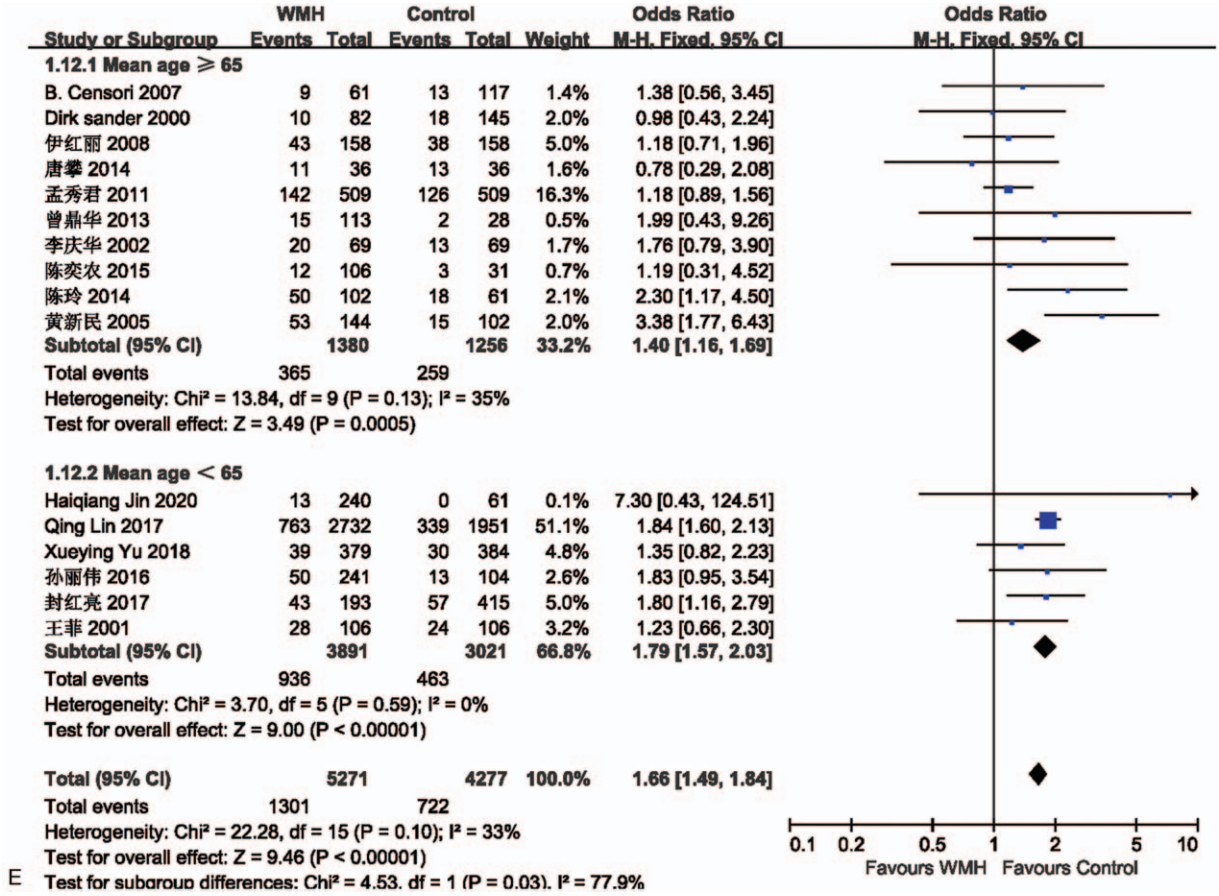

Figure 10. (Continued).

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 case-control 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 years 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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