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COMPREHENSIVE ANALYSIS OF RISK FACTORS FOR CAROTID PLAQUE IN TYPE 2 DIABETES MELLITUS: A META-ANALYSIS

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Article Info

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Type 2 Diabetes Mellitus, Carotid Plaque Formation, Risk Factors, Meta-Analysis, Cardiovascular Complications

Abstract

Type 2 diabetes mellitus (T2DM) is a global health concern with a rising incidence and severe complications. Carotid plaque formation, indicative of diabetic macrovascular complications, serves as a significant predictor of cardiovascular and cerebrovascular diseases. This study conducts a comprehensive meta-analysis of risk factors contributing to carotid plaque formation in individuals with T2DM, aiming to provide valuable insights and a solid theoretical foundation for future research and intervention strategies. The increasing prevalence of T2DM makes understanding and addressing carotid plaque formation imperative to reduce the risk of cardiovascular morbidity and mortality.

1. Introduction

Type 2 diabetes mellitus (T2DM) has become a disease of concern at present. It has a high incidence, a long course and affects every system in the body. Statistics show that there were 451 million diabetes patients worldwide in 2017. This is expected to increase to 693 million by 2045 [1]. Patients with this disease will develop different types of complications, such as: diabetic peripheral neuropathy, diabetic retinopathy, diabetic nephropathy, etc. Carotid plaque formation is a direct manifestation of diabetic macrovascular lesions, a window of systemic arteriosclerosis, and a predictor of cardiovascular and cerebrovascular diseases [2]. It is the most common cause of death in type 2 diabetes.Although there are many studies on the risk factors of carotid plaque formation in type 2 diabetes at home and abroad, no comprehensive systematic evaluation has been reported. Therefore, this paper will conduct a meta-analysis of the risk factors of this disease to provide theoretical support for future research and intervention.

2. Data and Methods

2.1. Literature retrieval strategy

Foreign language retrieval was conducted in Pubmed using Diabetes/T2DM, Extremities,Lower Extremities and RiskFactors as search terms.With the subject words "Type 2 diabetes mellitus, carotid plaque formation AND risk factors" as the main search terms, the combination of subject words AND free words was adopted, and finally "(type 2 diabetes ORT2DM) AND (related factors OR risk factors OR influencing factors OR etiology OR factors) and carotid plaque formation" as the search mode.Chinese search was conducted in Chinese databases such as China Journal Full-Text Database (CNKI), Wanfang Digital Journal Full-Text Database (Wanfang) and VIP Journal Resource Integration Service Platform.

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2.2. Inclusion and exclusion criteria

2.2.1. Inclusion criteria

(1) The design type was case-control study; (2) Patients with carotid plaque formation of type 2 diabetes diagnosed by medical institutions. The control group was patients with age difference of less than 5 years from the case, living in the same area, or receiving treatment in the same hospital at the same time with greater similarity with the case in the above conditions; (3) From January 1, 2011 to February 28, 2023, the relevant risk factors were TG or TC, HbA1c, hypertension history, LDL-C, age, diabetes course, smoking, and SBP. (4) The data of the research results can be converted by 95% confidence interval (CI), OR (oddsratio) value, and standard error (SE).

2.2.2. Exclusion criteria

(1) Incomplete basic data, no control group and excessive loss of follow-up; (2) Repeated publication of literature; (3) Review literature; (4) non-Chinese or English literature; (5) Documents from the same region in the same year; (6) The definition of risk factors differs significantly from the general standard or most research standards.

2.3. Literature Screening, data Extraction and quality evaluation

By reading the title, the irrelevant literature and repeated published clinical research results were eliminated, and the full text was read to find out the literature meeting the inclusion criteria.Then, with reference to the Newcastle-Ottawa Scale (NOS) [3], the quality of the studies meeting the inclusion criteria was evaluated by two evaluators.

2.4. Data Processing

ReviewManager5.4 was used for Meta-analysis in data processing.Heterogeneity among studies was analyzed using CochraneQ test, and the heterogeneity was evaluated using $I.^2$If $P > 0.1$ and $I2< 50\%$, it means that there is no statistical heterogeneity in each study, so the fixedeffectsmodel (FE) is used.Conversely, randomeffectsmodel (RE) is used.oddsratio (OR) was selected as the combined statistic for binary data, and each effect size was expressed with 95% confidence interval (CI). The sensitivity of heterogeneity was analyzed, and the funnel plot was used to analyze and judge whether there was publication bias.For missing data in literature, data need to be converted first [4].

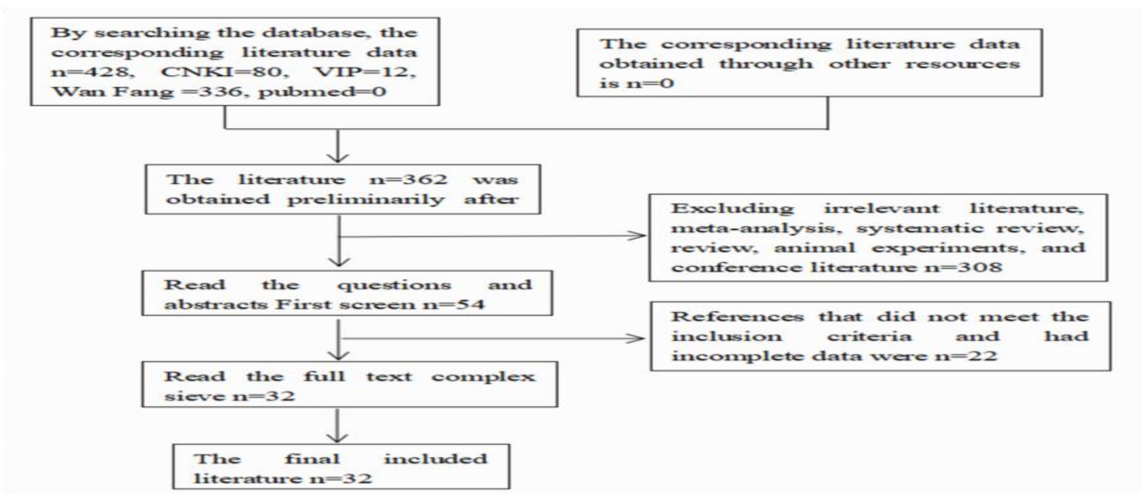

Figure 1: Literature screening process and results

After preliminary search in the database, 428 literatures were obtained, 362 literatures were initially screened out after the elimination of duplicate literatures, 308 literatures were excluded after reading the title and abstract, and 54 literatures were included in the second screening. After reading the full text, 22 literatures were excluded and the full text was intensively read. Following the inclusion and exclusion criteria, a total of 32 literatures meeting the criteria were included. (Figure 1)

3. Results

3.1. Basic Features of Literature Inclusion and Quality Evaluation

The 32 literatures included were case-control studies, published between 2003 and 2023, with a total of 5710 cases in the case group and 5405 cases in the control group. (Table 1)

Table 1: General characteristics of meta-analysis literature included

No.	First author	Year of publication	Study area	Research type	Case group (example)	Control group (example)	Research factor	NOS score
1	Dong Xia[5]	2021	Hebei	Case control	105	50	(6)	7
2	Gao Yueqin[6]	2003	Shanxi	Case control	44	47	(6)	7
3	Gong Li li[7]	2022	Shandong	Case control	100	100	(3)(5)(6)	8
4	Guo Li yan[8]	2018	Shanxi	Case control	279	354	(6)(7)(8)	7
5	He HuiJin[9]	2017	Tienjin	Case control	257	213	(3)(4)(6)(7)	7
6	He Liangjun[10]	2017	Maanshan	Case control	100	100	(3)(6)	8
7	Huang Minting [11]	2022	Changsha	Case control	146	61	(6)	8
8	Jin Hui[12]	2021	Hefei	Case control	426	526	(6)(7)(8)	7
9	Li Caiqin[13]	2018	Baoling	Case control	647	339	(4)(5)(6)(8)(9)	8
10	Li Jing[14]	2018	Qinghai	Case control	21	34	(1)(6)	8
11	Li Juan[15]	2023	Fuyang	Case control	77	70	(3)(5)(6)	7
12	Shang Shuxia[16]	2015	Handan	Case control	123	167	(2)(6)(9)	7
13	Wang Rui[17]	2016	Shenyang	Case control	70	140	(1)(6)(9)	7
14	Wang Yu Rong [18]	2017	Zhengzhou	Case control	178	136	(3)(4)(5)(6)(7)	7
15	Wu Chengxiang [19]	2020	Nanjing	Case control	203	186	(4)(7)	7
16	Xie Liping[20]	2017	Tongling	Case control	70	80	(4)(5)(6)(7)(9)	8
17	Xu Yeting[21]	2013	Guangxi	Case control	104	134	(3)(4)(5)(7)(9)	8
18	Zhang Qingxia [22]	2013	Beijing	Case control	86	172	(1)(6)(9)	7
19	Zhang Rui[23]	2019	Chengde	Case control	101	91	(3)(5)(7)(8)	8
20	Wu Wenhao[24]	2020	Shanxi	Case control	54	20	(7)	8

21	Jiang YongBin [25]	2019	Wuxi	Case control	568	495	(4)(6)(7)(8)(9)	8
22	Xu Hui[26]	2017	Tianjin	Case control	162	401	(6)(8)	8
23	LiangMeiyan[27]	2018	Shenzhen	Case control	32	50	(2)(5)	7
24	Wang Qi[28]	2021	Anhui	Case control	1161	809	(6)(7)(9)	7
25	Lin Yuanyuan[29]	2020	Nanning	Case control	54	46	(8)	7
26	Zheng Ying[30]	2020	Liaoning	Case control	220	249	(7)(8)	8
27	Hao Shaofeng[31]	2015	Zhangjiakou	Case control	92	102	(3)(5)	7
28	Ge XinLian[32]	2014	Hebei	Case control	31	24	(1)	7
29	Yuan Heju[33]	2019	Shanxi	Case control	31	32	(6)	8
30	Zhao Qian[34]	2021	Kunming	Case control	48	25	(6)(7)(9)	8
31	Pan Juan[35]	2020	Yan'an	Case control	57	97	(3)	7
32	Lu Ming xue[36]	2015	Nanjing	Case control	63	55	(2)(5)	7

Note: (1) TG; (2) TC; (3) glycosylated hemoglobin; (4) History of hypertension; (5) LDL-C; (6) Age; The course of diabetes; (8)
Smoking; (9) SBP

3.2. Results of Meta-analysis

Meta-analysis of risk factors for carotid plaque formation in type 2 diabetes mellitus Results: There was no heterogeneity in TG, TC, HbA1c and hypertension history (P>0.1, I<²50%), so fixed effect model was adopted.For other reasons of large heterogeneity (P≤0.1, I2≥50%), random effects model was adopted.Meta-analysis showed that the above 9 factors were all risk factors for carotid plaque formation in type 2 diabetes mellitus, as shown in Table 2.

Table 2: Meta-analysis of risk factors for carotid plaque formation in type 2 diabetes mellitus

Risk factor	Number of documents	OR(PE)	95%CI	Heterogeneity test			Population effect test	
				Q	P	I 2 (%)	Z	P
TG	4	2.74	2.25-3.33	5.25	0.15	43	10.08	P<0.00001
TC	3	2.50	2.22-2.83	1.47	0.48	0	14.65	P<0.00001
HbA1c	9	1.41	1.33-1.50	13.59	0.09	41	10.78	P<0.00001
History of hypertension	7	2.03	1.69-2.44	11.26	0.08	47	7.66	P<0.00001
LDL-C	10	1.64	1.31-2.06	53.11	P<0.00001	83	4.32	P<0.00001

age	21	1.12	1.09-1.14	120.53	P<0.00001	83	9.33	P<0.00001
Course of diabetes	13	1.04	1.03-1.06	238.69	P<0.00001	95	8.01	P<0.00001
smoking	8	1.30	1.18-1.44	86.54	P<0.00001	92	5.04	P<0.00001
SBP	9	1.04	1.02-1.05	41.20	P<0.00001	81	4.54	P<0.00001

3.2.1. Relationship between TG and carotid plaque formation in Type 2 diabetes

Mellitus: A total of 4 studies were included. After the heterogeneity test, P=0.15, I²=43%, the fixed effect model was adopted and the forest map was drawn, as shown in Figure 2. The effect combination OR=2.74, 95%CI: 2.25-3.33, the difference was statistically significant (P < 0.00001), and the ratio of carotid plaque formation was higher in the case group.

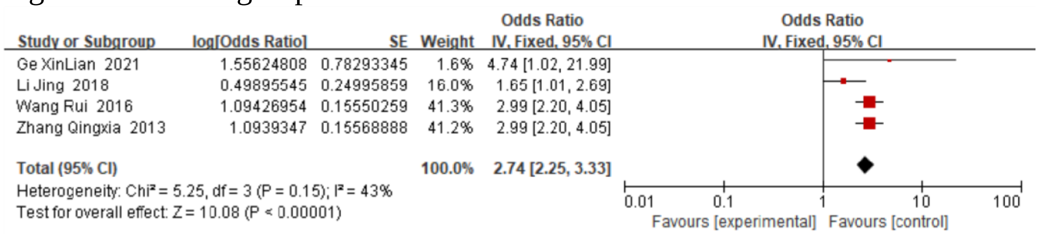

Figure 2: Forest map of TG analysis

3.2.2. Relationship between TC and carotid plaque formation in Type 2 diabetes

Mellitus: A total of 3 studies were included. After the heterogeneity test, P=0.48, I=²0%, the fixed effect model was used to plot the forest map, as shown in Figure 3. The effect combination OR=2.50, 95%CI: 2.22-2.83, the difference was statistically significant (P < 0.00001), and the ratio of carotid plaque formation was higher in the case group.

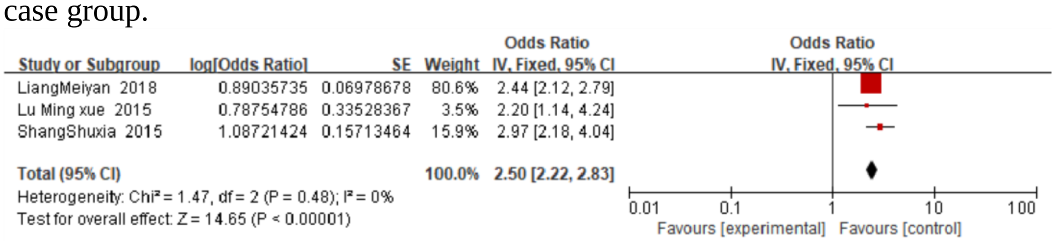

Figure 3: Forest map analyzed by TC

3.2.3. Relationship between HbA1c and carotid plaque formation in Type 2 diabetes

Mellitus: A total of 9 studies were included. After the heterogeneity test, P=0.09, I²=41%, the fixed effect model was used to plot the forest map, as shown in Figure 4. The effect combination OR=1.41, 95%CI: 1.33 ~ 1.50, the difference was statistically significant (P < 0.00001), and the ratio of carotid plaque formation was higher in the case group.

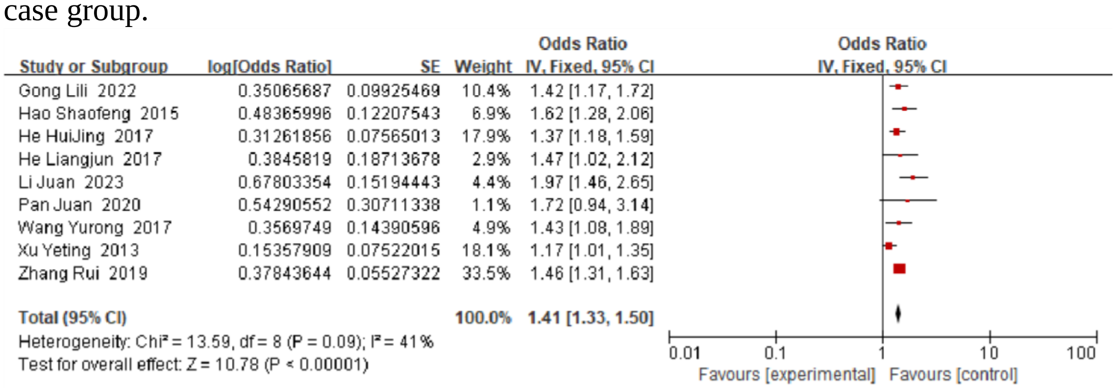

Figure 4: Forest map analyzed by HbA1c

3.2.4. Relationship between history of hypertension and carotid plaque formation in Type 2 diabetes

Mellitus: A total of 7 studies were included. After the heterogeneity test, P=0.08, I²=47%, the fixed effect model was adopted and the forest map was drawn, as shown in Figure 5. The effect combination OR=2.03, 95%CI: 1.69 ~ 2.4, the difference was statistically significant (P < 0.00001), and the ratio of carotid plaque formation was higher in the case group.

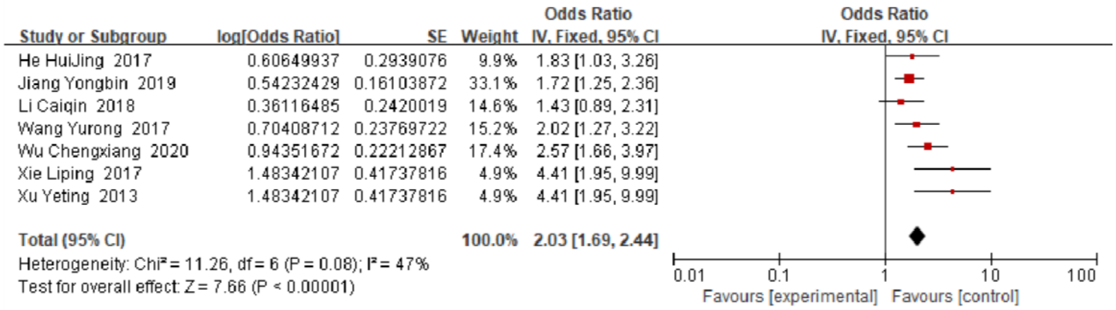

Figure 5: Forest map of hypertension history analysis

3.2.5. *Relationship between LDL-C and carotid plaque formation in Type 2 diabetes*

Mellitus: A total of 10 studies were included. After the heterogeneity test, P<0.00001, I²=83%, the random effects model was adopted and the forest map was drawn, as shown in Figure 6. The effect combination OR=1.64, 95%CI: 1.31-2.06, the difference was statistically significant (P <0.00001), and the ratio of carotid plaque formation was higher in the case group.

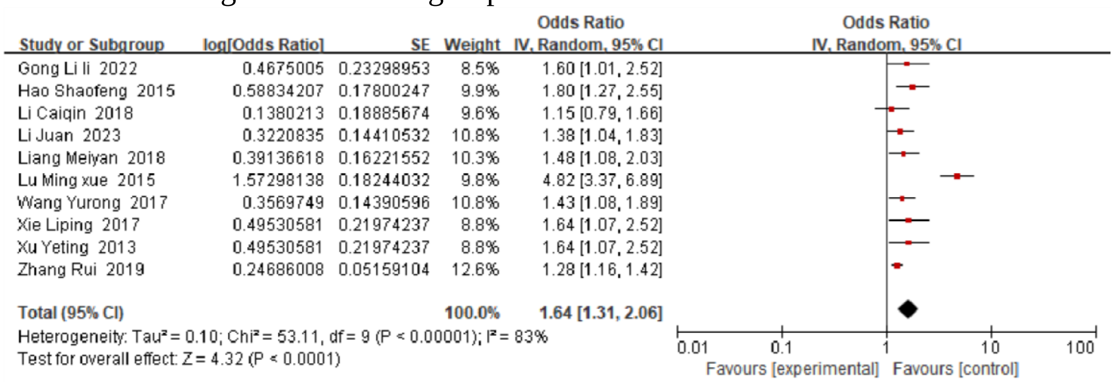

Figure 6: Forest map of LDL-C analysis

3.2.6. *Relationship between age and carotid plaque formation in Type 2 diabetes*

Mellitus: A total of 21 studies were included. After the heterogeneity test, P<0.00001, I²=83%, the random effects model was used to plot the forest map, as shown in Figure 7. The effect combination OR=1.12, 95%CI: 1.09-1.14, the difference was statistically significant (P <0.00001), and the ratio of carotid plaque formation was higher in the case group.

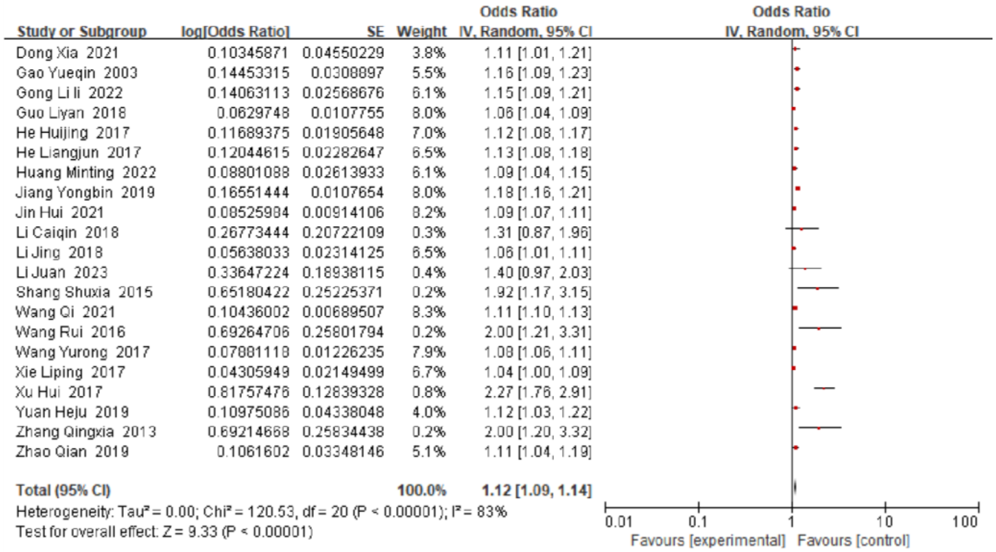

Figure 7: Forest map for age analysis

3.2.7. *Relationship between diabetes course and carotid plaque formation in Type 2 diabetes*

Mellitus: A total of 13 studies were included. After the heterogeneity test, P<0.00001, I²=95%, the random effects model was used to map the forest, as shown in Figure 8. The effect combination OR=1.04, 95%CI: 1.03 ~ 1.06, the difference was statistically significant (P <0.00001), and the ratio of carotid plaque formation was higher in the case group.

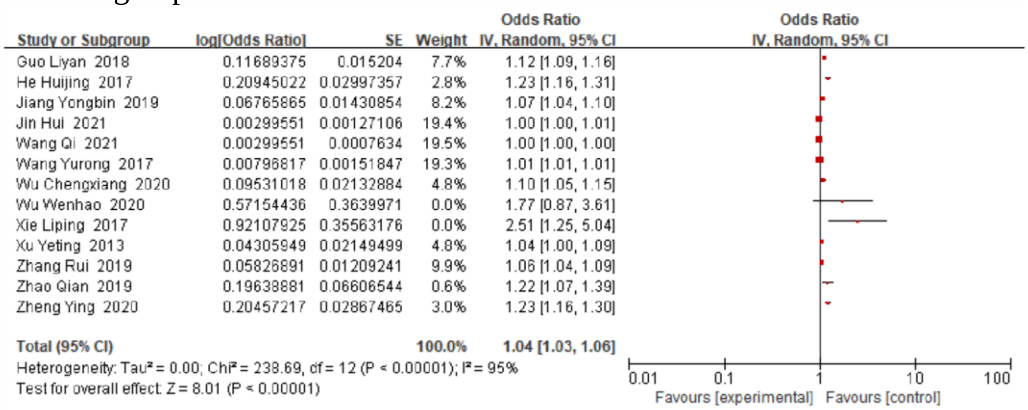

Figure 8: Forest map of diabetes course analysis

3.2.8. *Relationship between smoking and carotid plaque formation in Type 2 diabetes*

Mellitus: A total of 8 studies were included. After the heterogeneity test, P<0.00001, I²=92%, the random effects model was used to plot the forest map, as shown in Figure 9. The effect combination OR=1.30, 95%CI: 1.18 ~ 1.44, the difference was statistically significant (P <0.00001), and the ratio of carotid plaque formation was higher in the case group.

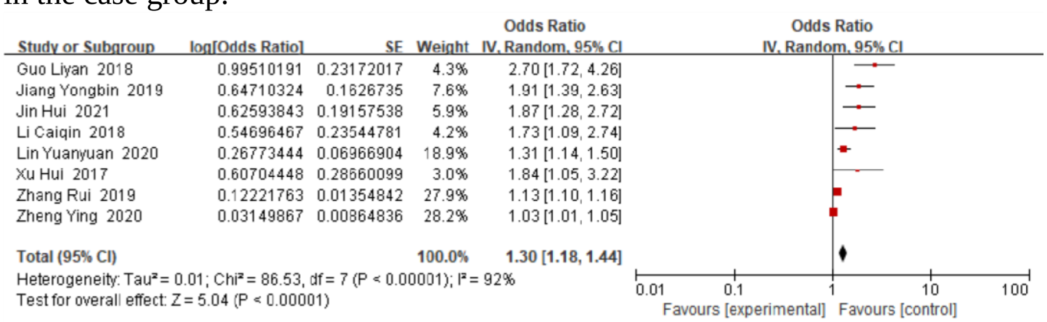

Figure 9: Forest map of diabetes course analysis

3.2.9. *Relationship between SBP and carotid plaque formation in Type 2 diabetes*

Mellitus: A total of 9 studies were included. After the heterogeneity test, P<0.00001, I=²81%, the random effects model was used to map the forest, as shown in Figure 10. The effect combination OR=1.04, 95%CI: 1.02 ~ 1.05, the difference was statistically significant (P <0.00001), and the ratio of carotid plaque formation was higher in the case group.

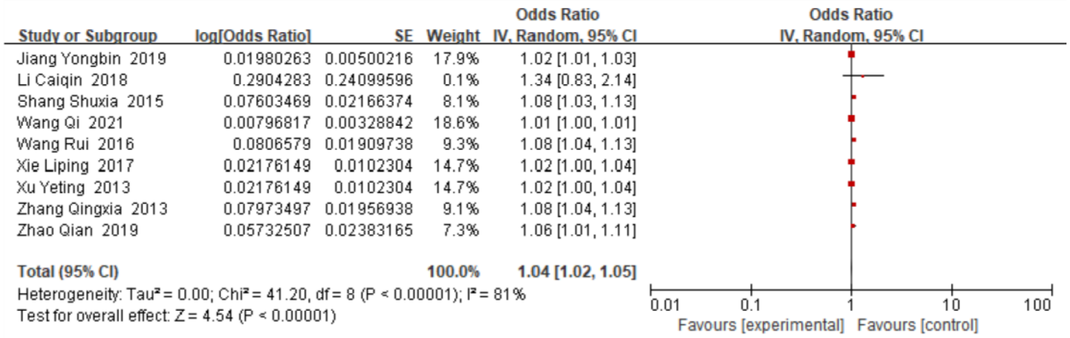

Figure 10: Forest map of SBP analysis

3.3. *Sensitivity analysis*

For the risk factors of carotid plaque formation in type 2 diabetes mellitus, the combined OR values and 95%CI were calculated using fixed and random effects models respectively in this study, and the results were highly similar, reflecting that the combined results obtained in this study were generally reliable. (Table 3)

Table 3: Sensitivity analysis

Risk factor	Fixed effect model		Random effects model	
	Combined OR value	95%CI	Combined OR value	95%CI
TG	2.74	2.25-3.33	2.65	1.98-3.55
TC	2.50	2.22-2.83	2.50	2.22-2.83
HbA1c	1.41	1.33-1.50	1.43	1.31-1.57
History of hypertension	2.03	1.69-2.44	2.15	1.65-2.80
LDL-C	1.34	1.24-1.46	1.64	1.31-2.06
age	1.11	1.10-1.11	1.12	1.09-1.14
Course of diabetes	1.00	1.00-1.01	1.04	1.03-1.06
smoking	1.07	1.05-1.08	1.30	1.18-1.44
SBP	1.02	1.01-1.02	1.04	1.02-1.05

3.4. *Publication bias analysis*

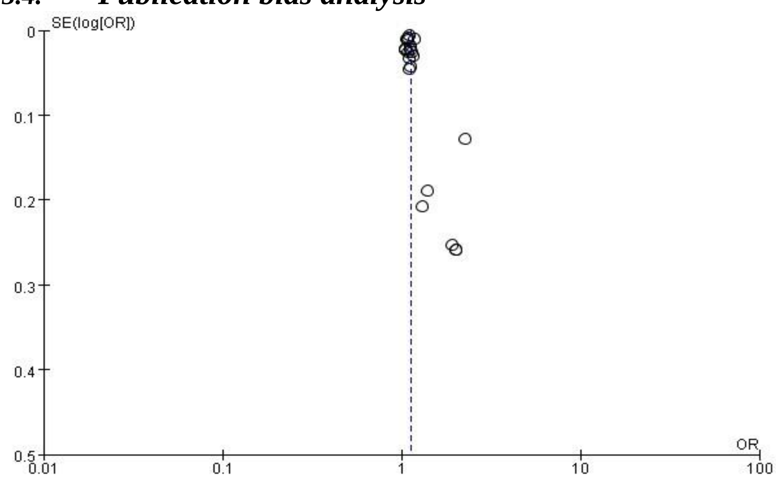

Figure 11: Funnel plot of age analysis of carotid plaque formation in T2DM

There is a certain degree of asymmetry in the scattered points corresponding to diabetes course, smoking and SBP, suggesting the possible existence of publication bias, which may be caused by the small sample size of these studies.Funnel plots of other risk factors generally maintained a symmetric relationship, which reflected that the results of meta-analysis had good stability.Funnel plot was drawn for the risk factor index (age) with more studies, indicating that publication bias was basically well controlled, as shown in Figure 11.

4. Discussion

In the early 19th century, some scholars have made relevant explanations on the generation of carotid plaque [37], pointing out that lipid stripe and fibrous plaque are the main pathogenic factors of carotid plaque, and that endometrial lipid deposition and changes in the structure of the endometrial wall are its pathogenesis. Carotid plaque formation is the most common in diabetic patients. In order to prevent and reduce the prevalence of this disease, this study summarized the latest research results related to carotid plaque formation of T2DM during 2003-2023, and made a comprehensive summary of the intensity of association between exposure factors and the risk of this disease.

4.1. TG, TC, LDL-C

Elevated levels of TC and TG are risk factors for the formation of carotid plaque in patients with T2DM, and lipid metabolism disorder is associated with the formation process of carotid plaque in T2DM [38]. The results of this study also indicate that TG and TC are risk factors for carotid plaque formation in T2DM.LDL-C is also a risk factor for carotid plaque formation in T2DM.This is consistent with what was reported in the study [39]. Studies have shown that patients with LDL- C levels higher than 3.45mmol/L have a 1.595 times higher risk of developing carotid atherosclerotic plaque than patients with normal LDL- C [40].

4.2. HbA1c

With the increase of FBG and HbA1c, the risk of carotid plaque formation also increases [41]. In patients with diabetes, HbA1c level is continuously correlated with the risk of diabetic microanglopathy and macroanglopathy [42]. HbA1c is a risk factor for carotid plaque formation in T2DM, which is consistent with the positive correlation between HbA1c level and CIMT reported [43].

4.3. History of hypertension and SBP

Hypertension and hyperglycemia promote each other, increase oxidative stress, damage vascular endothelium, and lead to atherosclerosis or accelerate the process of atherosclerosis [44]. Studies have shown that for patients with type 2 diabetes mellitus with hypertension, the risk of atherosclerosis increases by 77% for every 10mmHg increase in systolic blood pressure [45].

4.4. Age and diabetes course

According to domestic and foreign epidemiological data, age is the most important and independent risk factor for atherosclerotic plaque formation [46]. Cao et al. [47] suggested that age is one of the risk factors for carotid plaque formation, and the incidence of carotid plaque in patients over 80 years old with T2DM could reach 100%. This meta-analysis showed that age would increase the formation of carotid plaque in T2DM. With the increase of age, the chance of plaque occurrence increases, and age is closely related to the occurrence of carotid plaque.In addition, for patients with type 2 diabetes, the course of diabetes increases with the increase of age. Long-term stimulation of hyperglycemia will gradually deposit lipid in the blood vessels and eventually lead to the formation of plaque [48].

4.5. Smoking

Duration of smoking is an independent risk factor for carotid atherosclerosis in male patients [49]. Smoking is a risk factor for carotid plaque formation in T2DM, which is consistent with research reports [50]. The study of Kweon et al. [51] confirmed that the carotid intima thickness of smokers was significantly higher than that of non-smokers, and smoking environment would lead to the formation of unstable plaques.Yang Li et al. [52] suggested that smoking, hypertension, elevated blood lipids, HbA1c > 7% and any of the other factors could lead to the increase of carotid plaque in T2DM.

4.6. Limitations of this paper

(1) Risk factors such as TG, TG, hypertension history and smoking were not included in the literature, which may affect the conclusions of meta-analysis; (2) The retrieval language of this study is limited to Chinese and

English, which has a certain language bias; (3) All the included literatures were case controls, which made it difficult to comprehensively analyze the risk factors of carotid plaque formation in T2DM; (4) Among the literatures published in public, some of them do not have available data, or the research results are incomplete, so they cannot be applied to the analysis, resulting in information loss, or the included literatures have a large time span, inevitably facing various biases, and grey literatures are not searched.

In conclusion, the formation of carotid plaque in T2DM is affected by a variety of factors, including TG, TC, HbA1c, hypertension history, LDL-C, age, diabetes course, smoking and SBP.Therefore, attention should be paid not only to the control of blood sugar in diabetic patients, but also to the large vascular complications, and early carotid artery screening, diagnosis and intervention should be carried out in high-risk groups, so as to reduce the incidence of carotid plaque, reduce hospitalization costs and improve the quality of life.

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