



Research Article

Meta-analysis of the epidemiology of microvascular complications in people with Type 2 diabetes in mainland China

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Abstract

Objective: This study aims to estimate the overall prevalence of microvascular complications of type 2 diabetes in mainland China, and to identify any associated risk factors.

Methods: A systematic literature search was conducted to collect the prevalence information of microvascular complications over the past 5 years (2014 -2019) in CNKI, Wanfang, PubMed and the Cochrane Library. A meta-analysis was conducted using R3.4.3 following normal transformations given the skewed raw data. Due to high heterogeneity, a random effect model was selected. A meta-regression analysis was performed to investigate risk factors.

Results: A total of 171 studies were included in the meta-analysis. Of which, 86 studies in diabetic retinopathy, 61 in diabetic nephropathy and 24 in diabetic foot. Results of the meta-analysis showed that the prevalence of diabetic retinopathy was 26.19% [95% CI: 23.02%-29.50%], diabetic nephropathy 27.09% [95% CI: 23.55%-30.79%], and diabetic foot 7.41% [95% CI: 5.48%-10.03%], respectively. Duration of type 2 diabetes was identified as the risk factor which was significantly associated with the prevalence of all three microvascular complications ($p < 0.05$).

Conclusion: In mainland China, the prevalence of microvascular complications in patients with type 2 diabetes is high. Early diagnosis and treatment of type 2 diabetes may prevent or delay the development of microvascular complications.

Introduction

The International Diabetes Federation (IDF) reported that Chinese adult diabetes patients (20-79 years old) reached 116 million in 2019 [1], making China the largest diabetic population in the world. One of the most important aspects of diabetes prevention is the prophylaxis of chronic complications so as to improve patients' quality of life and to prolong their life expectancy.

Diabetic microvascular complications mainly include diabetic retinopathy (DR), diabetic nephropathy (DN) and diabetic foot (DF) caused by diabetic neuropathy. These

complications not only lead to patient disability and death, but also heavy social burdens. A comprehensive understanding of the prevalence of diabetes complications is imperative to reducing the diabetes disease burden. By evaluating the prevalence of microvascular complications nationwide, the number of diabetic patients with complications and the corresponding treatment costs can be estimated to ensure a rational allocation of public health resources. This meta-analysis estimated the prevalence of microvascular complications in patients with type 2 diabetes mellitus (T2DM) nationwide and analyzed any associated risk factors to provide evidence for the prevention and control of diabetic complications.

Data source and methods

Search strategy: A systematic literature search was conducted to investigate the prevalences of DR, DN and DF in Chinese patients with T2DM. Both Chinese and English databases were searched for the past 5 years (January 2014–August 2019), including Chinese National Knowledge Infrastructure (CNKI), Wanfang, PubMed and the Cochrane Library. According to the respective clinical guidelines, DR is defined as damages to retinal due to diabetes [2]; DN is defined as the presence of proteinuria or estimated glomerular filtration rate (eGFR) < 60ml/ (min 1.73m²) [3]; and DF is defined as diabetic patients accompanied with neuropathy and with lower limb infections, ulcers, or deep tissue damages due to peripheral vascular lesions [4]. The literature search strategies were as follows:

DR prevalence search strategy: ('Type 2 Diabetes' OR 'Non-Insulin-Dependent Diabetes') AND ('Epidemiology' OR 'Prevalence' OR 'Incidence' OR 'Disease Burden' OR 'Natural History') AND ('Eye' OR 'Retinal' OR 'Macular' OR 'Microaneurysms' OR 'Optic nerve')

DN prevalence search strategy: ('Type 2 Diabetes' OR 'Non-Insulin-Dependent Diabetes') AND ('Epidemiology' OR 'Prevalence' OR 'Incidence' OR 'Disease Burden' OR 'natural history') AND ('Kidney' OR 'Protein Urine')

DF prevalence search strategy: ('Type 2 Diabetes' OR 'Non-Insulin-Dependent Diabetes') AND ('Epidemiological' OR 'Prevalence' OR 'Incidence' OR 'Disease Burden' OR 'natural history') AND ('Foot' OR 'Ulcer' OR 'Lower Limb' OR 'Limb')

Inclusion and exclusion criteria

Studies potentially eligible for inclusion in this meta-analysis must meet the following inclusion and exclusion criteria. Inclusion criteria were: people aged over 18 years old and lived in mainland China; the prevalence of microvascular complications of T2DM was reported. Exclusion criteria were: the study population were not from mainland China, or patients with gestational diabetes, type 1 diabetes, latent autoimmune diabetes of the adult or patients who have had the targeted complication; did not report the prevalence of microvascular complications; case-control studies, newsletters, reviews, reports, etc. Literature annotation was conducted independently by two researchers (Y Liu and Y Zhang). Discrepancies were resolved through discussion or with the assistance of a third researcher.

Data extraction

Data were extracted using a standardized form to collect the following information: the prevalence of diabetic complications, average age of the study population, male proportion, glycosylated hemoglobin (HbA_{1c}) levels, body mass index (BMI), duration of diabetes, and region (Northeast /North China /East China /South China /Central China /Northwest / Southwest), etc.

It was noted that different definitions for the prevalence of complications were applied in different literatures. In

order to be consistent in our meta-analysis, the prevalence of complications was defined as the proportion of patients with the targeted microvascular complication against the investigated T2DM patients.

Statistical analysis

The normal distribution of the raw prevalence data included in the meta-analysis was tested. Mathematical conversions were applied to bring the skewed raw prevalence data back to normal or near-normal distributions [5]. Specifically, the arcsine transformation was applied in the raw prevalence data of DR and DN and logarithmic transformation was applied in the DF data. The heterogeneity test was performed and a random-effect model was used to estimate the prevalence of diabetes complications due to the significant heterogeneity among studies ($I^2 > 50\%$). Risk factors affecting the prevalence of diabetic microvascular complications were investigated via univariate meta-regression analysis. All analyses were conducted in R3.4.3.

Results

- Literature search results:** A total of 2,682 articles were retrieved during the systematic literature search. After removing duplicate studies, title and abstract screening, and full text scrutiny, a total of 171 articles were finally included in the meta-analysis. Among them, 86 were included in the analysis of Wang 2018 [6] was considered as two studies because the DR prevalence was reported in community and hospital, respectively. Sixty-one articles were identified for the analysis of DN and 24 for DF. The PRISMA flow chart of the literature review was shown in Figure 1.
- Meta-analysis results:** The meta-analysis showed that in Chinese patients with T2DM, the pooled prevalences were 26.19% [95% CI: 23.02% - 29.50%] for DR, 27.09% [95% CI: 23.55% - 30.79%] for DN, and 7.41% [95% CI: 5.48% - 10.03%] for DF, respectively. The forest plots of three meta-analyses using random effects model are illustrated in Figure 2.

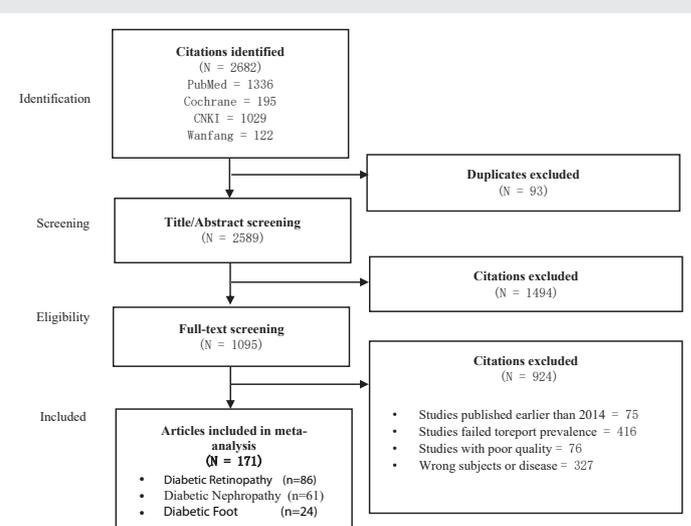


Figure 1: PRISMA flowchart of the systematic review.



3. Meta-regression analysis: Meta-regression analyses of the prevalence of DR, DN, and DF were conducted to identify any potential risk factors of diabetic microvascular complications. Age, gender, HbA_{1c}, BMI,

duration of diabetes, and region were tested (Table 1). The study found that the duration of diabetes was a risk factor for the prevalences of DR, DN and DF. The prevalences of all three complications demonstrated

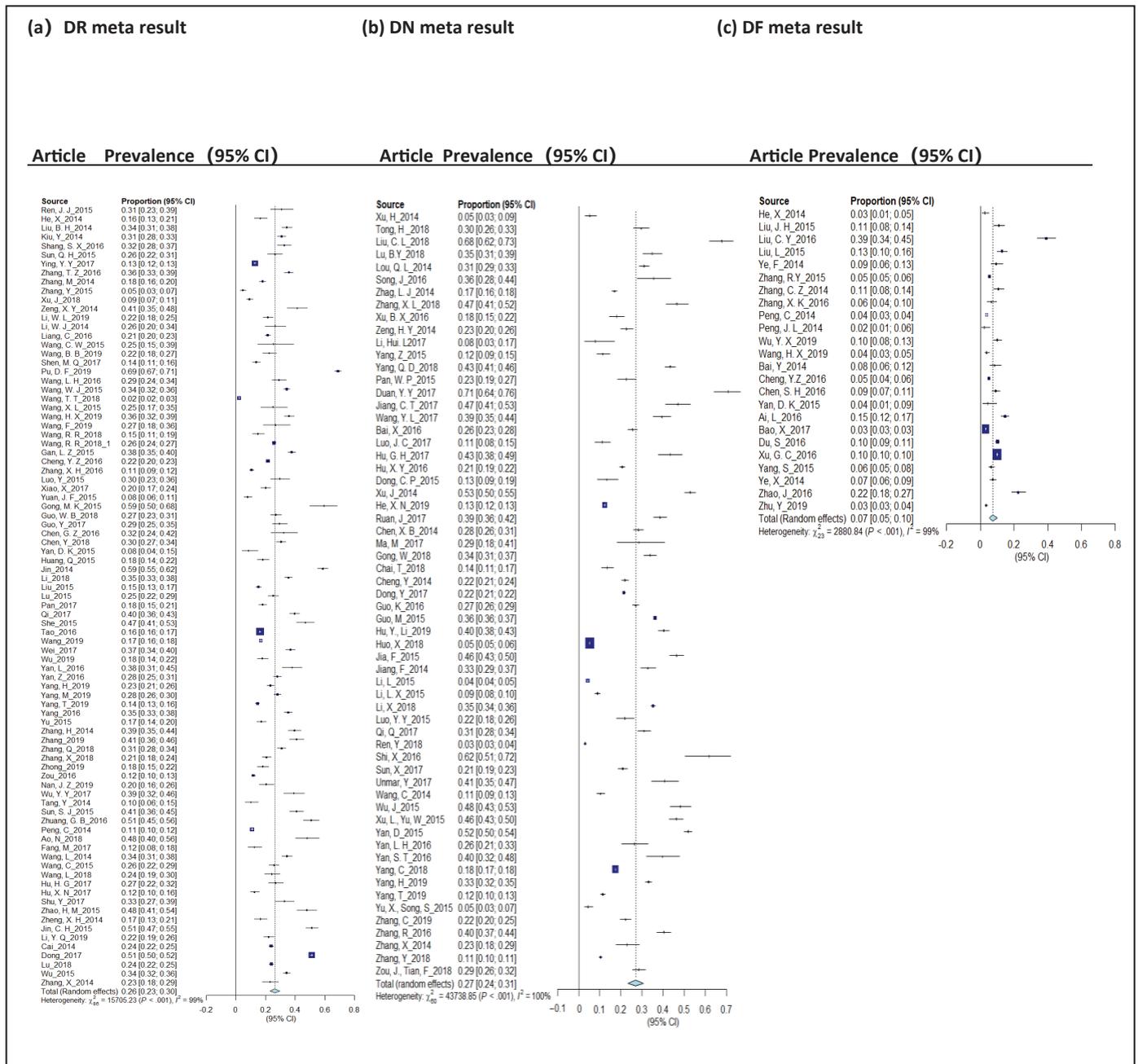


Figure 2: Meta-analysis Forest Plots.

Table 1: Meta-regression results.

Variable	DR			DN			DF		
	Coefficient	95% CI	p value	Coefficient	95% CI	p value	Coefficient	95% CI	p value
Average age	-0.04	[-0.09, 0.02]	0.22	0.03	[-0.03, 0.09]	0.29	-0.08	[-0.63, 0.47]	0.76
Percentage of male	-0.05	[-0.16, 0.02]	0.18	0.00	[-0.09, 0.09]	0.99	-0.28	[-0.97, 0.41]	0.43
Region (East China/North China/South China/...)	-0.03	[-0.05, 0.01]	0.23	0.01	[-0.02, 0.03]	0.60	-0.05	[-0.24, 0.13]	0.56
Diabetes duration (Years)	0.06	[0.02, 0.11]	0.0066*	0.04	[0.02, 0.06]	<0.0001*	0.85	[0.56, 1.13]	<0.0001*
BMI	0.01	[-0.09, 0.10]	0.89	0.08	[-0.04, 0.19]	0.19	-0.16	[-0.82, 0.49]	0.63
HbA _{1c} (%)	0.02	[-0.03, 0.07]	0.50	-0.01	[-0.08, 0.06]	0.80	-0.24	[-0.60, 0.13]	0.21

Note: *p<0.05



Table 2: Prevalences of diabetic microvascular complications by duration of diabetes.

Duration (years)	DR			DN			DF		
	N of articles	Prevalence	95% CI	N of articles	Prevalence	95% CI	N of articles	Prevalence	95% CI
<4	2	0.16	[0.04, 0.34]	2	0.20	[0.00, 0.72]	-	-	-
4~<8	25	0.23	[0.20, 0.26]	19	0.23	[0.17, 0.29]	8	0.06	[0.04, 0.07]
8~<12	30	0.30	[0.25, 0.36]	6	0.23	[0.15, 0.33]	8	0.11	[0.08, 0.15]
12~<16	6	0.42	[0.26, 0.59]	11	0.32	[0.26, 0.38]	1	0.39	[0.34, 0.45]
≥16	2	0.25	[0.22, 0.29]	7	0.44	[0.32, 0.57]	-	-	-

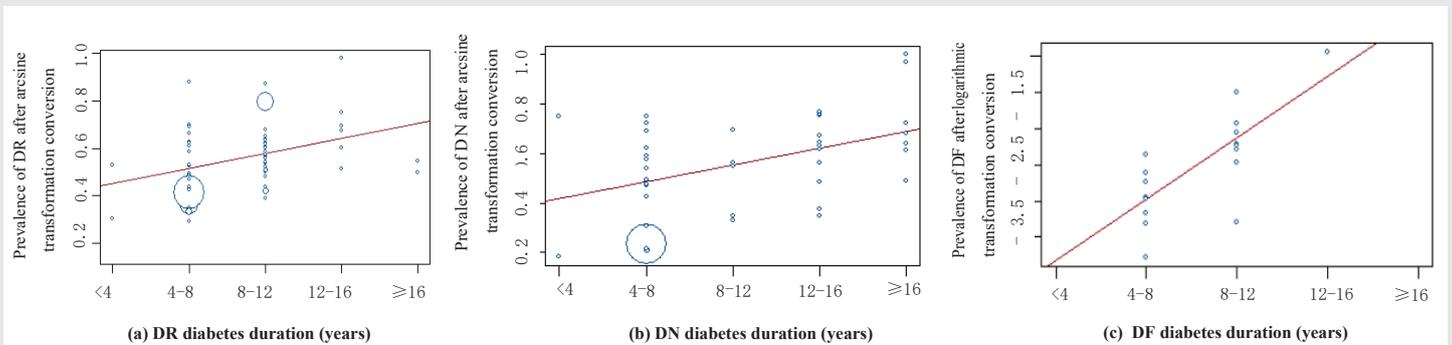


Figure 3: Meta-regression Analysis Bubble Charts.

an upward trend with the increase of the duration of diabetes ($p < 0.05$). Details are shown in Table 2 and Figure 3.

Discussion

With the increasing prevalence of diabetes, the metabolic disorders and vascular complications caused by diabetes impose heavy burdens on Chinese economy. Diabetic microvascular complications can affect almost every organ in the body, resulting in a high rate of fatality and disability in patients with T2DM. The probability of vision loss due to DR can be as high as 50% [7]. DN accounts for 25–50% of all chronic kidney diseases [8]. Once it progresses to end-stage kidney disease, it is more intractable than other kidney diseases given its complex metabolic disorders [3]. The mortality rate of patients with diabetic foot ulcer is as high as 11%, and that of amputees is even higher at 22% [4]. In 2015, a research report using an economic model to evaluate the burden of diabetes showed that the direct cost of diabetes in China reached ¥621 billion, of which 95.5% was spent on the treatment of complications [9]. In 2012, about 61% of the expenditure on T2DM was for complications in the United States [10], and data from the United Kingdom showed that the proportion of cost for complications was as high as 80% [11].

So far, investigations of the epidemiology of diabetes complications are scant in China. In 2018, Jia and her team carried out the world’s first multi-stage, stratified large-scale epidemiological study on diabetes complications, which covered 120 research centers in 30 provinces with more than 50,000 diabetes patients enrolled in China. Results are expected to be published in 2020 [12]. This systematic literature review and meta-analysis was a pooled analysis of the prevalence of diabetic microvascular complications across China, including 171 published studies and 807,313 patients. Results showed that the prevalence rates of DR, DN and DF in patients with T2DM

in mainland China in 2014 – 2019 were 26.19%, 27.09% and 7.41%, respectively. Liu 2012 [13], and Chen 2015 [14], reported a prevalence of DR in mainland China of 23% and 25% in 1986 – 2009 and 2009 – 2014, respectively. It appears an upward trend of DR prevalence in T2DM patients in China when our meta-analysis of DR prevalence was taken into account. The prevalence of DN in our report was slightly higher than that of the United States and the United Kingdom (25%) [15,16], however, it was lower than that of a domestic epidemiological study (29.6%) [17]. A 12-month study showed that the prevalence of DF in Chinese diabetic patients was about 8.1% [18]. By pooling the results of a number of epidemiological studies, our study further proved that the prevalences of DR, DN and DF in China was high with a serious disease burden. Duration of diabetes were a risk factor for the pre-mentioned three diabetic microvascular complications (DR, DN and DF), indicating that there is a higher probability of developing diabetic microvascular complications with the extension of the duration of diabetes. Liu 2010 [19], also demonstrated a significant positive correlation between the duration of diabetes and all diabetic microvascular complications.

The pathogenesis of diabetic microvascular complications has not yet been fully understood. Studies have shown that the greater the glycemic variability, the higher the incidence of microvascular complications and the worse the prognosis. Active control of blood glucose fluctuation, blood pressure and lipids is the basis for preventing and delaying the development of diabetic microvascular complications. In the last year or two, a metric of time percent during a 24-hour period when the blood glucose remains within the proposed target range (usually 3.9 to 10.0 mmol/L), time in range (TIR), has attracted more and more attention. The American Diabetes Association’s Standards of Medical Care in Diabetes – 2020 has added a new recommendation on the use of TIR for assessment of glycemic management [20]. As one of the important indicators of



continuous blood glucose monitoring, TIR can provide more valuable information such as glucose fluctuations over time while HbA_{1c} cannot. Several studies have shown that TIR was closely correlated with the occurrence of diabetic microvascular complications [21,22]. Although there are many different classes of anti-diabetic medications available, there is still a lack of clinical data on the improvement of glycemic fluctuation. In the future, the collection of clinical data related to TIR should be strengthened. It is also expected that more new drugs with novel mechanisms be developed, such as glucokinase activators, which can restore the normal physiological regulation of glucose, maintain glucose homeostasis, target the underlying causes of diabetes, and thus to reduce and delay the onset and development of diabetic complications effectively.

Diabetic microvascular complications should be detected and treated at the early stage as early intervention can delay the occurrence and development of these chronic complications. If the complications are treated after progressing into late stages, medical treatments will often be more expensive and less effective. The awareness of diabetic complications among Chinese patients is poor let alone the associated preventive and therapeutic treatments. Early screening, prevention and intervention of complications for diabetic patients can improve patients' quality of life and reduce the disease burden.

The limitation of this study is that the prevalences of diabetic microvascular complications were sourced from different studies, resulted in high heterogeneity due to various factors including research group, subjects investigated, study design and implementation, and varied diagnostic criteria for complications, etc. Publication bias cannot be ruled out when performing subgroup analysis. However, meta-analysis can pool the original researches in the most extensive and comprehensive way while making sure the included original researches have met certain quality requirements, which can partially offset the limitations in each original research. Therefore, meta-analysis can enhance the study power and the credibility of the aggregated overall effect estimate.

Since the tiered healthcare delivery service has not been well established in China, patients may elect to go to either a hospital as an outpatient or a community clinic at their own discretion. As such, there is no difference between the hospital outpatients and the community patients in terms of disease characteristics. Most of the studies included in our analysis failed to specify the patient status as of being hospital outpatients or inpatients. Therefore, an analysis by treatment setting (hospital or community) could be largely confounded. This meta-analysis did not investigate the potential difference in prevalences of diabetic microvascular complications between hospitals and community clinics.

Conclusion

The prevalences of DR, DN and DF in patients with T2DM are high in mainland China, leading to heavy disease burdens. Duration of diabetes is positively associated with diabetic microvascular complications, indicating that the government should focus on early diagnosis and treatment of diabetes,

as well as early screening and intervention of any potential complications. In the future, more anti-diabetic drugs with novel mechanisms are expected to be developed to restore glucose homeostasis so as to prevent and delay the onset of diabetic microvascular complications effectively.

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