Meta-Analysis and Meta-Regression of the Prevalence of Diabetic Peripheral Neuropathy Among Patients with Type 2 Diabetes Mellitus

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Abstract

The aim of the present study was to investigate the prevalence of diabetic peripheral neuropathy (DPN) among patients with type 2 diabetes mellitus (DM) using a systematic review and meta-analysis. An electronic search was conducted in the PubMed, Embase, Cochrane and other databases. This search employed articles published from July 1983 to December 2014. Only cross-sectional studies conducted with individuals aged 18 to 75 years old that investigated the prevalence of DPN among type 2 DM were included. Meta-regression and sensitivity analyses were performed to investigate the sources of heterogeneity. Publication bias was assessed via funnel plots and the Begg test. The meta-analysis was performed using the R 3.1.1 software. The study selection process resulted in the inclusion of 27 articles in the meta-analysis. In total, the occurrence of DPN was investigated in 16,337 individuals with type 2 DM. The global prevalence of DPN among patients with type 2 DM was 35.78% (95% CI: 27.86-44.55%). The sensitivity analysis by continent where the studies were performed showed that the prevalence of DPN was higher in Europe (48.14%; 95% CI: 33.31-63.30%). A meta-regression analysis did not show 44.91%. The any cofactors as a cause of the heterogeneity. Our data suggest that the prevalence of DPN among individuals with type 2 DM is high. Due to the impact of the complications of DPN on the quality of life of the affected patients and the cost of care for these complications, this condition should be considered a significant public health problem.

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Keywords

Type 2 Diabetes Mellitus; Diabetic Peripheral Neuropathy; Prevalence, Systematic Review; Meta-Analysis, Evidence-Based Healthcare.

Introduction

Diabetes mellitus (DM) is one of the most common metabolic diseases, and the number of cases has increased worldwide. According to the International Diabetes Federation (IDF), the number of patients with diabetes will increase from 387 million in 2014 to 592 million in 2035. With a global prevalence of 8.3%, DM represents a worldwide problem [1].

This pandemic mainly involves type 2 DM, which remains asymptomatic over a long period of time in many cases and is only diagnosed once the associated complications appear [2].

The most common neuropathies are symmetrical generalized polyneuropathy, especially the distal symmetric polyneuropathy or sensorimotor, called peripheral diabetic neuropathy, followed by the autonomic, sensory-acute; and focal and multifocal, less frequent [3, 4].

More than half of all individuals with diabetes exhibit one or more microvascular complications, including diabetic nephropathy (DN), diabetic peripheral neuropathy (DPN), or diabetic retinopathy (DR), which have a serious negative impact on the quality of life of patients [5, 6].

DPN is a well-known microvascular complication of type 2 DM. DPN is attributed to chronic hyperglycemia and is defined as the presence of peripheral nerve dysfunction in individuals with diabetes after the exclusion of other causes. DPN is associated with infections and is directly associated with increased risk for foot ulceration and nontraumatic amputation. The estimates of foot infections in type 2 DM patients range from a risk of 4% to 7% annually [2, 7].

The symptoms of DPN are intermittent and include persistent limb pain with a tingling or burning sensation, among others. DPN is one of the most debilitating factors for patients. The prevalence of DPN ranges from 30% to 90%. Patients might also develop hypoesthesia or paresthesia with numbness or an "electric shock" sensation [8].

Based on the afore mentioned considerations, as well as the lack of systematic reviews and meta-analyses assessing the association of DPN with DM the results of the present study might contribute to formulating strategies for early screening of DPN patients to achieve more effective diabetic control and reduce the risk of ulceration, gangrene, amputation, and other related consequences [8].

Thus, the aim of the present study was to assess the prevalence of DPN among patients with type 2 DM via a systematic review and meta-analysis.

Methods

Search strategy

An electronic search was conducted in the MEDLINE (via PubMed), Embase, LILACS [Literatura Latino-Americana e do Caribe em Ciências da Saúde (Latin American and Caribbean Health Sciences Literature)], Scopus, Cochrane Central Register of Controlled Trials, IBECs [Índice Bibliográfico Español de Ciencias de la Salud (Spanish Bibliographic Index on Health Sciences)], BIOSIS, and Web of Science databases and was restricted to articles published from July 1983 to December 2013 based on the following MeSH keywords and synonyms: "diabetic neuropathy", "diabetic neuropathies" combined with "Diabetes Mellitus, Type 2", "2 diabetes", "type 2 diabetes", "type 2 diabetes mellitus", and "2 diabetes mellitus type". The search terms were combined using the Boolean operators "AND", "OR", and "NOT".

The references listed in all of the primary studies were retrieved, and a search was also performed in the gray literature. No restrictions regarding publication language were applied, and the search was limited to studies on humans.

The titles and abstracts of articles retrieved via the application of the aforementioned search strategy to the databases were independently analyzed by four researchers. The studies considered to

be potentially relevant and that met the required criteria were selected for full-text reading, which was performed by four researchers. In both steps, instances of disagreement regarding the inclusion or exclusion of studies were resolved by consensus with additional researchers.

Study selection

Cross-sectional studies that included individuals aged 18 to 75 years and that assessed the prevalence of DPN among patients with type 2 DM were included for analysis. Regarding the diagnostic criteria used, individuals with fasting blood glucose levels ≥ 7 mmol/L, casual glucose levels > 11.11 mmol/L, associated with the presence of classic symptoms of diabetes, blood glucose levels > 11.11 mmol/L, two hours after the intake of a 75 g dose of glucose (oral glucose tolerance test), glycated hemoglobin (HbA1c) levels $\geq 6.5\%$ or under medical follow up after having been diagnosed with diabetes before the onset of the corresponding studies were considered diabetic.

The diagnosis of DPN was considered to be adequate when specific validated tests were used, electroneuromyography was performed, and the clinical diagnosis was established by a properly trained professional [9-13].

To minimize interference with the diagnosis of DPN, individuals with myopathies, peripheral vascular diseases, central or peripheral neurological disorders not associated with DM, hypothyroidism, alcoholism, poisoning, moderate-to-severe vitamin deficiencies, uremia, and paraneoplastic or inflammatory conditions were excluded from the meta-analysis.

Data synthesis and statistical analysis

The following data were recorded from the articles: publication year, country, patient ages and genders, and the number of patients with DPN and type 2 DM.

In the meta-analysis, the data regarding the prevalence of DPN among individuals with type 2 DM

were clustered using the random effects method [14, 15] heterogeneity was calculated using the τ^2 and Cochran's Q tests, and inconsistency was expressed as I^2 [16, 17], which describes the percentage of variability that is due to heterogeneity rather than chance [15].

Because heterogeneity was observed, sensitivity analyses were performed to identify the associated cofactors (such as continent) that accounted for the heterogeneity. Potential cofactors associated with heterogeneity (publication year, duration of diabetes, duration of DPN, and average HbA1c level) were also analyzed by a meta-regression [15, 18].

The possible occurrence of publication bias (tendency not to publish studies with negative results) was investigated using the Begg test [19] and analysis by funnel plots [20]. Each point in the funnel plots represents a study, its effect measure, or the prevalence and standard error [20]. A logit transformation of prevalence was performed in each included study to analyze the publication bias [20].

The meta-analysis was performed with R 3.1.1 software (Comprehensive R Archive Network, <http://cran.r-project.org/>), and the results were represented as forest plots [21-23].

Results

The database searches yielded 635 studies eligible for analysis of titles and abstracts. However, 450 articles were excluded due to their experimental or clinical design or association with other diseases, or because they did not report data on the occurrence of DPN among individuals with type 2 DM. As a result, only 186 articles were selected for full-text reading.

Following full-text reading, 158 studies were excluded due to reporting of insufficient data, data duplication, the presence of associated diseases, or meeting the exclusion criteria. Thus, 27 articles were selected for the meta-analysis. The study selection process is depicted in **Figure 1**.

Figure 1: Flowchart representing the process of study selection .

Among the included studies, 08 were conducted in Europe, 11 in Asia, six in the Americas, and two in Oceania, and all studies were published from 1984 to 2013. In total, the occurrence of DPN was

analyzed in 16.337 individuals with type 2 DM (cases) (**Table 1**). The average global prevalence of DPN was 35.78% (95% confidence interval (CI): 27.86%-44.55%) varying from 8.43% (95% CI: 6.21%-

Table 1. Studies included in the meta-analysis.

Author	Country	Continent	Patients with DPN/ T2DM	Prevalence (T2DM) % (95% CI)	Men with T2DM	Women with T2DM	Men with DPN	Women with DPN
Abougambou et al. 2012 [24]	Saudi Arabia	Asia	589/1077	54.60 (51.57-57.60)	476	601		
Acker et al. 2009 [25]	Belgium	Europe	389/767	50.72 (47.12-54.31)	436	331		
Al-Maskari and El-Sadig 2007 [26]	Arab Emirates United	Asia	156/423	36.88 (32.27-41.67)				
Bagavathiappan et al. 2010 [27]	South India	Asia	33/112	29.46 (21.23-38.82)			20	13
Bin Lu et al. 2013 [28]	China	Asia	45/534	8.43 (6.21-11.11)	230	304	13	32
Charles et al. 2011 [29]	Denmark	Europe	329/507	64.89 (60.56-69.05)				
Codogno et al. 2011 [30]	Brazil	America	32/121	26.45 (18.84-35.24)	72	49	23	9
Delcourt et al. 1996 [31]	France	Europe	136/427	31.85 (27.45-36.50)				
Hamdan et al. 2012 [32]	USA	America	29/100	29.00 (20.36-38.93)	59	41		

Author	Country	Continent	Patients with DPN/ T2DM	Prevalence (T2DM) % (95% CI)	Men with T2DM	Women with T2DM	Men with DPN	Women with DPN
Hanley et al. 2004 [33]	Canada	America	147/318	46.23 (40.65-51.88)	111	207		
Jang et al. 2013 [34]	Korea	Asia	64/175	36.57 (29.43-44.17)				
Janghorbani et al. 2006 [35]	Iran	Asia	608/810	75.06 (71.93-78.01)	289	521	216	392
Jarmuzewska and Mangoni 2005 [36]	Australia	Oceania	28/55	50.91 (37.07-64.65)				
Jianbo et al. 2011 [37]	China	Asia	80/227	35.24 (29.04-41.84)				
Kamenov et al. 2010 [38]	Bulgaria	Europe	1344/1705	78.83 (76.81-80.74)	744	961	585	759
Kastenbauer et al. 2003 [39]	Austria	Europe	96/256	37.50 (31.55-43.74)	130	126		
Kiani et al. 2013 [40]	Iran	Asia	264/521	50.67 (46.29-55.05)				
Liang et al. 2005 [41]	Japan	Asia	35/166	21.08 (15.15-28.08)				
Liu et al. 2010 [42]	China	Asia	117/1193	9.81 (8.18-11.64)	594	599		
Paisey et al. 1984 [43]	Mexico	America	205/503	40.76 (36.43-45.19)	199	304	89	116
Pop-Busui et al. 2009 [44]	USA	America	1173/2314	50.46 (48.43-52.50)	1681	687	642	553
Pradeepa et al. 2008 [45]	India	Asia	425/1629	26.09 (23.97-28.29)			195	230
Shaw et al. 1998 [46]	Australia	Oceania	70/847	8.26 (6.50-10.33)	387	460	45	25
Sloten et al. 2011 [47]	Netherlands	Europe	40/100	40.00 (30.33-50.28)	69	31		
Tahrani et al. 2012 [48]	United Kingdom	Europe	112/234	47.86 (41.31-54.47)	136	98		
Voulgari et al. 2011 [49]	Greece	Europe	122/400	30.50 (26.02-35.27)	178	222		
Wang et al. 2011 [50]	USA	America	78/816	9.56 (7.63-11.79)	369	447	37	41
Total			6746/16337	35.37 (27.77-43.80)	6160	5989	1865	2170

CI = Confidence Interval; DPN = Diabetic Peripheral Neuropathy; T2DM = Type 2 Diabetes Mellitus

11.11%) to 78.83% (95% CI: 76.81%-80.74%) (**Figure 2**). The heterogeneity among the studies was high ($I^2 = 99.0\%$; $\tau^2 = 0.9236$; $p < 0.0001$).

In the sensitivity analysis per continent, the prevalence of DPN was higher in Europe (48.14%; 95% CI: 33.31-63.30%) than in the Americas (31.61%; 95% CI: 18.93-47.78%), Asia (32.24%; 95% CI: 20.53-46.69%), and Oceania (23.20%; 95% CI: 2.68-76.80%) (**Figure 3**).

The average age of the participants with type 2 DM was calculated in 22 studies and was found to range from 46.5 ± 13.3 to 64.0 ± 11.6 years old. The average age of the participants with DPN was

included in 10 studies and varied from 53.8 ± 9.8 to 69.6 ± 9.5 years old (**Table 2**). The distribution of the participants with type 2 DM by gender did not indicate any differences (women, $n = 5,989$; men, $n = 6,160$). These characteristics are described in **Table 1**.

The sources of heterogeneity among the studies were investigated by a meta-regression analysis that included clinical cofactors such as year, duration of DM, average duration of DPN, and average HbA1c level. However, the results did not indicate any cofactors as a cause of the heterogeneity (**Figure 4**).

Figure 2: Prevalence of Diabetic Peripheral Neuropathy in Type 2 Diabetes Mellitus patients.

The analysis of the publication bias for the 27 studies included in the meta-analysis is depicted in the funnel plot presented in **Figure 5**. In the plot, which represents the prevalence of cases, the x-axis corresponds to the logit of prevalence, and the y-axis corresponds to the standard error of the

studies. The almost symmetric distribution of the points is suggestive of the absence of publication bias, which was confirmed by the result of the Begg test ($p=0.0764$).

Figure 3. Prevalence of diabetic peripheral neuropathy in type 2 diabetes mellitus patients by continent.

Table 2. Features of the studies included in the meta-analysis.

Author	Mean age ($\pm$ SD or 95% CI) or age group in patients with T2DM (years)	Mean age ($\pm$ SD or 95% CI) or age group in patients with DPN (years)	Duration of diabetes (years)	Duration of DPN (years)	Glycated hemoglobin level in patients with T2DM (mean $\pm$ SD or 95% CI)	Glycated hemoglobin level in patients with DPN (mean $\pm$ SD or 95% CI)
Abougambou et al. 2012 [24]	51-65				8.7 $\pm$ 2.3	
Acker et al. 2009 [25]	63.6 $\pm$ 11.0		11 (6-18)		7.58 $\pm$ 1.29	
Al-Maskari and El-Sadig 2007 [26]	53.0 $\pm$ 13.0					
Bagavathiappan et al. 2010 [27]		62.3 $\pm$ 12.0		15.2 $\pm$ 10.1		8.6 $\pm$ 2.4
Bin Lu et al. 2013 [28]	64.0 $\pm$ 9.9	69.6 $\pm$ 9.5				
Charles et al. 2011 [29]	40-69					
Codogno et al. 2011 [30]	60.1 $\pm$ 8.9					
Delcourt et al. 1996 [31]	35-74					
Hamdan et al. 2012 [32]	53.46 $\pm$ 9.51					
Hanley et al. 2004 [33]	46.5 $\pm$ 13.3		9.0 (3-11)			
Jang et al. 2013 [34]	56.0 $\pm$ 14.0		10.3 $\pm$ 8.3		9.9 $\pm$ 2.3	
Janghorbani et al. 2006 [35]	52.7 $\pm$ 9.9	53.8 $\pm$ 9.8	8.2 $\pm$ 6.8	9.1 $\pm$ 6.9	11.0 $\pm$ 2.4	
Jarmuzewska and Mangoni 2005 [36]	62.6 $\pm$ 8.0	64.9 $\pm$ 8.2	13.0 $\pm$ 9.6	16.3 $\pm$ 10.8	5.7 $\pm$ 1.0	5.8 $\pm$ 1.2
Jianbo et al. 2011 [37]	40-70	65.5 (59.0-70.9)		13.3 (10.2-20.5)		9.0 $\pm$ 3.1
Kamenov et al. 2010 [38]	60.0 $\pm$ 11.9	men 63 (56-70), women 60 (51-67)	men 6 (1-12) women 8(4-13)	men 9(3-15) women 10(5-16)	men 8.7 (7.5-10.5) women 8.7 (7.5-10.1)	men 8.6 (7.5-10.4), women 8.7 (7.5-10.1)
Kastenbauer et al. 2003 [39]	64.0 $\pm$ 11.6		10.3 $\pm$ 8.3		7.9 $\pm$ 1.3	
Kiani et al. 2013 [40]	57.0 $\pm$ 10.6	59.3 $\pm$ 11.6	9.2 $\pm$ 7.4	11.4 $\pm$ 8.0		
Liang et al. 2005 [41]	35-74	54 (44-62)		6 (2-14)		
Liu et al. 2010 [42]	59.17 $\pm$ 11.82		6.45 $\pm$ 6.32		7.41 $\pm$ 1.86	
Paisey et al. 1984 [43]			13.7			

Author	Mean age (±SD or 95% CI) or age group in patients with T2DM (years)	Mean age (±SD or 95% CI) or age group in patients with DPN (years)	Duration of diabetes (years)	Duration of DPN (years)	Glycated hemoglobin level in patients with T2DM (mean±SD or 95% CI)	Glycated hemoglobin level in patients with DPN (mean±SD or 95% CI)
Pop-Busui et al. 2009 [44]	62.4±8.9		10.4±8.7		7.7±1.6	
R. Pradeepa et al. 2008 [45]		60.0±9.0		6.7±6.7		9.0±2.3
Shaw et al. 1998 [46]		56.0±11.0		5 (1-11)		
Sloten et al. 2011 [47]	64.5±9.4		4.0 (2.0-7.0)		6.8±0.8	
Tahrani et al. 2012 [48]						
Voulgari et al. 2011 [49]	58.7±10.1		7.0 (3.0-41.0)		9.17±3.41	
Wang et al. 2011 [50]	57.0±14.0					

DPN = Diabetic Peripheral Neuropathy; T2DM = Type 2 Diabetes Mellitus; SD = Standard Deviation; CI = Confidence Interval

Figure 4: Meta-regression: bubble plot of duration of diabetes in years (a), duration of diabetic peripheral neuropathy in years (b), average glycated hemoglobin level (c), and publication year (d); and Q-Q norm plot of duration of diabetes in years (e), duration of diabetic peripheral neuropathy in years (f), average glycated hemoglobin level (g), and publication year (h).

Figure 5: Funnel plot for the estimation of publication bias.

Discussion

DPN is defined as a neurological disorder caused by progressive loss of the motor, sensory, and autonomic functions of the nerve fibers, which affects the main divisions of the peripheral nervous system in patients with DM [51].

When associated with DM, chronic peripheral neuropathy is a progressive and insidious pathological process. Its severity is associated not only with the signs and symptoms exhibited by patients but also with the fact that it represents the beginning of a pathophysiological process that leads to ulceration and amputation when it is not controlled early in its course [52-54].

The signs and symptoms of sensory-motor neuropathies vary according to the type of nerve fibers that are affected. Damage to the thick fibers might cause reduction of the sensitivity to touch and vibration and decreased sensitivity of proprioception. In turn, damage to the thin fibers causes changes in the sensitivity to pain, temperature, and affective touch. Other associated symptoms include neuropathic pain and paresthesia. In general, both the thick and thin fibers are affected by the neuropathic process; the motor symptoms become more common as the disease progresses [55].

We did not include the prevalence of DPN by gender in the meta-analysis because only a few studies have investigated the occurrence of this condition in men and women separately. However, it is worth noting that in the studies in which this information was available, no gender differences in the predominance of DPN were detected (women, $n = 2,170$; men, $n = 1,865$). This finding is consistent with reports in the literature indicating that the development of DPN does not differ between genders. Previously studies showed no clear association to gender [56]. However, it has been suggested previously that ethnicity may affect the development of neuropathy [57].

The average ages of the individuals with type 2 DM varied from 46.5 ± 13.3 to 64.0 ± 9.5 years old, and the average ages of patients with DPN from varied from 53.8 ± 9.8 to 69.6 ± 9.5 years old. Older age, having diabetes for 10 years or more, and inadequate glycemic control are well-known risk factors for DPN. In addition, smoking, retinopathy, hypertension, obesity, hyperlipidemia, and microalbuminuria have been described as possible risk markers [58].

Several studies have described a longer duration of diabetes as a risk factor for DPN [59-62]. However, the association between diabetes duration and prevalence of DPN might partially depend on the patient's age, which is a risk factor by itself [63]. Our meta-analysis investigated the association

between diabetes duration, age and prevalence of DPN, however, we find no statistically significant of this association.

Our analysis revealed high heterogeneity among the studies ($I^2=99.0\%$; $\tau^2=0.9236$; $p<0.0001$). To investigate this heterogeneity more thoroughly, sensitivity and meta-regression analyses were performed.

Our results showed that the prevalence of DPN was higher in Europe [48.14%, 95% CI: 33.31%-63.30%) than in the Americas (31.61%, 95% CI: 18.93%-47.78%), Asia (32.24%, 95% CI: 20.53%-46.69%), and Oceania (23.20%, 95% CI: 2.68%-76.80%). This distribution is different from that of DM prevalence, which is lower in Europe (7.9%) than the global average (8.3%). In the remaining continents, the prevalence of DM is 11.4% in North America, 8.1% in South America, 8.3% in Asia, and 8.5% in Oceania. It should be noted that the global prevalence of DM is not uniform, with 77% of the affected population living in low- and middle-income countries [1].

Regional characteristics and potential risk factors may have influenced the differences presented, as glycemic control, age, height and duration of T2DM. For every 10 years of T2DM, duration of the risk of DPN increases 73%[64]. The prevalence of DPN, ulcers and amputations is lower among Asian and african-Caribbean compared with European [65], can the person's height explain the DPN be more common among men: longer axons are more exposed to damage [66]. Other modifiable risk factors are metabolic syndrome and its components, such as smoking, also are associated with T2DM [67].

The diagnostic methods used differed among studies due to differences in the study aims. Rather than selecting a diagnostic method based on its efficacy alone, one should also consider the possibility of applying a method specific for the target population. For example, the consensus statement published in January 2012 by the American Diabetes Association attributes a particular value to the entire

scope of clinical aspects (clinical signs and symptoms) as a standard protocol for the screening of DPN instead of using quantitative laboratory tests. The latter are not mandatory due to their restricted availability resulting from their high cost and complexity. In addition, the published studies had small, non-representative samples or even biased designs [68].

However, previously published and ongoing studies describe promising diagnostic methods for DPN, allowing for earlier diagnosis than that based on the clinical signs and symptoms. These methods, particularly the neurophysiological tests, are reproducible and less subjective than the clinical methods [68].

The main tests used for the diagnosis of DPN in the studies included in the meta-analysis were the Neuropathy Disability Score (NDS), Neuropathy Symptom Score (NSS), Michigan Neuropathy Screening Instrument (MNSI), 10 g Semmes-Weinstein Monofilament Examination (SWME), and quantitative sensory testing by the vibration perception threshold (VPT), usually combined with clinical assessment and/or electromyography. These tests are useful for evaluating DPN in research and in the clinic, showing similarities and differences between them. The most of diagnosed neuropathies with these tools are related to T2DM and the reason of high prevalence of DPN in adult with T2DM and more ability of these three tools for large fiber neuropathy screening [69-71].

Regarding the accuracy of the tests, the NDS, NSS, and VTP exhibited 92.31%, 82.05%, and 86.00% sensitivity and 47.62%, 66.67%, and 76.00% specificity, respectively. For the MNSI score cutoff points of 1.5, 2.0, 2.5, and 3.0, the test exhibits 79%, 65%, 50%, and 35% sensitivity and 65%, 83%, 91%, and 94% of specificity, respectively [12].

The accuracy of the SWME was assessed in a systematic review conducted in 2009, which found that its sensitivity ranged from 41% to 93%, and its specificity ranged from 68% to 100% [11].

The evidence regarding the ideal screening method for DPN is currently limited. Nevertheless, many advances have been made for the detection of DPN regarding the results of tests, electrophysiological techniques, and quantitative sensory tests [13].

In our meta-analysis, the global prevalence of DPN among individuals with type 2 DM was 35.78% (95% CI: 27.86-44.55%). According to data in the literature, DPN is the most common long-term complication of diabetes, affecting approximately 50% of patients with type 2 DM (ranging from 30% to 90%). In addition, DPN is characterized as a factor that contributes the most to weakening of patients [8, 63, 68, 70, 72].

Conclusion

The data collected in the present study suggest that the prevalence of DPN among individuals with type 2 DM is high. For that reason, and given the impact of the complications of DPN on the quality of life of the affected patients and the cost of care for these complications, this condition should be considered a significant public health problem.

We recommend interpreting the data reported here cautiously due to the high heterogeneity found among the studies.

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