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Adverse Events Induced by Metformin Treatment in Patients with Type 2 Diabetes Mellitus: Metaanalysis

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Keywords: Metformin; Type 2 Diabetes Mellitus; Vitamin B12, Cardiovascular Disease, Neuropathy

ABSTRACT

Background: Metformin is used as a first-line treatment in patients with type 2 diabetes mellitus and have a significant impact on the prevention of complications associated with type 2 diabetes mellitus.

Aim: To evaluate the effect of metformin treatment on vitamin B12 level and associated events in patientsliving with type 2 diabetes mellitus and further evaluate the efficacy of this drug in the prevention ofcardiovascular disease associated with type 2 diabetes mellitus.

Methods: A literature search was conducted on PubMed-Medline database up to the 07 March 2020. Elevenstudies investigating the impact of metformin in type 2 diabetes mellitus were included in final synthesis after critical evaluation.

Result: Metformin increases risk of vitamin B12 deficiency OR, 95%CI[2.41 [1.58,3.68], p<0.0001],heterogeneity[Chi2=2.47, I2=0%, p=048]; the risk of stroke, retinopathy, anaemia, neuropathy andmyocardial infarction [1.05[0.94,1.18]], heterogeneity [Chi2=3.58, I2=0%, p=0.76].Additionally, metformin treatment was not associated with CVD including hypertension in T2DM OR,95%CI [0.92[0.73,1.16], heterogeneity [Chi2=93.18, I2=89%, P<0.00001].

Conclusion: In this meta-analysis, we conclude that metformin in patients with type 2 diabetes mellitus is associatedwith an increased risk of vitamin B12, stroke, retinopathy, anaemia, neuropathy and myocardialinfarction. Secondly, it prevents cardiovascular diseases and hypertension.

Introduction

Type 2 diabetes mellitus [T2DM] is a metabolic condition characterised by hyperglycaemia resultingfrom insulin resistant or impaired insulin function [1]. T2DM have a high risk of developingcardiovascular disease [CVD] compared to individuals without diabetes [2,3]. The pharmacological therapies currently used in the prevention of secondary complications associatedwith T2DM include metformin; this class of drugs improve insulin sensitivity and reduce body weight [4]. Although this drug provides therapeutic benefits in T2DM patients and associated CVD, there areother concerns it poses to individuals using it, including decreasing serum vitamin B12 levels [5]. In aclinical setting, when it is not detected early or if there is an incorrect diagnosis, this deficiency remainsuntreated, resulting in severe deficiency. Ultimately, this causes megaloblastic anaemia, alteration ofmental states and neurological damage [5-7]. In most cases, diabetic neuropathy symptoms can overlap with pricking, impaired vibration and musclesensation [8].

Thus, peripheral neuropathy as a result of vitamin B12 deficiency may contribute to theaggravation of diabetic peripheral neuropathy [6,7]. The progression of neurologic damage due tovitamin B12 deficiency can be treated if diagnosed early with the administration of vitamin B12 [9]. However, if there is

misdiagnosis, permanent neurological damage may not be reversed [7]. Additionally, these patients present with gastric abnormalities, including diarrhoea, nausea, and loss ofappetite, others may present with a sore and reddened tongue. These abnormalities may result in anunexpected reduction in body weight. Similarly, hepatomegaly and jaundice around the eyes and skinmay also be observed [10]. Although previous studies have reported vitamin B12 deficiency associated with metformin, there iscontradicting outcomes presented. Moreover, some studies show no association [11]; others areshowing positive association. Therefore, we aimed to conduct a first meta-analysis on the effect ofmetformin treatment on vitamin B12 level and associated events in patients living with type 2 diabetesmellitus. Furthermore, to assess the efficacy of this drug in ameliorating cardiovascular diseaseassociated with type 2 diabetes mellitus.

Material and Methods

Preferred Reporting Item for Systematic Reviews and Meta-Analysis [PRISMA] Guidelines [12]

was used when preparing this meta-analysis [Appendix file 1]. The ethics approval was not needed as this study only assess data extracted from already published studies.

Research question

Does metformin treatment alleviate type 2 diabetes mellitus related adverse events?

Search Strategy and Information Source

PubMed-Medline electronic database was used to search for published literature using the MedicalSubject Headings [MeSH] terms ''metformin'', "vitamin B12 deficiency" and ''diabetes mellitus''without language restriction. The studies meeting eligibility criteria were subjected to critical evaluationand included in the final synthesis. The search was for studies published since inception until 07 March2020. The exact search strategy is attached in appendix 1.

Study Selection

The selection procedure was conducted by two authors independently [KM and MSM]. Referencemanager software, Mendeley Desktop version 1.19.4 [Elsevier, Amsterdam, Netherlands] was used tostore retrieved studies. Firstly, we screened studies based on the title and abstract for relevance. Subsequently, the full-text studies were retrieved and critically evaluated for eligibility in the systematicreview and meta-analysis. Additionally, we screened the bibliographical lists of included studies toidentify additional eligible studies that might have been missed on electronic database search.

PECO: P: patients with type 2 diabetes mellitus; E: diabetes status; C: healthy control participants; O: adverse events, including cardiovascular disease, neuropathy, nephropathy, myocardial infarction,hypertension, stroke and anaemia.

Eligibility Criteria

Inclusion Criteria: Randomised control trials, cross-sectional, prospective or retrospective observational and cohortstudies. Mainly studies reporting on the impact of metformin treatment on the development of adverseevents including vitamin B12 deficiency, neuropathy, nephropathy, hypertension, anaemia, myocardialinfarction, retinopathy and stroke were included. Study selection was carried out by KM and MSM, andwhere there was disagreement, the same authors reached a conclusion through discussion and reevaluatingthe study.

Exclusion Criteria: We excluded editorials, letters to editors, case reports, reviews, the study on other treatment other than metformin and studies with no proper control.

Data Extraction and Data Items

Two independent authors [KM and MSM] reviewed each abstract, retrieved full-text studies and extracted information from each study. Relevant data items extracted from each study were primaryauthor surname and year of publication, the country, study design, population size, age and events. Where there was disagreement between the two independent authors, a resolution was reached through discussion and consensus and re-evaluation of study in question. Mendeley reference manager version (1.19.4) software [Elsevier, Amsterdam, Netherlands] was used to save collected data.

Assessment of Risk and Quality

The assessment of the quality of each included study was evaluated using a standard score by independent authors investigators. Cochrane tool was used to assess the risk of bias and quality of the studies. The disagreement between the two independent authors was resolved through discussion and re-evaluation of study in question.

Data Synthesis and Analysis

The Review Manager [RevMan] version 5.3 software [The Nordic Cochrane Centre, The Cochrane Collaboration, 2014] data analysis was used to carry out all the dichotomous data analysis. To determine the odds ratio [OR], the number of events and the total number of participants in the metformin and placebo group were computed. Effects measures were reported as OR and 95% confidence intervals [CI]. OR<1, OR=1, OR>1, classified as not associated with exposure of metformin, metformin not affecting odds of adverse events and metformin-associated with higher odds of adverse events respectively [13]. Heterogeneity was tested with Cochrane chi-square statistics and measured with the Higgins [I2] statistic tests [14]. In the case where heterogeneity was observed, an attempt to find sources of heterogeneity was made through

subgroup analysis and sensitivity tests. The I2 = 0%, I2 = 50%, were no and substantial level of heterogeneity respectively. Considering high clinical heterogeneity, a random effects model was used for meta-analyses in case of substantial heterogeneity while the fixed-effect model was used for studies which showed no presence of heterogeneity. Subgroup analyses were performed according to different events, including CVD, anaemia, neuropathy, retinopathy, nephropathy, stroke, hypertension and vitamin B12 deficiency. Publication bias was visually assessed using the funnel plots [symmetrical shape demonstrating an absence of publication bias]. A probability values of less than 0.05 were considered significant statistically.

Result

Selected Studies

A search on PubMed database yielded 64 studies, based on our eligibility criteria 12 studies [5,15,16-23,24] were critically analysed and further included in the final synthesis (Figure 1).

Figure 1: Flow diagram showing the study selection.

Overview of the Included Studies

All included studies were published in peer-review journals from 2003 to 2018, and their characteristicsare shown in Table 1. The included studies comprised of 25936 participants, 14720 [56.8%] of whomwere T2DM on metformin, and 11216 [43.2%] were T2DM on placebo. The sample size of includedstudies ranged between 31 and 7493 participants. Among the included 11 studies, three wererandomized control trials; three were cross-sectional, two retrospective cohorts, one observationalretrospective cohort, one longitudinal study and one study that was a mixture of an observational, crosssectionalcohort. These studies were conducted all over the world with four studies conducted inNetherland, two in the United States, one in each of the following country [China, Japan, south Arabia,Sweden, and Taiwan] (Table 1S -3S).

Table 1S: Characteristics of included studies.

Study	Country	Design	Population size	Age (years)	CVD	Neuropathy	B12	Anaemia	Nephropathy	Stroke	Hypertension	Retinopathy	MI
Allarbi, 2018	South Arabia	Observational retrospective cohort	Metformin (319)	57.8 ± 0.6	NR	96	30	NR	NR	NR	NR	NR	NR
			Placebo (93)	56.6 ± 1.4	NR	18	2		NR	NR	NR	NR	NR
Aroda, 2016	United States	longitudinal	Metformin (n=859)	56.7 ±10.1	NR	83	37	123	NR	NR	NR	NR	NR
			Placebo (n=856)	56.0 ± 9.9	NR	85	20	90	NR	NR	NR	NR	NR

De Groot-Kamphuis,2013	Netherland	Cross sectional	Metformin (n=164)	62.6 ±11.9	NR	28	23	NR	30	NR	NR	41	NR
			Placebo (n=134)	67.2 ±10.8	NR	38	6	NR	29	NR	NR	29	NR
De Jager resident, 2010	Netherland	Randomised control trial (RCT)	Metformin (n=193)	64 ±10	NR	NR	NR	NR	NR	8	NR	NR	24
			Placebo (n=191)	59 ±11	NR	NR	NR	NR	NR	8	NR	NR	21
Wuffel,2003	Netherland	RCT	Metformin (n=171)	63.2 ±9.8	59	NR	NR	NR	NR	NR	NR	NR	NR
			Placebo (n=182)	58.9 ±11.1	53	NR	NR	NR	NR	NR	NR	NR	NR
Reinstatler,2012	United States	Cross sectional	Metformin (n=575)	63.4 ±11.99	NR	NR	NR	104	NR	NR	NR	NR	NR
			Placebo(n=1046)	66.4 ±16.17	NR	NR	NR	222	NR	NR	NR	NR	NR
Sato,2013	Japan	Cross sectional	Metformin (n=46)	61±11	NR	NR	NR	NR	NR	9	NR	NR	NR
			Placebo (n=38	62±10	NR	NR	NR	NR	NR	7	NR	NR	NR
Hermann, 2004	Sweden	Observational, cross-sectional cohort study	Metformin (n=53)	58.75±11	NR	NR	8	NR	NR	22	28	NR	19
			Placebo (n=31)	64.5±8.25	NR	NR	3	NR	NR	7	18	NR	13
Fung ,2015	China	Retrospective cohort	Metformin (n=7493)	61.70 ± 10.75	NR	NR	NR	NR	NR	NR	5126	NR	NR
			Placebo (n=3800)	62.75 ±10.97	NR	NR	NR	NR	NR	NR	2971	NR	NR
Out, 2018	Netherland	RCT	Metformin (n=196	64 ±10	24	167	NR	NR	NR	NR	NR	NR	NR
			Placebo (n=194)	59 ±11	21	162	NR	NR	NR	NR	NR	NR	NR
Kuan, 2017	Taiwan	Retrospective cohort	Metformin (n=4651)	64.7 ±9.46	NR	NR	NR	NR	NR	NR	3406	641	NR
			Placebo (n=4651)	64.7 ±10.0	NR	NR	NR	NR	NR	NR	3408	623	NR

Note: CDV: Cardiovascular Disease, B12: Vitamin B12, MI: Myocardial Infarction.

Table 2S

Section/Topic	#	Checklist Item	Reported on Page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A

Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-Apr
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data Collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	5

Table 3S

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-Jul
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-Jul
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-Aug
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data), role of funders for the systematic review.	11

Data Synthesis

Vitamin B12 In Type 2 Diabetes Mellitus Patients on Metformin Treatment: The current meta-analysis has shown that T2DM patient on metformin has an increased risk ofdeveloping vitamin B12 deficiency when compared to healthy patient OR, 95%CI[2.41 [1.58,3.68],p<0.0001], interestingly the analysed studies showed no level of heterogeneity[Chi2=2.47, I2=0%,p=048] (Figure 2).

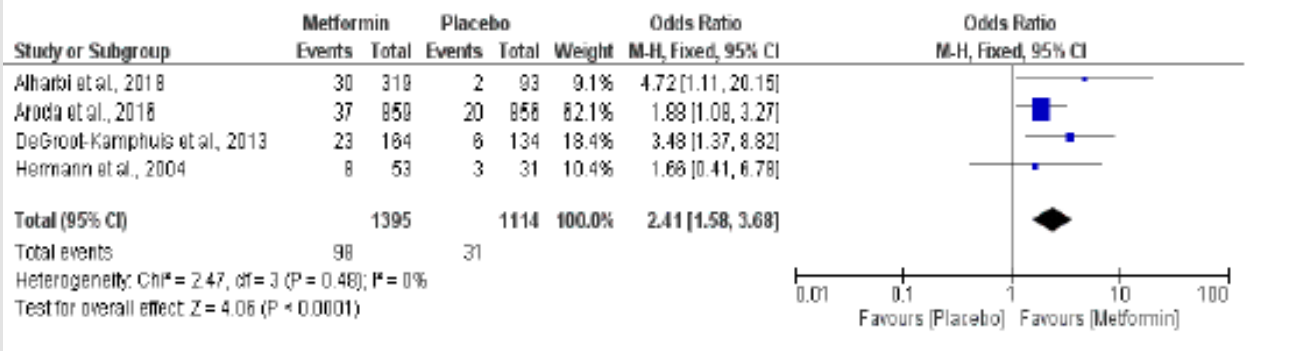

Figure 2: Metformin-induced vitamin B12 deficiency in type 2 diabetes mellitus versus patients onplacebo.

Adverse Events Induced by Metformin Treatment in Type 2 Diabetes Mellitus: According to the current study, patient with type 2 diabetes mellitus on metformin have increased riskof been attacked by stroke compared to T2DM not on metformin treatment OR, 95%CI[1.44 [0.80,2.60], Chi2=1.72, I2=0%, p=0.42], retinopathy [1.04[0.93, 1.17], Chi2=0.30,I2=0%, p=0.58], myocardialinfarction [1.01[0.61,1.69], Chi2=0.50, I2=0%, p=0.96]. The overall effect estimates for these adverseevents also indicated that metformin is associated with an increased risk of stroke, retinopathy andmyocardial infarction [1.05[0.94,1.18]] of interest was absence of heterogeneity which was alsoconfirmed by subgroup analysis[Chi2=1.17, I2=0%, p=0.56] (Figure 3).

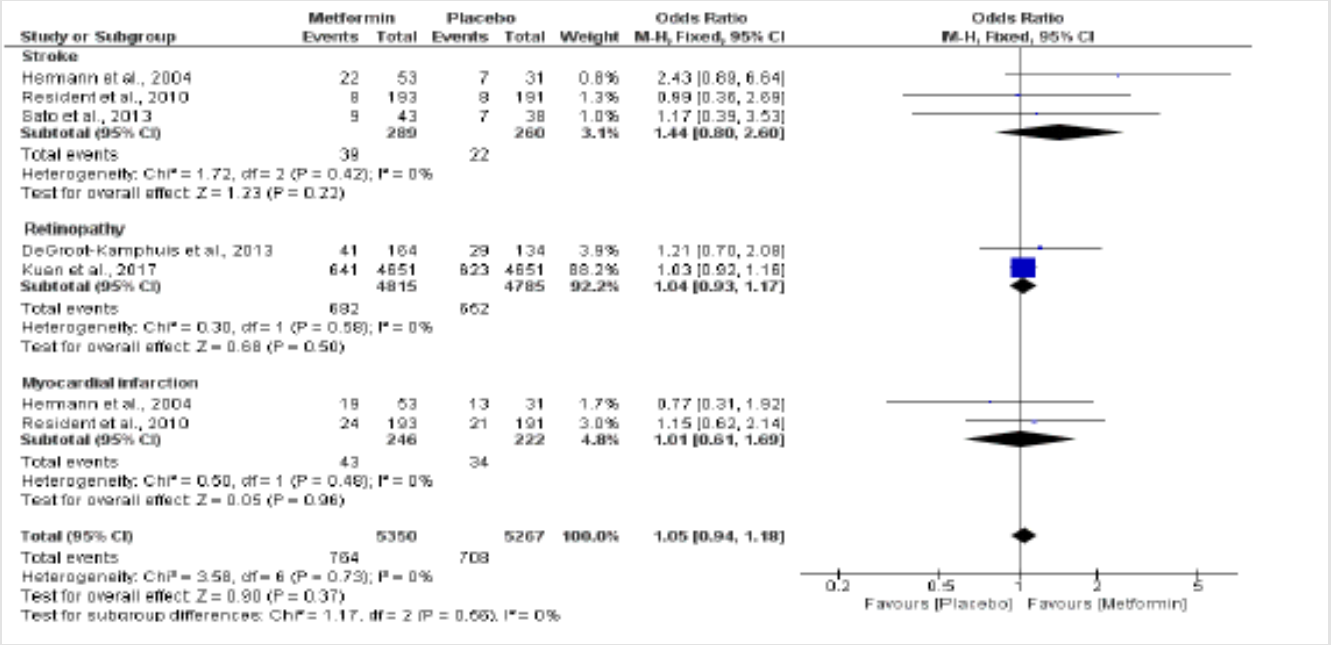

Figure 3: Metformin-induced adverse events in type 2 diabetes mellitus compared to diabetes patientson placebo.

Other Adverse Events Induced by Metformin Treatment: Current metanalysis shows that metformin treatment in type 2 diabetes mellitus patients reduces therisk of developing cardiovascular disease OR, 95%CI [0.81[0.31,2.10], Chi2=5.86, I2=83%, p=0.02],including hypertension [0.78[0.50,1.22], Chi2=57.79, I2=97%. P<0.00001] however shows an increasedrisk of neuropathy [1.00[0.65,1.55], Chi2=9.68, I2=69%] and anaemia [1.08[0.63,1.85], Chi2=7.72,I2=87%, p=0.0005] (Figure 4). The overall pooled effect estimate revealed that metformin treatment isnot associated with these adverse events in T2DM [0.92[0.73,1.16], Chi2=93.18, I2=89%, p<0.00001],as a result of moderate level of heterogeneity, subgroup analysis was performed and it revealed noheterogeneity [Chi2=1.05, I2=0%, p<0.00001] (Figure 4).

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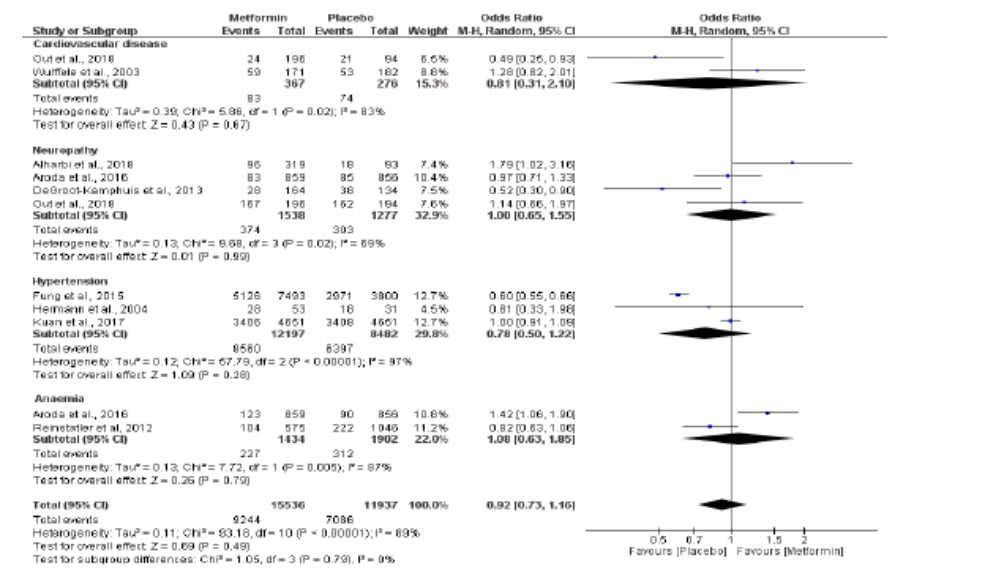

Figure 4: cardiovascular disease and related adverse events triggered by metformin treatment in type2 diabetes mellitus compared to placebo.

Table 1: Sensitivity analysis.

Study weight	OR, 95%CI	I^2	p
Low weight study	0.92(0.73, 1.18)	90	<0.00001
High weight study	0.92(0.71, 1.18)	90	<0.00001

Sensitivity Analysis for Studies That Showed A Substantial Level Of Heterogeneity: A sensitivity test was performed by removing one study at a time, and recalculating the effect measures,by removing low weight study, the OR did not change; however, the direction of confidence intervalslightly changed from [0.92[0.73, 1.16] to [0.92[0.73,1.8]], similarly when high weight study wasremoved we noted a slight change in confidence interval [0.92[0.71,1.18]] (Table 1).

Risk of Bias and Quality Assessment: Studies were scored as good quality when it has four or more positive, which showed a low risk of biasor fair if it has three scores out of six domains. Three studies scored all six positive, thus low risk ofbias in all domains. Four scored four out of possible six domains with two domains classified as a highrisk this included allocation and blinding of participants and personnel. One study was rated high riskin terms of the blinding and incomplete outcome however other four domains were of low risk, andlastly, one study had a fair quality as it has scored 3 points out of possible six domains (Figure 5 & Figure 1S-4S).

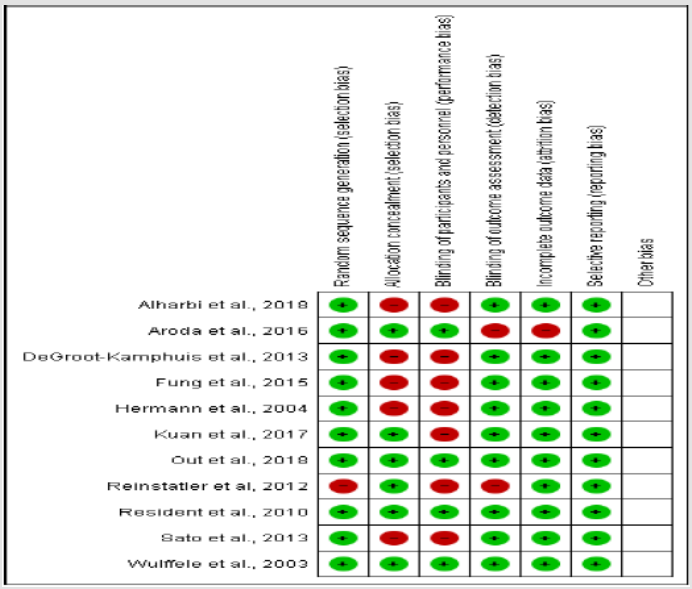

Figure 5: Risk of bias assessment.

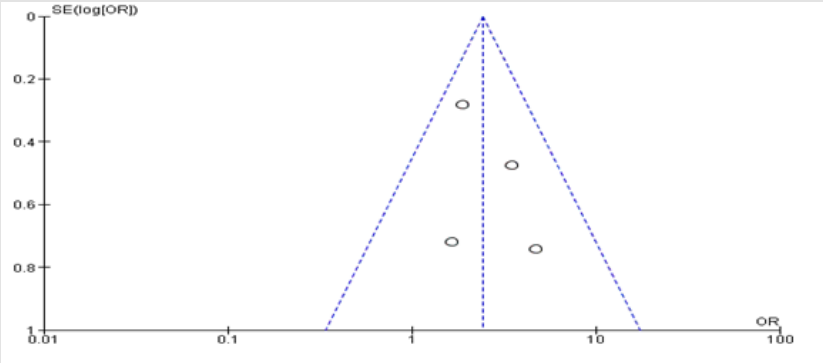

Figure 1S: Symmetrical presentation using funnel plot of vitamin B12 amongst the included studies showing no publication bias.

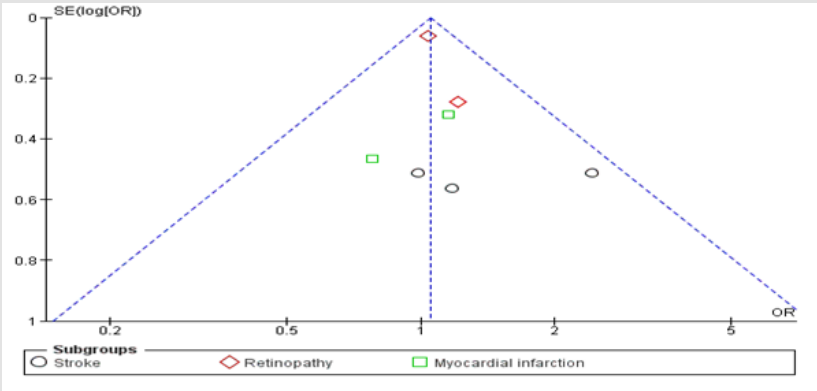

Figure 2S: Funnel plot of adverse events showing no publication bias.

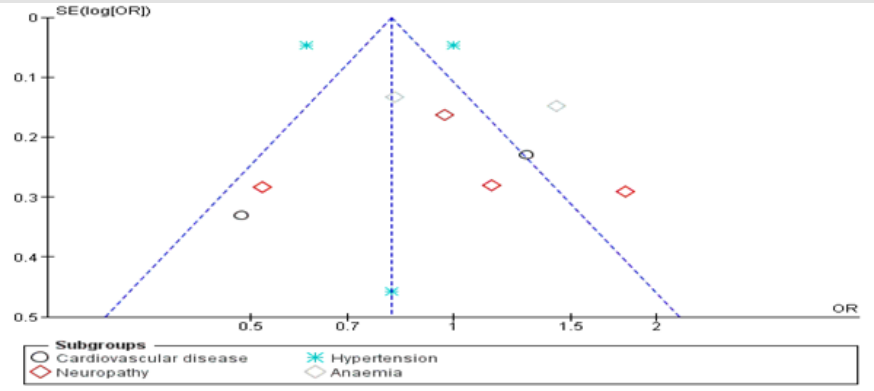

Figure 3S: symmetrical presentation of adverse events showing the absence of publication bias.

Figure 4S: Quality assessment and risk of bias amongst the included studies.

Publication Bias

The risk of publication bias was assessed graphically by use of funnel plots, and amongst all adverseevents in the included studies, there was no evidence of publication bias trough graphical presentationsof funnel plots as indicated in (Figures 1S-3S).

Discussion

This is the primary meta-analysis to evaluate the effect of metformin on the development of adverseevents in patients with type 2 diabetes mellitus. With the current high prevalence of T2DM andcardiovascular disease worldwide we found it necessary to synthesise the current meta-analysis onmetformin treatment and risk of adverse events, to highlight and weigh the therapeutic benefits ofmetformin and its adverse effects in patients with type 2 diabetes.Metformin has been prescribed worldwide as first-line treatment in patients with type 2 diabetesmellitus [16,25], and have a significant impact in reducing secondary complications associated with T2DM. The findings obtained from this meta-analysis included a high risk of developing vitamin B12deficiency associated with metformin treatment. Vitamin B12 deficiency if is prolonged lead tosubsequent adverse events, including neuropathy and anaemia [15-17,20,22,23], and this was evidentin the current study as revealed increased risk of neuropathy and anaemia associated with metformintreatment.This further supports previously published studies which demonstrated an increased risk of anaemiaand neuropathy arising from metformin-induced vitamin B12 deficiency [5,16,17]. Diabetic neuropathycan also manifest other symptoms, including impaired vibration and muscle sensation [8]. Thus,peripheral neuropathy induced by vitamin B12 deficiency due to metformin treatment may contribute tothe severe diabetic peripheral neuropathy [6,7]. The progression of neurological trauma associated withvitamin B12 deficiency is treatable if diagnosed early with the administration of vitamin B12 [9].However, if there is misdiagnosis, neurological damage may not be reversed [7].

Diabetic patients frequently present with anaemia which is common blood disorders resulting intodevelopment and exacerbation into micro and macrovascular complications [26]. It is considered anindicator of kidney disease and increases the risk of developing cardiovascular disease [CVD][27,28]As the first line of defence against cardiovascular disease, it was also revealed in our meta-analysis thatmetformin could alleviate cardiovascular disease, including hypertension. However, we observed anincreased risk of stroke, retinopathy, and myocardial infarction associated with metformin treatment.Our results are suggesting that metformin treatment has therapeutic benefits in terms of preventing CVDin patients living with T2DM; however, we suggest its impact on vitamin B12 levels not to be overlookedas it might result into the manifestation of other complications including neuropathy and anaemia.

Conclusion

Based on the finding synthesised in this meta-analysis, we have shown that type 2 diabetes mellituspatients on metformin treatment have a high risk of developing vitamin B12 deficiency which furtherpredisposes them to neuropathy, and other related adverse events including anaemia, retinopathy, nephropathy, stroke and myocardial infarction, of importance, is its beneficial effects in reducingcardiovascular disease including hypertension.

Strength and Limitation

One of the limitations includes different study design amongst the included studies. With that been said,the study has its strength which ranges from good quality of studies been included. The literature searchwas from inception until 07 march, to make sure we get old studies with background knowledge aboutmetformin and its impacts on type 2 diabetes. Pooling all these studies have increased the statisticalpower as compared to individual study. The combined sample size was sufficient; thus, we can concludethat our meta-analysis was not statistically underpowered. The studies showed no heterogeneity in manyadverse events, and the sensitivity analysis also showed a slight change in effect measures and thefunnels plots showed no presence of publication bias amongst the included studies. The studies werepublished in different regions of the world.

Ethical Considerations

Not required as this is review and analysis of studies that are already published.

Source of Funding

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships thatcould have appeared to influence the work reported in this manuscript.

Author Contribution

KM and MSM contributed equally from conceptualisation, screening, analysis, first draft to the finalapproval for publication of this manuscript.

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