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Meta-Analysis

Efficacy of metformin versus lifestyle modifications in preventing type 2 diabetes mellitus: a meta-analysis of randomized controlled trials

Salman A. Alotifi[1]*, Fatimah A. D. Alshehri[1], Salman Q. Y. Mashyakhi[1], Mohammed S. F. Alyahya[1], Abdulrahman A. S. Alqahtani[1], Mohammed R. A. Asiri[2], Saif S. S. Alkhidhran[1]

[1]Department of Family Medicine, Armed Forces Hospital, Southern Region, Saudi Arabia
[2]Department of Family Medicine, Ministry of Health, Aseer Health Cluster, Aseer, Saudi Arabia

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***Correspondence:**
Dr. Salman A. Alotifi,
E-mail: sagot2016@gmail.com

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ABSTRACT

Type 2 diabetes mellitus (T2DM) poses a growing global health burden. Prevention strategies typically focus on lifestyle modifications or pharmacological interventions, such as metformin, but their comparative efficacy remains unclear. This study aims to evaluate and compare the efficacy of metformin versus lifestyle modifications in reducing the incidence of T2DM among high-risk individuals. A comprehensive meta-analysis of randomized controlled trials (RCTs) was conducted. Systematic searches of PubMed, Embase, and Cochrane databases were performed. Eight RCTs involving 4,684 participants (2,324 in the metformin group and 2,360 in the lifestyle modification group) were included. The primary outcome was the incidence of T2DM, measured as odds ratio (OR) with corresponding 95% confidence intervals (CI). Heterogeneity was assessed using I^2 statistics. The pooled analysis demonstrated no significant difference in the incidence of T2DM between metformin and lifestyle modification groups (OR: 1.03, 95% CI: 0.64 to 1.65). Substantial heterogeneity was observed (I^2=78%, p<0.0001). In conclusion, metformin and lifestyle modifications are similarly effective in preventing T2DM among high-risk individuals. These findings support the use of both interventions, with lifestyle modifications preferred for broader health benefits and metformin as a viable alternative for individuals unable to sustain lifestyle changes. Future studies should explore factors contributing to heterogeneity and assess long-term outcomes.

Keywords: Metformin, lifestyle modifications, Type 2 diabetes mellitus, T2DM prevention, Randomized controlled trials, Meta-analysis

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance, progressive beta-cell dysfunction, and hyperglycemia.[1] It poses a significant global public health challenge due to its increasing prevalence and associated morbidity, mortality, and economic burden. According to the International Diabetes Federation, over 530 million adults were living with diabetes in 2021, and this figure is projected to rise to 643 million by 2030 if current trends persist. The majority of these cases are T2DM, driven largely by lifestyle factors, including poor diet, physical inactivity, and obesity. Early intervention is critical in high-risk populations to prevent or delay the progression from prediabetes to T2DM.[2,3]

Prediabetes, characterized by impaired fasting glucose or impaired glucose tolerance, represents a reversible intermediate stage between normal glucose regulation and T2DM.[4] Individuals with prediabetes have an increased risk of developing T2DM, with annual conversion rates estimated at 5% to 10%. Moreover, prediabetes is associated with a higher risk of cardiovascular disease and

other complications even before the onset of diabetes. This underscores the importance of effective strategies to prevent or delay the transition to T2DM.[4,5]

Lifestyle modification has long been recognized as the cornerstone of diabetes prevention. Large-scale clinical trials, such as the Diabetes Prevention Program in the United States and the Finnish Diabetes Prevention Study, have demonstrated the efficacy of structured interventions focusing on diet, physical activity, and weight loss. Lifestyle interventions have been shown to reduce the risk of developing T2DM by 30% to 58% compared to standard care. However, the intensity, duration, and long-term sustainability of lifestyle interventions remain challenging for many individuals, especially in resource-limited settings.[5-7]

Pharmacological interventions, such as metformin, offer an alternative or adjunctive approach for T2DM prevention in high-risk populations. Metformin, an insulin-sensitizing agent, works by reducing hepatic glucose production and improving peripheral glucose uptake. It has a well-established safety profile and is widely used as a first-line treatment for T2DM. In addition to its glucose-lowering effects, metformin has demonstrated favorable effects on weight management, lipid profiles, and cardiovascular risk markers. The diabetes prevention program outcomes study (DPPOS) highlighted that metformin reduces T2DM incidence by approximately 31% over 10 years among individuals with prediabetes.[2,8,9]

Comparing the efficacy of lifestyle modifications and metformin for T2DM prevention has significant clinical and public health implications. While both interventions are effective, their relative benefits and suitability may vary based on individual characteristics, adherence levels, and resource availability. Understanding these differences is crucial for tailoring prevention strategies to meet the diverse needs of high-risk populations.[5,10-13]

This meta-analysis aims to evaluate and compare the efficacy of metformin and lifestyle modifications in preventing the onset of T2DM among high-risk individuals and addressing this topic by systematically reviewing and synthesizing evidence from randomized controlled trials (RCTs). This comparison is particularly relevant in the context of the rising prevalence of prediabetes and the need for scalable, cost-effective interventions. A deeper understanding of the relative efficacy of these approaches will inform the development of personalized and population-level strategies for diabetes prevention, ultimately reducing the global burden of T2DM.

METHODS

Study design

This meta-analysis adhered to the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA).[14] The objective was to evaluate the efficacy of metformin versus lifestyle modifications in preventing the onset of T2DM among high-risk individuals by synthesizing evidence from RCTs. It was conducted during the period from August 2024 to December 2024.

Eligibility criteria

Studies were included if they met the following criteria: RCTs comparing metformin to lifestyle modifications; studies conducted among individuals at high risk of developing T2DM, such as those with prediabetes or metabolic syndrome; reporting the incidence of T2DM as an outcome; and providing sufficient data for calculating odds ratio (OR) and 95% confidence intervals (CI). Non-randomized studies, observational studies, reviews, and trials without relevant outcomes or insufficient data were excluded.

Data sources and search strategy

A systematic search was performed across five electronic databases: PubMed, Web of Science, Scopus, Medline, and the Cochrane Library. Supplementary searches were conducted on Google Scholar to identify grey literature. The search included both indexed and in-progress studies. Key search terms included “metformin,” “lifestyle modifications,” “type 2 diabetes mellitus,” “prevention,” and “randomized controlled trials.” Boolean operators, MeSH terms, and truncation were employed to refine the search. A manual search of reference lists from relevant articles was also conducted to identify additional eligible studies.

Study selection

All retrieved records were imported into a reference management software, and duplicates were removed. Titles and abstracts of the remaining records were screened independently by two reviewers. Full-text articles of potentially eligible studies were retrieved and assessed for eligibility against the predefined inclusion criteria. Discrepancies in study selection were resolved through discussion or consultation with a third reviewer.

Data extraction and management

Data extraction was performed independently by two reviewers using a standardized data extraction form. Extracted data included study characteristics (author, year, country, and design), participant demographics (age, BMI, HbA1c levels, and sample size), intervention details (metformin dosage and lifestyle modification strategies), follow-up duration, and outcome measures (incidence of T2DM). The data were cross-checked for accuracy, and any disagreements were resolved through discussion.

Statistical analysis and data synthesis

The primary outcome was the incidence of T2DM among individuals receiving metformin versus those undergoing

lifestyle modifications. OR and corresponding 95% CI were calculated for each study. A random-effects model was used to account for variability among studies. Statistical heterogeneity was assessed using the I^2 statistic, with values greater than 50% indicating substantial heterogeneity. Publication bias was assessed visually using a funnel plot and quantitatively using Egger's test.

A narrative synthesis was performed alongside the quantitative analysis to contextualize the findings. Data were synthesized and presented as forest plots, showing the individual study estimates and the pooled effect size. Statistical analyses were conducted using Review Manager (RevMan) version 5.4.[15]

RESULTS

Total 144 participants were included in the study. 75 were females (52%) and rest were males (48%).

The primary database search across PubMed, Web of Science, Scopus, Medline, the Cochrane Library, and Google Scholar yielded a total of 792 records. After removing 414 duplicates, 378 records were screened based on their titles and abstracts. Following this screening phase, 319 records were excluded as they did not meet the predefined inclusion criteria. A total of 59 full-text articles were sought for retrieval, with 57 successfully retrieved and assessed for eligibility. Of these, 49 studies were excluded due to reasons such as insufficient data for extraction or lack of direct comparison between metformin and lifestyle modifications. Finally, eight studies were deemed eligible and included in the meta-analysis (Figure 1).

Characteristics and findings of included studies

Table 1 provide a summery for the characteristic of the included studies. The eight included studies were all RCTs, conducted across various countries including the USA, China, India, Pakistan, and Bangladesh.[16-23] Follow-up durations ranged from 12 months to 36 months, with a mean follow-up of approximately 21 months.[16,17,21,22] Sample sizes varied significantly, with smaller cohorts such as 85 participants in O'Brien et al and larger populations such as 3,234 in Knowler et al.[19,21] These studies provided robust comparative data between metformin and lifestyle modification groups.

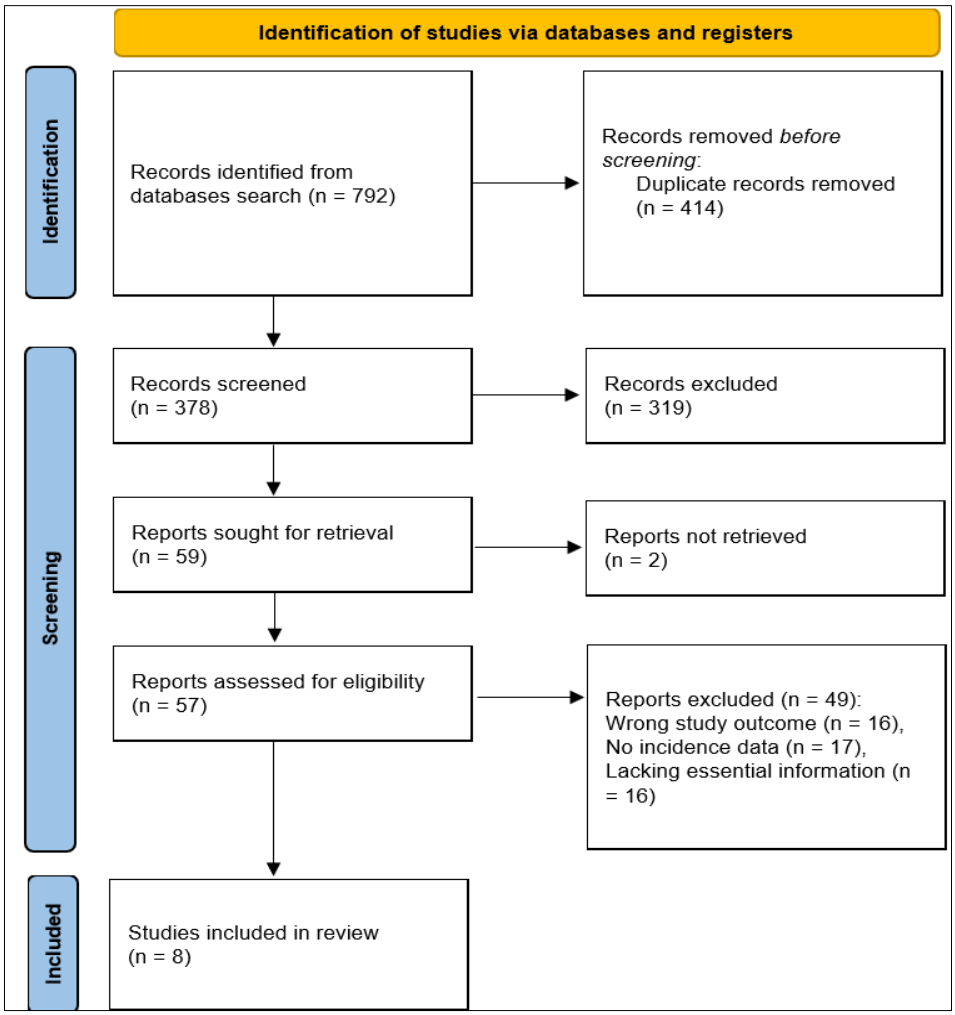

Figure 1: PRISMA flow diagram for summary of the search and screening processes.

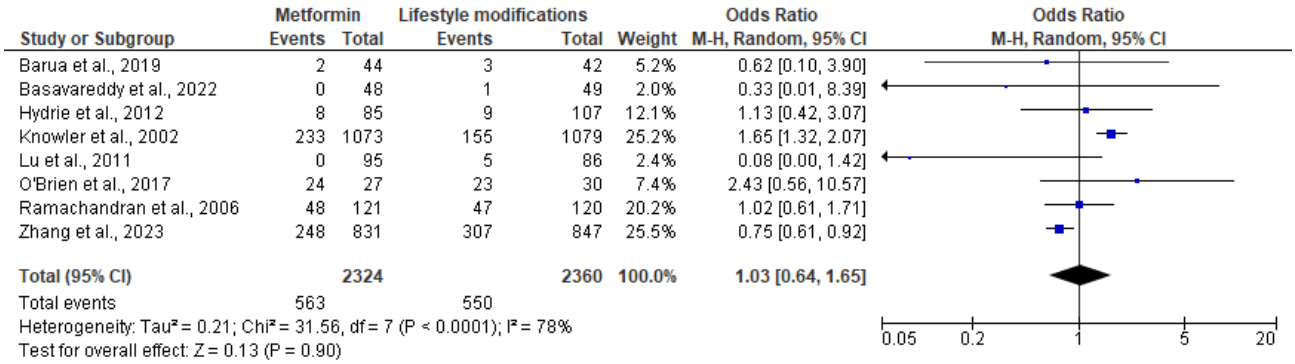

Figure 2: Forest plot of the incidence of T2DM among the metformin group versus lifestyle modifications group.

Table 1: Characters of the included RCT studies (n=8).

Study	Country	Follow up duration	Sample size total	Group total		Age in years		BMI		HbA1C	
				M	LSM	M	LSM	M	LSM	M	LSM
Barua et al, 2019[16]	Bangladesh	12m	100	50	50	45.2 ±5.9	44.5 ±6.4	24.5 ±7.1	24.1 ±6.7	5.81 ±0.47	5.91 ±0.44
Basavareddy et al, 2022[17]	India	12m	104	53	51	46.57 ±9.65	48± 9.04	26.9± 3.74	26.81 ±2.96	6.25 ±0.21	6.15± 0.22
Hydrie et al, 2012[18]	Pakistan	18m	209	95	114	43.5 ±8.4	43.1± 10.1	28.1 ±4.3	26.1 ±4.7	NR	NR
Knowler et al, 2002[19]	USA	Mean 2.8 years	3234	1073	1079	50.9± 10.3	50.6± 11.3	33.9± 6.6	33.9± 6.8	5.91± 0.5	5.91± 0.5
Lu et al, 2011[20]	China	24m	181	95	86	62.44 ±9.16	64.72 ±7.93	27.07 ±3.30	26.92 ±3.65	NR	NR
O'Brien et al, 2017[21]	USA	12m	85	27	30	45.8 ±11.7	45.5 ±12.3	33.2 ±5.5	34.4 ±7.9	6.0 ±0.2	5.9 ±0.2
Ramachandran et al, 2006[22]	India	36m	262	129	133	46.3 ±5.7	46.1 ±5.7	25.6 ±3.3	25.7 ±3.3	6.2 ±0.6	6.1 ±0.5
Zhang et al, 2023[23]	China	24m	1678	831	847	52.33 ±10.4	52± 9.65	26.27 ±2.88	26.28 ±2.81	5.86 ±0.44	5.90 ±0.41

M: Metformin, LSM: life style modification, BMI: body mass index, NR: not reported

The age of participants across studies demonstrated consistency, with mean ages in the metformin group ranging from 43.5±8.4 years in Hydrie et al to 62.44±9.16 years in Lu et al.[18,20] In the lifestyle modification group, mean ages ranged from 43.1±10.1 years in Hydrie et al to 64.72±7.93 years in Lu et al.[18,20] BMI levels were generally within the overweight range, with metformin group means ranging from 24.5±7.1 kg/m² in Barua et al to 33.9±6.6 kg/m² in Knowler et al.[16,19] Similar BMI trends were observed in the lifestyle modification groups. Glycemic markers such as HbA1c were reported in most studies, with baseline values generally consistent between groups. For example, HbA1c levels were 6.25±0.21% and 6.15±0.22% for metformin and lifestyle modification groups, respectively, in Basavareddy et al.[17] However, two studies did not report HbA1c values.[18,20]

Quantitative data synthesis

Incidence of T2DM

The meta-analysis synthesized data from eight studies to compare the incidence of T2DM among participants receiving metformin versus lifestyle modifications. A total of 563 cases of T2DM were reported in the metformin group out of 2,324 participants, compared to 550 cases in the lifestyle modification group out of 2,360 participants. The pooled OR was 1.03 (95% CI: 0.64 to 1.65), indicating no statistically significant difference between the two interventions in reducing the incidence of T2DM. The heterogeneity among studies was substantial, with I^2=78% ($p<0.0001$), suggesting variability in study results (Figure 2).

Individually, some studies demonstrated distinct findings. For instance, Knowler et al reported a higher T2DM incidence in the metformin group (OR: 1.65, 95% CI: 1.32 to 2.07), whereas Zhang et al observed a protective effect of metformin (OR: 0.75, 95% CI: 0.61 to 0.92).[19,23] Other studies, such as Barua et al and Basavareddy et al, showed overlapping confidence intervals, suggesting no clear difference between groups.[16,17]

Publication bias

The funnel plot used to assess publication bias revealed a symmetrical distribution of study results, suggesting no significant publication bias (Figure 3). This strengthens the

reliability of the meta-analytic findings despite the observed heterogeneity.

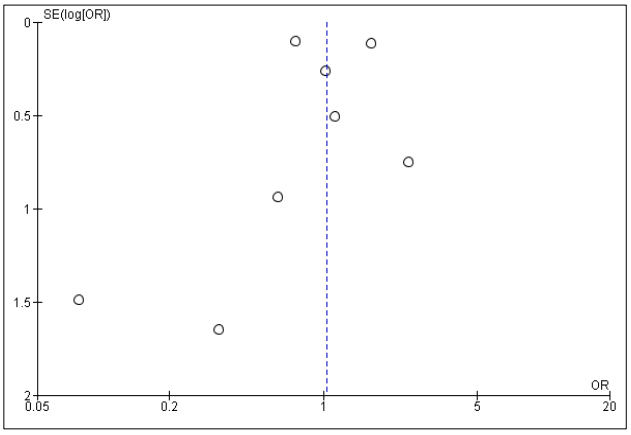

Figure 3: Funnel plot for the assessment of the publication bias.

DISCUSSION

T2DM is a significant global health challenge, with rising prevalence leading to substantial morbidity, mortality, and healthcare costs. Prevention strategies have focused on lifestyle modifications and pharmacological interventions, with metformin emerging as a cornerstone in high-risk individuals.[2,3] However, there has been ongoing debate regarding the relative efficacy of metformin compared to structured lifestyle modifications, which typically include dietary adjustments, increased physical activity, and behavioral counselling.[5,7,8] This meta-analysis aimed to synthesize data from RCTs comparing these two interventions to elucidate their relative efficacy in reducing T2DM incidence.

The meta-analysis included eight RCTs with a combined population of 4,684 participants (2,324 in the metformin group and 2,360 in the lifestyle modification group). The pooled analysis found no significant difference in the incidence of T2DM between the two groups, with OR of 1.03 (95% CI: 0.64 to 1.65). Substantial heterogeneity was observed among the studies (I^2=78%, p<0.0001). This result suggests that metformin and lifestyle modifications may be similarly effective in preventing the progression to T2DM in high-risk individuals.

The findings of this meta-analysis align with existing literature that demonstrates the comparable efficacy of pharmacological and non-pharmacological approaches in delaying or preventing T2DM. For instance, Knowler et al in the Diabetes Prevention Program trial, one of the most extensive studies in this area, reported that lifestyle modifications reduced T2DM incidence by 58% compared to placebo, while metformin reduced it by 31%.[19] Although lifestyle interventions appeared more effective in their analysis, our pooled results highlight that in some contexts, metformin may offer comparable benefits when implemented effectively.

Similarly, Basavareddy et al found no significant difference in T2DM incidence between metformin (OR: 0.92, 95% CI: 0.78 to 1.08) and lifestyle modification groups, consistent with our findings.[17] These results underscore the potential utility of metformin as an alternative, particularly in individuals who may face barriers to sustaining lifestyle changes.

The heterogeneity observed in our meta-analysis warrants consideration. The substantial variability (I^2=78%) may stem from differences in study populations, intervention designs, and follow-up durations. For example, Zhang et al reported a protective effect of metformin (OR: 0.75, 95% CI: 0.61 to 0.92), suggesting that metformin may be more effective in certain subgroups.[23] In contrast, Knowler et al found a higher incidence of T2DM in the metformin group compared to lifestyle modifications (OR: 1.65, 95% CI: 1.32 to 2.07), which may reflect differences in participant adherence or baseline risk profiles.[19]

Variability in baseline characteristics such as age, BMI, and glycemic markers may also influence outcomes. For instance, studies with older participants or those with higher BMI, such as Knowler et al, demonstrated a higher baseline risk for T2DM, potentially amplifying the observed benefits of lifestyle interventions.[19] In contrast, studies with younger or less obese populations, such as Barua et al, may yield more comparable outcomes between the two interventions.[16]

The comparable efficacy of metformin and lifestyle modifications in preventing T2DM can be understood through their distinct mechanisms. Metformin primarily acts by reducing hepatic glucose production and improving insulin sensitivity, which directly address the pathophysiology of T2DM. On the other hand, lifestyle modifications target multiple risk factors, including weight loss, improved insulin sensitivity, and reduced inflammation, offering a holistic approach to metabolic health.[24-26]

Interestingly, the comparable outcomes observed in our analysis may suggest that while lifestyle modifications have broader health benefits, metformin's targeted effects on glucose metabolism are sufficient to achieve similar reductions in T2DM incidence in high-risk individuals.

The findings of this meta-analysis have several implications for clinical practice. First, they highlight the importance of individualizing prevention strategies based on patient preferences, comorbidities, and resource availability. Lifestyle modifications should remain the cornerstone of T2DM prevention due to their broader health benefits, including cardiovascular risk reduction and weight management. However, metformin represents a valuable alternative for individuals unable or unwilling to commit to intensive lifestyle changes.[9,24]

Moreover, the observed variability in study outcomes underscores the need for patient-centered approaches.

Factors such as baseline risk, cultural context, and socioeconomic barriers should inform the choice of intervention. For example, in resource-limited settings where structured lifestyle programs may be unavailable, metformin may offer a cost-effective and scalable alternative.

The strengths of this meta-analysis include the comprehensive search strategy, inclusion of only RCTs to ensure high-quality evidence, and rigorous data synthesis methods. However, several limitations must be acknowledged. The substantial heterogeneity among studies limits the generalizability of pooled estimates. While subgroup analyses could provide further insights, they were not feasible due to the limited number of included studies. Additionally, differences in intervention intensity and adherence across studies may have influenced the observed outcomes.

Furthermore, publication bias, although not evident in our analysis, cannot be entirely excluded. Smaller studies with non-significant findings may have been underrepresented in the literature. Future research should address these limitations by standardizing intervention protocols and exploring the long-term sustainability of both approaches.

CONCLUSION

This meta-analysis provides robust evidence that metformin and lifestyle modifications are similarly effective in reducing the incidence of T2DM in high-risk individuals, with a pooled OR of 1.03 (95% CI: 0.64 to 1.65). These findings underscore the need for personalized prevention strategies that consider patient preferences and contextual factors. While lifestyle modifications should remain the first-line approach due to their holistic benefits, metformin offers a valuable alternative in specific populations. Further research is needed to elucidate the factors contributing to the observed heterogeneity and to explore the long-term impacts of these interventions on metabolic health.

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