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Cost-effectiveness of metformin in the prevention of Type 2 diabetes mellitus: A systematic review

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ABSTRACT

Background and aims: Type 2 diabetes mellitus (T2DM) is a common metabolic disorder with serious complications. Prediabetes treatment with metformin or lifestyle changes has been shown to delay the progression of prediabetes to T2DM, thus alleviating the overall economic burden associated with T2DM. This systematic review was conducted to evaluate the cost-effectiveness of metformin in the treatment of prediabetes. Methods and results: A PRISMA-guided systematic review was performed on databases: Pubmed, Cochrane, and Embase with appropriate keywords and phrases. CHEERS checklist was used to evaluate the studies' quality. Research characteristics and outcomes were examined, and Incremental cost-effective ratio (ICER) was converted to the USD 2020. With 402 articles identified through the search strategies, 16 articles that met the selection criteria were included for analysis in this review. All articles were deemed to be of relatively good quality according to CHEERS checklist. These analyses were conducted in developed countries from different perspectives and time frames. One of 16 studies revealed metformin as cost-saving compared to placebo, while the remaining studies reported metformin to be cost-effective compared to placebo, no intervention, or standard care, with ICERs below the willingness-to-pay threshold (ranging from $457/QALY to $164,621/QALY). However, conclusions regarding the cost-effectiveness of metformin versus lifestyle changes varied depending on different perspectives and program intensity. Conclusion: Metformin was dominant or cost-effective compared to placebo and no interventions in the treatment of prediabetes. However, the question about cost-effectiveness of metformin versus lifestyle change remained a subject of controversy among the studies. Further investigation into the cost-effectiveness of metformin compared to lifestyle change was recommended, particularly in developing countries where there is a high prevalence rate and limited healthcare resources.

Keywords*: systematic review, cost-effectiveness, metformin, prediabetes*

1. INTRODUCTION

Prediabetes is a metabolic condition that remains between normoglycemia and diabetes, including impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or both disorders [1]. Prediabetes diagnostic criteria have evolved over time and vary based on the institution of origin. Individuals with IGT and IFG face an elevated risk of developing diabetes. Within 3 to 5 years, around 25% of patients with prediabetes progress to T2DM, and up to 70% of those with prediabetes develop overt diabetes during their lifetime [2]. Besides, according to the report of the International Diabetes Federation (IDF) in 2019, people over 65 years old accounted for 20% of the total 483 million diabetic patients. In low and middle-income countries, the proportion of diabetes in urban areas is 64.24% and 79%, respectively. The report also indicates that global health expenditure related to diabetes comprise 10% of total healthcare costs, amounting to

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approximately 60 billion USD annually [3]. Therefore, early detection and prevention through effective medications and lifestyle intervention have been shown to have a positive impact on health outcomes and reduce the economic burden of the disease. The Diabetes Prevention Program (DPP) is one of the clinical trials that demonstrated the effectiveness of metformin in reducing conversion rate by 31% at 3 years of follow-up and 18% at 10 years in prediabetic patients [4]. The cost-effectiveness Metformin in the treatment of prediabetes presents a significant consideration for medication use, particularly within constrained healthcare budgets. As a result, this review study aims to thoroughly synthesize the current evaluations of the cost-effectiveness of metformin in the treatment of prediabetes, thereby providing a foundation for its pharmacological application in other countries.

2. MATERIALS AND METHODS

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline following four steps, including searching, screening and selecting, evaluating research quality, and extracting and synthesizing data. Two researchers independently reviewed and selected articles based on the titles and abstracts. Reports which met the eligibility criteria underwent quality assessed, followed by data extraction and synthesis. Any disagreements were resolved through discussion with a third researcher until a consensus was reached. The same procedures were applied for both quality assessment and data extraction.

Search strategy

The study objective was formalized using the PICOS format:

- Population: Prediabetes patients.
- Intervention: Metformin
- Comparators: Any type of treatment for prediabetes.
- Outcome: Incremental cost-effectiveness ratio (ICER), incremental cost-utility ratio (ICUR), net monetry benefit (NMB).

We searched on PubMed, Cochrane Library, and EMBASE using a combination of terms such as “metformin”, “impaired glucose tolerance”, “prevention diabetes”, “impaired fasting glucose”, “prediabetes”, “cost-effectiveness”, “cost-benefit”, “cost analysis”, “cost-utility”, “economic evaluation”, and boolean conjunctions including “AND”, “OR” to find related studies from the databases until October 1, 2021. Detailed search strategies are presented in the Supplementary file.

Eligibility criteria for screening and selecting

We included original studies that evaluated the cost-effectiveness of metformin in the treatment of prediabetes. Only publications written in English were accepted, with no restrictions on the publication date. Articles that did not report the aforementioned outcomes as well as systematic reviews, conference abstracts, treatment guidelines, case reports, were excluded.

Quality evaluation

The quality of the selected studies was assessed according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [5]. This checklist consisted of 24 criteria recommendations for reporting to provide clear and comprehensive picture of health economic evaluations. We assigned 0 to criteria that were not stated, 0.5 to criteria that were partially mentioned, and 1 to criteria that were fully mentioned.

Data extraction and synthesis

Information of qualified studies were extracted. These included study characteristics (author name, country, study year, population, opinion, currency), study design (interventions and comparisons, model, duration, outcome measures, sensitivity analysis, discount rates, cost reference dates), and study results (clinical outcomes, cost results, ICER value). ICERs were converted to US dollars in 2020 using the Consumer Price Index (CPI) and exchange rates from the World Bank Database 2020 [6] according to the following formula:

$$ICER_{2020} = ICER_{\text{year of the study}} * (CPI_{2020}/CPI_{\text{year of the study}})* \text{Exchange rate}$$

3. RESULTS AND DISCUSSIONS

3.1. RESULTS

3.1.1. Study selection

A total of 402 articles were identified, including 128 articles from Pubmed, 102 articles from Cochrane, and 172 studies from Embase. Of these, 47 relevant studies met the inclusion criteria,

while 31 articles were subsequently eliminated based on the exclusion criteria. Specifically, 11 articles did not involve the cost-effectiveness analysis, 15 articles did not report ICER index, 3 articles were the review, 1 article lacked full text, and 1 article was not written in English. Eventually, 16 qualified articles were detected for the overview (Figure 1).

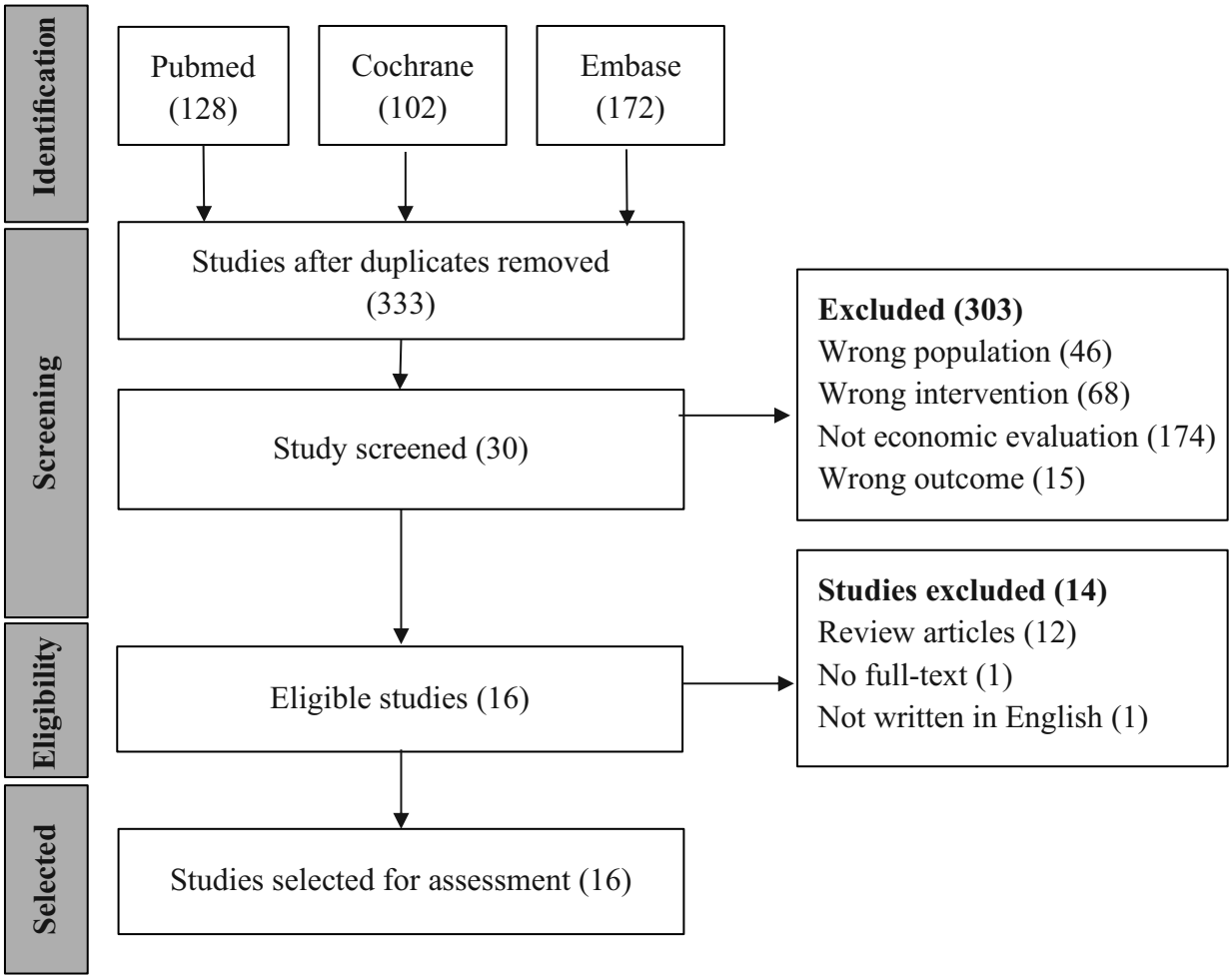

Figure 1. PRISMA flowchart of search results and selection

3.1.2. Quality evaluation

Table 1 presents reporting assessment of the selected studies based on CHEERS checklist. Quality of the studies did not differ significantly with a mean value of 20.94, ranging from 19.5 to 22.5 points. In which, the study of Eddy (2005) [7] satisfied most of the evaluation criteria with the highest total score (22.5/24).

Table 1. Evaluation of research quality

Author (year)	DPP Research Group (2003) [8]	Palmer et al. (2004) [9]	Caro et al. (2004) [10]	Eddy et al. (2005) [7]	Herman et al. (2005) [11]	Icks et al. (2006) [12]	Ramachandran et al. (2007) [13]	Bertram et al. (2010) [14]
Total score	19.5	22	22	22.5	19.5	20.5	22	20
Author (year)	Schaufler and Wolff (2010) [15]	Palmer et al. (2012) [16]	DPP Research Group (2012) [17]	Herman et al. (2013) [18]	Png et al. (2014) [19]	Roberts et al (2018) [20]	Islek et al. (2020) [21]	Vanden-berghe et al. (2021) [22]
Total score	20.5	20	21	20.5	21	21	20	22

DPP, diabetes prevention program

3.1.3. Study characteristics

Table 2 presents the characteristics of 16 selected studies.

Studies were carried out across various regions from Asia (Singapore, India) [13, 19, 21] to Europe (UK, Germany, Switzerland, France, Belgium) [9, 12, 15, 18, 22], America (USA, Canada) [8, 10, 11, 17, 20] and Oceania (Australia) [9, 14, 16], which publication years ranging from 2003 to 2021. The primary subjects were patients at risk of diabetes with various types of intermediate hyperglycemia such as IFG (Impaired Fasting Glucose), IGT (Impaired Glucose Tolerance), and HbA1c-at-risk. Seven studies conducted from the health system perspective [8, 11, 13, 14, 17, 19, 22], 9/16 studies were based on societal perspective [7, 8, 11, 12, 17, 19-22], 6/16 studies based on the payer's perspective [9, 10, 12, 15, 16, 21]. In addition, research by David M. Eddy in the US was carried out from the perspective of the patient [7].

Most research applied modelling techniques: decision tree [18, 19], Markov [9-11, 15, 16, 18, 22], discrete-time micro-simulation [14], generalized γ regression [21], decision analytic ''[12], Archimedes [13], and hypothetical models Ramachandran (2007) [13], with the exception of Herman et al.[18] and DPP Research Group (2003) [8, 17]. The time horizon varied across studies, ranging from 3 years to 50 years with a cycle from 1 month to 1 year. Patient's lifetime was also a common time frame for the cost-effectiveness studies[9, 11, 14, 15].

Based on the study perspectives, All studies evaluated direct costs while some assessed indirect costs, such as those by Bertram (2010) [14], Png (2014) [19], Eddy (2005) [7], Désirée Vandenberghe [22], A. Icks [12]. However, certain studies that adopted the perspective of societal did not include indirect costs [11, 14, 17, 21]. Therefore, the cost of interventions might be underestimated.

In terms of efficacy outcomes, QALYs (Quality Adjusted Life Years) [7, 11, 15-20, 22] were used in 9 out of 16 studies, DALYs (Disability Adjusted Life Years) in 1 study [14], LYGs (life-years gained) in 2 studies [9, 10], 1 case of diabetes prevented in 2 studies [12, 13]. Some research reported more than one outcomes, i.e. DPP Research Group (2003) (QALYs and 1 case of diabetes delayed prevented) [8], D. Islek et al. (2020) (1% point diabetes risk reduction, a case of diabetes prevented/delayed, QALYs, VAS-ALY) [21].

Nearly all studies applied a discount rate of 3% for both costs and clinical outcomes, except W.H. Herman (2013) [18], which used a rate of 3.5%. The discount rate at 5% was applied in the study of Palmer (2012) [16], Schaufler (2010) [15], Caro (2004) [10], and Islek (2020) [21]. Désirée Vandenberghe (2021) [22] discounted at 3% for costs, and 1,5% for effectiveness. Palmer (2004) [9] applied various discount rates of 1.5%, 5%, and 6% according to the subject countries. No discount rate was applied in the study of Ambady Ramachandran (2007) [13] and A. Icks (2006) ''[12] due to the short horizon (3 years).

All studies performed at least one sensitivity analysis to assess the model uncertainty. Most of these were deterministic sensitivity analysis, which examined the uncertainty of base case results by varying specific parameters. Other techniques were applied such as probabilistic analysis[11, 12, 16, 22], scenario analysis.

Table 2. Characteristics of selected studies

Author (Year)	Country	Perspective	Study design	Time horizon	Type of cost	Effectiveness	Discount rate	Sensitivity analysis
Eddy et al (2005) [7]	USA	Patient, society	Archimedes model	5-30 years	Direct and indirect cost	QALY	3%	DSA
DPP Research Group (2003) [8]	USA	Healthcare system, society	Trial-based	3 years	Direct and indirect cost	QALY, a case of diabetes delayed or prevented	3%	DSA

Author (Year)	Country	Perspective	Study design	Time horizon	Type of cost	Effectiveness	Discount rate	Sensitivity analysis
Palmer et al (2004) [9]	Australia, Germany, France, Switzerland, UK	Third-party reimbursement payer	Markov model	Lifetime	Direct cost	LYG	Australia, Germany, France, Switzerland: 5% UK: 1.5% (effec-tiveness), 6% (cost)	DSA, PSA, scenario analysis
Caro et al (2004) [10]	Canada	Payer	Markov model	10 years	Direct cost	LYG	5%	DSA
Herman et al (2005) [11]	USA	Healthcare system, society	Markov model	Lifetime	Direct cost	QALY	3%	DSA, PSA
Icks et al (2006) [12]	Germany	Health insurance, society	Decision analytic model	3 years	Direct and indirect cost	A case of diabetes prevented	0%	PSA
Ramachandran et al (2007) [13]	India	Healthcare system	Hypothetical models	3 years	Direct cost	A case of diabetes prevented	0%	PSA
Bertram et al (2010) [14]	Australia	Healthcare system	Discrete-time micro-simulation model	Lifetime	Direct cost	DALY	3%	PSA
Schaufler and Wolff (2010) [15]	Germany	Health insurance	Markov Monte Carlo micro-simulation model	Lifetime	Direct cost	QALY	5%	DSA
Palmer et al (2012) [16]	Australia	Third-party payer	Semi-Markov model	10 years	Direct cost	QALY	5%	DSA, PSA
DPP Research Group (2012) [17]	USA	Healthcare system, society, modified society	Trial-based	10 years	Direct cost	QALY	3%	DSA
Herman et al (2013) [18]	USA	Healthcare system, society, modified society	Trial-based	10 years	Direct cost	QALY	3%	DSA
Png et al (2014) [19]	Singapore	Healthcare system, society	Decision tree model	3 years	Direct and indirect cost	QALY	3%	DSA, scenario analysis

Author (Year)	Country	Perspective	Study design	Time horizon	Type of cost	Effectiveness	Discount rate	Sensitivity analysis
Roberts et al (2018) [20]	UK	Healthcare system	Decision tree, Markov model	50 years	Direct cost	QALY	3.5%	DSA, PSA, scenario analysis
Islek et al (2020) [21]	India	Multipayer, society	Generalized γ regression, linear model	3 years	Direct cost	VAS-ALY. 1% diabetes risk reduction, a case of diabetes prevented; QALY	5%	DSA, PSA
D. Vandenberghe (2021) [22]	Belgium	Healthcare system, society	Semi-Markov model	Intervention: 3 years; costs: 10 years	Direct and indirect cost	QALY	Cost: 3%; Effecti-veness: 1.5%	DSA, PSA

QALYs, Quality Adjusted Life Years; DALYs, Disability Adjusted Life Years; LYGs, life-years gained; VAS-ALY, Visual Analog Scales; PSA, probabilistic sensitivity analysis; DSA, deterministic sensitivity analysis; DPP, diabetes prevention program; a: Excluding participant time

Studies were carried out across various regions from Asia (Singapore, India) [13, 19, 21] to Europe (UK, Germany, Switzerland, France, Belgium) [9, 12, 15, 18, 22], America (USA, Canada) [8, 10, 11, 17, 20] and Oceania (Australia) [9, 14, 16], which publication years ranging from 2003 to 2021. The primary subjects were patients at risk of diabetes with various types of intermediate hyperglycemia such as IFG (Impaired Fasting Glucose), IGT (Impaired Glucose Tolerance), and HbA1c-at-risk. Seven studies conducted from the health system perspective [8, 11, 13, 14, 17, 19, 22], 9/16 studies were based on societal perspective [7, 8, 11, 12, 17, 19-22], 6/16 studies based on the payer's perspective [9, 10, 12, 15, 16, 21]. In addition, research by David M. Eddy in the US was carried out from the perspective of the patient [7].

Most research applied modelling techniques: decision tree [18, 19], Markov [9-11, 15, 16, 18, 22], discrete-time micro-simulation [14], generalized γ regression [21], decision analytic ''[12], Archimedes [13], and hypothetical models Ramachandran (2007) [13], with the exception of Herman et al.[18] and DPP Research Group (2003) [8, 17]. The time horizon varied across studies, ranging from 3 years to 50 years with a cycle from 1 month to 1 year. Patient's lifetime was also a common time frame for the cost-effectiveness studies [9, 11, 14, 15].

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Nearly all studies applied a discount rate of 3% for both costs and clinical outcomes, except W.H. Herman (2013) [18], which used a rate of 3.5%. The discount rate at 5% was applied in the study of Palmer (2012) [16], Schaufler (2010) [15], Caro (2004) [10], and Islek (2020) [21]. Désirée Vandenberghe (2021) [22] discounted at 3% for costs, and 1,5% for effectiveness. Palmer (2004)[9]

applied various discount rates of 1.5%, 5%, and 6% according to the subject countries. No discount rate was applied in the study of Ambady Ramachandran (2007) [13] and A. Icks (2006) "[12] due to the short horizon (3 years).

All studies performed at least one sensitivity analysis to assess the model uncertainty. Most of these were deterministic sensitivity analysis, which examined the uncertainty of base case results by varying specific parameters. Other techniques were applied such as probabilistic analysis[11, 12, 16, 22], scenario analysis.

3.1.4. Data synthesis

Metformin versus placebo

Table 3 compares the cost-effectiveness of metformin versus placebo. From the healthcare system perspective, metformin was found to be relatively cost-effective to placebo, with ICER ranging from US$7,236/QALY to US$149,712/QALY. From the societal perspective, the majority of studies concluded that metformin was cost-saving, resulting in lower costs but non-inferior clinical benefits[17, 18].

Metformin versus no interventions

In comparision to no intervention, metformin demonstrated either dominant or highly cost-effective outcomes from the perspectives of payers, the healthcare system, and society. The combination of lifestyle and metformin resulted in an incremental cost of US$1,745 for a case prevented in 3 years, which is also considered as a cost-effective treatment. Roberts et al. assessed ICER across different subgroups of intermediate hyperglycemia, including those with IFG, IGT and HbA1c-at-risk. From the healthcare system perspective, patients with high-risk HbA1c had the lowest ICER (USD$577/QALY), followed by IGT cohort (USD$8,104/QALY), and IFG cohort (USD$10,613/ QALY)[20](Table 4).

Metformin versus lifestyle

In comparision to lifestyle modification alone, metformin was not the most effective alternative in the prevention of T2DM, as most studies concluded that changes in lifestyle were either dominant or cost-effective from different perspectives. However, the addition of metformin to diet and exercise yielded an additional US$83,690/DALY, rendering it an unprofitable option. Regarding subgroups with prediabetes, metformin proved to be less costly and resulted in more life-years gained relative to low-intensity lifestyle in cohort with IFG or IGT, while those with HbA1c had an ICER of US$930/QALY (Table 5).

Metformin versus other interventions

When compared to standard care (regular visits to practitioners), metformin was associated with higher costs but achieved greater QALYs, thus representing a cost-effective alternative for the prevention of T2DM, with ICER values ranging from US$457/QALY to US$19,609/QALY. In fact, it was deemed a dominant choice in the settings of Australia, France, Germany, Switzerland from the perspective of third party reimbursement payer. However, metformin was found to be less cost-effective relative to acarbose – another pharmacological control, resulting in an ICER of US$2,005/LYG (Table 6).

Table 3. Metformin versus placebo

Author (Year)	Perspective	ICER (Year of study)	ICER (2020)	WTP	Conclusion
DPP Research Group (2003) [8]	Healthcare system	US$31,338/diabetes case prevented	US$47,100/diabetes case prevented	US$100,000	Cost-effective
		US$99,611/QALY	US$149,712/QALY		
	Society	US$34,489/diabetes case prevented	US$51,836/diabetes case prevented		
		US$99,171/QALY	US$149,051/QALY		
Herman et al (2005) [11]	Healthcare system	US$31,286/QALY	US$47,022/QALY	US$100,000	Cost-effective
	Society	US$29,900/QALY	US$44,937/QALY		
DPP Research Group (2012) [17]	Society	Cost-saving		-	Cost-saving
	Modified society	Cost-saving			
	Healthcare system	Cost-saving			

Author (Year)	Perspective	ICER (Year of study)	ICER (2020)	WTP	Conclusion
Herman (2013) [18]	Healthcare system	US$20,183/QALY	US$24,052/QALY	-	Cost-effective
	Society	Cost-saving			Cost-saving
	Modified society	Cost-saving			
Png et al. (2014) [19]	Healthcare system	US$21,065/QALY	US$23,941/QALY	US$53,000	Cost-effective
	Society	US$6,367/QALY	US$7,236/QALY		

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WTP, willingness-to-pay threshold; DPP, diabetes prevention program.

Table 4. Metformin versus no interventions

Author (Year)	Comparator	Perspective	ICER (Year of study)	ICER (2020)	WTP	Conclusion
DPP Research Group (2003) [8]	Metformin - no interventions	Healthcare system	US$34,458/diabetes case prevented	US$51,789/diabetes case prevented	US$100,000	Cost-effective
			US$109,531/QALY	US$164,621/QALY		
		Society	US$37,609/diabetes case prevented	US$56,525/diabetes case prevented		
			US$109,090/ QALY	US$163,958/QALY		
Caro et al (2004) [10]	Metformin - no interventions	Healthcare payer	Dominant		-	Dominant
Eddy (2005) [7]	Metformin - no interventions	Society	US$35,400/QALY	US$53,205/QALY	-	Cost-effective
Icks et al (2006) [12]	Metformin - no interventions	Health insurance	Dominant		-	Dominant
		Society	Dominant			
Ramachandran et al (2007) [13]	Metformin - no interventions	Healthcare system	US$1,095/diabetes case prevented	US$1,406/diabetes case prevented	-	Cost-effective
	Lifestyle + metformin – no intervention	Healthcare system	US$1,359/diabetes case prevented	US$1,745/diabetes case prevented		
Bertram et al. (2010) [14]	Metformin - no interventions	Healthcare system	AUD$21,500/DALY	US$22,214/DALY	AUD$50,000	Cost-effective
	Metformin + diet + exercise - no interventions		AUD$81,000/DALY	U$83,690/DALY		Not cost-effective
Roberts et al (2018) [20]	Metformin - no interventions	Healthcare system	IGT cohort: £5,224/QALY	US$8,104/QALY	£20,000	Cost-effective
			IFG cohort: £6,842/QALY	US$10,613/QALY		
			HbA1c-at-risk cohort: £372/QALY	US$577/QALY		
Vandenberghe (2021) [22]	Metformin - no interventions	Healthcare system	€8,609/QALY	US$7,900/QALY	€80,000	Cost-effective
		Society	€31,774/QALY	US$29,158/QALY		Cost-saving

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WTP, willingness-to-pay threshold; DALY, disability Adjusted Life Years; DPP, diabetes prevention program

Table 5. Metformin versus lifestyle

Author (Year)	Comparator	Perspective	ICER (Year of study)	ICER (2020)	WTP	Conclusion
Palmer et al (2004) [9]	ILC vs metformin	Third-party reimbursement payer	Australia, France, Germany, Switzerland: Dominant		-	Dominant
			UK: €7,144/LYG	US$10,977/LYG		Cost-effective
Caro et al (2004) [10]	ILC vs metformin	Healthcare payer	CAD$7,252/LYG	US$8,088/LYG	-	Cost-effective
DPP Research Group (2012) [17]	Lifestyle vs metformin	Healthcare system	US$14,885/QALY	US$7,667/QALY	-	Cost-effective
		Modified society	US$45,867/QALY	US$54,440/QALY		
		Society	US$28,634/QALY	US$33,986/QALY		
Herman et al. (2013) [18]	Lifestyle vs metformin	Healthcare system	US$19,662/QALY	US$23,431/QALY	-	Cost-effective
		Society	US$25,644/QALY	US$30,560/QALY		
		Modified society	US$33,149/QALY	US$39,504/QALY		
Roberts et al. (2018) [20]	Metformin vs LIL	Healthcare system	IGT cohort: dominant		£20,000	Dominant
			IFG cohort: dominant			
			HbA1c-at-risk cohort: £600/QALY	US$930/QALY		Cost-effective
Vandenberghe (2021) [22]	Lifestyle vs metformin	Healthcare system	€6289QALY	US$5,771/QALY	€80,000	Cost-effective
		Society	€12,201/QALY	US$11,197/QALY		Cost-saving

ILC, intensive lifestyle control; LIL, low-intensity lifestyle; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; LYG, life-year gained; WTP, willingness-to-pay threshold; DPP, diabetes prevention program

Table 6. Metformin versus other interventions

Author (Year)	Comparator	Perspective	ICER (Year of study)	ICER (2020)	WTP	Conclusion
Palmer et al (2004) [9]	Metformin – standard care	Third-party payer	Australia, France, Germany, Switzerland: Dominant		-	Dominant
			UK: €5,400/LYG	US$8,297/LYG		Cost-effective
Caro et al (2004) [10]	Acarbose - metformin	Healthcare payer	CAD$1,798/LYG	US$2,005/LYG	-	Cost-effective
Schaufler et al (2010) [15]	Metformin – standard care	Health insurance	€325/QALY	US$457/QALY	-	Cost-effective
Palmer et al (2012) [16]	Metformin – standard care	Third-party payer	AUD$10,142/QALY	US$8,800/QALY	AUD$50,000	Cost-effective
Islek (2020) [21]	Metformin + lifestyle – routine care	Multipayer	US$79/1% diabetes risk reduction	US$80/1% diabetes risk reduction	US$22,000	Cost-effective
			US$7,866/diabetes case prevented	US$8,008/diabetes case prevented		

Author (Year)	Comparator	Perspective	ICER (Year of study)	ICER (2020)	WTP	Conclusion
Islek (2020) [21]	Metformin + lifestyle – routine care	Multipayer	US$8,107/QALY	US$8,254/QALY	US$22,000	Cost-effective
			US$6,633/VAS-ALY	US$6,753/VAS-ALY		
		Society	US$117/1% diabetes risk reduction	US$119/1% diabetes risk reduction		
			US$11,739/diabetes case prevented	US$11,951/diabetes case prevented		
			US$12,099/QALY	US$12,318/QALY		
			US$9,899/VAS-ALY	US$10,078/VAS-ALY		
	Metformin + lifestyle – routine care (screening costs included)	Multipayer	US$145/1% diabetes risk reduction	US$148/1% diabetes risk reduction		Cost-effective
			US$14,539/diabetes case prevented	US$14,802/ diabetes case prevened		
			US$14,986/QALY	US$15,257/QALY		
			US$12,261/VAS-ALY	US$12,483/VAS-ALY		
		Society	US$187/1% diabetes risk reduction	US$190/1% diabetes risk reduction		
			US$18,686/diabetes case prevented	US$19,024/diabetes case prevented		
			US$19,260/QALY	US$19,609/QALY		
			US$15,758/VAS-ALY	US$16,043/VAS-ALY		

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; VAS-ALY, visual analog scale–adjusted life-year; LYG, life-year gained; WTP, willingness-to-pay threshold

3.2. DISCUSSION

The review was conducted in accordance with PRISMA guideline and identified 16 eligible studies based on the inclusion criteria. The reporting quality of these articles was assessed according to CHEERS checklist. Overall, most criteria were met, indicating reliable results. However, aspects related to analytical methods, and the characterization of heterogeneity were neglected.

Most of these studies were conducted in developed countries but limited representation from developing nations, despite the fact that 79% of individuals with diabetes come from low- and middle-income countries [23]. The healthcare system perspective was the most commonly adopted in the reviewed studies, leading researchers to primarily focus on direct costs, while indirect costs were assessed in only a few cases. Even so, hidden costs associated with productivity losses were often underestimated in studies that adopted a societal perspective [11, 17, 21]. As a result, these ICERs derived from these studies should be interpreted with caution. The prevalent use of QALY in the economic evaluation facilitates comparisons between studies. While QALY is recommended for health economic assessments, clinical indicators such as the number of diabetic cases prevented, or 1% risk reduction provide policy makers and even patients with tangible insights the clinical benefits of interventions. For example, an ICER of US$18,686/diabetes case prevented can be understood as an additional expenditure of US$18,686 to avert one patient from developing diabetes. This intuitive framework makes economic evaluations more accessible to the public. However, the absence of established thresholds based on these clinical efficacy indicators limits their utility in cost-effective analyses.

Despite variations in reported ICERs across different countries, the conclusions regarding the cost-effectiveness of metformin in the treatment of prediabetes were largely consistent. All studies concluded that metformin was either cost-effective

or associated with reduced costs compared to placebo, no intervention, and standard care (screening and regular medical visits). This is not surprising, given that metformin exerts a significant pharmacological effect on human receptors, providing clinically meaningful efficacy in delaying the onset of Type 2 Diabetes Mellitus (T2DM) and its associated complications. However, compared to lifestyle modification, metformin was not the optimal alternative. In the three-year period, prediabetic patients who initiated lifestyle intervention experienced a 58% reduction in risk (95% CI = 48-66%), nearly double the 31% reduction (95% CI = 17-43%) associated with metformin [24]. the risk of diabetes progression was reduced by 34% (95% CI = 24-42%) in the lifestyle arm, compared to 18% (95% CI = 7-28%) in the metformin arm, relative to placebo [4]. Moreover, a long-term lifestyle programme was expected to improve cardiovascular risk and mortality rate more effectively than metformin therapy [25]. While lifestyle interventions offer significant health benefits and appear to incur comparable direct medical costs to metformin from the healthcare system perspective, they may not be cost-effective from a societal standpoint when accounting for the value of participants' time (including travel and participation time). Therefore, lifestyle adjustments—such as regular physical activity, stress reduction, healthy dietary practices, and weight management—should be carefully integrated into national programs alongside metformin for high-risk individuals.

This systematic review provides a comprehensive assessment of the economics and benefits of metformin for T2DM prevention by synthesizing and analyzing cost-effectiveness studies across a variety of research perspectives. Prior to this study, we identified three additional cost-effectiveness reviews: T. Moin et al. (12 studies)[26], S. Roberts et al. (27 studies, in which 12 studies evaluated metformin) [27], S. Gebregergish et al. (14 articles and 8 abstracts) [28]. However, these reviews included fewer articles and had not been updated to the present. Our findings align with those of S. Gebregergish et al. [28] and T. Moin et al. [26], indicating that metformin is cost-effective compared to placebo and no intervention. In the review conducted by S. Roberts et al., the effects of various intensity lifestyle changes on different subtypes of prediabetes were examined in greater detail – an aspect that was not explored in this study [27]. Our study has several limitations. We restricted our search to publications in English and only searched three electronic databases (PubMed, Cochrane, and Embase). Consequently, our review may not fully encompass all relevant studies published in other languages or unpublished data from grey literature sources. Additionally, the exclusion of conference abstracts due to insufficient data for evaluation may have omitted potential evidence to support our conclusions.

4. CONCLUSION

Metformin was dominant or cost-effective compared to placebo and no interventions in the treatment of prediabetes. However, the question about cost-effectiveness of metformin versus lifestyle change remained controversial among studies. Further investigation on the cost-effectiveness of metformin compared to lifestyle change was recommended, especially in developing countries where there is a high prevalence rate and limited healthcare resources.

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Chi phí – Hiệu quả metformin trong điều trị đái tháo đường Type 2: Nghiên cứu tổng quan hệ thống

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TÓM TẮT

Tổng quan và mục tiêu: Đái tháo đường type 2 (DTDT2) là một rối loạn chuyển hóa phổ biến với nhiều biến chứng nghiêm trọng. Việc điều trị tiền đái tháo đường bằng metformin hoặc thay đổi lối sống đã cho thấy khả năng làm chậm sự tiến triển từ tiền đái tháo đường sang DTDT2, từ đó giảm bớt gánh nặng kinh tế tổng thể liên quan đến DTDT2. Nghiên cứu hệ thống này được thực hiện nhằm đánh giá tính hiệu quả về chi phí của metformin trong điều trị tiền đái tháo đường. Phương pháp và kết quả: Một nghiên cứu tổng quan hệ thống theo hướng dẫn PRISMA được thực hiện trên các cơ sở dữ liệu: Pubmed, Cochrane và Embase với các từ khóa và cụm từ phù hợp. Danh sách kiểm tra CHEERS được sử dụng để đánh giá chất lượng của các nghiên cứu. Các đặc điểm nghiên cứu và kết quả đã được xem xét, và tỷ lệ chi phí hiệu quả gia tăng (ICER) được chuyển đổi sang USD 2020. Trong số 402 bài báo được xác định qua các chiến lược tìm kiếm, 16 bài báo đáp ứng tiêu chí chọn lọc đã được đưa vào phân tích trong nghiên cứu này. Tất cả các bài báo đều được đánh giá là có chất lượng tương đối tốt theo danh sách kiểm tra CHEERS. Các phân tích này được thực hiện ở các quốc gia phát triển từ các góc độ và khung thời gian khác nhau. Một trong số 16 nghiên cứu cho thấy metformin là tiết kiệm chi phí so với giả dược, trong khi các nghiên cứu còn lại báo cáo metformin là hiệu quả chi phí so với giả dược, không can thiệp hoặc chăm sóc tiêu chuẩn, với các ICER dưới ngưỡng sẵn sàng chi trả (từ USD 457/QALY đến USD 164,621/QALY). Tuy nhiên, kết luận về tính hiệu quả chi phí của metformin so với thay đổi lối sống khác nhau tùy theo góc độ và cường độ chương trình. Kết luận: Metformin là lựa chọn ưu vượt trội hoặc đạt chi phí - hiệu quả so với giả dược và các can thiệp không có trong điều trị tiền đái tháo đường. Tuy nhiên, câu hỏi về tính hiệu quả chi phí của metformin so với thay đổi lối sống vẫn là một vấn đề gây tranh cãi trong các nghiên cứu. Cần tiếp tục nghiên cứu về tính hiệu quả chi phí của metformin so với

thay đổi lối sống, đặc biệt ở các quốc gia đang phát triển, nơi có tỷ lệ mắc cao và nguồn lực chăm sóc sức khỏe hạn chế.

Từ khóa: *nghiên cứu tổng quan hệ thống, chi phí – hiệu quả, metformin, tiền đái tháo đường*

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