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Systematic Review

Cost-effectiveness of gestational diabetes screening in middle-income countries: a systematic review

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Abstract
The majority of GDM occurs in low- and middle-income countries. GDM is associated with increased maternal and infant complications as well as an increased burden of health financing. Accurate and cost-effective screening is needed for prevention and further treatment. Unfortunately, there is a lack of research on the cost-effectiveness of GDM screening in middle-income countries. The objective of this study was to uncover scientific proof concerning the cost-effectiveness analysis of screening for gestational diabetes in middle-income countries. We conducted a systematic review using Pubmed and ScienceDirect. Four reviewers screened the title and abstract of each article, followed by the selection of the full text based on the inclusion criteria (cost-effectiveness analysis studies of GDM screening and original research). Quality articles were assessed using the CHEC-Extended tool. A total search of 1239 articles found 3 studies that met the inclusion criteria. A screening program is more cost-effective than no screening, this represents a savings of $1,329,671. The ICER value is less than 3x GDP per capita, which indicates that the intervention is cost-effective. Compared to two-step screening, one-step screening is more likely to be cost-effective since it detects more cases. As the prevention of DALYs is mainly due to the prevention of T2DM, middle-income countries should focus more on postnatal care for women with GDM in the future. It is advised that long-term follow-up studies be a major focus of future research in order to evaluate the follow-up GDM screening intervention's possible long-term health benefits and financial effects.

Keywords: Cost-effectiveness analysis; economic evaluation; gestational diabetes mellitus; GDM screening; middle-income countries

1. Introduction

In 2020, approximately 287,000 women died from pregnancy and childbirth. Almost 95% of all maternal deaths in 2020 occurred in low- and middle-income countries (WHO, 2024). Complications during pregnancy, childbirth, and postpartum account for 75% of maternal deaths (WHO, 2024). Gestational diabetes mellitus (GDM) is associated with an increased risk of complications during pregnancy and postpartum in the mother and her baby (Bhandiwad et al., 2015; Jafari-Shobeiri et al., 2015). Some previous studies have shown that GDM increased risk of preeclampsia (Lee et al., 2017; Yang & Wu, 2022), macrosomia (Bai et al., 2023; Sweeting et al., 2022; Ye et al., 2022), instrumental delivery (Ye et al., 2022), preterm birth (Ye et al., 2022), cesarean section delivery (Akinyemi et al., 2023; Ye et al., 2022; Zhuang et al., 2020), and stillbirth (Ye et al., 2022). Even within 8 to 10 years after pregnancy, women with GDM have a 10-fold risk of developing type 2 DM (Eades et al., 2015; Herath et al., 2017). Gestational diabetes mellitus also has the potential to increase the economic burden of healthcare. The results of a study on the economic burden of GDM in Italy showed that, compared to normal pregnant women, antenatal costs in pregnant women with GDM were greater than €326.9 (8 times), while the cost of maternity hospitalization was greater than €234 (1.39 times) for mothers and

€257 (1.3 times) for infants. As a result, in 2014, the national economy bore the financial burden of about €44.8 million due to the overall cost per case differential between GDM and normal pregnancies of €817.8 (Meregaglia et al., 2018).

The serious impact of GDM requires serious prevention and treatment. One of them involves GDM screening. Unfortunately, there isn't a "gold standards" on GDM screening strategies and diagnostic criteria; hence, the standards used in each nation vary. Some frequently used diagnostic criteria for GDM include: World Health Organization (WHO), American Diabetes Association (ADA), Society of Obstetricians and Gynecologists of Canada, International Federation of Gynecology and Obstetrics, American College of Obstetricians and Gynecologist (ACOG), and International Association of the Diabetes and Pregnancy Study Group (IADPSG) (American Diabetes Association, 2019; Li-zhen et al., 2019). There are two GDM screening strategies: the one-step strategy and the two-step strategy. One-step strategy: the average fasting, 1-hour, and 2-hour plasma glucose assessments during a 75-g oral glucose tolerance test (OGTT) in women at 24–28 weeks of gestation were the diagnostic cut points for GDM established by the IADPSG and WHO (American Diabetes Association, 2019; Behboudi-Gandevani et al., 2019). Meanwhile, a two-step screening strategy is recommended by American Diabetes Association (ADA). Step 1: Using a non-fasting 50 g glucose challenge test (GCT), Step 2: 0-hour, 1-hour, 2-hour, and 3-hour plasma glucose measured during 100 g OGTT. Step 2 is advised if the one-hour GCT value is greater than 140 mg/dl (American Diabetes Association, 2019).

The heterogeneity of screening strategies and diagnostic criteria for GDM identification has an impact on the variation and accuracy of GDM prevalence estimates, making it challenging to estimate and compare the prevalence of GDM globally. In 2021, it was estimated that the global prevalence of GDM will reach 14%, while in low- and middle-income countries, it will reach 12.7% and 9.2%, respectively (H. Wang et al., 2022). According to Cho et al., (2018), 88% of GDM occurs in low- and middle-income countries, where access to healthcare is limited. The IADPSG diagnostic criteria for GDM have a 1.75 to 11-fold increase in prevalence over the previous diagnostic criteria (Behboudi-Gandevani et al., 2019; Saeedi et al., 2021). In addition, several barriers to the application of OGTT for GDM screening in developing countries such as high cost and lack of laboratories particularly when IADPSG criteria are applied (Mohan et al., 2014). It is a challenge for governments and health care providers in developing countries to determine a cost-effective, safe, and accurate GDM screening strategy.

Evaluation of a health-care intervention's influence on costs is necessary in addition to its clinical effectiveness. In order to improve health outcomes, healthcare providers and policymakers can make the most efficient use of limited resources by choosing which healthcare interventions to implement and/or reimburse based on the relative cost-effectiveness of those interventions, as informed by such analyses (Haque et al., 2024). Unfortunately, although there have been many studies on gestational diabetes, many studies have centred on the impact of GDM, types of care, and patient characteristics, there is a lack of studies about the cost-effectiveness of GDM screening, especially in middle-income countries. The objective of this study was to uncover scientific proof concerning the cost-effectiveness analysis of screening for gestational diabetes in middle-income countries.

2. Research Methods

This study is a systematic review that is organized based on The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline (Page et al., 2021). According to Page et al. (2021), a systematic review employs explicit and systematic methods to gather and synthesize research results by answering formulated questions.

2.1.Search Strategy

We used the PICOS framework (Population, Intervention/Exposure, Comparison, Outcomes and Study design) to help identify search terms to be used in the literature search, as shown in Table 1.

Tabel 1. PICOS Framework

PICOS Elemen	Determinants
Population	Pregnant women in middle-income countries that have been registered with the World Bank Low and Middle-Income Countries (LMIC)
Intervention /Exposure	GDM Screening
Comparison	There are no screening or other preventive measures for Gestational Diabetes Mellitus
Outcomes	Effectiveness cost of GDM screening
Study Design	Cost-Effectiveness Analysis (CEA)

An extensive literature review was conducted in the PubMed, and ScienceDirect databases to obtain English articles examining the cost-effectiveness of screening GDM. A systematic search process on June 14, 2023, then, we updated the search again on June 21, 2023. In searching for articles, we determined the following keywords: "Pregnant* OR Perinatal OR Gestation*OR Pregnancy AND Screen* OR Early detection* OR Mass screening AND Gestational diabetes mellitus AND Cost-effectiveness analysis, OR cost utility analysis." The search was expanded using word synonyms and controlled vocabulary (MESH) on Pubmed.

2.2.Studies Selection and Eligibility Criteria

Articles obtained from our search are combined into Mendeley as a reference manager to identify and eliminate duplicate articles. Following this, the four reviewers (YS, DL, PA, and AR) were further divided into two groups as follows: (YS with PA) and (DL with AR). Each group filters the title and abstract of each article using the RAYYAN application. The results of filtering articles in the application that are considered doubtful are then searched to find the full article to evaluate its relevance to the study.

Article studies can be included if they comply with the criteria for the population's eligibility in the PICOS framework in Table 1. We determined the inclusion criteria using English and Indonesian, original research, and studies discussing cost-effectiveness analysis in GDM screening and exclusion criteria, namely review studies, opinions, documents or reports, and research without full text.

2.3.Quality Appraisal of the Included Articles

Four reviewers (YS, DL, PA, and AR) assessed the quality of studies using the Consensus Health Economic Criteria (CHEC-Extended) tool, which is reported in Table 2. The CHEC-Extended tool is an assessment guide assessing the quality of the articles related to the economic assessments of health interventions (Odnoletkova et al., 2014; van Delft et al., 2023).

Table 2. Quality Appraisal of the Included Articles Using CHEC-Extended Tool

No	QUESTIONS	(Marseille et al., 2013)	(Zhang et al., 2015)	(Celen et al., 2012)
1.	Is the study population clearly described?	1	1	1
2.	Are competing alternatives clearly described?	0	0	1
3.	Is a well-defined research question posed in answerable form?	0	0	1

No	QUESTIONS	(Marseille et al., 2013)	(Zhang et al., 2015)	(Celen et al., 2012)
4.	Is the economic study design appropriate to the stated objectives?	1	1	1
5.	Are the structural assumptions and the validation methods of the model properly reported?	1	1	0
6.	Is the chosen time horizon appropriate in order to include relevant costs and consequences?	1	1	1
7.	Is the actual perspective chosen appropriate?	0	0	0
8.	Are all important and relevant costs for each alternative identified?	0	0	1
9.	Are all costs measured appropriately in physical units?	1	1	1
10.	Are costs worth appropriately?	1	1	1
11.	Are all important and relevant outcomes for each alternative identified?	1	1	1
12.	Are all outcomes measured appropriately?	1	1	1
13.	Are outcomes valued appropriately?	1	1	1
14.	Is an appropriate incremental analysis of costs and outcomes of alternatives performed?	1	1	1
15.	Are all future costs and outcomes discounted appropriately?	1	1	1
16.	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	1	1	0
17.	Do the conclusions follow from the data reported?	1	1	1
18.	Does the study discuss the generalizability of the results to other settings and patient/client groups?	1	1	1
19.	Does the article/report indicate that there is no potential conflict of interest of the study researcher(s) and funder(s)?	0	0	1
20.	Are ethical and distributional issues discussed appropriately?	0	0	0
		14	**14**	**16**
	TOTAL "YES" ANSWER			
	TOTAL SCORE (%)	**70**	**70**	**80**
	EVALUATION	**Moderate**	**Moderate**	**Good**

Assessment Grade:
Low <50
Moderate 51-75
Good 76-95
Excellent >95

2.4.Extracted Information

We extracted the features of the studies reviewed based on countries classified as middle-income countries, population, and interventions reported in Table 3. In addition, we also documented the studies reviewed based on sensitivity analysis such as time horizon, perspective, discount rate, probabilistic sensitivity analysis, one-way sensitivity analysis, scenario analysis, and model validation, which have been reported in Table 4.

Table 3. Characteristics of the Studies Reviewed

Author Year	Country (Income level)	Study design	Economical	Population	Intervention
(Marseille et al., 2013)	**India** (Middle income)	Model-based	CEA	1,000 pregnant women	Screening with a glucose tolerance test or Oral Glucose Tolerance Test (OGTT)
(Zhang et al., 2015)	**China** (Middle income)	Observation	CEA	1,000 pregnant women	IADPSG guidelines, one-step OGTT
(Celen et al., 2012)	**Türkiye** (Middle income)	Observation	CEA	2,724 pregnant women in the first procedure and the second step of the procedure in 185 pregnant women.	One and two-step OGTT GDM screening.

Table 4. Study Characteristics Reviewed by Sensitivity Analysis

Author Year	Time Horizons	Perspective	Discount Rate	Probabilistic sensitivity analysis	One-Way Sensitivity Analysis	Scenario Analysis	Model Validation
(Marseille et al., 2013)	**Life–years**	**Society**	**3.0%**	**Yes**	**No**	**No**	**No**
(Zhang et al., 2015)	**Life-year**	**Society**	**3.0%**	**No**	**Yes**	**No**	**No**
(Celen et al., 2012)	**-**	**Health care**	**4.2%**	**No**	**No**	**No**	**No**

Finally, we document the results of the cost-effectiveness of the study based on the author, the effectiveness of the results of measuring parameters, currency and year, ICER, and conclusions by the author (quality of study CHEC-Extended Tool), which have been reported in Table 5.

Table 5. Article Cost-effectiveness Results

Author Year	Effectiveness of parameter measurement results	Currency, Year	ICER	Conclusion by the author (Quality of study according to check)
(Marseille et al., 2013)	**DALY**	**$ (2014)**	**cost-effectiveness of $1626**	GDM screening, taking into account perinatal adverse events and future diabetes, demonstrated a moderate incremental cost-effectiveness of $1626.
(Zhang et al., 2015)	**DALY**	**$ (2015)**	**cost-effectiveness of $1,329,671**	Based on IADPSG standards, interventions for GDM are cost-effective in China's urban areas. As the prevention of DALYs is mainly due to the prevention of T2DM, China should focus more on postnatal care for women with GDM in the future.

Author Year	Effectiveness of parameter measurement results	Currency, Year	ICER	Conclusion by the author (Quality of study according to check)
(Celen et al., 2012)	Unclear	Lira (2012)	-	The one-step approach test cost per woman was 0.75 Turkish Lira lower than the two-step approach test; however, the test took 18.6 minutes longer and required 1.08 times more blood sample procedures (Good)

3. Results and Discussion

The search for articles we carried out in stages according to the selection is reported in Figure 1. The search process with two databases produced a total 1240 articles. The PubMed database produced 257 articles, and ScienceDirect produced 983 articles. We used Mendeley to see duplicates, and we got 1 duplicate article, so the number of articles was 1239. Then, we filtered these articles based on the title and abstract using RAYYAN, excluding 1202 articles, so the number of articles became 37. Then, 37 articles were viewed in full text. Eleven articles were excluded because they could not be accessed in full text, bringing the total number of articles to 26. We reviewed 26 articles in detail, so we excluded 23 articles again because they failed to satisfy the criteria for inclusion. There are 3 articles used in this systematic review.

3.1.Article Characteristics

The studies obtained came from middle-income countries, including India (Marseille et al., 2013), China (Zhang et al., 2015), and Turkey (Celen et al., 2012). Based on study design, there are two type of study desain: model-based study design (Marseille et al., 2013) and observations (Celen et al., 2012; Zhang et al., 2015). Both of these studies use cost-effectiveness analysis to calculate costs.

In healthcare, cost-effectiveness analysis (CEA) is a crucial and frequently applied method for establishing such priorities. The incremental cost-effectiveness ratio (ICER), which is the ratio of incremental costs to incremental outcomes, is a common way to express CEA results. Generic efficacy measurements, such disability-adjusted life-years (DALYs) and quality-adjusted life-years (QALYs), are frequently used in CEA investigations (Daroudi et al., 2021).

The population in this systematic review was carried out on 1,000 pregnant women (Marseille et al., 2013; Zhang et al., 2015), and on 2,909 pregnant women (Celen et al., 2012). Then, interventions were carried out on IADPSG OGTT screening (Marseille et al., 2013; Zhang et al., 2015), as well as one-step and two-step OGTT screening strategy (Celen et al., 2012). IADPSG and WHO recommend a one-step strategy: fasting, 75-g OGTT, plasma glucose measured after 1 hour, and 2 hours of glucose administration (American Diabetes Association, 2019; Behboudi-Gandevani et al., 2019). Two-step screening strategy is recommended by American Diabetes Association (ADA). Step 1 is glucose challenge test (GCT) use 50 g glucose. If after 1 hour plasma glucose shows abnormal results (more than 140 mg/dl), then continue step 2 by giving of 100 g of glucose, and plasma glucose is measures at 0, 1, 2, and 3 hours (American Diabetes Association, 2019). Currently, the majority countries of the world applies the one-step approach, but the United States and a few other countries use two-step approach (Behboudi-Gandevani et al., 2019).

There is time limit (time horizon) in implementing screening, there was no age limit (Marseille et al., 2013) and no a time limit for implementation (Celen et al., 2012; Zhang et al., 2015) (Table 4). From the cost perspective: a social or general view (Marseille et al., 2013; Zhang et al., 2015), and a view of one's own health (Celen et al., 2012). The discount rate obtained in financing GDM screening was 3.0% (Marseille et al., 2013; Zhang et al., 2015) and 4.2% (Celen et al., 2012). The sensitivity

analysis: sensitivity probability analysis (Marseille et al., 2013), and one-way sensitivity analysis (Zhang et al., 2015). In this study, an assessment was carried out on three articles using the CHEC-Extended tool. The results obtained were scores 70 (moderate grade) (Marseille et al., 2013; Zhang et al., 2015), and a score of 80 (good grades) (Celen et al., 2012).

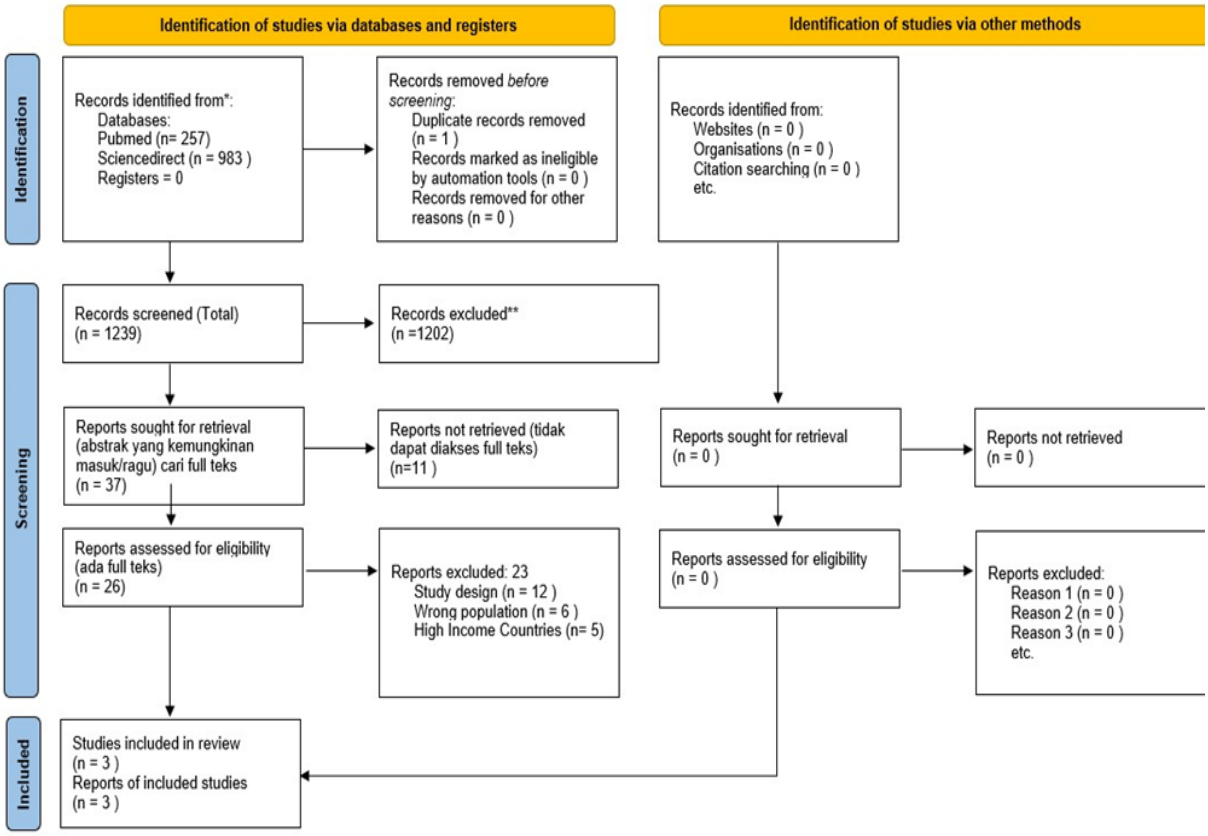

Figure 1. PRISMA Flowchart 2020

3.2.Cost-Effectiveness Screening GDM

A glucose challenge test using 50 g of glucose was performed on 2,724 pregnant women, of whom 628 continued step two, with the administration 100 g of glucose. While a one-step approach test with 75 g of glucose was performed on 185 pregnant women (Celen et al., 2012). The result of this study has shown that the one-step approach test cost per woman was 0.75 Turkish Lira lower than the two-step approach test; however, the test took 18.6 minutes longer and required 1.08 times more blood sample procedures (Celen et al., 2012). A screening program is more cost-effective than no screening. Compared to two-step screening, one-step screening is more likely to be cost-effective since it detects more cases. This result is the same as the results of Mo et al., (2021) study. Several studies have proven that the one-step method of IADPSG has the potential to increase the prevalence of GDM by 1.75 to 11-fold compared to others (Behboudi-Gandevani et al., 2019; Ramezani Tehrani et al., 2023; Saeedi et al., 2021). Due to its potential to detect and treat GDM sooner, the IADPSG criteria is the only outcome-based criteria that can reduce the complication related GDM in maternal and fetal (Rani & Begum, 2016). If GDM is detected early, treatment can be taken immediately to prevent worse impacts including preventing Type 2 DM in mothers and babies in the future. This will have an effect on reducing health costs due to DALYs.

The "WHO-CHOICE threshold" of 1-3× Gross Domestic Product (GDP) per capita has been frequently mentioned as a criterion for cost-effectiveness in the majority of research carried out in

LMICs (Leech et al., 2018; Ochalek et al., 2015). The WHO-CHOICE criterion states that if an intervention's ICER is less than 1× GDP per capita (highly cost-effective), less than 3× GDP per capita (cost-effective), and 3× GDP per capita or higher (not cost-effective) (Daroudi et al., 2021; Neumann et al., 2016). The GDM screening in India, taking into account such as perinatal adverse events and future diabetes, demonstrated a moderate incremental cost-effectiveness ratio (ICER) of $1626 (Marseille et al., 2013). Meanwhile, India's GDP per capita in 2013 was $1,438.1 (World Bank, 2016). This shows that the ICER value is less than 3x GDP per capita, which indicates that the intervention is cost-effective.

Zhang et al. (2015) found that in the GDM screening group, the overall expenditures of GDM screening, intervention, and lifetime treatment for 1000 pregnant women came to $7,092,398; this represents a savings of $1,329,671 when compared to the non-screening group. In the screening group, 277.4 DALYs were avoided, primarily due to GDM postpartum therapy for the prevention of type 2 diabetes. Sensitivity studies proved how reliable the findings were. Y.-Y. Wang et al. (2019) reported that 55% of women with a history of GDM in a previous pregnancy who had recurrent GDM in subsequent pregnancies. In addition, the risk of developing type 2 diabetes mellitus increases up to 10 times within 8 to 10 years after pregnancy (Eades et al., 2015; Herath et al., 2017). This will certainly have an impact on increasing the economic burden associated with diabetes, as DM is one of the non-communicable diseases that is the largest contributor to morbidity and mortality globally. Follow-up postnatal screening for mothers with a history of GDM is a major concern. Some high-income countries have implemented this intervention, but in low- and middle-income countries, it has not been widely implemented. Barriers to follow-up screening for GDM in low- and middle-income countries include the absence of guidelines, patients' and providers' lack of knowledge about GDM, the cost and distance of accessing regular monitoring and follow-up care, the unavailability of services, the lack of adequate testing equipment, patients' lack of motivation and adherence to recommended therapy, and a lack of communication (Utz & De Brouwere, 2016).

Short-term maternal and neonatal outcomes can be improved by GDM screening using IADPSG guidelines (a 2-hour 75 g OGTT) in 24-28 gestational weeks (He et al., 2020; Ramezani Tehrani et al., 2023). The risk of preterm delivery, cesarean section, macrosomia, neonatal hypoglycemia, and admission to the neonate intensive care unit (NICU) was significantly lower for women who were screened using the one-stage approach than for those a two-step screening method (Saccone et al., 2019). According to Rani & Begum (2016), the advantage of the one-step method is ease of implementation, more patient-friendly, more accurate diagnosis and nearly to international consensus.

4. Conclusion

This systematic review study found that GDM screening. A screening program is more cost-effective than no screening, this represents a savings of $1,329,671. The ICER value is less than 3x GDP per capita, which indicates that the intervention is cost-effective. Compared to two-step screening, one-step screening is more likely to be cost-effective since it detects more cases. As the prevention of DALYs is mainly due to the prevention of T2DM, the middle income countries should focus more on postnatal care for women with GDM in the future. It is advised that long-term follow-up studies be a major focus of future research in order to evaluate the follow-up GDM screening intervention's possible long-term health benefits and financial effects.

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