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Management of Gestational Diabetes Mellitus in Middle East and North Africa: Systematic review

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ABSTRACT

Background: Overweight and high parity are two of the many risk factors for gestational diabetes mellitus that affect women in Saudi Arabia. In order to minimize complications for both the mother and the fetus, care of gestational diabetes mellitus should involve keeping the patient's plasma glucose levels within normal ranges and avoiding significant weight gain. Insulin was the first line of therapy for diabetes during pregnancy. Metformin safety was approved recently, and it was administered more frequently to pregnant diabetes patients when insulin cannot be provided. **Method:** We conducted a thorough search of the Cochrane database, Embase, and PubMed (from 2015 to 2022). We looked for randomized controlled trials that contrasted metformin with insulin. **Results:** In the systematic review, we considered 6 studies with 996 patients overall. Five studies excluded mothers with pre-gestational diabetes, and one research did not state whether pre-gestational diabetes was present. In these six RCTs, 498 participants got insulin therapy, and 498 patients got metformin treatment. In Ashoush et al., (2016) study, 22% of the metformin group needed insulin throughout the follow-up period. In most of the included studies the two groups differed statistically significantly regarding gestational age at birth. **Conclusion:** our study shows that, when compared to insulin treatment, metformin can provide some benefits and acceptable glycemic control without increasing the risk of certain outcomes for mothers and neonates. More researches were needed in Middle East and especially in Saudi Arabia.

Keywords: Gestational diabetes mellitus, management, insulin, metformin

1. INTRODUCTION

The World Health Organization defines gestational diabetes mellitus (GDM) as hyperglycemia brought on by a carbohydrate intolerance that is initially detected

during pregnancy, excluding individuals who satisfy the requirements for type 2 diabetes mellitus (WHO, 2013). Global incidence of GDM is increasing along with rising rates of obesity and maternal ages at delivery (Vince et al., 2020). GDM affected 1 in 6 mothers in 2019, demonstrating its importance as a global public health concern. The prevalence of GDM (13.0%) Al-Rifai et al., (2021) was comparable to that of sub-Saharan Africa (14.0%) but frighteningly larger than that of European nations (2–6%) (Buckley et al., 2012). Saudi Arabia's prevalence was more than the prevalence estimates for Asia (11.5%) (Lee et al., 2018). Prevalence estimates from Saudi Arabia, Iran, and Qatar were included in the Asian meta-analysis; these estimates were 3.5% and 7.4% lower, respectively, for Saudi Arabia and Iran, and 7.4% higher, for Qatar (Lee et al., 2018).

In patients with GDM, the one-day clinic DM management model can effectively control blood glucose levels and weight gain during pregnancy. This leads to a higher rate of blood glucose and islet function recovery after delivery as well as a lower incidence of premature rupture of membranes, neonatal jaundice and macrosomia. Therefore, there may be significant effects from the one-day clinic GDM care strategy in terms of preventing or postponing the establishment of type 2 diabetes in individuals with GDM after giving birth (Cao et al., 2021). The predictors of GDM include increasing maternal age, BMI, blood pressure and weight, multiparity, prior recurrent abortions, GDM in prior pregnancies, a history of delivering a child with a malformation, family history of diabetes, and prior preterm births (Alfadhli et al., 2015). According to the result of a trial carried out in Saudi Arabia by the FDA, 363 women who were allocated to metformin, 92.6% remained to take the medication until delivery, and 46.3% got additional insulin.

In the metformin group, the primary composite outcome rate was 32%, whereas in the insulin group, it was 32.2%. Compared to the insulin group, a greater number of women in the metformin group said they would want to continue receiving their prescribed therapy. There was no discernible difference in the rates of other secondary outcomes between the groups. The usage of metformin was not linked to any significant side effects. Compared to insulin, metformin does not appear to be linked to a higher risk of perinatal problems in women with gestational diabetes mellitus. Insulin therapy was not chosen by the women over metformin. Uncontrolled hyperglycemia during pregnancy may be harmful to the developing foetus and mother. Maternity-related problems in people with GDM are well-known to include an increased caesarean sections risk and preeclampsia (ACOG, 2018). Offspring of women with uncontrolled blood sugar during pregnancy also had higher newborn macrosomia rates, hypoglycemia, shoulder dystocia, and birth trauma during labour (ACOG, 2018).

Furthermore, increasing maternal plasma glucose levels during pregnancy are associated with a higher stillbirth risk (ACOG, 2018). In addition, children exposed to high blood sugar levels in utero have an increased chance of becoming obese adults, and 50% of women with a history of GDM go on to develop T2DM in the ensuing 5–10 years. These are possible long-term implications of GDM for the mother and child (OECD, 2024). When gestational diabetes mellitus is identified, it is critical to treat it because of the risks associated with hyperglycemia. High postprandial blood sugars have been increased risk of labour problems due to a large-for-gestational-age (LGA) foetus, and raised maternal mean fasting blood glucose increased risk of obesity throughout the child's life (ACOG, 2018).

Since low foetal birth weight is linked to maternal hypoglycemia, extremely low blood sugar levels are also dangerous. High levels of ketonaemia in third trimester, which have been linked to impaired foetal brain development, can potentially result from insufficient calorie intake or insulin levels. This condition is primarily seen in type 1 diabetes pregnant women, though it can also occur to a lesser extent in patients with GDM (Hod et al., 2015; American Diabetes Association, 2021). Therefore, the best courses of action should minimise hypoglycemia and minimise ketonaemia, and regularly manage blood glucose levels both during fasting and after meals. Drugs that do not penetrate the placenta are beneficial since there is a lower chance that they will have a negative effect on the fetus. Remarkably, most GDM patients can manage postprandial hyperglycemia and fasting throughout pregnancy by altering their dietary and lifestyle habits.

To achieve target plasma glucose, 15–30% of people with GDM require medication in addition to lifestyle modification. Insulin treatment includes a number of drawbacks, such as the need for more injections, the possibility of hypoglycemia, weight gain in the mother, and increased expense (Simmons, 2010). The patient's motivation to utilize insulin may be diminished by these drawbacks. On the other hand, metformin is a substitute that can enhance peripheral and hepatic insulin sensitivity. Although metformin can penetrate the placenta and may directly impact fetal physiology, there is no proof to support the concern that it is teratogenic. Metformin exposure during the first trimester did not raise the incidence of any nongenetic congenital malformations, according to recent research that analyzed data from eleven European congenital abnormality databases (Bergman et al., 2018).

2. METHOD

In compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), this systematic review and meta-analysis was presented. From 2015 to 2022, we conducted a thorough electronic search using Embase, PubMed, and the Cochrane Library in an effort to find all pertinent randomized controlled trials, independent of language. We looked through related systematic reviews to find other studies that qualified. Studies that satisfied the following requirements were accepted: (1) Patients with gestational diabetes mellitus made up the population; (2) Metformin and insulin were used as interventions; and (3) One or more maternal and neonatal outcomes were included. RCTs were used in the design. Furthermore, research involving pregnant women with pre-pregnancy diabetes were omitted, and the same studies that were published in multiple publications were only included once.

Maternal and neonatal outcomes were the two areas of focus for the results. Newborn outcomes included birth weight, congenital abnormalities, less than 7 Apgar score at 5 minutes, RDS, hyperbilirubinemia, newborn hypoglycemia, SGA, macrosomia, NICU, and pH of the umbilical cord. Premature birth, caesarean delivery, preeclampsia, PIH, gestational age at delivery, weight gain, and glycemic control were among the maternal outcomes. Each review author evaluated the included papers' titles and abstracts on their own. Until an agreement was reached, any differences were explored with group discussion. In order to gather pertinent data, such as the author, the nation, the year of publication, the definition of GDM, the number of patients, the intervention, and the patient's characteristics, we created a data extraction form.

3. RESULTS

There were 216 records found in the first search. 165 records remained after duplicates were eliminated. 137 studies were eliminated following a review of abstracts and titles. We entered six investigations and reviewed the complete contents of 28 publications (Figure 1). 996 people in all were enrolled in the 6 RCTs. Pre-gestational diabetic mothers was eliminated from five trials Hamadani et al., (2017), Ghomian et al., (2019), Eid et al., (2018), Saleh et al., (2016), Ainuddin et al., (2015), while the remaining one study (Ashoush et al., 2016) did not specify whether pre-gestational diabetes was present. 498 individuals in these 6 RCTs received insulin treatment, while 498 patients received metformin treatment (Table 1). In single research, the metformin group required insulin in this study 22% of the metformin group needed insulin during the follow up period (Ashoush et al., 2016).

In most of the included studies regarding gestational age at birth, differences were statistically significant. Maternal age, body mass index, and gestational age did not differ significantly before therapy in the included studies. According to Hamadani et al., (2017) compared to women on insulin treatment, who gained an average of 9.36 kg, metformin-group women gained an average of 8.96 kg. In the insulin group, the rate of caesarean sections was 36.7%, whereas in the group received metformin, it was 43.3%. In the insulin group, the mean birth weight of the neonates was 3.67 kg, whereas in the group received metformin, it was 3.2 kg. Following the period of therapy, there were no appreciable differences in the two groups' plasma glucose, fasting plasma glucose, or HbA1c. There was also no appreciable difference between the two groups in terms of the cause for the caesarean section, the manner of delivery, birth weight, birth trauma, neonatal hypoglycemia, Apgar score, and hospitalization in the neonatal intensive care unit (Ghomian et al., 2019) (Table 2).

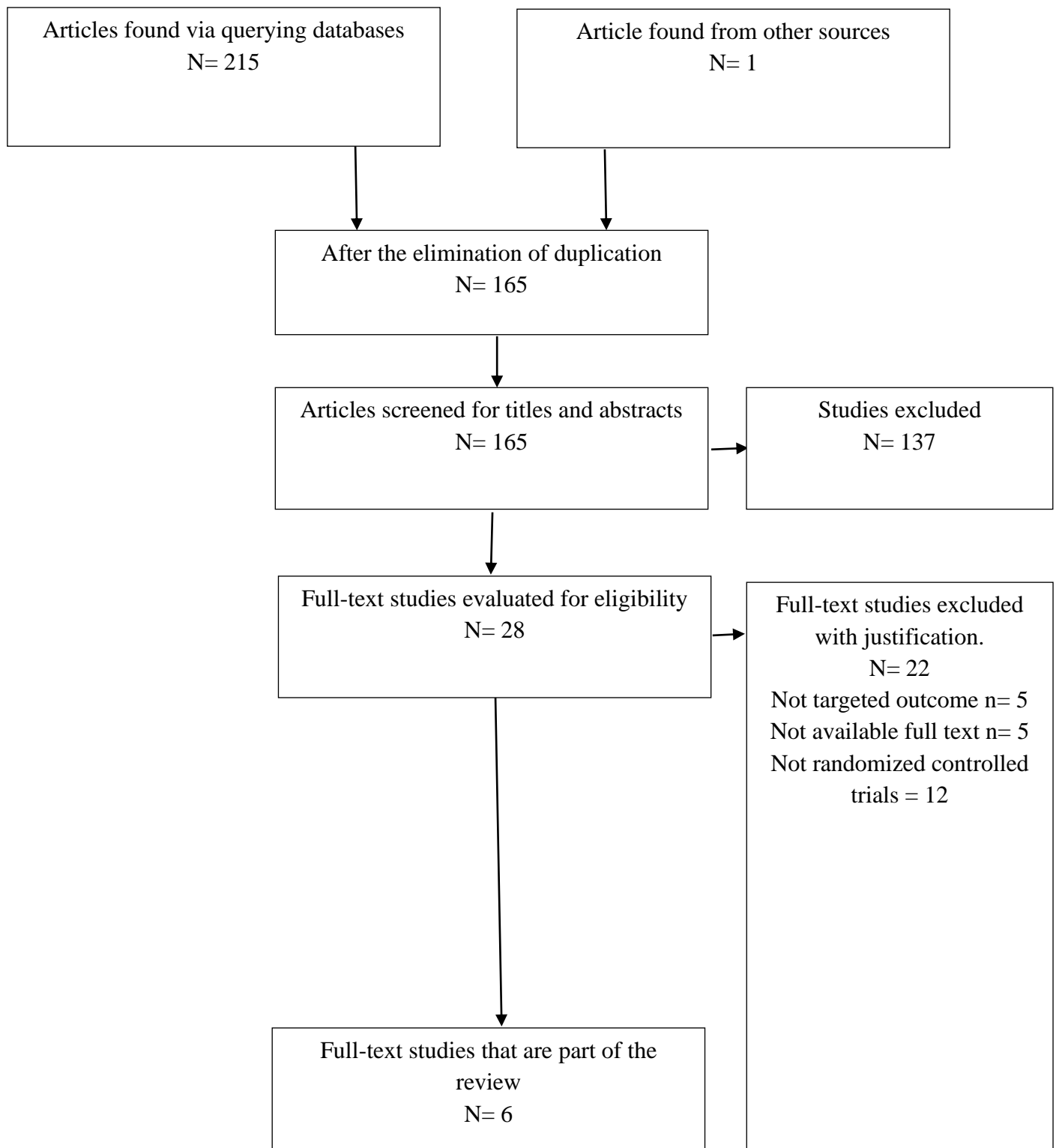


Figure 1 Consort chart of selection process

Table 1 Characteristics of included studies

Citation	Study participants	Country	Participants		Dose		Group of metformin needed insulin (%)
			Insulin	Metformin	Insulin	Metformin	
Hamadani et al., 2017 (25)	Singleton	Pakistan	30	30	NR	500 to 2000	NR
Ghomian et al., 2019 (28)	18 to 40 years old women	Iran	143	143	NR	500 to 1500	NR
Eid et al., 2018 (27)	Singleton GA 30 to 40 weeks	Egypt	125	125	NR	500 to 2500	0
Ashoush et al., 2016 (23)	Singleton	Egypt	50	50	NR	1000 to 2500	22
Saleh et al., 2016 (24)	GA 26 to 34	Egypt	75	75	NR	500 to 3000	NR
Ainuddin et al., 2015 (22)	Singleton GA 20 to 36 weeks	Pakistan	75	75	43	500 to 2500	NR
GA; gestational age, NR; not reported							

Table 2 Conclusion and main findings of selected studies

Citation	Main findings	Conclusion
Hamadani et al., 2017	At the time of study enrollment, the patients' mean gestational ages were 28.13 weeks for the metformin group and 28.26 weeks for the insulin group. Women on metformin medication gained an average of 8.96 kg, whereas those on insulin therapy gained an average of 9.36 kg. The rate of caesarean sections was 36.7% in the insulin group and 43.3% in the group received metformin. The mean birth weight of the newborns in the insulin group was 3.67 kg, whereas it was 3.2 kg in the group received metformin.	Because of its minimal monitoring requirements and relatively similar adverse effects for mothers, metformin is a safe medication for the treatment of GDM. Lower birth weight in newborns is the only issue with metformin medication.
Ghomian et al., 2019	Mother's age, body mass index, family history of diabetes, prior history of GDM, parity, FPG, postprandial glucose tolerance test, did not vary statistically between the two groups before treatment. After the treatment course, there were no discernible variations in PG, Fasting plasma glucose, or HbA1c between the two groups. Regarding the reason for caesarean section, mode of delivery, birth trauma, birth weight, Apgar score, neonatal hypoglycemia and neonatal intensive care unit hospitalization, there was similarly no discernible difference between the two groups.	Given that there was no statistically significant difference in mean Fasting plasma glucose or postprandial blood glucose level between the two groups, metformin appears to be a viable option to replace insulin in the treatment of GDM. Nevertheless, there are still certain unfavorable risk factors associated with both therapies that might endanger both the mother and the infant.
Eid et al., 2018	In two groups, blood glucose levels two hours after a meal and after fasting were statistically similar. Throughout pregnancy, both groups met their treatment target without a statistically significant difference. Compared to the insulin group, the metformin group's	Metformin-treated women can achieve greater results than insulin-treated ones, at least in some areas, and their neonates did not show any appreciable side effect. Neonatal

	mean fasting blood sugar was somewhat lower but not statistically significant. The metformin group's mean 2-hour post prandial glucose level was 95.9 mg/dl, whereas the insulin group's was 101.4 mg/dl; however, this difference was not statistically significant. No significant variation was seen in the HbA1c levels before to delivery within the examined cohorts.	hypoglycemia, hospital stays, and birth weight can all be considerably reduced with metformin. Currently, insulin treatment is the gold standard for treating GDM; however, metformin is becoming more and more well-liked as a good substitute.
Ashoush et al., 2016	Compared to women receiving insulin monotherapy, metformin-using women gained less weight and experienced lower fasting glucose levels over the initial and last two weeks of treatment. The mean glucose level in first week, GTT, HbA1c, and baseline body mass index were all correlated with insulin supplementation in the group received metformin. The two independent factors linked to the need for additional insulin were the 1-hour level of glucose during the first GTT and fasting glucose level mean over the first week of medication.	In cases of GDM, metformin is a safe and efficient substitute for insulin. Metformin-using women had comparable rates of adverse effects, decreased weight gain, and comparable glycemic control to those on insulin only.
Saleh et al., 2016	There is no discernible difference between using insulin or metformin to manage elevated plasma glucose in GDM. With the exception of the fact that the insulin group experienced greater hypoglycemia, there was no discernible difference between the two groups' maternal side effects or fetal outcomes.	Metformin used orally can help improve glycaemic control in GDM without raising the risk of hypoglycemia in the mother and providing a healthy outcome for the newborn.
Ainuddin et al., 2015	The group who received metformin had less weight gain. Preeclampsia was much lower in group receiving metformin. In the research, there were no perinatal fatalities. The group treated with metformin had a considerably lower mean birth weight. There was less neonatal morbidity in the group received metformin. Of the patients in the group received metformin, 42.7% needed extra insulin. Mean GA was 31.8 weeks at which insulin was introduced.	For GDM women, metformin is an affordable, efficient therapy option that may be used with or without additional insulin.
GDM; gestational diabetes mellitus, PG; plasma glucose, GTT; glucose tolerance test		

4. DISCUSSION

The safety and efficacy of metformin need to be confirmed given its growing usage in GDM patients. We provided a thorough systematic review. In women with GDM, glucose management is highly correlated with the outcome. According to Rowan et al., (2010) postprandial glucose predicted preeclampsia and LGA newborns, fasting capillary glucose predicted neonatal complications, and HbA1c% predicted LGA infants. According to our analysis, women on metformin had all acquired good control over their HbA1c, and their glycemic management was not poorer. We observed that metformin considerably decreased the 2-hour postprandial glucose levels, which is consistent with the previous review's findings Moore et al., (2007), even though there was no significant change in HbA1c between the two groups prior to delivery. Metformin group show, glucose level targets appeared to be reached sooner (Ashoush et al., 2016). For those with GDM who wish to promptly regulate their blood sugar, this discovery is encouraging.

But some of the women in the group received metformin needed the extra insulin to get proper glycemic control, and these patients typically had high blood sugar and a high body mass index prior to therapy. Insulin is promptly started when the glycemic aim could not be reached with metformin alone. Therefore, even if insulin is later required, using metformin during pregnancy has no negative

effects on glycemic control or the results of glycemic control responses. Maintaining weight control is crucial for GDM women. Excessive weight gain raises the risk of RDS, PIH, LGA, and caesarean birth. While in our study review the majority of studies indicate that women who took metformin during pregnancy experienced significantly decreased weight gain. Metformin also decreased LGA risk and macrosomia.

These findings further demonstrate the potential benefits of metformin for blood glucose regulation. The second most frequent cause of maternal mortality that occurs directly is gestational hypertension. GDM women are more likely to develop hypertension, and stated rates may not accurately reflect the current incidence of the disease due to the rising diabetes prevalence in women (Vest et al., 2014). Furthermore, intrauterine growth retardation, placental abruption, intrauterine haemorrhage, preterm, and intrauterine mortality are all possible outcomes of hypertension during pregnancy. Thus, blood pressure management is equally crucial to blood glucose management. Metformin may lower the risk of PIH, according to earlier reviewers' findings (Butalia et al., 2017). Unlike other studies Gui et al., (2013), Balseells et al., (2015), we did not find a higher incidence of preterm birth in GDM patients who were assigned randomly to the metformin group. Different findings might arise with enrolling more trials.

Our findings also indicate that metformin considerably shortens pregnancy, which may be one of the reasons doctors are hesitant to employ metformin more frequently in clinical practice. Thus, before more widespread use, additional study in this field is required. Associated with metformin medication, the most frequent gastrointestinal symptoms include nausea, vomiting, diarrhoea, bloating in the abdomen, and abdominal discomfort. There have also been reports of headache, anxiety, fatigue, and dizziness as side effects (Sakouhi et al., 2023). Women with normal weight may benefit from focusing on diet and insulin therapy to reduce adverse pregnancy outcomes, while those with higher pre-pregnancy BMI or excessive weight may benefit from metformin combination with supplemental insulin to alleviate insulin resistance and further weight gain (Bastian et al., 2022).

5. CONCLUSION

Overall, our research demonstrates that metformin can offer some advantages and adequate glycemic control when compared to insulin therapy, all without raising the risk of specific outcomes for mothers and newborns. Further studies regarding gestational diabetic mothers and their management protocols were required throughout the Middle East, particularly in Saudi Arabia.

List of abbreviations

LGA: Large for gestational age

GDM: Gestational diabetes mellitus

RDS: Respiratory distress syndrome

PIH: Pregnancy-induced hypertension

SGA: Small for gestational age

NICU: Neonatal intensive care unit

HbA1c: Glycosylated hemoglobin

T2DM: Type 2 diabetes mellitus

Ethical approval

Not applicable.

Informed consent

Not applicable.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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