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Association between Maternal Hypothyroidism and Miscarriage Risk: A Community Based Cohort Study

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Abstract

Introduction:

Maternal hypothyroidism is a frequent endocrine disorder during pregnancy and has been increasingly associated with miscarriage. However, many previous studies were limited by hospital based populations and insufficient control for psychological and medical confounders. This study aimed to assess the relationship between maternal hypothyroidism and miscarriage using a large communitybased cohort.

Methods:

Data were extracted from the Sina Electronic Health Record System covering 66279 pregnant women receiving prenatal care across health centers affiliated with Mashhad University of Medical Sciences (2017–2025). Thyroid status, pregnancy outcomes, psychological factors (depression, anxiety, domestic violence), and comorbidities were recorded. Univariate and multivariate logistic regression models were used to estimate adjusted odds ratios (AOR) with 95% confidence intervals (CI).

Results:

Maternal hypothyroidism was identified as a significant independent predictor of miscarriage (AOR = 1.60; 95% CI: 1.51–1.70; $p < 0.001$). Several additional risk factors showed strong independent associations, including advanced maternal age (AOR = 1.75 for 30–40 years; AOR = 1.90 for > 40 years; $p < 0.001$), Iranian nationality (AOR = 5.30; $p < 0.001$), residence in small cities (AOR = 2.23; $p < 0.001$) or suburban areas (AOR = 1.99; $p < 0.001$), and high parity (AOR = 3.20 for second pregnancy; 6.60 for third; 12.24 for ≥ 4 pregnancies; all $p < 0.001$). Psychosocial factors such as domestic violence (AOR = 1.25; $p < 0.001$), depression (AOR = 1.17; $p < 0.001$), and anxiety (AOR = 1.19; $p < 0.001$) were also associated with increased miscarriage risk. Medical comorbidities including obesity (AOR = 1.19; $p < 0.001$), diabetes (AOR = 1.21; $p < 0.001$), hypertension (AOR = 1.51; $p < 0.001$), cancer history (AOR = 1.40; $p < 0.001$), and genitourinary disorders (AOR = 1.37; $p < 0.001$) further contributed to risk.

Conclusion:

Maternal hypothyroidism is a significant and potentially modifiable risk factor for miscarriage. Our findings support the need for early thyroid screening during pregnancy, particularly in populations with high prevalence of thyroid disorders. Personalized management rather than universal treatment of mild subclinical hypothyroidism may offer more beneficial outcomes. Future research should examine treatment timing, autoantibody status and fetal developmental markers to develop clearer clinical guidelines.

Contributions to the Literature

This large population based cohort demonstrates that maternal hypothyroidism is an independent risk factor for miscarriage.

The study integrates medical, psychological and socioeconomic determinants, revealing a multidimensional risk profile.

High parity emerges as one of the strongest predictors of miscarriage, a finding rarely quantified in the region.

By using a national electronic health registry, the study fills a major geographic gap and supports targeted screening and maternal care strategies.

1. Introduction

Hypothyroidism is one of the common chronic conditions in pregnant women. In adults, hypothyroidism refers to a state in which thyroid hormone levels are below the normal range. During pregnancy, maternal hypothyroidism is classified into two categories: clinical and subclinical(1). Thyroid dysfunction during pregnancy has emerged as an important central issue in clinical endocrinology and is recognized as the second most common endocrine disorder in this critical period following diabetes(2). Hypothyroidism is very common during pregnancy(3). Approximately 2–3 percent of pregnant women develop overt hypothyroidism, while around 4 percent experience subclinical hypothyroidism(4)..Various studies in Iran have shown that thyroid dysfunction affects 18.10% of pregnant women. Among these, hypothyroidism is the most common, occurring in 13.01% of women, including 1.35% with clinical hypothyroidism and 11.90% with subclinical hypothyroidism. Hyperthyroidism is less frequent, affecting 3.31% of women, of whom 1.06% have clinical hyperthyroidism and 2.56% have subclinical hyperthyroidism(3). Both iodine deficiency and excessive iodine intake are considered major causes of hypothyroidism during pregnancy. In regions where dietary iodine intake is sufficient chronic autoimmune thyroiditis becomes the primary risk factor for maternal hypothyroidism(5). Other contributing risk factors include iron deficiency previous partial or total thyroidectomy Radioactive iodine therapy for prior hyperthyroidism radiation exposure to the head and neck inadequate treatment of clinical or subclinical hypothyroidism and thyroid dysgenesis(6). Hypothyroidism during pregnancy is linked to a wide range of adverse maternal and fetal outcomes. Even subclinical forms of the disorder can increase the likelihood of complications such as recurrent miscarriage, preeclampsia, gestational hypertension, gestational diabetes, placental abruption, low birth weight, preterm birth, fetal distress, intrauterine fetal demise, and impaired neurocognitive development(7–12). These potential consequences highlight the importance of early identification and appropriate management of thyroid dysfunction during pregnancy(13). Despite the substantial evidence highlighting the adverse outcomes of hypothyroidism during pregnancy, there is still no complete consensus regarding the extent and strength of its association with miscarriage risk(14, 15). Previous studies have reported inconsistent finding which may be due to methodological differences variations in study populations diverse diagnostic criteria or the lack of population-based

data in many regions. Therefore, conducting a community-based cohort study becomes particularly important. Such a design allows researchers to follow a defined population over time enabling a more accurate assessment of causal relationships and precise documentation of outcomes. Moreover, a population based approach can provide more realistic estimates of the incidence of maternal hypothyroidism and its consequences including miscarriage while overcoming limitations commonly seen in hospital based studies. The findings of this research can help fill existing gaps in the scientific literature and serve as a foundation for developing optimized strategies for screening early diagnosis, and effective management of hypothyroidism during pregnancy ultimately contributing to improved maternal and fetal health.

2. Method

2.1 Participants and Study Design:

Pregnant women receiving routine prenatal care at health centers affiliated with Mashhad University of Medical Sciences were included in this population based cohort study. Data were obtained from the Sina Health Information System (16). The study covered the period from March 1, 2017, to September 20, 2025. In this study, participants were divided into two groups based on their thyroid status during pregnancy. The exposed group included pregnant women who had been diagnosed with hypothyroidism and whose condition was documented in the registry. The unexposed group comprised pregnant women who did not have a diagnosis of hypothyroidism and had no record of the condition in the registry. This classification allowed for a clear comparison of outcomes between women with and without maternal hypothyroidism.

2.2 Study variables:

1. Outcome variable: The outcome variable in this study was miscarriage. Miscarriage was defined as the spontaneous loss of pregnancy before 20 weeks of gestation, as documented in the medical record. This definition allowed for consistent and standardized identification of the outcome across all participants and ensured comparison between exposed and unexposed groups.

2. Exposure variable: Age, place of residence, number of the mother's pregnancies, nationality, mother’s education level, mother’s job, domestic violence, depression, anxiety, history of cancer, diabetes, maternal obesity, hypertension and genitourinary disease.

2.3 Measurement tool:

In this study, the HITS short questionnaire was used to measure domestic violence; a tool designed by Sherin et al. in the United States with the aim of rapid screening for domestic violence. This questionnaire consists of 4 questions that focus on verbal and physical violence. Each question has 5 answer options and is scored from 1 to 5; therefore, the total score ranges from 4 to 20. A score greater than 10 is considered a positive result and indicates the presence of domestic violence(17).

2.4 Sampling technique and procedure:

In this study the exposed participants were identified through a census of pregnant women who had attended primary healthcare centers affiliated with Mashhad University of Medical Sciences over several years for routine prenatal care. A total of 33079 women with documented hypothyroidism during pregnancy were included as the exposed group. The unexposed participants were randomly selected from among pregnant women who did not have a diagnosis of hypothyroidism during pregnancy. Overall 66279 women participated in the study.

2.5 Definitions:

In this study the diagnosis of hypothyroidism during pregnancy was made by a physician. Women who received this diagnosis and had it recorded in the healthcare system were considered as cases. All diagnoses were based on thyroid function tests and clinical evaluation by the physician and their registration in the system ensured accuracy and consistency of the data across the study population. All other variables included in the study were also recorded and confirmed by physicians and healthcare personnel, ensuring the accuracy and reliability of the collected data.

2.6 Statistical Analysis:

After data collection, the information was coded and subsequently entered into Excel software. It was then transferred to Stata version 16 for analysis purposes. Frequencies and percentages were calculated to describe the characteristics of categories and quantitative variables in both case and control groups. Initially, bivariate analysis including chi-square test was performed to assess the unadjusted relationships between each factor and low birth weight. Variables that were statistically significant were entered into univariate regression model, then if significant, into multivariate regression model. The final model estimated the adjusted odds ratio (OR) and 95% confidence intervals indicating independent relationships. The final model estimated the adjusted odds ratio (AOR) and 95% confidence intervals indicating independent relationships between variables entered into the model. An alpha level of 0.05 determined statistical significance in the regression analysis. Statistical analysis was performed using Stata software version 16.

3. Results

A total of 66279 pregnant women were included in the present population-based cohort, of whom 33079 had documented hypothyroidism during pregnancy and 33200 were nonhypothyroid. Overall, 5723 miscarriages occurred, corresponding to an 8.6% miscarriage rate in the total sample. The distribution of miscarriage varied substantially across demographic, clinical and psychosocial factors, revealing a multifactorial risk pattern. Maternal age demonstrated a clear gradient of increasing risk. Miscarriage occurred in 5% of women younger than 20 years and 9% of those aged 20–30 years; however, the rate increased to 10% among women aged 30–40 and remained elevated (10%) in women older than 40. Regression analyses confirmed age as an independent predictor: women aged 30–40 exhibited a 75%

higher risk (AOR = 1.75, 95% CI: 1.57–1.95), while women aged > 40 had almost double the odds of miscarriage compared with those < 20 (AOR = 1.9, 95% CI: 1.63–2.44). These findings underscore the strong biological influence of maternal age on early pregnancy viability. Geographical disparities were also evident. Women living in suburban and small city settings experienced markedly higher miscarriage rates (12% and 13%, respectively) compared with women in metropolitan areas (5%). (Table 1)

Multivariable models showed that residence in small cities (AOR = 2.23, 95% CI: 2.02–2.46) or suburban areas (AOR = 1.99, 95% CI: 1.81–2.19) remained significantly associated with elevated miscarriage risk. These findings likely reflect differences in socioeconomic status, healthcare access and environmental stressors. Parity emerged as one of the strongest determinants of miscarriage. While only 3% of nulliparous women experienced miscarriage, the proportion increased to 8% among women with one prior pregnancy, 13% with two prior pregnancies, and 19% among those with four or more pregnancies. In adjusted analyses, the risk of miscarriage increased dramatically with parity: women with ≥ 4 pregnancies had 12.24 times higher odds of miscarriage (95% CI: 10.97–13.65) than those in their first pregnancy, making parity the single most powerful predictor in the final model.

Maternal educational status and employment were both protective factors. Women with education above a diploma had the lowest miscarriage rate (6%), while illiterate women and women with a diploma both had a miscarriage rate of 10%. After adjustment, illiteracy was associated with a 35% increased risk (AOR = 1.35) and diploma level education with a 23% increased risk (AOR = 1.23). Employment was consistently protective; employed and self employed women exhibited lower odds of miscarriage than housewives (AOR = 0.7 for both). This pattern highlights the influence of socioeconomic empowerment and health-seeking behavior on pregnancy outcomes. Psychosocial determinants also contributed significantly. Exposure to domestic violence increased the risk of miscarriage (AOR = 1.25, 95% CI: 1.15–1.46). Maternal depression (AOR = 1.17, 95% CI: 1.07–1.28) and anxiety (AOR = 1.19, 95% CI: 1.15–1.35) were similarly associated with higher odds of miscarriage, independent of other risk factors. Collectively, these findings point to the importance of mental health and social stability in safeguarding pregnancy. Several medical comorbidities demonstrated strong associations with miscarriage. Obesity increased miscarriage risk by 19% (AOR = 1.19) and diabetes by 21% (AOR = 1.21). Hypertension was associated with a 51% higher risk (AOR = 1.51), while a history of cancer increased the risk by 40% (AOR = 1.4). Genitourinary disease showed one of the strongest clinical associations, with affected women experiencing a 16% miscarriage rate and a 37% increase in adjusted odds (AOR = 1.37). Each of these comorbidities likely contributes through mechanisms such as inflammation, vascular dysfunction, metabolic stress, or impaired hormonal regulation.

The primary exposure of interest maternal hypothyroidism demonstrated a clear and independent association with miscarriage. Miscarriage occurred in 11% of hypothyroid women compared with 7% of non hypothyroid women. In unadjusted analysis, hypothyroidism increased the odds of miscarriage by 75%. After controlling for all demographic, clinical, and psychosocial variables, hypothyroidism remained a significant independent predictor, increasing the odds of miscarriage by 60% (AOR = 1.6, 95% CI: 1.51–1.7). This robust association suggests that even when key confounders such as age, parity, obesity,

mental health and socioeconomic factors are accounted for, thyroid dysfunction exerts a substantial biological influence on early pregnancy loss. Taken together, the final multivariable model identified the most influential determinants of miscarriage as high parity (AOR = 12.24), Iranian nationality (AOR = 5.3), advanced maternal age (AOR = 1.9), hypothyroidism (AOR = 1.6), hypertension (AOR = 1.51), domestic violence (AOR = 1.25), depression and anxiety (AORs 1.17–1.19), obesity and diabetes (AORs 1.19–1.21), and genitourinary infections (AOR = 1.37). Employment and higher education acted as meaningful protective factors. (Table 2)

Table 1
Demographic Characteristics and Risk Factors for Miscarriage in the Hypothyroid and Healthy Groups

Variable		Miscarriage		P-value
		NO	YES	
		N (%)	N (%)	
Age	< 20	3219(95)	162(5)	< 0.001
	20–30	25850(91)	2372(9)	
	30–40	26195(90)	2607(10)	
	> 40	5292(90)	582(10)	
Place of residence	Metropolis	17414(95)	736(5)	< 0.001
	Small city	10201(87)	1435(13)	
	Village	16428(93)	1215(7)	
	Suburban	16513(88)	2337(12)	
Number of pregnancies of the mother	First	23431(97)	518(3)	< 0.001
	Second	15520(92)	1214(8)	
	Third	11380(87)	1639(13)	
	Fourth and more	10225(81)	2352(19)	
Nationality	Foreign	4189(98)	63(2)	< 0.001
	Iranian	56367(90)	5660(10)	
Mother's education	Illiterate	14589(90)	1513(10)	< 0.001
	Diploma	32683(90)	3458(10)	
	Above the diploma	13284(94)	752(6)	
Mother's Job	Housewife	53197(91)	5151(9)	< 0.001
	Self-employed	1145(93)	78(7)	
	Employee	1743(93)	118(7)	
	Student	4471(92)	376(8)	
Domestic Violence	No	59931	5630	< 0.001
	Yes	625	93	
Depression	No	55673(91)	5007(8)	< 0.001
	Yes	4883(87)	716(13)	

Variable		Miscarriage		P-value
		NO	YES	
		N (%)	N (%)	
Anxiety	No	56139(91)	5154(9)	< 0.001
	Yes	4417(88)	569(12)	
History of Cancer	No	60020(92)	5641(8)	< 0.001
	Yes	536(86)	82(14)	
Hypothyroid	No	31055(93)	2145(7)	< 0.001
	Yes	29501(89)	3578(11)	
Diabetes	No	59722(91)	5601(9)	< 0.001
	Yes	834(87)	122(13)	
Mother's Obesity	No	57561(91)	5332(9)	< 0.001
	Yes	2995(88)	391(12)	
Hypertension	No	59394(92)	5549(8)	< 0.001
	Yes	1162(87)	174(13)	
Genitourinary disease	No	55333(92)	4753(8)	< 0.001
	Yes	5223(84)	970(16)	

Table 2: Adjusted and Unadjusted Logistic Regression Analysis of Maternal Risk Factors Associated with Miscarriage

Variables	Categories	Univariate regression analysis			Multivariate logistic regression		
		Odds Ratio	p-value	Confidence Interval	Odds Ratio	p-value	Confidence Interval
Hypothyroid	No	1	< 0.001	1.66–1.85	1	< 0.001	1.51–1.7
	Yes	1.75			1.6		
Age	< 20	1	< 0.001	1.54–2.14	1	0.13	0.97–1.19
	20–30	1.82		1.68–2.32	1.08	< 0.001	1.57–1.95
	30–40	1.97	< 0.001	1.82–2.62	1.75		1.63–2.44
	> 40	2.18	< 0.001		1.9	< 0.001	
Nationality	Foreign	1	< 0.001	5.16-8 51	1	< 0.001	4.11–6.8
	Iranian	6.67			5.3		
Place of residence	Metropolis	1	< 0.001	3.03–3.65	1	< 0.001	2.02–2.46
	Small city	3.3		1.59–1.92	2.23		1.27–1.55
	Village	1.7	< 0.001	3.07–3.68	1.4	< 0.001	1.81–2.19
	Suburban	3.34	< 0.001		1.99	< 0.001	
Mother's Job	Housewife	1	< 0.001	0.55–0.88	1	< 0.001	0.55–0.88
	Self-employed	0.7		0.5–0.84	0.7		0.58–0.85
	Employee	0.69	< 0.001	0.77–0.96	0.7	< 0.001	0.82–1.03
	Student	0.8	0.01		0.92	0.15	
Mother's education	Above the diploma	1	< 0.001	1.67–2.006	1	< 0.001	1.11–1.29
		1.83		1.73–2.02	1.23		1.14–1.45
	Diploma	1.86	< 0.001		1.35	< 0.001	
	Illiterate						
Number of pregnancies of the mother	First	1	< 0.001	3.1–3.9	1	< 0.001	2-87-3.56
	Second	3.5		5.8–7.2	3.2		5.93–7.36
	Third	6.5	< 0.001	9.4–11.4	6.6	< 0.001	10.97–13.65
	Fourth and more	10.4	< 0.001		12.24	< 0.001	

Depression	No	1	< 0.001	1.5–1.77	1	< 0.001	1.07–1.28
	Yes	1.63			1.17		
Domestic Violence	No	1	< 0.001	1.27–1.97	1	< 0.001	1.15–1.46
	Yes	1.58			1.25		
Anxiety	No	1	< 0.001	1.28–1.53	1	< 0.001	1.15–1.35
	Yes	1.41			1.19		
Mother's Obesity	No	1	< 0.001	1.26–1.57	1	< 0.001	1.06–1.34
	Yes	1.4			1.19		
Diabetes	No	1	< 0.001	1.28–1.89	1	< 0.001	1.14–1.41
	Yes	1.56			1.21		
History of Cancer	No	1	< 0.001	1.28–2.05	1	< 0.001	1.24–165
	Yes	1.62			1.4		
Hypertension	No	1	< 0.001	1.36–1.88	1	< 0.001	1.3–17
	Yes	1.6			1.51		
Genitourinary disease	No	1	< 0.001	2.07–2.33	1	< 0.001	1.26–1.7
	Yes	2.16			1.37		

4. Discussion

In both univariate and multivariate regression analyses, several factors were associated with an increased risk of miscarriage. Hypothyroid, maternal age, Iranian nationality, living in small cities or suburban areas higher number of previous pregnancies and lower maternal education were all linked to higher miscarriage risk. Additionally, psychological factors such as maternal depression, anxiety and exposure to domestic violence as well as medical conditions including maternal obesity, diabetes, hypertension, genitourinary diseases and a history of cancer were also associated with increased risk. Maternal occupation appeared protective, with employed or self-employed mothers showing a lower likelihood of miscarriage compared to homemakers.

Hypothyroidism, particularly in the presence of thyroid autoantibodies such as anti-TPO is associated with an increased risk of miscarriage. Studies have shown that overt hypothyroidism in women with a history of recurrent pregnancy loss can increase the risk of miscarriage up to fourfold by 20 weeks of gestation(18). Even subclinical hypothyroidism during the first trimester may elevate miscarriage risk especially when thyroid autoantibodies are present(19). However, evidence regarding the benefit of levothyroxine treatment in euthyroid women with positive antibodies is limited and inconclusive. Screening for serum TSH levels and thyroid autoantibodies in women with a history of miscarriage can

help identify those at higher risk and guide management(20, 21). In our study, we also observed an association between hypothyroidism and miscarriage, supporting previous evidence that thyroid dysfunction increases the risk of pregnancy loss(22).

Our findings Consist with a recent study confirm that genetically predicted hypothyroidism is causally linked to spontaneous abortion, even when major confounders are eliminated through genetic instrumental variables(23). This evidence indicates that thyroid dysfunction is not merely correlated with miscarriage but may be a direct etiological contributor, especially during the first trimester. This is consistent with another recent investigation which reported that persistent maternal hypothyroxinemia in early pregnancy impairs placental development and increases miscarriage risk emphasizing the critical window before 12 weeks of pregnancy(24). Previous systematic reviews and meta analyses reinforce our findings. For example, a meta-analysis including 12 studies concluded that subclinical hypothyroidism before 20 weeks of pregnancy is associated with significantly higher miscarriage risk, particularly among antibody positive women(19). More broadly, a review demonstrated that subclinical hypothyroidism is strongly associated with several adverse outcomes, including miscarriage and hypertensive disorders(25).

This aligns with our data, which suggest that the strongest association with miscarriage occurred among clinically diagnosed hypothyroid cases rather than borderline thyroid dysfunction. A related prospective study confirmed worse feto maternal outcomes among hypothyroid mothers, but highlighted that treatment timing and antibody status may modify the effect of therapy(26).

In the context of Middle Eastern populations, our findings are particularly relevant. A systematic review by Sepasi, Rashidian, Azami and colleagues showed that 18.10% of Iranian pregnant women experience thyroid dysfunction, with subclinical hypothyroidism being the most prevalent (11.9%)(27). This prevalence is substantially higher than that reported in many European countries, confirmed the need for community based population studies, such as ours, rather than small hospital based samples. Our results therefore provide important real world evidence that may support future national screening recommendations in Iran and other similar regions.Interestingly, our data showed higher miscarriage rates among women with coexisting depression, anxiety, or domestic violence. This finding agrees with multiple studies that psychological stress elevated risk of miscarriage(28, 29).These factors indicate the need for a multidimensional antenatal screening approach, where thyroid function is assessed not only biochemically but in relation to nutritional, psychological, and social risk factors.

Finally, this study has several strengths. First, it utilizes a large community-based cohort rather than a hospital-based sample, allowing greater generalizability and reducing selection bias. Second, the classification of thyroid status was confirmed by physicians using medical records, increasing the reliability of exposure assessment. Third, multiple confounders known to affect miscarriage risk were included in the multivariate analysis, strengthening the internal validity of the findings. However, it also has limitations. Our design does not account for variations in thyroid hormone treatment timing, dosage, or adherence, which may have influenced the results. We also did not assess TPO antibody status for

stratification, which recent evidence suggests may modify treatment effectiveness. In addition, residual confounding from iodine status, nutritional factors, or inflammation markers cannot be fully excluded. The lack of data on fetal thyroid morphology or head circumference also limits our ability to comment on subtle developmental effects reported in recent clinical studies. Larger prospective trials with biomarker stratification and detailed follow-up of fetal growth parameters are therefore necessary

5. Conclusion

The present study supports increasing evidence that maternal hypothyroidism particularly overt or antibody positive cases is a significant and potentially modifiable risk factor for miscarriage. Screening during early pregnancy, ideally in the first trimester, may be a cost-effective strategy to reduce pregnancy loss. However, the treatment of mild subclinical hypothyroidism should be personalized rather than universally recommended. Future trials should stratify participants by thyroid antibody status, treatment timing, and gestational age at diagnosis, and include fetal outcome measurements such as placental function and thyroid morphology. This precision based approach may help establish clear clinical thresholds for intervention and ultimately improve maternal and fetal outcomes.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (2013 version) as adopted by the World Medical Association. Ethical approval was obtained from Mashhad University of Medical Sciences (Approval Code: IR.MUMS.FHMPM.REC.1403.218). Informed consent to participate was obtained from all participants prior to their inclusion in the study. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

not applicable

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Author Contribution

MN is the principal investigator and research leader. AM and EM designed the Study and drafted the manuscript and analyzed the data. SA contributed to the conception, design, data interpretation, and revising the manuscript. All authors read and approved the final manuscript.

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Not Applicable.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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