

The Influence of Interpregnancy Interval on the Subsequent Risk of Stillbirth and Early Neonatal Death

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OBJECTIVE: To study whether interpregnancy interval is associated with increased risks of stillbirth and early neonatal death and whether this possible association is confounded by maternal characteristics and previous reproductive history.

METHODS: In a Swedish nationwide study of 410,021 women's first and second singleton deliveries between 1983 and 1997, we investigated the influence of interpregnancy interval on the subsequent risks of stillbirth and early neonatal death. Odds ratios (ORs) with 95% confidence intervals (CIs) estimated using unconditional logistic regression were adjusted for maternal characteristics and previous pregnancy outcome categorized into stillbirth, early neonatal death, preterm, or small for gestational age delivery.

RESULTS: Compared with interpregnancy intervals between 12 and 35 months, very short interpregnancy intervals (0–3 months) were, in the univariate analyses, associated with increased risks of stillbirth and early neonatal death (crude OR 1.9; 95% CI 1.3, 2.7; and 1.8; 1.2, 2.8, respectively). However, after adjusting for maternal characteristics and previous reproductive history, women with interpregnancy intervals of 0 to 3 months were not at increased risks of stillbirth (adjusted OR 1.3; 95% CI 0.8, 2.1) or early neonatal death (adjusted OR 0.9; 95% CI 0.5, 1.6). Women with interpregnancy intervals of 72 months and longer were at increased risk of stillbirth (adjusted OR 1.5; 95% CI 1.1, 2.1) and possibly early neonatal death (adjusted OR 1.3; 95% CI 0.9, 2.1).

CONCLUSION: Short interpregnancy intervals appear not to be causally associated with increased risk of stillbirth and early neonatal death, whereas long interpregnancy intervals were associated with increased risk of stillbirth and possibly early neonatal death. (*Obstet Gynecol* 2003;102:101–8. © 2003 by The American College of Obstetricians and Gynecologists.)

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Both short and long interpregnancy intervals have been associated with low birth weight, preterm delivery, and delivery of a small for gestational age infant.^{1–12} Results from studies investigating the influence of interpregnancy interval on stillbirth and neonatal death are conflicting.^{13–18} The discrepancy in these studies could be attributed to small sample size¹⁷ or lack of control for confounders, such as maternal characteristics^{13,14,16} and previous reproductive history.^{13,15,18}

The increased risk of adverse pregnancy outcomes related to short interpregnancy intervals has been attributed to a number of mechanisms including maternal depletion (nutritional stresses of successive pregnancies and lactations),¹⁹ hormonal imbalance,⁵ and postpartum stress⁸; recently, Smits and Essed²⁰ hypothesized that maternal folate depletion may play a major role. However, previous adverse pregnancy outcomes and maternal characteristics such as low socioeconomic status, smoking, and other lifestyle factors are associated with extreme interpregnancy intervals.^{2,20–22} Thus, such factors may confound the association between interpregnancy interval and risk of a subsequent adverse pregnancy outcome.

In this large, population-based, cohort study, we included information on the first two deliveries of 410,000 women to investigate whether interpregnancy interval is associated with increased risks of stillbirth and early neonatal death. As a secondary aim, we wanted to study whether possible associations between interpregnancy interval and risks of stillbirth and early neonatal death were confounded by maternal characteristics and previous reproductive history.

MATERIALS AND METHODS

The population-based Swedish Medical Birth Register recorded 410,021 women who delivered consecutive first and second singletons between 1983 and 1997. The Birth Register includes the mothers' and infants' unique national registration numbers, which facilitates linkage

of successive births as well as individual record linkage to other data sources. Information about stillbirth (defined as fetal death occurring at 28 or more completed weeks of gestation), the duration of gestation, birth weight, sex, and date of delivery was obtained from the standardized pediatric record, which is routinely filled out immediately after delivery. Information about early neonatal death (death during the first week after delivery) was obtained through individual record linkage between the Birth Register and the Cause of Death Register. Gestational age was determined using information from early second-trimester ultrasonography when available; otherwise, the last menstrual period was used. The use of ultrasound screening to date pregnancies became increasingly common during the study period, and after 1990, all pregnant women were offered routine ultrasound screening.²³ In a Swedish population-based study of stillbirth between 1987 and 1996, gestational age was estimated by ultrasonography in 94% of all cases and randomly selected controls, respectively.²⁴ We stratified preterm delivery into two categories: very preterm (before 32 weeks) and moderately preterm (32–36 weeks). Small for gestational age infants were defined as those with birth weights more than two standard deviations below the mean birth weight for gestational age, according to a Swedish reference curve.²⁵

For each woman, we defined the interpregnancy interval as the time that elapsed between the birth of the first child and the estimated conception date of the following child.⁵ The interval was calculated in days and converted into completed months (30 days was assumed to equal 1 month). We obtained information about maternal characteristics from the standardized prenatal record.²⁶ At the time of registration for prenatal care, women were categorized as nonsmokers, moderate smokers (one to nine cigarettes per day), or heavy smokers (at least ten cigarettes per day). Women were also classified as either living with or not living with the infant's father. Maternal age at delivery was registered in delivery records and categorized according to Table 1. Maternal disorders classified according to International Classification of Diseases, 8th, 9th, and 10th Revisions (ICD-8, ICD-9, and ICD-10) were noted in the delivery records by an obstetrician at the time of the woman's discharge from the hospital. We defined diabetes as pregestational and gestational diabetes (ICD-8 code 250.0; ICD-9 codes 648A and 648W; and ICD-10 code O24). Hypertensive disease was defined as chronic hypertension, gestational hypertension, preeclampsia, and eclampsia (ICD-8 codes 637.0, 637.1, and 637.9; ICD-9 code 642; and ICD-10 codes O10, O11, and O13–15). We obtained information on the mother's years of formal education as of December 31, 1998, by individual

record linkage to the Education Register, maintained by Statistics Sweden. We obtained information on the mother's country of birth through record linkage with the Immigration Register. We divided countries of birth into Nordic countries (Sweden, Denmark, Norway, Finland, and Iceland) and other countries. Calendar year of second delivery was obtained from the pediatric records and was categorized according to Table 1. The study was approved by the research ethics committee at Karolinska Institutet, Stockholm, Sweden.

We used unconditional logistic regression analysis to model the risks of adverse outcomes in the second pregnancy as a function of interpregnancy interval, maternal characteristics during the second pregnancy, and the outcome of the first pregnancy. Adverse outcomes in the first pregnancy were categorized as stillbirth, early neonatal death, and preterm or small for gestational age delivery. The analysis of early neonatal death was restricted to live-born infants. In all analyses, we adjusted for interpregnancy interval, maternal age at delivery, cigarette smoking, educational level, whether the mother was living with the infant's father, mother's country of birth, diabetes, hypertensive disease, and year of second delivery. In additional analyses, we also adjusted for previous pregnancy outcome. We excluded from our analysis 47,653 women (12% of the total study population) for whom information on covariates was missing. We studied whether there were any interactions between interpregnancy interval and adverse outcomes in the first pregnancy (stillbirth, early neonatal death, preterm, and small for gestational age delivery). That is, for each of the two outcomes, we modeled four interaction terms and tested statistical significance using the Wald test.²⁷ Odds ratios were calculated to approximate relative risks and are presented with 95% confidence intervals. All analyses were performed using SAS 6.12 (SAS Institute, Cary, NC).

RESULTS

Among the 410,021 second births, there were 1062 stillbirths (rate 2.6 per 1000) and 773 early neonatal deaths (rate 1.9 per 1000 live births). Compared with interpregnancy intervals of 12 to 35 completed months, very short (0–3 months) and long (36 months and longer) intervals were associated with increased risks of stillbirth in the univariate analyses (Table 1). Short interpregnancy intervals (0–3 months and 4–7 months) were associated with increased risk of early neonatal death, whereas long intervals were not. Adverse pregnancy outcomes in the first pregnancy (stillbirth, early neonatal death, very and moderately preterm delivery, and small for gestational age delivery) were all strongly associated

Table 1. Characteristics of Women Who Delivered Two Successive Singleton Infants Between 1983 and 1997 in Sweden and Univariate Associations With the Risk of Stillbirth and Early Neonatal Death in the Second Pregnancy*

Characteristic	No. of second deliveries (<i>n</i> = 410,021)	Stillbirth (<i>n</i> = 1062)		Early neonatal death (<i>n</i> = 773)	
		<i>n</i>	OR (95% CI)	<i>n</i>	OR (95% CI)
Interpregnancy interval (mo)					
0-3	6835	31	1.9 (1.3, 2.7)	22	1.8 (1.2, 2.8)
4-7	27,299	65	1.0 (0.8, 1.3)	68	1.4 (1.1, 1.8)
8-11	51,127	116	0.9 (0.8, 1.1)	89	1.0 (0.8, 1.2)
12-35	245,283	593	1.0 (referent)	435	1.0 (referent)
36-71	66,182	199	1.2 (1.1, 1.5)	133	1.1 (0.9, 1.4)
≥72	13,295	58	1.8 (1.4, 2.4)	26	1.1 (0.7, 1.6)
Stillbirth in first delivery					
Yes	1842	14	3.0 (1.8, 5.1)	15	4.4 (2.7, 7.4)
No	408,179	1048	1.0 (referent)	758	1.0 (referent)
Early neonatal death in first delivery [†]					
Yes	1241	9	2.9 (1.5, 5.5)	14	6.3 (3.7, 10.7)
No	406,938	1039	1.0 (referent)	744	1.0 (referent)
Gestational age at first delivery* (wk)					
<32	2344	19	3.3 (2.1, 5.2)	18	4.6 (2.9, 7.3)
32-36	21,003	70	1.3 (1.1, 1.7)	70	2.0 (1.5, 2.5)
≥37	382,989	948	1.0 (referent)	653	1.0 (referent)
Data missing	602	2		3	
Delivery of small for gestational age infant in first delivery [‡]					
Yes	14,083	85	2.5 (2.0, 3.1)	37	1.5 (1.1, 2.0)
No	390,849	950	1.0 (referent)	702	1.0 (referent)
Data missing	2006	4		5	
Smoking status					
Nonsmoker	311,488	733	1.0 (referent)	521	1.0 (referent)
One to nine cigarettes per day	49,054	137	1.2 (1.0, 1.4)	93	1.1 (0.9, 1.4)
More than ten cigarettes per day	27,604	96	1.5 (1.2, 1.8)	60	1.3 (1.0, 1.7)
Data missing	21,875	96		99	
Maternal age (y)					
≤24	82,427	202	1.0 (0.9, 1.2)	172	1.2 (1.0, 1.4)
25-29	178,343	434	1.0 (referent)	312	1.0 (referent)
30-34	115,432	293	1.0 (0.9, 1.2)	211	1.0 (0.9, 1.2)
≥35	33,817	133	1.6 (1.3, 2.0)	78	1.3 (1.0, 1.7)
Data missing	2	0		0	
Education (y)					
≤11	280,361	748	1.1 (1.0, 1.3)	533	1.1 (0.9, 1.2)
≥12	123,420	293	1.0 (referent)	220	1.0 (referent)
Data missing	6240	21		20	
Living with the infant's father					
Yes	372,766	930	1.0 (referent)	659	1.0 (referent)
No	10,294	31	1.2 (0.8, 1.7)	17	0.9 (0.6, 1.5)
Data missing	26,961	101		97	
Mother's country of birth					
Nordic country	381,438	928	1.0 (referent)	702	1.0 (referent)
Other country	27,856	104	1.5 (1.3, 1.9)	62	1.2 (0.9, 1.6)
Data missing	727	30		9	
Diabetes					
Yes	3722	21	2.2 (1.4, 3.4)	10	1.4 (0.8, 2.7)
No	406,299	1041	1.0 (referent)	763	1.0 (referent)
Hypertensive disease					
Yes	9608	37	1.5 (1.1, 2.1)	41	2.3 (1.7, 3.2)
No	400,413	1025	1.0 (referent)	732	1.0 (referent)
Year of second delivery					
1983-1989	124,056	320	1.0 (0.8, 1.1)	316	1.9 (1.6, 2.2)
1990-1993	151,676	382	0.9 (0.8, 1.1)	274	1.3 (1.1, 1.6)
1994-1997	134,289	360	1.0 (referent)	183	1.0 (referent)

OR = odds ratio; CI = confidence interval.

* For early neonatal death, values are based on live births in the second pregnancy.

[†] Includes live born in first pregnancy.

[‡] Includes live born in first pregnancy without early neonatal deaths.

Table 2. Distribution of Interpregnancy Interval According to Outcome in First Pregnancy for All Second Deliveries Among Women Who Delivered Two Successive Singleton Infants Between 1983 and 1997 in Sweden*

Outcome in first pregnancy	Interpregnancy interval					
	0–3 mo (n = 6835)	4–7 mo (n = 27,299)	8–11 mo (n = 51,127)	12–35 mo (n = 245,283)	36–71 mo (n = 66,182)	≥72 mo (n = 13,295)
All deliveries	1.7	6.7	12.5	59.8	16.1	3.2
Stillbirth						
Yes	31.9	27.7	14.0	20.5	5.3	0.7
No	1.5	6.6	12.5	60.0	16.2	3.3
Early neonatal death						
Yes	27.7	26.8	14.8	23.5	6.0	1.1
No	1.5	6.5	12.5	60.1	16.2	3.3
Gestational age (wk)						
<32	7.4	11.2	9.4	49.0	18.8	4.3
32–36	2.5	6.9	11.4	57.7	17.8	3.8
≥37	1.4	6.5	12.5	60.2	16.1	3.2
Delivery of a small for gestational age infant						
Yes	2.8	7.1	12.0	55.4	19.0	3.8
No	1.5	6.5	12.5	60.2	16.1	3.2

* Percentages may not add to 100.0 because of rounding. For early neonatal death, gestational age, and delivery of a small for gestational age infant, values are based on live births in first pregnancy.

with risks of stillbirth and early neonatal death in the second pregnancy. Risk of stillbirth was also influenced by maternal characteristics (foremost cigarette smoking, high maternal age, a non-Nordic country of birth, diabetes, and hypertensive disease), whereas risk of early neonatal death was above all associated with year of second delivery and hypertensive disease.

Interpregnancy intervals were substantially influenced by previous reproductive history (Table 2). For example, 32% of women with previous stillbirth and 28% of women with previous early neonatal death had interpregnancy intervals of less than 4 months, whereas the corresponding percentages among women without previous stillbirth or early neonatal death were both 1.5%. Compared with women who delivered at term or a non-small for gestational age infant in the first pregnancy, short and long interpregnancy intervals were consistently more common among women who delivered a preterm or a small for gestational age infant in the first pregnancy. Maternal characteristics were also related to interpregnancy intervals. Both short (less than 8 months) and long (at least 36 months) interpregnancy intervals were more common among smokers (9.6% and 27.1%, respectively) compared with nonsmokers (7.9% and 17.5%, respectively), among women with a low (11 years or less) level of formal education (8.7% and 20.9%, respectively) compared with women with high (12 years or more) education (7.1% and 16.2%, respectively), and among women born outside the Nordic countries (16.4% and 22.5%, respectively) compared with women born in the Nordic countries (7.7% and 19.2%, respectively). Long interpregnancy intervals (at least 36 months) were

more common among noncohabiting (44.7%) compared with cohabiting women (18.6%). Interpregnancy intervals increased with increasing maternal age. For example, among women younger than 25, 15.3% had an interpregnancy interval of less than 8 months compared with 5.4% among women 35 years and older. For interpregnancy intervals of 36 months and longer, the proportions were 8.8% and 36.2%, respectively. Long (at least 36 months) interpregnancy intervals were more common among women with diabetes and hypertensive disease (26.8% and 26.7%, respectively) compared with women without these diseases (19.3% and 19.2%, respectively).

Compared with results from the univariate analysis, the risk of stillbirth associated with very short (0–3 months) and very long (72 months or longer) interpregnancy intervals decreased when we adjusted for maternal characteristics (Table 3). When outcomes of the first pregnancy were also included in the model, the risk further decreased, and very short interpregnancy intervals were no longer significantly associated with stillbirth risk. In contrast, the risk of stillbirth associated with long (36–71 and 72 months or longer) interpregnancy intervals was not influenced by previous pregnancy outcomes.

Similarly, compared with the univariate results, the risk of early neonatal death associated with very short (0–3 months) and short (4–7 months) interpregnancy intervals decreased when we adjusted for maternal characteristics (Table 4). When adjustments for outcomes in the first pregnancy were included in the model, there was no association between very short and short intervals

Table 3. Adjusted Odds Ratios for Stillbirth in the Second Pregnancy Associated With Interpregnancy Interval

	Stillbirth	
	Adjusted for maternal characteristics* (<i>n</i> = 881)	Adjusted for maternal characteristics and outcome of first pregnancy† (<i>n</i> = 876)
	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Interpregnancy interval (mo)		
0–3	1.6 (1.1, 2.5)	1.3 (0.8, 2.1)
4–7	1.0 (0.8, 1.3)	1.0 (0.7, 1.3)
8–11	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)
12–35	1.0 (referent)	1.0 (referent)
36–71	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)
≥72	1.5 (1.1, 2.1)	1.5 (1.1, 2.1)
<i>P</i> *	0.032	0.096

Abbreviations as in Table 1.

*The ORs have been adjusted for smoking, maternal age, education, living arrangements of the infant's father, mother's country of birth, diabetes, hypertensive disease, and year of second delivery.

†The ORs have been adjusted for smoking, maternal age, education, living arrangements of the infant's father, mother's country of birth, diabetes, hypertensive disease, year of second delivery, and outcome of the first pregnancy (stillbirth, early neonatal death, preterm or small for gestational age delivery).

*Wald test for the overall effect (test of general heterogeneity).

and early neonatal death, and the risks associated with longer intervals did not reach statistical significance. Finally, we tested for interactions between interpregnancy interval and adverse pregnancy outcomes in the first pregnancy. Of the eight interactions tested, one was statistically significant at the 5% level. The association between long interpregnancy intervals and early neonatal death was restricted to women who delivered preterm (before 37 gestational weeks) in the first pregnancy ($P = .025$).

DISCUSSION

The associations between short interpregnancy intervals and risks of stillbirth and early neonatal death were

substantially confounded by maternal characteristics and previous reproductive history. Long interpregnancy intervals (36 months or longer) were associated with increased risks of stillbirth and possibly early neonatal death.

Consistent with findings from previous studies, interpregnancy intervals were associated with maternal characteristics and previous adverse pregnancy outcomes.^{1–3,5,7,9,12,14,17,18} Short interpregnancy intervals were especially common among women with previous stillbirth or early neonatal death, which may foremost be explained by a strong tendency to replace deaths in previous pregnancies.¹⁷ Moreover, as deliveries complicated by stillbirth and early neonatal death are not

Table 4. Adjusted Odds Ratios for Early Neonatal Death in the Second Pregnancy Associated With Interpregnancy Interval

	Early neonatal death	
	Adjusted for maternal characteristics* (<i>n</i> = 624)	Adjusted for maternal characteristics and outcome of first pregnancy† (<i>n</i> = 620)
	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Interpregnancy interval (mo)		
0–3	1.5 (0.9, 2.5)	0.9 (0.5, 1.6)
4–7	1.3 (1.0, 1.7)	1.1 (0.8, 1.5)
8–11	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)
12–35	1.0 (referent)	1.0 (referent)
36–71	1.2 (0.9, 1.5)	1.2 (0.9, 1.5)
≥72	1.3 (0.9, 2.1)	1.3 (0.9, 2.1)
<i>P</i> *	0.21	0.58

Abbreviations as in Table 1.

Values are based on live births in second pregnancy.

*The ORs have been adjusted for smoking, maternal age, education, living arrangements of the infant's father, mother's country of birth, diabetes, hypertensive disease, and year of second delivery.

†The ORs have been adjusted for smoking, maternal age, education, living arrangements of the infant's father, mother's country of birth, diabetes, hypertensive disease, year of second delivery, and outcome of the first pregnancy (stillbirth, early neonatal death, preterm or small for gestational age delivery).

*Wald test for the overall effect (test of general heterogeneity).

followed by lactation, there is a shorter period of anovulation. Shortening or absence of lactation may also be the mechanism for the association between delivery of a preterm or small for gestational age infant in the first pregnancy and short interpregnancy intervals.

Most studies have found that short interpregnancy intervals are associated with neonatal death, preterm, and small for gestational age delivery,^{1-7,9-11,13-18} and one study has also found an association with stillbirth.¹⁸ Whether the effect of short interpregnancy interval on adverse pregnancy outcomes is causal or not remains a matter of disagreement.²⁰ It is generally accepted that there is a tendency to repeat adverse pregnancy outcomes, such as stillbirth, early neonatal death, preterm delivery, or delivery of a small for gestational age infant.^{21,28-31} The basis for repeating adverse pregnancy outcomes in the subsequent pregnancy is not well known, but may include chronic or recurrent upper genital tract infections, repeated placental complications, chronic maternal diseases, and repeated pregnancy-related diseases.^{21,32,33} The risks of adverse pregnancy outcomes also increase with maternal characteristics, such as high maternal age, smoking, and low educational attainment. We found that women with short interpregnancy intervals were more likely to have experienced an adverse outcome in the first pregnancy, and these women were also more likely to have an overrepresentation of maternal risk factors. When we controlled for this in multivariate analyses, a short interpregnancy interval was not associated with increased risks of stillbirth and early neonatal death. It has been suggested that short interpregnancy intervals may increase risks of adverse pregnancy outcomes by maternal depletion or other mechanisms, but our results suggest that this is an effect of mothers' characteristics and the tendency to repeat adverse pregnancy outcomes. Previous studies on the association between short interpregnancy intervals and adverse pregnancy outcomes may have overestimated the risk associated with short intervals because of inadequate control for previous pregnancy outcomes as well as maternal characteristics.

Our finding of an increased risk of stillbirth for long interpregnancy intervals is consistent with some,^{13,16} but not all studies.^{14,18} Although diabetes and hypertensive disease were more common among women with long interpregnancy intervals, this could not explain the increase in risk of stillbirth. The association between long intervals and stillbirth may be attributed to metabolic or anatomical factors that are associated with delayed fertility as well as adverse birth outcomes.² The relative benefit of a previous pregnancy on the risk of adverse outcome in the subsequent pregnancy may also decrease over time. We found that long interpregnancy intervals

also appeared to increase the risk of early neonatal death for women with a history of preterm delivery.

The size of this population-based cohort study enabled us to investigate risks of rare pregnancy outcomes such as stillbirth and early neonatal death, and by using the unique national registration number, we could study information from successive births. By restricting the study population to only include first and second births, we minimized the effect of previous pregnancy outcomes on number of desired future pregnancies. In the present study, we did not have information on previous spontaneous or induced abortions. As spontaneous abortion is associated with subsequent risks of preterm delivery, neonatal death, and stillbirth,³⁴ as well as shorter interpregnancy intervals,¹⁴ this may have caused misclassification of the interpregnancy intervals. As noted by Fuentes-Afflick and Hessol,¹ such a bias would result in underestimating the effect of short interpregnancy intervals and overestimating the effect of long intervals. We were not able to investigate, on an individual basis, whether gestational age was based on ultrasound examination or date of last menstrual period, which may be an additional potential for misclassification of interpregnancy intervals. However, a second-trimester ultrasound scan is, since 1990, offered to all pregnant women in Sweden, and more than 95% of pregnant women avail themselves of this opportunity.³⁵ Thus, it is likely that the proportion of women with gestational age estimated by ultrasound examination was large, and because we also adjusted for year of delivery, misclassification of gestational age is not likely to have a substantial influence on our findings. Twelve percent of the women in the study population had incomplete exposure data, and were therefore excluded from the multivariate analyses. Because we made comparisons within the cohort, this is not a problem for the internal validity, but external validity (ie, the generalizability) may have been affected to some extent. We did not have information on lifestyle and environmental risk factors such as alcohol, drug use other than tobacco, and caffeine consumption during pregnancy. In this cohort study, we may have introduced a selection bias because women with short interpregnancy intervals were more likely to be included in the study population. However, because of the long time period, this is unlikely to have a substantial effect on our findings.

In conclusion, we found that previous reproductive history and maternal characteristics substantially confounded the association between interpregnancy interval and risks of stillbirth and early neonatal death, and risks were only found for long intervals. The role of short interpregnancy interval as an independent risk factor for

stillbirth and early neonatal death may have been overestimated in previous studies.

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