Gestational Diabetes and Incident Heart Failure: A Cohort Study

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Diabetes Care 2021;44:2346–2352 | https://doi.org/10.2337/dc21-0552

OBJECTIVE

To assess whether gestational diabetes mellitus (GDM) is associated with an increased risk of heart failure (HF).

RESEARCH DESIGN AND METHODS

We conducted a population-based cohort study using information from the Ministry of Health and Long-Term Care of Ontario (Canada) health care administrative databases. We identified all women in Ontario with a GDM diagnosis with a live birth singleton delivery between 1 July 2007 and 31 March 2018. Women with diabetes or HF before pregnancy were excluded. GDM was defined based on laboratory test results and diagnosis coding. The primary outcome was incident HF hospitalization over a period extending from the index pregnancy until 31 March 2019. The secondary outcome was prevalent peripartum cardiomyopathy at index pregnancy. Estimates of association were adjusted for relevant cardiometabolic risk factors.

RESULTS

Among 906,319 eligible women (mean age 30 years [SD 5.6], 50,193 with GDM [5.5%]), there were 763 HF events over a median follow-up period of 7 years. GDM was associated with a higher risk of incident HF (adjusted hazard ratio [aHR] 1.62 [95% CI 1.28, 2.05]) compared with no GDM. This association remained significant after accounting for chronic kidney disease, postpartum diabetes, hypertension, and coronary artery disease (aHR 1.39 [95% CI 1.09, 1.79]). GDM increased the odds of peripartum cardiomyopathy (adjusted odds ratio 1.83 [95% CI 1.45, 2.33]).

CONCLUSIONS

In a large observational study, GDM was associated with an increased risk of HF. Consequently, diabetes screening during pregnancy is suggested to identify women at risk for HF.

Heart failure (HF) and diabetes are common and co-occurring conditions (1,2). While it is clear that diabetes is associated with a two- to fourfold increase in the risk of incident HF (3), the relation between gestational diabetes mellitus (GDM) (a known forerunner of type 2 diabetes [4]) and the future risk of HF is less well defined. While accruing evidence suggests that women with GDM have a significantly increased risk of developing atherosclerotic cardiovascular disease (CVD) in the years after pregnancy (5), studies on the influence of GDM on cardiac dysfunction are scarce. There have been suggestions of a positive relation between GDM and peripartum cardiomyopathy (6), and a handful of studies that included cardiac imaging indicated that GDM

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Received 11 March 2021 and accepted 15 July 2021

This article contains supplementary material online at https://doi.org/10.2337/figshare.14999628.

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leads to cardiac remodeling (7,8). To our knowledge, studies on the adverse cardiovascular complications associated with GDM have sel-dom specifically explored the relation of GDM and incident HF events (9,10). The few extant studies that have done so have not been comprehensive or rigorous in their approach and are inconclusive (11,12).

In examining the link between GDM and HF, it is important to consider the method of GDM diagnosis. While the detection of GDM is a globally accepted as a standard of obstetrical care, the approaches to testing and the diagnostic criteria used have been heterogeneous across settings (13). In 2010, the International Association of Diabetes and Pregnancy Study Group proposed the adoption of a universal one-step screening strategy with new diagnostic criteria based on a 75-g oral glucose tolerance test (OGTT) (14). However, this recommendation has not been widely implemented for a number of reasons. It creates an increase in testing burden, leads to a higher prevalence of women diagnosed with GDM (15,16), and may be costly (17). Several professional organizations (e.g., the National Institutes of Health panel [18] and the most recent Canadian guidelines [19]) have continued to recommend a two-step screening strategy consisting of a 50-g glucose challenge test (GCT) in pregnant women followed by a diagnostic OGTT only in those individuals with an abnormal GCT (defined by a 1-h postchallenge plasma glucose concentration $\geq$140 mg/dL [7.8 mmol/L]).

Using data from the health care administrative databases from the Ontario Ministry of Health and Long-Term Care (MOHLTC) in Canada, we sought to examine the association of GDM and the risk of future HF. We hypothesized that GDM would be associated with an increased risk of HF, and thus, identification of GDM in young women can help in the stratification of the risk of future HF.

RESEARCH DESIGN AND METHODS

Study Population

Our sample of participants consisted of women who have data captured in the health care administrative databases from the MOHLTC in Ontario, which is the most populous province in Canada.

Data Sources

The databases include the Canadian Institute for Health Information (CIHI) Discharge Abstract Database from all hospitalizations in the province; the Ontario Health Insurance Plan physician service claims for reimbursement for virtually all consultations, procedures, and visits; and the Registered Persons Database for demographic information for all residents eligible for health care in Ontario. The Ontario Diabetes Database is a validated registry of physician-diagnosed nongestational diabetes that is derived using these data as well as prescription records (20). The MOMBABY database is derived from hospitalization data and links hospitalization records of delivering mothers with their newborn babies. The results of the GCT and OGTT tests were obtained from the Ontario Laboratory Information Service, which includes data for laboratory test orders and results from community, hospital, and public health laboratories across Ontario. Laboratories have gradually enrolled in Ontario Laboratory Information Service to contribute their data, starting in 2007. Individuals are linked between data sources through a unique and reproducibly encrypted health card number. These data sets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES).

Inclusion and Exclusion Criteria

In the current study, we included all women with a live birth singleton delivery, during a period spanning from 1 July 2007 to 31 March 2018. We excluded women with a history of diabetes before pregnancy or a history of HF prior to the index pregnancy. The additional criteria of exclusion from the study are detailed in the Supplementary Fig. 1.

The use of data in this study was authorized under section 45 of Ontario's Personal Health Information Protection Act and hence does not require review by a Research Ethics Board.

The data set from this study is held securely in coded form at ICES. While legal data-sharing agreements between ICES and data providers (e.g., health care organizations and government) prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at https://www.ices.on.ca/DAS (e-mail: das@ices.on.ca). The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

GDM Ascertainment

The algorithm for identification of GDM in our study is shown in Supplementary Fig. 2. It is based on the screening strategy recommended in Canada (19).

Our definition of GDM was initially based on the 1-h 50 g GCT result of $\geq$200 mg/dL (11.1 mmol/L) (19). Women whose GCT result was $\leq$139 mg/dL (7.7 mmol/L) were defined as not having GDM. For those with results between 140 mg/dL (7.8 mmol/L) and 200 mg/dL (11.0 mmol/L) and women for whom no GCT result was available, we then searched for 75-g OGTT results. The diagnosis of GDM was made based on one of the following thresholds being exceeded: fasting blood glucose $\geq$95 mg/dL (5.3 mmol/L), 1-h glucose levels $\geq$190 mg/dL (10.6 mmol/L), or 2-h glucose levels $\geq$162 mg/dL (9.0 mmol/L) (19). If no OGTT result was available, we identified women who had a diagnosis code for diabetes on the delivery hospitalization record as having GDM. The *International Classification of Diseases*, 10th Revision, Canada (ICD-10-CA) codes of E1 and O24 were used to identify GDM in the hospital records at index pregnancy.

HF Events and Peripartum Cardiomyopathy

The primary outcome was incident hospitalization for HF (HHF), identified through linkage with hospital admission records starting from 6 months after delivery of the index gestation up to 31 March 2019. HHF was identified using the ICD-10-CA code I50. The secondary outcome was prevalent peripartum cardiomyopathy, which was identified through linkage with hospital admission records from the 32nd week of the index gestation to 6 months after delivery (6). The ICD-10-CA codes for peripartum cardiomyopathy were I50, J81, and O90.3. Women with preexisting CVD identified before 32 weeks of the index gestation since 1 April 1988 were not considered as having peripartum cardiomyopathy. Preexisting CVD was identified using ICD-

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9-CA codes (390–459) and ICD-10-CA codes (I00–I99). Women who met the definition of peripartum cardiomyopathy at the index pregnancy were excluded from the analysis of the primary outcome. Women who had preexisting CVD before pregnancy (ICD-9-CA codes 390–459 and ICD-10CA codes I00–I99) were excluded from the analysis of the secondary outcome.

Covariates

The covariates used in the analyses included age at index delivery, socioeconomic status (ascertained ecologically based on neighborhood household income quintile), rurality of residence (ascertained using the Rurality Index of Ontario) (21), ethnicity (ascertained using a validated surnames algorithm) (22), parity, hypertension, chronic kidney disease (defined using a previously validated algorithm (23), preeclampsia in the current pregnancy, preterm delivery, postpartum progression to diabetes (based on the Ontario Diabetes Database), postpartum coronary artery disease, and postpartum hypertension.

Statistical Analyses

The baseline characteristics of the study population were presented by GDM status. Hypothesis tests are greatly affected by sample size; thus, in a large study as ours, clinically unimportant differences could be statistically significant. Therefore, we used standardized differences, calculated as the difference in means or proportions divided by a pooled estimate of the standard deviation (SD), to compare baseline characteristics between the two study groups (24). We considered a standardized difference >0.1 as indicating important imbalance between the study groups.

We assessed the association of GDM and incident HHF using Cox proportional hazards regression models. We conducted initial adjustments for age at index delivery, socioeconomic status, rurality of residence, ethnicity (ascertained using a validated surnames algorithm) (22), parity, pregestational hyper-tension, preeclampsia at the index pregnancy, preterm delivery, and preexisting CVD, and chronic kidney disease. We additionally adjusted for postpartum progression to diabetes, hypertension, or coronary artery disease as a time-varying covariates. Women were followed from 6 months after the index pregnancy until HHF event, death, migration, or 31 March 2019, whichever came first.

We examined an association of GDM and peripartum cardiomyopathy (occurring at the index pregnancy). This was done using logistic regression models, with adjustment for age, socioeconomic status, rurality of residence, ethnicity, parity, pregestational hypertension, preeclampsia at the index pregnancy, chronic kidney disease, and preterm delivery; we excluded women who had CVD prior to the index pregnancy.

Two-sided P values of <0.05 were considered statistically significant. All analyses were done using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

The study population consisted of 906,319 women (mean age 30 years [SD 5.6]), among whom 50,198 (5.5%) had GDM. Table 1 shows the baseline characteristics of the study population by GDM status. Women with GDM were older and more likely have a Chinese and south Asian ethnicity, an urban residence, a low socioeconomic status (as assessed by income quintile), a higher parity, a premature delivery, pregestational hypertension, preeclampsia, and postpartum diabetes, and postpartum hypertension (all standardized differences $>10\%$) (Table 1).

Over a median follow-up of 7 years (interquartile range 4–10; total follow-up >6.3 million person-years), there were 763 HHF events in the study population. At the time of the HF event, the mean age of participants was 34 years (SD 6.3). GDM was positively and significantly associated with a higher risk of incident HHF (Table 2). Indeed, after adjustment for potential confounders, individuals with GDM had a 62% higher risk of HHF (adjusted hazard ratio [HR] 1.62 [95% CI 1.28, 2.05]; $P < 0.0001$) compared with those without GDM. Additionally, accounting for chronic kidney disease status, postpartum diabetes, hypertension, and coronary artery disease attenuated the effect estimate for incident HHF, which however remained significant (adjusted HR 1.39 [95% CI 1.09, 1.79]; $P = 0.009$).

A total of 585 women had peripartum cardiomyopathy during the index pregnancy. In the fully adjusted model (Table 3), GDM was significantly associated with an 83% higher odds of peripartum cardiomyopathy at the index pregnancy (adjusted odds ratio [OR] 1.83 [95% CI 1.45, 2.33]; $P < 0.0001$).

CONCLUSIONS

In this large population-based cohort study, we showed that GDM was associated with the future risk of HHF among women. The association of GDM with incident HHF persisted after accounting for postpartum diabetes and postpartum coronary artery disease. GDM was also associated with increased odds of peripartum cardiomyopathy. Despite the understandably low HHF event rates in young women (mean age 34 years at the time of HHF event), we observed robust associations, which suggest the potential potency of GDM as a predictor of future HHF.

Our results are supported by some of the prior studies, which, albeit small and not including HF events, have suggested that GDM affects cardiac remodeling, possibly leading to cardiac dysfunction (7,8). These studies demonstrated an association of GDM with long-term changes in left ventricular mass and left ventricular mass index (7), as well as with alterations in diastolic dysfunction during pregnancy (8). The few extant population-based studies of GDM and incident HF events found either a borderline significant association (12) or no association (11) between GDM and HF risk (11,12). Regarding peripartum cardiomyopathy, our results align with that of a prior study, which described a higher frequency of peripartum cardiomyopathy among women with GDM compared with those without GDM (6).

GDM is a known forerunner of type 2 diabetes (4), and extant data have demonstrated that GDM increases the risk of developing CVD (5,25). However, most of the prior studies on CVD related to GDM did not specifically examine the risk of HF in relation to GDM (9,10). The few studies that examined the GDM and HF risk have a number of important limitations (11,12). These include being small in size (12), an ascertainment of GDM not based on biochemical data (11,12), relying on self-reported history of HF (12), not differentiating between peripartum cardiomyopathy and long-term incident

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Table 1—Baseline characteristics of study participants by gestational diabetes mellitus (GDM) status

	Total (N = 906,319)	No GDM (N = 856,126)	GDM (N = 50,193)	Standardized difference*
Age at index pregnancy (years)	29.74 ± 5.58	29.59 ± 5.56	32.32 ± 5.28	0.5
Ethnicity				
Chinese	53,136 (5.9)	48,404 (5.7)	4,732 (9.4)	0.14
General population	811,524 (89.5)	770,600 (90.0)	40,924 (81.5)	0.24
South Asian	41,659 (4.6)	37,122 (4.3)	4,537 (9.0)	0.19
Neighborhood income quintile				
1 (lowest)	207,754 (22.9)	193,980 (22.7)	13,774 (27.4)	0.11
2	186,621 (20.6)	175,611 (20.5)	11,010 (21.9)	0.03
3	184,881 (20.4)	174,598 (20.4)	10,283 (20.5)	0
4	183,203 (20.2)	174,241 (20.4)	8,962 (17.9)	0.06
5 (highest)	140,591 (15.5)	134,634 (15.7)	5,957 (11.9)	0.11
Rurality				
Rural	62,756 (6.9)	60,443 (7.1)	2,313 (4.6)	0.10
Semiurban	150,534 (16.6)	145,025 (16.9)	5,509 (11.0)	0.17
Urban	693,029 (76.5)	650,658 (76.0)	42,371 (84.4)	0.21
Gestational age at delivery (weeks)	38.92 ± 1.84	38.96 ± 1.84	38.23 ± 1.72	0.41
Preterm delivery (gestational age ≤36 weeks)	57,775 (6.4)	52,974 (6.2)	4,801 (9.6)	0.13
Number of previous live births, mean	0.52 ± 0.90	0.52 ± 0.89	0.64 ± 1.02	0.13
Parity (number of previous births)				
0	595,792 (65.7)	565,249 (66.0)	30,543 (60.9)	0.11
1	199,252 (22.0)	187,466 (21.9)	11,786 (23.5)	0.04
≥2	111,275 (12.3)	103,411 (12.1)	7,864 (15.7)	0.10
Pregestational hypertension	19,749 (2.2)	17,342 (2.0)	2,407 (4.8)	0.15
Preeclampsia	54,176 (6.0)	49,142 (5.7)	5,034 (10.0)	0.16
Prevalent chronic kidney disease	2,587 (0.3)	228 (0.5)	2,815 (0.3)	0.02
Proportion without 50-g GCT data	546,732 (60.3)	517,894 (60.5)	28,838 (57.5)	0.06
50-g GCT, mmol/L	6.53 ± 1.72	6.32 ± 1.48	9.85 ± 1.89	2.08
Preexisting CVD	8,455 (0.9)	7,924 (0.9)	531 (1.1)	0.01
Postpartum diabetes	20,459 (2.3)	11,759 (1.4)	8,700 (17.3)	0.57
Postpartum hypertension	28,704 (3.2)	25,481 (3.0)	3,223 (6.4)	0.16
Postpartum CAD	491 (0.1)	442 (0.1)	49 (0.1)	0.02

Data are mean ± SD or N (%). CAD, coronary artery disease. CVD, cardiovascular disease. GCT, glucose challenge test. *An absolute standardized difference of >0.1 is considered to indicate imbalance between the groups.

HF (11,12), and not comprehensively accounting for potential confounding factors (e.g., postpartum diabetes, postpartum hypertension, or postpartum coronary artery disease) as done in the current study (11,12). Our cohort allowed a more robust exploration of the relation of GDM and incident HHF, and our findings hold potential future implications for clinical practice. These suggest that implementation of universal screening for GDM during pregnancy offers a unique widow of opportunity for HF prevention. Our findings are parti-cularly relevant for a number or reasons. The burden of CVD, including HF, has been increasing in the younger population (26); GDM is emerging as a robust risk factor for CVD (5,25); and there is a context of a dramatic increase in the prevalence of GDM over the last three

Table 2—Event rates and relative risk (95% CI) for the association of gestational diabetes mellitus (GDM) and incident hospitalization for heart failure

	Crude incidence rate per 10,000 person-years (95% CI)	Hazard ratio (95% CI)		
		Unadjusted	Adjusted model 1	Adjusted model 2
No GDM	1.14 (1.05, 1.23)	1 (Reference)	1 (Reference)	1 (Reference)
GDM	2.58 (2.08, 3.20)	2.21 (1.76, 2.78)	1.62 (1.28, 2.05)	1.39 (1.09, 1.79)

Model 1: adjusted for age, ethnicity, neighborhood income quintile, rurality, parity, preterm delivery pregestational hypertension, preeclampsia, and preexisting cardiovascular disease. Model 2: model 1 plus chronic kidney disease, postpartum diabetes, postpartum hypertension, and postpartum coronary artery disease as time-varying covariates.

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Table 3—OR (95% CI) for the association of gestational diabetes mellitus (GDM) and peripartum cardiomyopathy

Case subjects/number at risk		Odds ratio* (95% CI) Unadjusted	Adjusted*
No GDM	502/848,202	1 (Reference)	1 (Reference)
GDM	83/49,662	2.83 (2.24, 3.57)	1.83 (1.45, 2.33)

*Adjusted for age, ethnicity, neighborhood income quintile, rurality, parity, preterm delivery (gestational age ≤36 weeks), pregestational hypertension, preeclampsia, and chronic kidney disease.

decades in Canada (27) and the U.S. (28). Given that >80% of women will become pregnant during their lifetime (29), universal GDM screening provides a platform for HF risk stratification, leading to a more effective risk factor surveillance and modification in young women. Indeed, this prevention opportunity is congruent with the plea of the American College of Obstetricians and Gynecologists for a new paradigm of individualized postpartum care to improve long-term health in women (30,31).

The mechanistic pathways linking GDM to a higher risk of HF largely remain to be clearly elucidated. One of the putative mechanisms includes the development of type 2 diabetes in the aftermaths of pregnancy among women with GDM, which will then pave the way to HF (3,32). However, extant evidence suggests that diabetes may not be a sine qua non interim stage between GDM and HF. First, a pathway that could explain a direct link between GDM and HF is that of microvascular alterations related to endothelial dysfunction (with a reduced endothelium-dependent vasodilatation), a mechanism that has also been described as diabetic cardiomyopathy (33–35). Indeed, GDM has been shown to induce endothelial dysfunction in the absence of type 2 diabetes, a phenomenon that can persist for years after pregnancy (36,37). Second, women with GDM have been shown to develop atherosclerotic CVD without having progressed to type 2 diabetes (5,38). Third, in our analyses, adjusting for postpartum progression to diabetes did affect the magnitude and significance of the association of GDM with subsequent HF. Four, a 7-year follow-up period may have been short for postpartum progression to type 2 diabetes to fully explain the occurrence of HF. Women who develop GDM most probably have an adverse pregravid cardiovascular risk factor profile, with pregnancy actually uncovering a high-risk cardiometabolic phenotype early in its natural history (39,40). GDM may reflect a latent underlying and intrinsic high-risk phenotype characterized by cardiometabolic dysregulation and hence heighten the HF risk potential. However, this theoretical explanatory model remains to be validated by empirical data, but GDM clearly appears to signal a high risk of HF within the first 7 years postpregnancy.

Our study has strengths that include the assessment of a large and multiethnic population-based sample drawn from a health care system, in which GDM screening is a standard of care for all pregnant women. Furthermore, our study included population-level data that capture all women in Ontario and their utilization of health care services, with no loss to follow-up. We also examined multiple aspects of cardiac dysfunction, including the incident HF and peripartum cardiomyopathy outcomes. The study also benefited from rigorous adjustment for known risk factors, including accounting for postpartum diabetes, postpartum hypertension, and postpartum coronary artery disease.

There are limitations to our study. First, we lacked data on cardiovascular risk factors, including biological (e.g., lipid levels and BMI) and behavioral (e.g., smoking, alcohol use, and physical activity) factors, which could have helped in the exploration of pathways linking GDM to HF. Indeed, some of these factors like BMI have been shown to relate to HF outcomes in pregnancy, such as prevalent peripartum cardiomyopathy (41). Second, we did not have access to cardiac imaging data that would have allowed us to define the subtypes of incident HF and refine our definition of peripartum cardiomyopathy, especially as the clinical signs and symptoms of HF often overlap with those of normal pregnancy, making peripartum cardiomyopathy a particularly challenging diagnosis (42). Third, we did have data on GCT or OGTT data for all of the women with the diagnosis of diabetes of GDM and had to rely on diagnostic codes to identify GDM in ∼60% of the cohort. Fourth, women identified under a two-step screening strategy for GDM (the preferred screening method in Canada to date [19]) may differ from those identified under other screening strategies, such as the International Association of Diabetes and Pregnancy Study Group or World Health Organization strategies used in many countries (14). Given the consistency of the findings of an association of GDM and atherosclerotic CVD irrespective of the method used to diagnose GDM (5,25) and the high degree of overlap between the GDM populations identified using a 50-g GCT and 75-g OGTT (43), one can reasonably think that the observed relation with HF most likely exists for the GDM state diagnosed using a one-step strategy including a 75-g OGTT. Lastly, we lacked detailed data on the use of medications relevant to diabetes and HF during and/or after the pregnancy period, as well as on albuminuria and estimated glomerular filtration rate, measures to further charac-terize the renal function, as this is a risk factor for HF. Additional studies including a longer follow-up period are needed to further establish the long-term HF risk related to GDM women and thus reinforce the notion that GDM detection in pregnancy has the potential to inform strategies for primary prevention of HF in young women.

Conclusion

In conclusion, GDM is associated with an elevated risk of subsequent HHF among young pregnant women. The universal screening for GDM as current implemented in obstetrical practice can be leveraged to identify young women at high-risk of future HF and thus offer an opportunity for primary HF prevention.

Funding. J.B.E.-T. was supported by National Heart and Lung Institute grant K23 HL153774 and the Johns Hopkins School of Medicine Diversity Award. R.R. holds the Boehringer Ingelheim Chair in Beta-Cell Preservation, Function and Regeneration at Mount Sinai Hospital (Toronto, Ontario, Canada), and his research program is supported by the Sun Life Financial Program to Prevent Diabetes in Women.

ICES is a nonprofit research institute funded by the Ontario MOHLTC that provided data

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used in the study. Parts of this report are based on data or information compiled and provided by CIHI. The opinions, results and conclusions reported in this study are those of the authors. No endorsement by ICES, MOHLTC, or CIHI is intended or should be inferred.

Duality of Interest. R.R. reports grants and personal fees from Novo Nordisk and Merck, grants from Boehringer Ingelheim, and personal fees from Eli Lilly and Company, Takeda Bio, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. J.B.E.-T. designed the study and drafted the manuscript. J.G. conducted the statistical analyses. J.B.E.-T., J.G., R.R., and B.R.S. provided data interpretation and meaningful contributions to the revision of the manuscript. J.B.E.-T. and B.R.S. are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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