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Incidence of Heart Failure Related to Co-Occurrence of Gestational Hypertensive Disorders and Gestational Diabetes

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Abstract

BACKGROUND—The extent to which their co-occurrence of gestational hypertensive disorders (GHTD) and gestational diabetes mellitus (GDM) influences heart failure (HF) risk is unclear.

OBJECTIVES—The purpose of this study was to characterize the risk of HF related to concomitant GHTD and GDM.

METHODS—We conducted a population-based cohort study using the Ministry of Health and Long-Term Care of Ontario (Canada) health care administrative databases. We included women with a livebirth singleton delivery between July 1, 2007, and March 31, 2018, and excluded those with prepregnancy diabetes, hypertension, HF, or coronary artery disease. GDM, GHTD, peripartum cardiomyopathy (at index pregnancy) were identified using diagnosis coding. Incident HF was assessed from index pregnancy until March 31, 2020. We estimated associations of GDM and/or GHTD with peripartum cardiomyopathy and incident HF.

RESULTS—Among 885,873 women (mean age: 30 years, 54,015 with isolated GDM, 43,750 with isolated GHTD, 4,960 with GDM and GHTD), there were 489 HF events over 8 years. Compared to no-GDM and no-GHTD, isolated GDM (adjusted hazard ratio [aHR]: 1.44; 95%

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APPENDIX For a supplemental table and figure, please see the online version of this paper.

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CI: 1.02-2.04) and isolated GHTD (aHR: 1.65; 95% CI: 1.17-2.31) were associated with a higher risk of incident HF. The co-occurrence of GDM and GHTD was associated with a higher HF risk (aHR: 2.64; 95% CI: 1.24-5.61). GDM and GHTD increased the risk of peripartum cardiomyopathy (adjusted risk ratio [aRR]: 7.30; 95% CI: 6.92-7.58), similarly to isolated GHTD (aRR: 7.40; 95% CI: 7.23-7.58).

CONCLUSIONS—The co-occurrence of GDM and GHTD was associated with a significantly high risk of incident HF.

Keywords

gestational diabetes mellitus; gestational hypertensive disorders

Cardiovascular disease (CVD) is common,[1] and increasingly frequent among young individuals, including women of childbearing age.[2] Accumulating evidence suggest that gestational diabetes mellitus (GDM)[3,4] and gestational hypertensive disorders (GHTD)[5-9] are each associated with an increased risk of developing heart failure (HF) in the years after pregnancy. However, there is a dearth of data on the concomitant and joint influences of GDM and GHTD on the incidence of HF. Prior studies that have examined the joint influence of GDM and GHTD on CVD outcomes,[10] have not included the HF outcome as an independent outcome, as opposed to a combined outcome. Given that HF may occur in the absence of coronary heart disease (CHD),[11] there are potentially specific implications for preventive and clinical care resulting from the links between GDM and/or GHTD and HF among young women in the postpartum period. It therefore appears logical to examine the individuals and joint influence of GHTD and GDM on the occurrence of HF. Indeed, common pathways between GDM and GHTD, including, eg, insulin resistance,[12,13] and pregnancy-induced microvascular (endothelial) dysfunction,[14,15] can contribute the potentiation of HF risk in the setting of joint occurrence of GHTD and GDM.

Using data from the health care administrative databases from the Ontario Ministry of Health in Canada, we examined the individual and conjoint associations of GDM and GHTD (gestational hypertension or pre-eclampsia/eclampsia) with the risk of HF. We hypothesized that the combined presence of GDM and GHTD (gestational hypertension or preeclampsia/eclampsia) would be associated with a greater HF risk as compared to each of these individual conditions.

METHODS

STUDY POPULATION.

The sampling frame for the selection of participants consisted of all women in Ontario, the most populated Canadian province, where there is universal coverage for hospital and physician services. Consequently, these women have their health data captured in administrative databases from the Ministry of Health, which include the Canadian Institute for Health Information Discharge Abstract Database from all hospitalizations in Ontario, the Ontario Health Insurance Plan database of 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 non-GD that is derived using these data as well as prescription records in the Ontario Drug Benefit database.[16] The Ontario Hypertension Database is a validated registry of physician-diagnosed nongestational hypertension that is derived using these data.[17] The MOMBABY database is derived from hospitalization data and links hospitalization records of delivering mothers with their newborn babies. The datasets were linked using unique encoded identifiers and analyzed at Institute of Clinical Evaluative Sciences (ICES).

In the present study, we included women with a livebirth singleton delivery, from July 1, 2007 to March 31, 2018. The exclusion criteria used in our study are shown in the Supplemental Figure 1. In particular, we excluded women with a pre-pregnancy history of diabetes, hypertension, or HF or CHD. Additionally, among women with multiple deliveries during this time period (July 1, 2007-March 31, 2018), only the first one was included.

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

IDENTIFICATION OF GHTD AND GESTATIONAL DIABETES.

We ascertained GDM using a validated algorithm relying on the delivery hospitalization record (including the International Classification of Diseases-10th Revision-Canada [ICD-10-CA] codes of E1 and O24 at index pregnancy), and physician billings within 90 days prior to delivery.[18] We identified GHTD using the ICD-10-CA codes O13, O14, and O15 in the hospital delivery record and any hospitalization within 24 weeks prior to delivery. The ICD-10-CA codes used for identifying the various forms of GHTD have been used before including in administrative databases from the Ontario province of Canada.[19,20] The women were categorized according to their GDM or GHTD and GDM statuses as having neither of the conditions, either, or both.

ASCERTAINMENT OF OUTCOMES–PERIPARTUM CARDIOMYOPATHY AND INCIDENT HF.

The primary outcome was incident hospitalization for HF identified through linkage with hospital admission records, using the ICD-10-CA code I50. In order to ascertain the HF outcome, the women were followed from 6 months after the index gestation until HF hospitalization, death, migration, or March 31, 2020. The secondary outcome that we examined was peripartum cardiomyopathy at index pregnancy, which was identified through linkage with hospital admission records from the 32nd week of the index gestation to 6 months after delivery.[21] The ICD-10-CA codes for peripartum cardiomyopathy were I50, J81, and O90.3. Women with peripartum cardiomyopathy were excluded from the analysis of the primary outcome.

COVARIATES.

The covariates considered in the current investigation included age at index delivery, socioeconomic status (assessed as the neighborhood household income quintile, which is an ecological level variable), rurality of residence (evaluated using the Rurality Index of Ontario),[22] parity, chronic kidney disease (ascertained using a previously validated

algorithm[23]), GDM at prior pregnancy, GHTD at prior pregnancy, postpregnancy type 2 diabetes, and postpregnancy hypertension, and postpregnancy coronary artery disease.

STATISTICAL ANALYSES.

We grouped the study participants into the following 4 categories: no-GDM and no-GHTD, isolated GHTD, isolated GDM, GDM and GHTD. The baseline characteristics of these groups at were compared using chi-square test tests for categorical variables and *t*-tests for continuous variables.

Using Cox proportional hazards regression models, we estimated the relative risk of incident HF hospitalization by exposure categories (with the no-GDM and no-GHTD group as the reference). We also conducted a direct comparison of isolated GHTD state and the isolated GDM state (as the reference group). The estimates of association between the exposure and incident HF were adjusted for age at index delivery, socioeconomic status, rurality of residence, parity, preterm delivery, chronic kidney disease, pre-existing CVD other than HF and coronary artery disease, GDM in a previous pregnancy, GHTD in a previous pregnancy. Additional adjustment variables included the postpartum development of each of the following conditions: diabetes, hypertension, and coronary artery disease, which were all included in the models as time-varying covariates. We tested for the proportional hazard assumption using log-log plots and Schoenfeld residuals.

We used a modified Poisson regression (corrected for under-dispersion) to examine the association between the GDM/GHTD exposure categories (with the no-GDM and no-GHTD group as the reference) and peripartum cardiomyopathy (occurring at the index pregnancy), adjusting for age, socioeconomic status, rurality of residence, parity, preterm delivery, chronic kidney disease, prior GDM and prior GHTD.

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

RESULTS

The study population included 885,873 women (mean age 29.8 ± 5.57 years), of whom 54,015 (6.0%) had isolated GDM, 43,750 (5.3%) had isolated GHTD, 4,960 (0.6%) had a combination of GDM and GHTD. The baseline characteristics of the study population by GDM and/or GHTD status are displayed in Table 1. Women with GDM and GHTD were older, more likely to have a history of premature delivery, chronic kidney disease, prior GHTD, prior GDM, or pre-existing CVD other than HF or CHD (Table 1). The baseline characteristics of the study sample in those who did vs did not develop incident HF are shown in Supplemental Table 1.

INCIDENCE OF HEART FAILURE.

Over a median follow-up period of 8 years (IQR: 5-11 years, total follow-up 7.02 million person-years), 489 women experienced a HF hospitalization event. The highest incidence rate of HF was observed among women with both GDM and GHTD, followed in descending order by those with isolated GHTD, women with isolated GDM, and women with neither

GHTD nor GDM (Table 2). The crude HF incidence rate among women with GDM and GHTD was ~3-fold higher than that of women without GHTD and GDM (Table 2), whereas those with isolated GHTD had ~2-fold higher incidence of HF.

The median age at the time of the diagnosis of HF was 34 years (IQR: 30-39 years), 33 years (IQR: 29-38 years), 39 years (IQR: 32-44 years), 35 years (IQR: 33-40 years) for the no GDM and no GHTD, isolated GHTD, isolated GDM, and both the GDM and GHTD groups, respectively (*P* for between groups difference = 0.005). The corresponding values for the time to HF diagnosis for these groups were 6 years (IQR: 3-8 years), 6 (IQR: 3-8 years), 5 years (IQR: 2-8), and 6 years (IQR: 3-9 years), respectively (*P* for between groups difference = 0.718).

Women who experienced a combination of GDM and GHTD had a higher relative risk of incident HF, as compared to women without any of these 2 conditions (Table 2, Central Illustration). After initial adjustment for potential confounders (Table 2, Model 1), those with both GDM and GHTD had a higher relative risk of HF (adjusted hazard ratio [aHR]: 2.64; 95% CI: 1.24-5.61; $P = 0.012$) compared to those without GDM nor GHTD. The corresponding HRs for the isolated GHTD and isolated GDM groups were 1.65 (95% CI: 1.17-2.31; $P = 0.004$) and 1.44 (95% CI: 1.02-2.04; $P = 0.039$), respectively. Additional adjustment for postpartum hypertension, postpartum diabetes, and postpartum coronary artery disease (Table 2, Model 2) attenuated the extent of the HF risk associated with GHTD and GDM (aHR: 1.46; 95% CI: 0.67-3.17). This corresponding risk was lower for women with isolated GHTD (aHR: 1.32; 95% CI: 0.93-1.86) compared to those with neither GDM nor GHTD, and lower still for women with isolated GDM (aHR: 1.15; 95% CI: 0.80-1.66).

In a direct comparison between isolated GHTD and isolated GDM, there was no significant difference between the 2 conditions for the incidence of HF, in models before (aHR: 1.17; 95% CI: 0.71-1.93) and after adjustment for postpartum hypertension, postpartum diabetes, and postpartum coronary artery disease (aHR: 1.12; 95% CI: 0.67-1.90).

PERIPARTUM CARDIOMYOPATHY.

A total of 408 women had peripartum cardiomyopathy during the index pregnancy. Compared to no-GDM and no-GHTD (Table 3, Model 2), the co-occurrence of GDM and GHTD was also associated with a higher risk of peripartum cardiomyopathy (adjusted risk ratio [aRR]: 7.30; 95% CI: 6.92-7.69), similar to the risk of peripartum cardiomyopathy associated with isolated GHTD (aRR: 7.40; 95% CI: 7.23-7.58). Isolated GDM was associated with a higher risk of peripartum cardiomyopathy (aRR: 2.07; 95% CI: 2.01-2.14). In a direct comparison, isolated GHTD was associated with significantly higher odds of peripartum cardiomyopathy as compared to isolated GDM (aRR: 3.38; 95% CI: 3.16-3.61).

DISCUSSION

In a large population-based cohort study, we observed significant individual associations of GDM and GHTD with an increased risk of HF hospitalization. More importantly, while the women who had a combination of GDM and GHTD during the same pregnancy had a higher rate of HF events as compared to those without any of these conditions, the relative

risk of HF events in the GDM and GHTD group was higher than that conferred by isolated GDM or isolated GHTD. Our results suggest that these associations are in part mediated by intermediate postpartum factors such as diabetes, hypertension, and coronary artery disease. The extent to which the concomitance of GDM and GHTD is associated with an increased risk of peripartum cardiomyopathy at index pregnancy was comparable to that of isolated GHTD.

Our observations suggest that the concomitance of GDM and GHTD is a potent marker of peripartum CM or the future HF risk, and that there is a high degree of imbrication of the pathways linking both GDM and GHTD to cardiac dysfunction. Our results also suggest that in the case of peripartum cardiomyopathy, there is possibly a dominance of processes related to GHTD in the pathogenesis of the condition. The latter results are consistent with the prevailing knowledge on the pathogenesis of peripartum cardiomyopathy.[24]

To our knowledge, our study is one of the first investigations to assess the individual and joint associations of GDM and GHTD with cardiac dysfunction. A prior study examined the joint effects of GDM and GHTD on the composite outcome of CVD and overall mortality, but did not explore HF.[10] Our findings are congruent with prior reports on the individual associations of GHTD[5-7,9] and GDM[3,25] with a higher risk of HF postpartum, as well their respective effect on subclinical adverse cardiac remodeling.[26,27] Our study complements the extant evidence on the links between pregnancy-related disorders (GDM, GHTD) and HF, by providing novel data on the extent to which the simultaneous occurrence of GDM and GHTD affects the future HF risk postpartum, which suggest a compounding effect of the concomitance of the 2 conditions GDM and GHTD. Our study also provides novel data on the combined effects of GDM and GHTD on the risk of peripartum cardiomyopathy, especially as prior studies have examined these conditions separately in relation to peripartum cardiomyopathy.[21,28]

Our findings are particularly relevant in the context of a rise in the trends in overall CVD[2] and pregnancy-related cardiometabolic disorders,[29-31] among young women. A significant proportion of women (>80%) will experience pregnancy during their lifespan.[32] Consequently, a systematic antenatal detection of GHTD and GDM can help foster HF prevention in the postpartum period, as advocated in the guidelines of various professional associations.[33-35] Indeed, HF risk prediction among young women would benefit from accounting for the history of both GDM and GHTD. Furthermore, women with a history of GDM and GHTD may particularly benefit from early intensive lifestyle modifications for HF and overall CVD preventative.

The pathways linking GDM and/or GHTD to HF risk remain to be fully elucidated. Postpartum diabetes among women with GDM[36] and hypertension among those with GHTD[37] may contribute to HF incidence, as evidenced by the attenuation of the effect sizes in our study after adjustment for these conditions. Common pathways between GDM and GHTD that could contribute to HF include insulin resistance,[12,13] and pregnancy-induced microvascular (endothelial) dysfunction that can persist postpartum.[14,15] There are also GHTD-specific potential mechanisms that can significantly affect cardiac remodeling, thus explaining the predominance of GHTD when it cooccurs with GDM. These include a

renin-angiotensin-aldosterone system dysregulation, which is particularly relevant to pre-eclampsia,[38,39] and whereby there is suppression of circulating renin, aldosterone, and angiotensin II levels.[38,40] Such a dysregulation may persist postpartum with augmented vasoconstrictor sensitivity to angiotensin II,[41] possibly contributing to the occurrence of hypertension and adverse left ventricular remodeling. Alterations in antiangiogenic proteins such as soluble fms-like tyrosine kinase-1 and soluble endoglin may also drive left ventricular remodeling among women with GHTD.[42]

There are limitations to our study. First, the HF diagnosis was based on hospitalization records; thus, HF cases seen in the outpatient setting (ie, potentially less severe forms of HF) were not captured. Because of the low rate of events, we lacked power to examine the individuals' subtypes of GHTD (preeclampsia/eclampsia and gestational hypertension) or to explore outcomes by differential parity, especially given that pre-eclampsia is more common during the first pregnancy. Another possible reason for underestimating the effect of GHTD and/or GDM is their relative low frequencies in our sample compared to estimates at the population levels. For example, in the United States, frequency estimates in 2019 to 2020 were 16% for GHTD and 7% for GDM.[43,44] We also did not have data on cardiac imaging to define the subtypes of HF (HF with preserved ejection fraction and HF with reduced ejection fraction), and also to better define peri- partum cardiomyopathy, as this may share signs and symptoms with those of normal pregnancy.[45] It is important to assess HF subtypes, given the emerging evidence on the association of GHTD with HF with preserved ejection fraction.[9] Second, cardiovascular risk factors such as smoking, lipid levels, body mass index, were not captured in the administrative databases used. However, prior reports on body have shown that women with GHTD or GDM have an adverse cardiovascular risk factor profile irrespective of body mass index before[46-50] and after pregnancy.[51-55] Third, we did not rely on glucose tolerance testing data for GDM identification, but used International Classification of Diseases-codes from administrative data, which has been shown to be reliable,[56] as is also the case for the International Classification of Diseases-codes based GHTD definition.[57] Fourth, we lacked data on postpartum use of cardioprotective medications (eg, statins, blood pressure lowering therapies, and antidiabetic medication therapies) that could modulate the HF risk, but which we anticipate would be infrequently used in women of childbearing age. Lastly, one cannot exclude residual confounding.

The strengths of our study include leveraging a large population-based cohort of women constituted using multiple linked administrative databases and postpartum follow-up, in a health care system with universal health coverage, and thus allowing a systematic detection of both GHTD and GDM during pregnancy. We explored multiple cardiac dysfunction outcomes including incident HF and peripartum cardiomyopathy, a pregnancy-specific outcome. We conducted adjustments for known cardiovascular risk factors, and assessed the mediating effects of postpregnancy determinants of outcomes such as diabetes, hypertension, and coronary artery disease, as well as pregnancy-specific factors such as prior history of GDM and GHTD.

CONCLUSIONS

In a large population-based cohort of young women, we showed that GHTD and GDM were individually associated with increased risk of HF in the postpartum period. The co-occurrence of GDM and GHTD was associated with a higher longer term of HF risk as compared to the isolated forms of these conditions, but GHTD may be a more potent driver of peripartum cardiomyopathy as compared to GDM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

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ABBREVIATIONS AND ACRONYMS

aHR	adjusted hazard ratio
CHD	coronary heart disease
CVD	cardiovascular disease
GDM	gestational diabetes mellitus
GHTD	gestational hypertensive disorder
HF	heart failure
ICD-10-CA	International Classification of Diseases-10th Revision-Canada
IQR	interquartile range

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

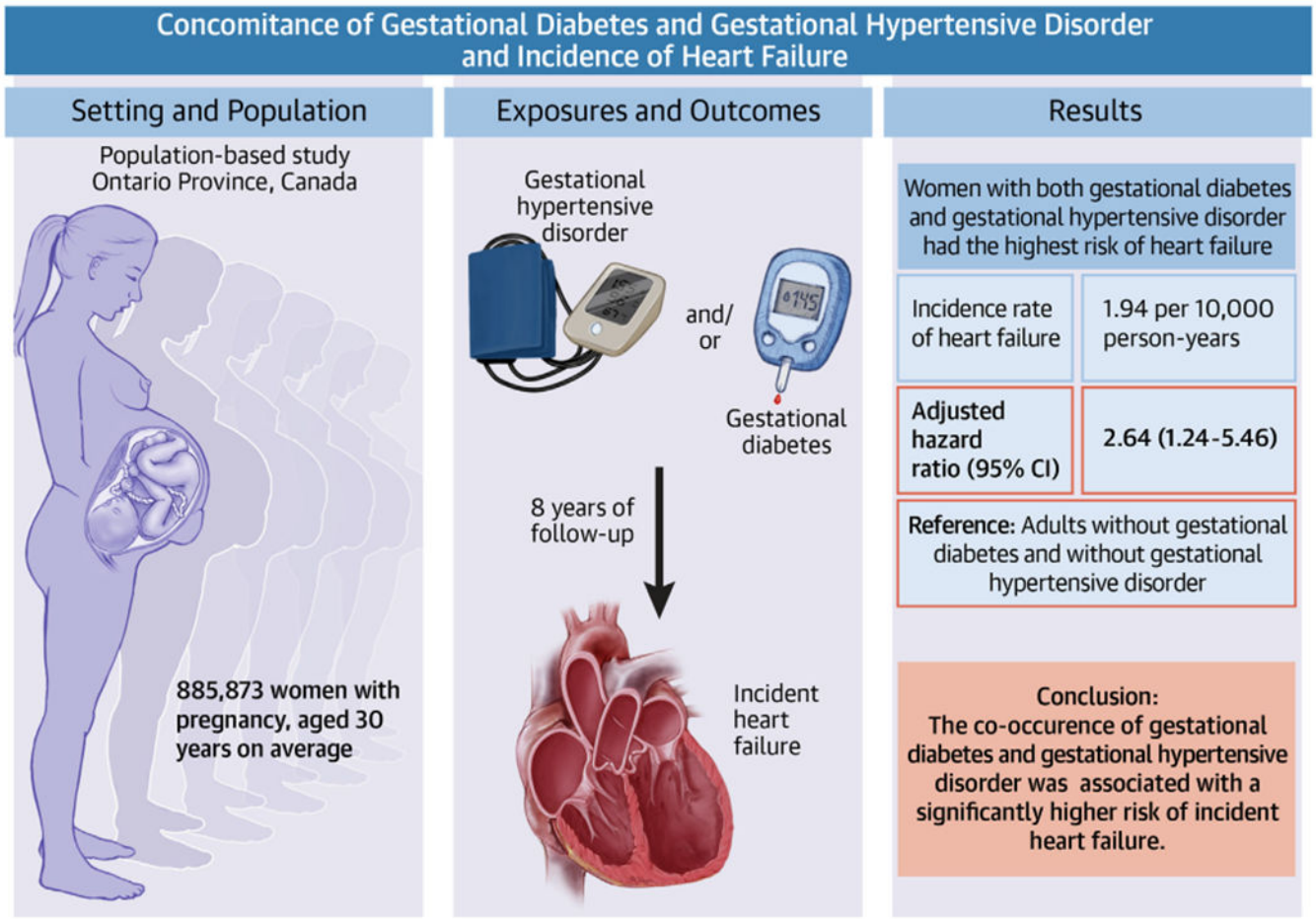
The extent to which the co-occurrence of concomitant GHTD and GDM influence the risk of HF is unclear.

COMPETENCY IN PATIENT CARE:

The co-occurrence of GHTD and GDM is strongly associated with high risks of peripartum-cardiomyopathy and incident HF, suggesting that active HF prevention may be needed in this population.

TRANSLATIONAL OUTLOOK:

The results of our study can help refine the assessment of the risk of HF among young women in the aftermath of pregnancy and thus better implement primary and secondary Cardiovascular preventive care among individuals care among individuals at risk, possibly through lifestyle changes and possibly aggressive use of cardioprotective therapies.



CENTRAL ILLUSTRATION.

Relation of gestational Hypertensive Disorder and/or gestational Diabetes With Heart Failure

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TABLE 1

Baseline Characteristics of Study Participants by GHTD and/or Gestational Diabetes Status

	No GDM and no GHTD (n = 783,148)	Isolated GDM (n = 54,015)	Isolated GHTD (n = 43,750)	GDM and GHTD (n = 4,960)	*P* Value
Age	29.60 ± 5.54	32.20 ± 5.23	29.60 ± 5.72	31.91 ± 5.75	<0.001
Income quintile					
1 (lowest)	177,758 (22.7)	14,750 (27.3)	9,522 (21.8)	1,338 (27.0)	<0.001
2	159,516 (20.4)	11,814 (21.9)	9,220 (21.1)	1,058 (21.3)	
3	159,369 (20.3)	11,044 (20.4)	9,181 (21.0)	1,038 (20.9)	
4	159,579 (20.4)	9,719 (18.0)	8,955 (20.5)	920 (18.5)	
5 (highest)	123,972 (15.8)	6,494 (12.0)	6,654 (15.2)	572 (11.5)	
Missing	2,954 (0.4)	194 (0.4)	218 (0.5)	34 (0.7)	
Rurality					
Urban	595,988 (76.1)	46,115 (85.4)	30,820 (70.4)	3,815 (76.9)	<0.001
Semiurban	130,910 (16.7)	5,671 (10.5)	9,165 (20.9)	754 (15.2)	
Rural	56,250 (7.2)	2,229 (4.1)	3,765 (8.6)	391 (7.9)	
Number of previous births					
0	514,159 (65.7)	32,083 (59.4)	35,281 (80.6)	3,567 (71.9)	<0.001
1	173,586 (22.2)	13,327 (24.7)	5,422 (12.4)	797 (16.1)	
2+	95,403 (12.2)	8,605 (15.9)	3,047 (7.0)	596 (12.0)	
Preterm delivery (≤36 wk gestation)	42,721 (5.5)	4,444 (8.2)	6,579 (15.0)	1,028 (20.7)	<0.001
Chronic kidney disease	1,840 (0.2)	158 (0.3)	243 (0.6)	52 (1.0)	<0.001
Gestational diabetes in a prior pregnancy	5,312 (0.7)	3,374 (6.2)	257 (0.6)	242 (4.9)	<0.001
Hypertensive disorder in prior pregnancy	7,303 (0.9)	774 (1.4)	1,981 (4.5)	258 (5.2)	<0.001
Pre-existing cardiovascular disease (other than heart failure or coronary artery disease)	6,631 (0.8)	463 (0.9)	544 (1.2)	69 (1.4)	<0.001

Values are mean ± SD or n (%). Women who had peripartum-cardiomyopathy (n = 422) were excluded.

GDM = gestational diabetes mellitus; GHTD = gestational hypertensive disorder.

table 2

Event Rates and HR (95% CI) for the Association of GHTD and Gestational Diabetes With Incident HF

	Crude Incidence Rate per 10,000 Person-Years (95% CI)	HR (95% CI)		
		Unadjusted	Adjusted Model 1	Adjusted Model 2
No GHTD and no-GDM	0.65 (0.59-0.72)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Isolated GDM	0.92 (0.67-1.27)	1.45 (1.04-2.03)	1.44 (1.02-2.04)	1.15 (0.80-1.66)
Isolated GHTD	1.17 (0.85-1.60)	1.84 (1.32-2.55)	1.65 (1.17-2.31)	1.32 (0.93-1.85)
GHTD and GDM	1.94 (0.92-4.07)	3.09 (1.47-6.53)	2.64 (1.24-5.61)	1.46 (0.67-3.17)

Model 1: adjusted for age, neighborhood income quintile, rurality, parity, chronic kidney disease, prior gestational diabetes, prior hypertensive disorder of pregnancy, and pre-existing cardiovascular disease other than heart failure or coronary artery disease. Model 2: Model 1 plus post-partum diabetes, and post-partum hypertension, and post-partum coronary artery disease.

GDM = gestational diabetes mellitus; GHTD = gestational hypertensive disorder; HF = heart failure.

table 3

Relative Risk (95% CI) for the Association of GHTD and Gestational Diabetes With Prevalent Peripartum Cardiomyopathy

		Relative Risk[a] (95% CI)	
	Cases/No. at Risk	Unadjusted	Adjusted[a]
No GHTD and no-GDM	242/776,759	1.00 (Reference)	1.00 (Reference)
Isolated GDM	43/53,595	2.58 (2.49-2.66)	2.07 (2.01-2.14)
Isolated GHTD	108/43,314	8.02 (7.84-8.21)	7.40 (7.23-7.58)
GHTD and GDM	15/4,906	9.85 (9.35-10.38)	7.30 (6.92-7.69)

[a]Adjusted for age, neighborhood income quintile, rurality, parity, preterm delivery (gestational age ≤36 weeks), gestational diabetes at prior pregnancy, gestational hypertensive disorder at prior pregnancy, chronic kidney disease, and pre-existing cardiovascular disease other than heart failure or coronary artery disease.

GDM = gestational diabetes mellitus; GHTD = gestational hypertensive disorder.