Diabetes Care
American Diabetes Association

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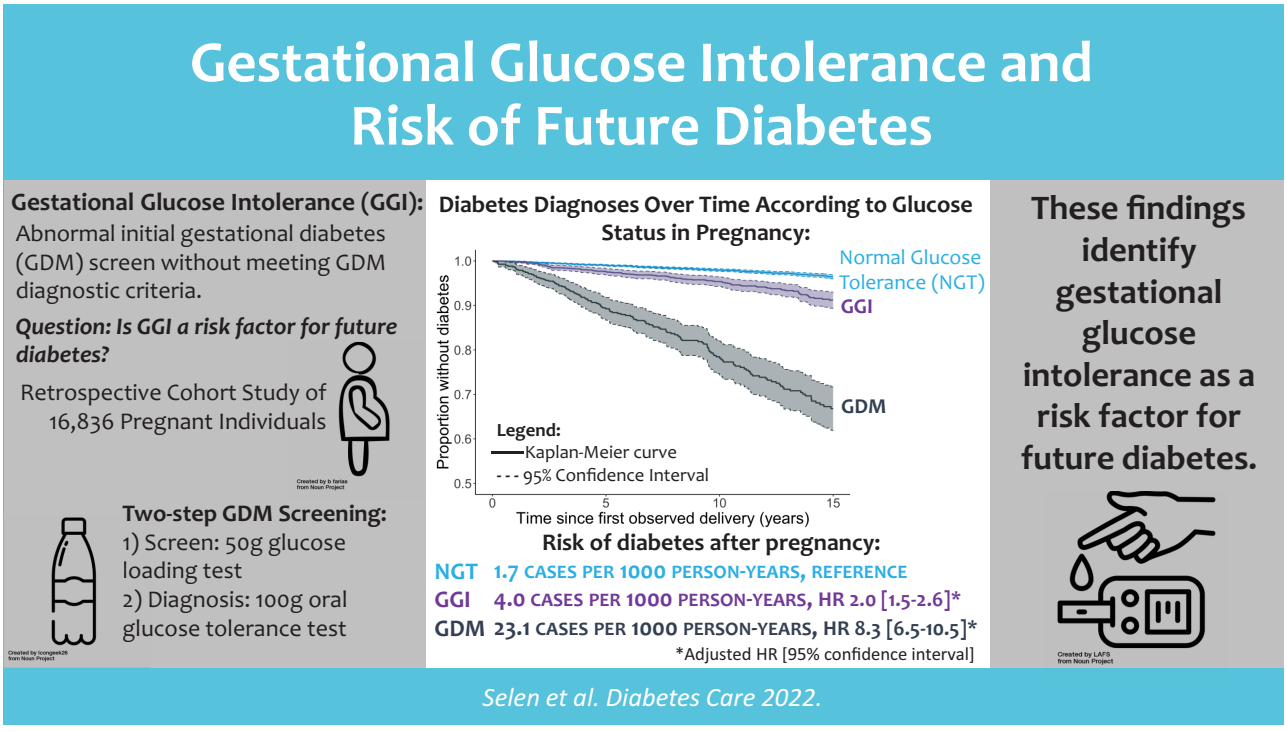
Diabetes Care 2023;46(1):83–91 | https://doi.org/10.2337/dc22-1390



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OBJECTIVE

Pregnant individuals are universally screened for gestational diabetes mellitus (GDM). Gestational glucose intolerance (GGI) (an abnormal initial GDM screening test without a GDM diagnosis) is not a recognized diabetes risk factor. We tested for an association between GGI and diabetes after pregnancy.

RESEARCH DESIGN AND METHODS

We conducted a retrospective cohort study of individuals followed for prenatal and primary care. We defined GGI as an abnormal screening glucose-loading test result at ≥24 weeks' gestation with an oral glucose tolerance test (OGTT) that did not meet GDM criteria. The primary outcome was incident diabetes. We used Cox proportional hazards models with time-varying exposures and covariates to compare incident diabetes risk in individuals with GGI and normal glucose tolerance.

RESULTS

Among 16,836 individuals, there were 20,359 pregnancies with normal glucose tolerance, 2,943 with GGI, and 909 with GDM. Over a median of 8.4 years of follow-up, 428 individuals developed diabetes. Individuals with GGI had increased diabetes risk compared to those with normal glucose tolerance in pregnancy (adjusted hazard ratio [aHR] 2.01 [95% CI 1.54–2.62], $P < 0.001$). Diabetes risk increased with the number of abnormal OGTT values (zero, aHR 1.54 [1.09–2.16], $P = 0.01$; one, aHR 2.97 [2.07–4.27], $P < 0.001$; GDM, aHR 8.26 [6.49–10.51], $P < 0.001$ for each compared with normal glucose tolerance). The fraction of cases of diabetes 10 years after delivery attributable to GGI and GDM was 8.5% and 28.1%, respectively.

CONCLUSIONS

GGI confers an increased risk of future diabetes. Routinely available clinical data identify an unrecognized group who may benefit from enhanced diabetes screening and prevention.

The diabetes epidemic affects 13% of nonpregnant adults in the U.S. and 4.5% of women of childbearing age (1,2). Guidelines recommend screening for diabetes in nonpregnant adults <35 years of age only if risk factors are present (3,4). In contrast, during pregnancy, universal screening for GDM has been widely implemented (4–6), with the goal of treating affected pregnant individuals to optimize perinatal outcomes (7–9). GDM is a strong risk factor for diabetes, with the lifetime prevalence of diabetes among affected individuals as high as 50% (10–13). Thus, universal screening during pregnancy provides the opportunity to systematically identify young adults at risk for diabetes.

Due to the recommendation for universal GDM screening, blood glucose levels are available from the vast majority of pregnancies cared for in the U.S. (14,15).

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Received 15 July 2022 and accepted 10 October 2022

This article contains supplementary material online at https://doi.org/10.2337/figshare.21308007.

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

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A two-step screening method is most commonly used (4,5). Between 24 and 28 weeks' gestation, an initial 1-h nonfasting 50-g glucose-loading test (GLT) is performed. If this screening test is abnormal, a 3-h 100-g diagnostic oral glucose tolerance test (OGTT) is conducted (4–6). Thus, it is possible to have an abnormal screening GLT with a diagnostic OGTT that does not meet criteria for GDM. Pregnancies in this intermediate category have been described as having gestational glucose intolerance (GGI) (16). While GGI has been shown to be associated with adverse pregnancy outcomes (16–20), there is limited information on GGI and future risk of maternal diabetes (18,22–24). Therefore, GGI has not been recognized as a diabetes risk factor and no enhanced screening or intervention to prevent diabetes is currently recommended for individuals with a GGI history.

We conducted a retrospective cohort study to test the hypothesis that individuals with GGI carry an increased risk of incident diabetes compared with those with normal glucose tolerance during pregnancy.

RESEARCH DESIGN AND METHODS

Study Population

Participants were from the Massachusetts General Hospital (MGH) Maternal Health Cohort (MHC), which contains data from >90% of pregnancies with babies delivered at MGH between September 1998 and March 2016. The MHC was linked to the MGH Primary Care Practice-Based Research Network (PBRN), a longitudinal cohort of all primary care patients at MGH beginning in 2000 (25,26). Data sources for these cohorts include the MGH electronic medical record and the Mass General Brigham Research Patient Data Registry, which holds clinical data from the Mass General Brigham health system. The Mass General Brigham Institutional Review Board approved this study and waived the informed consent requirement.

We included individuals with singleton pregnancies in the MHC who, after their first recorded delivery, had clinical encounters with an MGH adult primary care physician recorded in the PBRN (Fig. 1*A*). Pregnancies ending in miscarriage or termination were excluded from the analysis, as they did not have a recorded delivery date.

Among the aforementioned individuals, we performed additional pregnancy-level exclusions by censoring at the time of the delivery date for the first excluded pregnancy. We excluded pregnancies without delivery at MGH and pregnancies that occurred after the last nonobstetric clinical encounter. Additionally, we excluded pregnancies that occurred after diabetes diagnosis identified in the PBRN and pregnancies with incomplete GDM screening (where completeness was defined as glucose testing at ≥24 weeks' gestation: completion of 1-h 50-g GLT and, if indicated [1-h GLT glucose level ≥140 mg/dL], completion of the 3-h 100-g OGTT) (4,5). Reasons for incomplete screening data (obtained on chart review of a random sample) included preexisting diabetes, clinical data entry errors, patient preference, and nausea or bariatric surgery resulting in inability to complete GLT/OGTT testing. We also excluded pregnancies without the necessary data to calculate first-trimester BMI (see Supplementary Material) and multiple gestation (27,28).

Exposure, Outcome, and Covariate Assessment

Universal GDM screening was practiced during the study period. Maternal glucose was measured in hospital-affiliated clinical laboratories. Glucose data were entered prospectively by clinicians into the obstetric electronic medical record and downloaded into the research database. The Mass General Brigham Research Patient Data Registry was used to fill in missing values. Approximately 1% of charts (N = 547) were reviewed for verification or correction of outliers and for understanding of missing data.

Participants with GLT glucose level <140 mg/dL and no OGTT were categorized as having normal glucose tolerance. A GLT glucose level ≥140 mg/dL was considered an abnormal GDM screen, and patients underwent a 3-h OGTT for determination of whether GDM was present. Carpenter-Coustan thresholds were applied to the OGTT (abnormal values met or exceeded thresholds): fasting 95 mg/dL, 1 h 180 mg/dL, 2 h 155 mg/dL, and 3 h 140 mg/dL (4,29). GDM was defined as two to four abnormal OGTT values according to these criteria (4,29). GGI (16) was defined as zero or one abnormal value on the OGTT according to the same thresholds.

The primary outcome was diabetes diagnosis, defined in the PBRN as *1*) hemoglobin A_{1c} (HbA_{1c}) >6.5%, *2*) two clinical encounters with two diabetes problem list terms (doctor or hospital visits where diabetes was specified in the electronic medical record for documentation), or *3*) one ICD-9 or -10 diagnosis (codes used for billing) plus one problem list term for diabetes (30). This diabetes definition was previously validated (sensitivity 99%, specificity 93%) (30). Prediabetes was not included in the diabetes outcome. After an electronic medical record change in 2016, the diabetes definition was updated. In this updated definition, diabetes was defined as *1*) HbA_{1c} ≥6.5%, *2*) two clinical encounters with two diabetes problem list terms, or *3*) one ICD-9 or -10 billing diagnosis plus one problem list term for diabetes. Additionally, participants who met other criteria after 2016 but had normal (<6.5%) recorded HbA_{1c} without being on a diabetes medication were not considered to have diabetes. The updated definition was internally validated with blinded chart review for 100 randomly selected participants with apparent diabetes and 100 randomly selected participants without apparent diabetes and was found to have a sensitivity of 100% and specificity of 98%.

Age was calculated at the time of delivery of the first recorded pregnancy. Marital status was dichotomized between those who were partnered or married and those who were single or had another status. Race and ethnicity were based on that recorded in the electronic medical record and divided into five categories: Asian, Black, Hispanic or Latina, White, and none of the above. It was possible for an individual to belong to more than one race and ethnicity category if more than one was recorded. Parity was dichotomized as nulliparous or multiparous. Prenatal BMI and diastolic blood pressure were standardized to 12-week values with an interpolation/extrapolation procedure using restricted cubic splines (see Supplementary Material). After the interpolation/extrapolation procedure, there were 76 pregnancies excluded due to missing data for BMI. Gestational weight gain was also calculated with interpolated/extrapolated values (see Supplementary Material). Parity, prenatal measures, and gestational weight gain were all permitted to vary with each subsequent pregnancy. For individuals

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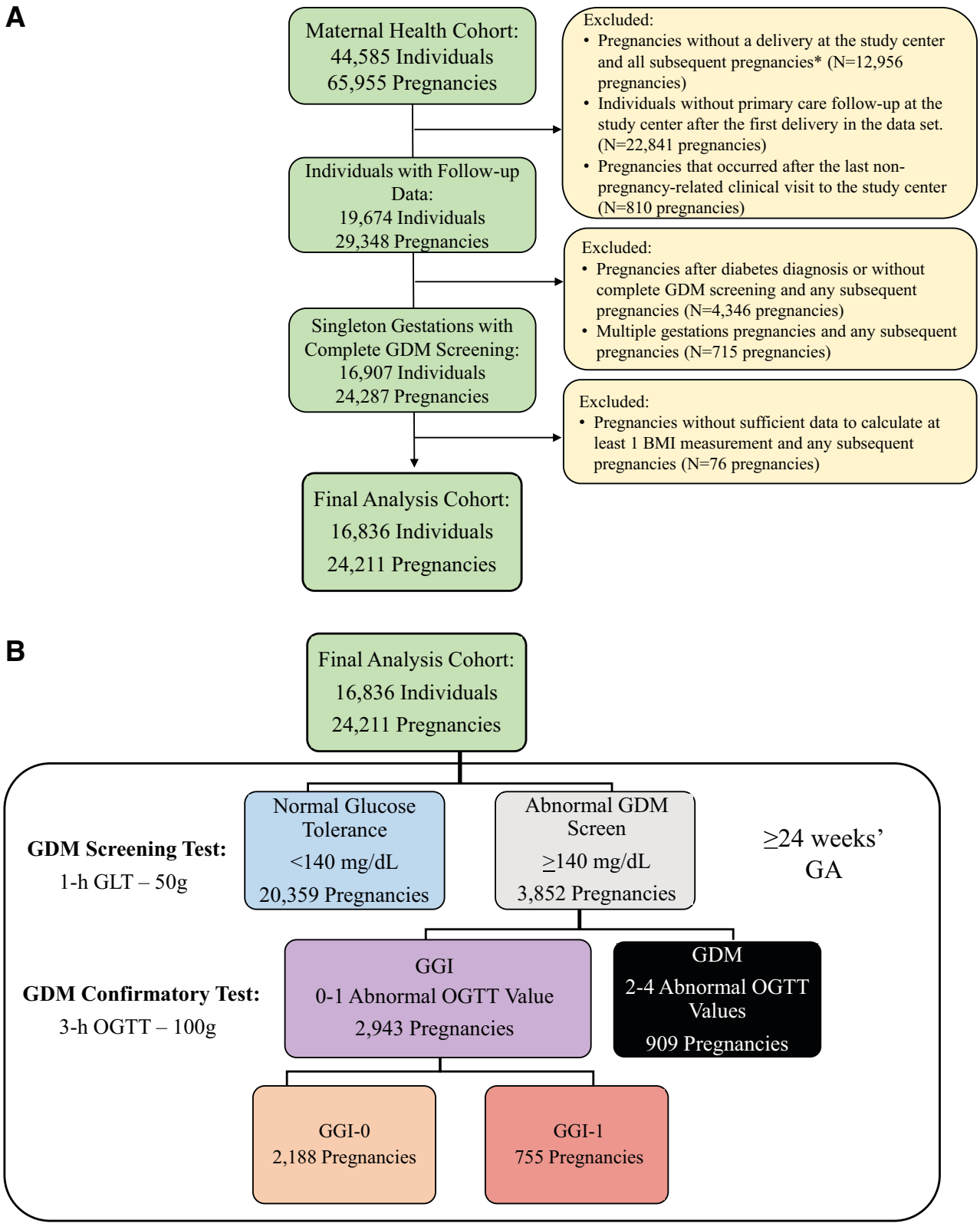

Figure 1—Final analysis cohort and exposure groups based on glucose tolerance status in pregnancy. *A*: Flowchart describing exclusion criteria used to determine final analysis cohort from the Maternal Health Cohort. *B*: Total numbers included in our final analysis cohort are shown for individuals and pregnancies. Total numbers of pregnancies in each glucose tolerance exposure group used for analyses are shown. GDM screening was done according to the two-step screening test at ≥24 weeks' gestation with a 1-h GLT of 50 g glucose with a glucose cutoff of 140 mg/dL used at MGH. If the GLT glucose result was ≥140 mg/dL, a confirmatory 3-hour OGTT of 100 g glucose was performed. GGI (zero [GGI-0] or one [GGI-1] abnormal OGTT value) and GDM (two to four abnormal OGTT values) were diagnosed according to Carpenter-Coustan criteria. GA, gestational age in weeks. *Where delivery for the first pregnancy in the data set did not occur at the study center, but at least one subsequent delivery did occur at the study center, individuals were still included. For these individuals (*N* = 1,847), follow-up began at the first delivery at the study center and subsequent consecutive pregnancies with deliveries at the study center were included.

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with missing parity, nulliparity was assumed prior to the first recorded pregnancy.

Statistical Analyses

We compared participant and pregnancy characteristics between pregnancy glucose tolerance categories (normal glucose tolerance, GGI, GDM) including the first recorded pregnancy for each individual in the final analysis cohort. We also examined the proportion of individuals with GGI pregnancy who would not have met U.S. Preventative Services Task Force (USPSTF) criteria for diabetes screening (age $<$35 years or BMI $<$25 kg/m^2) (3).

Time-to-event analyses were conducted to assess the association between each pregnancy glucose category and time to diabetes diagnosis. Individuals in the study were followed starting at the time of the first recorded delivery in MHC. Follow-up ended at the time of diabetes diagnosis (primary outcome), the last nonobstetric clinical encounter, or 31 December 2020—whichever came first. Individuals were also censored at the delivery date for excluded pregnancies. Kaplan-Meier curves were constructed accounting for pregnancy glucose category as a time-varying exposure that potentially changed with each delivery date (31,32). Time-varying Cox regression models were also fitted (33), with adjustment for age at first delivery, marital status, insurance status, race and ethnicity (four indicator variables for each category, permitting individuals to belong to zero, one, or more categories), parity, prenatal BMI, and prenatal diastolic blood pressure. These covariates were chosen because they were considered to be potential confounders due to an expected relationship with both the GGI exposure and diabetes outcome. A second set of models was also fit with additional adjustment for gestational weight gain. Schoenfeld residuals were generated to evaluate the assumption of proportional hazards in the Cox regression model (34).

The primary comparison was the adjusted rate of incident diabetes in individuals with GGI versus that in the normal glucose tolerance referent group. Power calculations are provided in Supplementary Material. We also examined the adjusted rate of incident diabetes in individuals with GDM compared with that in those with normal glucose tolerance. Secondary comparisons included the rate of incident diabetes in individuals with one abnormal OGTT value (GGI-1) and zero abnormal OGTT values (GGI-0), each compared with that in those with normal glucose tolerance.

Population-attributable fraction of diabetes after 10 years of follow-up was estimated for each of the exposure categories (see Supplementary Material).

To address potential ascertainment bias, we repeated the analysis, restricted to only those who were screened for diabetes, defined as those with an HbA_{1c} measurement occurring at least 3 months after first delivery in the cohort. In this analysis, individuals without diabetes diagnoses were censored at the time of the last HbA_{1c} measurement if this was before the censoring date in the main analysis.

Due to the dates of data availability, some individuals continued to contribute follow-up time in the PBRN (data available through December 2020) despite no longer being followed in the MHC (data available through March 2016). We conducted a sensitivity analysis to exclude individuals age $<$45 years at the end of 2016, who could have become pregnant again after the MHC ended.

Since the diabetes definition changed after the electronic medical record system changed, a sensitivity analysis in which follow-up time ended on 31 December 2015 was performed.

The validated definition of diabetes used in this study includes all types of diabetes (30). We conducted a sensitivity analysis excluding individuals who ever had an ICD-9 or -10 billing code or problem list term indicating type 1 diabetes.

We also performed a subgroup analysis dichotomizing the population based on age at first delivery: individuals with age $<$35 years and individuals age $\geq$35 years.

Statistical analyses were performed in R, version 4.1.1. Time-varying Cox regressions and associated time-to-event analyses were performed with the survival package in R.

RESULTS

Within the overall MHC, 19,674 individuals had long-term follow-up after a delivery date (Fig. 1*A*). After exclusions for diabetes diagnosis, complete GDM screening, multiple gestation pregnancies, and missing BMI data, there were 16,836 individuals left in our final analysis cohort (Fig. 1*A*). Of 24,211 pregnancies in 16,836 individuals in the final analysis cohort (Fig. 1*A*), there were 20,359 pregnancies with normal glucose tolerance (84.1%), 2,943 with GGI (12.2%), and 909 with GDM (3.8%) (Fig. 1*B*).

Participant characteristics from the first pregnancy in the cohort categorized by pregnancy glucose tolerance category are shown in Table 1. Characteristics of participants included in the final analysis cohort were similar to those who were excluded, except that excluded individuals were more likely to have no or limited health insurance (Supplementary Table 1). Individuals with GGI had mean BMI (GGI 25.7 kg/m^2, normal glucose tolerance 25.1 kg/m^2) and gestational weight gain (GGI 29.2 lb, normal glucose tolerance 30.1 lb) similar to those of subjects with normal glucose tolerance, while individuals with GDM had a higher mean BMI (28.1 kg/m^2) and less gestational weight gain (25.3 lb) (Table 1). Eighty-six percent of individuals with GGI in their first pregnancy were age $<$35 years or had BMI $<$25 kg/m^2 and thus would not have met USPSTF criteria for diabetes screening outside of pregnancy. The characteristics of participants by GGI subcategories (GGI-0 and GGI-1) in the first pregnancy are shown in Supplementary Table 2. Of the 16,836 individuals studied, 1,395 (8.3%) had a subsequent pregnancy with a glucose tolerance category different from that in their first pregnancy (Supplementary Table 3).

Over a median of 8.4 years (interquartile range [IQR] 4.0–14.3) of follow-up, 2.5% (N = 428) of individuals were diagnosed with diabetes, resulting in an overall incidence rate of 2.8 per 1,000 person-years. Individuals were diagnosed with diabetes at mean ± SD age 41.1 ± 8.5 years, at a median of 9.7 years (IQR 5.0–14.0) from the first observed delivery. Individuals with GGI had a diabetes incidence of 4.0 cases per 1,000 person-years, while individuals with normal glucose tolerance had a diabetes incidence of 1.7 cases per 1,000 person-years. The diabetes incidence rate in individuals with GDM was 23.1 cases per 1,000 person-years (Table 2). Kaplan-Meier curves, by pregnancy glucose tolerance category, depicting the proportion of the population without diabetes over time since first observed delivery, are shown in Fig. 2.

In adjusted models, individuals with GGI had an adjusted hazard ratio (aHR) of 2.01 (95% CI 1.54–2.62, $P < 0.001$) for incident

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Table 1—Characteristics of participants in the final analysis cohort categorized by glucose tolerance category of the first observed pregnancy

	Normal glucose tolerance	GGI (zero or one abnormal OGTT value)	GDM (two to four abnormal OGTT values)
Individuals	14,089 (83.7)	2,056 (12.2)	691 (4.1)
Participant characteristics			
Age (years), mean (SD)	30 ± 6.1	31 ± 5.7	33 ± 5.7
Nulliparous	10,326 (73.3)	1,451 (70.6)	434 (62.8)
Race and ethnicity			
Asian	1,113 (7.9)	253 (12.3)	76 (11.0)
Black	1,094 (7.8)	128 (6.2)	75 (10.9)
Latina	1,806 (12.8)	252 (12.3)	94 (13.6)
White	8,661 (61.5)	1,194 (58.1)	358 (51.8)
None of the above	1,715 (12.2)	270 (13.1)	102 (14.8)
Multiracial	298 (2.1)	40 (1.9)	14 (2.0)
Insurance status			
Private	8,922 (63.3)	1,325 (64.4)	368 (53.3)
Public	4,123 (29.3)	563 (27.4)	267 (38.6)
None/limited	1,044 (7.4)	168 (8.2)	56 (8.1)
Marital status			
Married/partnered	9,536 (67.7)	1,429 (69.5)	462 (66.9)
Single/other	4,553 (32.3)	627 (30.5)	229 (33.1)
Prenatal BMI at 12 weeks' gestation (kg/m^2)	25.1 ± 5.0	25.7 ± 5.1	28.1 ± 6.2
<25	8,301 (58.9)	1,087 (52.9)	239 (34.6)
25 to <30	3,833 (27.2)	596 (29.0)	237 (34.3)
≥30	1,955 (13.9)	373 (18.1)	215 (31.1)
Prenatal diastolic BP at 12 weeks' gestation (mmHg)	66 ± 6.9	67 ± 6.7	68 ± 6.7
Gestational weight gain (lb)	30.1 ± 9.4	29.2 ± 9.0	25.3 ± 9.4
Follow-up time (years from 1st delivery to last visit in cohort), median (IQR)	8.4 (4.0–14.2)	8.9 (4.1–14.2)	8.3 (3.9–14.7)

Data are *n* (%) or mean ± SD unless otherwise indicated. We stratified individuals by the glucose tolerance category of their first observed pregnancy in the cohort, even if categories changed in subsequent pregnancies. GGI (zero or one abnormal OGTT value) and GDM (two to four abnormal OGTT values) were diagnosed according to Carpenter-Coustan criteria. For race and ethnicity, individuals could belong to multiple categories and were categorized as multiracial if they so identified. BMI and blood pressure (BP) data were interpolated/extrapolated to 12 weeks' gestation for all missing data (details in Supplementary Material). We measured gestational weight gain by subtracting the 12-weeks' interpolated/extrapolated weight from the extrapolated weight at delivery (see Supplementary Material).

diabetes compared with those with normal glucose tolerance (Table 2). The increased risk of diabetes in individuals with GGI compared with those with normal glucose tolerance was not attenuated after adjustment for gestational weight gain (Table 2). Individuals with GDM had increased risk of incident diabetes compared with those with normal glucose tolerance (8.26 [6.49–10.51], $P < 0.001$) (Table 2), with no attenuation after gestational weight gain adjustment (Table 2). The population-attributable fraction of diabetes at 10 years of follow-up was 8.5% for GGI and 28.1% for GDM.

When GGI was separated into component categories, the diabetes incidence rates were 2.7 cases per 1,000 person-years for GGI-0 and 7.7 cases per 1,000 person-years for GGI-1 (Table 2). In both categories, the adjusted risk of diabetes was significantly greater than in individuals with normal glucose tolerance (GGI-0 aHR 1.54 [95% CI 1.09–2.16], $P = 0.01$; GGI-1 2.97 [2.07–4.27], $P < 0.001$) (Table 2), with no attenuation after adjustment for gestational weight gain (Table 2). Among individuals with GDM, an increasing number of abnormal OGTT values also appeared to confer a greater risk of incident diabetes (Supplementary Fig. 1).

When the study population was restricted to the screened cohort (HbA_{1c} ≥3 months after first delivery), results were similar to those in the primary analyses, but the diabetes incidence rates were greater among the screened population (Supplementary Table 4). When the study population was restricted to individuals who were unlikely to have additional pregnancies after the MHC ended (age ≥45 years in 2016) results were similar to those of the primary analyses (Supplementary Table 4). When the study follow-up period was terminated on 31 December 2015, prior to the adoption of a new electronic medical record, results were similar to the primary analyses (Supplementary Table 4). Of the 428 individuals in the study who were diagnosed with diabetes, 52 had an ICD-9 or -10 code or problem list term indicating type 1 diabetes at some point; results were similar to those of the primary analyses after exclusion of these individuals (Supplementary Table 4).

When the study population was dichotomized by age at first delivery, individuals with GGI had a greater risk of future diabetes compared with individuals with normal glucose tolerance in both age-groups: individuals age <35 years at delivery, as well as individuals age ≥35 years (Supplementary Table 5), though the effect size in the older age-group appeared to be attenuated.

In the model for the primary comparison of incident diabetes in GGI versus

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Table 2—Risk of diabetes diagnosis after GGI or GDM compared with normal glucose tolerance in pregnancy

	NGT	GGI (zero or one abnormal OGTT value)		GDM (two to four abnormal OGTT values)	
No. of diabetes diagnoses	212	77		139	
Follow-up time (1,000 person-years)	128.4	19.4		6.0	
Rate of diabetes/1,000 person-years	1.7	4.0		23.1	
		GGI (zero or one abnormal OGTT value)		GDM (two to four abnormal OGTT values)	
	NGT	HR (95% CI)	*P*	HR (95% CI)	*P*
Fully adjusted model	Ref	2.01 (1.54, 2.62)	<0.001	8.26 (6.49, 10.51)	<0.001
Fully adjusted model + gestational weight gain	Ref	2.00 (1.54, 2.61)	<0.001	8.15 (6.40, 10.39)	<0.001
	NGT	GGI-0 (zero abnormal OGTT values)	GGI-1 (one abnormal OGTT value)	GDM (two to four abnormal OGTT values)	
No. of diabetes diagnoses	212	39	38	139	
Follow-up time (1,000 person-years)	128.4	14.5	4.9	6.0	
Rate of diabetes/1,000 person-years	1.7	2.7	7.7	23.1	

		GGI-0 (zero abnormal OGTT values)		GGI-1 (one abnormal OGTT value)		GDM (two to four abnormal OGTT values)	
	NGT	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Fully adjusted model	Ref	1.54 (1.09, 2.16)	0.014	2.97 (2.07, 4.27)	<0.001	8.33 (6.55, 10.61)	<0.001
Fully adjusted model + gestational weight gain	Ref	1.53 (1.08, 2.15)	0.016	2.99 (2.08, 4.30)	<0.001	8.21 (6.45, 10.47)	<0.001

Absolute risk (in rate of diabetes per 1,000 person-years) and relative risk (in hazard ratios) for primary and secondary analyses are shown. GGI (zero and one abnormal OGTT value) and GDM (two to four OGTT values) were diagnosed according to Carpenter-Coustan criteria. All hazard ratios shown are from fully adjusted Cox proportional hazards models with adjustment for age at first delivery, marital status, insurance status, race and ethnicity, parity, prenatal BMI, and prenatal diastolic blood pressure (BP). The second models also include adjustment for gestational weight gain between 12 weeks' gestation and delivery with use of interpolated/extrapolated weights (N = 22 were excluded from these Cox models with adjustment for gestational weight gain as these data were missing; see Supplementary Material for details). HR, hazard ratio; NGT, normal glucose tolerance; Ref, reference.

normal glucose tolerance, the *P* value for the Schoenfeld residual corresponding to the primary comparison was 0.002. Inspection of the residual plot revealed a slightly diminishing time-varying effect of the exposure on the hazard of incident diabetes (Supplementary Fig. 2). Schoenfeld residual *P* values and plots were similar for the other models (between 0.001 and 0.002; plots not shown).

CONCLUSIONS

The results of this large U.S.-based retrospective study demonstrate that individuals with an abnormal initial GDM screen (1-h GLT) who do not meet criteria for GDM (GGI) have an increased risk of incident diabetes after pregnancy. Among these individuals, the degree of risk increases with more abnormal values on the diagnostic 3-h OGTT. As expected, individuals with GDM have the highest risk of future diabetes (20% developed diabetes over a median of 8.3 years). This risk was within the range of risks found in prior studies: an average of 21.5% of individuals in North American studies developed diabetes after GDM according to a recent meta-analysis (13). Together, the GDM and GGI risk factors account for 37% of the incident diabetes occurring in the 10 years after pregnancy. Although GDM is a recognized diabetes risk factor, many individuals with GGI do not meet current guideline-based criteria for diabetes screening outside of pregnancy (3,4). While GDM is a stronger risk factor for incident diabetes than GGI, GGI affects more individuals (12%) than GDM (4%), representing an expanded group who may benefit from postpartum diabetes prevention.

The 2018 American College of Obstetricians and Gynecologists guidelines on the management of GDM recognize the possibility of an increased risk of adverse perinatal outcomes among individuals with GGI (specifically, those with one abnormal OGTT value) (16–21) and call for more research on long-term maternal risks after a GGI-affected pregnancy (5). Our data are responsive to this call, as we have demonstrated that, like GDM, GGI is associated with an increased risk of future diabetes. In our study we identify a large group of individuals who may benefit from intervention after pregnancy to prevent diabetes. Since universal GDM screening is recommended during pregnancy, primary care physicians and health care systems could leverage available pregnancy glucose data to shape population screening and preventative strategies.

The current study includes a large population of pregnant individuals from an academic medical center in the U.S., where the two-step method is most commonly used for universal GDM screening and diagnosis. Though results from previous studies with examination of the risk of future diabetes after subclinical hyperglycemia in pregnancy are consistent with our findings, these studies were smaller or were conducted with screening procedures that cannot be generalized to those currently used in the U.S. (18,22–24,35,36). For example, in the Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study investigators found an increased prevalence

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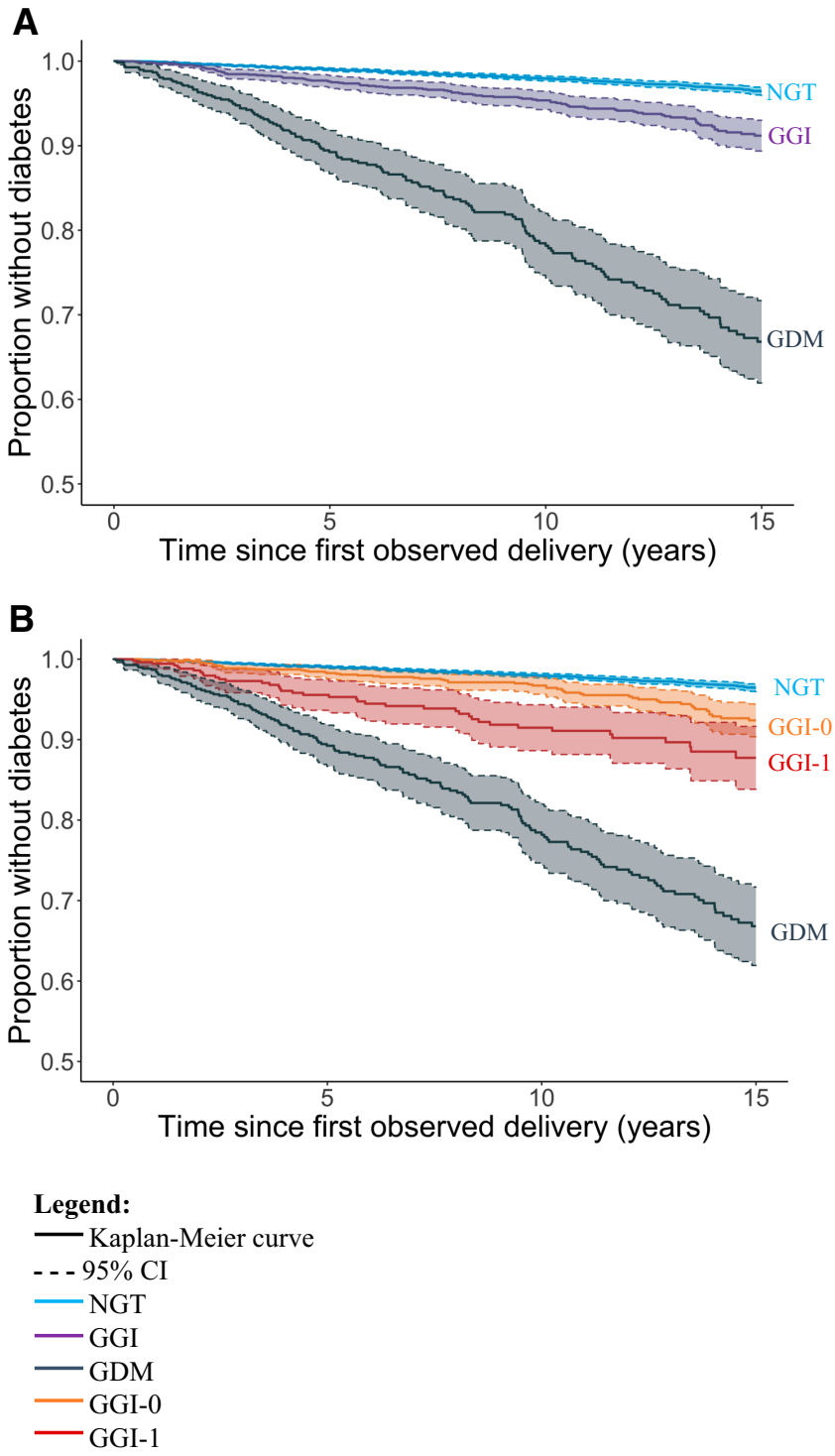

Figure 2—Kaplan-Meier curves depicting time to diabetes diagnosis according to glucose tolerance status in pregnancy. Kaplan-Meier curves (solid lines) with 95% CIs (dashed lines) shown of unadjusted data with time since first observed delivery in years on the *x*-axis and proportion without diabetes on the *y*-axis. *A*: Normal glucose tolerance (NGT) (control group) is shown in blue, GGI in purple, and GDM in gray. *B*: NGT (control group) is shown in blue, and GDM in gray. GGI is divided into its components: zero abnormal OGTT values (GGI-0) in orange and one abnormal OGTT value (GGI-1) in red.

of maternal diabetes and prediabetes a median of 11.4 years after pregnancies with GDM diagnosed with a one-step 75-g OGTT screening procedure according to International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria (35,37). The thresholds for IADPSG criteria are lower than Carpenter-Coustan criteria (37), and only one abnormal OGTT value is needed for diagnosis. Thus, the IADPSG GDM categorization includes some individuals who would have been categorized as having GGI in the current study. Berezowsky et al. (22), based in Israel and Canada, conducted a large retrospective cohort study, finding that one abnormal value on a 3-h 100-g OGTT during pregnancy is associated with increased risk of incident type 2 diabetes as compared with no abnormal OGTT values in those undergoing this testing. Notably, this study did not examine the results of the GLT screening test (22). Thus, unlike the current study, there is limited ability to directly apply the results of these prior studies to current U.S. clinical practice.

Strengths and Limitations

Strengths of this study include the large sample size, the detailed laboratory and clinical data available, the ability to include multiple pregnancies in the same individual using time-varying exposures, and the length of follow-up. Limitations do exist. First, there is a threat of bias by confounding inherent to observational data. To address this, we adjusted for potential confounders in our statistical models including age, parity, race and ethnicity, marital and insurance status, and baseline BMI and blood pressure. Second, our data set was limited to individuals who had prenatal and primary care at a single academic center, which may limit the generalizability. Our results may be less generalizable to the U.S. population as our cohort has a higher proportion of White, insured individuals. This population of White and insured individuals may be more likely to have postpartum diabetes screening and prevention than the general U.S. population. While we conducted a single-center study, our overall results are corroborated by those of other studies in other settings where increased risk of diabetes after subclinical hyperglycemia in pregnancy was found (18,22–24,35,36). Third, individuals need to be screened to be diagnosed with diabetes after pregnancy, possibly resulting in ascertainment bias if only those with established risk factors were screened. To evaluate this limitation, we conducted a sensitivity analysis in which only individuals screened by HbA_{1c} were included, with findings similar to those of our primary analysis. U.S. studies suggest that between 38 and 67% of individuals with

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GDM are screened for diabetes postpartum (38,39). Fourth, while we looked at gestational weight gain during pregnancy, we did not evaluate postpartum weight gain or BMI after pregnancy. Finally, it is possible that individuals had additional pregnancies that were not captured in our database. To address this limitation, we conducted a sensitivity analysis in which we only included individuals who were unlikely to become pregnant after the pregnancy data collection ended; results were similar to those of the primary analyses.

Calculation of the Schoenfeld residuals indicated that the proportional hazards assumption did not hold for the pregnancy glucose categories in the Cox regression models. However, the trend observed in the residual plots (a gradually diminishing effect of glucose category over time) is biologically plausible, as we would expect the effect of a pregnancy-related risk factor to diminish over time. Further, the hazard ratios obtained from the Cox regression models correspond to a time-averaged multiplicative effect of the exposure over time, which is valuable to estimate.

Conclusion

Pregnant individuals with GGI, those who had an initial abnormal screening test for GDM without meeting GDM diagnostic criteria, have increased risk of future diabetes compared with those with normal glucose tolerance. Clinical data universally available from prenatal care identify a large, previously unrecognized group of individuals who may benefit from diabetes screening and prevention postpartum. Recognizing GGI as a risk factor may provide additional opportunities to diagnose and prevent future diabetes, as well as cardiovascular disease (40).

Acknowledgments. The authors thank Chu Yu (former biostatistician at the Massachusetts General Hospital Biostatistics Center) for her statistical expertise during initial stages of this project and Jacqueline Maya (Pediatric Endocrinology Fellow at Massachusetts General Hospital for Children, Boston, MA) for her assistance with chart reviews.

Funding. D.J.S. was supported by a National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) T32 training grant for Endocrinology (T32DK007028). J.B.M. was supported by NIDDK grant UM1DK078616. This study was supported by the Massachusetts General Hospital Physician Scientist Development Award and the Claflin Distinguished Scholar Award (to C.E.P.).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. D.J.S. designed the study, researched data, and wrote the manuscript. T.T. contributed to study design, researched data, contributed to the results and methods, and reviewed and edited the manuscript. C.C.M.S. researched data, contributed to the results and methods, and reviewed and edited the manuscript. S.H. researched data and reviewed the manuscript. W.H. researched data and reviewed the manuscript. K.J. researched data and reviewed the manuscript. A.K. reviewed and edited the manuscript. J.B.M. contributed to study design and reviewed and edited the manuscript. C.E.P. contributed to study design, researched data, obtained funding, reviewed and edited the manuscript, and supervised the work. C.E.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 81st Scientific Sessions of the American Diabetes Association, New Orleans, LA, 25–29 June 2021.

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