SUPPLEMENTARY DATA

ADDITIONAL INFORMATION for RESEARCH DESIGN AND METHODS

Study Population

The first dietary questionnaire was administered in 1991, and thus 1991 was used as our baseline year. Women were included in our analysis if they reported at least one pregnancy lasting greater than 6 months between the 1991 and 2001 questionnaire cycles. The first pregnancy reported from baseline was considered the index pregnancy. Participants were restricted from entry into the study population if they reported prevalent hypertension, type 2 diabetes, use of blood pressure medication, a prior cardiovascular disease event, a history of pregnancy-related hypertension disorders, or GDM prior to the index pregnancy. Participants were censored during follow-up if they reported a cardiovascular disease event or if they died. In all, there were 25,305 participants included in our analysis.

Assessment of Exposure

A physician diagnosis of pregnancy-related diabetes (GDM) was ascertained by self-report on each questionnaire biannually from 1989 through 2001. A validation study among a subgroup of this cohort was previously conducted with 94% of GDM reports verified by medical records (1). Among the confirmed GDM diagnoses, physicians were most likely to use the National Diabetes Data Group criteria. Of a random sample of parous women without GDM, 83% reported a glucose screening test during pregnancy, suggesting similar screening practices. Self-reported type 2 diabetes has been previously validated in the Nurses' Health Study I cohort, comprised of similar participants (2). Among these participants, diabetes mellitus was confirmed in 98% of a random sample upon a blinded review of medical records.

GDM is an established risk factor for type 2 diabetes (3). Type 2 diabetes is also a well known correlate of hypertension. In a secondary analysis, we re-categorized our exposure into 4 groups to examine the joint effect of GDM and type 2 diabetes: women without self-reported GDM or type 2 diabetes, women with GDM only, women with type 2 diabetes only, and women with both GDM and subsequent type 2 diabetes.

Assessment of Outcome

Participants were asked on each questionnaire if they received a physician's diagnosis of high blood pressure (yes/no) and the date of diagnosis. For the validation of self-reported hypertension in this cohort, we obtained relevant medical records from a subset of randomly selected NHS II participants who self-reported a new diagnosis of hypertension on the 2005 questionnaire, as well as randomly selected participants who denied ever receiving this diagnosis. The sensitivity of self-reported hypertension was 94%. The specificity of a nurse reporting no diagnosis of hypertension was 85%. Incident cases were counted from the first follow-up questionnaire (1993) through June, 2007.

Assessment of Covariates

Age, in months, was computed from reported date of birth to date of questionnaire return. Participants reported their current weight on each biennial questionnaire. Self-reported weight was highly correlated with measured weight, among a random subset of Boston-area cohort participants (r=0.97) (4). Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared. Total physical activity was ascertained by frequency of engaging in common recreational activities. The questionnaire-based estimates correlated with detailed activity diaries (r=0.56) (5). Dietary information was assessed with a self-administered semi-quantitative food frequency questionnaire (FFQ), which has been extensively validated (6). Information from the FFQ was used to

quantify alcohol intake, as well as to compute DASH (Dietary Approaches to Stop Hypertension) score (7). Possible scores range from 8-40 points, with a higher score indicating greater adherence to the 8 dietary components, including a high intake of fruits, vegetables, nuts and legumes, low-fat dairy, and whole grains, while low in sodium, sugar-sweetened beverages, and red or processed meats.

Regular use of analgesics including acetaminophen, non-steroidal anti-inflammatory drugs, and aspirin, as well as parity, history of toxemia, preeclampsia, or gestational hypertension was also ascertained at each questionnaire cycle. In addition, we ascertained information about the participants' birthweight, weight at age 18 years, self-reported race and ethnicity, smoking status, and family history of hypertension and diabetes. These data have also been previously validated (8; 9).

Statistical Analysis

Baseline differences between GDM and non-GDM participants were compared using a chi^2 test (categorical variables) and univariate linear regression (continuous variables). Women were skipped from any biennial risk set in which they failed to return the questionnaire, but were eligible for reentry with return of successive questionnaires. Missing values for food frequency questionnaires were carried forward from the most recent previous questionnaire.

Crude cumulative incidence curves were generated comparing the incidence of hypertension between exposure groups. Age in months was modeled continuously, while BMI (<20, 20-20.9, 21-21.9, 22-22.9, 23-23.9, 24-24.9, 25.0-26.9, 27-28.0, 29-29.9, 30-31.9, 32-34.9, 35-39.9, 40+), BMI at age 18 (<20, 20-24, 25-29, ≥30), DASH score (quintiles), physical activity (<30 minutes/week, 30-59, 60-119, 120-209, 210), alcohol (0-4 g/day, 5-9, 10-14, 15-30, 30+), parity (1, 2, 3, 4+), participants' birth weight (<5.5 lbs, 5.5-6.9, 7.0-8.4, 8.5-9.9+), oral contraceptive use (never, past, current), and smoking status (never, past, current) were entered into the model categorically. History of gestational hypertension, family history of hypertension and/or type 2 diabetes, race and ethnicity, and analgesic medication use were included in the models as yes/no binary response variables. Current age, BMI, parity, history of toxemia, preeclampsia, gestational hypertension, physical activity, medication use, alcohol, and usual diet was updated with each questionnaire cycle.

ADDITIONAL RESULTS & DISCUSSION

Appendix Figure 1 shows the unadjusted cumulative incidence of hypertension by GDM status. We did observed a significant interaction between GDM exposure and history of pregnancy hypertensive disorders (p=0.0008). Compared to participants without either pregnancy disorder, those with both GDM and toxemia or pregnancy hypertension had more than twice the risk of developing hypertension (HR=2.11 [1.65, 2.70], p<0.0001). Additionally, those with GDM only (no pregnancy hypertensive disorders) were at a 45% increased risk of developing hypertension during follow-up (HR=1.45 [1.25, 1.68], p<0.0001).

Appendix Figure 2 shows unadjusted cumulative incidence of hypertension when exposure is further stratified by exposure to type 2 diabetes. Overall, 244 (1.0%) study participants developed type 2 diabetes after the index pregnancy and prior to either the diagnosis of hypertension or a censoring event. Almost half (n=114; 47%) of these participants had been exposed to GDM prior to developing type 2 diabetes. Compared to participants without exposure to either GDM or type 2 diabetes, the multivariable hazard ratio of incident hypertension was 2.55 ([1.84, 3.55], p<0.0001) among those who had both GDM and subsequent type 2 diabetes. This was similar to the hazard ratio among subjects who had type 2 diabetes only (HR=2.98 [2.17, 4.08], p<0.0001). The association between GDM and hypertension

incidence remained significant among the participants who had GDM but did not subsequently develop type 2 diabetes (HR=1.18 [1.03, 1.36], p=0.02).

There are potential limitations to our study. First, incident GDM was ascertained by participant self-report. Although this has previously been validated with exceptional accuracy, some misclassification of the exposure is likely. Secondly, GDM is classified in our cohort as a dichotomous exposure, although glucose tolerance impairment can be measured on a continuous scale, and misclassification with attenuation of the observed effect estimate towards the null is possible. Thirdly, to compute the time-to event for the cumulative incidence curves of hypertension and make sure that our covariate data was captured prospectively, we excluded prevalent GDM events. However, the exclusion may differentially exclude more future hypertension cases among exposed participants at baseline, therefore, result in an underestimation of the association between GDM and hypertension. Additionally, despite careful control for lifestyle and other factors, there might be unmeasured or residual confounding, which is possible with measurement error or bias in response to the questionnaires. The toxemia and pregnancy hypertension variables might be particularly susceptible to misclassification due to complexity in diagnosing these conditions

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SUPPLEMENTARY DATA

Supplementary Table 1. Baseline (1991) characteristics for study participants (Nurses' Health Study II, N=25,444) with and without GDM

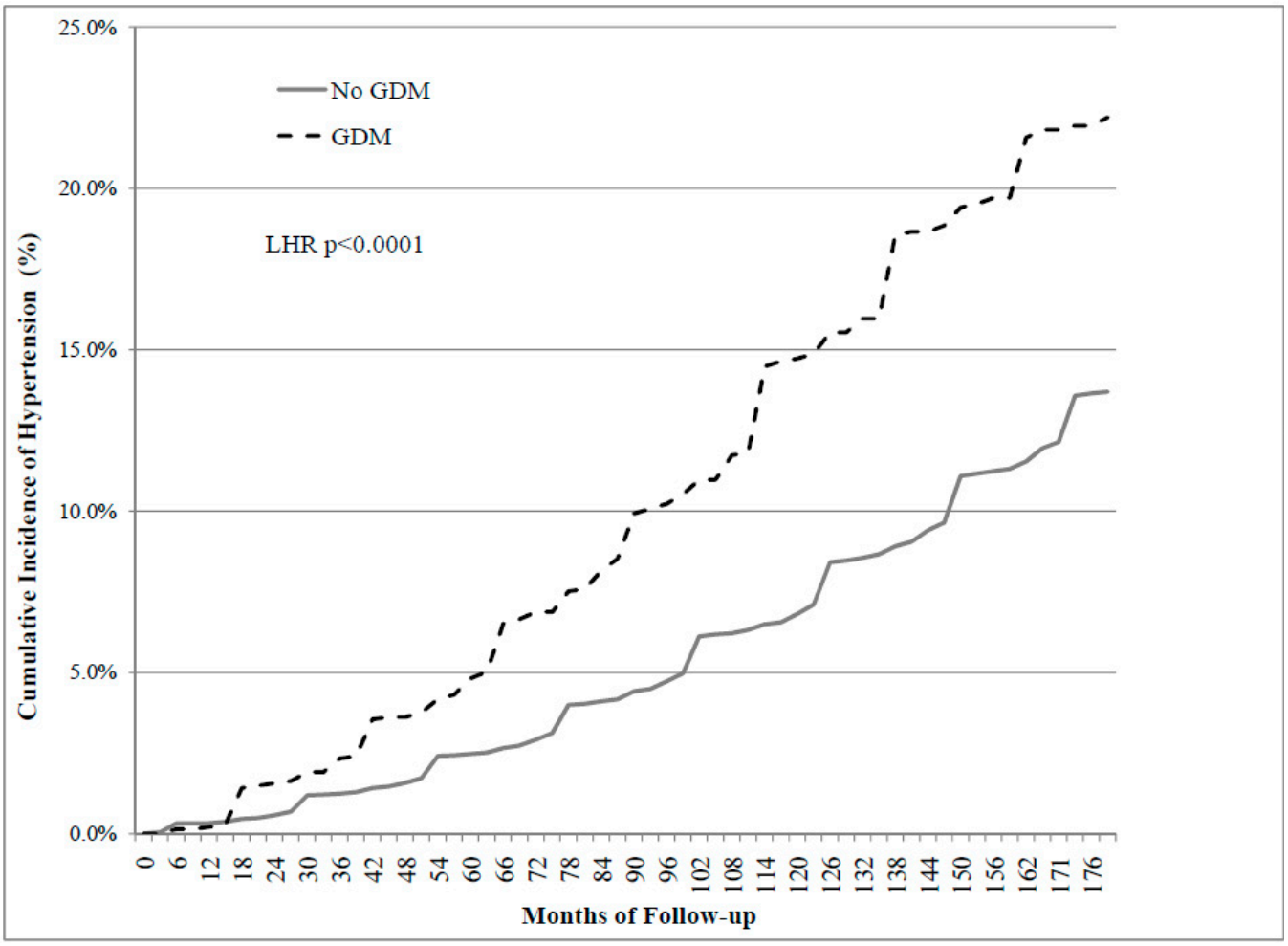
	GDM	non-GDM	
	n (%)	n (%)	
	1,414 (5.6)	23,891 (94.4)	
	Mean (SD)	Mean (SD)	p-value
Age (years)	32.7 (3.6)	32.7 (3.5)	0.9
BMI (kg/m^2)	25.2 (5.1)	23.4 (4.1)	<0.0001
BMI at Age 18 (kg/m^2)	21.2 (3.2)	20.9 (2.9)	0.0002
DASH Score (8-40)	23.7 (5.1)	24.4 (5.1)	<0.0001
Total Physical Activity (minutes/week)	243 (283)	257 (300)	0.09
Vigorous Physical Activity (minutes/week)	86 (153)	98 (172)	0.006
Smoking Pack-Years	7.8 (70)	6.2 (60)	0.40
Alcohol Consumption (g/day)	2.4 (4.7)	2.8 (5.0)	0.003
	%	%	
History of Toxemia/Pre-Eclampsia/Pregnancy Hypertension	12.1	5.9	<0.0001
Family History			
Hypertension	51.3	45.8	<0.0001
Diabetes	20.2	10.6	<0.0001
Race			
White	90.6	92.7	<0.0001
Black	1.1	0.9	
Hispanic	2.1	1.0	
Asian	2.8	1.8	
Other	1.3	1.9	
Parity			

0	37.9	28.2	<0.0001
1	31.8	28.1	
2	19.4	26.6	
3+	10.9	17.1	
Women's Birthweight			0.0001
<5.5 pounds	7.9	6.1	
5.5-6.9 pounds	32.1	28.3	
7.0-8.4 pounds	42.1	46.5	
8.5+ pounds	11.5	13.9	
Unknown	6.4	5.2	
Smoking Status			
Never	69.9	69.5	0.5
Past	21.9	22.9	
Current	8.5	7.1	
Ever Oral Contraceptive Use			
Never	16.6	15.9	0.7
Past	65.4	66.2	
Current	18.0	17.9	
Current Analgesic Medication Use			
Acetaminophen	21.9	18.6	0.002
Aspirin	8.3	6.4	0.005
Other Anti-Inflammatory	16.1	11.8	<0.0001

GDM=gestational diabetes mellitus
SD=standard deviation
BMI=body mass index
kg=kilograms; m=meters; g=grams
DASH=Dietary Approaches to Stop Hypertension

SUPPLEMENTARY DATA

Supplementary Figure 1. Cumulative incidence of hypertension by GDM status



SUPPLEMENTARY DATA

Supplementary Figure 2. Cumulative incidence of hypertension by GDM & type 2 diabetes status