Fetal Exposure to Parental Smoking and the Risk of Type 2 Diabetes in Adult Women

Vincent W.V. Jaddoe,[1,2] Layla L. de Jonge,[2,3] Rob M. van Dam,[1,4] Walter C. Willett,[1,5,6] Holly Harris,[3] Meir J. Stampfer,[1,5,6] Frank B. Hu,[1,5,6] and Karin B. Michels[3,5,6]

Diabetes Care 2014;37:2966–2973 | DOI: 10.2337/dc13-1679

OBJECTIVE

We evaluated the associations of both maternal and paternal smoking during pregnancy with the risk of type 2 diabetes in daughters and explored whether any association was explained by weight at birth or BMI throughout life.

RESEARCH DESIGN AND METHODS

We used data from 34,453 participants of the Nurses' Health Study II. We used Cox proportional hazards models to examine the associations of maternal and paternal smoking during pregnancy with incidence of type 2 diabetes in daughters between 1989 and 2009.

RESULTS

Maternal smoking during the first trimester only was associated with the risk of type 2 diabetes in the offspring, independent of confounders, birth weight, and later-life BMI (fully adjusted hazard ratio 1.34 [95% CI 1.01, 1.76]). In the age-adjusted models, both continued maternal smoking during pregnancy and paternal smoking tended to be associated with an increased risk of type 2 diabetes in daughters. Perinatal and adult life variables did not explain these associations, but additional adjustment for current BMI fully attenuated the effect estimates.

CONCLUSIONS

The associations of maternal and paternal smoking during pregnancy with the risk of type 2 diabetes in daughters were largely explained by BMI throughout the life course. Further studies are needed to explore the role of first-trimester-only maternal smoking on insulin resistance in the offspring. Also, similar effect estimates for maternal and paternal smoking suggest that the associations reflect shared family-based or lifestyle-related factors.

Adverse fetal exposures may lead to early developmental adaptations, including changes in the anatomy, physiology, and metabolism of various organ systems (1). These adaptations may be beneficial in the short-term but may have adverse consequences at birth and in later life, such as increased risks of low birth weight and common diseases in adulthood (2). This hypothesis is supported by studies showing consistent associations of low birth weight with increased risks of type 2 diabetes and cardiovascular disease (3–5). Not much is known about the specific adverse fetal exposures leading to low weight at birth and type 2 diabetes in later life. Maternal smoking during pregnancy is common in Western countries and might be one of the specific adverse fetal exposures involved in these pathways (6,7). Cigarette smoke contains many different substances including nicotine, carbon monoxide, and

[1]Department of Nutrition, Harvard School of Public Health, Boston, MA
[2]Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands
[3]Obstetrics and Gynecology Epidemiology Center, Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
[4]Saw Swee Hock School of Public Health and Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore
[5]Department of Epidemiology, Harvard School of Public Health, Boston, MA
[6]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Corresponding author: Vincent W.V. Jaddoe, v.jaddoe@erasmusmc.nl.

Received 17 July 2013 and accepted 9 July 2014.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-1679/-/DC1.

V.W.V.J. and L.L.d.J. contributed equally to this study.

cadmium and other toxic factors that have direct adverse effects and might affect placental function and the fetal supply line (8). Maternal smoking leads to restricted blood flow in the vascular beds of specific fetal organs (8). Animal studies demonstrated adverse effects of high maternal nicotine levels on metabolic development (9). Studies in rats demonstrated that fetal exposure to nicotine alters development of the pancreatic islets, control of fat storage, homeostasis of energy expenditure, and blood vessel structure and reactivity (9,10). Continued smoking during pregnancy is strongly associated with fetal growth retardation and increased risks of low birth weight (11,12). Follow-up studies in children and adults suggested increased risks of obesity in children from mothers who smoked during pregnancy (13–15). Results from the British National Child Development Study (NCDS) suggested that maternal smoking during pregnancy is associated with obesity and type 2 diabetes in the adult offspring (16). However, whether the observed association of maternal smoking during pregnancy with type 2 diabetes is explained by obesity is not known. Moreover, any association of maternal smoking during pregnancy with risk of type 2 diabetes in the offspring may be explained by intrauterine effects or just reflect confounding by various unmeasured shared family and lifestyle-related exposures. Stronger effect estimates for the associations of maternal smoking than for paternal smoking with the risk of type 2 diabetes in the offspring may suggest direct intrauterine effects, whereas similar effect estimates suggest that the associations are largely explained by unmeasured common family-based or lifestyle-related exposures (13,17).

We evaluated the associations of both maternal and paternal smoking during pregnancy with the risk of type 2 diabetes in daughters and explored whether any association was explained by weight at birth or BMI throughout life. We used data from 34,453 participants of the Nurses' Health Study II (NHSII) and their mothers. In the same cohort as the current study, we previously observed that maternal and paternal smoking during pregnancy was associated with obesity in the offspring throughout the life course.

RESEARCH DESIGN AND METHODS

Study Design

The NHSII is an ongoing prospective cohort study among 116,430 female registered nurses in the U.S. that started in 1989 and has been previously described in detail (18). Briefly, registered nurses who lived in 1 of 11 states and fulfilled the eligibility criteria (female, age range 25–42 years) were mailed a baseline questionnaire in 1989. The birth years of the nurses ranged from 1947 to 1964. Follow-up questionnaires were sent to participating nurses biennially to update the information of lifestyle risk factors and disease occurrence. In 2001, the mothers of 35,794 nurses participated in the Nurses' Mothers' Cohort Study (19). These participating mothers completed a questionnaire on the prenatal, perinatal, and early-life exposures of their nurse daughters. We excluded 113 nurses who were adopted, 1,013 nurses without information about maternal and paternal smoking during pregnancy, and 215 nurses with existing diagnosis of type 1 or type 2 diabetes reported at baseline. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard School of Public Health.

Assessment of Maternal and Paternal Smoking

Information on fetal smoke exposure was collected with the 2001 Nurses' Mothers' Cohort questionnaire (20). Mothers were asked to report whether they ever smoked cigarettes during pregnancy with the nurse daughter, the number of cigarettes they smoked daily during pregnancy, and whether they stopped smoking during pregnancy and, if so, during which trimester. Maternal smoking was categorized as never smoked, smoked until first trimester of pregnancy, continued smoking $<$15 cigarettes per day during pregnancy, and continued smoking $\geq$15 cigarettes per day during pregnancy. The questionnaire also inquired whether the nurse's father ever smoked cigarettes during pregnancy and the number of cigarettes he smoked. Paternal smoking was categorized as never smoked, smoked $<$15 cigarettes per day, and smoked $\geq$15 cigarettes per day. For investigation of the associations of both parents smoking independently and combined with the risk of type 2 diabetes, maternal and paternal smoking during pregnancy data were categorized into no parental smoking during pregnancy, only paternal smoking during pregnancy, and maternal or both parents smoking during pregnancy.

Ascertainment of Type 2 Diabetes

Participants with self-reported diagnoses of diabetes were mailed a supplementary questionnaire regarding symptoms, diagnostic tests, and hypoglycemic therapy. Cases before 1998 were defined by using the National Diabetes Data Group criteria (21). The American Diabetes Association criteria were used for cases after 1998 (22). The validity of the supplementary questionnaire has been established in two previous studies through medical record reviews. In both studies, diagnosis of type 2 diabetes was confirmed in 98% of the cases (23,24). Follow-up information about type 2 diabetes development was available until June 2009.

Assessment of Covariates

Information about covariates was obtained from the Nurses' Mothers' Cohort and the NHSII questionnaires (20). The 2001 Nurses' Mothers' Cohort questionnaire collected data on the nurse daughter's gestational age, birth weight, and breast-feeding status; maternal and paternal age at birth of the nurse daughter, educational level, and occupation and home ownership at the time of the daughter's birth; maternal prepregnancy weight and gestational weight gain; paternal weight; and the occurrence of pregnancy complications during the pregnancy of the nurse daughter. The 1989 NHSII questionnaire assessed age, height, weight at age 18 years, self-classified race of the nurse, and family history of type 2 diabetes at baseline. Nurses' weight and smoking status were additionally ascertained from the 1989 NHSII questionnaire and were updated with data from each biennial questionnaire cycle. BMI at age 18 years and current BMI were calculated as weight in kilograms divided by the square of height in meters as assessed in 1989. Information on alcohol and total calorie intake was also retrieved from the 1991 semiquantitative food frequency questionnaire and

updated every 4 years. Physical activity (hours per week) was expressed in MET scores and was ascertained in 1989 and updated every 4 years.

Statistical Analysis

We used *t* tests and χ^2 tests to explore differences in subject characteristics between nonsmoking in pregnancy and smoking in pregnancy groups. Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% CIs for incident type 2 diabetes by maternal and paternal smoking. Participants contributed follow-up time from the return of the 1989 questionnaire to the report of physician-diagnosed diabetes, death, or end of follow-up in June 2009. The proportional hazards assumption in all models was checked by visual inspection of the plots, along with the testing of time-dependent covariates. We considered birth weight and BMI in adolescence and adulthood as potential explanatory variables for the associations of maternal and paternal smoking during pregnancy with the risk of type 2 diabetes. Regression models were adjusted for age (model 1) and in addition for perinatal variables (maternal and paternal age at delivery, maternal prepregnancy BMI and weight gain during pregnancy, paternal BMI, maternal and paternal educational level, occupation, house ownership at the time of the daughter's birth, smoking by the other parent, and nurses' ethnicity, gestational age, breast-feeding status, and family history of type 2 diabetes) (model 2) and for adult life variables (nurses' husbands' educational level, pretax household income, smoking, height, total energy and alcohol intake, and physical activity) (model 3). We considered model 3 to be the model adjusted for all potential confounders. Subsequently, we explored whether any association was mediated through birth weight (model 4), BMI at age 18 years (model 5), current BMI (model 6), or both birth weight and BMI at age 18 years and in adulthood (model 7). We estimated the proportion of the associations explained by birth weight and current BMI using an SAS macro that calculates the explained proportion by each intermediate variable (Mediate SAS; Harvard School of Public Health [available from http://www.hsph.harvard.edu/faculty/donna-spiegelman/software/mediate]) (25). This analysis was performed for both statistically significant and nonsignificant effect estimates and gives for each mediating factor (birth weight and BMI) the percentage and 95% CI explained by the mediating factor. The percentage for each mediation effect is significant when zero is not included within the 95% CI range. To investigate the association of both parents smoking independently and combined with the risk of type 2 diabetes, we compared the effect estimates for smoking by father only and by mother only or both parents combined, with no parental smoking during pregnancy. Tests for trend were performed across the level of the number of cigarettes smoked. All statistical analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Participant characteristics are presented in Table 1. In total, 8,935 (25.9%) mothers reported that they smoked during the pregnancy with their nurse daughter. Compared with daughters of mothers who did not smoke during pregnancy, those of mothers who did smoke during pregnancy were born with lower birth weight, were less frequently breast-fed, were more often smokers in adulthood, and had a higher alcohol intake in adulthood. Supplementary Table 1 gives the subject characteristics for each category of maternal smoking during pregnancy. During 664,576 person-years of follow-up in 34,453 participants, 1,451 incident cases of physician-diagnosed type 2 diabetes were reported.

In the age-adjusted Cox proportional hazards model, first-trimester-only maternal smoking was associated with an increased incidence of type 2 diabetes in adult daughters compared with no maternal smoking during pregnancy (age-adjusted HR 1.32 [95% CI 1.02, 1.72]) (Table 2). Adjustment for perinatal variables and adult life variables only slightly changed this effect estimate. Also, birth weight and BMI at age 18 years and in later life did not explain this association.

In the crude models and models adjusted for perinatal variables and adult life variables, maternal continued smoking of $<$15 cigarettes per day was associated with the risk of type 2 diabetes in their daughters (adjusted HR 1.22 [95% CI 1.04, 1.43]). The association of maternal continued smoking of $\geq$15 cigarettes per day with the risk of type 2 diabetes in daughters was not significant (adjusted HR 1.16 [95% CI 0.95, 1.42]). Additional adjustment for birth weight slightly changed the effect estimate, and including BMI at age 18 years or in adulthood in the model further attenuated the associations. The estimated mediation proportion indicated that current BMI tended to account for 59% (95% CI $-$59, 178) of the association of maternal smoking of $\geq$15 cigarettes per day with the risks of type 2 diabetes.

We used similar models to examine the associations of the number of cigarettes smoked during pregnancy by the father with the risk of type 2 diabetes in the adult daughters (Table 2). We observed in the age-adjusted models and models adjusted for perinatal variables and adult life variables that paternal smoking of $\geq$15 cigarettes per day was associated with an increased risk of type 2 diabetes in the adult offspring compared with no paternal smoking during pregnancy (adjusted HR 1.21 [95% CI 1.06, 1.37]). Birth weight did not explain this association, but including BMI in adulthood in the models attenuated the associations into nonsignificance. Overall, the effect estimates for paternal smoking of $\geq$15 cigarettes per day were stronger than those for maternal smoking of the same number of cigarettes. A similar, but weaker, pattern was observed for the associations of paternal smoking of $<$15 cigarettes per day with the risk of type 2 diabetes in their daughters. Current BMI was estimated to mediate 53% (95% CI 5, 101) of this association. The percentages of the associations explained by birth weight and BMI are given in Supplementary Tables 2 and 3.

Next, we combined the maternal and paternal smoking categories. Because of the small numbers of mothers who smoked without their partner smoking, we used the categories no parental smoking, paternal smoking only, and maternal or both parents smoking. We observed that both paternal smoking only and maternal or both parental smoking were associated with type 2 diabetes in daughters in the models

Table 1—Age-standardized maternal, paternal, and offspring characteristics according to maternal smoking during pregnancy status in participants of the NHSII cohort

	Maternal cigarette smoking during pregnancy		
	No maternal smoking during pregnancy	Maternal smoking during pregnancy	*P*
N	25,518	8,935	
Maternal characteristics			
Age at daughter's birth (years)	26.4 (5.1)	25.9 (4.7)	<0.05
Prepregnancy BMI (kg/m^2)	21.4 (2.7)	20.9 (2.5)	<0.05
Weight gain during pregnancy <9.1 kg (%)	35	35	NS
Attended college (%)	35	41	<0.05
Professional occupation (%)	3	3	
History of diabetes (%)	11	10	
Paternal characteristics			
Age at daughter's birth (years)	29.2 (5.7)	28.9 (5.4)	<0.05
BMI (kg/m^2)	23.6 (2.8)	23.5 (2.8)	NS
Attended college (%)	41	49	<0.05
Professional occupation (%)	30	34	<0.05
Smoked during pregnancy (%)	50	74	<0.05
History of diabetes (%)	16	15	NS
Family-owned house at daughter's birth (%)	49	43	<0.05
Pregnancy and childhood characteristics			
Gestational age at birth (weeks)	39.4 (2.3)	39.3 (2.4)	<0.05
Birth weight (g)	3,335 (503)	3,157 (514)	<0.05
White ethnicity (%)	96	97	NS
Breast-fed in infancy (%)	56	44	<0.05
BMI at age 18 years (kg/m^2)	21.0 (3.1)	21.4 (3.3)	<0.05
Adulthood characteristics			
Age (years)[a]	34.4 (4.7)	33.8 (4.5)	<0.05
Height (cm)	165 (7)	165 (7)	NS
BMI (kg/m^2)	23.6 (4.7)	23.6 (4.7)	NS
Smoking behavior (%)			<0.05
Never	71	61	
Past	20	25	
Current <15 cigarettes/day	4	6	
Current ≥15 cigarettes/day	5	8	
Pretax household income >75,000 USD (%)	55	59	<0.05
Husband attended college (%)	81	83	<0.05
Alcohol intake (g/day)	2.9 (5.7)	3.6 (5.4)	<0.05
Total energy intake (kcal/day)	1,808 (539)	1,786 (509)	NS
Physical activity (MET h/week)[b]	24.0 (33.9)	25.4 (35.9)	<0.05

Data are means (SD) unless otherwise indicated and are standardized to the age distribution of the study population. *P* values are based on *t* tests and χ^2 tests for continuous and categorical variables, respectively. NS, nonsignificance. [a]Value is not age adjusted. [b]MET hours per week from recreational and leisure-time activities.

adjusted for age, perinatal variables, and adult life variables (Table 3). When we additionally adjusted these models for both weight at birth and BMI in adulthood, both paternal smoking only and maternal or both parental smoking were no longer associated with the risk of type 2 diabetes (paternal smoking only HR 1.08 [95% CI 0.95, 1.24]; maternal or both parents smoking HR 1.13 [95% CI 0.98, 1.31]).

CONCLUSIONS

We observed in a cohort study among U.S. women that maternal and paternal smoking during pregnancy tend to be associated with the risk of type 2 diabetes in the adult offspring. These associations were not explained by growth in early life but may be explained by BMI in adulthood.

An accumulating body of evidence suggests that a suboptimal fetal environment may be important for development of type diabetes (26). The association of low birth weight with type 2 diabetes has been observed in various populations and appears to be independent of socioeconomic status and adult BMI (4). Preterm birth has also been suggested to be associated with insulin resistance (27). The association of birth weight with insulin resistance seems to be stronger in adults with catch-up growth or higher growth rates in early childhood (28,29). Low birth weight is not likely the causal factor per se in this association but may reflect developmental adaptations in response to different fetal exposures (2,30). Reports from the Dutch and Chinese Famine Studies showed increased risks of type 2 diabetes among adults who experienced severe undernutrition during fetal life (31,32).

Maternal smoking during pregnancy is a common adverse fetal exposure. Children of mothers who smoked during pregnancy had higher BMI, blood pressure, and total cholesterol levels (33,34). We have recently reported that the associations of parental smoking during pregnancy with the risk of hypertension in the offspring are largely

Table 2—Maternal and paternal cigarette smoking during pregnancy in different periods of pregnancy and the risk of type 2 diabetes in participants of the NHSII cohort during 20 years of follow-up (1989–2009)

	Maternal smoking					Paternal smoking			
	Nonsmoker	Quit smoking in 1st trimester	Continued smoking <15 cigarettes/day	Continued smoking ≥15 cigarettes/day	*P* for trend*	Nonsmoker	<15 cigarettes/day	≥15 cigarettes/day	*P* for trend*
Person-years	492,349	21,875	85,003	52,696		284,919	142,340	225,580	
No. of cases	1,041	59	201	121		537	329	560	
Model 1: adjusted for age	Reference	1.32 (1.02, 1.72)	1.15 (0.99, 1.34)	1.19 (0.98, 1.44)	0.03	Reference	1.16 (1.01, 1.34)	1.30 (1.15, 1.46)	<0.01
Model 2: additionally adjusted for perinatal variables[a]	Reference	1.34 (1.03, 1.75)	1.18 (1.01, 1.38)	1.14 (0.93, 1.39)	0.11	Reference	1.10 (0.95, 1.27)	1.18 (1.04, 1.34)	0.01
Model 3: model 2 + adjusted for adult life variables[b]	Reference	1.39 (1.06, 1.83)	1.22 (1.04, 1.43)	1.16 (0.95, 1.42)	0.06	Reference	1.15 (0.99, 1.32)	1.21 (1.06, 1.37)	<0.01
Model 4: model 3 + adjusted for birth weight	Reference	1.34 (1.03, 1.76)	1.16 (0.99, 1.36)	1.09 (0.89, 1.33)	0.28	Reference	1.13 (0.98, 1.31)	1.19 (1.05, 1.36)	0.01
Model 5: model 3 + adjusted for BMI at age 18 years	Reference	1.41 (1.07, 1.85)	1.14 (0.97, 1.34)	1.06 (0.86, 1.29)	0.44	Reference	1.12 (0.97, 1.29)	1.17 (1.03, 1.33)	0.02
Model 6: model 3 + adjusted for current BMI	Reference	1.40 (1.06, 1.85)	1.13 (0.96, 1.33)	1.06 (0.87, 1.31)	0.46	Reference	1.10 (0.95, 1.27)	1.09 (0.96, 1.25)	0.24
Model 7: model 3 + adjusted for birth weight, BMI at age 18 years, and current BMI	Reference	1.34 (1.01, 1.76)	1.06 (0.90, 1.25)	0.97 (0.79, 1.19)	0.76	Reference	1.07 (0.93, 1.24)	1.07 (0.93, 1.22)	0.41

Data are HRs (95% CI) unless otherwise indicated based on Cox proportional hazards regression models and reflect the risk of type 2 diabetes compared with the reference group. **P* for trend across nonsmokers, smoking 1–14 cigarettes/day, and smoking ≥15 cigarettes/day. [a]Maternal and paternal age at time of daughter's birth, maternal prepregnancy BMI, maternal weight gain during pregnancy, paternal BMI, maternal and paternal educational level, maternal and paternal occupation, house ownership of parents at the time of the daughter's birth, smoking by the other parent, and nurse's ethnicity, gestational age, breast-feeding status, and family history of diabetes. [b]Participant's husband's educational level, pretax household income, cigarette smoking, height, alcohol intake, total energy intake, and physical activity.

Table 3—Parental smoking during pregnancy and risk of type 2 diabetes in participants of the NHSII cohort during 20 years of follow-up (1989–2009)

	Parental smoking during pregnancy			
	No parental smoking	Paternal smoking only	Maternal or both parents smoking	*P* for trend
Person-years	247,520	244,829	172,227	
No. of cases	463	578	410	
Model 1: adjusted for age	Reference	1.21 (1.07, 1.36)	1.30 (1.14, 1.49)	<0.01
Model 2: additionally adjusted for perinatal variables[a]	Reference	1.14 (1.01, 1.29)	1.33 (1.16, 1.53)	<0.01
Model 3: model 2 + adjusted for adult life variables[b]	Reference	1.18 (1.05, 1.35)	1.41 (1.23, 1.62)	<0.01
Model 4: model 3 + adjusted for birth weight	Reference	1.18 (1.04, 1.33)	1.33 (1.15, 1.53)	<0.01
Model 5: model 3 + adjusted for BMI at age 18 years	Reference	1.15 (1.01, 1.31)	1.29 (1.12, 1.48)	<0.01
Model 6: model 3 + adjusted for current BMI	Reference	1.11 (0.97, 1.26)	1.24 (1.07, 1.43)	<0.01
Model 7: model 3 + adjusted for birth weight, BMI at age 18 years, and current BMI	Reference	1.08 (0.95, 1.23)	1.13 (0.98, 1.30)	0.10

Data are HRs (95% CI) unless otherwise indicated based on Cox proportional hazards regression models and reflect the risk of type 2 diabetes compared with the reference group. [a]Maternal and paternal age at time of daughter's birth, maternal prepregnancy BMI, maternal weight gain during pregnancy, paternal BMI, maternal and paternal educational level, maternal and paternal occupation, house ownership of parents at the time of the daughter's birth, and nurse's ethnicity, gestational age, breast-feeding status, and family history of diabetes. [b]Participant's husband's educational level, pretax household income, cigarette smoking, height, alcohol intake, total energy intake, and physical activity.

explained by body weight throughout life (20). Results from a substudy within the British NCDS showed that adults aged 33 years who were exposed to maternal smoking during pregnancy had increased risk of diabetes compared with those who were not exposed (16). A study among 7,518 participants of the 1958 British Birth Cohort observed that maternal prepregnancy obesity, maternal smoking, and lower socioeconomic position were associated with impaired glucose tolerance at 45 years of age (35). These associations were not explained by size at birth, but adjustment for adult adiposity attenuated these associations. In line with findings from these previous studies, we observed tendencies for associations of maternal smoking during pregnancy with type 2 diabetes in the offspring. Adjustment for potential confounders or birth weight only partly explained the effect estimates. However, adding BMI in adulthood to the models attenuated the effect estimates toward nonsignificant.

BMI is strongly associated with the risk of type 2 diabetes and might be an intermediate in the association of maternal smoking during pregnancy with the risk of type 2 diabetes. This hypothesis is supported by studies showing consistent associations between fetal smoke exposure and offspring adiposity (13–15). In the same cohort as the current, we previously observed that maternal smoking during pregnancy was associated in a dose-response manner with overweight and obesity in the daughter across adolescence and adult life (15). In addition, paternal smoking was also associated with the risk of overweight and obese in the adult daughter, and this association persisted after adjustment for maternal smoking. The lack of association of maternal smoking during pregnancy with type 2 diabetes after adjustment for BMI in the current study may be explained by the known strong correlation between BMI and type 2 diabetes in adults.

We performed mediation analyses to explore the role of birth weight and adult BMI in the associations of maternal and paternal smoking with the risk of type 2 diabetes. The adult BMI mediation analysis was only significant for paternal smoking ≥15 cigarettes. However, the mediation analysis for the association of maternal smoking with the risk of type 2 diabetes was based on much smaller numbers than the corresponding analysis for paternal smoking. The point estimates from the mediation analyses were almost similar for maternal and paternal smoking (59.6% and 52.9%, respectively). Therefore, our interpretation that the associations of maternal and paternal smoking with type 2 diabetes were largely explained by BMI in adulthood was not only based on the overall significance results from mediation analyses but also based on the different adjustment models and the point estimates from the mediation analyses.

We observed that maternal smoking during the first trimester only was associated with type 2 diabetes in the offspring. In contrast to the effect of continued maternal smoking during pregnancy, the effect of first-trimester-only smoking was independent of birth weight and BMI in adulthood. Previous studies showed that adverse exposures may affect first-trimester fetal development (36). However, first-trimester smoking is not related to a low birth weight (7,11). We cannot explain why first-trimester-only maternal smoking was associated with type 2 diabetes in the offspring independent of BMI in adulthood, whereas continued maternal smoking was not associated. It might be that, in contrast to the effects of continued maternal smoking, the effects of first-trimester-only smoking on glucose metabolism in the offspring are not overshadowed by weight and BMI throughout the life course. Previous studies, also from the same cohort as the current study, did show that first-trimester-only smoking was not, or was to a limited extent, associated with obesity in later life, whereas strong associations have been reported for continued maternal smoking (15). A biological explanation for our observations might be that maternal first-trimester-only smoking leads to other adaptations and adverse postnatal

metabolic consequences than maternal continued smoking during pregnancy. The observed association might also be explained by mothers at risk for adverse health outcomes during pregnancy who quit smoking when pregnancy is acknowledged or just reflect a chance finding.

We observed similar associations of maternal and paternal smoking with the risk of type 2 diabetes in the offspring. Similar, or even stronger, effect estimates for the associations of paternal smoking than for maternal smoking suggest that the associations are explained by unmeasured environmental exposures (13,17). If fetal smoke exposure leads to direct intrauterine programming of insulin resistance, the effects of maternal smoking would be expected to be stronger than the effects of paternal smoking. Therefore, further studies in humans and animals are needed to explore the causality of the associations of fetal smoke exposure with type 2 diabetes in adulthood.

Some methodological issues need to be discussed. To our knowledge, this is the largest study that evaluated the associations of maternal and paternal smoking during fetal life with the risk of type 2 diabetes in the offspring. The major strengths of this study are the large sample size, high follow-up rate, and detailed information about potential confounders. Our study was based on a large cohort study of adult women only. Although we do not expect that the associations of maternal smoking during pregnancy with BMI and type 2 diabetes in adults would differ between men and women, further studies are needed in men. A limitation might be that although the study was embedded in an ongoing prospective cohort study, information about parental smoking during pregnancy was recalled and could not be validated. Also, the mother reported information about paternal smoking. The data collection about smoking during pregnancy was performed without reference to the outcome of the current study. Misclassification of parental smoking might be present, especially for paternal smoking, but is most likely not to be nondifferential with respect to the outcome of interest and would therefore lead to an underestimation of the observed effect estimates. No information about maternal smoking before pregnancy was available. Classifying mothers who quitted smoking before pregnancy as nonsmokers might have led to the underestimation of the effect estimates. Response rates of the follow-up questionnaires were generally higher than 90%. Nonresponse would have led to biased effect estimates only if the associations between maternal smoking during pregnancy and risk of type 2 diabetes would be different among those included and not included in the study. This seems unlikely. Our models were focused on incident cases of type 2 diabetes. We did not include women diagnosed with diabetes before enrollment in the study because of the missing information about year of diagnosis and about type 2 diabetes. Our effect estimates would be underestimated if the associations of maternal smoking during pregnancy with type diabetes in the offspring were stronger in younger cases. This seems unlikely but cannot be excluded. We performed stepwise adjustments for potential confounders related to fetal and early postnatal life and adulthood. However, as in any observational study, our results might still be explained by residual confounding from factors we did not measure, or measured imperfectly, such as maternal or offspring dietary factors or early growth patterns. Also, we did take into account smoking in the adult offspring but had no detailed information about childhood environmental tobacco smoke exposure available. It should be further explored whether the role of residual confounding could be different between the observed associations of maternal and paternal smoking with offspring outcomes.

In conclusion, maternal and paternal smoking during pregnancy tends to be associated with the risk of type 2 diabetes in their daughters. Not early growth but, rather, BMI throughout the life course largely explained these associations. Similar effect estimates for the associations of maternal and paternal smoking with the risk of type 2 diabetes suggest that these associations are caused not only by direct intrauterine mechanisms but also by shared common family-based or lifestyle-related exposures. Results from this study add to the accumulating body of evidence that first-trimester-only and continued fetal smoke exposure not only lead to fetal complications but may also have long-term consequences for body fatness and the corresponding adverse metabolic outcomes.

Funding. The study was supported by a grant from the Netherlands Organization for Scientific Research (NOW-VIDI 016.136.361 to V.W.V.J.).

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

Author Contributions. V.W.V.J., L.L.d.J., and R.M.v.D. analyzed data and wrote the manuscript. W.C.W., H.H., M.J.S., F.B.H., and K.B.M. contributed to the discussion and reviewed the manuscript. V.W.V.J. and L.L.d.J. are the guarantors of this work and, as such, had full access to all 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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