ORIGINAL ARTICLE: ASTHMA

PEDIATRIC PULMONOLOGY **WILEY**

Influence of maternal vomiting during early pregnancy on school-age respiratory health

Sunayna D. Poeran-Bahadoer MSc[1] | Evelien R. van Meel MD[1,2] |
Romy Gaillard MD, PhD[1,3] | Vincent W. V. Jaddoe MD, PhD[1,3] |
Liesbeth Duijts MD, PhD[2,4]

[1]The Generation R Study Group, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

[2]Department of Pediatrics, Division of Respiratory Medicine and Allergology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

[3]Department of Pediatrics, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

[4]Department of Pediatrics, Division of Neonatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

Correspondence
Liesbeth Duijts, MD, PhD, Department of Pediatrics, Division of Respiratory Medicine and Neonatology, Erasmus MC, University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, The Netherlands.
Email: l.duijts@erasmusmc.nl

Abstract

Background: Hyperemesis gravidarum, a clinical entity characterized by severe nausea and excess vomiting, might lead to a suboptimal maternal nutritional status during pregnancy and subsequently to adverse respiratory health in the offspring. The role of common vomiting symptoms on offspring's respiratory health is unclear. We examined the associations of maternal daily vomiting during early pregnancy with childhood respiratory outcomes, and potential explaining factors.

Methods: This study was embedded in a population-based prospective cohort study from early pregnancy onwards among 4232 mothers and their children. Maternal vomiting during early pregnancy was assessed by a questionnaire. At age 10 years, information on current wheezing and ever asthma was obtained by a questionnaire, and lung function was measured by spirometry at our research center. We used multiple regression analyses to assess the associations of maternal daily vomiting during early pregnancy with childhood respiratory outcomes.

Results: Compared to children from mothers without daily vomiting during early pregnancy, children from mothers with daily vomiting during early pregnancy had a higher forced expiratory flow when 75% of the forced vital capacity (FVC) is exhaled (Z-score difference [95% confidence interval, CI]: 0.13 [0.03, 0.23]), and an increased risk of current wheezing and ever asthma ([odds ratio, OR] [95% CI]: 1.75 [1.10, 2.79] and 1.61 [1.13, 2.31], respectively). These associations were fully explained by sociodemographic factors, but not sex or lifestyle-, infectious-, or growth-related factors. Maternal daily vomiting during early pregnancy was not associated with forced expiratory volume in 1 s (FEV_1), FVC, and FEV_1/FVC.

Conclusion: Only sociodemographic factors explain the associations of maternal daily vomiting during early pregnancy with childhood respiratory outcomes.

KEYWORDS
asthma, childhood, hyperemesis gravidarum, vomiting, wheezing

1 | INTRODUCTION

Childhood chronic respiratory diseases are highly prevalent and a major public health problem.[1,2] The fetal programming hypothesis proposes that adverse exposures in early life, including suboptimal maternal nutritional status during pregnancy, could influence the development of chronic respiratory diseases in later life.[3,4] Hyperemesis gravidarum, a clinical diagnosis prevailing in up to 10% of all pregnancies, is characterized by unrelenting nausea and pernicious vomiting and could lead to a suboptimal maternal nutritional status during pregnancy.[5–7] Suboptimal maternal nutritional status during pregnancy due to hyperemesis gravidarum is associated with adverse birth outcomes, such as fetal growth restriction and low birth weight.[8–12] Adverse birth outcomes are associated with increased risks of lower lung function and asthma.[13–15] Thus, hyperemesis gravidarum might be related to respiratory health and potentially mediated by adverse birth outcomes, such as preterm birth and low birth weight.[14,16–22] Hyperemesis gravidarum is difficult to measure in large-scale epidemiological studies.[7] More common and frequent symptoms, such as maternal daily vomiting in early pregnancy are often used, but its role on the development of adverse respiratory health is unclear. Also, sociodemographic and lifestyle factors might affect both maternal daily vomiting in early pregnancy and respiratory health.[6,15,23]

Therefore, we examined in a population-based prospective cohort study among 4232 mothers and their children, the associations of maternal vomiting during early pregnancy with school-age lung function, current wheezing, and ever asthma, measured at 10 years. We also explored whether any association was explained by sociodemographic, lifestyle-, infectious-, or growth-related factors.

2 | MATERIALS AND METHODS

2.1 | Study design

This study was embedded in the Generation R Study, a population-based prospective cohort study from early fetal life onwards in Rotterdam, The Netherlands.[24] The study has been approved by the Medical Ethical Committee of Erasmus MC, University Medical Center Rotterdam, The Netherlands (MEC-2012-165). Pregnant women with an expected delivery date between April 2002 and January 2006 living in Rotterdam were eligible for participation in the study. Of these mothers, 91% (n = 8879) were enrolled during pregnancy. Extensive assessments were performed on mothers, fathers, and their children. Measurements were planned in early pregnancy (gestational age <18 weeks), mid-pregnancy (gestational age 18–25 weeks), and late pregnancy (gestational age >25 weeks). The children formed a prenatally recruited birth cohort that is being followed at least until young adulthood.[24] Written informed consent was obtained from mothers and both parents or legal caregivers of the children. For the present study, we excluded those enrolled after 22 weeks of gestation (n = 1040), who did not have information on vomiting in early pregnancy available (n = 872), or without information on respiratory health (n = 1064). This left 4232 mothers and their children for the current analysis (Figure 1).

2.2 | Maternal vomiting and nausea during early pregnancy

Information on maternal vomiting and nausea during early pregnancy was obtained via questionnaires at enrollment in the study.[25] Pregnant women reported the number of times that they vomited or had nausea during early pregnancy which was divided into five categories: daily; a few days a week; once a week; less than once a week; and never. We compared maternal daily vomiting during early pregnancy, a proxy for hyperemesis gravidarum, with all other maternal vomiting categories combined. This approach is in line with previous studies.[8–12,26–29] Primary analyses were performed using maternal vomiting, and sensitivity analyses were performed using maternal nausea, across similar categories, to examine whether the associations differed between maternal vomiting and maternal nausea.

2.3 | School-age lung function and asthma

At age 10 years (median 9.7; 95% range 8.5–12.6) forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC, and forced expiratory flow when 75% of the FVC is exhaled (FEF_{75}) were measured by spirometry at our research center, according to the European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines.[30] Measures were converted into sex-, age-, height-, and ethnicity-adjusted z-scores, according to the global lung initiative reference criteria.[31] In addition, we included children with spirometry curves with a >5% deviation, but with at least one blow (according to ATS and ERS criteria) with adequate reach and duration of the plateau. We observed no difference in the size or direction of the effect estimates in our analyses when we in- or excluded these children. All spirometry curves and values were assessed by two well-trained researchers and discussed with a pediatric pulmonologist if necessary. Information on wheezing in the past 12 months and every doctor-diagnosis of asthma was obtained at the age of 10 years by questionnaires adapted from the International Study on Asthma and Allergies in Childhood.[32]

2.4 | Covariates

Maternal age and prepregnancy weight were obtained at enrollment. Maternal height (cm) was measured and prepregnancy body mass index (kg/m^2) was calculated. We defined gestational weight gain as the difference between weight before pregnancy and weight measured at 30 weeks of gestation (median 30.2; 95% range 25.5–37.1). Information on maternal educational level, parity, ethnicity, smoking during pregnancy, and psychological distress during pregnancy were obtained via questionnaires during pregnancy. The first-trimester nutritional status of the mother during pregnancy was obtained through a food frequency questionnaire, and total caloric intake (kcal) was calculated.[33] Information on a child's sex, gestational age at birth, and birth weight were available from medical records. We constructed gestational-age-adjusted standard deviation scores (SDS) for

FIGURE 1 Flowchart of the study population. FEF$_{75}$, forced expiratory flow when 75% of the FVC is exhaled; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity
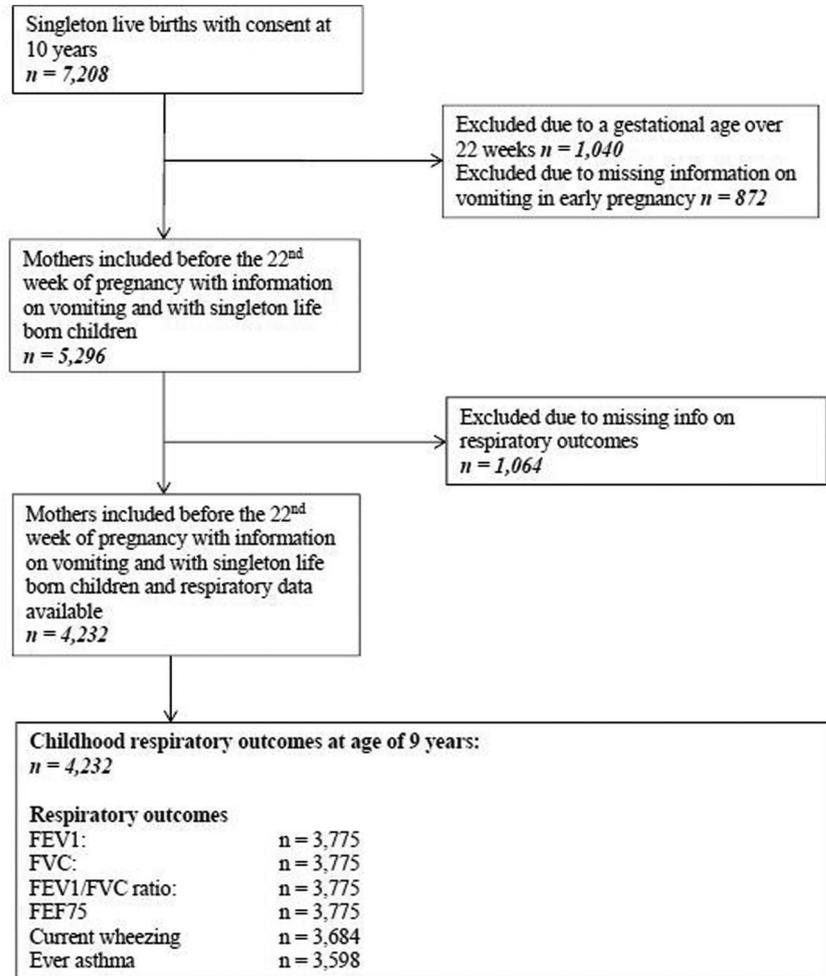
birth weight using North-European growth standards.[34] Infant growth was measured in community health centers according to standardized procedures at 24 months (median 24.9 months [95% range 22.8–34.9]). We created age- and sex-adjusted SDS of these infant anthropometrics within our study population using Dutch reference growth charts.[35] Information on breastfeeding, daycare attendance, and lower respiratory tract infections was obtained via multiple questionnaires until age 1 year.

2.5 | Statistical analysis

First, we examined differences in subject characteristics between mothers with and without daily vomiting during early pregnancy with analysis of variance tests and χ^2 tests. Second, we examined associations of daily vomiting with lung function, ever asthma, and current wheezing using linear and logistic regression models, respectively. For these analyses, we used the following models: (1) a basic model; (2) a sociodemographic factor confounder model (adjusted for child's gender, maternal age, educational level, ethnicity, parity and psychological distress separately) and a lifestyle-related factor confounder model (adjusted for prepregnancy body mass index, total caloric intake and smoking during pregnancy separately); (3) a full sociodemographic factor confounder model including all potential sociodemographic confounders; (4) a full lifestyle-related confounder model including all potential lifestyle-related confounders; (5) a fully adjusted confounder model including all sociodemographic and lifestyle-related confounders together; and (6) a fully adjusted model including all confounders and additionally all potential intermediating infectious and growth-related factors (gestational weight gain, gestational age at birth, gestational age-adjusted birth weight [SDS], infant growth from birth until 2 years of age, breastfeeding, daycare attendance, and lower respiratory tract infections). As correlations between these potential intermediates were lower than 0.6, we simultaneously included these potential intermediates in the model. We performed sensitivity analyses by comparing maternal daily vomiting with never vomiting; by assessing a dose-response relationship using maternal vomiting categories as a continuous variable, from category "never" up to category "daily," and by performing similar analyses using daily nausea during early pregnancy. Potential confounders were selected from literature first, after which they were tested for their relation with daily maternal vomiting and the outcomes of interest, or if the effect estimate of the unadjusted analyses changed ≥10% when we additionally adjusted for a

confounder. Missing data of confounders, assuming that they were missing at random, were imputed by the multiple imputation method using chained equations to select the most likely value for a missing response. Five new datasets were created. All analyses were performed using Statistical Package of Social Sciences version 25.0 for Windows (SPSS Inc).

3 | RESULTS

3.1 | Subject characteristics

In total, 8.8% of all women vomited daily during early pregnancy (Table 1). At age 10 years, 4.7% of all children had wheezing in the past 12 months, and 9.4% were ever diagnosed with asthma. Compared to mothers without daily vomiting during early pregnancy, mothers with daily vomiting during early pregnancy had a lower total caloric intake and total gestational weight gain were younger, more frequently lower educated, and of non-European descent ($p < 0.05$). As compared to mothers included in the analyses, those lost to follow-up more often vomited daily during early pregnancy; their children had a lower gestational age at birth (Table S1).

3.2 | Maternal vomiting and childhood respiratory health

Table 2 shows the associations of maternal daily vomiting during early pregnancy with childhood respiratory health at the age of 10 years. In the unadjusted model, children born to mothers with daily vomiting during early pregnancy had a similar FEV_1 and FVC, and a higher FEF_{75} as compared to those born to mothers without daily vomiting (Z-score difference in FEF_{75} [95% confidence interval, CI]: 0.13 [0.03, 0.23]). Additionally, these children had an increased risk of current wheezing and ever asthma (odds ratio [OR] [95% CI]: 1.75 [1.10, 2.79] and 1.61 [1.13, 2.31], respectively). The association of maternal daily vomiting with respiratory health attenuated into nonsignificant after adjustment for specific sociodemographic factors, explicitly ethnicity, educational level, and maternal psychological distress, but not after adjustment for child's gender, maternal age, parity, and lifestyle-related factors. Additional adjustment for potential infectious and growth intermediating factors did not further change the direction or magnitude of the effect estimates (Table 3). When we restricted the analyses to maternal daily vomiting versus never vomiting only, we found similar results (data not shown). In addition, when studying all categories of maternal vomiting separately, similar associations of maternal daily vomiting with current wheezing and ever asthma were observed (Table S2). In addition, maternal vomiting once a week, as compared to never, was associated with an increased FEF_{75}, even after adjustment for confounders and intermediates. Daily maternal vomiting, as compared to never, was associated with an increased risk of current wheezing and ever asthma, but attenuated into nonsignificant after adjustment for

confounders and intermediates. Sensitivity analyses demonstrated that maternal daily nausea, as compared to no daily nausea, was not associated with childhood respiratory outcomes (Table S3). Figure S1 depicts an overall conceptual model (directed acyclic graph) with all potential confounders and intermediate covariates for clarification of the strategy of analysis, and for interpretation of results.

4 | DISCUSSION

In this prospective cohort study, we observed that daily maternal vomiting during early pregnancy was associated with an increased $FEF_{75,}$ and an increased risk of current wheezing and ever asthma at age 10 years. These associations were fully explained by particular sociodemographic factors. We did not observe any associations of maternal daily vomiting during early pregnancy with other school-age respiratory outcomes.

4.1 | Methodological considerations

We used a population-based prospective cohort design including a large number of subjects whom we studied from fetal life onwards. Information on vomiting during early pregnancy was available for 5296 participants, of which 4232 mothers and their children were involved in childhood follow-up measurements. Comparison analyses of included versus non-included showed that our study group might have been skewed toward a relatively healthy population, which could affect the generalizability of our results. The observed associations would be biased if the associations of maternal vomiting during early pregnancy with childhood outcomes differed between those included and those lost to follow-up. This seems implausible, but cannot be excluded. We used daily maternal vomiting, comparable to previous epidemiological studies.[8–12,26–29] This indicator is only one element attributed to hyperemesis gravidarum, whereas the complete clinical picture also involves maternal weight loss, nutritional deficiencies, electrolyte imbalance, dehydration, and hospitalization. Our findings probably pertain to the less severe end of the spectrum of hyperemesis.

   We observed that women with daily vomiting during early pregnancy had a lower total caloric intake and total gestational weight gain. Considering the poor quantity of mothers with daily vomiting along with extreme weight loss, in this study, we were unable to determine the associations of these incorporated maternal components with respiratory outcomes at school age. More research is necessarily to evaluate the associations of a clinical diagnosis of hyperemesis gravidarum inclusive of different maternal characteristics related to hyperemesis gravidarum with respiratory morbidity and mortality. Detailed information about several maternal and childhood sociodemographic and lifestyle-, infectious-, and growth-related factors was available in this study. Extensive adjustment for sociodemographic factors in our analyses fully explained the associations of maternal daily vomiting during early pregnancy with childhood respiratory outcomes, while adjustment for lifestyle-,

TABLE 1 Maternal and childhood characteristics (N = 4232)[a]

	Total group n = 4232	No maternal daily vomiting during early pregnancy n = 3859	Maternal daily vomiting during early pregnancy n = 373	p
Maternal characteristics				
Age, years	30.8 (4.8)	31.0 (4.7)	28.8 (5.0)	<0.05
Body mass index, kg/m^2	23.5 (4.1)	23.3 (4.0)	25.0 (4.9)	<0.05
Total gestational weight gain, kg	10.6 (4.7)	10.8 (4.5)	8.4 (6.0)	<0.05
Parity (nulliparous), %	60.1 (2538)	60.8 (2343)	52.4 (195)	<0.05
Education (higher education), %	52.2 (2207)	54.9 (2117)	24.1 (90)	<0.05
Ethnicity (European), %	67.9 (2870)	71.0 (2737)	35.9 (133)	<0.05
Total caloric intake, kcal	2064 (543)	2075 (538)	1921 (593)	<0.05
Smoking during pregnancy (yes), %	23.5 (981)	23.6 (900)	22.0 (81)	<0.05
Psychological distress during pregnancy	0.26 (0.06, 0.31)	0.24 (0.06, 0.29)	0.46 (0.14, 0.67)	<0.05
Daily nausea during early pregnancy, %	32.4 (1364)	26.5 (1019)	93.0 (345)	<0.05
History of atopy or asthma, %	37.3 (1556)	37.3 (1422)	37.0 (134)	0.90
Pet keeping, %	47.9 (1652)	48.7 (1652)	38.2 (113)	<0.05
Birth characteristics				
Gestational age at birth, weeks	39.9 (39.1,41.0)	39.9 (39.1,41.0)	39.8 (39.0,41.0)	0.45
Birth weight, g	3443 (543)	3449 (545)	3377 (528)	<0.05
Gestational age adjusted birth weight (SDS)	−0.06 (0.99)	−0.05 (0.99)	−0.20 (0.96)	<0.05
Female sex, %	50.7 (2144)	51.0 (1969)	46.9 (175)	0.13
Child characteristics				
Breastfeeding (yes), %	92.6 (3220)	92.6 (2979)	92.3 (241)	0.89
Daycare attendance first year, %	64.3 (1751)	65.9 (1681)	40.5 (70)	<0.05
Infant weight growth from birth until 2 years, g	9574 (1450)	9558 (1425)	9751 (1701)	<0.05
Lower respiratory tract infections in first year, %	14.5 (322)	14.3 (299)	16.9 (23)	0.41
Body mass index at 9 years, kg/m^2	17.6 (2.7)	17.5 (2.7)	18.5 (3.3)	<0.05
Ever eczema at 9 years, %	23.0 (822)	22.8 (751)	25.4 (71)	0.32
Inhalant allergic sensitization, %	32.2 (948)	32.2 (868)	32.4 (80)	0.96
FEV$_1$, L	2.01 (0.30)	2.02 (0.30)	1.95 (0.30)	<0.05
FVC, L	2.33 (0.36)	2.34 (0.36)	2.25 (0.36)	<0.05
FEV$_1$/FVC, ratio (%)	0.87 (0.06)	0.87 (0.06)	0.87 (0.06)	0.11
FEF$_{75}$, L/s	1.14 (0.35)	1.14 (0.35)	1.14 (0.37)	0.69
Current wheezing at age 10 years, %	4.7 (172)	4.4 (150)	7.5 (22)	<0.05
Ever asthma at age 10 years, %	9.4 (339)	9.0 (300)	13.8 (39)	<0.05

Abbreviations: FEF$_{75}$, forced expiratory flow when 75% of the FVC is exhaled; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; SDS, standard deviation scores.

[a]Values represent means (standard deviation), median (25%–75% range), or percentages (absolute numbers). Differences in subject characteristics between the groups were evaluated using one-way analysis of variance tests for continuous variables and χ^2 tests for proportions.

TABLE 2 Maternal daily vomiting and childhood lung function and asthma (adjustment per confounder separately)

	Childhood lung functionThe difference in standard deviation score (95% confidence interval)					
	FEV_1 n = 3775	FVC n = 3775	FEV_1/FVC n = 3775	FEF_{75} n = 3775	Current wheezing n = 3684	Ever asthma n = 3598
Basic model[a]	−0.02 (−0.13, 0.09)	−0.07 (−0.17, 0.04)	0.09 (−0.02, 0.19)	0.13 (0.03, 0.23)*	1.75 (1.10, 2.79)*	1.61 (1.13, 2.31)*
Sociodemographic factor confounder model[b]						
Gender	−0.01 (−0.12, 0.10)	−0.06 (−0.16, 0.04)	0.09 (−0.02, 0.19)	0.13 (0.03, 0.23)*	1.69 (1.06, 2.69)*	1.55 (1.08, 2.22)*
Age	−0.02 (−0.13, 0.09)	−0.06 (−0.16, 0.05)	0.07 (−0.04, 0.18)	0.12 (0.01, 0.22)*	1.67 (1.05, 2.68)*	1.52 (1.06, 2.19)*
Educational level	−0.04 (−0.15, 0.07)	−0.08 (−0.18, 0.03)	0.07 (−0.04, 0.18)	0.09 (−0.01, 0.19)	1.46 (0.91, 2.34)	1.45 (1.01, 2.10)*
Ethnicity	−0.09 (−0.20, 0.02)	−0.11 (−0.22, −0.01)*	0.04 (−0.07, 0.15)	0.03 (−0.08, 0.13)	1.56 (0.96, 2.51)	1.45 (1.20, 1.75)*
Parity	−0.03 (−0.14, 0.08)	−0.07 (−0.17, 0.04)	0.08 (−0.03, 0.18)	0.12 (0.02, 0.22)*	1.75 (1.38, 2.22)*	1.62 (1.35, 1.94)*
Psychological distress	−0.05 (−0.17, 0.08)	−0.06 (−0.18, 0.06)	0.04 (−0.08, 0.16)	0.09 (−0.03, 0.20)	1.36 (0.84, 2.21)	1.35 (0.93, 1.96)
Lifestyle-related factor confounder model[c]						
Prepregnancy BMI	−0.05 (−0.16, 0.07)	−0.09 (−0.20, 0.03)	0.08 (−0.04, 0.19)	0.13 (0.02, 0.23)*	1.73 (1.09, 2.77)*	1.56 (1.09, 2.24)*
Total caloric intake	−0.03 (−0.13, 0.08)	−0.07 (−0.17, 0.04)	0.08 (−0.03, 0.19)	0.12 (0.02, 0.22)*	1.74 (1.09, 2.78)*	1.59 (1.11, 2.28)*
Smoking during pregnancy	−0.02 (−0.13, 0.09)	−0.06 (−0.16, 0.05)	0.07 (−0.04, 0.18)	0.13 (0.02, 0.23)*	1.75 (1.10, 2.79)*	1.61 (1.12, 2.30)*

Note: Values are Z-score differences or odds ratios (95% confidence interval) from linear or logistic regression models, respectively, with no daily maternal vomiting during early pregnancy as the reference category. Estimates are based on multiple imputed data.

Abbreviations: BMI, body mass index; FEF_{75}, forced expiratory flow when 75% of the FVC is exhaled; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

[a]Basic model is unadjusted.

[b]Sociodemographic factor confounder model is adjusted for each potential confounder separately (gender: child's sex, maternal age, educational level, ethnicity, parity and maternal psychological distress).

[c]Lifestyle-related confounder model is adjusted for each potential confounder separately (prepregnancy BMI, total caloric intake and smoking during pregnancy).

*$p < 0.05$.

infectious-, and growth-related factors did not. However, because of the observational design, residual confounding due to other socio-demographic and lifestyle-related determinants, such as sedentary lifestyle or maternal physical activity, residential area, and childhood nutritional intake, might still be an issue.

4.2 | Interpretation of main findings

Previous evidence suggests that adverse exposures in early life are significantly associated with respiratory morbidity throughout life.[36,37] To the best of our knowledge, no studies have examined the associations of maternal daily maternal vomiting in early pregnancy with respiratory

health in the offspring. Support for mechanisms by which maternal daily vomiting in early pregnancy interferes with respiratory health may lay in the undernutrition status of a mother during pregnancy. Restriction of fetal nutrition and growth due to exposure to maternal undernutrition, and low birth weight and prematurity, may induce tenacious modifications in lung development, leading to unfavorable effects on lung function and respiratory health in later life.[37] This is supported by various epidemiological human and animal studies elucidating mechanisms underlying the associations between maternal undernutrition during critical periods of pregnancy and structural effects on the developing lung and respiratory mechanics.[14,22,38–41] The results of a murine study indicated that undernutrition during pregnancy, in conjunction with hypoxic stress, instigate pulmonary vascular dysfunction in the offspring by an epigenetic

TABLE 3 Maternal daily vomiting and childhood lung function and asthma (fully adjusted models)

	Childhood lung function Difference in standard deviation score (95% confidence interval)					
	FEV$_1$ n = 3775	FVC n = 3775	FEV$_1$/FVC n = 3775	FEF$_{75}$ n = 3775	Current wheezing n = 3684	Ever asthma n = 3598
Full sociodemographic factor confounder model[a]	−0.09 (−0.20, 0.02)	−0.10 (−0.21, 0.01)	0.01 (−0.10, 0.13)	0.00 (−0.11, 0.10)	1.20 (0.73, 1.96)	1.21 (0.82, 1.77)
Full lifestyle-related factor confounder model[b]	−0.04 (−0.15, 0.07)	−0.08 (−0.19, 0.02)	0.08 (−0.03, 0.19)	0.12 (0.01, 0.22)*	1.72 (1.08, 2.76)*	1.54 (1.07, 2.22)*
Fully adjusted confounder model[c]	−0.09 (−0.21, 0.02)	−0.10 (−0.21, 0.00)	0.01 (−0.10, 0.12)	0.00 (−0.11, 0.10)	1.21 (0.73, 1.99)	1.20 (0.82, 1.76)
Fully adjusted model[d]	−0.07 (−0.19, 0.04)	−0.09 (−0.20, 0.02)	0.02 (−0.09, 0.13)	0.01 (−0.10, 0.12)	1.20 (0.72, 2.01)	1.19 (0.80, 1.78)

Note: Values are Z-score differences or odds ratios (95% confidence interval) from linear or logistic regression models, respectively, with no daily maternal vomiting during early pregnancy as the reference category. Estimates are based on multiple imputed data.

Abbreviations: BMI, body mass index; FEF$_{75}$, forced expiratory flow when 75% of the FVC is exhaled; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity.

[a]Full sociodemographic factor confounder model is adjusted for potential confounders (gender: child's sex, maternal age, educational level, ethnicity, parity and maternal psychological distress.

[b]Full lifestyle-related factor confounder model is adjusted for potential confounders (prepregnancy BMI, total caloric intake and smoking during pregnancy).

[c]Fully adjusted confounder model includes all potential confounders.

[d]Fully adjusted model includes all potential confounders and intermediates (gestational weight gain, birth characteristics: gestational age at birth and birth weight, infant growth: growth in weight from birth until 2 years of age, and child characteristics: breastfeeding, daycare attendance in the first year and lower respiratory tract infections in the first year).

*p < 0.05.

mechanism, implying a similar fetal programming effect on pulmonary circulation in humans.[40] However, none of the associations were explained by gestational age or size at birth, even though both characteristics are known to be related to impaired lung function in the offspring.[14,19,21] To this extent, growth-related factors do not play a role in the association of maternal daily vomiting with the respiratory health of the offspring.

Our findings suggest that the associations of daily maternal vomiting during early pregnancy with increased risks of childhood wheezing and asthma are fully explained by psychological distress during pregnancy, ethnicity, lower educational level, younger age, and primigravidas, which is in line with previous studies.[6,23] These potential factors in the psychosocial and sociodemographic pathway have further been delineated as women aged younger than 20 years, with less than 12 years of education, low-income levels, part-time employment status, psychiatric disease, nulliparity, and a non-Caucasian descent, as demonstrated in previous research.[26] We speculate that these women may have less access to healthcare with rare primary and antenatal care visits. Hence, effects may only unveil in extreme extents, such as hyperemesis gravidarum causing approximately famine status or equivalent.

5 | CONCLUSION

We observed that specifically sociodemographic factors explain the associations of maternal daily vomiting during early pregnancy with childhood respiratory outcomes. Future studies should mainly focus on the potential adverse effects to extreme extents.

writing, reviewing, or approval of this report. The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam area, Rotterdam, the Rotterdam Homecare Foundation, Rotterdam, and the Stichting Trombosedienst and Artsenlaboratorium Rijnmond, Rotterdam. The authors gratefully acknowledge the contribution of children and their parents, general practitioners, hospitals, midwives, and pharmacies in Rotterdam.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Romy Gaillard: Conceptualization (equal); writing – review and editing (supporting). **Vincent W. V. Jaddoe**: Supervision (supporting); writing – review and editing (supporting). **Sunayna D. Poeran-Bahadoer, Evelien R. van Meel and Liesbeth Duijts:** substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; drafting the manuscript, revising it critically for important intellectual content; given final; and agreed to be accountable for all aspects of the work.

ORCID

Sunayna D. Poeran-Bahadoer https://orcid.org/0000-0003-1413-0714

Evelien R. van Meel http://orcid.org/0000-0002-0826-9931

Liesbeth Duijts https://orcid.org/0000-0001-6731-9452

REFERENCES

1. Mallol J, Crane J, von Mutius E, Odhiambo J, Keil U, Stewart A. The International Study of Asthma and Allergies in Childhood (ISAAC) phase three: a global synthesis. *Allergol Immunopathol.* 2013;41(2): 73-85.
2. Papadopoulos NG, Arakawa H, Carlsen KH, et al. International consensus on (ICON) pediatric asthma. *Allergy.* 2012;67(8):976-997.
3. Duijts L, Reiss IK, Brusselle G, de Jongste JC. Early origins of chronic obstructive lung diseases across the life course. *Eur J Epidemiol.* 2014;29(12):871-885.
4. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med.* 2008;359(1):61-73.
5. Nurmi M, Rautava P, Gissler M, Vahlberg T, Polo-Kantola P. Incidence and risk factors of hyperemesis gravidarum: a national register-based study in Finland, 2005-2017. *Acta Obstet Gynecol Scand.* 2020;99:1003-1013.
6. Fejzo MS, Trovik J, Grooten IJ, et al. Nausea and vomiting of pregnancy and hyperemesis gravidarum. *Nat Rev Dis Primers.* 2019;5(1): 62.
7. Poeran-Bahadoer S, Jaddoe VWV, Gishti O, et al. Maternal vomiting during early pregnancy and cardiovascular risk factors at school age: the Generation R Study. *J Dev Orig Health Dis.* 2019;11:118-126.
8. Ayyavoo A, Derraik JG, Hofman PL, Cutfield WS. Hyperemesis gravidarum and long-term health of the offspring. *Am J Obstet Gynecol.* 2014;210(6):521-525.
9. Dodds L, Fell DB, Joseph KS, Allen VM, Butler B. Outcomes of pregnancies complicated by hyperemesis gravidarum. *Obstet Gynecol.* 2006;107(2 pt 1):285-292.
10. Vandraas KF, Vikanes AV, Vangen S, Magnus P, Stoer NC, Grjibovski AM. Hyperemesis gravidarum and birth outcomes-a population-based cohort study of 2.2 million births in the Norwegian Birth Registry. *BJOG.* 2013;120(13):1654-1660.
11. Veenendaal MV, van Abeelen AF, Painter RC, van der Post JA, Roseboom TJ. Consequences of hyperemesis gravidarum for offspring: a systematic review and meta-analysis. *BJOG.* 2011;118(11): 1302-1313.
12. Vlachodimitropoulou Koumoutsea E, Gosh S, Manmatharajah B, Ray A, Igwe-Omoke N, Yoong W. Pregnancy outcomes in severe hyperemesis gravidarum in a multi-ethnic population. *J Obstet Gynaecol.* 2013;33(5):455-458.
13. Arigliani M, Spinelli AM, Liguoro I, Cogo P. Nutrition and lung growth. *Nutrients.* 2018;10(7):919.
14. den Dekker HT, Sonnenschein-van der Voort AM, de Jongste JC, et al. Early growth characteristics and the risk of reduced lung function and asthma: a meta-analysis of 25,000 children. *J Allergy Clin Immunol.* 2016;137(4):1026-35.
15. den Dekker HT, Jaddoe VWV, Reiss IK, de Jongste JC, Duijts L. Fetal and infant growth patterns and risk of lower lung function and asthma. The Generation R Study. *Am J Respir Crit Care Med.* 2018; 197(2):183-192.
16. Chortatos A, Haugen M, Iversen PO, et al. Pregnancy complications and birth outcomes among women experiencing nausea only or nausea and vomiting during pregnancy in the Norwegian Mother and Child Cohort Study. *BMC Pregnancy Childbirth.* 2015;15:138.
17. Temming L, Franco A, Istwan N, et al. Adverse pregnancy outcomes in women with nausea and vomiting of pregnancy. *J Matern Fetal Neonatal Med.* 2014;27(1):84-88.
18. Grooten IJ, Painter RC, Pontesilli M, et al. Weight loss in pregnancy and cardiometabolic profile in childhood: findings from a longitudinal birth cohort. *BJOG.* 2015;122(12):1664-1673.
19. Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, et al. Preterm birth, infant weight gain, and childhood asthma risk: a meta-analysis of 147,000 European children. *J Allergy Clin Immunol.* 2014; 133(5):1317-1329.
20. Sonnenschein-van der Voort AM, Gaillard R, de Jongste JC, Hofman A, Jaddoe VW, Duijts L. Foetal and infant growth patterns, airway resistance and school-age asthma. *Respirology.* 2016;21(4):674-682.
21. Sonnenschein-van der Voort AM, Jaddoe VW, Raat H, et al. Fetal and infant growth and asthma symptoms in preschool children: the Generation R Study. *Am J Respir Crit Care Med.* 2012;185(7):731-737.
22. Lawlor DA, Ebrahim S, Davey Smith G. Association of birth weight with adult lung function: findings from the British Women's Heart and Health Study and a meta-analysis. *Thorax.* 2005;60(10): 851-858.
23. London V, Grube S, Sherer DM, Abulafia O. Hyperemesis gravidarum: a review of recent literature. *Pharmacology.* 2017;100(3–4): 161-71.
24. Kooijman MN, Kruithof CJ, van Duijn CM, et al. The Generation R Study: design and cohort update 2017. *Eur J Epidemiol.* 2016;31(12): 1243-64.
25. Jaddoe VW, van Duijn CM, Franco OH, et al. The Generation R Study: design and cohort update 2012. *Eur J Epidemiol.* 2012;27(9): 739-756.
26. Vikanes AV, Stoer NC, Magnus P, Grjibovski AM. Hyperemesis gravidarum and pregnancy outcomes in the Norwegian mother and child cohort—a cohort study. *BMC Pregnancy Childbirth.* 2013;13:169.
27. Peled Y, Melamed N, Hiersch L, Hadar E, Wiznitzer A, Yogev Y. Pregnancy outcome in hyperemesis gravidarum—the role of fetal gender. *J Matern Fetal Neonatal Med.* 2013;26(17):1753-1757.
28. Bailit JL. Hyperemesis gravidarium: epidemiologic findings from a large cohort. *Am J Obstet Gynecol.* 2005;193(3 pt 1):811-814.
29. Paauw JD, Bierling S, Cook CR, Davis AT. Hyperemesis gravidarum and fetal outcome. *JPEN J Parenter Enteral Nutr.* 2005;29(2):93-96.

30. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. *Eur Respir J*. 2005;26(1):153-161.

31. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324-1343.

32. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995; 8(3):483-491.

33. Heppe DH, Medina-Gomez C, Hofman A, Franco OH, Rivadeneira F, Jaddoe VW. Maternal first-trimester diet and childhood bone mass: the Generation R Study. *Am J Clin Nutr*. 2013;98(1):224-232.

34. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). *Acta Paediatr Scand*. 1991;80(8–9):756-762.

35. Fredriks AM, van Buuren S, Burgmeijer RJ, et al. Continuing positive secular growth change in The Netherlands 1955-1997. *Pediatr Res*. 2000;47(3):316-323.

36. Bobolea I, Arismendi E, Valero A, Agusti A. Early life origins of asthma: a review of potential effectors. *J Investig Allergol Clin Immunol*. 2019;29(3):168-179.

37. Maritz GS, Morley CJ, Harding R. Early developmental origins of impaired lung structure and function. *Early Hum Dev*. 2005;81(9):763-771.

38. Pike K, Jane Pillow J, Lucas JS. Long term respiratory consequences of intrauterine growth restriction. *Semin Fetal Neonatal Med*. 2012;17(2): 92-98.

39. Paek DS, Sakurai R, Saraswat A, et al. Metyrapone alleviates deleterious effects of maternal food restriction on lung development and growth of rat offspring. *Reprod Sci*. 2015;22(2): 207-222.

40. Rexhaj E, Bloch J, Jayet PY, et al. Fetal programming of pulmonary vascular dysfunction in mice: role of epigenetic mechanisms. *Am J Physiol Heart Circ Physiol*. 2011;301(1):H247-H252.

41. Dias CM, Pássaro CP, Cagido VR, et al. Effects of undernutrition on respiratory mechanics and lung parenchyma remodeling. *J Appl Physiol*. 2004;97(5):1888-1896.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.