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The role of maternal anorexia nervosa and bulimia nervosa before and during pregnancy in early childhood wheezing: Findings from the NINFEA birth cohort study

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Abstract

Objective

This study evaluates associations of maternal eating disorders (bulimia nervosa, anorexia nervosa, and purging behaviors) with infant wheezing and examines the effects of eating disorders on several wheezing determinants.

Method

We studied 5,150 singletons from the NINFEA birth cohort. Maternal bulimia nervosa and anorexia nervosa diagnoses were ascertained from the questionnaires completed in pregnancy and 6 months after delivery, and were analyzed as: ever diagnosis, only before pregnancy, and during pregnancy. Purging behaviors were assessed for 12 months before or during pregnancy. The associations with wheezing between 6 and 18 months of age were assessed in models adjusted for a priori selected confounders.

Results

Children born to mothers with lifetime eating disorders were at an increased risk of developing wheezing (adjusted OR 1.68; [95% CI: 1.08, 2.60]), and this risk further increased when the disorders were active during pregnancy (2.52 [1.23, 5.19]). Increased risk of offspring wheezing was observed also for purging behaviors without history of eating disorder diagnosis (1.50 [1.10, 2.04]). The observed associations were not explained by comorbid depression and/or anxiety. Bulimia nervosa and/or anorexia nervosa during pregnancy were also associated with several risk factors for wheezing, including maternal smoking, adverse pregnancy outcomes, shorter breastfeeding duration, and day care attendance.

Discussion

The associations of maternal eating disorders with offspring wheezing suggest long-term adverse respiratory outcomes in children of mothers with eating disorders. A better understanding of mechanisms implicated is necessary to help reduce the respiratory disease burden in these children.

1 INTRODUCTION

Wheezing is one of the most frequent respiratory symptoms in infancy (Mallol, Garcia-Marcos, Sole & Brand, 2010) and represents an important predictor of later lung function and asthma development (Duijts, Granell, Sterne & Henderson, 2016). Prenatal and early life are increasingly recognized as the most susceptible periods for lung development and immune system programming (Gollwitzer & Marsland, 2015; Wright, 2010), and several intrauterine and early life exposures are recognized risk factors for wheezing and asthma (Beasley, Semprini & Mitchell, 2015; Rusconi & Gagliardi, 2017).

Maternal mental disorders, particularly depression and anxiety, have been shown to influence fetal development, increase the risk of pregnancy complications, and affect perinatal and later childhood outcomes (Stein et al., 2014). Eating disorders have been also associated with several adverse perinatal and postnatal outcomes, including preterm birth, fetal and infant growth restriction (Micali, Stemmann Larsen, Strandberg-Larsen & Nybo Andersen, 2016; Perrin et al., 2015), different maternal breastfeeding practice (Micali, Simonoff, & Treasure, 2009), and abnormal neurodevelopmental outcomes (Micali, Stahl, Treasure & Simonoff, 2014). To date research on childhood asthma has focused predominantly on maternal depression and anxiety as potentially adverse prenatal mental health exposures, showing that these conditions are positively associated with both wheezing and asthma in children (Andersson et al., 2016; Guxens et al., 2014; Rusconi & Gagliardi, 2017). To our knowledge, no previous studies have evaluated maternal eating disorders in association with infant respiratory outcomes.

Anorexia nervosa and bulimia nervosa are complex disorders influenced both by genetic predisposition and environmental risk factors (Fairburn & Harrison, 2003). Several studies reported high comorbidity between eating and other mental disorders, especially anxiety and depression (Godart, Flament, Lecrubier & Jeammet, 2000; O'Brien & Vincent, 2003). Although it has been shown that anxiety generally precedes anorexia nervosa or bulimia nervosa onset (Godart et al., 2000), anxiety, depression, and eating disorders likely have common risk factors and similar underlying psychopathologic traits (Silberg & Bulik, 2005).

Mental disorders during pregnancy might increase the risk of wheezing and asthma in offspring via several mechanisms (Rusconi & Gagliardi, 2017). They are considered major stressors, which by activating the hypothalamic-pituitary-adrenal (HPA) axis, may increase the production of cortisol and corticotrophin-releasing hormone (CRH) (Beijers, Buitelaar & de Weerth, 2014; Tollenaar, Beijers, Jansen, Riksen-Walraven & de Weerth, 2011). Children prenatally exposed to increased levels of these hormones are likely to have disrupted immune system development, altered HPA axis responses, and airway inflammation (Beijers et al., 2014; Pincus-Knackstedt et al., 2006; Wright, 2010). Dysregulation of HPA axis and cortisol excess are also recognized endocrinopathies of eating disorders (Warren, 2011), and recently, an HPA axis dysfunction, represented by low cortisol decline throughout the day, has been reported in women with eating disorders in pregnancy (Easter et al., 2017).

Other potentially relevant mechanisms that might explain associations of maternal mental health with offspring health outcomes include alterations in maternal immune system and intestinal

microbiota, compromised placental functioning, and epigenetic modifications (Beijers et al., [2014](#)). Finally, maternal eating disorders are strongly associated with several lifestyle related factors (e.g., high smoking prevalence, poor diet) (Stein et al., [2014](#)), adverse pregnancy outcomes (e.g., low birth weight, preterm birth) (Micali et al., [2016](#); Perrin et al., [2015](#)), and postnatal child care (e.g., breastfeeding, mother-child attachment) (Micali et al., [2009](#); Sadeh-Sharvit, Levy-Shiff, Arnow & Lock, [2016](#)) that could be implicated in the associations with offspring health outcomes. For example, some of these factors, such as maternal smoking and pre-pregnancy obesity, have a recognized role also in the onset of childhood wheezing and asthma (Rusconi & Popovic, [2017](#); Silvestri, Franchi, Pistorio, Petecchia & Rusconi, [2015](#)).

In this study, we primarily aimed at determining whether maternal eating disorders, including bulimia nervosa, anorexia nervosa and purging behaviors before and during pregnancy are associated with the risk of infant wheezing. In addition, associations of purging behaviors with offspring wheezing were evaluated in mothers without history of bulimia nervosa and/or anorexia nervosa, capturing in this way subthreshold cases and other feeding or eating disorders characterized by an inappropriate compensatory behavior. To disentangle the role of maternal eating disorders independent of comorbid depression and anxiety, we further estimated the associations of eating disorders with infant wheezing separately in mothers with and without these two comorbidities. Lastly, potential pathways by which maternal eating disorders might influence offspring respiratory morbidity were studied by examining associations of maternal bulimia nervosa and/or anorexia nervosa during pregnancy with well-known pregnancy, perinatal and early-life determinants of infant wheezing.

2 METHOD

2.1 Sample

The NINFEA (Nascita ed INFanzia: gli Effetti dell'Ambiente) is a web-based birth cohort study started in 2005 in Italy (www.progettoninfea.it) (Firestone et al., [2015](#)). Members of the cohort are children of mothers who have access to the Internet and enough knowledge of Italian to complete online questionnaires. In the period 2005–2016 pregnant women were recruited actively, through obstetrics clinics, and passively, via Internet and the media. After the first baseline questionnaire completed anytime during pregnancy, the children are followed up by five additional questionnaires completed by mothers 6 and 18 months after delivery and when children turn 4, 7, and 10 years of age. More details on study design, follow-up periods and specific measures can be found in the Supporting Information (NINFEA study design and Supporting Information Figure S1). The Ethical Committee of the San Giovanni Battista Hospital and CTO/CRF/Maria Adelaide Hospital of Turin approved the NINFEA study (approval N. 0048362, and subsequent amendments) and the informed consent was obtained from all the participants.

Information on exposures, outcome, and potential confounding factors was retrieved from the first three questionnaires. We used the NINFEA database version 11.2017 that consists of 5,385 singletons with complete information on wheezing between 6 and 18 months of age. As missing values did not exceed 5% for any of the variables analyzed in this study, the complete case approach was used, and the final data set included 5,150 children (95.6% of the eligible population). The NINFEA cohort has an 82% response rate at the 18-month questionnaire (Pizzi, [2017](#)).

2.2 Exposures

Maternal eating disorders were assessed from the questionnaires completed during pregnancy (median gestational age at compilation 27.1 weeks, interquartile range 17.7–34.1 weeks) and 6

months after delivery. In particular, during pregnancy mothers were asked to respond to a pre-specified checklist with a number of doctor-diagnosed chronic conditions from which we selected bulimia nervosa and anorexia nervosa. Affirmative response to any of the conditions opens additional questions on whether mother suffered from a condition only before or also during pregnancy. Six months after delivery mothers were asked to respond if any of the conditions was present also during the third trimester of pregnancy.

Purging is a compensatory behavior specific for several eating disorders, including anorexia nervosa binge-eating/purging subtype, bulimia nervosa, purging disorder and other unspecified feeding or eating disorders (American Psychiatric Association, 2013). In the first NINFEA questionnaire, completed during pregnancy, mothers reported self-induced vomiting and laxative/diuretics use to lose weight for 12 months before pregnancy and for the first trimester. The same exposures regarding the third pregnancy trimester were assessed in the questionnaire completed six months after delivery. No information was available on the purging behaviors occurring during the second trimester. As 12 months before pregnancy are closely related to pregnancy itself, both in terms of specific exposures and their medium- and long-term effects, we combined the three exposure-windows available into single exposure (12 months before pregnancy and/or first trimester and/or third trimester), hereafter referred as “purging behaviors” only.

Maternal eating disorders, including doctor-diagnosed bulimia nervosa and anorexia nervosa were analyzed for the following windows of exposure: (a) ever diagnosis, (b) disorder present only before pregnancy, and (c) disorder present during pregnancy. For during pregnancy/close-to-pregnancy period we also combined doctor-diagnosed bulimia nervosa and anorexia nervosa during pregnancy with purging behaviors. Associations of purging behaviors with offspring wheezing were additionally evaluated in mothers without history of bulimia nervosa and/or anorexia nervosa, identifying in this way subthreshold cases, i.e., symptomatic women not diagnosed by a doctor, as well as other feeding or eating disorders characterized by inappropriate compensatory behaviors that were not assessed in the NINFEA study.

Despite the substantial crossover between bulimia nervosa and anorexia nervosa cases and their, at least in part, similar lifestyle and behavioral patterns (Eddy et al., 2008; Strober, Freeman, Lampert, Diamond & Kaye, 2000), the two conditions have distinct clinical presentations (American Psychiatric Association, 2013; Birmingham, Touyz & Harbottle, 2009; Mancuso et al. 2015); thus we performed an exploratory analysis in which we analyzed maternal bulimia nervosa and anorexia nervosa separately.

Due to a high comorbidity between eating disorders and depression and/or anxiety (O'Brien & Vincent, 2003), we also selected doctor-diagnosed maternal depression and anxiety from the checklist of chronic conditions to estimate the associations of maternal eating disorders with infant wheezing independent of these two comorbidities. We categorized the exposure according to the presence or absence of these two comorbidities as follows: (a) no eating disorders (bulimia nervosa during pregnancy and/or anorexia nervosa during pregnancy and/or purging behaviors), (b) eating disorders without comorbid lifetime depression and/or anxiety, and (c) eating disorders with comorbid lifetime depression and/or anxiety.

2.3 Outcome

Infant wheezing was assessed using a question from the standardized International Study on Asthma and Allergies in Childhood (ISAAC) questionnaire (Asher et al., 1995), and was defined as at least one episode of wheezing or whistling in the chest occurred between 6 and 18 months of age. Mothers were additionally asked if a pediatrician confirmed the reported symptoms, with 788 out of

870 (90.6%) of mothers confirming a doctor's diagnosis of wheezing. Hence, maternally reported wheezing was considered as a reliable alternative and was used as the outcome in this study.

2.4 Confounding factors

Potential confounding factors were selected a priori and included maternal age, maternal educational level (low, primary school or less; medium, secondary school; high, university degree or higher), ever maternal asthma, ever maternal atopy, and child's Region of birth (Piedmont Region, other Regions of North Italy, Tuscany Region, and other Regions of Center and South Italy).

2.5 Wheezing determinants

We selected a priori several well-known pregnancy-related and early life determinants of wheezing to assess their associations with maternal bulimia nervosa and/or anorexia nervosa during pregnancy, and in this way investigate possible pathways that might link maternal eating disorders and offspring respiratory morbidity. These data, collected in the first three NINFEA questionnaires, included: maternal smoking during pregnancy and 18 months after delivery, adverse pregnancy outcomes (caesarean delivery and/or gestational age <37 weeks and/or birth weight <2,500 grams), less than 6 months of breastfeeding, and day-care attendance between 6 and 18 months of age.

2.6 Data analysis

Crude and adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI) were estimated using logistic regression models. ORs were used instead of risk ratios as the outcome referred to a specific time-window (i.e., 6–18 months of age). As mothers could have participated in the NINFEA study with more than one pregnancy, cluster sandwich estimators were used to compute robust variance and allow for intragroup correlation. For each exposure two models were fitted: (a) a univariable model and (b) a model adjusted for the a priori selected confounding factors. Multicollinearity in the adjusted models was examined by checking the variance inflation factor (VIF).

We also estimated the adjusted marginal effects of maternal bulimia nervosa and anorexia nervosa on infant wheezing, that is the difference in the prevalence of infant wheezing among exposed and unexposed children when the other explanatory variables are set at their means.

The associations with infant wheezing were also estimated for maternal eating disorders during pregnancy in presence and absence of comorbid depression and/or anxiety. For completeness, we also analyzed the associations of maternal depression and anxiety with infant wheezing.

The associations of maternal bulimia nervosa and/or anorexia nervosa during pregnancy with wheezing determinants were analyzed using logistic regression models adjusted for maternal age and educational level (coded as reported above). When analyzed as single and not the composite “adverse pregnancy outcome”, gestational age (weeks) and birth weight (grams) were modeled as continuous unstandardized variables using linear regression.

Analyses were performed using Stata13 (Stata Corporation, College Station, TX).

3 RESULTS

The main characteristics of the study population are reported in Tables [1](#) and [2](#). Self-reported ever diagnosis of eating disorders (bulimia nervosa and/or anorexia nervosa) had a prevalence of 1.9%,

while 0.6% of mothers suffered from bulimia nervosa and/or anorexia nervosa during pregnancy (Table 1). The overlap between lifetime bulimia nervosa and anorexia nervosa was 32.8%. The prevalence of purging behaviors 12 months before or during pregnancy was 5.0%, and when combined with bulimia nervosa and/or anorexia nervosa active during pregnancy this prevalence increased to 5.5%. There were 891 (17.3%) children who experienced at least one episode of wheezing between 6 and 18 months of age (Table 2).

Table 1. Maternal characteristics

Maternal characteristics	N^a	% Or mean (SD)	Maternal mental disorders	N^a (%)
Age (years)	5,150	33.7 (4.2)	Bulimia nervosa	
Nationality			Ever	58 (1.1)
Born in Italy	4,908	95.3	Only before pregnancy	36 (0.7)
Other	242	4.7	During pregnancy	22 (0.4)
Educational level ^b			Anorexia nervosa	
Low	213	4.1	Ever	61 (1.2)
Medium	1,647	32.0	Only before pregnancy	48 (0.9)
High	3,290	63.9	During pregnancy	13 (0.3)
Parity			Purging behaviors ^c	
0	3,615	71.2	12 months before or during pregnancy	250 (5.0)
≥1	1,465	28.8		
Asthma history			Bulimia nervosa and/or anorexia nervosa	
Yes	418	8.1	Ever	100 (1.9)
No	4,732	91.9		
Atopy history ^d				
Yes	953	18.5	Only before pregnancy	69 (1.3)
No	4,197	81.5	During pregnancy	31 (0.6)
Pre-pregnancy BMI			Bulimia nervosa and/or anorexia nervosa and/or purging behaviors	
≤18.5	456	8.9	During pregnancy	281 (5.5)
18.5–24.9	3,675	71.8	Depression	
25.0–29.9	732	14.3	Ever	196 (3.8)
≥30.0	257	5.0	Only before pregnancy	91 (1.8)
Smoking during pregnancy ^e			During pregnancy	98 (1.9)
Yes	388	7.6	Anxiety	
No	4,733	92.4	Ever	463 (9.0)
Smoking after pregnancy ^f			Only before pregnancy	123 (2.4)
Yes	666	13.0	During pregnancy	330 (6.6)
No	4,447	87.0		

- *Note.* ^aTotal numbers may vary due to missing data. ^bLow, primary school or less; Medium, secondary school; High, university degree or higher. ^cSelf-induced vomiting and/or laxative and/or diuretics use to lose weight 12 months before pregnancy or during pregnancy

among women without history of anorexia nervosa and/or bulimia nervosa diagnosis. ^dEver diagnosed with atopic dermatitis and/or allergic rhinitis. ^eAny smoking during pregnancy. ^fSmoking in the first 18 months after delivery.

Table 2. Perinatal and postnatal children's characteristics

Children's characteristics	N^a	% or mean (SD)
Gender		
Females	2,516	48.9
Males	2,634	51.1
Gestational age (weeks)	5,147	39.7 (1.5)
Mode of delivery		
Caesarean	1,218	25.5
Vaginal	3,554	74.5
Birth weight (g)	5,024	3,267.4 (456.6)
Breastfeeding		
<6 months	1,498	29.5
≥6 months	3,580	70.5
Day□care attendance 6–18 months		
Yes	2,361	46.4
No	2,731	53.6
Wheezing 6–18 months		
Yes	891	17.3
No	4,259	82.7

- *Note.* ^aTotal numbers may vary due to missing data.

The crude and adjusted associations of maternal bulimia nervosa, anorexia nervosa, and purging behaviors with infant wheezing are shown in Table 3. Children born to mothers with lifetime eating disorder diagnosis (bulimia nervosa and/or anorexia nervosa) were at an increased risk of developing wheezing (OR_{adj} 1.68; [95% CI: 1.08, 2.60]), and this risk further increased when the disorders were active during the index pregnancy (OR_{adj} 2.52; [95% CI: 1.23, 5.19]). Moreover, an increased risk of wheezing was observed also in children born to mothers with purging behaviors who never had bulimia nervosa or anorexia nervosa diagnosis (OR_{adj} 1.50; [95% CI: 1.10, 2.04]), indicating the presence of the effect even for subthreshold cases and other eating disorders characterized by purging symptomatology. A positive association of similar magnitude was observed also when doctor□diagnosed bulimia nervosa and anorexia nervosa during pregnancy were combined with purging behaviors (OR_{adj} 1.60; [95% CI: 1.20, 2.13]).

Table 3. Associations between maternal eating disorders and infant wheezing

Maternal eating disorders	Total numbers	Number of cases (%)	Infant wheezing	
			OR_{Crude} [95% CI]	OR_{Adj}^a [95% CI]
Bulimia nervosa and/or anorexia nervosa				
Never	5,050	865 (17.1)	Reference	Reference

Maternal eating disorders	Total numbers	Number of cases (%)	Infant wheezing	
			OR _{Crude} [95% CI]	OR _{Adj} ^a [95% CI]
			(1.00)	(1.00)
Ever	100	26 (26.0)	1.70 [1.09, 2.65]	1.68 [1.08, 2.60]
Only before pregnancy	69	15 (21.7)	1.34 [0.77, 2.36]	1.35 [0.77, 2.35]
During pregnancy	31	11 (35.5)	2.66 [1.27, 5.57]	2.52 [1.23, 5.19]
Bulimia nervosa and/or anorexia nervosa and/or purging behaviors			Reference	Reference
Never	4,800	807 (16.8)	(1.00)	(1.00)
During pregnancy	281	69 (24.6)	1.61 [1.21, 2.14]	1.60 [1.20, 2.13]
Purging behaviors^b			Reference	Reference
No purging behaviors	4,800	807 (16.8)	(1.00)	(1.00)
12 months before or during pregnancy	250	58 (23.2)	1.49 [1.10, 2.03]	1.50 [1.10, 2.04]
Bulimia nervosa			Reference	Reference
Never	5,092	873 (17.1)	(1.00)	(1.00)
Ever	58	18 (31.0)	2.17 [1.25, 3.78]	2.10 [1.23, 3.59]
Only before pregnancy	36	11 (30.6)	2.13 [1.06, 4.25]	2.09 [1.06, 4.11]
During pregnancy	22	7 (31.8)	2.26 [0.92, 5.55]	2.12 [0.89, 5.07]
Anorexia nervosa			Reference	Reference
Never	5,089	880 (17.3)	(1.00)	(1.00)
Ever	61	11 (18.0)	1.05 [0.56, 1.99]	1.07 [0.56, 2.02]
Only before pregnancy	48	6 (12.5)	0.68 [0.30, 1.56]	0.70 [0.31, 1.62]
During pregnancy	13	5 (38.5)	2.99 [0.98, 9.16]	2.88 [0.96, 8.61]

- *Note.* ^aAdjusted for maternal age, educational level, maternal asthma and atopy, and child's region of birth. ^bSelf-induced vomiting and/or laxative and/or diuretics use to lose weight

12 months before pregnancy or during pregnancy among women without history of anorexia nervosa and/or bulimia nervosa diagnosis.

The analyses performed separately on bulimia nervosa and anorexia nervosa revealed an increased risk of wheezing in children born to mothers with bulimia nervosa irrespectively of the analyzed exposure time windows (ever diagnosis OR_{adj} 2.10; [95% CI: 1.23, 3.59], while an indication of an association with anorexia nervosa was observed only if the disease was present during pregnancy (OR_{adj} 2.88; [95% CI: 0.96, 8.61]). In the adjusted models variance inflation factors were less than two for all the variables included, indicating no collinearity problems.

The estimated adjusted prevalence of wheezing between 6 and 18 months of age for children unexposed to maternal bulimia nervosa and/or anorexia nervosa was 17% [95% CI: 16%–18%], with other explanatory variables set at their average values. By contrast, the estimated adjusted wheezing prevalence was 34% [95% CI: 18%–50%] for children of mothers with bulimia nervosa and/or anorexia nervosa during pregnancy (Figure 1).

The prevalence of lifetime depression and/or anxiety in mothers with eating disorders during pregnancy (anorexia nervosa and/or bulimia nervosa and/or purging behaviors) was 20%. Increased risk of wheezing in children born to mothers with eating disorders during pregnancy was observed regardless of presence or absence of maternal comorbid depression and/or anxiety (Table 4). Moreover, maternal anxiety and depression were both associated with infant wheezing (Supporting Information Table S1).

Table 4. Associations of maternal eating disorders during pregnancy in presence and absence of comorbid depression and/or anxiety with offspring wheezing

Maternal eating disorders ^a	Total numbers	Number of cases (%)	Infant wheezing	
			OR [95% CI]	OR_{Adj} ^b [95% CI]
No eating disorders	4,800	807 (16.8)	Reference (1.00)	Reference (1.00)
Eating disorders without depression and/or anxiety	225	54 (24.0)	1.56 [1.14, 2.15]	1.55 [1.12, 2.13]
Eating disorders with depression and/or anxiety	56	15 (26.8)	1.81 [1.00, 3.28]	1.83 [1.02, 3.30]

- *Note.* ^aBulimia nervosa and/or anorexia nervosa and or purging behaviors (self-induced vomiting and/or laxative and/or diuretics use to lose weight) during pregnancy. ^bAdjusted for maternal age, maternal educational level, maternal asthma, maternal atopy, and child's Region of birth.

The associations between maternal bulimia nervosa and/or anorexia nervosa during pregnancy and several prenatal and early life determinants of infant wheezing are presented in Table 5. Mothers with bulimia nervosa and/or anorexia nervosa during pregnancy had 2.5 higher risk of adverse pregnancy outcomes compared with mothers without eating disorders during pregnancy (OR_{adj} 2.51; [95% CI: 1.17, 5.38]). These mothers were also more likely to breastfeed their children for less than 6 months and to send them to day care (Table 5). There was also an indication of a positive association with smoking during and after pregnancy.

Table 5. Associations between maternal bulimia nervosa and/or anorexia nervosa during pregnancy and wheezing determinants

		Maternal smoking			
		Smoking during pregnancy (N=5,052) OR [95% CI] ^a		Smoking after pregnancy (N=5046) OR [95% CI] ^a	
Eating disorders during pregnancy	No	Reference (1.00)		Reference (1.00)	
	Yes	1.90 [0.66, 5.54]		2.05 [0.87, 4.80]	
		Adverse pregnancy outcomes			
		Any (N=4,669) OR [95% CI] ^a	Cesarean delivery (N=4,704) OR [95% CI] ^a	Gestational age (N=5,078) Coefficient [95% CI] ^c	Birth weight (N=4,955) Coefficient [95% CI] ^c
Eating disorders during pregnancy	No	Reference (1.00)	Reference (1.00)	Reference	Reference
	Yes	2.51 [1.17, 5.38]	1.94 [0.90, 4.19]	-0.28 [-0.84, 0.27]	-113.12 [-288.01, 61.78]
		Postnatal outcomes			
		Breastfeeding <6 months (N=5,009) OR [95% CI] ^a	Day care attendance 6–18 months (N=5,026) OR [95% CI] ^a		
Eating disorders during pregnancy	No	Reference (1.00)	Reference (1.00)		
	Yes	2.81 [1.38, 5.70]	2.47 [1.18, 5.17]		

- *Note.* ^aOR, odds ratio, adjusted for maternal age and education. ^bCaesarean delivery and/or preterm birth (<37 gestational weeks) and/or low birth weight (<25,00 gr). ^cUnstandardized regression coefficient, adjusted for maternal age and education. Gestational age in weeks; birth weight in grams.

4 DISCUSSION

Our results, based on the data from the large prospective NINFEA birth cohort study, show that maternal lifetime diagnosis of eating disorders (bulimia nervosa and/or anorexia nervosa) is associated with an increased risk of infant wheezing, and that this risk further increases when the disorders are active during pregnancy. The findings were consistent also for purging behaviors without history of eating disorder diagnosis, and robust to the adjustment for several potential confounding factors. Maternal bulimia nervosa increases the risk of infant wheezing independently of the analyzed exposure time windows, while the increased risk of wheezing for infants born to mothers with anorexia nervosa was found mainly when the disorder was present during pregnancy. Moreover, an increased risk of wheezing in offspring born to mothers with eating disorders was not explained by maternal comorbid depression and/or anxiety, which were also associated with infant

wheezing in our study. Finally, we showed that some of well-known risk factors for wheezing are associated with maternal bulimia nervosa and anorexia nervosa during pregnancy, shedding light on the potential pathways underlying the associations between maternal eating disorders and infant wheezing.

To our knowledge, this is the first study to explore the associations of maternal eating disorders with infant respiratory morbidity. So far, studies have found an increased risk of childhood wheezing and asthma after prenatal exposure to maternal stress, depression, and anxiety (Andersson et al., [2016](#); Guxens et al., [2014](#)), that has been explained by alterations in maternal and fetal HPA axis (Tollenaar et al., [2011](#); Wright, [2010](#)). As dysregulation of HPA axis and cortisol excess have been reported also in women with eating disorders (Easter et al., [2017](#); Warren, [2011](#)), the associations observed in our study might be explained by these hormonal disturbances. One might argue that the alterations caused by eating disorders occurring many years before pregnancy are less likely to have an impact on the developing fetus. In fact, we found stronger associations when eating disorders were active during pregnancy, and analyses focusing on purging behaviors 12 months before or during the index pregnancy confirmed the overall findings. For women reporting eating disorders only before pregnancy we did not have information on the age of onset and remission. Nevertheless, it has been shown that women with history of eating disorders have long-term adverse outcomes and long-lasting impacts on nutrition and body weight, as well as particular child-care practices that could affect the offspring pre- and postnatal development (Beijers et al., [2014](#); Micali & Treasure, [2009](#); O'Brien, Whelan, Sandler, Hall & Weinberg, [2017](#)).

Furthermore, the positive association between eating disorders during pregnancy and infant wheezing was observed irrespectively of comorbid depression and anxiety. However, we evaluated only severe depression and/or anxiety cases diagnosed by a doctor, and measures of subjective depressive/anxious symptoms or negative and stressful life events during pregnancy were not available in the NINFEA questionnaires. The possibility of residual confounding by maternal mental health cannot be thus entirely ruled out, but it is unlikely that residual confounding could fully explain these findings.

Interestingly, we found that even children born to mothers with subthreshold eating disorders and/or other feeding or eating disorders characterized by compensatory behaviors (e.g., purging disorder) are at an increased risk of developing wheezing in early childhood. As purging behaviors had much higher prevalence in the NINFEA cohort compared with bulimia nervosa and/or anorexia nervosa (5% vs. 1.9%) these findings indicate an important role of eating or feeding disorders that fall below the current diagnostic thresholds and highlight their clinical significance.

Maternal eating disorders encompass a complex mixture of asthma-related risk factors, including maternal behaviors and psychopathology, pregnancy-related conditions, perinatal events, and postnatal child-care practice that could be involved in pathways between maternal eating disorders and infant respiratory morbidity. Out of these factors, we selected well-known wheezing determinants and showed that maternal bulimia nervosa and/or anorexia nervosa are associated with several risk factors for wheezing. For example, our finding that mothers with bulimia nervosa and/or anorexia nervosa during pregnancy are at an increased risk of developing adverse pregnancy outcomes is in line with previous studies showing associations of maternal eating disorders with fetal growth restriction, low birth weight and preterm birth (Bulik et al., [2009](#); Micali et al., [2016](#); Watson et al., [2017](#)). In addition, we confirmed that mothers with eating disorders are more likely to smoke during pregnancy (Bulik et al., [2009](#)) and found an increased risk also for smoking after pregnancy that is a proxy for child's exposure to passive smoking. The association of eating disorders during pregnancy with earlier breastfeeding cessation found in our study is in line with findings from the large Norwegian Mother and Child Cohort Study (Torgersen et al., [2010](#)), and in

contrast with findings from the Dutch Generation R study (Nguyen et al., [2017](#)) and the UK ALSPAC study (Micali et al., [2009](#)) that assessed only lifetime eating disorders. Finally, we showed that mothers with eating disorders are more likely to send their children to day-care, which is a well-recognized trigger of early childhood respiratory infections and wheezing (Ball et al., [2000](#)). These findings give an indication of specific lifestyle-related patterns and possible pathways that may link maternal eating disorders to offspring wheezing that merit future, specifically focused, research.

Our study has the strength of being a large birth cohort with a number of maternal and childhood characteristics collected prospectively. Bulimia nervosa and anorexia nervosa are rare conditions whose prevalence in the NINFEA study is consistent with previously reported prevalence in European countries (Keski-Rahkonen & Mustelin, [2016](#); Preti et al., 2009). Despite the low prevalence, we were able to assess the associations of lifetime eating disorders and purging behaviors with infant wheezing by accounting for the most important confounding factors. However, the number of the exposed cases was relatively low for the specific exposure time-windows and in the analyses performed on bulimia nervosa and anorexia nervosa separately. Although the consistency and direction of the associations speak against chance findings, caution is needed when interpreting these results.

All the information collected in the NINFEA cohort is self-reported. Wheezing at this early age might be confused with other respiratory symptoms, but it has been shown that self-reported wheezing is reliable in determining asthma symptoms in the past 12 months (Jenkins et al., [1996](#)), and a physician confirmed >90% of wheezing cases in the NINFEA cohort. Similarly, maternal anorexia nervosa and bulimia nervosa were defined on the basis of a self-reported doctor-diagnosed disorder that could introduce misclassification of the exposure. Nevertheless, it has been shown that pregnant women with self-reported eating disorders are similar to those with hospital-diagnosed eating disorders in terms of demographic, reproductive, lifestyle, and mental health characteristics (Larsen, Nybo Andersen, Olsen, Micali & Strandberg-Larsen, 2016). Moreover, in contrast to health registers that generally include only severe eating disorder cases (Larsen et al., 2016; Watson et al., [2014](#)), self-reported prevalence more likely depicts the actual eating disorders prevalence.

The NINFEA study, as many other birth cohorts, is based on a selected group of participants, with an overrepresentation of highly educated women. However, it has been extensively shown that baseline selection does not imply biased associational estimates in cohort studies (Richiardi, Pizzi & Pearce, [2013](#); Rothman, Gallacher & Hatch, [2013](#)).

Finally, we did not have information on the most prevalent eating disorder diagnoses—binge-eating disorder and otherwise specified feeding or eating disorder (OSFED, e.g., purging disorder, atypical anorexia nervosa), although it is possible that some of the OSFED cases have been captured when analyzing purging behaviors.

In conclusion, we provide evidence linking maternal eating disorders, including bulimia nervosa, anorexia nervosa, and purging behaviors and wheezing in early childhood. The increased risk for children was particularly enhanced if mothers suffered from eating disorders during pregnancy, and was not explained by comorbid maternal depression and anxiety. Maternal bulimia nervosa and anorexia nervosa during pregnancy are also associated with several pre- and postnatal wheezing determinants, suggesting potential pathways that could link maternal eating disorders and infant wheezing. Our results do not allow us to determine whether maternal eating disorders will have long-term effects on the offspring respiratory health, but given the importance of early wheezing in later lung function and asthma development they could have important clinical implications. Further

investigation of the underlying mechanisms and longitudinal behavioral studies will suggest possible areas for preventive intervention.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this manuscript.

REFERENCES

- American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: APA.
- Andersson, N., Hansen, M., Larsen, A., Hougaard, K., Kolstad, H., & Schlunssen, V. (2016). Prenatal maternal stress and atopic diseases in the child: A systematic review of observational human studies. *Allergy*, 71(1), 15–26. <https://doi.org/10.1111/all.12762>
- Asher, M. I., Keil, U., Anderson, H. R., Beasley, R., Crane, J., Martinez, F., Williams, H. C. (1995). International study of asthma and allergies in childhood (ISAAC): Rationale and methods. *European Respiratory Journal*, 8(3), 483–491. <https://doi.org/10.1183/09031936.95.08030483>
- Ball, T. M., Castro-Rodriguez, J. A., Griffith, K. A., Holberg, C. J., Marti-nez, F. D., & Wright, A. L. (2000). Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *New England Journal of Medicine*, 343(8), 538–543. <https://doi.org/10.1056/NEJM200008243430803>
- Beasley, R., Semprini, A., & Mitchell, E. (2015). Risk factors for asthma: Is prevention possible? *Lancet* (London, England), 386(9998), 1075–1085. [https://doi.org/10.1016/s0140-6736\(15\)00156-7](https://doi.org/10.1016/s0140-6736(15)00156-7)
- Beijers, R., Buitelaar, J., & de Weerth, C. (2014). Mechanisms underlying the effects of prenatal psychosocial stress on child outcomes: Beyond the HPA axis. *European Child & Adolescent Psychiatry*, 23(10), 943–956. <https://doi.org/10.1007/s00787-014-0566-3>
- Birmingham, C. L., Touyz, S., & Harbottle, J. (2009). Are anorexia nervosa and bulimia nervosa separate disorders? Challenging the 'transdiag-nostic' theory of eating disorders. *European Eating Disorders Review*, 17(1), 2–13. <https://doi.org/10.1002/erv.896>
- Bulik, C. M., Von Holle, A., Siega-Riz, A. M., Torgersen, L., Lie, K. K., Hamer, R. M., . . . Reichborn-Kjennerud, T. (2009). Birth outcomes in women with eating disorders in the Norwegian mother and child cohort study (MoBa). *International Journal of Eating Disorders*, 42(1), 9–18. <https://doi.org/10.1002/eat.20578>
- Duijts, L., Granell, R., Sterne, J., & Henderson, A. (2016). Childhood wheezing phenotypes influence asthma, lung function and exhaled nitric oxide fraction in adolescence. *European Respiratory Journal*, 47(2), 510–519. <https://doi.org/10.1183/13993003.00718-2015>
- Easter, A., Taborelli, E., Bye, A., Zunszain, P. A., Pariante, C. M., Treasure, J., . . . Micali, N. (2017). Perinatal hypothalamic-pituitary-adrenal axis regulation among women with eating disorders and their infants. *Psychoneuroendocrinology*, 76, 127–134. <https://doi.org/10.1016/j.psy-neuen.2016.11.004>
- Eddy, K., Dorer, D., Franko, D., Tahilani, K., Thompson-Brenner, H., & Herzog, D. (2008). Diagnostic crossover in anorexia nervosa and bulimia nervosa: Implications for DSM-V. *American Journal of Psychiatry*, 165(2), 245–250. <https://doi.org/10.1176/appi.ajp.2007.07060951>
- Fairburn, C. G., & Harrison, P. J. (2003). Eating disorders. *Lancet* (London, England), 361(9355), 407–416. [https://doi.org/10.1016/s0140-6736\(03\)12378-1](https://doi.org/10.1016/s0140-6736(03)12378-1)
- Firestone, R., Cheng, S., Pearce, N., Douwes, J., Merletti, F., Pizzi, C., Richiardi, L. (2015). Internet-based birth-cohort studies: Is this the future for epidemiology? *JMIR Research Protocols*, 4(2), e71. <https://doi.org/10.2196/resprot.3873>
- Godart, N., Flament, M., Lecrubier, Y., & Jeammet, P. (2000). Anxiety disorders in anorexia nervosa and bulimia nervosa: Co-morbidity and chronology of appearance. *European Psychiatry*, 15(1), 38–45. [https://doi.org/10.1016/s0924-9338\(00\)00212-1](https://doi.org/10.1016/s0924-9338(00)00212-1)
- Gollwitzer, E., & Marsland, B. (2015). Impact of early-life exposures on immune maturation and susceptibility to disease. *Trends in Immunology*, 36(11), 684–696. <https://doi.org/10.1016/j.it.2015.09.009>
- Guxens, M., Sonnenschein-van der Voort, A. M. M., Tiemeier, H., Hofman, A., Sunyer, J., de Jongste, J. C., . . . Duijts, L. (2014). Parental psychological distress during pregnancy and wheezing in preschool children: The Generation R Study. *Journal of Allergy and Clinical Immunology*, 133(1), 59–67. <https://doi.org/10.1016/j.jaci.2013.04.044>
- Jenkins, M. A., Clarke, J. R., Carlin, J. B., Robertson, C. F., Hopper, J. L., Dalton, M. F., . . . Giles, G. G. (1996). Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *International Journal of Epidemiology*, 25(3), 609–616. <https://doi.org/10.1093/ije/25.3.609>
- Keski-Rahkonen, A., & Mustelin, L. (2016). Epidemiology of eating disorders in Europe: Prevalence, incidence, comorbidity, course, consequences, and risk factors. *Current Opinion in Psychiatry*, 29(6), 340–345. <https://doi.org/10.1097/ycp.0000000000000278>
- Larsen, P. S., Nybo Andersen, A. M., Olsen, E. M., Micali, N., & Strandberg-Larsen, K. (2016). What's in a self-report? A comparison of pregnant women with self-reported and hospital diagnosed eating disorder. *European Eating Disorders Review*, 24(6), 460–465. <https://doi.org/10.1002/erv.2464>

- Mallol, J., Garcia-Marcos, L., Sole, D., & Brand, P. (2010). International prevalence of recurrent wheezing during the first year of life: Variability, treatment patterns and use of health resources. *Thorax*, 65 (11), 1004–1009. <https://doi.org/10.1136/thx.2009.115188>
- Mancuso, S. G., Newton, J. R., Bosanac, P., Rossell, S. L., Nesci, J. B., & Castle, D. J. (2015). Classification of eating disorders: Comparison of relative prevalence rates using DSM-IV and DSM-5 criteria. *British Journal of Psychiatry*, 206(06), 519–520. <https://doi.org/10.1192/bjp.bp.113.143461>
- Micali, N., Simonoff, E., & Treasure, J. (2009). Infant feeding and weight in the first year of life in babies of women with eating disorders. *Journal of Pediatrics*, 154(1), 55–60.e1. <https://doi.org/10.1016/j.jpeds.2008.07.003>
- Micali, N., Stahl, D., Treasure, J., & Simonoff, E. (2014). Childhood psychopathology in children of women with eating disorders: Understanding risk mechanisms. *Journal of Child Psychology and Psychiatry*, 55(2), 124–134. <https://doi.org/10.1111/jcpp.12112>
- Micali, N., Stemann Larsen, P., Strandberg-Larsen, K., & Nybo Andersen, A. (2016). Size at birth and preterm birth in women with lifetime eating disorders: A prospective population-based study. *BJOG: An International Journal of Obstetrics & Gynaecology*, 123(8), 1301–1310. <https://doi.org/10.1111/1471-0528.13825>
- Micali, N., & Treasure, J. (2009). Biological effects of a maternal ED on pregnancy and foetal development: A review. *European Eating Disorders Review*, 17(6), 448–454. <https://doi.org/10.1002/erv.963>
- Nguyen, A. N., de Barse, L. M., Tiemeier, H., Jaddoe, V. W. V., Franco, O. H., Jansen, P. W., & Voortman, T. (2017). Maternal history of eating disorders: Diet quality during pregnancy and infant feeding. *Appetite*, 109, 108–114. <https://doi.org/10.1016/j.appet.2016.11.030>
- O'Brien, K. M., & Vincent, N. K. (2003). Psychiatric comorbidity in anorexia and bulimia nervosa: Nature, prevalence, and causal relationships. *Clinical Psychology Review*, 23(1), 57–74. [https://doi.org/10.1016/s0272-7358\(02\)00201-5](https://doi.org/10.1016/s0272-7358(02)00201-5)
- O'Brien, K. M., Whelan, D. R., Sandler, D. P., Hall, J. E., & Weinberg, C. R. (2017). Predictors and long-term health outcomes of eating disorders. *PLoS One*, 12(7), e0181104. <https://doi.org/10.1371/journal.pone.0181104>
- Perrin, E. M., Von Holle, A., Zerwas, S., Skinner, A. C., Reba-Harrelson, L., Hamer, R. M., . . . Bulik, C. M. (2015). Weight-for-length trajectories in the first year of life in children of mothers with eating disorders in a large norwegian cohort. *International Journal of Eating Disorders*, 48(4), 406–414. <https://doi.org/10.1002/eat.22290>
- Pincus-Knackstedt, M. K., Joachim, R. A., Blois, S. M., Douglas, A. J., Orsal, A. S., Klapp, B. F., . . . Arck, P. C. (2006). Prenatal stress enhances susceptibility of murine adult offspring toward airway inflammation. *Journal of Immunology*, 177(12), 8484–8492. <https://doi.org/10.4049/jimmunol.177.12.8484>
- Pizzi, C. (2017). Follow-up response rates. Retrieved from <https://www.progettoninfea.it/attachments/39> Preti, A., Girolamo, G. D., Vilagut, G., Alonso, J., Graaf, R. D., Bruffaerts, R., . . . Morosini, P. . . . ESEMeD-WMH Investigators. (2009). The epidemiology of eating disorders in six European countries: Results of the ESEMeD-WMH project. *Journal of Psychiatric Research*, 43(14), 1125–1132. <https://doi.org/10.1016/j.jpsychires.2009.04.003>
- Richiardi, L., Pizzi, C., & Pearce, N. (2013). Commentary: Representativeness is usually not necessary and often should be avoided. *International Journal of Epidemiology*, 42(4), 1018–1022. <https://doi.org/10.1093/ije/dyt103>
- Rothman, K., Gallacher, J., & Hatch, E. (2013). Why representativeness should be avoided. *International Journal of Epidemiology*, 42(4), 1012–1014. <https://doi.org/10.1093/ije/dys223>
- Rusconi, F., & Gagliardi, L. (2018). Pregnancy complications and wheezing and asthma in childhood. *American Journal of Respiratory and Critical Care Medicine*, 197(5):580–588. [Epub ahead of print]. <https://doi.org/10.1164/rccm.201704-0744PP>
- Rusconi, F., & Popovic, M. (2017). Maternal obesity and childhood wheezing and asthma. *Paediatric Respiratory Reviews*, 22, 66–71. <https://doi.org/10.1016/j.prrv.2016.08.009>
- Sadeh-Sharvit, S., Levy-Shiff, R., Arnov, K. D., & Lock, J. D. (2016). The interactions of mothers with eating disorders with their toddlers: Identifying broader risk factors. *Attachment & Human Development*, 18(4), 418–428. <https://doi.org/10.1080/14616734.2016.1164201>
- Silberg, J. L., & Bulik, C. M. (2005). The developmental association between eating disorders symptoms and symptoms of depression and anxiety in juvenile twin girls. *Journal of Child Psychology and Psychiatry*, 46(12), 1317–1326. <https://doi.org/10.1111/j.1469-7610.2005.01427.x>
- Silvestri, M., Franchi, S., Pistorio, A., Petecchia, L., & Rusconi, F. (2015). Smoke exposure, wheezing, and asthma development: A systematic review and meta-analysis in unselected birth cohorts. *Pediatric Pulmonology*, 50(4), 353–362. <https://doi.org/10.1002/ppul.23037>
- Stein, A., Pearson, R. M., Goodman, S. H., Rapa, E., Rahman, A., McCallum, M., . . . Pariante, C. M. (2014). Effects of perinatal mental disorders on the fetus and child. *Lancet (London, England)*, 384(9956), 1800–1819. [https://doi.org/10.1016/s0140-6736\(14\)61277-0](https://doi.org/10.1016/s0140-6736(14)61277-0)
- Strober, M., Freeman, R., Lampert, C., Diamond, J., & Kaye, W. (2000). Controlled family study of anorexia nervosa and bulimia nervosa: Evidence of shared liability and transmission of partial syndromes. *American Journal of Psychiatry*, 157(3), 393–401. <https://doi.org/10.1176/appi.ajp.157.3.393>
- Tollenaar, M., Beijers, R., Jansen, J., Riksen-Walraven, J., & de Weerth, C. (2011). Maternal prenatal stress and cortisol reactivity to stressors in human infants. *Stress*, 14(1), 53–65. <https://doi.org/10.3109/10253890.2010.499485>
- Torgersen, L., Ystrom, E., Haugen, M., Meltzer, H. M., Von Holle, A., Berg, C. K., . . . Bulik, C. M. (2010). Breastfeeding practice in mothers with eating disorders. *Maternal & Child Nutrition*, 6(3), 243–252. <https://doi.org/10.1111/j.1740-8709.2009.00208.x>
- Warren, M. P. (2011). Endocrine manifestations of eating disorders. *Journal of Clinical Endocrinology and Metabolism*, 96(2), 333–343. <https://doi.org/10.1210/jc.2009-2304>
- Watson, H. J., Torgersen, L., Zerwas, S., Reichborn-Kjennerud, T., Knoph, C., Stoltenberg, C., . . . Bulik, C. M. (2014). Eating disorders, pregnancy, and the postpartum period: Findings from The Norwegian mother and child cohort study (MoBa). *Norsk Epidemiologi*, 24(1–2), 51–62. <https://doi.org/10.5324/nje.v24i1-2.1758>
- Watson, H. J., Zerwas, S., Torgersen, L., Gustavson, K., Diemer, E. W., Knudsen, G. P., . . . Bulik, C. M. (2017). Maternal eating disorders and perinatal outcomes: A three-generation study in the Norwegian Mother and Child Cohort Study. *Journal of Abnormal Psychology*, 126 (5), 552–564. <https://doi.org/10.1037/abn0000241>
- Wright, R. (2010). Perinatal stress and early life programming of lung structure and function. *Biological Psychology*, 84(1), 46–56. <https://doi.org/10.1016/j.biopsycho.2010.01.007>