Prenatal Maternal Psychological Distress and Offspring Risk for Recurrent Respiratory Infections

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Abstract

Objective

To assess the relation between maternal prenatal psychological distress, comprising depression and anxiety symptoms and relationship quality, and the risk of recurrent respiratory infections (RRIs) in children up to two years of age. Children with RRIs frequently use health care services and antibiotics. Prenatal maternal psychological distress can be one, previously unidentified risk factor for RRIs.

Study design

The study population was drawn from a population-based pregnancy cohort in Finland (www.finnbrain.fi). Children with RRIs (n = 204) and a comparison group (n = 1,014) were identified by maternal reports at the child age of 12 or 24 months. The Edinburgh Postnatal Depression Scale (EPDS), Symptom Checklist-90 (SCL-90) anxiety subscale, the Pregnancy-Related Anxiety Questionnaire–Revised2 (PRAQ-R2) and the Revised Dyadic Adjustment Scale (RDAS) were used to assess maternal symptoms and parental relationship quality at gestational week 34. Adjustment for maternal postnatal depressive and anxiety symptoms was performed.

Results

Maternal prenatal EPDS (odds ratio [OR] 1.24, 95% confidence interval [CI] 1.08-1.44), SCL-90/Anxiety (OR 1.40, 95% CI 1.01-1.76), PRAQ-R2 (OR 1.28, 95% CI 1.11-1.47), and RDAS (OR 1.32, 95% CI 1.01-1.58) total sum scores were associated with child RRIs by the age of 24 months. Greater number of siblings, shorter duration of breastfeeding and the level of maternal education were also identified as risk factors for child RRIs.

Conclusions

Maternal prenatal psychological distress is linked with higher risk for child RRIs.

Introduction

Respiratory tract infections (RTIs) are the most common infectious diseases among infants and toddlers(1),(2). Most RTIs are caused by respiratory viruses circulating in the community(1). Even in the pneumococcal conjugate vaccine era, RTIs are often complicated by acute otitis media (AOM) and antibiotic use is common(3). Compared with prior decades, the incidence of AOM has decreased, but still almost half of infants experience AOM by age 12 months(3).

Children under two years of age have limited acquired immunity, which among other reasons may lead to recurrent respiratory tract infections (RRIs). About 10% of all children under two years of age suffer from recurrent upper and lower RTIs(4), although the definition of RRIs has not been broadly agreed upon. Previous research has consistently identified parental smoking during and after pregnancy(5),(6), lower socioeconomic status of the family(7), shorter duration of breastfeeding(3),(6), (greater) number of siblings(6), and outside-home daycare(6),(8) as risk factors for RRIs in children. Lately, increasing understanding has been reached, that also exposure to environmental psychosocial stressors prenatally may influence immunity and the risk of RRIs(9),(10). Several studies linking maternal prenatal psychological distress to atopic disorders of child indicate that the in utero environment influences immune development independently of genetic susceptibility (11).

Previous studies do suggest that maternal psychological distress during pregnancy is associated with long-lasting changes in immune function as well as alterations in disease resistance in the offspring(10),(12). Animal experiments have shown that prenatal maternal stress can increase susceptibility to infectious diseases in the offspring(10). However, only few human studies exist on this topic(9), (13), (14),(15). In the Norwegian Mother and Child Cohort Study 2015(14), it was noted that prenatal maternal relationship dissatisfaction and stressful life events were significantly associated with increased frequency of infectious diseases in the offspring after controlling for

crucial confounding factors. Beijers and collegues (13) found that maternal pregnancy related anxiety as well as mothers' circadian cortisol from saliva samples were both associated with an elevated risk for child RTIs. In addition, The Pregnancy-Related Anxiety Questionnaire (PRAQ) first subscale; fear of giving birth , was related to greater use of antibiotics during the first year of life(13).

The health and well-being of children are linked to their parents' physical and emotional health, social conditions, and child-rearing practices(16). The programming effect of early life stress on child RRIs may be driven not only by mothers' individual well-being but also by other environmental factors within the families. During pregnancy, the parental relationship is often the main source of psychological support for both adults. Thus, the parental relationship can be viewed as one of the fundamental sources of stress regulation and its declined quality one of the most important stressors in parents' lives during the prenatal period.

This study aimed at investigating prospectively the impact of maternal psychological distress as measured by maternal reports of depressive or anxiety symptoms and marital satisfaction during the third trimester on the risk of a child's RRIs up to two years of age. We hypothesized that the diverse measures of maternal prenatal psychological distress independently increase the risk of RRIs in infancy and toddlerhood after adjusting for other key environmental factors such as the duration of breastfeeding, number of siblings, parental smoking, socioeconomic status, and postnatal distress symptoms.

Methods

Participants

The FinnBrain Birth Cohort Study (www.finnbrain.fi) is a transgenerational prospective observational study investigating the effects of prenatal and early life stress exposure on child health(17). Recruitment took place at three maternal welfare clinics of a geographically defined

area, which performed pregnancy ultrasound scans for the women eventually referred to give birth at the Turku University Hospital in the Hospital District of Southwest Finland and the Åland Islands in Finland. The recruitment took place between December 2011 and April 2015 and relied on personal contact by research nurses who were placed at the recruitment sites. The cohort consists of 3808 women who attended the free-of-charge ultrasounds in early pregnancy (gestational week [gwk] 12), their 3837 babies and 2623 fathers/partners. Mothers and fathers were considered eligible to participate in the study if they had a verified pregnancy and sufficient knowledge of Finnish or Swedish (the official languages of Finland) to fill in the study questionnaires. Participating parents gave written informed consent for themselves and on behalf of the expected child. The participants were informed that they could discontinue at any time without having to give an explanation and that no monetary compensation was provided for participation. The Ethics Committee of the Hospital District of Southwest Finland approved the study protocol.

Identification of children with and without Recurrent Respiratory Infections (RRIs)

The study population was selected from among the Cohort participants who had responded to the questionnaires by December 2017 (*n*=1,443). Children with RRIs (*n*= 204, one child per family) were identified from maternal reports on a question "Has your child had recurrent infections" (yes/no) at the child age of 12 and/or 24 months. This single question was applied as a method to determine the RRI group, as no absolute consensus exists on the number of infections per year that would define recurrent infections(4). Information on the number and timing (child age) of infections and antibiotic treatments as well as the number of physician visits at ages 3, 6, 12 and 24 months and any physician-assessed pediatric diagnoses were inquired.

Of the entire RRI group, 91 children were included based on the 12-month questionnaire (6 % of cohort children) and the remaining 155 (11% of cohort children) based on the 24-month questionnaire. There were 40 families (20 %) out of the 204 who had responded "yes" to the

question on RRIs both at 12 and 24 months. The group of children without RRIs, later referred to as the comparison group, was also selected on the basis of parental responses on the 12-month and 24-month questionnaires. Responding "no" regarding recurrent infections at both time points was the criterion to be in the comparison group *n*= 1,014 (Figure 1. Flowchart).

Sociodemographic and Other Background Factors

The research questionnaires were either mailed to the participants or could be filled out online, according to each participant's choice. The parents answered the questionnaires at gwks 14, 24, and 34 as well as at child ages of 3, 6, 12, and 24 months. The data on background factors was collected from maternal questionnaires. Educational level was categorized into low (up to 12 years of education), medium (13-15 years) and high (over 15 years). Further, the number of siblings, smoking during pregnancy (yes/no) and during the postnatal period (yes/no), duration of breastfeeding (months), daycare attendance at the child age of 12 months (yes/no) and the number of daycare days per week were assessed. Pregnancy and infant birth characteristics were obtained from the Finnish Medical Birth Register kept by the National Institute for Health and Welfare (www.thl.fi).

Psychological Distress: Symptoms of Depression and Anxiety, and Relationship Satisfaction/Quality

Parental depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS). The EPDS is a widely used, sensitive meter of both postnatal and prenatal depressive symptoms, with 10 items each rated from 0 to 3 (higher scores indicating more depressive symptoms)(18).

Parental symptoms of anxiety were assessed using the Symptom Checklist 90 (SCL-90) anxiety subscale, a reliable and valid symptom measure consisting of 10 items each rated from 0 to 5 (19). Again, higher scores indicate more pronounced symptoms.

Pregnancy-specific anxiety was assessed using The Pregnancy-Related Anxiety Questionnaire–Revised (PRAQ-R2)(20), a 10-item shortened version of the PRAQ. The items of the PRAQ-R2 can be ordered into three subscales. The first subscale, Fear of giving birth, consists of three items such as “I am worried about the pain of contractions and the pain during delivery”. The second subscale, Worries about bearing a physically or mentally handicapped child, consists of four items, including “I sometimes think that our child will be in poor health or will be prone to illnesses“. The third subscale, Concern about own appearance, consists of three items, such as “I am worried about my enormous weight gain”. Scores on each item ranged from 1 to 5.

Relationship satisfaction was assessed using the Revised Dyadic Adjustment Scale (RDAS)(21), a 14-item version of the DAS24, measuring couple/partner adjustment in three domains. Factor 1(F1) Consensus consists items “Career decisions” and “Religious matters” (Always agree, almost always agree, occasionally agree, frequently disagree, almost always disagree, always disagree). Factor 2 (F2) Satisfaction consists items “How often do you discuss or have you considered divorce, separation, or terminating your relationship?” and “How often do you and your partner quarrel?” (All the time, most of the time, more often than not, occasionally, rarely, never). Factor 3(F3) Cohesion consists items “Work together on a project” and “Calmly discuss something” (Never, less than once a month, once or twice a month, once or twice a week, once a day, more often). Each item is scaled from 1 to 6, the total scores thus ranging from 14 to 84. Higher scores represent lower levels of relationship satisfaction. The cutoff score of 36 has been used to separate couples between two groups (distress vs. non-distress) in a previous study(22).

Continuous sum scores of the EPDS, SCL-90/anxiety PRAQ-R2 and RDAS subscale were used, as this general population-based sample was likely to yield a very low number of subjects scoring above the clinical thresholds available.

Statistical Analyses

All statistical analyses were conducted using IBM SPSS 24.0. Sociodemographic and other background data as well questionnaire data were compared between the RRI group and comparison group by using χ^2 or Mann-Whitney U test.

Binary logistic regression was used to study the association between maternal prenatal psychological distress and child RRI status. The dependent variable was RRIs (0=no, 1=yes) and independent variables were duration of gestation, duration of breastfeeding, number of siblings, maternal smoking, maternal level of education, maternal depressive (EPDS) and anxiety (SCL-90/anxiety) symptoms at the child age of 2 years. These covariates were included as they are previously identified and well-established risk factors for RRIs (3),(4),(5),(6),(7). Postnatal symptoms of depression or anxiety were included to control for possible maternal report bias (23),(24). As all the children were not born full-term, gestational age was also included as a potential covariate in the analyses. Due to multicollinearity, separate analyses were performed for each questionnaire (EPDS, SCL-90/anxiety, PRAQ-R2 and RDAS total sum scores). Analyses with prenatal EPDS and RDAS total sum scores were adjusted by maternal EPDS score at the child age of 2 years and the analyses with prenatal SCL-90/anxiety and PRAQ-R2 scores were adjusted by maternal SCL-90/anxiety score at the child age of 2 years.

Results

The distributions and between-groups differences in sociodemographic and other background factors of the children with RRIs (n=204) and the comparison group without RRIs (n=1,014) are presented in Table 1. The majority (77%) of children in the RRI group had more than five respiratory infections before two years of age while 16% of the comparison group reported more than five RTIs ($P < .001$). Children in the RRI group had much more frequent antibiotic treatments than the comparison group before two years of age, as 57% of children in RRI-group had more than

five antibiotic treatments ($P < .001$). Half of the children in the RRI group had tympanostomy tubes inserted, whereas in the comparison group only 4% of the children had tubes inserted (Table 1).

In univariate analyses, group comparisons showed significant differences in all maternal prenatal psychological distress questionnaires (Table 2). Thus, the RRI group mothers reported significantly higher scores on each scale (EPDS, PRAQ-R2, SCL-90/anxiety, RDAS), indicating elevated levels of symptoms of depression ($P < .001$), pregnancy-specific anxiety ($P = .001$), and anxiety ($P = .04$), and lower levels of parental relationship satisfaction ($P= .008$) when compared with the comparison group (Table 2). Also postnatally, the RRI group mothers reported more symptoms of depression, anxiety and lower levels of relationship satisfaction when the child was two years old ($P = .001$, $P = .03$, $P = .003$, respectively) (Table 2). Of the preselected covariates, a significant difference was seen in univariate analyses regarding duration of gestation, breastfeeding and number of siblings between the RRI group and comparison group. No significant difference was observed in maternal education and smoking.

Logistic regression analyses were performed to see if the associations between maternal prenatal psychological distress and child RRIs remained after adjusting for the selected covariates. Analyses with prenatal EPDS and RDAS total sum scores resulted in an OR of 1.24 (95% CI 1.08-1.44) and an OR of 1.32 (95% CI 1.01-1.58), respectively, for child RRIs. Number of siblings and shorter duration of exclusive breastfeeding were also risk factors (Table 3). Regarding the prenatal maternal anxiety symptom questionnaires, ORs for child RRIs were 1.40 (95% CI 1.01-1.76, SCL/90 anxiety scale) and 1.28 (95% CI 1.11-1.47, PRAQ-R2). Maternal level of education was also a significant risk factor in the models including the anxiety questionnaires (Table 3).

To conclude, after consideration of the number of siblings and the duration of breastfeeding, maternal prenatal psychological distress remained as an independent risk factor for the RRIs in our analyses covering the first 24 months of postnatal life (Table 3).

Discussion

Our cohort study demonstrated that maternal symptoms of depression and anxiety and declined marital satisfaction in late pregnancy are associated with recurrent respiratory infections in children after controlling for essential confounding factors. To our knowledge, this is the first study linking maternal psychological distress during pregnancy with offspring RRI risk. Previous research on this topic has not focused on RRIs but rather on a wider spectrum of pediatric infections(9),(13),(14),(15) and has not used such diverse queries on maternal psychological wellbeing as in this study. Prior research has also focused more on the postnatal distress effect of child RRIs on family relations (25).

Greater number of siblings and shorter duration of exclusive breastfeeding were also risk factors for child's RRIs. These findings are in line with previous studies(4). In this study, 57% of the mothers were primiparous. The number of outside-home daycare days is also a previously established risk factor for recurrent infections(4),(8). In our study, no significant difference was seen between the RRI group and comparison group regarding daycare attendance at 12 months of age, but a significant difference was seen regarding the number of daycare days. We did not conduct more detailed analyses on the associations between daycare characteristics and RRIs.

It should be noted that the data on child health and identification of the RRIs were based on maternal reports. Previous studies(24),(25) have suggested that stressed mothers are more likely to seek medical care for minor symptoms that could be managed with family-initiated care. A recent study by Huizink et al(26) suggested that particularly prenatal maternal anxiety—both general anxiety and pregnancy-specific anxiety—were important predictors of almost all aspects of parenting stress later on. It is likely that women with elevated stress levels during pregnancy continue to worry as a parent. In our analyses, maternal prenatal general and pregnancy-specific anxiety, were both risk factors for child's RRIs, along with level of education. This association

between RRIs and education was not seen in the analyses including EPDS and RDAS questionnaires.

Although we cannot completely distinguish the behavioral aspect (*e.g.* distressed mothers are more prone to take their child to doctor appointments, family health behavior(16)) from fetal programming, maternal psychological distress was an independent risk factor for RRIs after adjusting for other important environmental risk factors, placing our results in the context of prenatal and early life stress exposure and its potential effects on the development of the child's immune system. Although it remains unclear how exactly maternal prenatal stress affects the immune system of the offspring, it has been suggested that maternal hypothalamic-pituitary-adrenal (HPA) axis functioning would play a role (13), (27), (28). Both animal and human studies suggest that stress-related maternal cortisol increases fetal exposure to cortisol and can subsequently affect the development of the fetus' immune domains (12), (10). The fetus is exposed to elevated levels of endogenous glucocorticoids in conditions where the levels of glucocorticoids are elevated in the mother or when the placental 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) barrier decreases. Maternal stress may result in secretion of catecholamines, which may down-regulate human placental 11β-HSD2 during gestation (29). This may alter newborn HPA-axis function, which plays an important immunomodulatory role during viral infections (28).

Main strengths of this study are the large comparison group size, prospective study design, the longitudinal measurements during pre- and postnatal periods with extensive measurements of maternal psychosocial stress with validated questionnaires. As this was a questionnaire-based study, report bias may occur. However, the fact that our RRI group clearly differed from the control group in antibiotic treatments and insertion of tympanostomy tubes indicates that the maternal report actually depicts children with exceptionally high rates of RTIs.

During sensitive periods of fetal development, exposure to maternal psychological distress may cause programming effects on future health (30). Previous studies have found an association between maternal psychological distress and childhood atopic diseases (11). Our study showed that prenatal maternal distress should be considered as one potential risk factor for later childhood respiratory infections. As pediatricians, we should work to address maternal stress prenatally to enhance offspring health. We need additional research to further understand the mechanisms and to develop targeted and efficient interventions.

Abbreviations: Respiratory tract infections (RTIs); Recurrent respiratory tract infections (RRIs); Acute otitis media (AOM); The Edinburgh Postnatal Depression Scale (EPDS); Symptom Checklist-90 (SCL-90) anxiety subscale; the Pregnancy-Related Anxiety Questionnaire–Revised2 (PRAQ-R2) and the Revised Dyadic Adjustment Scale (RDAS)

References:

1. Toivonen L, Karppinen S, Schuez-Havupalo L, Teros-Jaakkola T, Vuononvirta J, Mertsola J, et al. Burden of Recurrent Respiratory Tract Infections in Children. Pediatr Infect Dis J. 2016 ;35:362–9.

2. Monto AS, Sullivan KM. Acute respiratory illness in the community. Frequency of illness and the agents involved. Epidemiol Infect. 1993;110:145–60.

3. Chonmaitree T, Trujillo R, Jennings K, Alvarez-Fernandez P, Patel JA, Loeffelholz MJ, et al. Acute Otitis Media and Other Complications of Viral Respiratory Infection. Pediatrics. 2016;137:e20153555–e20153555.

4. Nokso-Koivisto J, Pitkäranta A, Blomqvist S, Jokinen J, Kleemola M, Takala A, et al. Viral etiology of frequently recurring respiratory tract infections in children. Clin Infect Dis. 2002;35:540–6.

5. Jedrychowski W, Flak E. Maternal smoking during pregnancy and postnatal exposure to environmental tobacco smoke as predisposition factors to acute respiratory infections. Environ Health Perspect. 1997; 105:302–6.

6. Nicolai A, Frassanito A, Nenna R, Cangiano G, Petrarca L, Papoff P, et al. Risk Factors for Virus-induced Acute Respiratory Tract Infections in Children Younger Than 3 Years and Recurrent Wheezing at 36 Months Follow-Up After Discharge. Pediatr Infect Dis J. 2017;36:179–83.

7. Sonego M, Pellegrin MC, Becker G, Lazzerini M. Risk factors for mortality from acute lower respiratory infections (ALRI) in children under five years of age in low and middle-income countries: a systematic review and meta-analysis of observational studies. Sankoh OA, editor. PLoS One. 2015;10:e0116380.

8. Fairchok MP, Martin ET, Chambers S, Kuypers J, Behrens M, Braun LE, et al. Epidemiology of viral respiratory tract infections in a prospective cohort of infants and toddlers attending daycare. J Clin Virol. 2010;49:16–20.

9. Tegethoff M, Greene N, Olsen J, Schaffner E, Meinlschmidt G. Stress during pregnancy and

offspring pediatric disease: A National Cohort Study. Env Heal Perspect. 2011;119:1647–52.

10. Merlot E, Couret D, Otten W. Prenatal stress, fetal imprinting and immunity. Brain Behav Immun. 2008;22:42–51.

11. Andersson NW, Hansen M V, Larsen AD, Hougaard KS, Kolstad HA, Schlünssen V. Prenatal maternal stress and atopic diseases in the child: a systematic review of observational human studies. Allergy. 2016;71:15–26.

12. Howerton CL, Bale TL. Prenatal programing: at the intersection of maternal stress and immune activation. Horm Behav. 2012;62:237–42.

13. Beijers R, Jansen J, Riksen-Walraven M, de Weerth C. Maternal Prenatal Anxiety and Stress Predict Infant Illnesses and Health Complaints. Pediatrics. 2010;126:e401–9.

14. Henriksen RE, Thuen F. Marital quality and stress in pregnancy predict the risk of infectious disease in the offspring: The norwegian mother and child cohort study. PLoS One. 2015;10:1–12.

15. Nielsen NM, Hansen AV, Simonsen J, Hviid A. Prenatal stress and risk of infectious diseases in offspring. Am J Epidemiol. 2011;173:990–7.

16. Schor EL, American Academy of Pediatrics Task Force on the Family. Family pediatrics: report of the Task Force on the Family. Pediatrics. 2003;111:1541–71.

17. Karlsson L, Tolvanen M, Scheinin NM, Uusitupa H-M, Korja R, Ekholm E, et al. Cohort Profile: The FinnBrain Birth Cohort Study (FinnBrain). Int J Epidemiol. 2018;47:15–16.

18. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987;150.

19. Derogatis LR, Melisaratos N, Amenson CS, Lewinsohn PM, Campbell DT, Fiske DW, et al. The Brief Symptom Inventory: an introductory report. Psychol Med. Cambridge University Press; 1983;13:595.

20. Huizink AC, Delforterie MJ, Scheinin NM, Tolvanen M, Karlsson L, Karlsson H. Adaption of pregnancy anxiety questionnaire–revised for all pregnant women regardless of parity: PRAQ-R2. Arch Womens Ment Health. 2016 ;19:125–32.

21. Busby, D. M, Christensen, C, Crane, D. R, & Larson JH. J Marital Fam Ther. 1995;21:289–308.

22. Korja R, Piha J, Otava R, Lavanchy-Scaiola C, Ahlqvist-Björkroth S, Aromaa M, et al. Mother's marital satisfaction associated with the quality of mother-father-child triadic interaction. Scand J Psychol. 2016;57:305–12.

23. Louhi-Pirkanniemi K, Rautava P, Aromaa M, Ojanlatva A, Mertsola J, Helenius H, et al. Factors of early infancy and recurrent use of antibiotic therapy. Acta Paediatr. 2004 ;93:1386–90

24. Horwitz SM, Horwitz RI, Morgenstern H. Maternal employment, maternal care and pediatric visits for minor acute illnesses. J Clin Epidemiol. 1993;46:981–6.

25. Louhi-Pirkanniemi K, Rautava P, Aromaa M, Ojanlatva A, Mertsola J, Helenius H, et al. Recurrent antibiotic use in a small child and the effects on the family. Scand J Prim Health Care. 2004 ;22:16–21.

26. Huizink AC, Menting B, De Moor MHM, Verhage ML, Kunseler FC, Schuengel C, et al. From prenatal anxiety to parenting stress: a longitudinal study. Arch Womens Ment Health. 2017 ;20:663–72.

27. Beijers R, Buitelaar JK, de Weerth C. Mechanisms underlying the effects of prenatal psychosocial stress on child outcomes: beyond the HPA axis. Eur Child Adolesc Psychiatry. 2014 ;23:943–56.

28. Bailey M, Engler H, Hunzeker J, Sheridan JF. The hypothalamic-pituitary-adrenal axis and viral infection. Viral Immunol. 2003;16:141–57.

29. Sarkar S, Tsai SW, Nguyen TT, Plevyak M, Padbury JF, Rubin LP. Inhibition of placental 11beta-hydroxysteroid dehydrogenase type 2 by catecholamines via alpha-adrenergic signaling. Am J Physiol Regul Integr Comp Physiol. 2001;281:1966-74.

30. O'Donnell, K.J., Meaney, M.J. Fetal Origins of Mental Health: The Developmental Origins of Health and Disease Hypothesis. Am. J. Psychiatry 2017;174, 319–328.

Figure 1. Study Flow Chart.

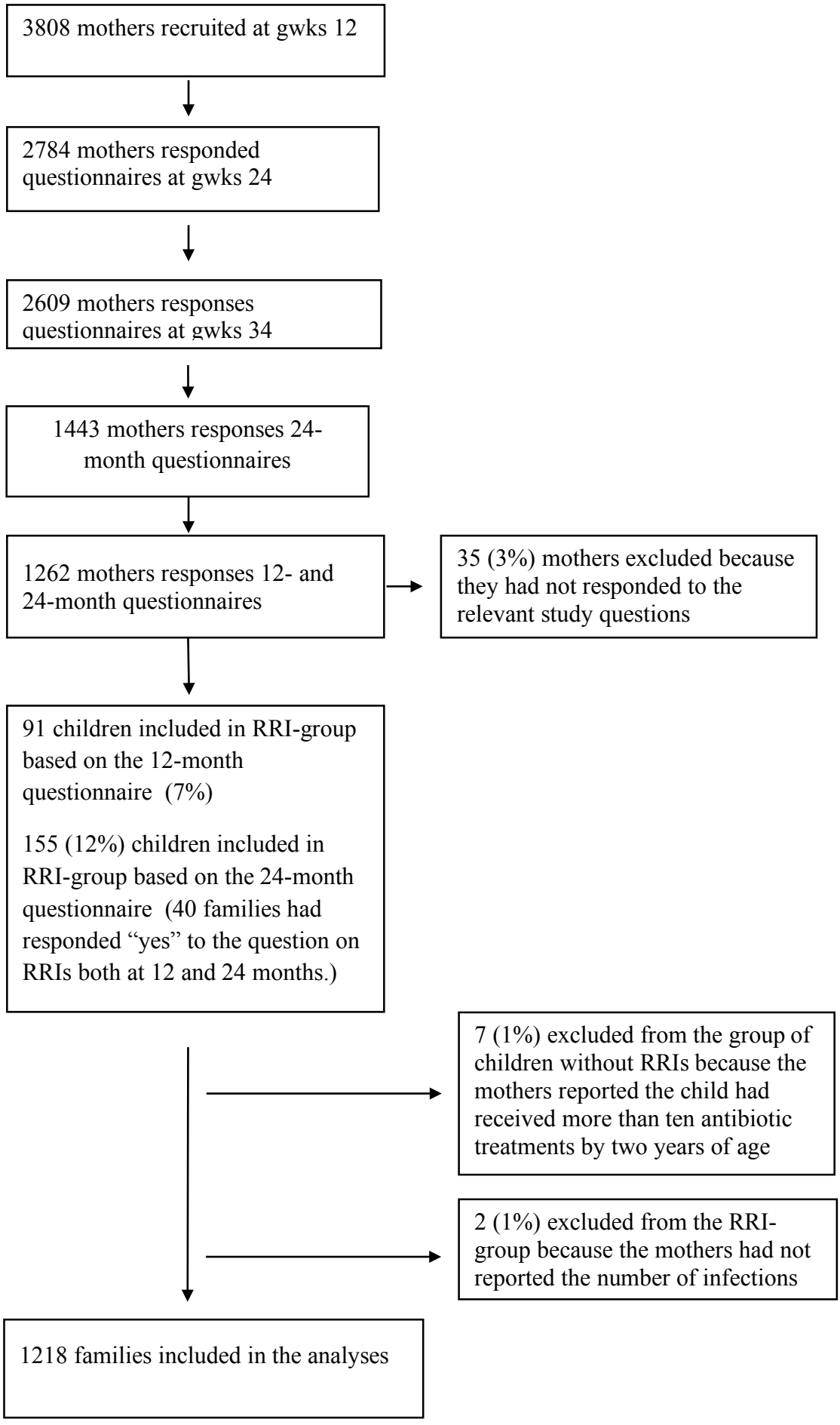

Table 1. Mean (SD) values or percentages of study population characteristics in children with recurrent respiratory tract infections (RRI) and comparison group without RRIs.

		RRI group n=204	Comparison group n=1014	P value
Mothers' age, mean		31.5 (4.4)	31.1(4.3)	.38
Maternal education (%)[a]	**Low**	28.0	28.3	.10
	Middle	35.0	27.7	
	High	37.0	44.0	
Maternal smoking at the child age of 3 months (%)[b] (yes/no)		10.0	6.6	.11
Exclusive breastfeeding/months, mean		3.3 (2.1)	3.7 (2.1)	.02
Child sex male (%)		56	53	.42
Gestational weeks, mean		39.6 (1.6)	39.7 (1.7)	.03
Siblings (%)[c]	**0**	43	60	< .001
	1	41	29	
	2	13	10	
	≥ 3	3	1	
Outside-home daycare at the child age of 12 months (%)[d]		22.0	16.0	.05
Daycare days/week		1.6 (2.1)	1 (1.8)	.02
Tympanostomy tube insertions (%)[e]		59	4	<.001
Antibiotic treatments before one year of age (%)				<.001
	0	39	75	
	1-4	41	24.4	
	5-10	20	0.6	
	>10	0	0	

Antibiotic treatments before two years of age (%)			<.001
0		9	57
1-4		33	38
5-10		49	5
>10		8	0
Infections before one year of age (%)			<.001
0		28	58
1-4		42	37
5-10		28	5
>10		2	0
Infections before two years of age (%)			<.001
0		0	44
1-4		24	40
5-10		53	15
>10		24	1

P values are based on χ^2 and Mann-Whitney U tests for categorical and continuous variables, respectively.

a) RRI-group n=189, comparison group n=973, b) RRI-group n=194, comparison group n=974, c) RRI-group n=187, comparison group n=1013, d) RRI-group n=186, comparison group n=1010, e) RRI-group n=173, comparison group n=984

Table 2. Mean (SD) values of total scores of the Pregnancy-Related Anxiety Questionnaire–Revised2 (PRAQ-R2), the Symptom Checklist 90 anxiety subscale (SCL90/Anxiety), the Edinburgh Postnatal Depression Scale (EPDS) and the Revised Dyadic Adjustment Scale (RDAS) questionnaires in recurrent respiratory tract infections (RRI) and comparison groups

		Mothers		
		RRI group[1]	Comparison group[2]	P value
PRAQ-R2	gwks 34	24.2(6.9)	22.6 (6.5)	.001
SCL90/Anxiety	gwks 34	3.8 (4.5)	3.0 (3.8)	.04
	child 24 mo	3.5 (4.3)	2.5 (3.8)	.03

EPDS	gwks 34	5.6 (4.2)	4.4 (4.0)	<.001
	child 24 mo	5.4 (4.1)	4.3 (4.1)	.001
RDAS	gwks 34	32.1 (8.0)	30.4 (6.0)	.008
	child 24 mo	34.0 (8.6)	31.7 (7.4)	.003

Data available N at gestational weeks (gwks) 34 /at child 24 months (mo): 1) PRAQ 188/-, SCL 191/177, EPDS 192/177, RDAS 189/169; 2) PRAQ 983/-, SCL/Anxiety 982/1006, EPDS 986/1006, RDAS 967/967

P values are based on Mann-Whitney U tests.

Table 3. Results of binary logistic regression analyses on maternal psychological distress at gestational weeks 34 predicting child recurrent respiratory tract infections (RRIs) by the age of two years (N= 1218) separately for each questionnaire (EPDS, SCL90/Anxiety, PRAQ-R2, RDAS).

MODEL 1	**B**	**P value**	**OR**	**95% CI**
EPDS at gwks 34	0.073	.003	1.24	1.08-1.44
The duration of breastfeeding	-0.106	.02	0.90	0.82-0.98
N siblings	0.278	.008	1.32	1.08–1.62
The duration of gestation	-0.038	.53	0.96	0.86-1.08
Maternal level of education (ref. High)		.06		
Low	-0.313	.21	0.73	0.45-1.20
Middle	0.295	.17	1.34	0.89-2.05
Maternal smoking	0.143	.70	1.15	0.57–2.34
EPDS at the child age of 2 years	0.014	.60	1.01	0.97-1.06
MODEL 2				
SCL90/Anxiety at gwks 34	0.067	.006	1.40	1.01-1.76
The duration of breastfeeding	-0.102	.02	0.9	0.83-0.99
N siblings	0.303	.003	1.36	1.11–1.67
The duration of gestation	-0.048	.42	0.95	0.85-1.07
Maternal level of education (ref. High)		.045		
Low	-0.306	.22	0.74	0.45-1.20
Middle	0.322	.14	1.38	0.90-2.11
Maternal smoking	0.187	.60	1.2	0.60–1.66
SCL90/Anxiety at the child age of 2 years	0.009	.74	1.00	0.96-1.1

MODEL 3				
PRAQ-R2 at gwks 34	0.049	.001	1.28	1.11-1.47
The duration of breastfeeding	-0.103	.02	0.90	0.83-1.00
N siblings	0.378	<.001	1.46	1.18-1.80
The duration of gestation	-0.034	.58	0.9	0.83-0.99
Maternal level of education (ref. High)		.048		
Low	-0.316	.21	0.73	0.45-1.20
Middle	0.311	.15	1.37	0.89-2.10
Maternal smoking	0.134	.72	1.14	0.55-2.38
SCL90/Anxiety at the child age of 2 years	0.020	.38	1.02	0.98-1.08
MODEL 4				
RDAS at gwks 34	0.046	.003	1.32	1.01-1.58
The duration of breastfeeding	-0.110	.02	0.90	0.82-0.98
N siblings	0.280	.007	1.32	1.08-1.62
The duration of gestation	-0.049	.42	0.95	0.85-1.07
Maternal level of education (ref. High)		.07		
Low	-0.286	.25	0.75	0.46-1.23
Middle	0.301	.17	1.35	0.88-2.08
Maternal smoking	0.132	.72	1.14	0.56-2.32
EPDS at the child age of 2 years	0.037	.08	1.04	1.00-1.08

Independent variables: EPDS, SCL90/Anxiety ,PRAQ-R2 total sum, RDAS total sum, at gestational weeks 34, duration of breastfeeding, number of siblings, duration of gestation, maternal smoking and level of education. Mothers' EPDS or SCL90/Anxiety score at the child age of 2 years.

The effect of a rise on the EPDS score on the RRI risk as OR was calculated by using a 3-point rise, i.e., minimum vs. maximum points per question (max. sum 30 points), SCL score OR by using a 5-point rise (max. sum 50), PRAQ-R2 total sum score OR by using a 5-point rise (max. sum 50) and RDAS total sum score OR was estimated by using a 6-point rise (max. sum 84)

RDAS: The Revised Dyadic Adjustment Scale; EPDS: The Edinburgh Postnatal Depression; SCL90/Anxiety: Symptom Checklist 90 (SCL-90)/anxiety subscale; The Pregnancy-Related Anxiety Questionnaire–Revised (PRAQ-R2)