Perinatal risk factors and reactive attachment disorder: a nationwide population-based study

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Short running title: Perinatal risk factors and reactive attachment disorder

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Abstract

Aim: To examine the association between several perinatal and obstetric risk factors and reactive attachment disorder in children diagnosed in specialized services.

Methods: In this nested case control study, 614 cases with reactive attachment disorder and 2,423 controls matched with age and sex were identified from Finnish national registers. Conditional logistic regression was used to examine the association between a number of perinatal risk factors and reactive attachment disorder.

Results: In the adjusted analysis, a low birthweight of <2,500 grams was associated with an increased odds of reactive attachment disorder, with an odds ratio (OR) of 1.96 and 95% confidence interval (CI) of 1.17, 3.30 and a birthweight of 4,000-4,499 grams was associated with decreased odds OR 0.49 (95% CI 0.31, 0.75). The odds for being diagnosed with reactive attachment disorder increased with a gestational age of <32 weeks OR 3.72 (95% CI 1.52, 9.10), induced labour OR 1.34 (95% CI 1.03, 1.75) and monitoring in a neonatal intensive care unit (NICU) OR 1.67 (95% CI 1.09, 2.55).

Conclusion: We found associations between low birthweight, preterm birth, NICU admission and reactive attachment disorder. The findings add to the current literature on the understanding of the development of reactive attachment disorder in children.

Keywords: Birthweight, obstetric risk factors, prematurity, reactive attachment disorder, socio-emotional development.

Key Notes

No previous studies have examined the perinatal and obstetrics risk factors associated with reactive attachment disorder in children.

Infants born very prematurely, or with a very low birth weight, have increased risks of reactive attachment disorder.

We demonstrated associations between low birth weight, preterm birth, NICU admission and reactive attachment disorder.

List of abbreviations:

CI: confidence interval

DSM: Diagnostic and Statistical Manual of Mental Disorders

ICD: International Classification of Diseases

NICU: neonatal intensive care unit

OR: odds ratio

SES: socioeconomic status

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Introduction

Reactive attachment disorder is a childhood disorder that affects social functioning. Children with reactive attachment disorder are ambivalent in seeking comfort from caregivers and demonstrate emotional withdrawal, lack of social approach, reduced positive affect and unexplained fearfulness or irritability (1,2). Reactive attachment disorder is generally diagnosed before the age of 5 years, and is mostly diagnosed among maltreated children, children in foster care and children experiencing severe deprivation (3). The diagnosis is made after careful clinical interview and observation, and is based on the criteria described in both the International Classification of Diseases, 10th Revision (ICD-10), published in 1992, and in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, published in 2013 (DSM-5). Reactive attachment disorder has been associated with increased risks of comorbidity, including emotional, behavioural and learning difficulties (3). Children with reactive attachment disorder symptoms have difficulties expressing their needs and desires in socially adaptive ways affecting their cognitive functioning (4). Reactive attachment disorder has been linked to a range of negative outcomes, including both externalizing and internalizing problems, depression and poor social relationships (5).

Most of the studies on reactive attachment disorder have been conducted in clinical settings and have concerned the prevalence, phenotypic characteristics and comorbidities of the disorder. The etiological studies on reactive attachment disorder have mostly been conducted among deprived populations and have concentrated almost solely on psychosocial factors. In particular, these have included insufficient caregiving such as social neglect or deprivation and repeated changes of primary caregivers, which is usually considered the strongest predictive factor (1,2,6). However, individual qualities, such as physical health, cognitive capacity and temperament, also influence the psychosocial circumstances of a developing child (7). In addition, a range of parental attributes may influence how the child forms attachments, such as psychopathology and adverse life events (8). Preterm birth influences the interaction between mothers and infants. Newborn infants are biologically pre-programmed to develop a secure bond with their caregiver (9). This

formation of mother-infant bond and/or interaction might be at risk in preterm infants due to interrupted psychological growth to become a mother, weak and unspecific behavioural cues of a preterm born infant, mother-infant separation during the care in Neonatal Intensive Care Unit (NICU) (10). In addition, preterm birth may predispose the child to cognitive or physical health problems (11). The mother-child attachment might be affected by the severe complications during and after pregnancy. The obstetric complications affect mother's recovery, altering the circumstances at beginning of attachment relationship with the infant (8). No previous clinical or population-based studies have examined perinatal risk factors, such as preterm birth and obstetric complications, in relation to childhood reactive attachment disorder.

The aim of this study was to examine the associations between a number of perinatal and obstetric risk factors and reactive attachment disorder in children. The perinatal risk factors included birthweight, gestational age, NICU admission, induced labour, uterine bleeding, maternal hypertension, birth presentation, birth type, Apgar score at one minute and umbilical artery pH. We hypothesized that both preterm birth and obstetric complications would be associated with increased risks for reactive attachment disorder.

Methods

This nationwide population-based study was based on a nested case-control design and it used a number of national registers to identify the cases, the controls and their parents. The potential study population comprised of 964,929 singleton children born alive in Finland between 1 January 1996 and 31 December 2012. The Care Register for Health Care (CRHC) was used to obtain the patient's personal identity code, date of birth, sex, the dates of any medical admissions and discharges and any primary diagnoses at discharge, along with three subsidiary diagnoses. The CRHC was also the source for any diagnoses of maternal and paternal psychopathology. The Finnish Central Population Register was used to retrieve the demographic characteristics of the cases and controls. The Finnish Maternal Birth Register was used to collect information on the child's birth place, the mother's marital

status, maternal smoking, maternal SES, growth indicators and obstetric complications. These registers, and their linkages, have previously been described in detail (12).

Study participants

We used the ICD-10 code F94.1 to identify all singleton children born alive with reactive attachment disorder (n=614) in the CRHC during the study period, and without any diagnosis of severe or profound intellectual disability (F72 and/or F73) or pervasive developmental disorders (F84). The controls (n=2,423) were also singleton children, who were born alive in Finland during the same time period without any diagnosis of reactive attachment disorder, severe or profound mental retardation (F72 and/or F73), pervasive developmental disorders (F84) or anxiety disorders (F 40-42 and/or F93). Each case was matched with four controls (1:4) based on their date of birth (±30 days) and sex.

The children with severe or profound intellectual disability were excluded from the cases and controls, because the severity of their illness would have caused difficulties in assessing reactive attachment disorder symptoms. Children diagnosed with pervasive developmental disorders were excluded from the cases and controls, to increase the reliability of the reactive attachment disorder diagnoses, as ICD-10 states that pervasive developmental disorder is an exclusion criterion for diagnosing reactive attachment disorder. (1) Children with pervasive developmental disorder display similar characteristics to those with reactive attachment disorder, and could be misdiagnosed as having reactive attachment disorder in the early years of life. Children with anxiety disorders were not included among controls because this study was a sub-study of larger anxiety related study and therefore the diagnosis of anxiety were excluded from controls in the initial sample.

Diagnosing reactive attachment disorder in Finland

The Government universally funds health care services in Finland. All children make at least 15 age-specific visits to child health clinics between birth and 7 years of age, with most of the appointments taking place during the first year of life. Registered nurses and

family doctors manage the appointments, and they can refer the children to psychologists and social workers if needed. During these visits, information on the child's physical, social and psychological development is documented, together with information about their family and living circumstances, including whether they attend school or day care. If a health care provider suspects reactive attachment disorder, or any more unspecific of social functioning problems, the child is referred to clinicians working in specialized mental health services.

Clinical diagnoses of reactive attachment disorder are based on ICD-10 criteria, which are routinely registered at each visit to specialized health care services in the country's CRHC for Health Care. In Finland, teams of professionals usually work together in child psychiatric clinics and these usually include child psychiatrists, psychologists and social workers or psychiatric nurses. Several professionals examine the child, on its own, and with primary caregivers, and the mental health team discusses the findings. Extensive interviews are conducted with the parents and information on the child is obtained from their day care centre and/or school. The child is observed in different surroundings to see how they interact with their peers and with adults.

Validation of reactive attachment disorder diagnoses

We conducted the validation of reactive attachment disorder diagnoses for a sub-group of cases (n=40) by reviewing their medical records. We searched the patient record system of the Hospital District of Southwest Finland that provides secondary and tertiary level treatment. The children were born between 1.1.1996 and 31.12.2011 and diagnosed by 31.12.2012.

Two reviewers assessed the medical records for all 40 cases: a registered psychiatric nurse and a 5th year medical student. Professor in child psychiatry (Andre Sourander) and specialist in child psychiatry (Terhi Luntamo) supervised the process. The medical records were studied for reactive attachment disorder diagnoses based on ICD-10 criteria shown in Table 1. In addition, we studied for inadequate childcare in the form of psychological abuse or neglect (harsh punishment, persistent failure to respond to the child's

overtures, or grossly inept parenting), or physical abuse or neglect (persistent disregard of the child's basic physical needs, repeated deliberate injury, or inadequate provision of nutrition). (1) To determine the final case status, the detailed recordings from each reviewer were compared and reviewed by the specialist in child psychiatry (Terhi Luntamo).

Growth indicators

In our study, birthweight was categorized as under 2,500 grams, 2,500- 3,999 (reference), 4,000-4,499 and 4,500 grams or more. Gestational age was classified into four categories: less than 32 weeks, 32-36, 37-41 (reference) and 42 weeks or more. The subjects' gestational ages were calculated according to the mothers' last menstrual period.

Obstetric complications

The Apgar score at one minute was classified as less than 7, 7-8 and 9-10 (reference). Neonatal treatment was classified as either normal follow up (reference) or monitoring, either in a maternal postpartum department or a NICU. Birth presentation was classified as cephalic (reference), breech, or other. Birth type was classified as vaginal cephalic (reference), vacuum extractor or forceps, or vaginal breech, planned Caesarean section, other Caesarean section including urgent and emergency Caesarean section, and unknown. Uterine bleeding that required hospitalization, induced labour and maternal hypertension that required hospitalization were all dichotomized as yes or no (reference). Umbilical artery pH was analysed as a continuous variable.

Covariates

The covariates were considered for inclusion in the analyses based on our previous study (13). They included maternal age, paternal age, maternal SES, maternal smoking, marital status, previous births, maternal psychopathology and paternal psychopathology. The covariates were considered for inclusion in the statistical models, if they met both of the following criteria: 1) association with perinatal and obstetric risk factors ($p < 0.1$); 2)

association with childhood reactive attachment disorder ($p < 0.1$). This is in accord with standard epidemiologic texts, and limits the possibility for over adjustment of the variables that can reduce the efficiency of the estimation process, without reducing the bias (14). Each examined risk factor was adjusted with their respective covariates meeting the criteria mentioned above. Maternal and paternal age were both split into two categories based on whether they were below or above the median values, which were 29 years for the mothers and 31 years for the fathers. Maternal SES was categorized as upper white collar workers, lower white collar workers, blue collar workers and others. Maternal smoking was dichotomized as yes or no. Marital status was dichotomized as being single or as married/ in a relationship. Previous birth was split into none or more than one. Maternal and paternal psychopathology were both defined as having a history of any psychiatric disorder (ICD-10 codes F10-99, ICD-9 codes 291-316 and ICD-8 codes 291-308 in the CRHC. Maternal and paternal psychopathology were dichotomized as yes or no. The data on paternal characteristics were missing if the paternity of the child was unknown.

Statistical analysis

The associations between covariates and risk factors, and between covariates and reactive attachment disorder, were examined using Pearson's chi-square test and the statistical significance for selecting the covariates was $p<0.1$.

We analysed the associations between the various risk factors and a diagnosis of reactive attachment disorder using conditional logistic regression. The associations for each risk factor were measured using odds ratios (ORs) and two-sided 95% confidence intervals (95% CI). The results were then adjusted for the covariates i.e. each risk factor was adjusted with the respective covariates that met our a priori criteria (see "Methods / Covariates"). A two-sided p value of <0.05 was used to test the significance.

The statistical analyses were performed with SAS statistical software, version 9.4 (SAS Institute Inc, Cary, NC, USA).

Ethical approval

The approval for the validation study was obtained from the ethics committee of the Hospital District of Southwest Finland and Turku Clinical Research Centre. The approval for overall study was provided by the Ministry of Social Affairs of Health and the National Institute of Health and Welfare.

Results

The total number of reactive attachment disorder cases included in this study was 614. Of total reactive attachment disorder cases, 61% were male.

Of the total cases (n=614) included in the study, 40 cases were selected for validation purposes. Of 40 cases, three cases had incomplete information and the evaluation was therefore not possible. Only two cases did not fulfil the diagnostic criteria. The full ICD-10 diagnostic criteria for reactive attachment disorder were fulfilled in 35 out of 37 cases (94.5%). In all the examined cases, psychological and/or physical abuse or neglect was present.

Relationships between the covariates and each perinatal and obstetric risk factor, and reactive attachment disorder, are provided in Table 2. The covariates that were associated with any perinatal and obstetric risk factors and reactive attachment disorder were maternal age, paternal age, maternal SES, maternal smoking, marital status, maternal psychopathology and paternal psychopathology.

The perinatal and obstetric risk factors associated with increased odds of reactive attachment disorder in the unadjusted analyses were, a low birthweight of under 2,500 grams OR 2.90 (95% CI 1.99, 4.22), a gestational age of less than 32 weeks OR 6.73 (95% CI 3.38, 13.40), a gestational age of 32-36 weeks OR 2.04 (95% CI 1.41, 2.97), a low Apgar score of less than 7 at one minute OR 1.94 (95% CI 1.34, 2.82), and admission to a NICU OR 2.48 (95% CI 1.92, 3.20). A birthweight of 4,000–4,499 grams OR 0.38 (95% CI 0.27, 0.53) was associated with decreased odds of reactive attachment disorder. In the adjusted analyses, a low birthweight of less than 2,500 grams OR 1.96 (95% CI 1.17, 3.30), a low

gestational age of less than 32 weeks OR 3.72 (95% CI 1.52, 9.10), induced labour OR 1.34 (95% CI 1.03, 1.75) and admission to a NICU OR 1.67 (95% CI 1.09, 2.55) remained as significant risk factors for reactive attachment disorder. A birthweight of 4,000-4,499 grams OR 0.49 (95% CI 0.31, 0.75) remained a protective factor, as it continued to be associated with decreased odds of reactive attachment disorder in the adjusted analyses (Table 3).

Discussion

This was the first population-based study to show that neonatal and obstetric risk factors, including low birthweight, preterm birth below 32 weeks of gestation, admission to the NICU and induced labour, were associated with reactive attachment disorder.

There are several possible mechanisms that might explain the association between low birth weight, preterm birth and reactive attachment disorder. The physical and psychosocial environment of the NICU might affect the preterm infant's developing brain (15). They leave the adaptive environment of their mothers' uterus too early, and are exposed to medical care and procedures that induce stress or trauma. Moreover, perinatal adversity can predispose them to poor stress management and reduced resiliency (16). At the same time, the normal psychological process that the mother goes through during pregnancy, as she develops a growing emotional attachment to her unborn baby, is suddenly and prematurely interrupted. Mothers' mental representations of the baby may be far from the real baby when the baby is born preterm (17). Moreover, parents of preterm infants might have difficulty in understanding the infant's attachment needs and signals seeking for closeness as preterm infants are less alert and less responsive than full-term infants (18). The mothers of preterm infants have been reported to experience increased levels of psychological distress during neonatal period, including anxiety, depressive symptoms, and post-traumatic stress disorder (19). The preterm infants themselves often show disturbances in their cortisol production as a result of a combination of stressful environment, brain immaturity and maternal separation (20). The elevated level of distress in

mothers, which may persist over several months after discharge from NICU (19), and in preterm infants may disrupt the development of normal attachment in the mother-child dyad.

The NICU admission itself was a risk factor for later reactive attachment disorder. It was observed already during 1970s by Fanaroff, Kennell and Klaus (21) that prolonged mother-infant separation during NICU care associated with a risk for child abuse and failure-to-thrive. Long periods of parent-infant separation are still common during neonatal hospital care (22), and may disturb the formation of the attachment between preterm infant and the parents. Family centred care promotes parent-infant closeness and parents' role as primary caregivers (23). Furthermore, new NICU architecture with an opportunity for the parents to stay overnight increases parents' presence and the duration of parent-infant skin-to-skin contact (22). Increased maternal contact can lower stress and improve cortisol reactivity in preterm infants (24). In addition, increased maternal proximity has been shown to increase oxytocin production in mother and child, and to improve infant neuro-behavioural maturation as well as maternal sensitivity and bonding (25). The role of sensitive and responsive care for the development of attachment relationship has also been shown in children living in institutions (26), and in primates (27). Therefore, it would be interesting to see the changes in risks for reactive attachment disorder among children admitted in NICU care, during the era of family centred care and single family rooms. Nevertheless, it should be kept in mind that the development of reactive attachment disorder involves a complex interplay of nature and nurture, and improvements in neonatal care could only partly address the risks involved.

There may be other underlying pregnancy-related reasons, for the development of reactive attachment disorder when infants are born with a low birthweight and are admitted in a NICU. Numerous studies have suggested how several mechanisms, such as maternal depression and smoking during pregnancy, can affect the intrauterine growth of the foetus (28). These maternal adversities, together with a lack of facilities that enable parents and infants to be together in the NICU, might worsen maternal-infant relationships.

When we examined obstetric factors, we found that induced labour was associated with reactive attachment disorder in the adjusted analysis. To date, no previous studies have

examined the association between obstetric risk factors and reactive attachment disorder. It has been suggested that the mechanism related to exposure to exogenous oxytocin contributes to these associations, as oxytocin signalling might play an important prosocial role, by influencing attachment behaviour and social and cognitive functions (29). It is important for future studies with larger sample sizes to examine obstetric factors and the risk of later reactive attachment disorder.

Strengths and limitations

The present nationwide register-based study includes large sample size, addresses recall bias, and uses a comprehensive list of potential risk factors in a cost-effective prospective design. Earlier studies on reactive attachment disorder were based on deprived populations and/or clinical samples, and have concerned the prevalence, phenotypic characteristics and comorbidities of the disorder. No previous clinical or population-based study has examined the perinatal risk factors associated with reactive attachment disorder. Availability of population-based epidemiological studies will contribute in better understanding of etiology of reactive attachment disorder.

There are several limitations that need to be considered when interpreting our findings. First, national Finnish registers were used to identify cases with reactive attachment disorder. Standardized interviews, or scales designed and validated for diagnosing reactive attachment disorder in children, would have been more reliable than clinical diagnoses in the CRHC. However, the Finnish registers have been reported to provide good accuracy with regard to the diagnoses of mental disorders (30). The chart review of reactive attachment disorder diagnoses showed that 94.5% meet the ICD-10 diagnostic criteria of reactive attachment disorder. Second, the use of national registers to identify cases may not have completely represented all the cases of reactive attachment disorder in Finland. We are likely to have missed a number of undiagnosed or less severe cases, as the national registers we used only covered cases that had visits at specialized health care services. However, all children below school age, namely the age of 7, periodically visit child health

clinics in Finland. Children with moderate or severe symptoms that suggest psychiatric disorders are referred to specialized services by these clinics. Moreover, health care services in Finland are universally financed by state or municipalities and children are exempt from the generally low patient fees. Third, we did not have access to information about child abuse, neglect or child custody among study population. However, psychological and/or physical abuse or neglect was present in all cases that were evaluated for validation of reactive attachment disorder diagnoses in this study. Fourth, since the study variables were derived from the national registers, the risk factors and outcomes would probably not have been measured with the same accuracy and consistency throughout. Finally, the umbilical artery pH value was only available for half of the study population, but it was missing for a similar proportion of cases and controls.

Conclusions

This study found novel associations between reactive attachment disorder and several neonatal risk factors, such a low birthweight, low gestational age and NICU admission. These associations may be due to biological factors related to neonatal immaturity and potentially exacerbated by psychosocial effects of parent-infant separation in early life. Therefore, it is important to help parents with preterm infants to promote parental-infant attachment and to develop positive environment already during the neonatal period. The findings add to the current literature on the understanding of development of reactive attachment disorder in children.

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Conflict of interest

None.

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Table 1. ICD-10 criteria for reactive attachment disorder

A	Onset is before the age of 5 years.
B	The child exhibits strongly contradictory or ambivalent social responses that extend across social situations (but that may show variability from relationship to relationship).
C	Emotional disturbance is shown by lack of emotional responsiveness, withdrawal reactions, aggressive responses to the child's own or other's distress, and/or fearful hypervigilance.
D	Some capacity for social reciprocity and responsiveness is evident in interactions with normal adults.
E	The criteria for pervasive developmental disorders (F84) are not met.

Note: In ICD-10, pathogenic care is not considered as a diagnostic criterion, but the clinician is cautioned against making the diagnosis if there is no history of abuse or neglect

Table 2. Covariates in relation to perinatal risk factors among controls and in relation to the risk of reactive attachment disorder

Covariates	**n (%)**	**Association of covariate and outcome‡**	**Associations between covariate and exposures among controls***									
			Birth weight[a]	Gestational age[b]	Bleeding[c]	Hypertension[c]	Birth Presentation[c]	Birth type	Induced labor[c]	Apgar 1 min[c]	Monitoring[d]	pH[e]
Maternal age		<0.001	0.23	0.15	0.02	0.03	0.46	<0.001	0.21	0.38	0.90	0.69
<29	1055 (43.5)											
29-	1368 (56.4)											
Paternal age[1]		<0.001	0.93	0.32	0.15	0.11	0.33	<0.001	0.003	0.41	0.28	0.25
<31	1071 (44.5)											
31-	1335 (55.5)											
Maternal SES[2]		<0.001	0.82	0.68	0.81	0.04	0.47	<0.001	0.03	0.97	0.94	0.11
Upper white collar	398 (16.4)											
Lower white collar	1014 (41.8)											
Blue collar	371 (15.3)											
Other or Missing	640 (26.4)											
Maternal Smoking[3]		<0.001	<0.001	0.02	0.49	0.59	0.50	0.45	0.54	0.76	0.04	0.43
Yes	351 (14.9)											
No	1994 (85.0)											
Marital status[4]		<0.001	0.66	0.68	0.07	0.33	0.26	0.75	0.12	0.09	0.97	0.13
Married/in a relationship	2138 (95.3)											
Single	104 (4.6)											
Previous birth[5]		0.57	<0.001	0.48	0.52	0.009	<0.001	<0.001	0.03	<0.001	0.07	0.64

0	993 (41.2)											
>1	1416 (58.7)											
Maternal psychiatric history		<0.001	0.74	0.21	0.63	0.01	0.34	0.02	0.59	0.02	0.04	0.02
Yes	311 (12.8)											
No	2112 (87.1)											
Paternal psychiatric history[1]		<0.001	<0.001	<0.001	0.06	0.46	0.22	0.47	0.79	0.92	0.001	0.17
Yes	269 (11.1)											
No	2137 (88.8)											

[*]Associations of covariates and exposure among controls analyzed by Pearson's chi-square test.[‡] Associations between covariate and reactive attachment disorder by conditional logistic regression in case–control pairs.[1]Data missing for 56 cases and 17 controls.[2]Data missing for 107 cases and 181 controls.[3] Data missing for 19 cases and 78 controls.[4]Data missing for 4 cases and 14 controls. [a] Data missing for 4 cases and 14 controls. [b] Data missing for 7 cases and 20 controls. [c] Data missing for 3 cases and 10 controls. [d] Data missing for 4 cases and 17 controls. [e] Data missing for 256 cases and 1118 controls.

Table 3. Unadjusted and adjusted association for perinatal and obstetric risk factors, and reactive attachment disorder

	Cases (n=614), N (%)	**Controls (n=2423), N (%)**	**Unadjusted OR (95% CI)**	**P value**	**Adjusted OR[*] (95% CI)**	**P value**
Birth weight (grams)[a]						
<2500	54 (8.8)	68 (2.8)	2.90 (1.99, 4.22)	<0.001	1.96 (1.17, 3.30)	0.01
2500–3999	499 (81.8)	1832 (76.0)	1.00 (Reference)		1.00 (Reference)	
4000–4499	43 (7.0)	421 (17.4)	0.38 (0.27, 0.53)	<0.001	0.49 (0.31, 0.75)	0.001
4500 and above	14 (2.3)	88 (3.6)	0.59 (0.33, 1.05)	0.072	0.93 (0.44, 1.94)	0.85
Gestational age (weeks)[b]						
<32	22 (3.6)	14 (0.5)	6.73 (3.38, 13.40)	<0.001	3.72 (1.52, 9.10)	0.003
32–36	45 (7.4)	93 (3.8)	2.04 (1.41, 2.97)	<0.001	1.20 (0.71, 2.02)	0.48
37–41	510 (84.0)	2169 (90.2)	1.00 (Reference)		1.00 (Reference)	
42 and above	30 (4.9)	127 (5.3)	0.98 (0.65, 1.48)	0.95	0.68 (0.38, 1.22)	0.20
Bleeding [c]	13 (2.1)	39 (1.6)				
Yes	598 (97.8)	2374 (98.)	1.31 (0.70, 2.47)	0.39	0.86 (0.34, 2.16)	0.75
No			1.00 (Reference)		1.00 (Reference)	
Hypertension [c]						

Yes	19 (3.1)	88 (3.6)	0.83 (0.50, 1.38)	0.48	1.04 (0.52, 2.07)	0.90
No	592 (96.9)	2325 (96.3)	1.00 (Reference)		1.00 (Reference)	
Birth presentation [c]						
Cephalic	578 (94.6)	2263 (93.7)	1.00 (Reference)		1.00 (Reference)	
Breech	16 (2.6)	62 (2.5)	0.99 (0.56, 1.72)	0.97	0.99 (0.56, 1.72)	0.97
Others	17 (2.7)	88 (3.6)	0.77 (0.45, 1.30)	0.33	0.77 (0.45, 1.30)	0.33
Birth type						
Vaginal cephalic	467 (76.0)	1842 (76.0)	1.00 (Reference)		1.00 (Reference)	
Vaginal breech	2 (0.3)	10 (0.4)	0.79 (0.17, 3.62)	0.76	1.06 (0.12, 8.86)	0.95
Suction + forceps	36 (5.8)	175 (7.2)	0.81 (0.56, 1.18)	0.28	0.87 (0.52, 1.46)	0.61
Cesarean planned	43 (7.0)	176 (7.2)	0.96 (0.68, 1.36)	0.85	0.85 (0.53, 1.37)	0.51
Cesarean other	60 (9.7)	205 (8.4)	1.15 (0.85, 1.56)	0.34	0.86 (0.55, 1.33)	0.50
Unknown	6 (0.9)	15 (0.6)	1.57 (0.61, 4.06)	0.34	0.75 (0.24, 2.32)	0.62
Induced labor [c]						
Yes	109 (17.8)	380 (15.7)	1.17 (0.92, 1.48)	0.19	1.34 (1.03, 1.75)	0.02
No	502 (82.1)	2033 (84.2)	1.00 (Reference)		1.00 (Reference)	
Apgar score at 1 min [d]						

<7	46 (7.5)	103 (4.2)	1.94 (1.34, 2.82)	<0.001	1.40 (0.78, 2.53)	0.25
7-8	128 (20.3)	440 (18.3)	1.24 (0.99, 1.55)	0.059	0.98 (0.70, 1.37)	0.92
9-10	436 (71.4)	1863 (77.4)	1.00 (Reference)		1.00 (Reference)	
Monitoring [c]						
Normal	498 (81.5)	2205 (91.3)	1.00 (Reference)		1.00 (Reference)	
Monitoring/NICU	113 (18.5)	208 (8.6)	2.48 (1.92, 3.20)	<0.001	1.67 (1.09, 2.55)	0.01
	Mean (SD)	**Mean (SD)**				
Umbilical artery pH [e]						
Mean (SD)	7.2 (0.09)	7.2 (0.09)	1.14 (0.27, 4.70)	0.85	1.02 (0.12, 8.35)	0.98

[a] Data missing for 4 cases and 14 controls; [b] Data missing for 7 cases and 20 controls; [c] Data missing for 3 cases and 10 controls; [d] Data missing for 4 cases and 17 controls; [e] Data missing for 256 cases and 1118 controls. OR odds ratio; SES socio-economic status; NICU neonatal intensive care unit; SD standard deviation.

[*]Birth weight and gestational age adjusted for paternal psychiatric history and maternal smoking. Bleeding adjusted for maternal age. Hypertension adjusted for maternal age, maternal SES and maternal psychiatric history. Birth type adjusted for maternal age, paternal age, maternal SES, and maternal psychiatric history. Induced labor adjusted for paternal age, maternal SES. Apgar score adjusted for marital status and maternal psychiatric history. Monitoring adjusted for paternal psychiatric history, maternal smoking and maternal psychiatric history. Umbilical artery pH adjusted for maternal psychiatric history.

Table S1. Covariates in relation to exposures among controls and in relation to the risk of RAD (continued)

Covariates	**n (%)**	**Association of covariate and outcome ‡**	**Association of covariates and exposures among controls***									
			Birth weight [a] n (%)				**P value**	**Gestational age [b] n (%)**				**P value**
Maternal age		<0.001	<2500	2500-3999	4000-4499	4500-	0.23	<32	32-36	37-41	42-	0.15
<29	1055 (43.5)		31 (45.59)	820 (44.76)	168 (39.90)	34 (38.64)		9 (64.29)	36 (38.71)	943 (43.48)	63 (49.61)	
29-	1368 (56.4)		37 (54.41)	1012 (55.24)	253 (60.10)	54 (61.36)		5 (35.71)	57 (61.29)	1226 (56.52)	64 (50.39)	
Paternal age[1]		<0.001					0.93					0.32
<31	1071 (44.5)		30 (45.45)	817 (44.89)	181 (43.20)	40 (45.45)		7 (50)	35 (38.40)	959 (44.52)	64 (50.39)	
31-	1335 (55.5)		36 (54.55)	1003 (55.11)	238 (56.80)	48 (54.55)		7 (50)	57 (61.96)	1195 (55.48)	63 (49.61)	
Maternal SES[2]		<0.001					0.82					0.68
Upper white collar	398 (16.4)		11 (16.18)	302 (16.48)	73 (17.34)	12 (13.64)		2 (14.29)	10 (10.75)	359 (16.55)	26 (20.47)	
Lower white collar	1014 (41.8)		32 (47.06)	762 (41.59)	184 (43.71)	36 (40.91)		6 (42.86)	45 (48.39)	913 (42.09)	47 (37.01)	
Blue collar	371 (15.3)		6 (8.82)	288 (15.72)	60 (14.25)	17 (19.32)		1 (7.14)	12 (12.90)	338 (15.58)	20 (15.75)	
Other or Missing	640 (26.4)		19 (27.94)	480 (26.20)	104 (24.70)	23 (26.14)		5 (35.71)	26 (27.96)	559 (25.77)	34 (26.77)	
Maternal Smoking[3]		<0.001					<0.001					0.02
Yes	351 (14.9)		22 (32.84)	275 (15.43)	40 (9.80)	14 (15.91)		2 (14.29)	24 (26.09)	306 (14.50)	19 (15.32)	
No	1994 (85.0)		45 (67.16)	1507 (84.57)	368 (90.20)	74 (84.09)		12 (85.71)	68 (73.91)	1804 (85.50)	105 (84.68)	
Marital status[4]		<0.001					0.66					0.68
Married/in a relationship	2138 (95.3)		60 (95.24)	1618 (95.06)	380 (96.45)	80 (96.39)		12 (92.31)	84 (95.45)	1923 (95.29)	115 (97.46)	
Single	104 (4.6)		3 (4.76)	84 (4.94)	14 (3.55)	3 (3.61)		1 (7.69)	4 (4.55)	95 (4.71)	3 (2.54)	
Previous birth[5]		0.57					<0.001					0.48
0	993 (41.2)		32 (47.06)	820 (44.78)	120 (28.57)	21 (23.86)		6 (42.86)	35 (37.63)	889 (41.01)	60 (47.24)	
>1	1416 (58.7)		36 (52.94)	1011 (55.22)	300 (71.43)	67 (76.14)		8 (57.14)	58 (62.37)	1279 (58.99)	67 (52.76)	
Maternal psychiatric history		<0.001					0.74					0.21
Yes	311 (12.8)		11 (16.18)	234 (12.77)	53 (12.59)	9 (10.23)		2 (14.29)	18 (19.35)	268 (12.36)	19 (14.96)	
No	2112 (87.1)		57 (83.82)	1598 (87.23)	368 (87.41)	79 (89.77)		12 (85.71)	75 (80.65)	1901 (87.64)	108 (85.04)	
Paternal psychiatric history[1]		<0.001					<0.001					<0.001
Yes	269 (11.1)		20 (30.30)	201 (11.04)	42 (10.02)	5 (5.68)		7 (50)	22 (23.91)	222 (10.31)	16 (12.60)	
No	2137 (88.8)		46 (69.70)	1619 (88.96)	377 (89.98)	83 (94.32)		7 (50)	70 (76.09)	1932 (89.69)	111 (87.40)	

Table S1. Covariates in relation to exposures among controls and in relation to the risk of RAD (continued)

Covariates	**Association of covariates and exposures among controls***										
	Birth Presentation [c] n (%)			**P value**	**Birth type [c] n (%)**						**P value**
Maternal age	Cephalic	Breech	Other	0.46	Cephalic	Breech	Suction+forceps	C planned	C other	Unknown	<0.001
<29	984 (43.48)	26 (41.94)	44 (50)		823 (44.68)	3 (30)	92 (52.57)	55 (31.25)	79 (38.54)	3 (20)	
29-	1279 (56.52)	36 (58.06)	44 (50)		1019 (55.32)	7 /70)	83 (47.43)	121 (68.75)	126 (61.46)	12 (80)	
Paternal age[1]				0.33							<0.001
<31	995 (44.28)	28 (45.16)	46 (52.27)		828 (45.20)	4 (40)	101 (58.38)	65 (37.14)	69 (34.16)	4 (28.57)	
31-	1252 (55.72)	34 (54.84)	42 (47.73)		1004 (54.80)	6 (60)	72 (41.60)	110 (62.86)	133 (65.84)	10 (71.43)	
Maternal SES[2]				0.47							<0.001
Upper white collar	371 (16.39)	10 (16.13)	17 (19.32)		299 (16.23)	1 (10)	36 (20.57)	30 (17.05)	32 (15.61)	0 (0)	
Lower white collar	945 (41.76)	31 (50)	38 (43.18)		756 (41.04)	8 (80)	70 (40)	79 (44.89)	101 (49.27)	0 (0)	
Blue collar	347 (15.33)	7 (11.29)	17 (19.32)		284 (15.42)	0 (0)	26 (14.86)	26 (14.77)	34 (16.59)	1 (6.67)	
Other or Missing	600 (26.51)	14 (22.58)	16 (18.18)		503 (27.31)	1 (10)	43 (24.57)	41 (23.30)	38 (18.54)	14 (93.33)	
Maternal Smoking[3]				0.50							0.45
Yes	326 (14.82)	12 (20.34)	13 (14.94)		268 (14.93)	0 (0)	23 (13.14)	23 (13.69)	37 (18.78)	0 (0)	
No	1873 (85.18)	47 (79.66)	74 (85.06)		1527 (85.07)	9 (100)	152 (86.86)	145 (86.31)	160 (81.22)	1 (100)	
Marital status[4]				0.26							0.75
Married/in a relationship	2011 (95.40)	55 (98.21)	72 (92.31)		1643 (95.03)	7 (100)	146 (95.42)	159 (96.95)	182 (96.81)	1 (100)	
Single	97 (4.60)	1 (1.79)	6 (7.69)		86 (4.97)	0 (0)	7 (4.58)	5 (3.05)	6 (3.19)	0 (0)	
Previous birth[5]				<0.001							<0.001
0	903 (39.97)	38 (61.29)	52 (59.09)		651 (35.36)	4 (40)	139 (79.43)	71 (40.57)	128 (62.44)	0 (0)	
>1	1356 (60..03)	24 (38.71)	36 (40.91)		1190 (64.64)	6 (60)	36 (20.57)	104 (59.43)	77 (37.56)	3 (100)	
Maternal psychiatric history				0.34							0.02
Yes	285 (12.59)	10 (16.13)	15 (17.05)		221 (12)	0 (0)	25 (14.29)	24 (13.64)	36 (17.56)	5 (33.33)	
No	1978 (87.41)	52 (83.87)	73 (82.95)		1621 (88)	10 (100)	150 (85.71)	152 (86.36)	169 (82.44)	10 (66.67)	
Paternal psychiatric history[1]				0.22							0.47
Yes	258 (11.48)	6 (9.68)	5 (5.68)		197 (10.75)	1 (10)	16 (9.25)	23 (13.14)	30 (14.85)	2 (14.29)	
No	1989 (88.52)	56 (90.32)	83 (94.32)		1635 (89.25)	9 (90)	157 (90.75)	152 (86.86)	172 (85.15)	12 (85.71)	

Table S1. Covariates in relation to exposures among controls and in relation to the risk of RAD (continued)

Covariates	**Association of covariates and exposures among controls***									
	Bleeding [c] n (%)		**P value**	**Induced labor [c] n (%)**		**P value**	**Apgar 1 min [c] n (%)**			**P value**
Maternal age	Yes	No	0.02	Yes	No	0.21	<7	7-8	9-10	0.38
<29	10 (25.64)	1044 (43.98)		155 (40.79)	899 (44.22)		51 (49.51)	185 (42.05)	816 (43.80)	
29-	29 (74.36)	1330 (56.02)		225 (59.21)	1134 (55.78)		52 (50.49)	255 (57.95)	1047 (56.20)	
Paternal age[1]			0.15			0.003				0.41
<31	13 (33.33)	1056 (44.78)		143 (37.73)	926 (45.89)		52 (50.98)	192 (43.94)	823 (44.46)	
31-	26 (66.67)	1302 (55.22)		236 (62.27)	1092 (54.11)		50 (49.02)	245 (56.06)	1028 (55.54)	
Maternal SES[2]			0.81			0.03				0.97
Upper white collar	6 (15.38)	392 (16.51)		57 (15)	341 (16.77)		20 (19.42)	75 (17.05)	303 (16.26)	
Lower white collar	18 (46.15)	996 (41.95)		178 (46.84)	836 (41.12)		41 (39.81)	179 (40.68)	793 (42.57)	
Blue collar	4 (10.26)	367 (15.46)		65 (17.11)	306 (15.05)		16 (15.53)	70 (15.91)	285 (15.30)	
Other or Missing	11 (28.21)	619 (26.07)		80 (21.05)	550 (27.05)		26 (25.24)	116 (26.36)	482 (25.87)	
Maternal Smoking[3]			0.49			0.54				0.76
Yes	7 (18.92)	344 (14.90)		59 (15.99)	292 (14.78)		17 (16.67)	68 (15.70)	265 (14.67)	
No	30 (81.08)	1964 (85.10)		310 (84.01)	1684 (85.22)		85 (83.33)	365 (84.30)	1542 (85.33)	
Marital status[4]			0.07			0.12				0.09
Married/in a relationship	33 (89.19)	2105 (95.46)		348 (96.94)	1790 (95.06)		95 (98.96)	372 (93.94)	1668 (95.48)	
Single	4 (10.81)	100 (4.54)		11 (3.06)	93 (4.94)		1 (1.04)	24 (6.06)	79 (4.52)	
Previous birth[5]			0.52			0.03				<0.001
0	18 (46.15)	975 (41.14)		138 (36.32)	855 (42.14)		57 (55.34)	212 (48.18)	724 (38.90)	
>1	21 (53.85)	1395 (58.86)		242 (63.68)	1174 (57.86)		46 (44.66)	228 (51.82)	1137 (61.10)	
Maternal psychiatric history			0.63			0.59				0.02
Yes	6 (15.38)	304 (12.81)		52 (13.68)	258 (12.69)		17 (16.50)	71 (16.14)	218 (11.70)	
No	33 (84.62)	2070 (87.19)		328 (86.32)	1775 (87.31)		86 (83.50)	369 (83.86)	1645 (88.30)	
Paternal psychiatric history[1]			0.06			0.79				0.92
Yes	8 (20.51)	261 (11.07)		44 (11.61)	225 (11.15)		12 (11.76)	51 (11.67)	205 (11.08)	
No	31 (79.49)	2097 (88.93)		335 (88.39)	1793 (88.85)		90 (88.24)	386 (88.33)	1646 (88.92)	

Table S1. Covariates in relation to exposures among controls and in relation to the risk of RAD (continued)

Covariates	**Association of covariates and exposures among controls***							
	Hypertension [c] n (%)		**P value**	**Monitoring [d] n (%)**		**P value**	**PH [e] Mean (SD)**	**P value**
Maternal age	Yes	No	0.03	NICU	Normal	0.90		0.69
<29	29 (32.95)	1025 (44.09)		90 (43.27)	964 (43.72)		7.26 (0.09)	
29-	59 (67.05)	1300 (55.91)		118 (56.73)	1241 (56.28)		7.26 (0.08)	
Paternal age[1]			0.11			0.28		0.25
<31	32 (36.36)	1037 (44.91)		85 (41.06)	984 (44.93)		7.26 (0.09)	
31-	56 (63.64)	1272 (55.09)		122 (58.94)	1206 (55.07)		7.26 (0.08)	
Maternal SES[2]			0.04			0.94		0.11
Upper white collar	24 (27.27)	374 (16.09)		32 (15.38)	366 (16.60)		7.25 (0.08)	
Lower white collar	33 (37.50)	981 (42.19)		86 (41.35)	928 (42.09)		7.26 (0.09)	
Blue collar	13 (14.77)	358 (15.40)		33 (15.87)	338 (15.33)		7.26 (0.09)	
Other or Missing	18 (20.45)	612 (26.32)		57 (27.40)	573 (25.99)		7.25 (0.08)	
Maternal Smoking[3]			0.59			0.04		0.43
Yes	11 (12.94)	340 (15.04)		40 (19.80)	311 (14.51)		7.26 (0.09)	
No	74 (87.06)	1920 (84.96)		162 (80.20)	1832 (85.49)		7.26 (0.09)	
Marital status[4]			0.33			0.97		0.13
Married/in a relationship	80 (97.56)	2058 (95.28)		187 (95.41)	1951 (95.36)		7.26 (0.09)	
Single	2 (2.44)	102 (4.72)		9 (4.59)	95 (4.64)		7.27 (0.07)	
Previous birth[5]			0.009			0.07		0.64
0	48 (54.55)	945 (40.72)		98 (47.12)	895 (40.66)		7.24 (0.08)	
>1	40 (45.45)	1376 (59.28)		110 (52.88)	1306 (59.34)		7.27 (0.08)	
Maternal psychiatric history			0.01			0.04		0.02
Yes	4 (4.55)	306 (13.16)		36 (17.31)	274 (12.43)		7.26 (0.07)	
No	84 (95.45)	2019 (86.84)		172 (82.69)	1931 (87.57)		7.26 (0.09)	
Paternal psychiatric history[1]			0.46			0.001		0.17
Yes	12 (13.64)	257 (11.13)		37 (17.87)	232 (10.59)		7.27 (0.08)	
No	76 (86.36)	2052 (88.87)		170 (82.13)	1958 (89.41)		7.26 (0.09)	

*Associations of covariates and exposure among controls analyzed by Pearson's chi-square test.‡ Associations between covariate and reactive attachment disorder by conditional logistic regression in case–control pairs.[1]Data missing for 56 cases and 17 controls.[2] Data missing for 126 cases and 201 controls.[3] Data missing for 19 cases and 78 controls.[4] Data missing for 107 cases and 181 controls. [5]Data missing for 4 cases and 14 controls. [a] Data missing for 4 cases and 14 controls. [b] Data missing for 7 cases and 20 controls. [c] Data missing for 3 cases and 10 controls. [d] Data missing for 4 cases and 17 controls. [e] Data missing for 256 cases and 1118 controls.

Table S2. Unadjusted association for perinatal and obstetric risk factors, and RAD with and without anxiety disorders

	Reactive attachment disorder with or without anxiety disorders Unadjusted OR (95% CI), n=614	**P value**	**Reactive attachment disorder without anxiety disorders Unadjusted OR (95% CI), n=453**	**P value**
Birth weight (grams)				
<2500	2.90 (1.99, 4.22)	<0.001	3.52 (2.28-5.45)	<0.001
2500–3999	1.00 (Reference)		Ref	
4000–4499	0.38 (0.27, 0.53)	<0.001	0.27 (0.17-0.42)	<0.001
4500 and above	0.59 (0.33, 1.05)	0.07	0.71 (0.37-1.34)	0.29
Gestational age (weeks)				
<32	6.73 (3.38, 13.40)	<0.001	6.52 (3.06-13.88)	<0.001
32–36	2.04 (1.41, 2.97)	<0.001	2.60 (1.68-4.00)	<0.001
37–41	1.00 (Reference)		1.00 (Reference)	
42 and above	0.98 (0.65, 1.48)	0.95	0.92 (0.57-1.50)	0.76
Bleeding				
Yes	1.31 (0.70, 2.47)	0.39	1.54 (0.77-3.11)	0.22
No	1.00 (Reference)		1.00 (Reference)	
Hypertension				
Yes	0.83 (0.50, 1.38)	0.48	0.85 (0.47-1.54)	0.59
No	1.00 (Reference)		1.00 (Reference)	
Birth presentation				
Cephalic	1.00 (Reference)		1.00 (Reference)	
Breech	0.99 (0.56, 1.72)	0.97	1.00 (0.52-1.92)	0.9
Others	0.77 (0.45, 1.30)	0.33	0.78 (0.42-1.44)	0.43
Birth type				
Vaginal cephalic	1.00 (Reference)		1.00 (Reference)	
Vaginal breech	0.79 (0.17, 3.62)	0.76	0.80 (0.17-3.65)	0.77
Suction + forceps	0.81 (0.56, 1.18)	0.28	0.82 (0.53-1.26)	0.36
Cesarean planned	0.96 (0.68, 1.36)	0.85	0.94 (0.62-1.42)	0.78
Cesarean other	1.15 (0.85, 1.56)	0.34	1.28 (0.91-1.80)	0.14
Unknown	1.57 (0.61, 4.06)	0.34	1.79 (0.62-5.17)	0.28
Induced labor				
Yes	1.17 (0.92, 1.48)	0.19	1.05 (0.80-1.39)	0.69
No	1.00 (Reference)		1.00 (Reference)	
Apgar score at 1 min				
<7	1.94 (1.34, 2.82)	<0.001	2.11 (1.39-3.20)	<0.001
7-8	1.24 (0.99, 1.55)	0.06	1.32 (1.02-1.72)	0.03
9-10	1.00 (Reference)		1.00 (Reference)	
Monitoring				
Normal	1.00 (Reference)		1.00 (Reference)	
Monitoring/NICU	2.48 (1.92, 3.20)	<0.001	2.82 (2.08-3.81)	<0.001
Umbilical artery pH				
Mean (SD)	1.14 (0.27, 4.70)	0.85	1.08 (0.31-10.34)	0.50