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CLINICAL TRAIL

Infant colic and abdominal pain; associations with infant multimorbidity and maternal perceived stress up to 3 months postpartum—A cross-sectional/cohort study in the PreventADALL study

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Abstract

Aims and Objectives: The primary aim was to explore whether infants with pain symptoms (colic, abdominal pain and visit to healthcare provider with pain or other discomforts) had increased multimorbidity (common infections, eczema and food sensitivity) compared with infants without these conditions. Secondarily, we aimed to determine whether infant pain symptoms were associated with maternal perceived stress in pregnancy and 3 months postpartum.

Background: Infant colic and abdominal pain are common concerns in early infancy. Nevertheless, to our knowledge, little research exists on the relationship between infant pain and common infant infections, eczema and food sensitization as comorbidities, and the impact of infant pain on the development of maternal perceived stress from pregnancy to infancy is inconsistent.

Design: This study was cross-sectional and partly prospective.

Methods: The sample consisted of mother–infant pairs ($N = 1852$); information regarding infant pain and multimorbidity was collected from the 3-month questionnaire and postpartum visits in the PreventADALL prospective cohort study. Chi-square tests and regression analyses were conducted. The STROBE checklist was followed.

Results: Our results showed a statistically significant higher proportion of respiratory and other infections in infants with pain symptoms. The odds of infant pain were higher for infants with multimorbidity compared to those with no comorbidity. Mothers of infants with colic and of infants visiting healthcare with pain and other discomforts

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reported statistically significant higher perceived stress by 3 months compared with mothers of infants with no reported pain.

Conclusion: Our results indicate an association between infant pain symptoms and the presence of infections. Mothers of infants with colic and visiting healthcare had higher perceived stress compared to the no pain group.

Implications for Practice: Our study indicates that infant pain is associated with infant multimorbidity and maternal perceived stress, which may be useful when planning diagnostic, treatment and coping strategies in infant and family care.

Patient or Public Contribution: The PreventADALL is a collaborative study with governmental and patient organisation representation. Selected infants with parents were also contributing during calibrating courses on eczema assessment for the data collectors.

Trial Registration: The study was approved by the Regional Committee in Norway (2014/518) and Sweden (2014/2242–31/4) and registered at clinicaltrial.gov (NCT02449850). Link for clinical trials: https://clinicaltrials.gov/ct2/show/NCT02449850

KEYWORDS
abdominal pain, colic, eczema, infant, infection, maternal stress

1 | INTRODUCTION

Infant colic and abdominal pain are common and distressing concerns for parents and clinicians (Wolke et al., 2017). Infant colic is a condition appearing from the first weeks of life up to 3–4 months, characterised by prolonged periods of crying. The diagnosis is based upon the infant's medical history, excluding other causes (Johnson et al., 2015). Characteristics of colic are crying, including clenching of fists and flexion of hips. The suggestion is that these behaviours are related to abdominal discomfort (Mai et al., 2018). All infants cry, but for infants with colic the term excessive crying is used. It usually occurs in the evenings and the infants are difficult to calm and comfort (Turner et al., 2018; Zeevenhooven et al., 2017). The crying is associated with more pain for the infant, measured in intensity and durations, compared to fussing or hungry cries (Parga et al., 2020).

Colic has also been suggested to be an extreme variation of normal infant crying caused by different physiological and psychosocial factors (Sung, 2018). 'The ROME IV criteria for infant colic are: "… parents have to report that their infant has cried or fussed for 3 or more hours per day, during 3 or more days in the preceding week. In addition, parents have to keep a 24-hour behaviour diary to confirm that the total amount of crying and fussing is more than 3 hours per 24 hours.' (Zeevenhooven et al., 2017). Parents, however, are less likely to perceive colic based on this strict criterion (Helseth & Begnum, 2002). Recent findings from the Preventing Atopic Dermatitis and ALLergies in children (PreventADALL) study demonstrated that symptoms of infant colic and abdominal pain overlapped, most likely due to the similarity of the symptoms and subjective perceptions (Despriee et al., 2022). Causes of infant colic are unclear, as multiple factors may contribute to discomfort and pain, including extra-abdominal origins (Lucassen, 2010).

What does this paper contribute to the wider global clinical community?

- The current study identifies association between both infant multimorbidity and maternal perceived stress with infant colic, abdominal pain and visits to healthcare provider with pain or other discomforts.
- The results highlight and confirm the multifactorial associations with the infant pain symptoms.
- Implication for clinical use: a contribution to new insight on infant pain, which may provide a better understanding and be useful when planning diagnostic, treatment, information and stress coping strategies in infant and family care.

2 | BACKGROUND

Infant colic has been associated with inflammation and changes in gut microbial diversity and colonisation (Hofman et al., 2022; Pärtty et al., 2017), it has also been associated with later migraines (Gelfand et al., 2015). It is still unclear whether parents of infants with colic report more diseases in their infants than parents of children without colic. In a retrospective study, about 5% of 237 infants less than 1 year of age with afebrile pain symptom had severe illness

(Freedman et al., 2009). Viral bronchiolitis is a common disease in early infancy and respiratory infections, gastroenteritis, and urinary tract infections may be associated with abdominal pain in children (Reust & Williams, 2016). Urinary tract infection has also been found to be associated with colic-like symptoms in infants within the first year of life (Freedman et al., 2009). To our knowledge, research on the association between colic and infections in early infancy is lacking.

Severe infantile colic has been associated with later allergic rhinitis, conjunctivitis, atopic dermatitis and food allergies in children above 10 years of age in a Swedish prospective birth cohort study (Savino et al., 2005). One of three infants present with eczema before 12 months of age (Martin et al., 2013) and in our cohort, eczema was observed in 30% of 3-month-old infants while 9% fulfilled the diagnostic criteria for atopic dermatitis in the first year of life (Endre et al., 2022). Although atopic dermatitis is common in children, we are unaware of studies exploring possible associations with colic. Abdominal pain may be a symptom of food allergy or food intolerance; however, an association between colic and food intolerance in early infancy remains uncertain (Nocerino et al., 2015).

Excessive crying is a hallmark of colic and may disturb the relationship between parent and child (Landgren & Hallström, 2011; Viragova & O'Curry, 2021). It also has important associations with maternal stress (Türkmen et al., 2022). We recently showed a trend of high perceived stress in pregnancy, but it was not a significant predictor of colic or abdominal pain at 3 months of age in a general population in Norway and Sweden (Caroline-Aleksi Olsson et al., 2022; Despriee et al., 2022). Maternal stress levels in pregnancy may indicate a susceptibility to stress that may manifest 3 months postpartum, in line with recent findings that high maternal stress in pregnancy was associated with infant colic (Caparros-Gonzalez et al., 2021).

Infant colic and abdominal pain has to some degree the same features, and colic could appear as a cause of abdominal pain (Kim, 2013). Infant colic symptoms overlap with other infant pain symptoms and may it be difficult to distinguish (Despriee et al., 2022). Due to the unclear aetiology (Sarasu et al., 2018), our hypothesis was that infants with colic are at increased risk of multimorbidity, including common infections and allergic sensitization. To our knowledge, there are few studies on different infant colic and pain symptoms and the association with common morbidities in infants as early as up to 3 months of age. Further, our prospective follow up on maternal perceived stress from pregnancy up to 3 months postpartum explore if there are similar associations with the three different pain symptoms and how the maternal stress develop during these months. To our knowledge is this not done in previous studies.

The primary aim was to explore whether infants with pain symptoms (colic, abdominal pain and visit to healthcare provider with pain or other discomfort) had increased multimorbidity (common infections, eczema and food sensitivity) compared with infants without these conditions. Secondarily, we aimed to determine whether infant pain symptoms were associated with maternal stress in pregnancy and at 3 months postpartum.

3 | METHODS

3.1 | Study design

We used a cross-sectional design to respond to the primary aim of this study, and a prospective design for the secondary aim. All mother–infant pairs with available questionnaire data at 3 months postpartum from PreventADALL were included in the present study.

PreventADALL is a prospective interventional birth cohort study in Norway and Sweden that enrolled pregnant women at their 18-week routine ultrasound scanning from December 2014 to October 2016, at Østfold and Oslo in Norway and collaborating obstetric units in Stockholm, Sweden. All women attending their midpregnancy ultrasound screening got a letter at site inviting them to participate and got oral information at the respective hospitals, excluding those with severe maternal or foetal disease, plans to move outside a reasonable travel distance from the hospital within 1 year, more than two foetuses, and insufficient Scandinavian language skills. Informed consent forms were signed by the women at 18 weeks enrolment and by both parents at birth of the infants if they still accepted to continue. (Lødrup Carlsen et al., 2018). The offspring of participating mothers were included in the study at birth, provided a gestational age of at least 35.0 weeks and no severe diseases at birth.

The study was approved by the Regional Committee in Norway (2014/518) and Sweden (2014/2242–31/4) and registered at clinicaltrial.gov *(NCT02449850)*.

3.2 | Study population

The study population consisted of 1852 of the recruited 2397 mother–infant pairs from three regions in Norway and Sweden from 2015 to to 2017 (Lødrup Carlsen et al., 2018). Three mothers withdrew consent after inclusion, while 3-month questionnaire data were not available for 542 children (Figure 1).

3.3 | Data collection and definitions

Baseline characteristics and level of maternal perceived stress and background data were assessed using electronic questionnaires administered when the women were 18 and 34 weeks pregnant, and further data were collected by electronic questionnaire and visits at 3 months postpartum, see details in the next section 'Variables and outcomes'. For details concerning maternal enrollment and information on infants at 3 months of age, as well as information on and around delivery retrieved from medical charts, see (Lødrup Carlsen et al., 2018). We got one response to each questionnaire on each time point from each mother–infant pair.

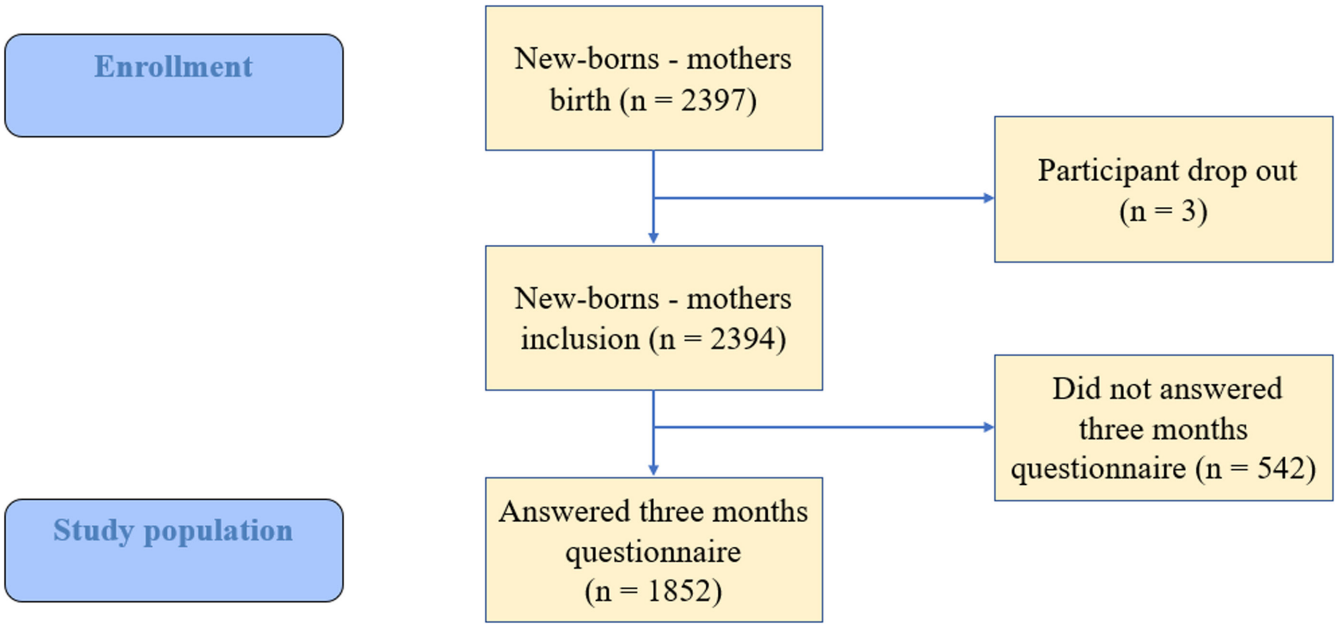

FIGURE 1 Flow chart of included participants. [Colour figure can be viewed at wileyonlinelibrary.com]

We do not know which one of the parents answered or if they did it together. For maternal perceived stress questions, it was the mother who answered.

3.4 | Variables and outcomes

The outcome variables—infant pain symptoms—were defined as positive if parents answered in the affirmative to the following questions: *In the last 3 months, did your child experience any of the following*: *'colic,' 'abdominal pain (not colic),' and/or 'visit to health care with pain or other discomforts?'* We retained these reported pain symptoms as three separate subgroups. In addition, we created a new variable by recoding all three pain symptoms into one group, labelled '*Pain sum group*.' We did not use a definition of colic in the questionnaire, only the parents' subjective perception. Pain and discomfort are subjective perceptions (IASP, 2020), so it may be difficult for the parent to assess what kind of pain their infant is experiencing.

All variables were dichotomous, with yes affirming the condition while all other responses (do not know, never or uncertain) were coded as no.

For maternal perceived stress and other background variables the missing data was treated as missing data, for example, the proportion of missing values was small thus no imputation of missing data was performed. Further, the questionnaire was designed as follows, the participants had to indicate that a morbidity or infant pain symptoms were present by clicking on a box. Thus, when this box was not clicked on, the answer was coded as no.

Infant pain symptoms and infant diseases from 0 to 3 months of age were reported using the electronic questionnaire collected at 3 months of age, while allergic sensitization was determined by serum-specific immunoglobulin E (s-IgE) analyses at a clinical visit at 3 months of age.

Parent reported infectious diseases from 0 to 3 months of age included upper respiratory tract infections (common cold), lower respiratory tract infections (bronchiolitis/pneumonia/other), conjunctivitis, otitis, gastroenteritis, urinary tract infection and others (fever with unknown cause, influenza, flu-like symptoms and virus without further diagnosis). Eczema was defined as the presence of clinical eczema, diagnosed by trained clinicians excluding differential diagnosis to atopic dermatitis at the 3-month follow-up examination (Endre et al., 2022). Allergic sensitization was determined by serum samples collected at the 3-month clinical investigation, analysing for s-IgE (Thermo-Fisher Scientific, Uppsala, Sweden) at the Furst Medical Laboratory in Oslo, as previously reported (Wärnberg Gerdin et al., 2022). Allergic sensitization to food was defined as an s-IgE of at least .1 kU/l to wheat, milk, eggs and/or peanuts.

Maternal stress was assessed at 18 and 34 weeks of pregnancy as well as at 3 months postpartum. Maternal perceived stress was assessed using the Perceived Stress Scale (PSS), including 14 questions within domains covering stressors, irritations, poor coping, anger and difficulties (Cohen, 1994; Kamarck et al., 1983), with scores ranging from 0 to 56 (higher scores indicating higher stress level). Based on previous results of stress in pregnancy from the PreventADALL study, we used a cut-off score of 28 to indicate high stress in the three assessments, as used in other studies (Magi et al., 2020). To assess the association between infant pain and high maternal perceived stress in pregnancy at 18 or 34 weeks and at 3 months postpartum, we recoded three variables: low maternal perceived stress at 3 months (coded 0), high maternal perceived stress at 3 months and low maternal perceived stress in pregnancy (coded 1), and high maternal stress at 3 months and in pregnancy (coded 2).

3.5 | Statistical analyses

Categorical data are presented as number (*n*) and percentages (%), while continuous variables are described with mean, (minimum–maximum) and standard deviation (SD). Possible differences regarding selected background variables between responders and nonresponders were assessed using chi-square tests (categorical variables) or *t*-tests/Mann–Whitney U tests (continuous variables). To determine a normal distribution of the data set we conducted Shapiro–Wilk test and used histogram to assess the bell-shaped symmetrical curve cantered around the mean. Crude between groups comparisons were performed using independent samples *t*-test for continuous, normally distributed variables or a nonparametric Mann–Whitney U-test for variables that were skewed (maternal body mass index). Further, chi-square test was conducted to compare pairs of categorical variables.

Bivariate analyses of categorical data were performed using chi-square tests for categorical variables. To identify potential associations between maternal stress and the pain outcomes (colic, abdominal pain and visits to healthcare with pain or discomfort), we used logistic regression. The results are presented as odds ratios (OR) with 95% confidence intervals (CI).

All tests were two-sided and *p*-values <.05 were considered statistically significant. We consider our study exploratory so no correction for multiple testing was performed. All analyses were conducted using SPSS version 27. The STROBE checklist was followed (Appendix S1).

4 | RESULTS

The baseline characteristics of the 1852 included mother–infant pairs were largely similar to the characteristics of the 542 mother–infant pairs who did not return the 3-month questionnaire (Table 1), except for significantly higher family income, maternal education and more first-time mothers among the respondents.

Overall, 478/1852 (26%) infants were reported to suffer from infant pain symptoms: 59 (3%) with colic, 415 (22%) with abdominal pain and 119 (6%) visited healthcare with other pain or discomfort, with no significant differences between boys and girls overall or for each symptom group (Table 2). In 1347/1852 (73%) infants, there were no reported multimorbidities; infections, eczema or allergic sensitization, while one of these conditions was observed or reported in 226/1852 (12%) infants, two conditions in 65/1852 (4%) infants and three or more conditions in 33/1852 (2%) infants (Table 3).

Parents of infants with pain symptoms reported that the child more often had infections in the upper as well as lower respiratory tract, other possible viral infections and gastroenteritis, but there were no significant associations with urinary tract infections, eczema or allergic sensitization to foods compared to infants without infant pain symptoms (Table 2).

Similarly, in subgroup analyses stratified by type of pain, statistically significant differences in reported morbidity were observed between infants with and without each of the three pain subgroups outcome (colic, abdominal pain or visited healthcare provider with pain or other discomforts) (Table 2).

Urinary tract infections and eczema were more often reported in infants with abdominal pain compared to the no pain group (Table 2).

In univariate analyses, the odds of infant 'pain sum' increased by 8.3 [6.16–11.07] for those with one morbidity compared to infants with no reported morbidities. The infants with two and three morbidities had about 10 times higher odds of infant 'pain sum' compared to infants with no morbidity (OR = 10.3 [6.3–16.9]) and (OR = 10.4 [5.4–20.0]), for two and three morbidities, respectively (Table 3).

Mothers with high level of perceived stress at 3 months postpartum were more likely to report that their infants had colic (OR = 2.5 [1.2–5.0]) or visited healthcare with pain and other discomfort (OR = 2.8 [1.7–4.6]) compared to mothers with low levels of perceived stress. For details, see Table 4. High maternal perceived stress levels were not significantly associated with 'pain sum' and the abdominal pain subgroup, compared to the group with low maternal perceived stress at 3 months.

Mothers with high level of perceived stress in pregnancy combined with high perceived stress at 3 months had statistically significant higher odds of reporting colic. Further high maternal perceived stress increased the odds of reporting infants visiting healthcare with pain and other discomfort, compared with mothers' low maternal stress at 3 months (Table 5). In the colic group, mothers with low perceived stress in pregnancy and high perceived stress only postpartum did not have significantly higher levels of reported colic compared with the mothers with low perceived stress at 3 months postpartum, indicating that high maternal stress in pregnancy is a predictor of high stress at 3 months for the colic group (Table 5).

5 | DISCUSSION

Both infant multimorbidity and higher maternal perceived stress were significantly associated with reported infant pain at 3 months postpartum, compared with infants with no reported pain.

We found that multimorbidity was significantly more common in infants with reported pain than in those without, for gastroenteritis (9% vs. 2%), conjunctivitis (19% vs. 4%), otitis (2% vs. 0%), upper respiratory infections (70% vs. 19%) and lower respiratory infections (10% vs. 2%) (Table 2). Urinary tract infections were statistically significantly more often reported in infants with abdominal pain (1.2% vs. .3%) compared to the no-pain group. To our knowledge, few studies exist on infant pain and association with common multimorbidity in 3-month-old infants. In accordance with our findings, Freedman et al.'s study of colic-like symptoms and severe illness found a prevalence of 1.3% (3/237) with urinary tract infection in infants less than 1 year of age visiting healthcare (Freedman et al., 2009). Supporting our findings on otitis, Hestbaek et al. found an association of colic with ear infection in children under 2 years of age (Hestbaek et al., 2014). Respiratory infections, gastroenteritis and urinary tract infections

TABLE 1 Baseline characteristics are shown for the 1852 included mother–infant pairs and for the 542 who did not complete the three-months questionnaire.

Characteristics	Responder *N* = 1852	Nonresponder *N* = 542	*p*-Value
Maternal			
Age (years)	*n* = 1852	*n* = 542	.073
Mean (min-max) SD	32.5 (20–48) 4.0	32.1 (21–47) 4.5	
Body mass index	*n* = 1822	*n* = 532	.882
Mean (min-max) SD	24.8 (17.2–48.2) 3.6	24.8 (18.1–41.7) 3.8	
Asthma, allergies or eczema n (%)			
No	1781 (76.3)	351 (81.3)	.215
Yes	422 (23.7)	103 (22.7)	
Sick leave n (%)			
No	852 (47.8)	218 (48.0)	.900
Yes	810 (45.5)	203 (44.7)	
Not applicable	119 (6.7)	33 (7.3)	
Country of origin n (%)			
Norway	1157 (67.1)	286 (64.0)	.124
Sweden	388 (22.5)	104 (23.3)	
Nordic	21 (1.2)	7 (1.6)	
Other	158 (9.2)	50 (11.2)	
Living area n (%)			
City high/less populated	1331 (77.2)	337 (75.4)	.201
Suburb/village	307 (17.8)	84 (18.8)	
Countryside	86 (5.0)	26 (5.8)	
Education n (%)			
Primary or high school	173 (10.1)	66 (14.8)	.001
High <4 years	527 (30.7)	163 (36.6)	
High =/>4 years, PhD	1017 (59.2)	216 (48.5)	
Family income			
Low, <600,000	216 (12.7)	86 (19.9)	<.01
600,000–1000 000	719 (42.3)	165 (38.1)	
High>1000 000	766 (45.0)	182 (42.0)	
Marital status n (%)			
Married	746 (43.1)	187 (41.6)	.322
Cohabitant	943 (54.5)	247 (54.9)	
Other	40 (2.3)	16 (3.6)	
Previous pregnancies n (%)			
0	1140 (61.6)	289 (53.3)	.004
1	561 (30.3)	186 (34.3)	
2	132 (7.1)	56 (10.3)	
3	17 (0.9)	11(2.0)	
Caesarean section *n* (%)			
No	1548 (83.7)	446 (82.3)	.431
Yes	301 (16.3)	96 (17.7)	
Infant			
Boys *n* (%)	963 (52.0)	292 (54.0)	.421
Girls	889 (48.0)	250 (46.0)	

TABLE 1 (Continued)

Characteristics	Responder $N = 1852$	Nonresponder $N = 542$	p-Value
Gestational age in days (n)	$n = 1847$	$n = 542$	.077
Mean (min-max) SD	280.5 (245–298) 9.5	279.7 (250–296) 9.1	
Birth weight (kg) (n)	$n = 1844$	$n = 540$	.960
Mean (min-max) SD	3.57 (1.8–5.6) .48	3.6 (1.9–5.0) .49	

are known causes of abdominal pain in school children (Reust & Williams, 2016), but we are not aware of studies on this in infancy. Gastroenteritis is inflammation of the stomach with abdominal pain as one of the symptoms (Dalby-Payne & Elliott, 2011; Graves, 2013), and colic has characteristic behaviours related to abdominal discomfort and pain (Mai et al., 2018).

In our study, eczema was more common (14% vs. 10%) in the subgroup reporting abdominal pain than in the no-pain group (Table 2). In a previous study, we found that 30% of the infants had eczema at 3 months of age, but the research on this early in life measurement is uncertain and further research is needed (Endre et al., 2022). A study on atopic dermatitis and comorbidities in children under 2 years of age found an association with colic (Petriashvili & Jorjoliani, 2020). In an Italian follow-up study of 52 children with severe infant colic, an association was found with various allergic diseases (e.g. allergic rhinitis, conjunctivitis, asthmatic bronchitis and food allergies) and atopic eczema at 10 years of age (Savino et al., 2005). In our study, there were no statically significant differences on eczema between infants with colic and the no-pain group.

We did not find a statistically significant association between positive IgE for food and infant pain symptoms in our study. Food allergies affect up to 10% of young children in Western countries and are associated with gastrointestinal symptoms like colic, but this association is not conclusive (Nocerino et al., 2015).

In our study, the odds of infant 'pain sum' increased by eight times for those with one morbidity and 10 times for the infants with two and three multimorbidities, compared with infants with no morbidities (Table 3). A likely explanation for our findings of associations between infant pain in all pain groups and common infections may be that these conditions are uncomfortable and cause infants to have pain symptoms.

We found that the odds of high maternal perceived stress at 3 months were significantly higher among mothers of infants with colic (OR 2.5) and infants visiting healthcare (OR 2.8) compared with those without any reported pain. Colic and excessive crying are a distressing concern to parents in infancy (Caparros-Gonzalez et al., 2021). Furthermore, in our study, high maternal perceived stress in pregnancy combined with high maternal perceived stress at 3 months seems to be a predictor of reporting colic at 3 months postpartum (Table 5), while high maternal perceived stress at 3 months but not during pregnancy was not significant at 3 months postpartum, compared to mothers with low levels of perceived stress (Table 5). In a previous study we conducted on the same population, mothers with high perceived stress at 34 weeks of pregnancy reported higher odds of infants with colic at 3 months postpartum, although our findings did not reach the level of statistical significance (OR 1.56, 95% CI [.70–3.48]) (Despriee et al., 2022). In line with our findings, Bolten et al. showed that 20% of the variance in infant crying behaviour was connected to maternal prenatal stress and self-efficacy. Further, mothers reported more symptoms of stress in pregnancy if their infants cried excessively (Bolten et al., 2012). Our results are also supported by a study on maternal stress and early regulatory disorders in infancy reporting that infant fussing and crying are associated with maternal stress (Georg et al., 2021). Higher levels of stress exposure, like excessive crying, are associated with increased difficulties in developing positive mother–infant relationships (Kim et al., 2020), and it is therefore important to support these families. While our colic and abdominal pain symptoms did not assess severity, a total of 119/478 (24%) of infants with pain in our population visited healthcare provider because of the pain (Table 2). Supporting our findings, Lucassen et al. (2001) found that many parents with crying infants do not seek or need professional help.

Our findings of the relationship between maternal stress and infant colic may contribute to early perinatal targeting and support, already from pregnancy. We found that 6% visited healthcare providers because of infant pain or discomfort after birth. Supporting parents to cope is recommended (Søndergaard et al., 2000; Zeevenhooven et al., 2018). A recommended management strategy to improve the parents stress and fears about their infant's condition is parental education and reassurance that colic is benign and self-limiting (Scott-Jupp, 2018; Zeevenhooven et al., 2018). Furthermore, sources of physical and emotional distress should be identified and met with the accurate support to help the parents to cope with their infant's symptoms and to provide support for the infant–family relationship. Our findings suggest that also other pain symptoms than colic were associated with higher maternal stress. The clinicians should recognise the parents' perceptions and offer continuous support, this may influence the parents view on their capability to care for their infant (Shamir et al., 2013; Zeevenhooven et al., 2017, 2018). Further, Stapleton et al found that mothers who perceived stronger social support from their partners in pregnancy had lower emotional distress postpartum (Stapleton et al., 2012). Use of support programmes with information about infant crying as well as strengthen parenting to improve parental well-being and coping are promising (Zeifman & St James-Roberts, 2017).

TABLE 2 Proportions of infants with selected multimorbidities and maternal perceived stress at 3 months postpartum.

				Subgroups infant pain								
	Infant pain sum[a] *n* = 478			Colic *n* = 59			Abdominal pain *n* = 415			Visit health care providers with pain or other discomforts *n* = 119		
Variables	No	Yes	*p*-value	No	Yes	*p*-value	No	Yes	*p*-value	No	Yes	p-value
Sex n (%)												
Boy	699 (50.9)	264 (55.2)	.101	930 (51.9)	33 (55.9)	.539	734 (51.1)	229 (55.2)	.141	895 (51.6)	68 (57.1)	0.246
Girl	675 (49.1)	214 (44.5)		896 (48.1)	26 (44.1)		703 (48.9)	186 (44.8)		838 (48.4)	51 (42.9)	
Eye infection n (%)												
No	1325 (96.4)	386 (80.8)	<.001	1662 (92.7)	49 (83.1)	.006	1379 (96.0)	332 (80.0)	<.001	1615 (93.2)	96 (80.7)	<.001
Yes	49 (3.6)	92 (19.2)		131 (7.3)	10 (16.9)		58 (4.0)	83 (20.0)		118 (6.8)	23 (19.3)	
Otitis *n* (%)												
No	1371 (99.8)	469 (98.1)	<.001	1785 (99.6)	55 (93.2)	<.001	1429 (99.4)	411 (99.0)	.363	1724 (99.5)	116 (97.5)	.008
Yes	3 (0.2)	9 (1.9)		8 (0.4)	4 (6.8)		8 (0.6)	4 (1.0)		9 (0.5)	3 (2.5)	
Upper respiratory tract infection(cold) *n* (%)												
No	1110 (80.8)	104 (21.8)	<.001	1196 (66.7)	18 (31.5)	<.001	1124 (78.2)	90 (21.7)	<.001	1175 (67.8)	39 (32.8)	<.001
Yes	264 (19.2)	374 (78.2)		597 (33.3)	41 (69.5)		313 (21.8)	325 (78.3)		558 (32.2)	80 (67.2)	
Lower respiratory tract infections (Bronchiolitis/RS/ Pneumonia/other) *n* (%)												
No	1344 (97.8)	432 (90.4)	<.001	1746 (97.4)	51(86.4)	<.001	1410 (98.1)	387 (93.2)	<.001	1685 (97.5)	108 (90.8)	.001
Yes	30 (2.2)	46 (9.6)		47 (2.6)	8 (13.6)		27 (1.9)	28 (6.8)		44 (2.5)	11 (9.2)	
Other infection symptoms (Fever/virus/flu and flulike symptoms) n (%)												
No	1321 (96.1)	379 (79.3)	<.001	1661 (92.7)	39 (74.1)	<.001	1360 (94.6)	340 (81.9)	<.001	1622 (93.6)	78 (65.5)	<.001
Yes	53 (3.9)	99 (20.7)		131 (7.3)	20 (33.9)		77 (5.4)	75 (18.1)		111 (6.4)	41 (34.5)	
Gastro enteritis *n* (%)												
No	1352 (98.4)	436 (91.2)	<.001	1734 (96.7)	54 (91.5)	.034	1410 (98.1)	378 (91.1)	<.001	1689 (97.5)	99 (83.2)	<.001
Yes	22 (1.6)	42 (8.8)		59 (3.3)	5 (8.5)		27 (1.9)	37 (8.9)		44 (2.5)	20 (16.8)	
Urinary tract infection *n* (%)												
No	1370 (99.7)	473 (99.0)	.055	1785 (99.6)	58 (98.3)	.175	1433 (99.7)	410 (98.8)	.017	1725 (99.5)	118 (99.2)	.556
Yes	4 (0.3)	5 (1.0)		8 (0.4)	1 (1.7)		4 (0.3)	5 (1.2)		8 (0.5)	1 (0.8)	
Eczema *n* (%)												
No	1200 (90.0)	409 (87.4)	.113	1553 (89.1)	56 (96.6)	.081	1256 (90.2)	353 (86.5)	.044	1508 (89.4)	101 (87.8)	.535
Yes	133 (12.0)	59 (12.6)		190 (10.9)	8 (13.4)		137 (9.8)	55 (13.5)		178 (10.6)	14 (12.2)	

TABLE 2 (Continued)

Variables	Infant pain sum[a] $n=478$			Colic $n=59$			Abdominal pain $n=415$			Visit health care providers with pain or other discomforts $n=119$		
	No	Yes	*p*-value	No	Yes	*p*-value	No	Yes	*p*-value	No	Yes	*p*-value
Sensitised to at least one food allergen (milk, wheat, egg, peanut) *n* (%)												
No	1329 (96.3)	460 (96.2)	1.000	1724 (96.2)	59 (100.0)	.168	1385 (96.4)	398 (95.9)	.657	1667 (96.2)	116 (97.5)	.621
Yes	51 (3.7)	18 (3.8)		69 (3.8)	0 (.0)		52 (3.6)	17 (4.1)		66 (3.8)	3 (2.5)	
Maternal Perceived Stress Scale (PSS) 3 months *n* (%)												
Low	1274 (92.7)	432 (90.4)	.001	1657 (92.4)	49 (83.1)	.009	1327 (92.3)	379 (91.3)	.497	1608 (92.8)	98 (82.4)	.001
High	100 (7.3)	46 (9.6)		136 (7.6)	10 (16.9)		110 (7.7)	36 (8.7)		125 (7.2)	21 (17.6)	

[a]Infant pain sum: at least one of the pain symptoms colic, abdominal pain and/or visit to health care providers with pain or discomfort. The pain symptoms have some overlap.

TABLE 3 Univariate regression of the degree of infant multimorbidity on infant 'pain sum'[a]

	N	OR	95% CI	*p*-value
Multimorbidity[b]				
0 (ref)	1347	1		
1	226	8.3	6.16–11.07	<.001
2	65	10.3	6.24–16.89	<.001
3 or more	33	10.4	5.43–20.01	<.001

[a]Colic, abdominal pain and/or visits to healthcare providers with pain or other discomfort.

[b]Multimorbidity: Infections, eczema and/or sensitised to at least one food allergen (milk, wheat, egg and peanut).

5.1 | Strengths and limitations

A strength is that this study is a part of a prospective study, with longitudinal design and frequent follow-up investigations and questionnaires. This reduces the risk of recall bias. Our study is a sub study in the PreventADALL-study. According to power analysis the sample size for the PreventADALL RCT was >2000 mother–infant pairs, and 2394 were included after birth (Lødrup Carlsen et al., 2018). There was not performed specific power analysis for this sub study, because all the mother–infant pairs were already included, however, the size of our study population is similar to some previous publications on infant colic (Wolke et al., 2017). Additionally, all the statistical methods and choice of analyses were approved by a professional statistician.

The Norwegian and Swedish translation of the validated and well-established Perceived stress scale (PSS) Questionnaire (Chan & La Greca, 2020; Cohen, 1994; Eskin & Parr, 1996; Østerås et al., 2018) was integrated in the electronic questionnaires sent to the mothers. However, specific validation studies for the remaining questions used in PreventADALL have not been performed. The electronic questionnaires were developed by the study team in close collaboration with experts in the field and the University Center for Information Technology (USIT) at the University of Oslo—for electronic responses via computers, tablets and smartphones. Electronic form (nettskjema.uio.no) tool administrating online data collection is used both for registering clinical data (including adverse events) by study personnel and the self-reported diaries/questionnaires from the mothers. Swift delivering of fully Pretty Good Privacy (PGP) encrypted answers to the projects secure infrastructure was ensured. This includes a set of virtual machines (VMs) for managing/post-processing data and dedicated secure storage within the central TSD system. Whenever possible, core questions were included from collaborating studies to facilitate harmonisation of follow-up investigations of children, such as the MeDALL core questionnaire (Hohmann et al., 2014), the two United Kingdom based studies Isle of Wight 3rd generation study (Mitchell et al., 2018) and the Barrier Enhancement for Eczema Prevention (BEEP) study (Munthe-Kaas et al., 2006) as described in the first publication from PreventADALL (Lødrup Carlsen et al., 2018). Some of the questions used were

TABLE 4 Univariate regression. Maternal stress at 3 months, infant pain subgroups.

	Colic			Abdominal pain			Visit to health care providers with pain or other discomforts		
Variables	**OR**	**CI 95%**	***p*-value**	**OR**	**CI 95%**	***p*-value**	**OR**	**CI 95%**	***p*-value**
Maternal stress 3 months PSS Low(ref) PSS High	1 2.49	1.23–5.03	.011	1 1.15	0.77–0.70	.497	1 2.76	1.66–4.57	<.001

TABLE 5 Associations between high maternal perceived stress at 3 months postpartum and high maternal perceived stress in pregnancy in subgroup of infants with pain.

	Pain sum[a] *n* = 475			Colic *n* = 59			Abdominal pain *n* = 412			Visits to healthcare with pain or other discomfort *n* = 117		
Variables for high maternal stress	**OR**	**CI**	***p*-value**	**OR**	**CI**	***p*-value**	**OR**	**CI**	***p*-value**	**OR**	**CI**	***p*-value**
Low maternal stress at 3 months (ref)	1			1			1			1		
High maternal stress at 3 months but NOT in pregnancy (1)	1.25	.70–2.24	.444	2.55	.89–7.33	.082	1.14	.62–2.11	.676	3.08	1.47–6.45	.003
High maternal stress at 3 months AND in pregnancy (2)	1.37	.85–2.21	.197	2.67	1.11–6.43	.028	1.06	.62–1.79	.839	2.28	1.14–4.55	.020

[a]'Pain sum' includes all three pain symptoms (colic, abdominal pain and/or visits to healthcare provider with pain or other discomforts).

based on other similar cohort studies such as *the* Environment and Childhood Asthma (ECA) study, the *Barn/Children*, *Asthma*, Milieu, Stockholm, Epidemiology (BAMSE) study (Wickman et al., 2002), as well as the *Norwegian Mother, Father and Child Cohort (MoBA) Study* (Magnus et al., 2006).

Prick tests and serum samples for IgE sensitization and examinations for assessing eczema were performed in hospital facilities by trained and experienced personnel.

All researchers were experienced nurses and doctors.

There are slight demographic differences between the populations who answered (77%) and did not answer the 3-month questionnaire (23%). The challenge of not answering/drop-outs is common in prospective studies and this may lead to selection bias (Laake et al., 2008; Polit et al., 2021). This is described in the results. Our study had frequent visits and questionnaires, this could be a load on the parents and lead to drop out.

It is important for the validity of a study that a concept is accurately measured (Roberta & Alison, 2015). 'Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors' p.1 (IASP, 2020). This makes it challenging for the parents to 'measure' the infants subjective pain symptoms and discomforts, we must rely on the reporting of a second part, this could lead to report bias. We did not use a definition of colic in the questionnaire, only the parents' subjective perception. Pain and discomfort are subjective perceptions, so it may be difficult for the parent to assess what kind of pain their infant is experiencing. Exploring different parent reported pain symptoms, colic, abdominal pains (not colic) and visits to healthcare with pains and other discomfort should be a strength, because Steutel et al. (2014) discussed in their review the difficulty of assessing the validity in definition of infant colic because half of the authors had their own definition of colic and the majority focused on the infants crying, this could be due to misclassification of infant colic and abdominal pains (Steutel et al., 2014).

6 | CONCLUSION

Colic is usually diagnosed after the elimination of other concerns. However, our results indicate that colic and infant pain are associated with higher likelihood of having common infections, eczema and/or high maternal perceived stress at 3 months of age. The odds of reporting infant pain increased with the presence of multimorbidity compared with infants with no multimorbidity. Our findings were consistent for all three pain outcomes. However, our results need to be replicated and confirmed in other studies.

Mothers with high perceived stress levels had higher odds of reporting having infants with colic and visiting healthcare services because of infant pain and other discomforts compared with mothers with low perceived stress. Our data indicate that high maternal perceived stress in pregnancy, combined with high perceived maternal stress at 3 months is a predictive factor for infant colic. Other studies need to be conducted to confirm these results.

7 | RELEVANCE TO CLINICAL PRACTICE

Colic, abdominal pain and visiting healthcare provider with pain or other discomforts are common concerns in infancy. Our study indicates that infant pain is associated with common infant infections, infant eczema and maternal perceived stress, which may be useful when planning diagnostic, treatment and coping strategies in infant and family care. Parental education and reassuring the parents that colic is benign and self-limiting is important (Zeevenhooven et al., 2018). Our findings, even though it must be confirmed, could contribute to a more precise approach and education of infant pain to parents, including attention to infection symptom. Further, the attention to maternal stress and supporting the family could start earlier. This is important for providing support to the infant and the family.

AUTHOR CONTRIBUTIONS

Åshild Wik Despriée carried out the data collection and data management in Norway, was responsible for the study design, data analysis and preformed and drafted the initial manuscript. Håvard Skjerven, Karin Lødrup Carlsen and Kari Glavin has conceptualised, supervised the study and critically reviewed and revised the manuscript. Milada Cvancarova Småstuen has contributed on data analysis and overview data work and critically reviewed and revised the manuscript. Cilla Söderhäll, Gunilla Hedin, Live Nordhagen and Caroline-Aleksi Olsson Mägi carried out the data collection, critically reviewed data analysis and revised the manuscript. Christine M Jonassen, Eva Maria Rehbinder and Björn Nordlund, local responsible leaders, critically reviewed data analysis and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest associated with this article.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

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