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Research paper

The efficacy of probiotics and/or n-3 long-chain polyunsaturated fatty acids intervention on maternal prenatal and postnatal depressive and anxiety symptoms among overweight and obese women

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ABSTRACT

Background: Maternal depression and anxiety may endanger well-being of both mother and child. We investigated the efficacy of probiotics and/or fish oil (FO) in modifying pre- and postnatal depressive and anxiety symptoms. Symptom trajectories were identified and the influence of lifestyle factors on symptoms was evaluated.

Methods: Overweight women ($n = 439$) were randomized to intervention groups (probiotics+FO, probiotics+-placebo, FO+placebo, placebo+placebo) from early pregnancy until six months postpartum, and assessed for depressive and anxiety symptoms with Edinburgh Postnatal Depression Scale (EPDS) and Anxiety subscale of Symptoms Checklist (SCL-90) at early and late pregnancy and three, six and 12 months postpartum. Latent growth mixture modeling was used to model the symptom courses. Dietary quality and physical activity were assessed with validated indices.

Results: Symptom scores were generally low. Statistically significant intervention effect was seen during pregnancy ($p = 0.017$): EPDS scores increased (by 1.11 points) in the FO+probiotics group and decreased (by 0.85 points) in the FO+placebo group. At 12 months postpartum, FO+placebo group had lower EPDS scores compared to probiotics+placebo group ($p = 0.039$). No differences in SCL scores were seen in response to the intervention. Irrespective of the intervention, three depressive and two anxiety symptoms trajectories were identified. Dietary quality correlated negatively with depressive symptoms in early pregnancy and six months postpartum and with anxiety symptoms in early pregnancy. Perinatal events including mother-reported colic were related to symptoms.

Limitations: Secondary outcomes of the primary trial.

Conclusions: Intervention had a modest impact on depressive symptoms. Diet and obstetric events were associated with depressive and anxiety symptoms.

1. Introduction

Symptoms of depression and anxiety are common among women in the perinatal period. Approximately 19% of women in high income countries suffer from anxiety symptoms of varying severities in the prenatal period and 14% in the postnatal period (Dennis et al., 2017). Symptoms of depression are also common, experienced by approximately 18% of women in the prenatal period and 19% in the postnatal period (Howard et al., 2014). It is likely that there is variation in the persistence and timing of depressive and anxiety symptoms (Korja et al.,

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2018), and they may differently affect both the mother's transmission to parenthood and the development of the infant. Depressive and anxiety symptoms during pregnancy are also predictors for postnatal depressive and anxiety symptoms (Heron et al., 2004). In addition to mothers' subjective suffering, these symptoms may have a fundamental negative effect on the development and the mental health of the child, and some of these effects may originate already from the prenatal period. For instance, this has been demonstrated in studies where antenatal maternal depressive symptoms contributed to the child's temperament assessed as negative affectivity (Rouse and Goodman, 2014) and increased the risk that the child may suffer from depression later in his/her life (Pearson et al., 2013). Maternal antenatal depressive or anxiety symptoms may affect fetal physiological development; together with insensitive maternal care, antenatal anxiety or mood diagnosis induce higher cortisol levels in children and thus may be associated with maladaptive physiological functioning (Kaplan et al., 2008). Considering these findings of maternal psychological distress on child's development, it is important to try to prevent and treat maternal symptoms of anxiety and depression from early pregnancy onwards.

The latest research has demonstrated that depressive and anxiety symptoms may be connected to the human gut microbiota (Naveed et al., 2020). In addition, maternal depressive symptoms in the pre- and postnatal period may be associated with the child's gut microbiome (Kang et al., 2018) indicating that one potential mechanism would be mediated via mother-child transfer through the gut-brain axis. Indeed, the consumption of probiotics has been claimed to ease maternal depressive and anxiety symptoms: in a recent randomized double-blind placebo-controlled trial, women receiving probiotic *Lactobacillus rhamnosus* HN001 during pregnancy and 6 months postpartum, if breastfeeding, were found to manifest with fewer depressive and anxiety symptoms postpartum (Slykerman et al., 2017). Thus, alongside the many benefits of n-3 long-chain polyunsaturated fatty acids (LC-PUFAs) such as their immunoregulatory properties and advancement of child neurodevelopment (Demmelmair and Koletzko, 2015), it seems that these fatty acids may also be associated with advantageous effects on pre- and postnatal depressive symptoms. Mothers with lower levels of total n-3 LC-PUFAs suffered more from depressive symptoms than those with higher levels (Lin et al., 2017). There are also some indications that the quality of diet and physical activity are associated with anxiety and depressive symptoms. A recent systematic review and meta-analysis concluded that a higher quality of diet was associated with a lower risk for the onset of depressive symptoms in females and males from all age groups (Molendijk et al., 2018). Furthermore, Lindwall et al. (2014) found that an increase in physical activity was associated with a reduction in depressive and anxiety symptoms.

Therefore, we hypothesized that the consumption of probiotics and n-3 LC-PUFAs as fish oil (FO) individually or in combination would be able to reduce the presence of pre- and postnatal depressive and anxiety symptoms during and after pregnancy. Furthermore, we speculated that lifestyle factors including high quality diet and high level of physical activity would associate with lower levels of depressive and anxiety symptoms. The aims of this study were 1) to investigate the effect of probiotics and/or FO on pre- and postnatal maternal depressive and anxiety symptoms, 2) to monitor the development of these symptoms from pregnancy up to one year after giving birth and 3) to study the extent to which lifestyle (diet and physical activity), obstetric and child related factors associate with the symptoms among healthy overweight and obese women, a risk group for metabolic and psychological aberrations.

2. Methods

2.1. Study design and participants

A total of 439 pregnant women were recruited into a mother-child dietary intervention study (ClinicalTrials.gov Identifier: NCT01922791) in the University of Turku and Turku University Hospital, Turku, Finland between October 2013 – July 2017. The study design has been described in detail previously (Pellonperä et al., 2019) with predefined secondary outcomes of the study being reported here. Briefly, the inclusion criteria were early pregnancy (<18 weeks of gestation), self-reported pre-pregnancy overweight (body mass index (BMI) $\geq$ 25) and the absence of chronic diseases (except for asthma and allergies). The exclusion criteria were multifetal pregnancy, the presence of inflammatory, metabolic or gastrointestinal diseases. The women who became pregnant again before 12 months postpartum were excluded from the postpartum analyses. At the first study visit in early pregnancy, the women were randomized in a double-blind manner into four intervention groups; probiotics+placebo (i.e. placebo for FO), FO+placebo (i.e. placebo for probiotics), FO+probiotics or placebo+-placebo (placebo for probiotics and placebo for FO). Dietary supplements were consumed from the first study visit throughout the pregnancy until 6 months after delivery. Women were instructed to take two FO capsules (a total of 2.4 g of n-3 LC-PUFA of which 1.9 g docosahexaenoic acid and 0.22 g eicosapentaenoic acid, Croda Europe Ltd., Leek, UK), and one probiotic capsule (*Lactobacillus rhamnosus* HN001 and *Bifidobacterium animalis* ssp. *lactis* 420, each 10^{10} CFU per capsule, ATCC SD5675 and DSM 22,089; Dupont Nutrition & Health, Niebüll, Germany) every day. Placebo for the probiotics consisted of microcrystalline cellulose and that for FO consisted of medium chain fatty acids. Subjects were instructed not to consume any other probiotic or FO products during the trial. Compliance with the consumption of capsules was assessed first by a phone call at mean 28 gestation weeks, subsequently by interview at the second study visit (good compliance being defined as taking study capsules $\geq$5 days/week reported at both time points), and thirdly by counting the numbers of consumed fish oil capsules, i.e., subtracting the capsules returned to the study unit from the total provided by a random sample of 62 women (14% of participants). Good compliance was reported by 88.4% of the women, with this value being similar in the four groups (P>0.98, data not shown). The compliance calculated from the returned fish oil capsules indicated that a mean of 91.8% (SD 15.9) of the capsules had been consumed.

This study was performed according to the guidelines of the Declaration of Helsinki and the protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland. Written informed consent was obtained from all subjects.

2.2. Measures

2.2.1. Depressive and anxiety symptoms

Maternal depressive and anxiety symptoms were assessed in early (mean: 13.9 +/- 2.1 gestational weeks) and late (mean: 35.2 +/- 0.9 gestational weeks) pregnancy and at three, six and 12 months postpartum. Depressive symptoms were assessed using the Edinburgh Postnatal Depression scale (EPDS) (Cox et al., 1987). EPDS is a 10 item self-report scale and each item is scored on a 4-point Likert-scale from 0 to 3. The total score ranges between 0 and 30 points with 0 being the minimum and 30 the maximum score. For example, the questionnaire includes questions of experiences of pleasure, sadness and guilt. The EPDS has been developed for assessing maternal postnatal depression but it can also be used to assess prenatal depression (Matijasevich et al., 2015). A score of 13 or above is considered as a cut-off for depression (Gaynes et al., 2005; Rubertsson et al., 2011) and is also considered in the Finnish maternal welfare system as an indicator of the possibility of a major depressive disorder, demanding further attention (Finnish Institute for Health and Welfare, 2019). Further, EPDS subscales were calculated to describe non-specific depressive symptoms (DEP), anhedonia (ANH) and anxietal symptoms (ANX). DEP consists of items 7, 8, 9 and 10, ANH items 1 and 2 and ANX items 3, 4 and 5 of the EPDS scale (Tuohy & McVey, 2008).

The SCL-90/anxiety subscale questionnaire was used to assess maternal general anxiety symptoms (the first study visit data missing

from 65 participants). The SCL-90 was developed to assess anxiety and other psychiatric symptoms (Derogatis, 1979). The anxiety dimension of SCL-90 consists of 10 items scored on a 5-point Likert scale (from 0 to 4). The total score ranges between 0 and 40 points with 0 being the minimum and 40 the maximum score. The subscale assesses nervousness, tension and feelings of panic and terror (Holi, 2003). A cut-point ≥ 11 is used as an indicator of anxiety in this study.

At baseline, the internal consistencies of EPDS (Cronbach's alpha 0.82) and SCL-90 (Cronbach's alpha 0.84) were good.

2.2.2. Dietary quality, physical activity and clinical characteristics

Dietary quality with respect to that recommended was inquired via the validated Index of Diet Quality (IDQ) (Leppälä et al., 2010). The IDQ comprises of 18 multiple-choice questions about the frequency and quality of consumed foods including whole-grain foods, vegetable oil based spreads and salad dressings, dairy, vegetables, fruit and berries and sugar-rich foods. The total IDQ score ranges from 0 to 15 points such that scores $\geq$ 10 are considered as health-promoting (good dietary quality), with a score $<$ 10 designated as a poor dietary quality with respect to dietary recommendations.

Physical activity was assessed with a questionnaire in which women were asked to report the intensity, frequency and duration of their habitual leisure-time physical activity during the preceding week. A metabolic equivalent index for leisure-time physical activity (MET-index) (Mansikkaniemi et al., 2012) was calculated from the product of intensity x frequency x duration of activity (MET h/wk) on all study visits. The coefficients for the intensity of physical activity were estimated from the existing tables (Ainsworth et al., 1993).

The prepregnancy BMI was calculated based on welfare clinics records of maternal self-reported pre-pregnancy weight and height that was measured at the first study visit in early pregnancy. Weight in kilograms was divided by height that was squared. The accuracy of the self-report weight was verified by a high correlation coefficient between BMI calculated from the self-report weight and BMI calculated from the weight measured at the first study visit: $r = 0.96$ ($p<0.001$; $n = 438$). Women filled in questionnaires concerning their health, family, education, smoking habits and child medical history. Mothers were also asked if they thought that their child had suffered from colic over the first three months of life. The obstetric history was viewed from hospital records.

2.3. Statistics

IBM SPSS Statistics version 25 was used for statistical analyses. First, descriptive statistics of all study variables were estimated. If the mother had a maximum of three missing items at a measurement point, the missing items were imputed using the mean of all responses of the item. The trajectories of symptoms from early pregnancy until 12 months postpartum were also modeled with Latent Growth Mixture Modelling (LGMM; Muthén and Muthén, 2000) in Mplus 6 (Muthén and Muthén, 1998). Maternal depressive and anxiety symptoms were evaluated as classified variables based on the clinical cut-off score and as continuous sum scores to estimate the effect of the intervention. Change scores of EPDS and SCL-90 from late to early pregnancy were subtracted. The differences in depressive, including subscales, and anxiety symptoms between intervention groups were tested with Kruskal-Wallis test, with the Bonferroni method being applied in further post-hoc comparisons. No confounding factors were included in the analyses as no differences in the clinical characteristics or IDQ score between the intervention groups were identified ($p>0.13$). The family history of diabetes was more common in FO+placebo group compared to the probiotics+placebo and placebo+placebo groups (Pellonperä et al., 2019), but this variable was not included in the analysis as it was considered not to influence the outcomes.

The associations between the mothers' diet and physical activity habits, and depressive and anxiety symptoms were modeled with Spearman correlations. The following variables were investigated to study the extent to which they associate with the depression and anxiety symptoms; mother's BMI, education (high education [university and college] and others), smoking before pregnancy, a diagnosis of gestational diabetes mellitus, primiparity, mode of delivery (vaginal unassisted, vacuum extraction, elective cesarean and acute and emergency cesarean), delivery before gestational week 37 and delivery after gestational week 42, being small for gestational age, infant's macrosomia, infant's admission to neonatal intensive care unit after birth and infant's congenital malformation. The associations were tested with Pearson chi-square test, Fisher's exact test, Mann-Whitney *U* test or Kruskal-Wallis test with the Bonferroni method in further post-hoc comparisons. Two-sided statistical tests were used, and p-values less than 0.05 were considered statistically significant.

2.3.1. Latent growth mixture modeling

In order to model the trajectories of depressive and general anxiety symptoms (the EPDS and SCL-90, respectively) Latent Growth Mixture Modelling (LGMM; Muthén and Muthén, 2000) was used in Mplus 6 (Muthén and Muthén, 1998–2011). In the LGMM approach, growth curves of symptoms are estimated for each individual, separately for each symptom category, and then prototypic curves are identified for the whole sample. The aim is to select latent curves, that is "the developmental patterns" in those symptoms that most optimally describe the data and are also interpretable. Individual item scores were used in the models, and participants with missing data were incorporated in the analyses with maximum likelihood under the missing-at-random assumption (Graham, 2009), in order to minimize bias (Nagin, 2005).

First, the factor structures of prenatal psychological distress questionnaires were examined separately for general anxiety and depressive symptoms using structural equation modelling. The longitudinal Confirmatory Factor Analysis of the EPDS and SCL-90 displayed a good fit with the data [*SCL-90*: χ^2 (1087)= 1962.703, $p < 0.0001$, comparative fit index (CFI) = 0.87, root mean square error of approximation = 0.04, standardized root mean square residual = 0.14. Items 3 and 6, 5 and 10, 7 and 10, and 5 and 7 were allowed to correlate to improve model fit; *EPDS*: χ^2 (1092)= 1729.412, $p < 0.0001$, comparative fit index (CFI) = 0.90, root mean square error of approximation = 0.04, standardized root mean square residual = 0.11. Consecutive Items 1 and 2, 3 and 4, and 4 and 5 were allowed to correlate to improve the model's fit.].

Second, the number of latent growth curves was established. This was done by increasing the number of subgroups in the LGMM models and comparing fit indices of the models as the number of subgroups increased. The following criteria were used for the decision about the optimal number of groups: Bayesian information criteria (BIC, where a lower value indicates a better model fit; Nylund et al., 2007), the posterior probability for each trajectory group (referring to the probability of an individual belonging to a group; here a score of $>$ 0.80 was preferred; Nagin, 2005), and entropy rate indexing classification accuracy ($>$ 0.80 indicating excellent accuracy; Lubke & Muthen, 2007). In addition, theoretical and clinical interpretabilities of the class solutions were used when selecting the best model.

In the SCL-90 LGMM, a 2-group solution was the best fit with the data (see Supplementary Table 1). Here, the two groups were "Low and stable" ($n = 397$, estimate of intercept = 4.31, estimate of slope = −0.42, $p = 0.08$) and "Moderate and increasing" ($n = 31$, estimate of intercept = 6.39, estimate of slope = 1.87, $p = 0.06$). In the EPDS LGMM, all the statistical indices continued to improve and/or were satisfactory up to a 3-group model (Supplementary Table 1). The groups were labelled as "Low and stable" ($n = 345$, estimate of intercept = 3.39, estimate of slope = −0.15, $p = 0.31$) and "Moderate and increasing" ($n = 47$, estimate of intercept = 5.21, estimate of slope = 1.74, $p < 0.01$), and "High and decreasing" ($n = 47$, estimate of intercept = 11.20, estimate of slope = −1.33, $p < 0.0001$).

3. Results

The flow chart of the study is shown in Fig. 1. EPDS scores were available from 438 women and SCL-90 scores from 373 women in the early pregnancy. Until the last measurement point at one year after delivery, 264 EPDS scores and 264 SCL-90 scores were available for the analyses.

3.1. Clinical characteristics

The characteristics of the participants are shown in Table 1. Most (60.7%) of the participating women were overweight (BMI ≥ 25 & <30) with the remaining 39.3% being classified as obese (BMI ≥ 30). The majority of the women were highly educated and approximately half were expecting their first child.

Generally, at the different time points, the levels of depressive (mean 3.87–4.54 at different time points) and anxiety symptoms (mean 1.88–2.90) were low. The following percentages of women scored above the clinical cut off of ≥13 for EPDS: early pregnancy 3.9%, late pregnancy 5.1%, three months 3%, six months 4.7% and 12 months 5.3% and SCL-90 cut off ≥11, early pregnancy 4.8%, late pregnancy 4.0%, three months 2.8%, six months 4.0% and 12 months 3.0%.

3.2. Trajectories of the maternal depressive and anxiety symptoms from early pregnancy until 12 months postpartum

Maternal depressive and anxiety symptoms were modeled using latent growth mixture modeling (LGMM). We identified three depressive symptoms trajectories: Low and stable ($n = 345$), Moderate and increasing ($n = 47$) and High and decreasing ($n = 47$) and two anxiety symptoms trajectories: Low and stable ($n = 397$) and Moderate and increasing ($n = 31$) (See Methods and Fig. 2). The latent groups did not exhibit any interactions with the intervention groups, i.e. the trajectories were independently distributed across the intervention groups, EDPS $p = 0.055$ and SCL-90 $p = 0.550$.

3.3. Impact of dietary intervention on depressive and anxiety symptoms

When evaluating each time point separately, the intervention groups differed in EPDS scores at three, six and 12 months postpartum. However, in the post hoc comparisons only one difference remained statistically significant; FO+placebo group values were lower compared to those in the probiotics+placebo group at 12 months postpartum (Table 2). When compared to baseline, the intervention had a significant impact on the change in EPDS mean scores during the pregnancy. This was attributable to an increase in depressive symptoms by 1.11 points in the FO+probiotics group as compared to a decrease by 0.85 points in the FO+placebo group from early to late pregnancy (Table 2). There were no other differences in the EPDS scores due to the intervention. In addition, no impact was detected on SCL-90 scores attributable to the consumption of probiotics and/or FO either during or after pregnancy (Table 3).

In the evaluation of the EPDS subscales (Supplementary Table 2), non-specific depressive symptoms differed statistically significantly between intervention groups in late pregnancy and three months postpartum. However, in the post hoc comparisons there was no statistically significant differences. When evaluating the change from early to late pregnancy, rise in non-specific depressive symptoms was detected FO+probiotics compared to a decrease in FO+placebo group. Also an increase in FO+probiotics group compared to placebo+placebo group

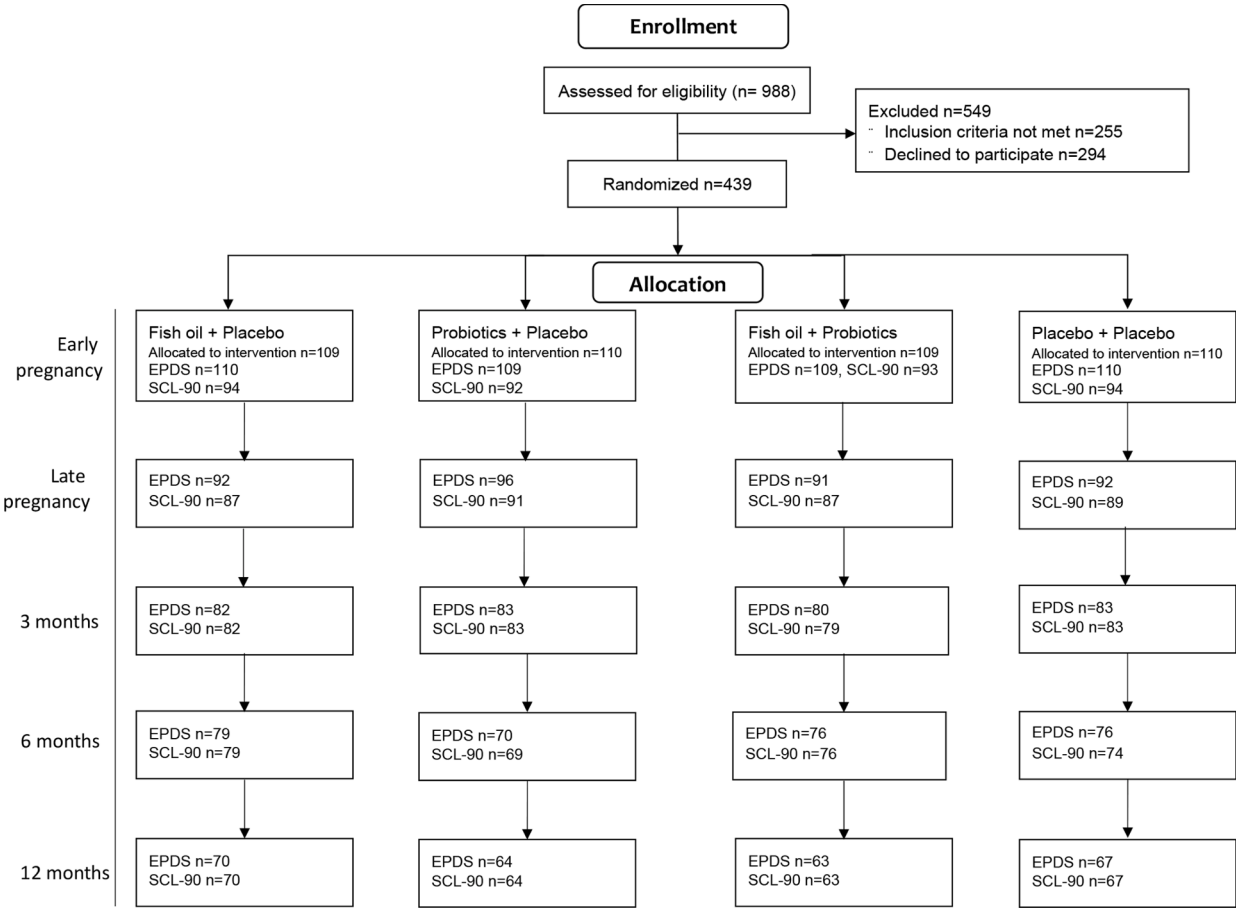

Fig. 1. Flow diagram.

Table 1
Clinical characteristics of the participating women.

Characteristics	
Age, Mean (SD)	30.6 (4.6)
BMI, n (%)	
Overweight	266 (60.7)
Obese	172 (39.3)
Primipara, n (%)	210 (47.9)
College or university education, n (%)	239 (61.1)
Smoking before pregnancy, n (%)	86 (21.9)
Mode of delivery, n (%)	
Vaginal unassisted	277 (73.1)
Vacuum extraction	39 (10.3)
Elective cesarean	25 (6.6)
Acute cesarean & emergency cesarean	38 (10.0)
Delivery < 37+0 gestational week, n (%)	22 (5.8)
Delivery > 42+0 gestational week, n (%)	5 (1.3)
Infant born small for gestational age ≤ −2 SD, n (%)	13 (3.4)
Infant born macrosomic ≥ +2 SD or ≥4500 g, n (%)	16 (4.2)
Infant admitted to neonatal intensive care unit, n (%)	52 (13.8)
Infant's congenital malformation, n (%)	14 (3.7)
Mother reported that her baby had colic (at 3 mo), n (%)	
Yes	27 (8.3)
No	269 (82.5)
Not sure	30 (9.2)
IDQ, mean (SD)	
Early pregnancy, $n = 437$	9.4 (2.1)
Late pregnancy, $n = 374$	9.6 (2.1)
3 months, $n = 323$	9.4 (2.1)
6 months, $n = 286$	9.4 (2.0)
12 months, $n = 264$	9.4 (2.1)
MET, mean (SD)	
Early pregnancy, $n = 434$	9.1 (10.9)
Late pregnancy, $n = 368$	5.3 (7.7)
3 months, $n = 323$	10.5 (12.5)
6 months, $n = 298$	11.3 (13.0)
12 months, $n = 263$	9.9 (10.6)

Abbreviations: BMI = Body Mass Index; IDQ = Index of diet quality, MET = Metabolic equivalent index for leisure-time physical activity.

was detected. In the anxiety subscale of EPDS there was a statistically significant difference at 3 months postpartum between FO+placebo group compared to probiotics+placebo group, the values being higher in the probiotics group. At 12 months postpartum a higher anxiety subscale values were detected in probiotics+placebo group compared to placebo+placebo group (Supplementary Table 2).

3.3.1. Clinical characteristics and trajectories of depressive and anxiety symptoms

Some differences between the EPDS and SCL-90 trajectories were detected with regard to the baseline characteristics of the participants. EPDS trajectories differed according to the subjects' smoking habits before pregnancy ($p = 0.037$) i.e. the frequency of smoking before pregnancy was highest in the High and decreasing symptoms group and lowest in the Low and stable group (details: supplementary Table 3). In the Low and stable SCL-90 group, there were significantly more obese (BMI ≥ 30) women than in the Moderate and increasing group ($p = 0.021$) (details: supplementary Table 4). No other statistically significant differences were detected in clinical characteristics among the EPDS or SCL-90 symptom trajectory groups.

3.3.2. Dietary quality and physical activity in relation to depressive and anxiety symptoms

The mean scores of depressive symptoms were negatively correlated with the dietary quality in early pregnancy and at six months postpartum; the poorer the dietary quality, the higher were the EPDS scores (Table 4). The mean scores of anxiety symptoms were also negatively correlated with the dietary quality in early pregnancy. The mean scores of physical activity did not correlate with depressive or anxiety symptom scores. Dietary quality or physical activity did not associate with EPDS or with SCL-90 symptom trajectories at any measurement point (data not shown).

3.3.3. Obstetric and child variables

The mother-reported infant colic groups differed in EPDS scores at three months postpartum ($p = 0.003$). In the post hoc comparisons, there was a statistically significant difference; the mothers that reported that their infant had colic reported a 3.46 units higher score in EPDS (median 7.0, interquartile range 9.0) than those mothers that stated their infant did not have colic (median 3.0, interquartile range 4.56) ($p = 0.002$). The mothers who were "not sure" if their infant had suffered from colic did not differ statistically significantly in EPDS scores from the mothers that reported colic in their infants or from the mothers who did not report colic. Furthermore, the mother-reported infant colic groups differed in SCL-90 scores at three months postpartum ($p = 0.006$). The mothers who reported that their infant had colic reported a 3.14 units higher score in SCL-90 (median 3.0, interquartile range 8.0) than the mothers who stated that their infant did not have colic (median 1.0, interquartile range 2.0) ($p = 0.004$). The mothers who were "not sure" if their infant had experienced colic did not differ statistically significantly in SCL-90 scores from the mothers that reported colic or from those

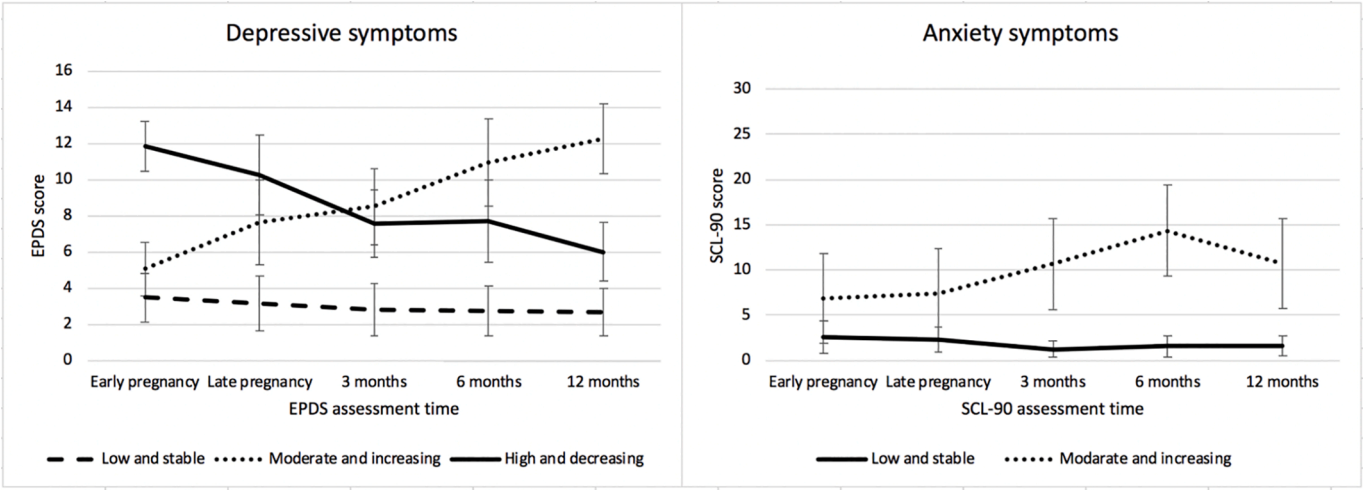

Fig. 2. The mean level of maternal depressive (EPDS) and anxiety symptoms (SCL-90) in the latent groups from early pregnancy to 12 months postpartum. Error bars represent standard deviations.

Table 2
Depressive symptom (EPDS) scores (mean (SD)) from early pregnancy to 12 months postpartum according to the intervention groups and in all women.

	n	FO + placebo	Probiotics + placebo	Probiotics + FO	Placebo + placebo	All	P-value[1]
Early pregnancy	110/109/109/110/438	4.37 (3.47)	5.22 (3.93)	4.11 (3.53)	4.49 (3.96)	4.54 (3.74)	0.150
Late pregnancy	92/96/91/92/371	3.58 (3.58)	4.82 (4.33)	4.98 (4.51)	3.83 (3.92)	4.30 (4.13)	0.068
3 months	82/83/80/83/328	3.15 (3.22)	4.68 (3.97)	4.36 (4.39)	3.29 (3.50)	3.87 (3.83)	0.025
6 months	79/70/76/76/301	3.68 (3.80)	5.10 (4.66)	4.63 (4.76)	3.41 (4.01)	4.18 (4.35)	0.041
12 months	70/64/63/67/264	3.74 (4.55)*	4.86 (3.63)*	4.00 (4.49)	4.18 (4.59)	4.19 (4.34)	0.044
Mean change (SD) from early pregnancy							
to late pregnancy		−0.85 (4.08)**	−0.21 (3.48)	1.11 (4.32)**	−0.43 (4.11)	−0.10 (4.05)	0.017
to 3 mo postpartum		−0.93 (3.44)	0.05 (3.83)	0.54 (4.68)	−0.85 (4.25)	−0.30 (4.10)	0.166
to 6 mo postpartum		−0.33 (4.27)	0.52 (3.55)	0.76 (5.19)	−0.48 (4.50)	0.10 (4.44)	0.376
to 12 mo postpartum		−0.37 (3.87)	0.33 (3.86)	0.25 (4.89)	0.23 (4.23)	0.10 (4.21)	0.525

[1] Kruskal-Wallis Test.
* Statistically significantly different between FO+placebo group compared to probiotics+placebo group; Bonferroni post hoc test, $p = 0.039$.
** Statistically significantly different between FO+placebo group compared to probiotics+FO group; Bonferroni post hoc test, $p = 0.014$.Abbreviation: EPDS = Edinburgh Postnatal Depression Scale.

Table 3
Anxiety symptoms (SCL-90) (mean (SD)) from early pregnancy to 12 months postpartum in all women and according to the intervention groups.

	n	FO + placebo	Probiotics + placebo	Probiotics + FO	Placebo + placebo	All	P-value[1]
Early pregnancy	94/92/93/94/373	2.38 (2.75)	3.41 (3.77)	2.39 (2.96)	3.41 (5.55)	2.90 (3.93)	0.165
Late pregnancy	87/91/87/89/354	2.22 (2.81)	3.12 (3.74)	2.93 (3.50)	2.36 (3.30)	2.66 (3.37)	0.083
3 months	82/83/79/83/327	1.41 (2.33)	2.10 (3.70)	1.92 (2.76)	2.07 (5.14)	1.88 (3.65)	0.475
6 months	79/69/76/74/298	1.63 (2.72)	2.63 (3.79)	3.16 (6.87)	1.88 (4.86)	2.31 (4.83)	0.087
12 months	70/64/63/67/264	1.71 (3.16)	2.15 (3.00)	2.07 (3.30)	2.96 (5.74)	2.22 (3.97)	0.291
Mean change (SD) from early pregnancy							
to late pregnancy		−0.13 (3.25)	−0.36 (2.44)	0.25 (2.51)	−0.77 (5.60)	−0.26 (3.70)	0.303
to 3 mo postpartum		−0.92 (2.87)	−1.00 (2.64)	−0.34 (2.88)	−0.99 (7.33)	−0.82 (4.41)	0.223
to 6 mo postpartum		−0.59 (3.22)	−0.34 (2.62)	1.23 (7.54)	−0.91 (7.32)	−0.16 (5.71)	0.324
to 12 mo postpartum		−0.42 (3.16)	−0.85 (2.73)	−0.32 (3.42)	−0.28 (7.80)	−0.46 (4.79)	0.609

[1] Kruskal-Wallis Test.Appreviations: SCL-90 = Symptoms Checklist.Explanatory factors for depressive and anxiety symptoms.

Table 4
Spearman correlations coefficients (p values) between depressive and anxiety symptoms (mean scores), dietary quality (IDQ score) and physical activity (MET index) in different time points.

	Pregnancy		Postpartum		
	Early	Late	3 months	6 months	12 months
EPDS score					
IDQ score	−0.12 (0.010)	−0.08 (0.114)	−0.09 (0.123)	−0.13 (0.030)	−0.06 (0.330)
MET index	−0.09 (0.070)	−0.08 (0.131)	0.03 (0.619)	−0.06 (0.303)	0.00 (0.963)
SCL-90 score					
IDQ score	−0.13 (0.010)	−0.09 (0.089)	−0.07 (0.189)	−0.09 (0.132)	−0.03 (0.667)
MET index	−0.02 (0.696)	−0.10 (0.062)	−0.04 (0.487)	−0.02 (0.719)	−0.02 (0.780)

Appreviations: EPDS = Edinburgh Postnatal Depression Scale, IDQ = Index of Diet Quality, MET = Metabolic index of leisure time physical activity, SCL-90 = Symptoms Checklist.

mothers who did not report colic in their infants.

The associations between mode of delivery and anxiety and depressive symptoms were studied using the symptom scores rated at 3 months postpartum. The mode of delivery groups (vaginal unassisted, vacuum extraction, elective cesarean and acute and emergency cesarean) differed statistically significantly in EPDS scores at this time point ($p = 0.018$). However, in the post hoc comparisons, only vaginal unassisted delivery group (median 2.36, interquartile range 5.14) when compared to vacuum extraction group (median 5.0, interquartile range 6.0) was associated with a statistically significant difference in EPDS scores ($p = 0.023$). The mothers with vacuum extraction delivery reported 2.11 point higher mean EPDS scores than the mothers with vaginal unassisted delivery. The women who had undergone either elective or acute and emergency cesarean delivery did not differ in their EPDS scores; there were no differences in SCL-90 scores linked with any of the modes of delivery groups.

In addition, the mothers that had delivery before gestational week 37 had 1.74 points higher score in SCL-90 at three months postpartum (median 2.0, interquartile range 4.50) in comparison with the mothers who had given birth after gestational week 37 (median 1.0, interquartile range 2.0) ($p = 0.016$). EPDS trajectories also differed in mother-reported colic ($p = 0.015$), mothers whose infants had most suffered from colic tended to be in the High and decreasing symptoms group and those whose infant had experienced that symptom the least were located in the Low and stable group (details: supplementary Table 5). In the SCL-90 Moderate and increasing group, there were also significantly more women who reported that their child had suffered from colic during her/his first three months of life than in the Low and stable group ($p = 0.003$) (details: supplementary Table 6).

4. Discussion

Here we demonstrated that an FO and probiotic intervention had a modest impact on anxiety and depressive symptoms. The intervention resulted in a small increase in EPDS scores (by 1.11 points) in the FO+probiotics group and a decrease (by 0.85 points) in the FO+placebo

group over pregnancy. The intervention groups also differed in EPDS scores at three, six and 12 months postpartum even though in the post hoc comparisons only the FO+placebo group when compared to the probiotics+placebo group displayed significantly different EPDS scores (by 1.12 points) at the 12 months' time point. In addition, we detected three separate courses of depressive symptoms and two courses of anxiety symptoms from early pregnancy to 12 months postpartum and observed that mother's diet, mother-reported infant colic and obstetric events (i.e. mode of delivery) were associated with depressive and/or anxiety symptoms. Although we found a significant effect of the intervention on depressive symptoms scores, it is unlikely that the effect would be clinically significant. However, based on these results, the varying trajectories of anxiety and depressive symptoms as well as the potential influences of mother-reported infant colic, mode of delivery and lifestyle factors on maternal depressive and anxiety symptoms should be recognized in maternal health care and clarified in future research.

4.1. Impact of dietary intervention on depressive and anxiety symptoms

Preventing or reducing the maternal symptoms of depression and anxiety during the perinatal period is of paramount importance due to their putative negative influence on the mother, the family system and the developing child (Korja et al., 2018; Pearson et al., 2013; Rouse and Goodman, 2014). It has been suggested that the gut-brain-axis could be one mechanism connecting maternal emotional well-being and child development (Sanders et al., 2019). We modelled the maternal symptoms of depression and anxiety, measured at five time points from early pregnancy onwards, with different statistical approaches, using the sum scores, subscale scores, and latent growth curves of symptoms. We found that there was a minor increase in depressive symptoms in the FO and probiotics group as compared to a minor decrease in the FO and placebo group from early to late pregnancy. Findings from the EPDS subscales were in line with the results from the total sum score analyses as a rise in non-specific depressive symptoms in FO+probiotics compared to a decrease in FO+placebo or placebo+placebo groups was seen. As far as we know, the possible synergistic effects of probiotics and FO on depressive and/or anxiety symptoms have not been previously evaluated. Even though in our study the difference in the amount of depressive symptoms between FO and probiotics and FO and placebo groups was small, and optimally the potential impact of the baseline LC-PUFA levels would be considered in the analyses (Weylandt et al., 2015), further investigations are warranted in order to clarify the interactive effects of these supplements.

Furthermore, EPDS scores differed between the intervention groups at three, six and 12 months postpartum even though only one post hoc comparison (lower score in FO+placebo group compared to probiotics+placebo group 12 months postpartum) was statistically significant. Also, in the anxiety subscale of the EPDS higher values in the groups receiving probiotics+placebo at late pregnancy and 12 months postpartum were seen. No other significant associations between probiotics and/or FO were found in our study. A minimum four points change in EPDS score is considered to have a real impact on the individual's mood and is not likely explained by measurement error (Matthey, 2004). The differences we found in EPDS scores in our study were smaller than that value and therefore likely to be clinically insignificant.

At odds with our results, a recent meta-analysis of healthy adults ($n = 1146$) concluded that probiotics may reduce subthreshold anxiety and depressive symptoms (Zhang et al., 2020) and another recent review concluded that the consumption of prebiotic and probiotic supplements may be a useful adjunctive treatment for anxiety and/or depression (Noonan et al., 2020). In addition, a randomized placebo-controlled trial probiotic supplement intervention from early pregnancy to 6 months postpartum was claimed to have a modest but statistically significant effect on postpartum depressive and anxiety symptoms (Slykerman et al., 2017). The participants who had consumed the probiotic (*Lactobacillus rhamnosus* HN001) had 1.3 units lower mean depressive score measured with EPDS and 1.0 unit lower mean anxiety score measured with State Trait Anxiety Inventory postpartum compared to the group that had consumed placebo. Instead of two supplements, only probiotic supplement was used in that trial. It is also noteworthy that the sample sizes of the intervention groups were larger ($n = 212$ & $n = 211$) than in our study.

Conflicting results of the effect of FO on depressive and anxiety symptoms in the perinatal period have been reported. Compared to our study, one previous smaller ($n = 42$) randomized placebo-controlled trial conducted in healthy women with a smaller dose (300 mg DHA supplement five days a week) and a shorter duration (from 24 to 40 weeks of gestation) reported fewer postpartum depressive and anxiety symptoms in women who had consumed DHA when compared to women who had not received the supplement (Judge et al., 2014). In addition, in a double-blind placebo-controlled trial, it was found that primiparous pregnant women with mild depression ($n = 80$) who consumed 1 g of n-3 LC-PUFA supplement per day for six weeks during late pregnancy exhibited significantly fewer symptoms of depression after the intervention in comparison to the placebo-group (Kaviani et al., 2014). In agreement with our results, some investigators have not found significant associations between n-3 LC-PUFA supplementation and depressive or anxiety symptoms. Makrides et al. (2010) reported in their study ($n = 2399$) that consumption of DHA-rich FO capsules (800 mg of DHA) during pregnancy was not able to reduce the levels of postpartum depressive symptoms. In addition, a recent meta-analysis ($n = 4052$) concluded that n-3 LC-PUFA supplementation reduced depressive symptoms in participants that were already depressed when the study started but exerted no effect on depressive symptoms in those participants that were not depressed at the starting point (Mocking et al., 2020). In our study, we also attempted to test whether the intervention resulted a different change in those women exhibiting more symptoms of depression and/or anxiety than those who had fewer symptoms but because our participants were a sample of the general population and were not suffering from depression and/or anxiety at the starting point, the 'more symptoms groups' was too small to allow a reliable evaluation. This might also partly explain why our FO supplementation did not demonstrate a clinically significant benefit in lowering depressive and anxiety symptoms.

Although there are plausible mechanisms to explain the putative benefits of both probiotics and FO, the results from the clinical trials are very conflicting. There has been significant heterogeneity in trial designs and composition and dosage of supplements. The meta-analyses that have been conducted have pointed to some benefits in women with symptoms. In summary, these discrepancies can only be clarified by conducting further studies.

4.2. Trajectories of the maternal depressive and anxiety symptoms from early pregnancy until 12 months postpartum

Several recent studies have shown that depressive and anxiety symptoms tend to vary and even fluctuate during the pre- and postnatal periods, and the temporal differences as well as the severity of symptoms may differently associate with maternal factors and child outcomes (Fredriksen et al., 2017; Korja et al., 2018; Vänskä et al., 2011). In our sample, we identified three different depressive symptom trajectories: Low and stable, Moderate and increasing and High and decreasing and two anxiety symptoms trajectories: Low and stable and Moderate and increasing. Korja et al. (2018) identified five different depressive and four anxiety symptom trajectories in their Finnish population-based sample from early to late pregnancy in mothers ($n = 3202$). Their larger sample size likely explains why they were able to detect more variance in the symptom courses. In another international sample of women with an onset of depressive symptoms in the perinatal period ($n = 663$), five different subtypes of depression were identified (Putnam et al., 2017). These findings reveal that there are different types of

depressive and anxiety patterns over the course of pregnancy and postpartum which should be taken into consideration both in health care and research. The screening of these symptoms should be more frequent and better organized in the maternal and child health care system, and the treatment and intervention guidelines should be revised to take account of these symptoms (American College of Obstetricians and Gynecologists, 2018).

Even though it has been reported that anxiety and obesity are positively correlated (Gariepy et al., 2010) and obesity increases the risk of depression and furthermore that depression might predict the development of obesity (Luppino et al., 2010), the mean depressive and anxiety symptom levels in this sample of overweight and obese women were generally low. Compared to a recent population based sample ($n = 3202$; Korja et al., 2018) from the same geographical area, the baseline scores in early pregnancy were somewhat lower in our study in EPDS (4.54 vs. 5.17) and in SCL-90 (2.90 vs. 3.31) indicating that the present study population represents women who typically participate in clinical trials.

4.3. Explanatory factors for depressive and anxiety symptoms

We found a statistically significant weak negative correlation between depressive and anxiety symptoms and an overall better dietary quality in early pregnancy as well as between depressive symptoms and a better dietary quality at six months postpartum; the better the overall dietary quality, the less likely it was for mothers to exhibit depressive and/or anxiety symptoms at those time points. A previous study (Baskin et al., 2017) found that when compared to a healthy dietary pattern (i.e. fruits, vegetables, fish), an unhealthy dietary pattern (i.e. sweets, fast foods) was associated with increased depressive symptoms at 32 weeks of gestation ($n = 167$). Another large ($n = 9530$) study reported that pregnant women who scored in the highest tertile of "health-conscious" (i.e. salad, fruit, fish, rice) or "traditional" (i.e. vegetables, red meat, poultry) diet patterns were less likely to report high levels of anxiety when compared to women scoring in the lowest tertile of these patterns (Vaz et al., 2013). In addition, women that scored in the highest or middle tertile of a "vegetarian" (e.g. consuming meat substitutes and nuts) diet pattern suffered more from anxiety symptoms than those in the lowest tertile. These findings demonstrate that there is a relationship between diet, and particularly diet patterns, with perinatal anxiety or depressive symptoms. This should be considered in health care even though firm conclusions about the assessment or potential treatment cannot be made based on this evidence and further investigations are evidently needed.

We also observed that vacuum extraction delivery was associated with higher maternal depressive symptoms than vaginal unassisted delivery and also that delivery before gestational week 37 was associated with higher maternal anxiety symptoms than delivery after gestational week 37. In addition, mother-reported infant colic at three months postpartum was associated with more maternal depressive and anxiety symptoms when compared to the mothers who reported that their infant did not have colic. Partly in agreement with our results, Eckerdal et al. (2018) ($n = 3888$) found that women that have emergency cesarean or vacuum extraction delivery and who experience the birthing process negatively are at risk to suffer a postpartum depression. Vik et al. (2009) also found that mother-reported infant colic at two months postpartum ($n = 1015$) was associated with a high amount of maternal depressive symptoms four months later. Another study ($n = 78$) also reported that infant colic was associated with high depressive symptoms but not with high anxiety symptoms (Abacı et al., 2013). These findings together indicate that obstetric and child related factors act as risk factors for postnatal depressive and/or anxiety symptoms and they should be recognized by health care professionals as a part of the counselling procedures. However, it is also possible that mother-reported factors such as the presence of colic in their infant and maternal mood are interrelated and reflect at least partly maternal well-being.

4.4. Strengths & limitations

The strengths are that this was a longitudinal study with five measurement points between early pregnancy and one year postpartum, i.e. approximately 1.5 years. The study was conducted in a clinical trial setting with detailed data collection. The study strengths also include the fact that our sample was similar to the general population of pregnant women in Finland in 2015 with regard to maternal age and delivery parameters (mean age in our sample 30.6 vs. perinatal statistics 30.6 years, delivery before gestational week 37 was 5.8% in our sample vs. 5.3% in the perinatal statistics, vacuum extraction delivery 10.3% in our sample vs 9.2% in perinatal statistics, elective cesarean delivery 6.6% in our sample vs. 6.2% in perinatal statistics and acute and emergency cesarean deliveries 10.0% in our sample vs. 9.8% in perinatal statistics), although it was slightly different with regard to primiparity (47.9% in our sample vs. 58.4% perinatal statistics) (Finnish Institute for Health and Welfare, n.d.).

Some limitations should be pointed; sample sizes of the intervention and trajectory groups at end of the study were affected by dropouts, possibly influencing the evaluation of the intervention's effects. We also chose to study a population of at risk women with regard to pregnancy complications, i.e. overweight and obese women, which limits the generalization of the results to normal weight pregnant women, although it is noteworthy that the depressive and anxiety scores reported here are similar to a population sample collected from the same geographical area. Limitations also include our finding of the significant effect of the intervention to increase depressive symptoms; this should be interpreted cautiously as the effect was small and likely clinically insignificant. We report here secondary outcomes of the intervention trial i.e. the primary outcomes were related to gestational glucose metabolism (Pellonperä et al., 2019) and child allergy (unreported).

4.5. Summary

As far as we are aware, this is the first study that has evaluated the potential synergistic effects of probiotics and FO. However, the association between these food supplements and the development of anxiety and depressive symptoms in pre- and postnatal period remains somewhat unclear. Further investigation of this subject will be required before devising recommendations and guidelines concerning the consumption of probiotics and FO in pregnancy and the postpartum period with regard to the symptoms of depression and anxiety. In the light of the findings reported here, mother's anxiety and depressive symptoms seem to vary both temporally and in severity in pregnancy and postpartum period. The screening of these symptoms should be more frequent in the maternal health care system and appropriate treatments should be implemented should they appear. In addition, we found that mother's diet, mother-reported colic in her infant and obstetric events (i.e. mode of delivery and delivery before gestational week 37) were related to symptoms; these findings should be recognized in maternal health care and as topics for future research.

Declaration of Competing Interest

All authors declare no competing interests.

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Contributors

KL designed the original clinical study, directed the project and acquired the financial support for the study; KL and E-LK conceptualized the research; EK, NH, OP and KM participated in data collection; PH and TV performed statistical analyses; KL, PH, E-LK and TV interpreted the

results, and HK contributed to the interpretation of the results. PH wrote the manuscript with support from KL and E-LK; all authors read, critically revised and approved the final version of the manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.04.006.

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