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Maternal psychological distress during gestation is associated with infant food allergy

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Supporting Information: Methods, Results, Tables S1 and S2 and Figure S1: Study Flow Chart.

Key words: Allergy, atopic diseases, child, cortisol, food allergy, HPA axis, infant, prenatal distress, programming.

Abbreviations:

EPDS	The Edinburgh Postnatal Depression Scale
gwk	Gestational week
PD	Psychological distress
SCL-90	The Symptom Checklist-90, anxiety scale

To the Editor,

Maternal psychological distress (PD, depressive and anxiety) symptoms during gestation are shown to relate to elevated risk of offspring atopic diseases.^{1,2} According to the Developmental Origins of Health and Disease theory, this association could result from the programming effect of maternal PD predisposing the offspring to aberrant stress and immune responses.³ The timing and duration of the PD exposure seem to be relevant but the chronicity aspect has not been studied earlier in humans.^{1,2,4,5} Therefore, we aimed to investigate how the timing, chronicity and severity of maternal PD symptoms associate with the outcome of food allergy at the infant age of 6 months, and expected that the chronic PD exposure might increase the risk. We suggest that the outcome of infant food allergy indicates very early aberrations in immune response, but it has not been studied prospectively in the context of PD since the widely used questionnaire of the International Study of Asthma and Allergies in Childhood (ISAAC) includes only the atopic outcomes of rhinitis, eczema, wheezing and asthma in older children.^{6,7}

The FinnBrain Birth Cohort Study is population-based and prospective consisting of 3808 women, 3837 children (29 twin pairs) and 2623 fathers enrolled at gestational week (gw) 12 in Southwestern Finland and Åland Islands in Finland 12/2011-04/2015.⁸ The study conforms to the Declaration of Helsinki, was approved by the Ethics Committee of the Hospital District of Southwest Finland, and commenced after obtaining written informed consent from the guardians. Current study included 1976 mother-infant dyads whose mothers initially replied “yes/no” about infant allergies on maternal questionnaire at infant age of 6 months (Figure S1). To increase the validity of the outcome, all mothers who replied affirmatively in the questionnaire were personally contacted by the author (EP) who reviewed in detail how the food allergy diagnosis was made; whether the food allergy was diagnosed by doctor, based on oral food challenge, and whether the symptoms were from skin, intestines or both.⁶ Based on this, the study outcome was the mother-reported doctor-diagnosed food allergy at the infant age of 6 months. Data for maternal body mass index (BMI), smoking and delivery were derived from the Finnish Medical Birth Register (www.thl.fi) and other data from the parental questionnaires (Tables 1 and S2). Atopic diseases of mothers and older siblings were identified by maternal report, and atopic diseases of fathers by paternal report: “Have you or at least one of your children had allergies, allergic rhinitis and/or eczema?” (yes/no). At gwks 14, 24 and 34 mothers filled out the standardized questionnaires of

depressive symptoms (Edinburgh Postnatal Depression Scale [EPDS]) and general anxiety (Symptom Checklist-90, anxiety scale [SCL-90]). Symptom chronicity and severity assessments was based on the EPDS and SCL-90 scores in all trimesters, and modelled as symptom trajectories using latent growth mixture modeling with imputed missing data in Mplus 6.0 (StatModel, Los Angeles, CA, USA)⁹ (Figure 1, Methods and Table S1 in Supporting information).

The risk for food allergy was assessed using the logistic regression. The unadjusted analyses included PD symptoms analyzed in different ways; the continuous symptom scores in separate trimesters demonstrated the timing, whereas the symptom trajectories across gestation illustrated the chronicity and severity. The trajectories were studied using the multi-nominal regression with consistently low symptom level trajectories as the reference groups. In unadjusted sensitivity analyses, the trajectories of high PD symptoms were excluded due to low number of infants in the respective food allergy group (Table 1). The adjusted analyses were done separately for same EPDS and SCL-90 trajectories as in the unadjusted sensitivity analyses, both adjusted for the exposures associating with outcome at the significance level of $P < 0.10$ in the unadjusted analyses *i.e.* maternal atopic diseases. This covariate selection was also based on the literature. Two-sided P value < 0.05 was considered significant. Analyses were done using the IBM SPSS 26.0 software (SPSS Inc, Chicago, Ill, USA).

Altogether, 1976/3837 (52%) infants were included (Results, Table S2, Figure S1 in Supporting information). At 6 months, 45/1976 (2.3%) infants had mother-reported doctor-diagnosed food allergy (Table 1). In the unadjusted analyses, mothers' and older siblings' atopic diseases, but not fathers', increased the risk of infant's food allergy (Table 2). Maternal depressive symptoms during gestation were analyzed in three ways; 1) continuous EPDS scores per time point: the risk of food allergy increased by 11% per EPDS point in the first and 10% per EPDS point in the third trimester; 2) the EPDS score above the highest quartile (≥ 7 points) throughout gestation elevated the risk, and 3) using the EPDS trajectories, the risk was elevated with moderate and stable symptom course (all $P < 0.05$, Table 2). The anxiety symptoms were analyzed in two ways; 1) continuous SCL-90 scores per time point: the risk of allergy increased by 7% per SCL-90 point in the first trimester and 2) using the SCL-90 trajectories, the risk was elevated with moderate and decreasing symptom courses (all $P < 0.05$, Table 2). The sensitivity analyses gave similar results (Table 2).

Due to strong correlation of mothers' and siblings' atopic diseases (Table 1), the multivariable analyses were adjusted for maternal atopic diseases. The risk of food allergy was elevated with the EPDS trajectory of moderate and stable symptom levels and for SCL-90 trajectory of moderate and decreasing symptom levels, both analysed separately and adjusted for maternal atopic diseases (all $P < 0.05$, Table 2). In two additional sets of analyses, maternal PD remained as independent risk factor when adjusted for 1) both maternal and siblings' atopic diseases (respective trajectories of EPDS: odds ratio 2.1; 95% confidence interval 1.1-4.0; $P = 0.021$ and SCL-90: 2.9; 1.3-6.7; 0.013, respectively), or for 2) maternal atopic diseases and educational level (up to 12 years, 13-15 years or over 15 years) (2.2; 1.1-4.1; 0.020 and 2.8; 1.2-6.5; 0.018, respectively).

Our findings suggest that chronic prenatal PD symptoms in mother predispose offspring to infant food allergy, and support the earlier hypothesis that the duration of PD exposure is relevant for the programming of the fetal/infant immune system towards atopic diseases.^{3,4} The novelty of our study was the trajectory-based approach to illustrate the chronic course of PD symptoms.⁹ In animal studies, chronic prenatal PD exposed the offspring to immune system changes, but human studies in this field are scarce.⁵ From multiple studies on prenatal PD shaping the offspring risk for atopic traits, only two prospective birth cohorts investigated stress in two trimesters showing that end-gestation, rather than mid-gestation stress predisposed older children to other atopic diseases than food allergy^{1,2}, whereas a retrospective study based on maternal reports investigating the influence of perinatal stress on developing offspring food allergy showed that significantly higher number of stressful events occurred during the perinatal period of food allergic children compared to their non-allergic siblings.¹⁰ Notably, analyses on the relevance of the timing of PD completed the trajectory results and further suggested that the chronicity of PD exposure is relevant

The other novelty was the selection of infant food allergy as the outcome reflecting the early aberration of immune system⁶, while earlier research in the context of maternal prenatal PD has mainly focused on the atopic outcomes in older children.⁷ Food allergy is a substantive risk factor for future asthma although most infants outgrow food allergy.^{6,7} The outcome assembled various underlying mechanisms; skin symptoms are usually atopy-prone/Th2-related, whereas intestinal symptoms derive from several origins.⁶ However, the food allergen-specific immunoglobulin E was not tested here as the test positivity indicating the Th2-related response appears later in childhood,

and is unsuitable for assessing allergies with intestinal symptoms.⁶ Our findings support the idea that maternal chronic PD symptoms predispose offspring to infant food allergy, while exact mechanisms are unknown.¹⁻⁴ Prenatal PD may affect through intrauterine processes including the functions of inter-related stress regulation and immune systems.^{4,11} Therefore, inadequate cortisol levels might have an adverse effect on fetal immune competence, Th1/Th2 balance and mucosal barrier functions.^{5,11}

The strengths of this study include the large sample of nearly 2000 non-selected mother-infant dyads from the prospective pregnancy cohort.⁸ The PD data uses standardized measures and the application of longitudinal symptom modeling is the true novelty. The validated questionnaire of ISAAC does not cover the outcome of infant food allergy and therefore, we were unable to use it for the outcome. Despite this limitation, we did an approach to make the outcome of mother-reported doctor-diagnosed infant food allergy as objective as possible, although we acknowledge that maternal report leaves some uncertainty to the assessment. Of note, the prevalence of this outcome was 2.3% and equals to previous studies.⁶ Adjusting for maternal level of education did not affect the results. Analyses on the association between maternal perinatal dietary patterns and infant food allergy were precluded by the lacking dietary information. Despite the large study population, groups with high maternal PD symptom levels and offspring outcome were small, as expected in this general population based cohort. In conclusion, mothers' chronic and moderate PD and especially depressive symptoms during gestation associated with the infant food allergy suggesting that chronic PD exposure may be relevant for the programming of fetal/infant immune system towards atopic diseases.

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AUTHOR CONTRIBUTIONS:

ML, EP and LK contributed to acquisition of data. ML, EP, E-LK, LK, HL, LK and HK were involved in the conception and design of the study. ML and E-LK analyzed and interpreted the data. ML wrote the initial draft. ML, EP, E-LK, LK, HL, LK and HK reviewed and edited the manuscript.

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TABLE 1. Population characteristics of the included at 6 months.

Exposures	Doctor-diagnosed food allergy	No food allergy	P*
	n = 45 (2.3)	n = 1931 (97.7)	
During gestation			
Maternal obesity; pre-gestational BMI ≥30 kg/m ²	7/44 (16)	218/1903 (12)	0.36
Maternal atopic diseases ^{†‡}	26 (59)	800 (43)	0.036
Maternal smoking during the first trimester	4 (8.9)	148 (7.7)	0.39
Maternal smoking throughout gestation	0 (0)	75 (3.9)	
Maternal education level low (up to 12 years)	14/43 (33)	599/1840 (33)	0.082
Maternal education level medium (13-15 years)	21/43 (49)	638/1840 (35)	
Maternal education level high (over 15 years)	8/43 (19)	603/1840 (33)	0.61
Paternal atopic diseases	12/38 (32)	438/1232 (36)	
Older siblings	19/44 (43)	858/1847 (47)	0.67
Older siblings with atopic diseases [†]	13/44 (30)	249/1852 (13)	0.002
Older siblings with asthma [‡]	5/44 (11)	47/1852 (2.5)	0.006
EPDS score medians (range 0-30)			
gwks 14 (IQR)	7.0 (4.0; 10.0), n = 43	4.0 (2.0; 7.0), n = 1830	<0.001
gwks 24 (IQR)	7.0 (2.0; 8.3), n = 44	4.0 (2.0; 7.0), n = 1857	0.070
gwks 34 (IQR)	6.0 (4.0; 8.0), n = 41	4.0 (2.0; 7.0), n = 1829	0.001
EPDS at highest quartile (≥7 points) throughout gestation	11/43 (26)	211/1878 (11)	0.004
EPDS at highest quartile (≥7 points) throughout gestation among mothers with atopic diseases	8/25 (32)	95/788 (12)	0.56
EPDS trajectories	n = 44	n = 1910	0.010
High and decreasing	2 (4.5)	20 (1.0)	
Moderate and increasing	2 (4.5)	48 (2.5)	
Moderate and stable	17 (39)	464 (24)	
Consistently low	23 (52)	1378 (72)	
EPDS trajectory “Moderate and stable” among mothers with atopic diseases	11/24 (46)	206/768 (27)	0.14

SCL-90 score medians (range 0-40)

gwks 14 (IQR)	3.0 (2.0; 7.0), n = 43	2.0 (0; 4.0), n = 1828	0.002
gwks 24 (IQR)	4.0 (2.0; 7.0), n = 43	2.0 (1.0; 5.0), n = 1856	0.016
gwks 34 (IQR)	3.0 (2.0; 5.0), n = 41	2.0 (0; 4.0), n = 1824	0.005

SCL-90 at highest quartile (≥ 4 points) throughout gestation among mothers with atopic diseases

0 (0)	1/624 (0.2)	1.0
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SCL-90 trajectories

n = 44	n = 1910
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High and decreasing

0 (0)	19 (1.0)
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Moderate and increasing

2 (4.5)	108 (5.7)	0.053
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Moderate and decreasing

7 (16)	114 (6.0)
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Consistently low

35 (80)	1669 (87)
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SCL-90 trajectory “Moderate and decreasing” among mothers with atopic diseases

5/24 (21)	58/741 (8)	0.060
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At delivery

Male sex	23 (51)	1026 (53)	0.79
Delivery with caesarean section	10 (22)	320 (17)	0.30
Duration of gestation, median (IQR), gwks	39.0 (38; 40.75)	40.0 (39; 40)	0.39
Mother age, mean (SD), years	30.2 (4.3)	30.7 (4.4)	0.74
Birth weight, median (IQR), g	3620 (3250; 4020)	3550 (3260; 3900)	0.82
Birth length, median (IQR), cm	50.0 (49.0; 53.0)	51.0 (49.0; 52.0)	0.40

At 6 months

Exclusive breastfeeding, mean (SD), months	5.0 (1.3), n = 12/731	4.6 (1.3), n = 719/731	0.33
Allergy diagnosis based on oral food challenge	30 (67)	0	
• intestinal symptoms	16 (36)	0	
• skin symptoms	15 (33)	0	
• intestinal and skin symptoms	8 (18)	0	
• no symptoms were reported	6 (13)	0	
• milk allergy	40 (89)	0	

BMI, Body mass index; EPDS: The Edinburgh Postnatal Depression Scale; gwks, Gestational weeks; SCL-90: The Symptom Checklist-90, anxiety scale.

Presented as numbers (percentages), means (standard deviations, SD), or medians (interquartile ranges, IQR).

*Indicates the group comparisons.

†The correlation between maternal and sibling atopic diseases, $P < 0.001$.

‡The correlation between maternal atopic diseases and sibling asthma, $P = 0.018$.

TABLE 2. Risk of mother-reported doctor-diagnosed food allergy at age 6 months.

Exposures			
Unadjusted analyses	Odds ratio	95% CI	P
Maternal obesity; pre-gestational BMI ≥ 30 kg/m ²	1.5	0.64-3.3	0.36
Maternal atopic diseases	1.9	1.03-3.4	0.039
Maternal smoking during the first trimester	1.1	0.40-3.2	0.82
Maternal smoking throughout gestation	N/A [†]	N/A [†]	N/A [†]
Maternal education level low (up to 12 years) as reference			
Maternal education level medium (13-15 years)	1.4	0.71-1.8	0.33
Maternal education level high (over 15 years)	0.57	0.24-1.4	0.21
Paternal atopic diseases	0.84	0.42-1.7	0.61
Older siblings	0.53	0.16-1.7	0.30
Older siblings with mother-reported atopic diseases [‡]	2.7	1.4-5.2	0.003
Older siblings with mother-reported asthma [‡]	4.9	1.9-13	0.001
Male sex vs. female sex	1.1	0.60-2.0	0.79
Delivery with caesarean section	1.5	0.71-3.0	0.30
Exclusive breastfeeding during 6 months	1.3	0.75-2.3	0.33
EPDS score as a continuous variable, risk increase per point			
at gwks 14	1.11	1.05-1.2	<0.001
at gwks 24	1.05	0.98-1.1	0.16
at gwks 34	1.10	1.03-1.2	0.005
EPDS at highest quartile (≥ 7 points) throughout gestation	2.4	1.2-5.0	0.015
EPDS trajectories with Consistently low as reference			
High and decreasing	2.7	0.59-13	0.20
Moderate and increasing	1.1	0.26-5.1	0.87
Moderate and stable	2.2	1.2-4.2	0.015
Sensitivity analyses: Moderate and stable vs. Consistently low ^{\$}	2.2	1.2-4.2	0.015
SCL-90 score as a continuous variable, risk increase per point			
at gwks 14	1.07	1.02-1.1	0.012
at gwks 24	1.05	0.99-1.1	0.078
at gwks 34	1.04	0.98-1.1	0.20
SCL-90 trajectories with Consistently low as reference			

Consistently high	N/A [†]	N/A [†]	N/A [†]
Moderate and increasing	0.88	0.21-3.7	0.86
Moderate and decreasing	2.9	1.3-6.7	0.012
Sensitivity analyses: Moderate and decreasing vs. Consistently low [§]	2.9	1.3-6.7	0.012

Adjusted analyses[¶]

Model 1:

Maternal atopic diseases	1.9	1.02-3.7	0.044
EPDS trajectory of Moderate and stable vs. Consistently low [§]	2.2	1.1-4.1	0.019

Model 2:

Maternal atopic diseases	1.7	0.92-3.2	0.091
SCL-90 trajectory of Moderate and decreasing vs. Consistently low [§]	2.7	1.2-6.3	0.018

BMI, Body mass index; CI, Confidence interval; EPDS: The Edinburgh Postnatal Depression Scale; gwks, Gestational weeks; N/A, Not applicable; SCL-90: The Symptom Checklist-90, anxiety scale.

[†]N/A due to 0 cells.

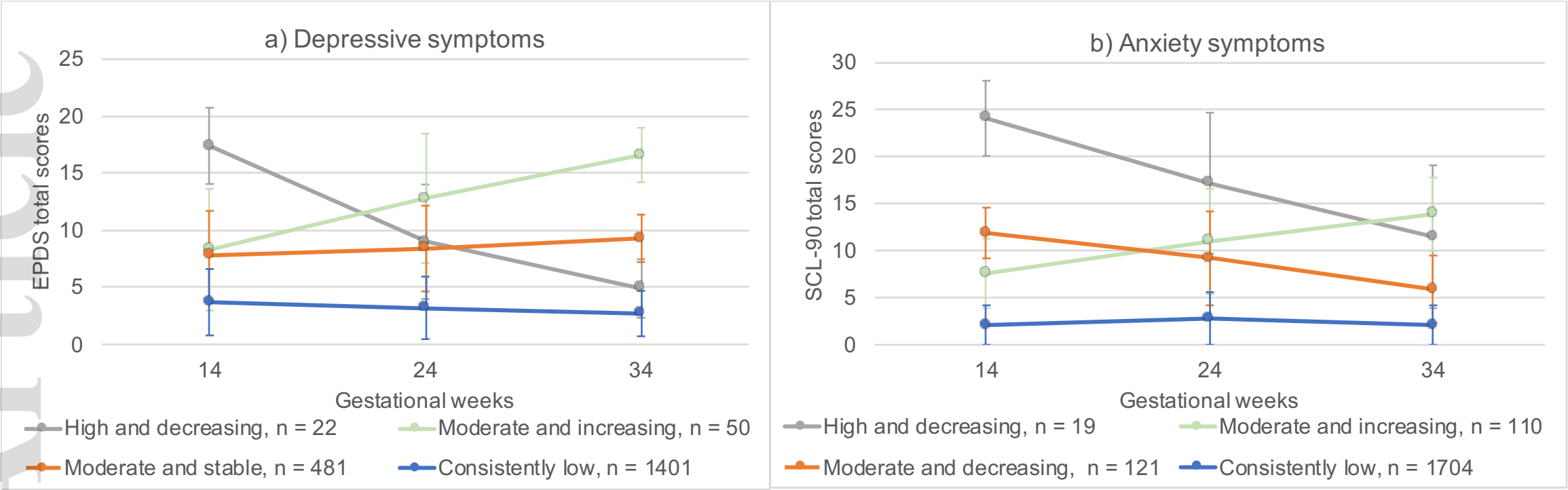
[‡]Excluded from the adjusted analyses due to strong correlation with maternal atopic diseases.

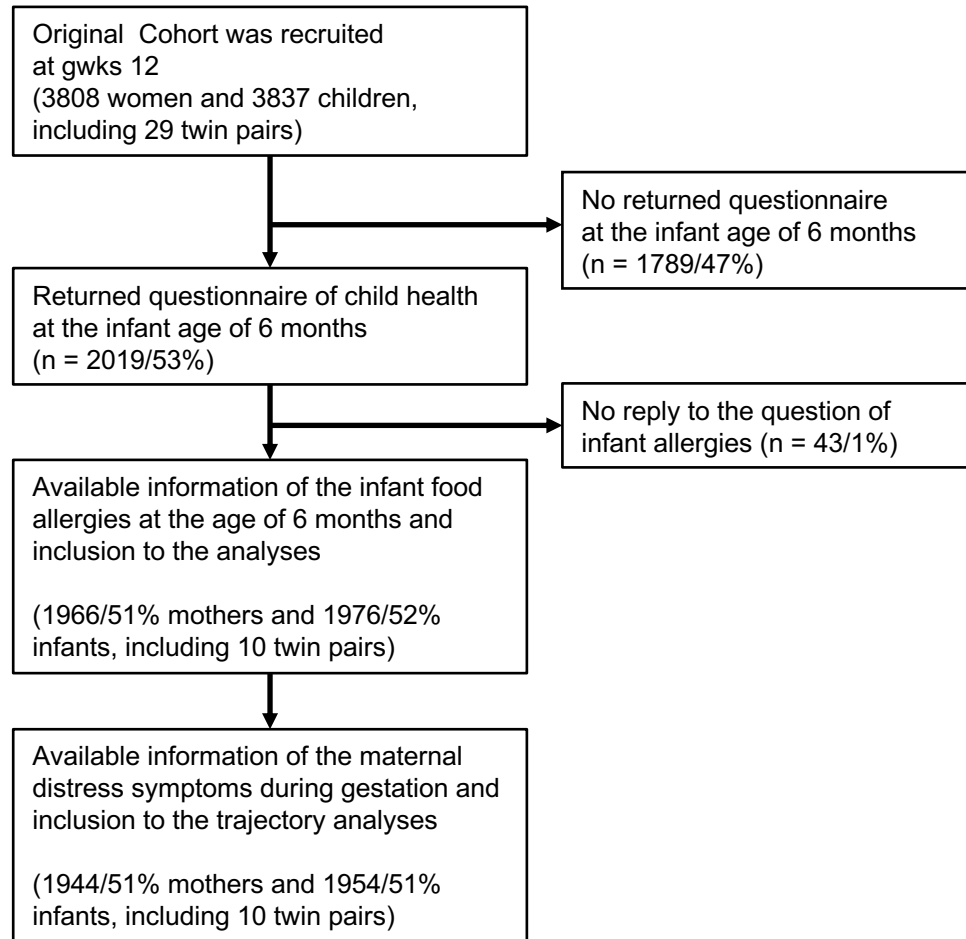
[§]The high score trajectories of EPDS and SCL-90 were excluded due to low numbers among infants with food allergy.

[¶]Adjusted for exposures that associated with the outcome at the significance level of $P < 0.10$ in the unadjusted analyses *i.e.* maternal atopic diseases. Adjusted analyses were grouped as models 1 and 2.

FIGURE LEGENDS

FIGURE 1: The four latent growth curve trajectories of maternal a) depressive and b) anxiety symptoms at three trimesters illustrating the severity and chronicity of the depressive and anxiety symptoms during pregnancy. The mean levels (whiskers representing the standard deviations) of symptom scores. *EPDS*, the Edinburgh Postnatal Depression Scale (range 0-30 points); *SCL-90*, the Symptom Checklist-90, anxiety subscale (range 0-40 points).





1 **Maternal psychological distress during gestation is associated with infant food allergy**

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15 **METHODS**

16 Firstly, the factor structures of both the Edinburgh Postnatal Depression Scale (EPDS) and the
17 Symptom Checklist-90, anxiety scale (SCL-90) questionnaires were examined with structural equation
18 modelling. The longitudinal confirmatory factor analysis of the questionnaires showed good fit with
19 the data; EPDS, $\chi^2(382) = 1316.217$, $P < 0.001$, comparative fit index (CFI) = .94, root mean square
20 error of approximation = .035, standardized root mean square residual = .047 (consecutive Items 1 and
21 2, 4 and 5, 8 and 9 were allowed to correlate to improve model fit); SCL-90, $\chi^2(385) = 1078.294$,
22 $P < 0.001$, CFI = .95, root mean square error of approximation = .030, standardized root mean square
23 residual = .044 (similar items 5 and 10, and 7 and 10 were allowed to correlate to improve model fit).
24 Table S1 presents the resultant fit indices.

25
26 Secondly, the number of latent curves was established by increasing the number of subgroups in the
27 latent growth mixture modeling models and comparing fit indices of the outputs with an increasing
28 number of subgroups. The optimal number of groups was defined by Bayesian information criteria
29 (BIC, where lower value indicates better model fit¹; the posterior probability (*i.e.* the probability of an
30 individual belonging to a group) for each trajectory group (a score of .80 or above is preferred²;
31 entropy rate indexing classification accuracy (>.80 indicating excellent accuracy³; and Vuong-Lo-
32 Mendell-Rubin likelihood ratio test (VLMR-LRT) and Bootstrapping Likelihood Ratio Test (BLRT)
33 for k versus $k-1$ groups (P values lower than .05 suggesting that $k + 1$ is superior in comparison to k
34 groups⁴ (Table S1).

35
36 Finally, four latent curve trajectories for both the EPDS and SCL-90 scores at gestational weeks 14,
37 24, and 34 were created (Figure 1 and Table S2). For the EPDS, these were Consistently low ($n =$
38 1401; estimate of intercept = 3.719; estimate of slope = -0.493; $P > 0.001$), Moderate and stable ($n =$
39 481; estimate of intercept = 7.550; estimate of slope = 0.710; $P > 0.001$), High and decreasing ($n = 22$;
40 estimate of intercept = 16.226; estimate of slope = -5.916; $P = 0.001$), Moderate and increasing ($n = 50$;

41 estimate of intercept = 8.802; estimate of slope = 3.716; $P < 0.001$). For the SCL-90, these were
42 Consistently low ($n = 1704$; estimate of intercept = 2.117; estimate of slope = -0.034, $P = 0.367$),
43 Moderate and increasing ($n = 110$; estimate of intercept = 7.683; estimate of slope = 3.043; $P < 0.001$),
44 Moderate and decreasing ($n = 121$; estimate of intercept = 11.617; estimate of slope = -2.960;
45 $P < 0.001$), and High and decreasing ($n = 19$; estimate of intercept = 23.922; estimate of slope = -6.158;
46 $P = 0.976$).

47

48 **RESULTS**

49 **Study population and characteristics**

50 Parental questionnaire regarding index child's health during the first 6 months was returned from
51 2019/3837 (53%) originally enrolled children, but 43 questionnaires lacked the reply about infant
52 allergies. Finally, 1976/3837 (52%) infants were included in current study (Figure S1). Based on
53 parental reports at gwk 14, 826/1896 (44%) infants had mothers and 450/1270 (35%) infants had
54 fathers with atopic diseases. Mother-experienced PD symptoms during gestation did not associate with
55 their own atopic diseases (Table S2). At the age of 6 months, 77/1976 (3.9%) infants were reported
56 having allergies (Table S2).

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67 **Table S1. The resultant fit indices of the distress trajectory classes.**

	Log L.	BIC	Entropy	Class Proportions	Average Latent Class Posterior Probabilities
EPDS					
1 Class	-14821.309	29703.239	1.000	1.000	1.000
2 Class	-14681.102	29445.558	.78	.82/.18	.96/.86
3 Class	-14602.732	29311.552	.83	.25/.3/.72	.87/.87/.94
4 Class	-14550.508	29229.836	.86	.01/.71/.03/.25	.84/.94/.89/.86
5 Class	-14493.465	29138.482	.85	.02/.24/.03/.02/.69	.86/.83/.76/.82/.94
SCL-90					
1 Class	-14652.029	29364.679	1.000	1.000	1.000
2 Class	-14280.514	28644.381	.96	.94/.06	.99/.93
3 Class	-14021.125	28148.337	.95	.89/.04/.06	.99/.94/.91
4 Class	-13920.657	27970.134	.95	.05/.07/.01/.88	.92/.92/.95/.98
5 Class	-13822.154	27795.862	.94	.07/.06/.02/.84/.01	.85/.89/.88/.98/.96

68 BIC, Bayesian information criteria; EPDS, the Edinburgh Postnatal Depression Scale; Log L., Log
69 Likelihood; SCL-90, the Symptom Checklist-90, anxiety scale.

TABLE S2. Population characteristics and loss analysis.

	Cohort n = 3837	Included (reply at 6 months) n = 1976 (52)	Excluded (no reply at 6 months) n = 1861 (48)	P*
During gestation				
Maternal obesity; pre-gestational BMI ≥30 kg/m ²	468/3684 (13)	225/1947 (12)	243/1737 (14)	0.027
Maternal atopic diseases	1299/3096 (42)	826/1896 (44)	473/1200 (39)	0.023
Maternal smoking during the first trimester	332/3769 (8.8)	152/1957 (7.7)	180/1794 (10)	<0.001
Maternal smoking throughout gestation	230/3769 (6.1)	75/1975 (3.8)	155/1794 (8.6)	
Maternal education level low (up to 12 years)	1205/3103 (39)	613/1883 (33)	585/1201 (49)	
Maternal education level medium (13-15 years)	1041/3103 (34)	659/1883 (35)	375/1201 (31)	<0.001
Maternal education level high (over 15 years)	857/3103 (28)	611/1883 (32)	241/1201 (20)	
Paternal atopic diseases	694/2012 (35)	450/1270 (35)	244/742 (33)	0.25
Older siblings	1500/3094 (49)	877/1891 (46)	623/1203 (52)	0.003
Older siblings with atopic diseases	444/3096 (14)	262/1896 (14)	182/1200 (15)	0.30
Older siblings with asthma	97/3096 (3.1)	52/1896 (2.7)	45/1200 (3.8)	0.12
EPDS score medians (range 0-30)				
gwks 14 (IQR)	4.0 (2.0; 7.0), n = 3050	4.0 (2.0; 7.0), n = 1873	5.0 (2.0; 8.0), n = 1177	0.001
gwks 24 (IQR)	4.0 (2.0; 7.8), n = 2770	4.0 (2.0; 7.0), n = 1901	5.0 (2.0; 8.0), n = 869	<0.001
gwks 34 (IQR)	4.0 (2.0; 7.0), n = 2602	4.0 (2.0; 7.0), n = 1870	5.0 (2.0; 8.0), n = 732	<0.001
EPDS at highest quartile (≥7 points) throughout gestation	306/3048 (10)	222/1921 (12)	84/1127 (8)	<0.001
EPDS at highest quartile (≥7 points) throughout gestation among mothers with atopic diseases	131/1233 (11)	103/813 (13)	28/420 (7)	0.21
EPDS trajectories				
		n = 1954		
High and decreasing	N/A	22 (1.1)	N/A	
Moderate and increasing	N/A	50 (2.6)	N/A	
Moderate and stable	N/A	481 (25)	N/A	
Consistently low	N/A	1401 (72)	N/A	
SCL-90 score medians (range 0-40)				
gwks 14 (IQR)	2.0 (0; 5.0), n = 3052	2.0 (0; 4.0), n = 1871	2.0 (1; 5.0), n = 1181	0.004
gwks 24 (IQR)	3.0 (1.0; 6.0), n = 2767	2.0 (1.0; 5.0), n = 1899	3.0 (1.0; 6.0), n = 868	<0.001
gwks 34 (IQR)	2.0 (0; 5.0), n = 2598	2.0 (0; 4.0), n = 1865	2.0 (0; 5.3), n = 733	<0.001
SCL-90 at highest quartile (≥4 points) throughout gestation among mothers with atopic diseases	3/978 (0.3)	1/648 (0.2)	2/330 (0.6)	0.15
SCL-90 trajectories				
		n = 1954		
High and decreasing	N/A	19 (1.0)	N/A	
Moderate and increasing	N/A	110 (5.6)	N/A	
Moderate and decreasing	N/A	121 (6.2)	N/A	
Consistently low	N/A	1704 (87)	N/A	
At delivery				
Male sex	1961/3748 (52)	1049 (53)	912 (52)	0.32
Delivery with caesarean section	623/3837 (16)	330 (17)	293 (16)	0.92
		n = 1935	n = 1735	
Duration of gestation, median (IQR), gwks	40.0 (39; 41)	40.0 (39; 40)	39.0 (39; 40)	0.073

Mother age, mean (SD), years	30.2 (4.7)	31.2 (4.4)	30.2 (5.0)	<0.001
Birth weight, median (IQR), g	3550 (3230; 3890)	3560 (3260; 3900)	3540 (3200; 3900)	0.71
Birth length, median (IQR), cm	50.5 (49.0; 52.0)	51.0 (49.0; 52.0)	50.0 (49.0; 52.0)	0.20

At 6 months

Exclusive breastfeeding, mean (SD), months	4.6 (1.3), n = 734	4.6 (1.3), n = 731/734	4.7 (1.2), n = 3/734	0.076
Mother-reported allergies on questionnaire	N/A	77 (3.9)	N/A	N/A
Mother-reported doctor-diagnosed food allergy	N/A	45 (2.3)	N/A	N/A

70 BMI, Body mass index; EPDS, The Edinburgh Postnatal Depression Scale; gwks, Gestational weeks;

71 N/A, Not applicable; SCL-90, The Symptom Checklist-90, anxiety scale.

72 Presented as numbers (percentages), means (standard deviations, SD), or medians (interquartile ranges,
73 IQR).

74 *The comparison of the included and excluded.

75 **FIGURE LEGENDS**

76

77 **FIGURE S1:** Study flow chart. *gwks*, Gestational weeks.