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Cohort Profile: The Little in Norway (LiN) Study

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Title: Cohort Profile: The Little in Norway (LiN) Study

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Abstract

Purpose:

The Little in Norway (LiN) project is a cross-disciplinary prospective longitudinal study starting in pregnancy. It was set up to investigate maternal and paternal mental health functioning in the transition to parenthood, detect pathways to healthy and aberrant child development, and generate new knowledge about mechanisms underlying differential child mental health susceptibility.

Participants:

The LiN cohort is a community-based sample comprising 1036 families (1036 mothers, 884 partners, 1017 children). All pregnant women and their partners receiving routine prenatal care at well-baby clinics at nine geographically selected sites across Norway were invited to participate. Enrolment took place from September 2011 to October 2012. This cohort profile focuses on ten data collection waves spanning from enrolment in pregnancy until 18 months.

Findings to date:

The most important findings so far relate to three domains of results. First, when examining risk factors for parental mental health problems, results showed how the parents' own adverse childhood experiences and attachment style were related to anxiety, depression, and stress in the perinatal period. The experience of difficult child temperament was also found to contribute to parenting stress in the first year after birth. Second, we studied how parental mental health risk factors were related to later child development and social emotional functioning, for example linking maternal symptoms to social-emotional outcomes and paternal symptoms to language outcomes. Third, we investigated the relation between maternal nutrition during pregnancy and aspects of early child development. Results showed that mild to moderate maternal iodine deficiency in pregnancy was associated with lower language skills up to 18 months, but not with reduced cognitive or fine- and gross motor skills

Future plans:

A data collection point at 36 months is completed and currently being analysed. A new data collection wave is planned when the children are 8 years old.

Keywords:

Community-based, Cross-disciplinary, Prospective longitudinal, Parental mental health, Nutrition, Child development

Strengths and limitations of this study

- Cross-disciplinary prospective, longitudinal community-based study of children and their parents from early pregnancy on.
- A multi-method and multi-informant design including biological sampling, direct observation of behaviour, assessment of the children's development and self-reported information from mothers and fathers.
- Many repeated in-depth assessments from early in pregnancy and onward makes it possible to identify differential developmental pathways and underlying mechanisms.
- This cohort alone may be underpowered when examining risk factors of outcomes with low prevalence, hence collaboration is encouraged.
- The participating parents tended to have a higher educational level than the general population at the different sites. A related concern is selective attrition, as dropout was shown to be related to depressive symptoms. However, appropriate statistical methods have been used to minimize the effect of selective attrition in papers based on this study population.

Introduction

Differential pathways to healthy and atypical development emerge early in life [1]. Human infants are malleable and take their course of growth in many directions, in part predisposed by biological factors and subsequently influenced by postnatal environmental characteristics in a continuous dynamic transactional interplay [2-4]. Such pathways have been identified in early childhood [2 5 6]. However, the knowledge of the pre- and perinatal precursors of child development and social-emotional functioning is still scarce. The Little in Norway (LiN) study is an on-going cross-disciplinary longitudinal and prospective multisite community-based study of children and their parents from early pregnancy on. It was set up to investigate maternal and paternal mental health functioning in the transition to parenthood, examine pre- and postnatal precursors of long-term child development and mental health, as well as disentangling mechanisms of transmission of developmental risk and protective factors. The study aims at integrating the research areas of mental health, developmental psychology, nutrition and molecular genetics. This Cohort Profile focuses on ten data collection waves spanning from enrolment in pregnancy until 18 months after birth.

A better understanding of early risk and protective factors, leading into pathways of later competence or adversity is needed, as there is a high potential for early interventions to adjust atypical pathways [7-9]. For example, parents' adverse childhood experiences [10 11] have been shown to influence later parental mental health, and are associated with insecure attachment, pre- and postnatal depression, parenting stress and atypical parenting behaviour toward their own children [10 12-17]. However, only few studies have examined the longitudinal implications of such risk factors on parenting and parent–child interaction in cohorts followed from the prenatal period [18]. One needs to elucidate the mechanisms of how parental adverse childhood experiences and mental health status, such as perinatal depression and anxiety, translate into aberrant child development, as such mechanisms are only partially understood [19 20]. In

addition, there is a need for including fathers in such studies [21 22]. Particularly, there is a lack of studies examining differential and joint effects of mothers' and fathers' impact on mental health functioning in infancy and early childhood [23].

Antenatal biological factors may also be decisive for later development. Some nutrients protect maternal health while others affect birth outcome and infant health. For example, an inadequate nutrient supply may cause biological competition between mother and foetus [24 25]. Evidence also suggests a role of long chain polyunsaturated fatty acid in the aetiology of postpartum depression [26-29]. Furthermore, suboptimal iodine nutrition during pregnancy is associated with language delay and lower verbal IQ scores [30 31]. This study comprises a food frequency questionnaire applied at several time points as well as biological samples to obtain information related to child and parental nutrition and its possible relation to child development and mental health functioning.

Cohort description

Who is in the cohort?

All pregnant women, receiving routine prenatal care at nine public well-baby clinics across Norway, were invited by midwives to participate. The clinics were chosen taking demographics and size of the population into account, to ensure a wide distribution of background conditions. Participants were recruited at their first prenatal care examination. At each site, one public health care nurse was trained as a research assistant. There is considerable variation in local and individual practices as to when pregnant women first receive prenatal care at a well-baby clinic. Although there are nationwide schedules for prenatal care, many choose to receive initial check-ups by their general practitioner while switching to midwives at the well-baby clinics when the due date approaches. Therefore,

despite all women being invited at their first prenatal visit to the well-baby clinic, the time frame for enrolment ranged from gestational week 8 to 34.

Initially, 1041 women consented; five later withdrew, leaving 1036 (99.5%) participating pregnant women. Their partners were also invited and 884 (878 men and six women) participated. No exclusion criteria were applied, but since the questionnaires were either in Norwegian or English, this might have excluded pregnant women and their partners who neither spoke Norwegian nor English. The participation rate is estimated to be 50.7%. At five of the clinics, the staff did not establish reliable routines to monitor rates of participation; this rate is based on records from the remaining four clinics. However, participation rates were probably relatively similar at all sites since all clinics shared recruitment strategies.

Table 1 shows demographic characteristics of the sample. Pearson chi-square tests were performed at each of the nine sites separately, comparing the participants' educational level with the mean educational level of the population at the nine sites in the same age (figures obtained from Statistics Norway). In general, participant showed higher educational level than the reference populations ($p < .001$).

Insert Table 1 here

Participants received written and oral information before giving their consent to their own and their children's participation. Confidentiality was assured, and it was emphasized that they could withdraw at any time. The Regional Committees for Medical and Health Research Ethics in Norway approved the study [2011/560]. The enrolment took place from September 2011 to October 2012. At time of birth, three families were lost due to stillbirth, while 26 families were lost for other reasons before childbirth (e.g., family moving out of the area, participation felt to be too time consuming). The remaining 1007 mothers delivered 1017 children (including ten twin pairs).

How often have the participants been followed up?

The participants have been followed-up from early in pregnancy with an intensive longitudinal design including data collection at ten time points. After enrolment, the prenatal data collection waves were at gestational weeks 8-21 (T1), weeks 22-27 (T2), weeks 28-31 (T3), weeks 32-35 (T4), and weeks 36-41 (T5). T6 comprises birth records. Postnatal data were collected at 6 weeks postpartum (T7), and again at 6 months (T8), 12 months (T9), and 18 months (T10) after birth, all with ± 2 weeks.

All participants completed the enrolment package (n = 1036 and 884, pregnant women and their partners, respectively). Data collection at T1 to T10 had limited time windows relative to gestational/child age for valid participation. This means that a sizeable proportion of participants was not enrolled in time to take part in the early data collection points during pregnancy. At T10, 925 families (88.9 %) of the original sample were still participants and remained in the study for future follow-up. Hence, there are three categories of missing data: late recruitment, study withdrawal or families lost to follow-up (n = 116), and intermittently missing data, which comprise participants that skipped one or more data collection waves, but then contributed at later time points. Figure 1 depicts the flow of recruitment, participation and attrition at each data point.

Insert Figure 1 here

Bivariate logistic regression analyses were conducted to investigate selective attrition at T10 (18 month after childbirth). High level of maternal education slightly increased the probability of participation at T10 (OR = 1.07, 95% CI [1.01, 1.15], p = .030). Neither partners' education (OR = 1.04, 95% CI [0.97, 1.11], p = .255), maternal age (OR = 1.00, 95% CI [0.97, 1.03], p = .886), partners' age (OR = 1.00, 95% CI [0.98, 1.03], p = .756), maternal parity (OR = 0.87, 95% CI [0.73, 1.04], p = .123), nor the number of partners' previous

children (OR = 0.98, 95% CI [0.80, 1.21], p = .879) were related to attrition. Attrition was further predicted by lower levels of mean prenatal (OR = 0.91, 95% CI [0.88, 0.95], p <.001) and postnatal (OR = 0.95, 95% CI [0.90, 1.00], p = .041) depressive symptoms for mothers, as well as lower levels of mean prenatal (OR = 0.92, 95% CI [0.87, 0.97], p = .004) and postnatal (OR = 0.93, 95% CI [0.86, 0.99], p = .030) depressive symptoms for partners.

What has been measured?

Data collected in the LiN-Study include multi-informant questionnaire data, observational and behavioural data, and biological samples. Data were collected at the local well-baby clinic and by means of web-based surveys filled out at home, at well-baby clinics or completed by the research assistants based on parent interviews. Types of measurements at each wave are shown in Table 2, while the specific measurement methods are shown in table 3.

Insert Table 2 and 3 here

Enrolment package in pregnancy

Mothers and fathers received a comprehensive questionnaire package concerning parental demographic information, somatic and mental health and dietary habits, as well as medication, smoking and alcohol habits, at the first meeting in pregnancy (enrolment package). In addition, possible adverse childhood experiences [10] and life stress events over the previous 12 months [32] were assessed. We also measured partner-related attachment style [33] since the quality of the parents' representations of attachment relationships is an important factor to consider for parental adaptation and parenting behaviour [34 35].

Repeated assessments during pregnancy (T1-T5)

Anxiety related to pregnancy and birth [36], and depressive symptoms in the perinatal period were measured at all assessments in pregnancy (T1-T5) [37 38]. We also included questions

about both parents' thoughts and feelings toward their unborn baby at all data points during pregnancy in order to capture mental representations of the coming child. To assess nutritional status and cortisol levels, hair and urine samples were collected from the mothers twice during pregnancy (T1 and T3). The urine samples have been analysed for iodine concentration. Blood samples were collected during pregnancy (T1) and have been analysed for fatty acid composition and vitamin D status (25(OH)D3). Dietary intake was measured using a web-based, and a food frequency questionnaire (FFQ) twice during pregnancy (T1 and T4) [39 40]. Three questions regarding seafood intake were included at T2, T3 and T5).

Postnatal assessments (T6-T10)

At birth (T6), we collected information from hospital birth records. At six weeks after birth (T7) the research assistants met with the parents and their baby to observe the infant and obtain information about the child's diurnal rhythm. The parents received questionnaires, and biological samples from mother and child were collected.

Depressive symptoms [37] in both parents were again assessed several times; at six weeks, six, 12, and 18 months (T7-T10.) Stress in the parenting role and in the parent–child relationship was also measured repeatedly postpartum [32].

Testing and observation of the children's development and videotaping of child–parent interaction were conducted at the local well-baby clinics at six, 12 and 18 months (T8-T10). Developmental skills were assessed by testing cognitive, language, and fine- and gross motor development [41]. We also observed the infants' possible social withdrawal reactions [42], and the parents were asked to evaluate their infants' temperament characteristics [43 44]. To assess the quality of parent–child interaction, the children and their parents participated in videotaped play sessions at 6, 12 and 18 months (T8-T10).

In a sub-sample (N = 102), child social emotional functioning was assessed by a standardized telephone interview with the main caregiver at 12 months (T9) [45]. At 18 months (T10) a questionnaire related to the child's social-emotional functioning was completed by all parents, and by the preschool teacher if the child attended a day-care centre. In another subsample children's stress levels were assessed 5-6 months after the children entered childcare by measuring salivary levels of cortisol at home and in childcare, and childcare quality was observed on a day when researchers visited the childcare centres in the same period as saliva was collected.

Dietary intake was also assessed repeatedly postpartum, both for mothers and infants [39 40]. Hair samples, non-fasting urine samples from the mothers were collected again at 6 weeks, 6, 12 and 18 months postpartum (T7-T10), and non-fasting venous blood samples were collected from a subsample 6 and 12 months postpartum (T8-T9). The blood samples have been analysed for fatty acid composition, thyroid hormone function and vitamin D status (25(OH)D3). Non-fasting blood samples were collected from a subsample from the child at 6 and 12 months postpartum (T8-T9). Hair from the child was collected at 6 weeks, 6, 12 and 18 months postpartum (T7-T10), and spot urine samples were collected at 18 months (T10). The urine samples have been analysed for iodine concentration, and a sub-sample of hair (T7) has been analysed for total mercury concentration. The blood samples have been analysed for fatty acid composition and 25-hydroxy vitamin D (vitamin D status). Saliva samples, to be used for assaying DNA-methylation, were collected at 6 weeks (T7) and 12 months (T9). The aim is to use genome-wide epigenetic approaches, which allow a non-biased screen for DNA methylation alterations associated with pre- and postnatal stress and maternal non-optimal food intake.

It should be noted that at age three years information about the children's social emotional functioning at home and (when applicable) in day care, as well as an update on the families'

living conditions were collected. The next data collection wave is planned when the children are 8 years old. The main aim of the 8-year longitudinal follow-up study will be to investigate a broad range of child outcomes, including mental health and social-emotional and cognitive functioning, during the key transitional phase of entering school, predicted by perinatal psychological, epigenetic and nutritional patterns and processes. Subsequent collection waves are planned at age 13 and later on.

Findings to date

The most important findings generated by the cohort so far relate to three groups of results. The first group concerns parental mental health functioning in the perinatal period and which factors were related to parental anxiety, depression and stress in mothers and fathers [18 22 46]. The second group of results is directed toward child functioning [23 47-49], while the third group concerns maternal nutrition during pregnancy and its possible relation to early child development [50-52].

Concerning the first group of results, we explored whether depressive symptoms in the perinatal period could be categorized into distinct trajectories of symptom development among subgroups of women, and further investigated predictors of these trajectory groups [46]. Four classes of depressive symptom trajectories were identified: only in pregnancy, only postpartum, moderate and persistent up to 12 months, and few symptoms presented (Figure 2). Membership in the pregnancy only and postpartum only classes was primarily associated with maternal pregnancy-related anxiety and previous psychopathology, respectively, whereas the moderate and persistent class was associated with several psychosocial adversity factors. Maternal antenatal and perinatal depressive symptoms seemingly do not follow a uniform course, but rather support a model of several distinct time courses of depressed mood associated with diverse psychosocial adversity factors.

Insert Figure 2 here

Moreover [22], we have examined the association between adverse childhood experiences and symptoms of antenatal depression and anxiety in prospective fathers. Fathers who reported several such experiences had more depressive symptoms and pregnancy-related anxiety than those with lower scores. In a related paper, we found that fathers' symptoms of anxiety and depression during pregnancy as well as adverse childhood experiences predicted stress and a negative perception of the children's behaviour at 6 months [53]. In a similar vein, we investigated the multiple determinants of mothers' parenting stress and found that attachment style assessed prenatally was a salient predictor 12 months after birth [18]. Concurrent infant temperament at 12 months also contributed to parenting stress experienced by the mothers. We further found a link between maternal adverse childhood experiences and later parenting stress and showed that attachment style operated as a mediator in this link.

So far, four studies have been directed toward child development and mental health. In one study we found that parental perinatal depressive symptoms predicted child social-emotional functioning, specifically externalizing, internalizing, and dysregulation problems, as well as language developmental delay [23]. Interestingly, a differential effect, linking maternal symptoms to social-emotional outcomes and paternal symptoms to language outcomes, was found. Parenting stress at 12 months mediated the relations between parental depressive symptoms and child outcomes 6 months later. In another study, we investigated social emotional functioning among 12 month olds in a subsample of children whose mothers participated in a structured interview based on a questionnaire for children between the ages of 12 and 36 months [47]. Results showed that clinically important social emotional problems and competence delays could be reliably detected even at the lowest age limit [47]. We have also examined the applicability of a temperament questionnaire that was constructed for intervention [48]. The temperamental dimensions of adaptability, persistence, and regularity had

coherent factor structures. The inclusion of concepts related to individual differences in infant response tendencies and regulatory efforts may broaden the understanding of parent–infant transactions and can supply the toolkit for individualized parent guidance at an early age. In a fourth study, we studied stress reactions in connection with childcare; the change of morning to mid-afternoon levels of cortisol at home and in childcare was explored in a subsample of 112 toddlers [49]. Saliva samples and observations in childcare were conducted 5-6 months after the children entered childcare. An increase in cortisol levels during the day in childcare compared to home, was found among the toddlers. Of special interest is the finding that longer hours (8-9 hours per day) in childcare were associated with greater increases in cortisol levels compared with shorter hours (5-7 hours), which were associated with a flat cortisol pattern from morning to mid-afternoon.

Three studies of maternal and child nutrition and later child development have been published [50-52]. In one study, we asked whether the pregnant women had sufficient iodine intake according to WHO criteria [50]. Dietary factors such as use of iodine supplements and intake of dairy products, and geographic factors such as residence and season of urine sampling were all associated with urinary iodine concentration (UIC). In many cases the diet of the women did not secure a sufficient iodine intake as the median UIC was 85 µg/L (n=954) which is below the WHO cut off value of 150 µg iodine/L. In another study, mild to moderate maternal iodine deficiency in pregnancy was associated with lower language skills up to 18 months, but not with reduced cognitive or fine- and gross motor skills [51]. In a third study [52] the iodine status and dietary iodine sources were studied cross-sectionally among the 18-month-old toddlers. Results showed that the iodine status among the children from different geographic areas in Norway was sufficient, indicated by a median UIC above the WHO cut off of 100 µg/L.

Strengths and limitations

This study has a cross-disciplinary nature with a frequent and in-depth assessment of mothers, fathers, and their children from early in pregnancy. The use of a multi-method and multi-informant design including biological sampling, direct observation of behaviour, assessment of the children's development and self-reported information from mothers and fathers is a main strength. Moreover, well-validated measures have been used to assess both child development, child socio-emotional functioning, and parental symptoms of depression, anxiety, adult attachment style and parenting stress.

The use of many repeated assessments may increase the odds for identifying developmental pathways and contributing parental and child risk- and promoting factors. However, the LiN-cohort alone may be underpowered to identify when examining risk factors of outcomes with low prevalence. National as well as international collaboration is therefore encouraged with the aim of increasing sample size in connection with targeted research questions.

Further, the parents who took part tended to have a higher educational level than was common in the general population at the different sites. The impact of educational level might be different if it had been more in line with that of the local populations. A related concern is selective attrition, as dropout was shown to be related to depressive symptoms [23 46]. However, appropriate statistical methods (i.e., full information maximum likelihood estimations) have been used to minimize the effect of selective attrition in papers based on this study population [18 23 46 53]. Several assessments were based on self-report. This applies to our measures of adverse childhood experiences, depressive and anxious symptoms, as well as attachment style. Hence, associations might be inflated due to shared methods variance.

Collaboration

The study is located at the Department of Psychology at the University of Oslo. Collaboration is encouraged. Further information and requests for collaboration can be obtained by

contacting the principal investigator Vibeke Moe: vibeke.moe@psykologi.uio.no. The Institute of Marine Research (IMR), Bergen, and Uni Research Centre for Child and Youth Mental Health and Child Welfare, Bergen, and the Regional Centre for Child and Adolescent Mental Health, Eastern and Southern Norway are all collaborating institutions.

Data availability statement

Data available upon reasonable request.

Funding declaration

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Competing interests

None declared.

Ethics approval

All procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. The study protocol and the assessment procedures were reviewed and approved by the Norwegian Regional Committees for Medical and Health Research Ethics, reference number 2011/560.

Patient and public involvement statement

The LiN cohort is population based and does not involve patients. However, all the four Regional Centres for Child and Adolescent Health in Norway were involved in the planning

and development of the design of the study, and the data collection involved collaboration with midwives and nurses from nine public well-baby clinics across the four different Norwegian health regions.

Contributorship statement

VM and LS planned and developed the Little in Norway study design. MK, LD, MWK and KMS planned the nutrition part of the study. VM, EF, MK, LD, MWK, KMS, TvS, KO, UTV and LS all contributed in planning of the design of the present paper. EF and VM performed analysis of data. VM took the main responsibility for drafting the article, while EF, MK, LD, MWK, KMS, TvS, KO, UTV and LS contributed substantially in revising it critically for important intellectual content. All authors approved the final draft for publication.

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Table 1

Demographic characteristics of participants in the LiN-study

	Mothers *n* = 1036 Mean (SD) / Proportion	Partners *n* = 884 (878 men) Mean (SD) / Proportion	Children *n* = 1017 Mean (SD) / Proportion
Parents			
Age	30.26 (4.78)	32.76 (5.90)	
Education in years	16.05 (2.13)	15.59 (2.37)	
College or University degree	77.1%	67.1%	
High school	19.8%	28.2%	
Elementary school	3.1%	4.8%	
Ethnic minority	6.1%	4.6%	
First-time parent	54.9%	56.2%	
One previous child	33.3%	32.7%	
Two or more previous children	11.8%	11.0%	
Work status:			
Full-time job	77.3%	91.0%	
Part-time job	7.4%	1.7%	
Student	11.6%	6.2%	
Disability/Unemployed/At home	3.8%	1.0%	
Relationship status:			
Married	36.2%	35.2%	
Living together	59.7%	62.4%	
Single	2.5%	0.9%	

Divorced	0.2%	0.2%	
Other	1.4%	1.2%	
Previous psychiatric problems	21.7%	11.2%	
Life stress at enrollment	7.08 (6.91)	7.38 (7.00)	
Children			
Gestational age (in weeks)			39.99 (1.81)
Sex (percentage of boys)			52.3%
Premature births (n = X)			6.3%

Note. SD = Standard Deviation.

Table 2

Overview of data collection types (questionnaires, biological samples, observation and developmental testing) and time points of repeated assessments

Types of data	Enrol-ment	T1 gwk 8-21	T2 gwk 22-27	T3 gwk 28-31	T4 gwk 32-35	T5 gwk 36-41	T6 Birth	T7 6 w	T8 6 mo	T9 12 mo	T10 18 mo
Both parents:											
Questionnaires on											
Self	X	X	X	X	X	X		X	X	X	X
Infant characteristics								X	X	X	X
Mothers:											
Hair	X			X				X	X	X	X
Urine	X			X				X	X	X	X
Blood									X	X	
Infants:											
Hospital birth records							X				

48h diurnal clock registration	X			
Observation of infant social withdrawal		X	X	X
Cognitive, language and motor testing		X	X	X
Hair		X	X	X
Urine				X
Blood		X	X	
Saliva	X		X	
Mother-infant interaction:				
Video observation		X	X	X
Father-infant interaction:				
Video observation		X	X	X
Child care center:				
Questionnaire				X

Note. gwk: gestational weeks, mo: months

Table 3

Phases of data collection and specific measurements in the LiN study

Phase	**Measurements**
Assessments during pregnancy	Enrolment package, T1 (Gwk 8-21) T2 (Gwk 22-27), T3 (Gwk 28-31), T4 (Gwk 32-35), T5 (Gwk 36-41)
Enrolment package in pregnancy, first visit to well-baby clinic (range Gwk 8-34) At well baby clinic° Web from home*	Mothers and fathers: demographic information°, somatic and mental health, medication/smoking/alcohol habits° (TWEAK[b]), thoughts about unborn child°, life stress° (PSI-ls[d]), relational experiences° (ECR[e]), adverse childhood experiences° (ACE[f]) Mothers only: food frequency questionnaire* (FFQ[g]), hair and urine samples°
T1 (Gwk 8- 21)	Both parents: pregnancy concerns° (PRAQ-R[a]), depressive symptoms° (EPDS[c]), TWEAK, thoughts about unborn child Mothers only: Brief FFQ
T2 (Gwk 22-27) Web from home	Both parents: PRAQ-R, TWEAK, EPDS, thoughts about unborn child Mothers only: Brief FFQ
T3 (Gwk 28-31) At well baby clinic	Both parents: PRAQ-R, TWEAK, EPDS, Thoughts about unborn child Mothers only: brief FFQ, blood, urine and hair samples
T4 (Gwk 32-35) Web from home	Both parents: PRAQ-R, TWEAK, EPDS, Thoughts about unborn child Mothers only: FFQ

T5 (Gwk 36-41) Web from home	Both parents: PRAQ-R, TWEAK, EPDS, Thoughts about unborn child Mothers only: brief FFQ
T6 birth	Birthweight; gestational age; birth complications
Follow-up At well baby clinic° Web from home*	T7 6 weeks, T8 6 months, T9 12 months, T10 18 months
T7 Child age 6 weeks At well baby clinic° Web from home*	Infant–mother assesment procedure° (MABI[h]) Infants: diurnal rhythm*; DNA extracted from saliva°, infant hair samples° Mothers: FFQ*, child nutrition and breast feeding*, maternal hair and urine samples° Both parents: EPDS°
T8 Child age 6 months At well baby clinic° Web from home*	Infants: Infant development° (Bayley III screen[i]); withdrawal behavior° (ADBB[j]); hair and blood samples° Mothers: Hair, urine and blood samples°, FFQ*, child nutrition and breast feeding* Both parents: Parenting Stress Index° (PSI[k]), infant–parent interaction° (RHS[l]), EPDS°, perceived infant temperament* (Cameron-Rice[m])
T9 Child age 12 months At well baby clinic° Web from home*	Infants: Bayley III screen°, ADBB°, DNA extracted from saliva, infant hair and blood samples° Mothers: FFQ*, child nutrition and breast feeding*, maternal hair, urine and blood samples° Both parents: PSI°, RHS°, EPDS°, Cameron-Rice*

T10 Child age 18 months. At well baby clinic° Web from home* Web from child care centres**	Infants: Bayley III full scale°,[n], ADBB°, infant hair and urine samples° Mothers: Maternal hair and urine samples° Both parents: PSI°, RHS°, EPDS°, child social emotional assessment* (ITSEA*,[o]) Childcare centre: ITSEA**

Note. Gwk: Gestational weeks, [a]PRAQ-R: Pregnancy Related Anxiety Questionnaire revised [36], [b]TWEAK: Tolerance, Worried, Eye-opener, Amnesia, Cut-down [54], [c]EPDS: Edinburgh Postnatal Depression Scale [37], [d]PSI-ls: Parenting Stress Index-life stress [32], [e]ECR: Experiences in Close Relationships scale [33], [f]ACE: Adverse Childhood Experiences scale [10], [g]FFQ: semi–quantitative food frequency questionnaire,[39 40] [h]MABI: Mothers's Assessment of the Behavior of the Infant [55], [i]Bayley Scales of Infant and Toddler Development, screening test, [j]ADBB: Alarm Distress Baby Scale [42], [k]PSI: Parenting Stress Index [32], [l]RHS: Relational Health Screen (Willis & Kahn, 2002), [m]Cameron-Rice perceived temperament scale [56], [n]Bayley Scales of Infant and Toddler Development, full scale [41][o]ITSEA: Infant-Toddler Social and Emotional Assessment [45]

Figure captions:

Figure 1

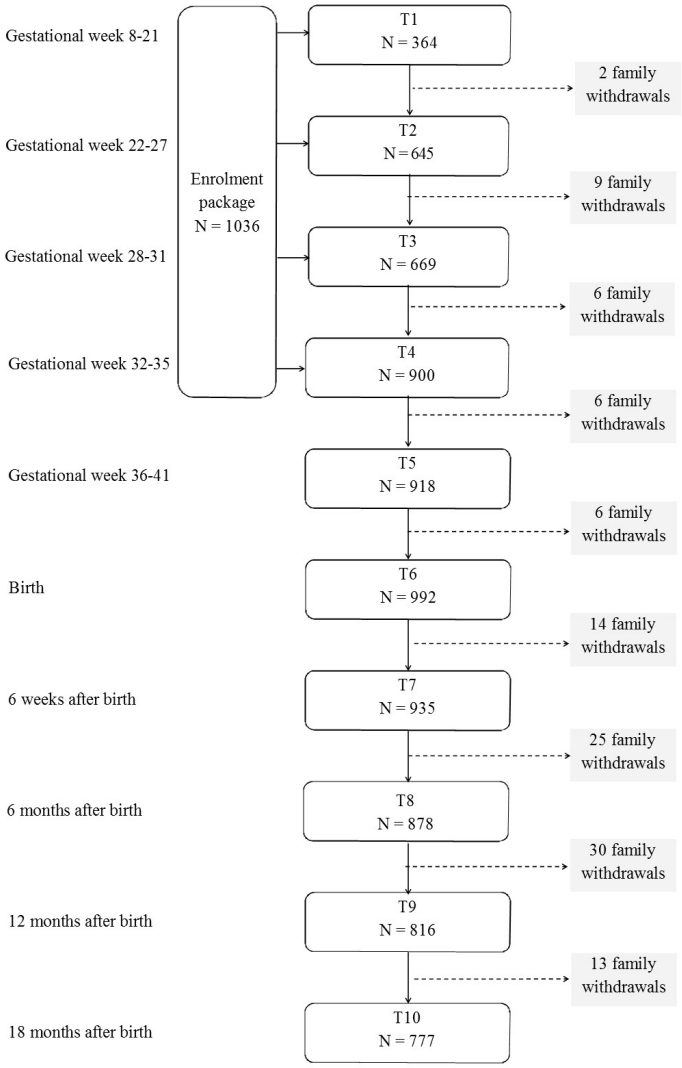
Recruitment, participation and attrition in the Little in Norway study

All participants received an enrollment package at entry into the study; subsequently they took part in the data collection wave corresponding to their gestational week at entry. The full *Little in Norway* sample was reached at T4. The *N*s represent the number of participants taking part at each time point; missingness comprises late recruitment, intermittent missingness (missing at current time point, but participating at later time points) and study drop-out. The grey boxes on the right indicate the number of participants that dropped out on a permanent basis.

Figure 2

Model of the course of depressive symptoms from pregnancy to 12 months

The figure shows the estimated mean trajectories of the of the 4-class growth mixture model of depressive symptoms in women from pregnancy to 12 months postpartum. From Fredriksen et al., 2018, (cf. reference list No. 46), reprinted with permission from APA.



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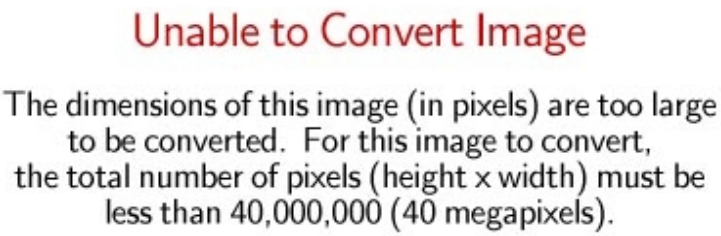
209x297mm (150 x 150 DPI)



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Cohort Profile: Little in Norway: a prospective longitudinal community-based cohort from pregnancy to child age 18 months

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Mental health, Nutrition and metabolism
Keywords:	Community-based, Cross-disciplinary, Prospective longitudinal, Parental mental health, Child development, NUTRITION & DIETETICS

Title: Cohort Profile: Little in Norway: a prospective longitudinal community-based cohort from pregnancy to child age 18 months

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Abstract

Purpose:

The Little in Norway (LiN) project is a cross-disciplinary prospective longitudinal study starting in pregnancy. It was set up to investigate maternal and paternal mental health functioning in the transition to parenthood, detect pathways to healthy and aberrant child development, and generate new knowledge about mechanisms underlying differential child mental health susceptibility.

Participants:

The LiN cohort is a community-based sample comprising 1036 families (1036 mothers, 884 partners, 1017 children). All pregnant women and their partners receiving routine prenatal care at well-baby clinics at nine geographically selected sites across Norway were invited to participate. Enrolment took place from September 2011 to October 2012. This cohort profile comprises ten data collection waves spanning from enrolment in pregnancy until child age 18 months.

Findings to date:

The most significant findings so far relate to three domains of results. First, when examining risk factors for parental mental health problems, results showed that the parents' own adverse childhood experiences and attachment style were related to anxiety, depression, and stress in the perinatal period. The experience of difficult child temperament was also found to contribute to parenting stress in the first year after birth. Second, we studied how parental mental health risk factors were related to later child development and social emotional functioning, for example linking maternal symptoms to social-emotional outcomes and paternal symptoms to language outcomes. Third, we investigated the relation between maternal nutrition during pregnancy and aspects of early child development. Results showed

that mild to moderate maternal iodine deficiency in pregnancy was associated with poorer language skills up to 18 months, but not with reduced cognitive or fine- and gross motor skills

Future plans:

A data collection point at 36 months is completed and currently being analysed. A new data collection wave is planned when the children are 8 years old.

Keywords:

Community-based, Cross-disciplinary, Prospective longitudinal, Parental mental health, Nutrition, Child development

Strengths and limitations of this study

- Cross-disciplinary prospective longitudinal community-based study of children and their parents from early pregnancy on.
- A multi-method and multi-informant design including biological sampling, direct observation of behaviour, assessment of the children's development and self-reported information from mothers and fathers.
- Many repeated in-depth assessments from early in pregnancy and onward makes it possible to identify differential developmental pathways and underlying mechanisms.
- This cohort alone may be underpowered when examining risk factors of outcomes with low prevalence, hence collaboration is encouraged.
- The participating parents tended to have a higher educational level than the general population at the different sites. A related concern is selective attrition, as dropout was shown to be related to depressive symptoms. However, appropriate statistical methods have been used to minimize the effect of selective attrition in papers based on this study population.

Introduction

Differential pathways to healthy and atypical development emerge early in life [1]. Human infants are malleable and take their course of growth in many directions, in part predisposed by biological factors and subsequently influenced by postnatal environmental characteristics in a continuous dynamic transactional interplay [2-4]. Such pathways have been identified in early childhood [2 5 6]. However, the knowledge of the pre- and perinatal precursors of child development and social-emotional functioning is still scarce. The Little in Norway (LiN) study is an on-going cross-disciplinary longitudinal and prospective multisite community-based study of children and their parents from early pregnancy on. It was set up to investigate maternal and paternal mental health functioning in the transition to parenthood, examine pre- and postnatal precursors of long-term child development and mental health, as well as disentangling mechanisms of transmission of developmental risk and protective factors. The study aims at integrating the research areas of mental health, developmental psychology, nutrition and molecular genetics. This Cohort Profile focuses on ten data collection waves spanning from enrolment in pregnancy until 18 months after birth.

A better understanding of early risk and protective factors, leading into pathways of later competence or adversity is needed, as there is a high potential for early interventions to adjust atypical pathways [7-9]. For example, parents' adverse childhood experiences [10 11] have been shown to influence later parental mental health, and are associated with insecure attachment, pre- and postnatal depression, parenting stress and atypical parenting behaviour toward their own children [10 12-17]. However, only few studies have examined the longitudinal implications of such risk factors on parenting and parent–child interaction in cohorts followed from the prenatal period [18]. One needs to elucidate the mechanisms of how parental adverse childhood experiences and mental health status, such as perinatal depression and anxiety, translate into aberrant child development, as such mechanisms are only partially understood [19 20]. In

addition, there is a need for including fathers in such studies [21 22]. Particularly, there is a lack of studies examining differential and joint effects of mothers and fathers' impact on mental health functioning in infancy and early childhood [23].

Antenatal biological factors may also be decisive for later development. Some nutrients protect maternal health while others affect birth outcome and infant health. For example, an inadequate nutrient supply may cause biological competition between mother and foetus [24 25]. Evidence also suggests that long chain polyunsaturated fatty acids, such as docosahexaenoic acid (DHA, 22:6, n3), play a role in the aetiology of postpartum depression [26-29]. DHA and arachidonic acid (AA, 20:4, n-6) are important structural components in the brain and the central nervous system and subsequently necessary for normal growth and development of the brain. Further, suboptimal iodine nutrition during pregnancy is associated with poorer child language development and lower child IQ [30 31 32]. This study comprises a food frequency questionnaire applied at several time points as well as biological samples to obtain information related to child and parental nutrition and its possible relation to child development and mental health functioning.

Cohort description

Who is in the cohort?

All pregnant women, receiving routine prenatal care at nine public well-baby clinics across Norway, were invited by midwives to participate. The clinics were chosen taking demographics and size of the population into account, to ensure a wide distribution of background conditions. Participants were recruited at their first prenatal care examination at the well-baby clinic. At each site, one public health care nurse was trained as a research assistant. In Norway, all pregnant women have the right to prenatal care and at least eight free consultations during pregnancy. If necessary, extra consultations are offered. Nearly all

pregnant women (93 %) in Norway choose to use the first line public health care system during pregnancy (general practitioners and well-baby clinics) [33]. Although there are nationwide schedules for prenatal care, many choose to receive initial check-ups by their general practitioner while switching to midwives at the well-baby clinics when the due date approaches. Therefore, despite all women being invited at their first prenatal visit to the well-baby clinic, the time frame for enrolment ranged from gestational week 8 to 34.

Initially, 1041 women consented; five later withdrew, leaving 1036 (99.5%) participating pregnant women. Their partners were also invited and 884 (878 men and six women) participated. No exclusion criteria were applied, but since the questionnaires were either in Norwegian or in English, this might have excluded pregnant women and their partners who spoke neither Norwegian nor English. The participation rate is estimated to be 50.7%. At five of the clinics, the staff did not establish reliable routines to monitor rates of participation; this rate is based on records from the remaining four clinics. However, participation rates were probably relatively similar at all sites since all clinics shared recruitment strategies.

Table 1 shows demographic characteristics of the sample. Pearson chi-square tests were performed at each of the nine sites separately, comparing the participants' educational level with the mean educational level of the population at the nine sites in the same age (figures obtained from Statistics Norway). In general, participant showed higher educational level than the reference populations ($p < .001$).

Insert Table 1 here

Participants received written and oral information before giving their consent to their own and their children's participation. Confidentiality was assured, and it was emphasized that they could withdraw at any time. The Regional Committees for Medical and Health Research Ethics in Norway approved the study [2011/560]. The enrolment took place from September

2011 to October 2012. At time of birth, three families were lost due to stillbirth, while 26 families were lost for other reasons before childbirth (e.g., family moving out of the area, participation felt to be too time consuming). The remaining 1007 mothers delivered 1017 children (including ten twin pairs).

How often have the participants been followed up?

The participants have been followed-up from early in pregnancy to infant age 18 months. The study has an intensive prospective, longitudinal design including data collection at ten time points. After enrolment, the prenatal data collection waves were at gestational weeks 8-21 (T1), weeks 22-27 (T2), weeks 28-31 (T3), weeks 32-35 (T4), and weeks 36-41 (T5). T6 comprises birth records. Postnatal data were collected at 6 weeks postpartum (T7), and again at 6 months (T8), 12 months (T9), and 18 months (T10) after birth, all with ± 2 weeks.

All participants completed the enrolment package (n = 1036 and 884, pregnant women and their partners, respectively). Data collection at T1 to T10 had limited time windows relative to gestational/child age for valid participation. This means that a sizeable proportion of participants was not enrolled in time to take part in the early data collection points during pregnancy. At T10, 925 families (88.9 %) of the original sample were still participants and remained in the study for future follow-up. Hence, there are three categories of missing data: late recruitment, study withdrawal or families lost to follow-up (n = 116), and intermittently missing data, which comprise participants that skipped one or more data collection waves, but then contributed at later time points. Figure 1 depicts the flow of recruitment, participation and attrition at each data point.

Insert Figure 1 here

Bivariate logistic regression analyses were conducted to investigate selective attrition at T10 (18 month after childbirth). High level of maternal education slightly increased the probability

of participation at T10 (OR = 1.07, 95% CI [1.01, 1.15], p = .030). Neither partners' education (OR = 1.04, 95% CI [0.97, 1.11], p = .255), maternal age (OR = 1.00, 95% CI [0.97, 1.03], p = .886), partners' age (OR = 1.00, 95% CI [0.98, 1.03], p = .756), maternal parity (OR = 0.87, 95% CI [0.73, 1.04], p = .123), nor the number of partners' previous children (OR = 0.98, 95% CI [0.80, 1.21], p = .879) were related to attrition. Attrition was further predicted by lower levels of mean prenatal (OR = 0.91, 95% CI [0.88, 0.95], p <.001) and postnatal (OR = 0.95, 95% CI [0.90, 1.00], p = .041) depressive symptoms for mothers, as well as lower levels of mean prenatal (OR = 0.92, 95% CI [0.87, 0.97], p = .004) and postnatal (OR = 0.93, 95% CI [0.86, 0.99], p = .030) depressive symptoms for partners.

What has been measured?

Data collected in the LiN-Study include multi-informant questionnaire data, observational and behavioural data, and biological samples. Data were collected at the local well-baby clinic and by means of web-based surveys filled out at home, at well-baby clinics or completed by the research assistants based on parent interviews. Types of measurements at each wave are shown in Table 2, while the specific measurement methods are shown in Table 3.

Insert Tables 2 and 3 here

Enrolment package in pregnancy

Mothers and fathers received a comprehensive questionnaire package concerning parental demographic information, somatic and mental health and dietary habits, as well as medication, smoking and alcohol habits, at the first meeting in pregnancy (enrolment package). To screen for possible alcohol problems the Tolerance, Worried, Eye-opener, Amnesia, Cut-down (TWEAK) screening questionnaire [34] was administered. In addition, possible adverse childhood experiences were assessed by means of the Adverse Childhood Experiences (ACE) Scale [10]. The scale comprises ten questions about possible adverse

experiences prior to age 18 years, such as physical or sexual assault, major separation or loss, or parental mental illness or drug abuse. The Life Stress Scale, a subscale of the Parenting Stress Index (PSI) [35], was used to measure life stress events. The PSI is a self-report questionnaire that contains a Life stress Scale, a Child Domain, reflecting how parents perceive their child, and a Parent Domain, consisting of items related to parental coping and the parenting role. The PSI was standardized for use with parents of children ranging from 1 month to 12 years of age. The Life stress Scale consists of 19 items measuring life stress events experienced in the previous 12 months.

We also measured partner-related attachment style by using the Experiences in Close Relationships (ECR) Scale [36] since the quality of the parents' representations of attachment relationships is an important factor to consider for parental adaptation and parenting behaviour [37 38]. The ECR Scale is a self-report measure designed to assess the dimensions of adult attachment styles in relationships. The instrument comprises two dimensions, avoidance and anxiety, consisting of 18 items each.

Repeated assessments during pregnancy (T1-T5)

Anxiety related to pregnancy and birth and depressive symptoms in the perinatal period were measured at all assessments in pregnancy in both parents (T1-T5). PRAQ-R is a short form of the Pregnancy Related Anxiety Questionnaire (PRAQ) [39], a 10-item scale designed to assess ongoing anxiety related to pregnancy and birth. The Edinburgh Postnatal Depression Scale (EPDS) [40] is a self-report measure to identify women at risk for postnatal depression in the previous seven days. Although EPDS was originally developed to screen for postnatal depressive symptoms in women, it has later been validated for prenatal use [41]. It has also been validated on male populations [42]. We also included questions about both parents' thoughts and feelings toward their unborn baby at all data points during pregnancy in order to capture

mental representations of the coming child. To assess nutritional status and cortisol levels, hair and urine samples were collected from the mothers twice during pregnancy (T1 and T3). The urine samples have been analysed for iodine concentration. Blood samples were collected during pregnancy (T1) and have been analysed for fatty acid composition and vitamin D status (25(OH)D3). Dietary intake was measured using a web-based food frequency questionnaire (FFQ) twice during pregnancy (T1 and T4) [43 44].

Three questions about seafood intake were included at T2, T3 and T5.

Postnatal assessments (T6-T10)

At birth (T6), we collected information from hospital birth records. At six weeks after birth (T7) the research assistants met with the parents and their baby to observe the infant [45] and obtain information about the child's diurnal rhythm. The parents received questionnaires, and biological samples from mother and child were collected.

Depressive symptoms [40 41] in both parents were again assessed (T7 to T10 by means of the EPDS. Stress in the parenting role and in the parent–child relationship was also measured repeatedly postpartum by using the Parenting Stress Index (PSI) [35]. Testing and observation of the children's development and videotaping of child–parent interaction were conducted at the local well-baby clinics at six, 12 and 18 months (T8-T10). Developmental skills were assessed by using the screening (6 and 12 months) and the full version (18 months) of the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III) [46]. The Bayley Scales is an individually administered test designed to assess developmental functioning of infants and toddlers from 1 to 42 months. The screener is composed of selected items from the full Bayley version to briefly assess current functioning in the domains of cognition, receptive and expressive language, as well as gross- and fine motor development. We also observed the infants' possible social withdrawal reactions using the Alarm Distress Baby Scale [47]. The

scale is a method aimed at evaluating social behaviours that can be observed during a brief observation of children from two to 24 months old. It was scored based on child behaviour when doing the Bayley.

The parents were also asked to evaluate their infants' temperament characteristics by means of the Cameron-Rice perceived temperament scale (CRITQ) [48 49]. The CRITQ comprises 46 items probing eight dimensions: sensitivity, movement, reactivity/intensity, persistence, adaptability, approach–withdrawal, regularity, and soothability.

To assess the quality of parent–child interaction (data not yet analysed), the children and their parents participated in videotaped play sessions at 6, 12 and 18 months (T8-T10). At 18 months (T10) the Infant-Toddler Social Emotional Assessment scale (ITSEA) [50] was completed by all parents, and by the preschool teacher if the child attended a day-care centre. The ITSEA is a parent report questionnaire assessing the child's social-emotional functioning in children from 12 to 36 months and comprises 166 items measuring four domains: externalising behaviour, internalising behaviour, dysregulation and competence.

In one sub-sample (N = 102, 10.03 %), children with high (N = 52) versus low risk scores (N = 50) on markers of developmental status and parenting stress obtained at 6 months were selected. Child social emotional functioning was assessed by a standardized telephone interview with the main caregiver at 12 months (T9) [51]. The aim was to assess the applicability of the ITSEA at its lowest age level (12 months), and whether infants at risk at 6 months had increased scores later (12 months).

In another sub-sample, the aim was to investigate if changes in toddlers' morning to mid-afternoon levels of cortisol were different on days spent in childcare compared with days spent at home [52]. The children's stress levels were assessed 5-6 months after they entered childcare by measuring levels of cortisol in saliva at home and in childcare. Childcare quality was observed on a day when researchers visited the childcare centres in the same period as

saliva was collected. From the whole sample, 459 eligible parents who had toddlers entering childcare in the autumn of 2013 and 2014 were invited to participate (192 parents consented, 122 childcare centres cooperated). Ten children missed saliva samples, thus the final sample comprised 112 children (58.30 % of the consenting parents, 11.01 % of the total child sample).

Dietary intake was assessed repeatedly postpartum, both for mothers and infants [39 40]. Hair samples and non-fasting urine samples from the mothers were collected at 6 weeks, 6, 12 and 18 months postpartum (T7-T10), and non-fasting venous blood samples were collected at 6 and 12 months postpartum (T8-T9). The blood samples have been analysed for fatty acid composition, thyroid hormone function and vitamin D status (25(OH)D3). Non-fasting blood samples were collected from the child at 6 and 12 months postpartum (T8-T9). Hair from the child was collected at 6 weeks, 6, 12 and 18 months postpartum (T7-T10), and spot urine samples were collected at 18 months (T10). The urine samples have been analysed for iodine concentration, and a sub-sample of hair (T7) has been analysed for total mercury concentration. The blood samples have been analysed for fatty acid composition and 25-hydroxy vitamin D (vitamin D status). Saliva samples, to be used for assaying DNA-methylation, were collected at 6 weeks (T7) and 12 months (T9). It should be noted that at age three years information about the children's social emotional functioning at home and (when applicable) in day care, as well as an update on the families' living conditions were collected.

The next data collection wave is planned when the children are 8 years old. The main aim of the 8-year longitudinal follow-up study will be to investigate a broad range of child outcomes, including mental health and social-emotional and cognitive functioning, during the key transitional phase of entering school, predicted by perinatal psychological, epigenetic and nutritional patterns and processes. We have so far used a genome-wide epigenetic approach, which allows a non-biased screen for DNA methylation alterations that may be associated

with prenatal maternal stress [53]. We will pursue this line of investigation in future studies. We plan to look at patterns of parental mental health and non-optimal nutrition, and possible relations to differential child methylation patterns. Subsequent collection waves are planned at age 13 and later on.

Patient and public involvement statement

The LiN cohort is population based and does not involve patients. However, all the four Regional Centres for Child and Adolescent Health in Norway were involved in the planning and development of the design of the study, and the data collection involved collaboration with midwives and nurses from nine public well-baby clinics across the four different Norwegian health regions.

Findings to date

The most important findings generated by the cohort so far can be summarised in three main domains. The first domain concerns parental mental health functioning in the perinatal period and factors related to parental anxiety, depression and stress in mothers and fathers [18 22 54]. The second domain is directed toward child functioning and early detection of infants and toddlers at risk [23 51 52 55], while the third domain concerns maternal nutrition during pregnancy and its possible relation to early child development [32 56 57].

Parental mental health in the transition to parenthood

First, we included an examination of the course of depressive symptoms in the ante- and postnatal period among subgroups of women[54]. We found that maternal antenatal and postnatal depressive symptoms do not follow a uniform course; results rather support a model of several distinct trajectories of depressed mood associated with different adverse psychosocial and relational factors. Four different symptom trajectories were identified; only in pregnancy, only postpartum, moderate and persistent up to 12 months postpartum . Both

researchers and clinicians should be aware of possible multiple courses of depressive mood and the risk factors behind these different trajectories, in order to better target intervention efforts in the perinatal period. Moreover, we have examined the association between adverse childhood experiences and symptoms of antenatal depression and anxiety in prospective fathers [22]. Fathers who reported several such experiences had more depressive symptoms and anxiety before birth of the child than those with lower scores. We also found that paternal symptoms of anxiety and depression during pregnancy as well as their own adverse childhood experiences predicted stress and a negative perception of the infants' behaviour [58]. In a similar vein, we investigated the multiple determinants of mothers' parenting stress and found that partner attachment style assessed prenatally was a salient predictor of such stress 12 months after birth [18]. We further found a link between maternal adverse childhood experiences and later parenting stress, and showed that partner attachment style operated as a mediator in this link. Perceived difficult infant temperament also contributed to the experience of parenting stress in the mothers. Altogether, these results point to the clinical importance of paying attention to both parents' mental health during pregnancy. It is especially important to recognise the role of parental adverse childhood experiences in determining later parenting stress, and the need to help parents with a background of difficult relational experiences and an unsecure couple relationship before childbirth.

Child development, infant mental health and early detection of infants at risk

So far, four studies have been directed toward early child development and infant mental health. In one study, we found that parental perinatal depressive symptoms predicted child social-emotional difficulties and language delay at infant age 18 months [23]. A differential effect, linking maternal symptoms to compromised social-emotional outcomes in children and paternal symptoms to poorer language outcomes was found. Perinatal depressive symptoms in both mothers and fathers may have a wide impact on child development, underscoring the

importance of being aware of depression in fathers as well as in mothers in the perinatal period. It should be noted that a majority of Norwegian children between 1 and 2 years of age are cared for in professional childcare during the day (83.5 %) [59]. Possible stress reactions among the youngest children in connection with childcare has been of concern. We therefore studied the change of morning to mid-afternoon levels of the stress hormone cortisol at home and in childcare among toddlers. An increase in cortisol levels during the day in childcare compared to home was found. Of special interest is the finding that longer hours (8–9 per day) were associated with a greater increase in cortisol levels among the children compared with shorter hours (5–7), suggesting that separation from parents and interaction with several caregivers and children during the day may be especially demanding for toddlers who spend the longest days in childcare [52].

In order to detect early deviance and to provide help to infants at risk for social-emotional difficulties as early as possible, it is important that assessment instruments are developmentally sensitive. To this aim, we investigated if the ITSEA scale could be reliably used as a screening instrument for children as young as 12 months [51]. Results showed that clinically important social emotional problems and competence delays could be reliably detected even at ITSEA's lowest age limit. We also examined the applicability of a temperament questionnaire constructed for intervention [55]. The temperamental dimensions of adaptability, persistence, and regularity had coherent factor structures. The inclusion of concepts related to individual differences in infant response tendencies and regulatory efforts when assessing infant behavior may broaden the understanding of parent-infant transactions, and can provide a valuable toolkit for individualized parent guidance at an early age

Maternal nutrition during pregnancy and later child development

So far, three studies of maternal and child nutrition and later child development have been published [32 56 57]. First, we asked whether the pregnant women had sufficient iodine intake

according to WHO criteria [56]. In many cases the women's diet did not secure a sufficient iodine intake. Second, mild to moderate maternal iodine deficiency in pregnancy was found to be associated with lower child language skills up to 18 months [32]. Third, the iodine status and dietary iodine sources were studied cross-sectionally among the toddlers [56]. Results showed that the iodine status among the children from different geographic areas in Norway was sufficient, indicated by a median UIC above the WHO cut off of 100 µg/L. To our knowledge, this is the largest and most complete study to date of maternal iodine status during pregnancy and its association with repeated measures of clinically assessed infant and toddler neurodevelopment. Preventing mild to moderate iodine deficiency in pregnant women by securing adequate iodine status before conception is an optimal strategy to counteract the detrimental effects of inadequate iodine intake.

Strengths and limitations

This study has a cross-disciplinary nature with a frequent and in-depth assessment of mothers, fathers, and their children from early in pregnancy. The use of a multi-method and multi-informant design including biological sampling, direct observation of behaviour, assessment of the children's development and self-reported information from mothers and fathers is a main strength. Moreover, well-validated measures have been used to assess both child development, child socio-emotional functioning, and parental symptoms of depression, anxiety, adult attachment style and parenting stress.

The use of many repeated assessments may increase the odds for identifying developmental pathways and contributing parental and child risk- and promoting factors. However, the LiN-cohort alone may be underpowered when examining risk factors of outcomes with low prevalence. National as well as international collaboration is therefore encouraged with the aim of increasing sample size in connection with targeted research questions.

Further, the parents who took part tended to have a higher educational level than was common in the general population at the different sites. The impact of educational level might be different if it had been more in line with that of the local populations. A related concern is selective attrition, as dropout was shown to be related to depressive symptoms [23 53]. However, appropriate statistical methods have been used to minimize the effect of selective attrition in papers based on this study population [18 23 53 57]. More specifically, in the majority of papers using longitudinal data from the study, full information maximum likelihood (FIML) was used to reduce bias relating to missing data, including late recruitment, intermittent missingness and study drop-out. FIML is regarded as a state-of-the-art missing data technique, providing unbiased parameter estimates under the missing at random (MAR) assumptions while at the same time providing high statistical power of the analyses [60].Several assessments were based on self-report. This applies to our measures of adverse childhood experiences, depressive and anxious symptoms, as well as attachment style. Hence, associations might be inflated due to shared methods variance.

Collaboration

The study is located at the Department of Psychology at the University of Oslo. Collaboration is encouraged. Further information and requests for collaboration can be obtained by contacting the principal investigator Vibeke Moe: vibeke.moe@psykologi.uio.no. The Institute of Marine Research (IMR), Bergen, and Uni Research Centre for Child and Youth Mental Health and Child Welfare, Bergen, and the Regional Centre for Child and Adolescent Mental Health, Eastern and Southern Norway are all collaborating institutions.

Data availability statement

Data available upon reasonable request. Further information and requests for collaboration can be obtained by contacting the principal investigator Vibeke Moe: vibeke.moe@psykologi.uio.no.

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Competing interests

None declared.

Ethics approval

All procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. The study protocol and the assessment procedures were reviewed and approved by the Norwegian Regional Committees for Medical and Health Research Ethics, reference number 2011/560.

Contributorship statement

VM and LS planned and developed the Little in Norway study design. MK, LD, MWM and KMS planned the nutrition part of the study. VM, EF, MK, LD, MWM, KMS, TvS, KO, UTV and LS all contributed in planning of the design of the present paper. EF and VM performed analysis of data. VM took the main responsibility for drafting the article, while EF, MK, LD, MWM, KMS, TvS, KO, UTV and LS contributed substantially in revising it

critically for important intellectual content. All authors approved the final draft for publication.

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Table 1

Demographic characteristics of participants in the LiN-study

	Mothers *n* = 1036 Mean (SD) / Proportion	Partners *n* = 884 (878 men) Mean (SD) / Proportion	Children *n* = 1017 Mean (SD) / Proportion
Parents			
Age	30.26 (4.78)	32.76 (5.90)	
Education in years	16.05 (2.13)	15.59 (2.37)	
College or University degree	77.1%	67.1%	
High school	19.8%	28.2%	
Elementary school	3.1%	4.8%	
Ethnic minority	6.1%	4.6%	
First-time parent	54.9%	56.2%	
One previous child	33.3%	32.7%	
Two or more previous children	11.8%	11.0%	
Work status:			
Full-time job	77.3%	91.0%	
Part-time job	7.4%	1.7%	
Student	11.6%	6.2%	
Disability/Unemployed/At home	3.8%	1.0%	
Relationship status:			
Married	36.2%	35.2%	
Living together	59.7%	62.4%	
Single	2.5%	0.9%	

Divorced	0.2%	0.2%	
Other	1.4%	1.2%	
Previous psychiatric problems	21.7%	11.2%	
Life stress at enrollment	7.08 (6.91)	7.38 (7.00)	
Children			
Gestational age (in weeks)			39.99 (1.81)
Sex (percentage of boys)			52.3%
Premature births (n = X)			6.3%

Note. SD = Standard Deviation.

Table 2

Overview of data collection types (questionnaires, biological samples, observation and developmental testing) and time points of repeated assessments

Types of data	Enrol-ment	T1 gwk 8-21	T2 gwk 22-27	T3 gwk 28-31	T4 gwk 32-35	T5 gwk 36-41	T6 Birth	T7 6 w	T8 6 mo	T9 12 mo	T10 18 mo
Both parents:											
Questionnaires on											
Self	X	X	X	X	X	X		X	X	X	X
Infant characteristics								X	X	X	X
Mothers:											
Hair	X			X				X	X	X	X
Urine	X			X				X	X	X	X
Blood									X	X	
Infants:											
Hospital birth records							X				

48h diurnal clock registration	X			
Observation of infant social withdrawal		X	X	X
Cognitive, language and motor testing		X	X	X
Hair		X	X	X
Urine				X
Blood		X	X	
Saliva	X		X	
Mother-infant interaction:				
Video observation		X	X	X
Father-infant interaction:				
Video observation		X	X	X
Child care center:				
Questionnaire				X

Note. gwk: gestational weeks, mo: months

Table 3

Phases of data collection and specific measurements in the LiN study

Phase	**Measurements**
Assessments during pregnancy	Enrolment package, T1 (Gwk 8-21) T2 (Gwk 22-27), T3 (Gwk 28-31), T4 (Gwk 32-35), T5 (Gwk 36-41)
Enrolment package in pregnancy, first visit to well-baby clinic (range Gwk 8-34) At well baby clinic° Web from home*	Mothers and fathers: demographic information°, somatic and mental health, medication/smoking/alcohol habits° (TWEAK[b]), thoughts about unborn child°, life stress° (PSI-ls[d]), relational experiences° (ECR[e]), adverse childhood experiences° (ACE[f]) Mothers only: food frequency questionnaire* (FFQ[g]), hair and urine samples°
T1 (Gwk 8- 21)	Both parents: pregnancy anxiety concerns° (PRAQ-R[a]), depressive symptoms° (EPDS[c]), medication/smoking/alcohol habits° (TWEAK), thoughts about unborn child° Mothers only: brief food frequency questionnaire (FFQ)
T2 (Gwk 22-27) Web from home	Both parents: pregnancy anxiety concerns (PRAQ-R), medication/smoking/alcohol habits (TWEAK), depressive symptoms (EPDS), thoughts about unborn child Mothers only: brief food frequency questionnaire (FFQ)
T3 (Gwk 28-31) At well baby clinic	Both parents: pregnancy anxiety concerns (PRAQ-R), medication/smoking/alcohol habits (TWEAK), depressive symptoms°(EPDS), thoughts about unborn child

	Mothers only: brief food frequency questionnaire (FFQ), blood, urine and hair samples
T4 (Gwk 32-35) Web from home	Both parents: pregnancy anxiety concerns (PRAQ-R), medication/smoking/alcohol habits (TWEAK), depressive symptoms (EPDS), thoughts about unborn child Mothers only: food frequency questionnaire (FFQ)
T5 (Gwk 36-41) Web from home	Both parents: pregnancy anxiety concerns (PRAQ-R), medication/smoking/alcohol habits (TWEAK), depressive symptoms (EPDS), thoughts about unborn child Mothers only: brief food frequency questionnaire (FFQ)
T6 birth	Birthweight; gestational age; birth complications
Follow-up At well baby clinic° Web from home*	T7 6 weeks, T8 6 months, T9 12 months, T10 18 months
T7 Child age 6 weeks At well baby clinic° Web from home*	Infant–mother assesment procedure° (MABI[h]) Infants: diurnal rhythm*; DNA extracted from saliva°, infant hair samples° Mothers: food frequency questionnaire (FFQ*), child nutrition and breast feeding*, maternal hair and urine samples° Both parents: depressive symptoms (EPDS°)
T8 Child age 6 months At well baby clinic° Web from home*	Infants: infant development° (Bayley III screen[i]); infant social withdrawal behaviour° (ADBB[j]); hair and blood samples° Mothers: Hair, urine and blood samples°, food frequency questionnaire (FFQ*), child nutrition and breast feeding*

	Both parents: Parenting Stress Index° (PSI[k]), infant–parent interaction°, depressive symptoms° (EPDS), perceived infant temperament* (Cameron-Rice[m])
T9 Child age 12 months At well baby clinic° Web from home*	Infants: infant development° (Bayley III screen), infant social withdrawal behaviour° (ADBB), genetic information extracted from saliva, infant hair and blood samples° Mothers: food frequency questionnaire (FFQ)*, child nutrition and breast feeding*, maternal hair, urine and blood samples° Both parents: Parenting Stress Index° (PSI), infant–parent interaction°, depressive symptoms (EPDS°), perceived infant temperament*(Cameron-Rice)
T10 Child age 18 months. At well baby clinic° Web from home* Web from child care centres**	Infants: infant development° (Bayley III full scale[n]), infant social withdrawal behaviour° (ADBB), infant hair and urine samples° Mothers: maternal hair and urine samples° Both parents: Parenting Stress Index° (PSI), infant–parent interaction°, depressive symptoms (EPDS°), child social emotional assessment* (ITSEA[o]) Childcare centre: child social emotional assessment** (ITSEA)

Note. Gwk: Gestational weeks, [a]PRAQ-R: Pregnancy Related Anxiety Questionnaire revised [39], [b]TWEAK: Tolerance, Worried, Eye-opener, Amnesia, Cut-down [38], [c]EPDS: Edinburgh Postnatal Depression Scale [40], [d]PSI-ls: Parenting Stress Index-life stress [35], [e]ECR: Experiences in Close Relationships scale [36], [f]ACE: Adverse Childhood Experiences scale [10], [g]FFQ: semi–quantitative food frequency questionnaire,[42 43] [h]MABI: Mothers's Assessment of the Behavior of the Infant [44], [i]Bayley Scales of Infant and Toddler Development, screening test [45], [j]ADBB: Alarm Distress Baby Scale [46], [k]PSI: Parenting Stress Index [35], [m]Cameron-Rice perceived temperament scale [47], [n]Bayley Scales of Infant and Toddler Development, full scale [45] [o]ITSEA: Infant-Toddler Social and Emotional Assessment [50].

Figure caption:

Figure 1

Recruitment, participation and attrition in the Little in Norway study

All participants received an enrollment package at entry into the study; subsequently they took part in the data collection wave corresponding to their gestational week at entry. Due to late recruitment, some participants missed early data collection waves and the full *Little in Norway* sample was reached at T4. The *N*s represent the number of participants taking part at each time point; missingness comprises late recruitment, intermittent missingness (missing at current time point, but participating at later time points) and study drop-out. The grey boxes on the right indicate the number of participants that dropped out on a permanent basis.

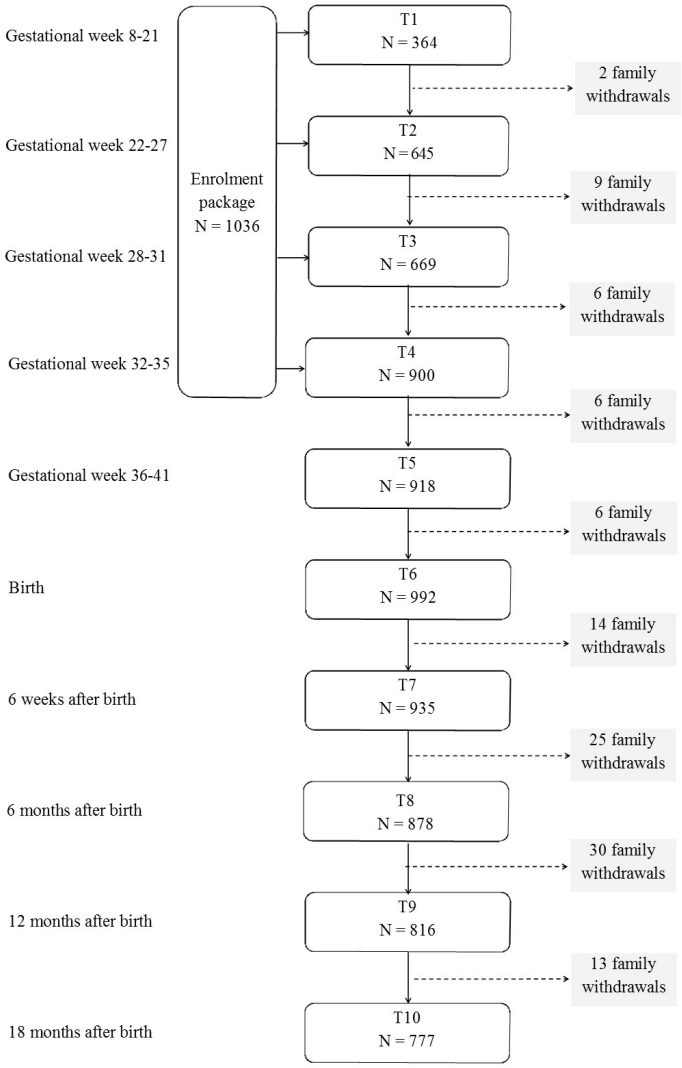

Figure 1
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Cohort Profile: Little in Norway: a prospective longitudinal community-based cohort from pregnancy to child age 18 months

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Title: Cohort Profile: Little in Norway: a prospective longitudinal community-based cohort from pregnancy to child age 18 months

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Abstract

Purpose:

The Little in Norway (LiN) project is a cross-disciplinary prospective longitudinal study starting in pregnancy. It was set up to investigate maternal and paternal mental health functioning in the transition to parenthood, detect pathways to healthy and aberrant child development, and generate new knowledge about mechanisms underlying differential child mental health susceptibility.

Participants:

The LiN cohort is a community-based sample comprising 1036 families (1036 mothers, 884 partners, 1017 children). All pregnant women and their partners receiving routine prenatal care at well-baby clinics at nine geographically selected sites across Norway were invited to participate. Enrolment took place from September 2011 to October 2012. This cohort profile comprises ten data collection waves spanning from enrolment in pregnancy until child age 18 months.

Findings to date:

Four types of information have been collected: multi-informant questionnaire-reports, direct observation of interaction, test data and biological samples. The most significant findings so far relate to three domains of results. First, when examining risk factors for parental mental health problems, results showed that the parents' own adverse childhood experiences and attachment style were related to anxiety, depression, and stress in the perinatal period. The experience of difficult child temperament was also found to contribute to parenting stress in the first year after birth. Second, we studied how parental mental health risk factors were related to later child development and social emotional functioning, for example linking maternal symptoms to social-emotional outcomes and paternal symptoms to language outcomes. Third, we investigated the relation between maternal nutrition during pregnancy

and aspects of early child development. Results showed that mild to moderate maternal iodine deficiency in pregnancy was associated with poorer language skills up to 18 months, but not with reduced cognitive or fine- and gross motor skills

Future plans:

A data collection point at 36 months is completed and currently being analysed. A new data collection wave is planned when the children are 8 years old.

Keywords:

Community-based, Cross-disciplinary, Prospective longitudinal, Parental mental health, Nutrition, Child development

Strengths and limitations of this study

- Cross-disciplinary prospective longitudinal community-based study of children and their parents from early pregnancy on.
- A multi-method and multi-informant design including biological sampling, direct observation of behaviour, assessment of the children's development and self-reported information from mothers and fathers.
- Many repeated in-depth assessments from early in pregnancy and onward makes it possible to identify differential developmental pathways and underlying mechanisms.
- This cohort alone may be underpowered when examining risk factors of outcomes with low prevalence, hence collaboration is encouraged.
- The participating parents tended to have a higher educational level than the general population at the different sites. A related concern is selective attrition, as dropout was shown to be related to depressive symptoms. However, appropriate statistical methods have been used to minimize the effect of selective attrition in papers based on this study population.

Introduction

Differential pathways to healthy and atypical development emerge early in life [1]. Human infants are malleable and take their course of growth in many directions, in part predisposed by biological factors and subsequently influenced by postnatal environmental characteristics in a continuous dynamic transactional interplay [2-4]. Such pathways have been identified in early childhood [2 5 6]. However, the knowledge of the pre- and perinatal precursors of child development and social-emotional functioning is still scarce. The Little in Norway (LiN) study is an on-going cross-disciplinary longitudinal and prospective multisite community-based study of children and their parents from early pregnancy on. It was set up to investigate maternal and paternal mental health functioning in the transition to parenthood, examine pre- and postnatal precursors of long-term child development and mental health, as well as disentangling mechanisms of transmission of developmental risk and protective factors. The study aims at integrating the research areas of mental health, developmental psychology, nutrition and molecular genetics. This Cohort Profile focuses on ten data collection waves spanning from enrolment in pregnancy until 18 months after birth.

A better understanding of early risk and protective factors, leading into pathways of later competence or adversity is needed, as there is a high potential for early interventions to adjust atypical pathways [7-9]. For example, parents' adverse childhood experiences [10 11] have been shown to influence later parental mental health, and are associated with insecure attachment, pre- and postnatal depression, parenting stress and atypical parenting behaviour toward their own children [10 12-17]. However, only few studies have examined the longitudinal implications of such risk factors on parenting and parent–child interaction in cohorts followed from the prenatal period [18]. One needs to elucidate the mechanisms of how parental adverse childhood experiences and mental health status, such as perinatal depression and anxiety, translate into aberrant child development, as such mechanisms are only partially understood [19 20]. In

addition, there is a need for including fathers in such studies [21 22]. Particularly, there is a lack of studies examining differential and joint effects of mothers and fathers' impact on mental health functioning in infancy and early childhood [23].

Antenatal biological factors may also be decisive for later development. Some nutrients protect maternal health while others affect birth outcome and infant health. For example, an inadequate nutrient supply may cause biological competition between mother and foetus [24 25]. Evidence also suggests that long chain polyunsaturated fatty acids, such as docosahexaenoic acid (DHA, 22:6, n3), play a role in the aetiology of postpartum depression [26-29]. DHA and arachidonic acid (AA, 20:4, n-6) are important structural components in the brain and the central nervous system and subsequently necessary for normal growth and development of the brain. Further, suboptimal iodine nutrition during pregnancy is associated with poorer child language development and lower child IQ [30 31 32]. This study comprises a food frequency questionnaire applied at several time points as well as biological samples to obtain information related to child and parental nutrition and its possible relation to child development and mental health functioning.

Cohort description

Who is in the cohort?

All pregnant women, receiving routine prenatal care at nine public well-baby clinics across Norway, were invited by midwives to participate. The clinics were chosen taking demographics and size of the population into account, to ensure a wide distribution of background conditions. Participants were recruited at their first prenatal care examination at the well-baby clinic. At each site, one public health care nurse was trained as a research assistant. In Norway, all pregnant women have the right to prenatal care and at least eight free consultations during pregnancy. If necessary, extra consultations are offered. Nearly all

pregnant women (93 %) in Norway choose to use the first line public health care system during pregnancy (general practitioners and well-baby clinics) [33]. Although there are nationwide schedules for prenatal care, many choose to receive initial check-ups by their general practitioner while switching to midwives at the well-baby clinics when the due date approaches. Therefore, despite all women being invited at their first prenatal visit to the well-baby clinic, the time frame for enrolment ranged from gestational week 8 to 34.

Initially, 1041 women consented; five later withdrew, leaving 1036 (99.5%) participating pregnant women. Their partners were also invited and 884 (878 men and six women) participated. No exclusion criteria were applied, but since the questionnaires were either in Norwegian or in English, this might have excluded pregnant women and their partners who spoke neither Norwegian nor English. The participation rate is estimated to be 50.7%. At five of the clinics, the staff did not establish reliable routines to monitor rates of participation; this rate is based on records from the remaining four clinics. However, participation rates were probably relatively similar at all sites since all clinics shared recruitment strategies.

Table 1 shows demographic characteristics of the sample. Pearson chi-square tests were performed at each of the nine sites separately, comparing the participants' educational level with the mean educational level of the population at the nine sites in the same age (figures obtained from Statistics Norway). In general, participant showed higher educational level than the reference populations ($p < .001$).

Insert Table 1 here

Participants received written and oral information before giving their consent to their own and their children's participation. Confidentiality was assured, and it was emphasized that they could withdraw at any time. The Regional Committees for Medical and Health Research Ethics in Norway approved the study [2011/560]. The enrolment took place from September

2011 to October 2012. At time of birth, three families were lost due to stillbirth, while 26 families were lost for other reasons before childbirth (e.g., family moving out of the area, participation felt to be too time consuming). The remaining 1007 mothers delivered 1017 children (including ten twin pairs).

How often have the participants been followed up?

The participants have been followed-up from early in pregnancy to infant age 18 months. The study has an intensive prospective, longitudinal design including data collection at ten time points. After enrolment, the prenatal data collection waves were at gestational weeks 8-21 (T1), weeks 22-27 (T2), weeks 28-31 (T3), weeks 32-35 (T4), and weeks 36-41 (T5). T6 comprises birth records. Postnatal data were collected at 6 weeks postpartum (T7), and again at 6 months (T8), 12 months (T9), and 18 months (T10) after birth, all within ± 2 weeks.

All participants completed the enrolment package (n = 1036 and 884, pregnant women and their partners, respectively). Data collection at T1 to T10 had limited time windows relative to gestational/child age for valid participation. This means that a sizeable proportion of participants was not enrolled in time to take part in the early data collection points during pregnancy. At T10, 925 families (88.9 %) of the original sample were still participants and remained in the study for future follow-up. Hence, there are three categories of missing data: late recruitment, study withdrawal or families lost to follow-up (n = 116), and intermittently missing data, which comprise participants that skipped one or more data collection waves, but then contributed at later time points. Figure 1 depicts the flow of recruitment, participation and attrition at each data point.

Insert Figure 1 here

Bivariate logistic regression analyses were conducted to investigate selective attrition at T10 (18 month after childbirth). High level of maternal education slightly increased the probability

of participation at T10 (OR = 1.07, 95% CI [1.01, 1.15], p = .030), measured in years of education. Neither partners' education (OR = 1.04, 95% CI [0.97, 1.11], p = .255), maternal age (OR = 1.00, 95% CI [0.97, 1.03], p = .886), partners' age (OR = 1.00, 95% CI [0.98, 1.03], p = .756), number of previous children for mothers (OR = 0.87, 95% CI [0.73, 1.04], p = .123), nor the number of partners' previous children (OR = 0.98, 95% CI [0.80, 1.21], p = .879) were related to attrition. Attrition was further predicted by lower levels of mean prenatal (OR = 0.91, 95% CI [0.88, 0.95], p <.001) and postnatal (OR = 0.95, 95% CI [0.90, 1.00], p = .041) depressive symptoms for mothers, as well as lower levels of mean prenatal (OR = 0.92, 95% CI [0.87, 0.97], p = .004) and postnatal (OR = 0.93, 95% CI [0.86, 0.99], p = .030) depressive symptoms for partners. Depressive symptoms were measured by the composite scores of Edinburgh Postnatal Depression Scale (EPDS) [34].

What has been measured?

Data collected in the LiN-Study include multi-informant questionnaire data, observational and behavioural data, and biological samples. Data were collected at the local well-baby clinic and by means of web-based surveys filled out at home, at well-baby clinics or completed by the research assistants based on parent interviews. Types of measurements at each wave are shown in Table 2, while the specific measurement methods are shown in Table 3.

Insert Tables 2 and 3 here

Enrolment package in pregnancy

Mothers and fathers received a comprehensive questionnaire package concerning parental demographic information, somatic and mental health and dietary habits, as well as medication, smoking and alcohol habits, at the first meeting in pregnancy (enrolment package). To screen for possible alcohol problems the Tolerance, Worried, Eye-opener, Amnesia, Cut-down (TWEAK) screening questionnaire [35] was administered. In addition,

possible adverse childhood experiences were assessed by means of the Adverse Childhood Experiences (ACE) Scale [10]. The scale comprises ten questions about possible adverse experiences prior to age 18 years, such as physical or sexual assault, major separation or loss, or parental mental illness or drug abuse. The Life Stress Scale, a subscale of the Parenting Stress Index (PSI) [36], was used to measure life stress events. The PSI is a self-report questionnaire that contains a Life stress Scale, a Child Domain, reflecting how parents perceive their child, and a Parent Domain, consisting of items related to parental coping and the parenting role. The PSI was standardized for use with parents of children ranging from 1 month to 12 years of age. The Life stress Scale consists of 19 items measuring life stress events experienced in the previous 12 months.

We also measured partner-related attachment style by using the Experiences in Close Relationships (ECR) Scale [37] since the quality of the parents' representations of attachment relationships is an important factor to consider for parental adaptation and parenting behaviour [38 39]. The ECR Scale is a self-report measure designed to assess the dimensions of adult attachment styles in relationships. The instrument comprises two dimensions, avoidance and anxiety, consisting of 18 items each.

Repeated assessments during pregnancy (T1-T5)

Anxiety related to pregnancy and birth and depressive symptoms in the perinatal period were measured at all assessments in pregnancy in both parents (T1-T5). PRAQ-R is a short form of the Pregnancy Related Anxiety Questionnaire (PRAQ) [40], a 10-item scale designed to assess ongoing anxiety related to pregnancy and birth. The Edinburgh Postnatal Depression Scale (EPDS) [34] is a self-report measure to identify women at risk for postnatal depression in the previous seven days. Although EPDS was originally developed to screen for postnatal depressive symptoms in women, it has later been validated for prenatal use [41]. It has also been

validated on male populations [42]. We also included questions about both parents' thoughts and feelings toward their unborn baby at all data points during pregnancy in order to capture mental representations of the coming child. To assess nutritional status and cortisol levels, hair and urine samples were collected from the mothers twice during pregnancy (T1 and T3). The urine samples have been analysed for iodine concentration. Blood samples were collected during pregnancy (T1) and have been analysed for fatty acid composition and vitamin D status (25(OH)D3). Dietary intake was measured using a web-based food frequency questionnaire (FFQ) twice during pregnancy (T1 and T4) [43 44].

Three questions about seafood intake were included at T2, T3 and T5.

Postnatal assessments (T6-T10)

At birth (T6), we collected information from hospital birth records. At six weeks after birth (T7) the research assistants met with the parents and their baby to observe the infant [45] and obtain information about the child's diurnal rhythm. The parents received questionnaires, and biological samples from mother and child were collected.

Depressive symptoms [34 41] in both parents were again assessed (T7 to T10 by means of the EPDS. Stress in the parenting role and in the parent–child relationship was also measured repeatedly postpartum by using the Parenting Stress Index (PSI) [36]. Testing and observation of the children's development and videotaping of child–parent interaction were conducted at the local well-baby clinics at six, 12 and 18 months (T8-T10). Developmental skills were assessed by using the screening (6 and 12 months) and the full version (18 months) of the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III) [46]. The Bayley Scales is an individually administered test designed to assess developmental functioning of infants and toddlers from 1 to 42 months. The screener is composed of selected items from the full Bayley version to briefly assess current functioning in the domains of cognition, receptive

and expressive language, as well as gross- and fine motor development. We also observed the infants' possible social withdrawal reactions using the Alarm Distress Baby Scale [47]. The scale is a method aimed at evaluating social behaviours that can be observed during a brief observation of children from two to 24 months old. It was scored based on child behaviour when doing the Bayley.

The parents were also asked to evaluate their infants' temperament characteristics by means of the Cameron-Rice perceived temperament scale (CRITQ) [48 49]. The CRITQ comprises 46 items probing eight dimensions: sensitivity, movement, reactivity/intensity, persistence, adaptability, approach–withdrawal, regularity, and soothability.

To assess the quality of parent–child interaction (data not yet analysed), the children and their parents participated in videotaped play sessions at 6, 12 and 18 months (T8-T10). At 18 months (T10) the Infant-Toddler Social Emotional Assessment scale (ITSEA) [50] was completed by all parents, and by the preschool teacher if the child attended a day-care centre. The ITSEA is a parent report questionnaire assessing the child's social-emotional functioning in children from 12 to 36 months and comprises 166 items measuring four domains: externalising behaviour, internalising behaviour, dysregulation and competence.

In one sub-sample (N = 102, 10.03 %), children with high (N = 52) versus low risk scores (N = 50) on markers of developmental status and parenting stress obtained at 6 months were selected. Child social emotional functioning was assessed by a standardized telephone interview with the main caregiver at 12 months (T9) [51]. The aim was to assess the applicability of the ITSEA at its lowest age level (12 months), and whether infants at risk at 6 months had increased scores later (12 months).

In another sub-sample, the aim was to investigate if changes in toddlers' morning to mid-afternoon levels of cortisol were different on days spent in childcare compared with days spent at home [52]. The children's stress levels were assessed 5-6 months after they entered

childcare by measuring levels of cortisol in saliva at home and in childcare. Childcare quality was observed on a day when researchers visited the childcare centres in the same period as saliva was collected. From the whole sample, 459 eligible parents who had toddlers entering childcare in the autumn of 2013 and 2014 were invited to participate (192 parents consented, 122 childcare centres cooperated). Ten children missed saliva samples, thus the final sample comprised 112 children (58.30 % of the consenting parents, 11.01 % of the total child sample).

Dietary intake was assessed repeatedly postpartum, both for mothers and infants [39 40]. Hair samples and non-fasting urine samples from the mothers were collected at 6 weeks, 6, 12 and 18 months postpartum (T7-T10), and non-fasting venous blood samples were collected at 6 and 12 months postpartum (T8-T9). The blood samples have been analysed for fatty acid composition, thyroid hormone function and vitamin D status (25(OH)D3). Non-fasting blood samples were collected from the child at 6 and 12 months postpartum (T8-T9). Hair from the child was collected at 6 weeks, 6, 12 and 18 months postpartum (T7-T10), and spot urine samples were collected at 18 months (T10). The urine samples have been analysed for iodine concentration, and a sub-sample of hair (T7) has been analysed for total mercury concentration. The blood samples have been analysed for fatty acid composition and 25-hydroxy vitamin D (vitamin D status). Saliva samples, to be used for assaying DNA-methylation, were collected at 6 weeks (T7) and 12 months (T9). It should be noted that at age three years information about the children's social emotional functioning at home and (when applicable) in day care, as well as an update on the families' living conditions were collected.

The next data collection wave is planned when the children are 8 years old. The main aim of the 8-year longitudinal follow-up study will be to investigate a broad range of child outcomes, including mental health and social-emotional and cognitive functioning, during the key transitional phase of entering school, predicted by perinatal, psychological, epigenetic and

nutritional patterns and processes. We have so far used a genome-wide epigenetic approach, which allows a non-biased screen for DNA methylation alterations that may be associated with prenatal maternal stress [53]. We will pursue this line of investigation in future studies. We plan to look at patterns of parental mental health and non-optimal nutrition, and possible relations to differential child methylation patterns. Subsequent collection waves are planned at age 13 and later on.

Patient and public involvement statement

The LiN cohort is population based and does not involve patients. However, all the four Regional Centres for Child and Adolescent Health in Norway were involved in the planning and development of the design of the study, and the data collection involved collaboration with midwives and nurses from nine public well-baby clinics across the four different Norwegian health regions.

Findings to date

The most important findings generated by the cohort so far can be summarised in three main domains. The first domain concerns parental mental health functioning in the perinatal period and factors related to parental anxiety, depression and stress in mothers and fathers [18 22 54 55]. The second domain is directed toward child functioning and early detection of infants and toddlers at risk [23 51 52 56], while the third domain concerns maternal nutrition during pregnancy and its possible relation to early child development [32 57 58].

Parental mental health in the transition to parenthood

First, we included an examination of the course of depressive symptoms in the ante- and postnatal period among subgroups of women[54]. We found that maternal antenatal and postnatal depressive symptoms do not follow a uniform course; results rather support a model of several distinct trajectories of depressed mood associated with different adverse

psychosocial and relational factors. Four different symptom trajectories were identified; only in pregnancy, only postpartum, moderate and persistent up to 12 months postpartum. Both researchers and clinicians should be aware of possible multiple courses of depressive mood and the risk factors behind these different trajectories, in order to better target intervention efforts in the perinatal period. Moreover, we have examined the association between adverse childhood experiences and symptoms of antenatal depression and anxiety in prospective fathers [22]. Fathers who reported several such experiences had more depressive symptoms and anxiety before birth of the child than those with lower scores. We also found that paternal symptoms of anxiety and depression during pregnancy as well as their own adverse childhood experiences predicted stress and a negative perception of the infants' behaviour [55]. In a similar vein, we investigated the multiple determinants of mothers' parenting stress and found that partner attachment style assessed prenatally was a salient predictor of such stress 12 months after birth [18]. We further found a link between maternal adverse childhood experiences and later parenting stress, and showed that partner attachment style operated as a mediator in this link. Perceived difficult infant temperament also contributed to the experience of parenting stress in the mothers. Altogether, these results point to the clinical importance of paying attention to both parents' mental health during pregnancy. It is especially important to recognise the role of parental adverse childhood experiences in determining later parenting stress, and the need to help parents with a background of difficult relational experiences and an unsecure couple relationship before childbirth.

Child development, infant mental health and early detection of infants at risk

So far, four studies have been directed toward early child development and infant mental health. In one study, we found that parental perinatal depressive symptoms predicted child social-emotional difficulties and language delay at infant age 18 months [23]. A differential effect, linking maternal symptoms to compromised social-emotional outcomes in children and

paternal symptoms to poorer language outcomes was found. Perinatal depressive symptoms in both mothers and fathers may have a wide impact on child development, underscoring the importance of being aware of depression in fathers as well as in mothers in the perinatal period. It should be noted that a majority of Norwegian children between 1 and 2 years of age are cared for in professional childcare during the day (83.5 %) [59]. Possible stress reactions among the youngest children in connection with childcare has been of concern. We therefore studied the change of morning to mid-afternoon levels of the stress hormone cortisol at home and in childcare among toddlers. An increase in cortisol levels during the day in childcare compared to home was found. Of special interest is the finding that longer hours (8–9 per day) were associated with a greater increase in cortisol levels among the children compared with shorter hours (5–7), suggesting that separation from parents and interaction with several caregivers and children during the day may be especially demanding for toddlers who spend the longest days in childcare. [52].

In order to detect early deviance and to provide help to infants at risk for social-emotional difficulties as early as possible, it is important that assessment instruments are developmentally sensitive. To this aim, we investigated if the ITSEA scale could be reliably used as a screening instrument for children as young as 12 months [51]. Results showed that clinically important social emotional problems and competence delays could be reliably detected even at ITSEA's lowest age limit. We also examined the applicability of a temperament questionnaire constructed for intervention [56]. The temperamental dimensions of adaptability, persistence, and regularity had coherent factor structures. The inclusion of concepts related to individual differences in infant response tendencies and regulatory efforts when assessing infant behavior may broaden the understanding of parent-infant transactions, and can provide a valuable toolkit for individualized parent guidance at an early age

Maternal nutrition during pregnancy and later child development

So far, three studies of maternal and child nutrition and later child development have been published [32 57 58]. First, we asked whether the pregnant women had sufficient iodine intake according to WHO criteria [57]. In many cases, the women's diet did not secure a sufficient iodine intake. Second, mild to moderate maternal iodine deficiency in pregnancy was found to be associated with lower child language skills up to 18 months [32]. Third, the iodine status and dietary iodine sources were studied cross-sectionally among the toddlers [57]. Results showed that the iodine status among the children from different geographic areas in Norway was sufficient, indicated by a median UIC above the WHO cut off of 100 µg/L. To our knowledge, this is the largest and most complete study to date of maternal iodine status during pregnancy and its association with repeated measures of clinically assessed infant and toddler neurodevelopment. Preventing mild to moderate iodine deficiency in pregnant women by securing adequate iodine status before conception is an optimal strategy to counteract the detrimental effects of inadequate iodine intake.

Strengths and limitations

This study has a cross-disciplinary nature with a frequent and in-depth assessment of mothers, fathers, and their children from early in pregnancy. The use of a multi-method and multi-informant design including biological sampling, direct observation of behaviour, assessment of the children's development and self-reported information from mothers and fathers is a main strength. Moreover, well-validated measures have been used to assess both child development, child socio-emotional functioning, and parental symptoms of depression, anxiety, adult attachment style and parenting stress.

The use of many repeated assessments may increase the odds for identifying developmental pathways and contributing parental and child risk- and promoting factors. However, the LiN-cohort alone may be underpowered when examining risk factors of outcomes with low

prevalence. National as well as international collaboration is therefore encouraged with the aim of increasing sample size in connection with targeted research questions.

Further, the parents who took part tended to have a higher educational level than was common in the general population at the different sites. The impact of educational level might be different if it had been more in line with that of the local populations. A related concern is selective attrition, as dropout was shown to be related to depressive symptoms [23 54]. However, appropriate statistical methods have been used to minimize the effect of selective attrition in papers based on this study population [18 22 23 54 55]. In publications where multiple assessments over time have been included, based on both mother, father, and in some instances child data, we have used a structural equation (SEM) framework (see for example [18 22 23 54]). In these papers using longitudinal data from the study, full information maximum likelihood (FIML) has been used to reduce bias relating to missing data, including late recruitment, intermittent missingness and study dropout. FIML is regarded as a state-of-the-art missing data technique, providing unbiased parameter estimates under the missing at random (MAR) assumptions while at the same time providing high statistical power of the analyses [60]. In another paper, we used mixed effects models that gives valid results under the MAR assumption for the repeated measurements (see [55]). Several assessments were based on self-report. This applies to our measures of adverse childhood experiences, depressive and anxious symptoms, as well as attachment style. Hence, associations might be inflated due to shared methods variance.

Collaboration

The study is located at the Department of Psychology at the University of Oslo. Collaboration is encouraged. Further information and requests for collaboration can be obtained by contacting the principal investigator Vibeke Moe: vibeke.moe@psykologi.uio.no. The Institute of Marine Research (IMR), Bergen, and Uni Research Centre for Child and Youth

Mental Health and Child Welfare, Bergen, and the Regional Centre for Child and Adolescent Mental Health, Eastern and Southern Norway are all collaborating institutions.

Data availability statement

Data available upon reasonable request. Further information and requests for collaboration can be obtained by contacting the principal investigator Vibeke Moe: vibeke.moe@psykologi.uio.no.

Funding declaration

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Competing interests

None declared.

Ethics approval

All procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. The study protocol and the assessment procedures were reviewed and approved by the Norwegian Regional Committees for Medical and Health Research Ethics, reference number 2011/560.

Contributorship statement

VM and LS planned and developed the Little in Norway study design. MK, LD, MWM and KMS planned the nutrition part of the study. VM, EF, MK, LD, MWM, KMS, TvS, KO, UTV and LS all contributed in planning of the design of the present paper. EF and VM

performed analysis of data. VM took the main responsibility for drafting the article, while EF, MK, LD, MWM, KMS, TvS, KO, UTV and LS contributed substantially in revising it critically for important intellectual content. All authors approved the final draft for publication.

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Table 1

Demographic characteristics of participants in the LiN-study

	Mothers *n* = 1036 Mean (SD) / Proportion	Partners *n* = 884 (878 men) Mean (SD) / Proportion	Children *n* = 1017 Mean (SD) / Proportion
Parents			
Age	30.26 (4.78)	32.76 (5.90)	
Education in years	16.05 (2.13)	15.59 (2.37)	
College or University degree	77.1%	67.1%	
High school	19.8%	28.2%	
Elementary school	3.1%	4.8%	
Ethnic minority	6.1%	4.6%	
First-time parent	54.9%	56.2%	
One previous child	33.3%	32.7%	
Two or more previous children	11.8%	11.0%	
Work status:			
Full-time job	77.3%	91.0%	
Part-time job	7.4%	1.7%	
Student	11.6%	6.2%	
Disability/Unemployed/At home	3.8%	1.0%	
Relationship status:			
Married	36.2%	35.2%	
Living together	59.7%	62.4%	
Single	2.5%	0.9%	

Divorced	0.2%	0.2%	
Other	1.4%	1.2%	
Previous psychiatric problems	21.7%	11.2%	
Life stress at enrollment	7.08 (6.91)	7.38 (7.00)	
Children			
Gestational age (in weeks)			39.99 (1.81)
Sex (percentage of boys)			52.3%
Premature births (n = X)			6.3%

Note. SD = Standard Deviation.

Table 2

Overview of data collection types (questionnaires, biological samples, observation and developmental testing) and time points of repeated assessments

Types of data	Enrol-ment	T1 gwk 8-21	T2 gwk 22-27	T3 gwk 28-31	T4 gwk 32-35	T5 gwk 36-41	T6 Birth	T7 6 w	T8 6 mo	T9 12 mo	T10 18 mo
Both parents:											
Questionnaires on											
Self	X	X	X	X	X	X		X	X	X	X
Infant characteristics								X	X	X	X
Mothers:											
Hair	X			X				X	X	X	X
Urine	X			X				X	X	X	X
Blood									X	X	
Infants:											
Hospital birth records							X				

48h diurnal clock registration	X			
Observation of infant social withdrawal		X	X	X
Cognitive, language and motor testing		X	X	X
Hair		X	X	X
Urine				X
Blood		X	X	
Saliva	X		X	
Mother-infant interaction:				
Video observation		X	X	X
Father-infant interaction:				
Video observation		X	X	X
Child care center:				
Questionnaire				X

Note. gwk: gestational weeks, mo: months

Table 3

Phases of data collection and specific measurements in the LiN study

Phase	**Measurements**
Assessments during pregnancy	Enrolment package, T1 (Gwk 8-21) T2 (Gwk 22-27), T3 (Gwk 28-31), T4 (Gwk 32-35), T5 (Gwk 36-41)
Enrolment package in pregnancy, first visit to well-baby clinic (range Gwk 8-34) At well baby clinic° Web from home*	Mothers and fathers: demographic information°, somatic and mental health, medication/smoking/alcohol habits° (TWEAK[b]), thoughts about unborn child°, life stress° (PSI-ls[d]), relational experiences° (ECR[e]), adverse childhood experiences° (ACE[f]) Mothers only: food frequency questionnaire* (FFQ[g]), hair and urine samples°
T1 (Gwk 8- 21)	Both parents: pregnancy anxiety concerns° (PRAQ-R[a]), depressive symptoms° (EPDS[c]), medication/smoking/alcohol habits° (TWEAK), thoughts about unborn child° Mothers only: brief food frequency questionnaire (FFQ)
T2 (Gwk 22-27) Web from home	Both parents: pregnancy anxiety concerns (PRAQ-R), medication/smoking/alcohol habits (TWEAK), depressive symptoms (EPDS), thoughts about unborn child Mothers only: brief food frequency questionnaire (FFQ)
T3 (Gwk 28-31) At well baby clinic	Both parents: pregnancy anxiety concerns (PRAQ-R), medication/smoking/alcohol habits (TWEAK), depressive symptoms°(EPDS), thoughts about unborn child

	Mothers only: brief food frequency questionnaire (FFQ), blood, urine and hair samples
T4 (Gwk 32-35) Web from home	Both parents: pregnancy anxiety concerns (PRAQ-R), medication/smoking/alcohol habits (TWEAK), depressive symptoms (EPDS), thoughts about unborn child Mothers only: food frequency questionnaire (FFQ)
T5 (Gwk 36-41) Web from home	Both parents: pregnancy anxiety concerns (PRAQ-R), medication/smoking/alcohol habits (TWEAK), depressive symptoms (EPDS), thoughts about unborn child Mothers only: brief food frequency questionnaire (FFQ)
T6 birth	Birthweight; gestational age; birth complications
Follow-up At well baby clinic° Web from home*	T7 6 weeks, T8 6 months, T9 12 months, T10 18 months
T7 Child age 6 weeks At well baby clinic° Web from home*	Infant–mother assesment procedure° (MABI[h]) Infants: diurnal rhythm*; DNA extracted from saliva°, infant hair samples° Mothers: food frequency questionnaire (FFQ*), child nutrition and breast feeding*, maternal hair and urine samples° Both parents: depressive symptoms (EPDS°)
T8 Child age 6 months At well baby clinic° Web from home*	Infants: infant development° (Bayley III screen[i]); infant social withdrawal behaviour° (ADBB[j]); hair and blood samples° Mothers: Hair, urine and blood samples°, food frequency questionnaire (FFQ*), child nutrition and breast feeding*

	Both parents: Parenting Stress Index° (PSI[k]), infant–parent interaction°, depressive symptoms° (EPDS), perceived infant temperament* (Cameron-Rice[m])
T9 Child age 12 months At well baby clinic° Web from home*	Infants: infant development° (Bayley III screen), infant social withdrawal behaviour° (ADBB), genetic information extracted from saliva, infant hair and blood samples° Mothers: food frequency questionnaire (FFQ)*, child nutrition and breast feeding*, maternal hair, urine and blood samples° Both parents: Parenting Stress Index° (PSI), infant–parent interaction°, depressive symptoms (EPDS°), perceived infant temperament*(Cameron-Rice)
T10 Child age 18 months. At well baby clinic° Web from home* Web from child care centres**	Infants: infant development° (Bayley III full scale[n]), infant social withdrawal behaviour° (ADBB), infant hair and urine samples° Mothers: maternal hair and urine samples° Both parents: Parenting Stress Index° (PSI), infant–parent interaction°, depressive symptoms (EPDS°), child social emotional assessment* (ITSEA[o]) Childcare centre: child social emotional assessment** (ITSEA)

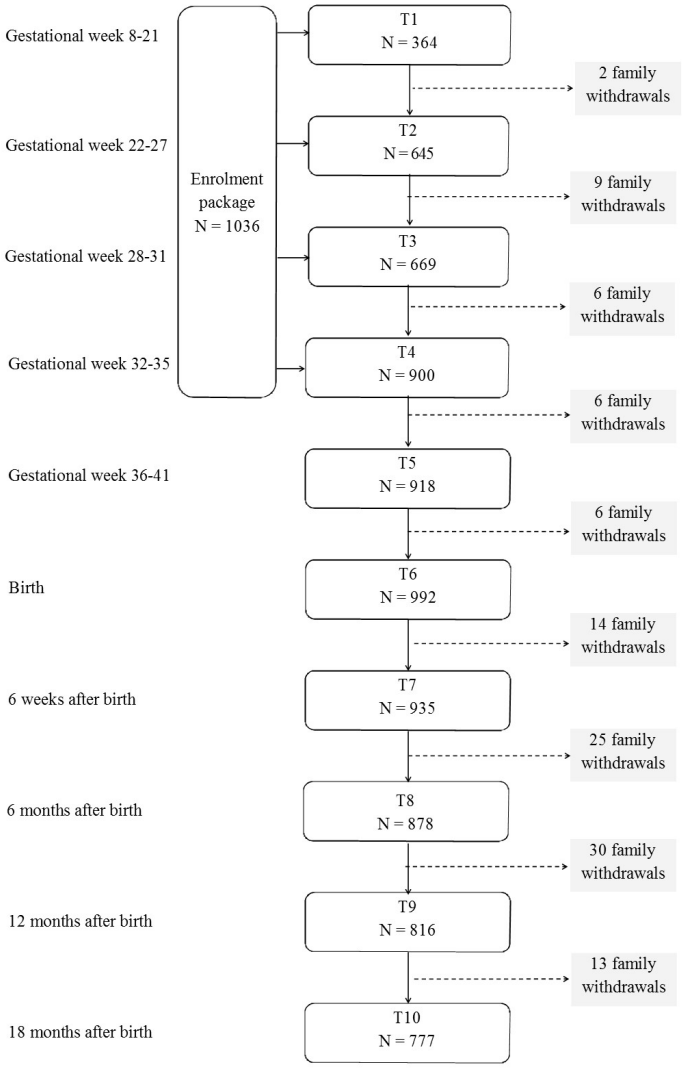
Note. Gwk: Gestational weeks, [a]PRAQ-R: Pregnancy Related Anxiety Questionnaire revised [40] [b]TWEAK: Tolerance, Worried, Eye-opener, Amnesia, Cut-down [35], [c]EPDS: Edinburgh Postnatal Depression Scale [34], [d]PSI-ls: Parenting Stress Index-life stress [36], [e]ECR: Experiences in Close Relationships scale [37], [f]ACE: Adverse Childhood Experiences scale [10], [g]FFQ: semi–quantitative food frequency questionnaire,[43 44] [h]MABI: Mothers's Assessment of the Behavior of the Infant [45], [i]Bayley Scales of Infant and Toddler Development, screening test [46], [j]ADBB: Alarm Distress Baby Scale [47], [k]PSI: Parenting Stress Index [36], [m]Cameron-Rice perceived temperament scale [48], [n]Bayley Scales of Infant and Toddler Development, full scale [46] [o]ITSEA: Infant-Toddler Social and Emotional Assessment [50].

Figure caption:

Figure 1

Recruitment, participation and attrition in the Little in Norway study

All participants received an enrollment package at entry into the study; subsequently they took part in the data collection wave corresponding to their gestational week at entry. Due to late recruitment, some participants missed early data collection waves and the full *Little in Norway* sample was reached at T4. The *N*s represent the number of participants taking part at each time point; missingness comprises late recruitment, intermittent missingness (missing at current time point, but participating at later time points) and study drop-out. The grey boxes on the right indicate the number of participants that dropped out on a permanent basis.



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209x297mm (150 x 150 DPI)