**Cohort Profile: The FinnBrain Birth Cohort Study (FinnBrain)**

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**Why was the cohort set up?**

Early life stress (ELS) is a major public health issue, as the consequences often persist into adulthood and impose negative effects on wide range of outcomes.[1-4] The FinnBrain Birth Cohort Study (www.finnbrain.fi) was established to study prospectively the effects of ELS, also comprising prenatal stress (PS), on child brain development and health. This population-based pregnancy cohort with a primarily neurodevelopmental focus eventually aims at identifying biomarkers related to PS and ELS exposures as well as trajectories for common psychiatric and somatic illnesses (e.g. depression, anxiety, and cardiovascular illness). Corresponding multidisciplinary efforts employing, for example, multimodal brain imaging techniques soon after birth in combination with molecular genetic and infant neuropsychological functional studies have been scarce.[5,6] Moreover, the availability of Finnish registers makes the research environment exceptionally suitable for cohort studies.

PS, often defined as maternal prenatal psychological symptoms of depression or anxiety or perceived stress related to major life events or daily hassles,[7-9] can be considered as one of the first ELS phenomena directly affecting offspring development but also rendering the child more vulnerable for the effects of postnatal exposures.[10-13] However, existing data on the offspring effects of ELS and especially PS remains inconclusive,[8,10,12,14,15] which partially owes to the large variation in both PS/ELS and offspring phenotype measures and subsequent differences in biological pathways underlying the associations. Additionally, timing and duration of the stress exposure matter, so the attempts to disentangle these complex pathways in prospective studies are important.[9,12] Finally, genetic factors naturally influence development, but especially research on how offspring genotype modifies the associations between PS/ELS to developmental outcomes, and vice cersa, is called for.[6,16,17]

Maternal PS is related to child aberrant behavioural, emotional and cognitive development and alterations in important regulatory functions of child stress reactions, emotional states, and attention,[18-22] as well as elevated risk for somatic conditions, such as wheezing or asthma [23,24] and obesity.[25,26] Importantly, moderate levels of stress might be also beneficial for development[27] and vulnerability to stress varies between individuals and also by sex.[28,29] It should be noted that many children who are exposed to PS or ELS are not affected at all[10,30] and in some individuals stress may even help in building resilience.[31] Therefore, understanding developmental trajectories and clusters of factors contributing to this variability is crucial for the development of improved preventive and therapeutic approaches.[32]

Paternal symptoms of depression during pregnancy also reportedly influence obstetric[33] and child psychosocial developmental outcomes[14], which suggests that the mechanisms behind these associations are complex. Research on the role of paternal health on child development has emerged and currently a few studies have followed both parents across pregnancy as well as during the postnatal period and reported on the roles of both maternal and paternal psychological symptoms or stress on later child development.[33-37] However, knowledge on the impact of paternal factors, both genetic and environmental, is still scarce compared to data on mothers and is essential in increasing our understanding on the mechanisms linking prenatal environment with child development.

Alterations in maternal hypothalamus-pituitary-adrenal (HPA) axis functioning and cortisol secretion, and subsequent foetal exposure to higher cortisol concentrations have been among the most studied mechanisms via which PS could affect offspring neurodevelopment.[38] Many studies fail to show a link between altered maternal HPA axis functioning and either PS or offspring outcomes.[10,12,39]. Thus, investigation of other stress-mediating mechanisms, such as alterations in the immune system[40], modifications in the functioning of the placenta[41], and composition and

functioning of the gut microbiota[42] is warranted.[10,38,39] Multidisciplinary assessment of brain structural and functional features starting in infancy have the potential to increase our understanding on the mechanism underlying the pathways from early exposures to later neuropsychological development and health outcomes.[43,44] The inclusion of postnatal environment characteristics (e.g. parent-child interaction and parental care) as factors shaping the developmental trajectories is of utmost importance in studies on PS.[45,46]

**Who is in the cohort?**

This paper focuses on the parental cohort profile across pregnancy and first postnatal infant assessments (Figure 1). Recruitment for the FinnBrain Birth Cohort Study (www.finnbrain.fi) took place at the three maternal welfare clinics of a geographically defined area performing pregnancy ultrasound scans for the women eventually referred to give birth at Turku University Hospital in the Southwest Finland Hospital District and the Åland Islands in Finland. The actual cohort follows a Pilot Study collected in 2010 (N=203 families). The recruitment took place between December 2011 and April 2015 (third site added in November 2012) and relied on personal contact by research nurses who were placed at the recruitment sites. According to the study inclusion criteria, the nurses approached families with sufficient knowledge of Finnish or Swedish and only following a normal screening result. Due to parallel visits and some other occasional resource constraints 5790 out of 8895 newly pregnant women visiting the recruitment sites during the specified time period were contacted and informed about the study (Figure 1). The Cohort population comprises consecutive women attending the free-of-charge ultrasounds [coverage close to 100% in the population, (www.thl.fi)] at the gestational week (gwk) 12, their children-to-be-born and fathers of the children/partners of the mothers. Of those informed about the study, a total of N=3808 (66%) mothers and N=2623 fathers or other partners of the mother decided to participate. The participation rate was higher (70-82%) in years 2011-2014 but declined during the last four months of

recruitment (Jan- April 2015) (58%). The main reasons for lower participation rate in 2015 were related to families already having a child in the cohort and changes in the recruitment resources. The women recruited in 2015 were more often nulliparous (67% vs. 51%) and belonged more often to the highest educational level category (44% vs. 33%) but were similar in parental age, gestational weeks, and psychological symptom scores when compared with the rest of the cohort.

The parents gave written informed consent on their own and on their child´s behalf. The children will be asked for personal consent at an appropriate age. Twenty-nine twin pairs were included so the total number of recruited children was N=3837. Children born preterm, with malformations or other severe medical conditions were included but they may not be eligible for subpopulation assessments. The Ethics Committee of the Hospital District of Southwest Finland has approved the study protocol.

Comparisons between the study participants' and source population characteristics as well as attrition analyses are presented in Tables 1 and 2, respectively. The Cohort population resembles the source population with the possible exceptions of lower prevalence of younger, multiparous and smoking women in the Cohort and the prevalence of preterm births being lower in the Cohort than among all the deliveries at the Turku University Hospital (Table 1). Data on the sociodemographic variables were drawn from the cohort questionnaires and from the national registries. The attrition analyses were performed among the subjects with data from the first prenatal assessment (gwk 14) providing the relevant information (Table 2). The analyses show that women who responded also to the gwk 34 questionnaires, were older (Cohen's d=0.13), more often nulliparous (OR 1.30), had longer duration of gestation (Cohen's d=0.25), had higher educational (Somer's d=0.11) and income levels (Somer's d=0.04), smoked less frequently (Somer's d=0.06), and reported lower depressive symptom scores at gwk 14 than those who did not return the third trimester

questionnaires (Cohen's d=0.12) (Table 2). In men, similar trends were noted as in women (Table 2) as well as when comparing the participants who responded to the first postnatal questionnaires (3 months) with those not returning them.

In all, n=310 families, comprising n=315 children, discontinued the study during pregnancy. Of these subjects, 35 and 8 were cases of miscarriage or stillbirth, respectively. Additionally, n=57 families/children (including 3 neonatal deaths) discontinued between delivery and the 3-month assessment (Figure 1). Shorter duration of gestation [mean gwks 39.4 (SD 2.4) vs. mean gwks 39.8 (SD 1.7), Cohen's d=0.16] and lower maternal level of maternal education (42.6% vs. 37.6% in the lowest educational category, Somer's d= -0.05) were associated with discontinuation. While lack of time was the most frequently actively communicated reason for withdrawing from the study, the subjects did not need to specify the reason for discontinuation.

**How often have the participants been followed up?**

The timeline of data collection sweeps including all of the ongoing assessments are presented in Table 3. The next up-coming assessment point will be at the child age of 5 years, and the study is planned to continue for decades with 12-36-month follow-up intervals.

After recruitment, the participants filled in a set of self-report questionnaires three times during pregnancy (Figure 1 and Table 3) and at delivery. Parental biological samples were collected prenatally during a separate laboratory visit at gwk 24 (mothers and fathers) and at delivery (mothers) (Figure 1 and Table 3). Data on the course of pregnancy and delivery was acquired from the Finnish Medical Birth Register administered by the National Institute of Health and Welfare. Register linkages to the domains of the Cohort data will be performed.

After birth, all Cohort families are followed up regularly by using questionnaires (Table 3). The

Cohort is divided into several substudies (see below), the aim of which is to acquire multidimensional, integrative data on various child brain and behavioral developmental intermediate and long-term illness and health outcomes. Subjects are recruited to these substudies according to distinct criteria and the time points for assessments may vary from the overall Cohort time-line (Table 3 and Table 4). Detailed information on the underlying research questions and corresponding methods will be specified in the reports resulting from these studies.

**What has been measured?**

*The whole cohort*

The measurements applying to the whole cohort during pregnancy include questionnaires (Figure 1), national registry data, and blood samples for analysis of serum as well as extraction of DNA from the blood leukocytes (Table 3). Registries provide data on medical and social issues related also to the participants who are not actively responding to the follow-up questionnaires (e.g. www.thl.fi; www.kela.fi; www.tilastokeskus.fi).

The questionnaires comprise standardized and internationally validated measures. The main focus of the survey data is on measuring various dimensions of PS and ELS and resilience both on an individual and family level. Family life events, daily hassles, life and relationship satisfaction, physical health, and symptoms of depression and anxiety, sleep, and substance use are assessed systematically and repeatedly. The main interest lies in the trajectories of emotion regulation skills and, thus, alexithymic traits and coping strategies are also investigated. Features considered important for later parenting, such as parents' childhood experiences and relationships with own parents, attachment to the foetus, parental own attachment patterns, parental reflective functioning and parenting stress, are assessed. Child questionnaires focus on temperament and emotion

regulation, aspects of psychosocial and language development, physical health (e.g. infections, atopic diseases), and sleep.

The DNA samples from the parents can be used for analyses on gene-environment correlations that could, in their own right, have an effect on the child's development.[47] When accompanied by analyses on DNA samples from the offspring (for parent-child pairs and trios, see Table 2 footnotes), they will enable studies on co-segregation of hypothesis-based genetic risk and resilience factors with traits of interest as well as on genomic imprinting mechanisms, considered to play an important role in neural development and functions related to brain plasticity, emotions, and cognition.[48] Parental serum samples are mainly used in assessing the associations between PS and ELS and the functioning of the immune system. The samples are processed according to standard procedures and stored in – 75 C freezers.

*Focus Cohort*

The Focus Cohort is a nested case-control study within the main cohort and was established to compare subjects exposed to PS with their non-exposed controls. The Criteria for the Focus Cohort were determined by using the first 500 participant mothers' questionnaire data in exploratory analyses and establishing cut-points for the approximately highest and lowest 25$^{th}$ percentiles of maternal PS during pregnancy. The questionnaires for depressive symptoms (Edinburgh Postnatal Depressive Scale, EPDS),[49] overall anxiety (Symptom Checklist -90, SCL-90/anxiety scale),[50,51] and pregnancy-specific anxiety (Pregnancy-Related Anxiety Questionnaire-Revised, PRAQ-R/PRAQ-R2)[52,53] symptoms at gwks 14, 24, and 34 were used for defining maternal PS. The total sum score cut-off points for "cases" and "controls" were as follows ≥12 and ≤ 6 for the EPDS, ≥10 and ≤ 4 for the SCL-90 anxiety subscale, and ≥ 34 and ≤ 25 points for PRAQ-R, respectively. Criteria for becoming identified as a case were: 1) scoring at least once above the selected threshold

on two different questionnaires, or 2) scoring at least twice above the selected threshold on the same instrument during pregnancy. The controls needed to remain below the thresholds in all assessments. All mothers reporting the use of serotonin reuptake inhibitors (SSRIs) during the index pregnancy were also included as cases (n=92; 2.42%). After the collection of the pregnancy data of the whole cohort, the PS case target group ultimately comprised 20% and the control group 27 % of all women in the Cohort. The first 500 subjects resembled the rest of the cohort in the distribution of sociodemographic characteristics and the mean symptom scores of depression and anxiety.

After birth, the children within the Focus Cohort as well as other defined subpopulations of potential interest are subjects for several assessments across the postnatal period. The focus is especially on infancy and early childhood and the aim is to acquire multidisciplinary, repeated measurements from same individuals in order to trace developmental trajectories and identify factors affecting their course (Table 3 and Table 4). For example, studies of multimodal structural and functional infant brain imaging (Table 3), child developmental neuropsychological functioning, sleep, paediatric studies on asthma and infections, gut-brain axis studies, and hypothesis-based studies on genetic mechanisms of health and development are included (www.finnbrain.fi; Table 3), each study being described in the context of later reports emerging from these studies.

*Other Subpopulations*

Additional subpopulation studies among the parents usually comprising but not limited to Focus Cohort subjects are, for example, hair, placenta, and breast milk sample collections, and parental neuropsychological assessments (Table 3 and Table 4). Maternal hair samples are used for analysing hair cortisol concentration (HCC), reflecting the average level of maternal cortisol during the past two to three months.[54,55] The purpose is to investigate the relevance of HCC as a biomarker for various sources of maternal PS and to investigate links between PS and later child outcomes.

The laboratory analyses are performed according to a protocol adapted from Davenport et al.[56] Placenta samples were taken both from the fetal side and maternal side of the placenta after removing decidua, both close to the insertion of the umbilical cord and halfway the placental radius.[57] The samples were snap frozen in liquid nitrogen within one hour of the delivery and stored in a -70 C freezer until analysed. Breast milk has been collected and stored with the aim of analyzing the concentrations of selected nutrients and hormones and their associations with environmental and child developmental factors.[58] Finally, parental neuropsychological functioning is assessed using the CogState computerized test battery (www.cogstate.com).[59] Associations between PS, parental executive functioning[60] and both parenting and child neuropsychological characteristics are investigated.

**What has it found? Key findings and publications**

Lower parental level of education was linked with elevated levels of depressive, anxiety and pregnancy-related anxiety symptoms (Table 5). These associations were highly consistent across pregnancy in both women and men, while the association remained evident only in women but not in men during the early postpartum period (Table 5). The uneven distribution of PS by socioeconomic status should be taken into account whenever assessing the impact of PS on child health and development.

We have previously reported that maternal pregnancy-related anxiety is predictive of increased infant negative emotional reactivity at the age of six months after adjusting for maternal postnatal symptoms of depression and anxiety,[21] supporting the importance of prenatal factors in the context of child emotion regulation development and emphasising the role of pregnancy-related worries as a source of PS. Our earlier reports also put forward the importance of infant temperament as one factor contributing to early parent-infant relationships, as infant negative emotionality was linked

with lower quality of mother-infant bonding.[61] Moreover, maternal alexithymic traits predicted infant emotion regulation or temperament traits,[62] while paternal alexithymic traits were related to fathers' own risk for anxiety symptoms.[63] Our findings also indicate that maternal prenatal depressive and anxiety symptoms are correlated with a potentially "proallergenic" set of cytokines or interleukins (IL) (e.g. IL-5, IL-9, and IL-13) providing hypotheses for further studies bridging maternal prenatal and later child health.[64]

Additionally, a 14-item questionnaire on parental prenatal reflective functioning (RF) has been produced and validated.[65] Parents' capacity to think of the child's perspective can now be explored already during pregnancy, which is important from stress regulation and early screening and intervention point of views.[65] One of the established measures of pregnancy-related anxiety, the PRAQ-R[52], was further developed into PRAQ-R2[53] to better apply to all pregnant women regardless parity. Finally, in need for neuropsychological assessment method suitable for population-based cohort we investigated correlations between the computerized CogState test battery (www.cogstate.com) and Wechsler Adult Intelligence Scale (WAIS-IV). It was discovered that the correlations between the two were rather modest and that their use should be strongly guided by the research questions, as they seem to have somewhat distinct profiles.[59] Interestingly, decline in maternal prenatal working memory performance in CogState was related to increased PRAQ-R2 symptom levels.[60]

**What are the main strengths and weaknesses?**

We have been able to launch a multidisciplinary, neurodevelopmentally oriented pregnancy cohort focusing on the offspring effects of PS and postnatal ELS and both environmental and genetic factors modifying the possible associations. The attrition analyses suggest that some of the effects will be diluted due to the lower socioeconomic status and somewhat higher symptom levels accumulating in the attrition. One of the challenges is to sustain families' adherence to the study as

well as the generalizability of the results, although when investigating associations between variables within a specified study population, generalizability is not always a major concern. By using the Focus Cohort design we have aimed at building a set of substudies with planned integration of measurements. The use of registry data strengthens our design. The amount of data in the Finnish registries is large covering e.g. the use of prescription medicines and social and medical services. The Finnish population is relatively homogenous genetically, environmentally, and socio-economically, which is likely to increase the power of analyses aiming at disentangling the distinct and joint effects of genetic and environmental factors.[66] We will likely be able to detect some unique infant brain developmental and neuropsychological phenotypes (Table 3 and Table 4) and then provide important hypotheses for additional experimental or intervention studies carried out either within the FinnBrain Cohort or in other populations.

The ultimate aim of this study is to perform longitudinal research on child (brain) development and health and the effects of PS and ELS on these trajectories. Our baseline population provides a valuable basis for subsequent research and the value of the cohort will increase as the follow-up progresses. The parental cohort can be treated as an independent cohort.

We have established collaboration networks that facilitate the integration of disciplines. To collect a database with repeated assessments on the same individuals and to keep as many of the families involved as possible are recognized as challenges. Our cohort alone is likely to be underpowered for identification of novel common genetic variants for developmental neurobehavioral disorders by genome-wide association studies (GWAS). However, by focusing on continuous measures rather than diagnostic categories, as well as on significant and well-characterized phenotypes and biomarkers, we will strengthen our odds to identify developmental trajectories and contributing parental and offspring genetic factors or polygenetic clusters in the context of PS research.

Collaboration also aims at increasing sample sizes in targeted research questions via combining data sources.

**Can I get hold of the data? Where can I find out more?**

Further information about FinnBrain can be obtained via www.finnbrain.fi or by e-mailing the PI prof. Hasse Karlsson (hasse.karlsson@utu.fi) and the co-PI MD, PhD Linnea Karlsson (linnea.karlsson@utu.fi). Requests for collaboration, including access to the data or the biosamples, are considered by the Steering Committee of the FinnBrain Birth Cohort Study. International and domestic collaboration is encouraged and inherent in the project and the ultimate goal is that the data will be available as easily as possible for the research community.

**Profile in a nutshell**

- The FinnBrain Birth Cohort Study is a transgenerational prospective observational study investigating the effects of prenatal and early life stress exposure on child health and brain development. This "Cohort Profile" covers the prenatal and early postnatal periods of the study.
- Women (n=3808), their spouses (n=2623), and babies to-be born (n=3837; including 29 twin pairs) were recruited at gestational week (gwk) 12 in Southwest Finland between 12/2011 and 04/2015.
- The prenatal follow-up comprised three assessments with questionnaires (gwks 14, 24, 34) and one blood sample from both mothers and fathers (serum, DNA, RNA) at gwk 24.
- Postnatal assessments of the whole cohort include questionnaires with 3- to 36-month intervals and registry data linkages.
- In all, 310 families (8.14%) with 315 children discontinued the study during pregnancy and another 57 families/children by the 3-month follow-up.
- A nested case-control population ("Focus Cohort") of women with elevated levels of

depressive and anxiety symptoms (highest 20%) and controls (lowest 27%) is included.

- Focus Cohort subjects and other selected subpopulations are invited to studies applying, for example, brain imaging techniques, neuropsychological assessments, and biological sample collections.
- The Cohort is located at the University of Turku, Finland. International and domestic collaboration is encouraged and inherent in the project (www.finnbrain.fi).

**Funding**

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**Acknowledgements and conflicts of interest**

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**Figure 1. Flow chart of the FinnBrain Birth Cohort Study participants**

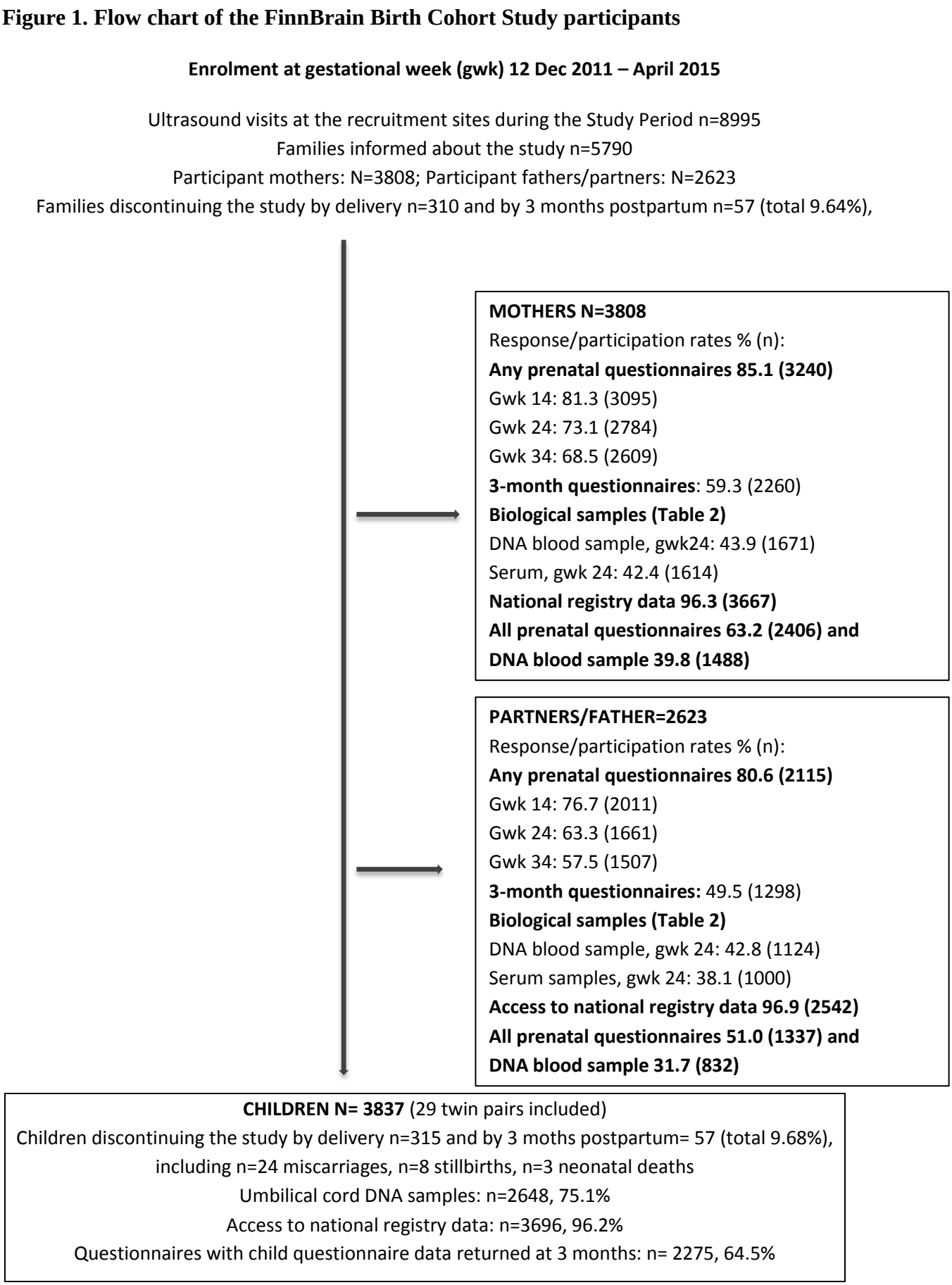

**Table 1. Demographic characteristics of the women giving birth at Turku University Hospital* in years 2012-2014 and the FinnBrain Birth Cohort Study participant women.**

| | | Deliveries at Turku University Hospital N = 12 285 | | FinnBrain participant, mother N = 3808 | |
|---|---|---|---|---|---|
| | | N** | | N** | |
| **Age, mean years** | | | NA | | 30.2 |
| **Age, Distribution (%)** | | 12 285 | | | |
| | 15–19 | | 1.9 | | 1.1 |
| | 20–24 | | 13.6 | | 10.2 |
| | 25–29 | | 31.0 | | 32.3 |
| | 30–34 | | 34.5 | | 37.7 |
| | 35–39 | | 15.6 | | 16.4 |
| | 40– | | 3.1 | | 2.3 |
| **Two adults in the household (%)** | | 11 935 | 94.3 | 3 469 | 94.7 |
| **Nulliparous (%)** | | 12 285 | 43.9 | 3 739 | 49.8 |
| **Smoking (%)** | | 12 242 | | 3 740 | |
| | No smoking | | 83.4 | | 87.3 |
| | Smoking ≤ 1st trimester | | 7.7 | | 8.8 |
| | Smoking >1st trimester | | 8.9 | | 5.9 |
| **Gestational weeks,** | | 12 277 | | 3 729 | |
| **Distribution (%)** | –31 | | 1.4 | | 0.7 |
| | 32–35 | | 3.0 | | 2.3 |
| | 36–37 | | 7.7 | | 7.3 |
| | 38–39 | | 38.5 | | 38.4 |
| | 40–41 | | 44.5 | | 46.5 |
| | 42– | | 4.8 | | 4.8 |
| **Gender of the child (%)** | Girl | 12 381 | 49.3 | 3 747 | 47.7 |
| **Birth weight (%)** | | 12 381 | | 3 696 | |
| | <1500g | | 1.9 | | 0.6 |
| | 1500–1999 | | 1.1 | | 0.8 |
| | 2000–2499 | | 3.4 | | 2.2 |
| | 2500–2999 | | 11.2 | | 10.4 |
| | 3000–3499 | | 31.2 | | 31.8 |
| | 3500–3999 | | 35.6 | | 35.8 |
| | 4000–4499 | | 14.4 | | 15.6 |
| | 4500– | | 2.5 | | 2.8 |
| **Apgar, 5 minutes (%)** | | 12 308 | | 3 673 | |
| | 0–3 | | 0.3 | | 0.2 |
| | 4–7 | | 4.2 | | 3.9 |
| | 8 | | 10.6 | | 9.8 |
| | 9 | | 64.8 | | 63.9 |
| | 10 | | 20.9 | | 22.2 |

* source population: defined geographical area ** N with valid data on the item

**Table 2. Attrition analyses on the parental prenatal questionnaire data, parental blood sample, and umbilical cord blood sample among mothers (n=3095) and fathers (n=2011) who returned the first prenatal (gwk 14) questionnaires in the FinnBrain Birth Cohort Study.**

| | | Returned gwk 34 questionn. | Did not return gwk 34 questionn. | P value ** | DNA blood sample | No DNA blood sample | P value ** | Umbilical cord sample *** | No umbilical cord sample | P value ** |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Mothers*** | n=3095 (%) | 2500 (80.8) | 595 (19.2) | | 1611(52.1) | 1484 (47.9) | | 2304 (74.4) | 791 (25.6) | |
| **Age, mean (SD)** | | 31.0 (4.5) | 30.4 (4.7) | 0.005 | 31.5 (4.3) | 30.3 (4.7) | <0.001 | 30.9 (4.5) | 31.0 (4.6) | 0.634 |
| **Education (%)** | < 10 years | 3.6 | 8.6 | <0.001 | 3.5 | 5.7 | <0.001 | 4.5 | 4.6 | 0.167 |
| | 10–12 years | 31.7 | 40.6 | | 26.2 | 41.2 | | 32.4 | 36.0 | |
| | 13–15 years | 35.1 | 30.4 | | 37.0 | 31.1 | | 34.3 | 34.2 | |
| | > 15 years | 29.6 | 20.4 | | 33.3 | 22.0 | | 28.8 | 25.2 | |
| **Income, €/month (%)** | ≤ 1000 | 22.0 | 23.1 | 0.012 | 20.0 | 24.6 | <0.001 | 21.9 | 23.2 | 0.613 |
| | 1001–1500 | 16.0 | 21.5 | | 15.0 | 19.3 | | 17.0 | 17.2 | |
| | 1501–2000 | 33.6 | 31.5 | | 34.7 | 31.6 | | 34.0 | 30.9 | |
| | 2001–2500 | 18.5 | 15.1 | | 20.0 | 15.5 | | 17.7 | 18.4 | |
| | > 2500 | 9.9 | 8.8 | | 10.3 | 9.0 | | 9.4 | 10.3 | |
| **Two adults in a household (%)** | | 95.2 | 93.4 | 0.076 | 96.0 | 93.1 | <0.001 | 95.1 | 93.2 | 0.034 |
| **Nulliparous (%)** | | 52.8 | 46.3 | 0.005 | 55.1 | 47.6 | <0.001 | 50.2 | 55.5 | 0.012 |
| **Smoking (%)** | No smoking | 88.1 | 83.4 | 0.001 | 89.3 | 85.0 | <0.001 | 86.9 | 86.9 | 0.539 |
| | Quit < 2nd trimester | 7.3 | 8.2 | | 7.5 | 8.0 | | 7.9 | 8.7 | |
| | Smoking > 1st trimester | 4.6 | 8.4 | | 3.2 | 7.1 | | 4.4 | 5.2 | |
| **Gestational weeks, mean (SD)** | | 39.8 (1.5) | 39.3 (2.5) | <0.001 | 39.7 (1.7) | 39.8 (1.6) | 0.883 | 39.8 (1.5) | 39.6 (2.2) | 0.009 |
| **Gender of the child, girl (%)** | | 47.9 | 47.2 | 0.802 | 49.5 | 45.5 | 0.052 | 48.0 | 46.9 | 0.641 |
| **Questionnaire symptom scores, mean (SD)** | | | | | | | | | | |
| EPDS | | 5.1 (4.0) | 5.6 (4.3) | 0.016 | 5.0 (3.9) | 5.3 (4.1) | 0.095 | 5.1 (4.0) | 5.3 (4.0) | 0.278 |
| SCL-90/anxiety | | 3.3 (3.9) | 3.5 (4.0) | 0.328 | 3.6 (5.1) | 3.6 (4.8) | 0.735 | 3.5 (4.9) | 3.7 (5.1) | 0.210 |
| PRAQ-R2 * | | 22.3 (6.5) | 22.2 (7.2) | 0.478 | 22.5 (6.5) | 21.9 (6.8) | 0.244 | 22.3 (6.5) | 22.1 (6.9) | 0.468 |
| ***Fathers*** | N=2011 (%) | 1433 (71.3) | 578 (28.7) | | 987 (49.1) | 1024 (50.9) | | | | |
| **Age, mean (SD)** | | 32.7 (5.3) | 32.4 (5.5) | 0.235 | 33.0 (5.4) | 32.2 (5.3) | 0.001 | 32.6 (5.4) | 32.8 (5.3) | 0.385 |
| **Education (%)** | < 10 years | 6.6 | 9.9 | <0.001 | 6.8 | 8.2 | <0.001 | 7.3 | 8.2 | 0.721 |
| | 10–12 years | 37.8 | 48.9 | | 37.0 | 44.9 | | 41.7 | 39.1 | |
| | 13–15 years | 31.9 | 26.2 | | 32.1 | 28.4 | | 29.9 | 31.14 | |
| | > 15 years | 23.7 | 15.0 | | 24.1 | 18.5 | | 21.1 | 21.6 | |
| **Income, €/month(%)** | ≤1000 | 10.0 | 11.0 | 0.784 | 10.2 | 10.4 | 0.580 | 10.9 | 8.6 | 0.304 |
| | 1001–1500 | 9.4 | 9.2 | | 10.3 | 8.5 | | 9.4 | 9.4 | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1501–2000 | 26.2 | 26.9 | | 25.2 | 27.5 | | 26.8 | 24.9 | |
| | 2001–2500 | 29.4 | 26.6 | | 29.0 | 28.2 | | 27.5 | 31.8 | |
| | >2500 | 25.0 | 26.3 | | 25.3 | 25.4 | | 25.4 | 25.3 | |
| **Questionnaire symptom scores, mean (SD)** | | | | | | | | | | |
| EPDS | | 3.6 (3.3) | 4.1 (3.6) | 0.008 | 3.6 (3.3) | 4.1 (3.6) | 0.039 | 3.7 (3.3) | 3.9 (3.6) | 0.362 |
| SCL-90/anxiety | | 2.4 (3.3) | 2.9 (4.0) | 0.034 | 3.3 (6.6) | 3.9 (7.2) | 0.634 | 3.6 (7.0) | 3.3 (5.9) | 0.763 |

EPDS= Edinburgh Postnatal Depression Scale; PRAQ-R2= Pregnancy-Related Anxiety, Revised2; SCL-90/anxiety= Symptom Checklist-90, the anxiety subscale

*PRAQ-R2 assessment at gwk 14 started July 2014, thus the numbers of subjects in the attrition analyses are n=474 and n=128, respectively

** t-test for age and gestational weeks; Mann-Whitney U test for symptom scores; $\chi^2$ test for all the other variables

*** matching sets of DNA samples: mother-child 1384; father-child 875; mother-father-child: n=847

**Table 3. Overview of data collection methods and time points of assessments in the FinnBrain Birth Cohort Study.**

| **ASSESSMENTS** | sub population* | gwk 14 | gwk 24 | gwk 34 | 0-3 days | 1-2.5 mo | 3 mo | 6 mo | 8 mo | 12-14 mo | 18-24 mo | 30 mo | 36-48 mo |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PARENTS** | | | | | | | | | | | | | |
| Questionnaires | | x | x | x | x | x | x | x | x | x | x | x | x |
| Blood sample: Mothers and fathers Mothers | x | | x | | | x | | | | | | | |
| Breast milk sample | x | | | | | x | | x | | x | x | | |
| Hair samples (cortisol), mothers** | x | | x | | x | | | | | | x | x | |
| Feces, mother | x | | x | x | | | | | | | | | |
| Neuropsychological assessment, mothers *** | x | | x | | | | | | | x | x | | |
| Facial emotion recognition tasks: both parents**** | x | | | | | | | | | | | | |
| Placenta sample | x | | | | x | | | | | | | | |
| **CHILDREN** | | | | | | | | | | | | | |
| Questionnaires | | | | | x | x | x | x | | x | x | x | x |
| Umbilical cord blood | | | | | x | | | | | | | | |
| ERP | x | | | | x | | | | | | | | x |
| Feces | x | | | | | x | | x | | x | x | x | |
| Brain MRI | x | | | | | x | | | | | x | | x |
| NIRS | x | | | | | x | | | | | x | | x |
| Saliva cortisol | x | | | | | x | | x | | x | | | |
| NPS | x | | | | | x | | x | | x | | | |
| Blood sample: DNA, RNA, serum | x | | | | | x | | | | | | | |
| Ultrasonography, aorta | x | | | | | x | | | | | | | |
| Hair sample (cortisol) | x | | | | | | | | | | | x | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Urine | x | | | | | | | | | | | x | |
| Eye movement tracking | x | | | | | | | | x | | | x | |
| Temperament (LabTab) | x | | | | | | | | x | | | x | |
| Cognition | x | | | | | | | | | | | x | |
| Mother-child interaction | x | | | | | | | | x | | | x | |
| Actigraphy | x | | | | | | | | | | | x | |

*Subpopulations are mainly drawn from the Focus Cohort but the target populations may vary for different assessments. Final number of samples or measurements indicated in Table 4 when available (measurements up to 3 months).

** a small population of fathers at gwk 24 included (Table 4)

*** a small population of fathers included (Table 4)

**** assessment times vary

gwk= gestational week; mo=months; ERP= event-related potential; MRI= magnetic resonance imaging; NIRS= near-infrared spectroscopy; NPS= nasopharyngeal sample

**Table 4. Frequencies of biological samples, neuropsychological assessments, and brain imaging in the FinnBrain Birth Cohort Study* by 3 months postpartum.**

| | Final number of samples* |
|---|---|
| **PARENTS** | |
| Hair samples | |
| Mother, gwk 24 | 953 |
| Father, gwk 24 | 58 |
| Delivery, mother | 275 |
| Feces | |
| Mother gwk 24 | 103 |
| Mother, gwk 36 | 55 |
| Cogstate, neuropsychological assessment | |
| Mother, gwk 24 | 274 |
| Father, varying time points | 91 |
| Placenta sample | 252 |
| Breast milk sample, 10 weeks postpartum | 443 |
| Serum sample, mother, 10 weeks postpartum | 352 |
| **CHILDREN**** | |
| Event-Related Potential (ERP), 0-3 days | 151 |
| Magnetic Resonance Imaging (MRI), 2-5 weeks | 183 |
| Near-Infrared Spectroscopy (NIRS), 8 weeks | 64 |
| Blood sample***, 10 weeks | 268 |
| Saliva cortisol, 10 weeks | 375 |
| Feces sample, 10 weeks | 516 |
| Nasopharyngeal sample (NPS), 10 weeks | 378 |
| Ultrasonograpghy/aorta, 10 weeks | 296 |

* Varying subpopulations, but mainly Focus Cohort subjects

** In all, 588 children with at least two and 387 children with at least three different types of measurements presented in Table 4. For example: 157 (85.8%) or 102 (55.7%) of the subjects with 2-5-week MRI scans also have provided a cord blood sample (DNA) or a 10-week faeces sample, respectively.

***serum, DNA, RNA

**Table 5. Mean (SD) values of EPDS, SCL-90/anxiety and PRAQ-R2 scores by years of education at different assessment points in the FinnBrain Birth Cohort Study.**

| | | | Years of Education | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | < 10 years | 10–12 years | 13–15 years | > 15 years | P value* | r |
| Mother | gwk 14 | EPDS | 6.7 (4.6) | 5.7 (4.1) | 4.8 (3.9) | 4.7 (3.8) | <0.001 | -0.129 |
| | | SCL-90/anxiety | 4.7 (4.9) | 4.1 (5.2) | 3.1 (4.3) | 3.3 (5.3) | <0.001 | -0.105 |
| | | PRAQ-R2 | 24.7 (9.1) | 23.4 (6.9) | 21.6 (6.2) | 21.6(6.5) | <0.001 | -0.057 |
| | gwk 24 | EPDS | 6.0 (4.3) | 5.5 (4.2) | 4.7 (4.0) | 4.5 (3.9) | <0.001 | -0.119 |
| | | SCL-90/anxiety | 5.3 (4.9) | 4.7 (5.4) | 3.9 (5.0) | 3.7 (5.0) | <0.001 | -0.100 |
| | | PRAQ-R2 | 23.7 (8.0) | 23.6 (6.9) | 22.6 (6.5) | 22.4(6.4) | 0.003 | -0.069 |
| | gwk 34 | EPDS | 5.8 (4.3) | 5.5 (4.2) | 4.5 (3.9) | 4.4 (3.9) | <0.001 | -0.121 |
| | | SCL-90/anxiety | 4.6 (4.7) | 4.4 (6.5) | 3.3 (5.0) | 3.2 (5.2) | <0.001 | -0.098 |
| | | PRAQ-R2 | 23.3 (8.0) | 24.0 (7.0) | 22.8 (6.7) | 23.0(6.4) | 0.004 | -0.050 |
| | 3 mo | EPDS | 4.8 (4.1) | 4.7 (4.0) | 4.0 (3.8) | 4.1 (3.6) | 0.004 | -0.058 |
| | | SCL-90/anxiety | 4.0 (5.0) | 2.8 (3.7) | 2.4 (3.6) | 2.4 (3.3) | 0.013 | -0.047 |
| Fathers | gwk 14 | EPDS | 4.7 (3.8) | 3.9 (3.5) | 3.5 (3.2) | 3.4 (3.3) | <0.001 | -0.092 |
| | | SCL-90/anxiety | 4.1 (5.0) | 3.6 (6.7) | 3.5 (7.4) | 3.1 (6.6) | 0.002 | -0.031 |
| | gwk 24 | EPDS | 4.4 (3.7) | 3.7 (3.5) | 3.1 (3.4) | 3.4 (3.1) | 0.001 | -0.094 |
| | | SCL-90/anxiety | 4.7 (7.4) | 3.4 (6.2) | 3.1 (5.6) | 3.8 (7.5) | 0.333 | -0.015 |
| | gwk 34 | EPDS | 4.3 (4.1) | 3.4 (6.2) | 2.7 (3.2) | 2.9 (3.0) | <0.001 | -0.108 |
| | | SCL-90/anxiety | 4.2 (7.8) | 2.9 (6.5) | 2.4 (5.3) | 3.1 (7.6) | 0.056 | -0.030 |
| | 3 mo | EPDS | 3.6 (3.8) | 3.5 (3.5) | 3.0 (3.3) | 3.5 (3.6) | 0.138 | -0.016 |
| | | SCL-90/anxiety | 3.3 (4.4) | 2.5 (3.9) | 2.2 (3.3) | 2.4 (3.5) | 0.405 | -0.025 |

*p value is based on the Kruskall-Wallis test
r= Spearman correlation co-efficient for effect size of the associations

EPDS= Edinburgh Postnatal Depression Scale; PRAQ-R2= Pregnancy-Related Anxiety, Revised2; SCL-90/anxiety= Symptom Checklist-90, the anxiety subscale; gwk=gestational week; mo=months