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Title:

Northern Babies: Predicting postpartum depression and improving parent-infant interaction with The Newborn Behavioral Observation Intervention: A non-randomized cluster controlled design nested in a longitudinal observational study

Research protocol of

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Abstract

Introduction

Postpartum depression (PPD) is a prevalent disorder. Studying the factors related to PPD will help to identify families at risk and provide preventive interventions. This can in turn improve the developmental trajectories for the children. Several previous studies have investigated risk factors for PPD. However, few studies have focused on cognitive vulnerability factors. The first aim of the present study is to explore a range of protective and risk factors, including cognitive factors, for PPD, parent-infant interactions and child development. The second aim of the study is to evaluate the effectiveness of The Newborn Behavioral Observation (NBO) as a universal preventive intervention delivered in routine practice. The NBO is a brief relationship-enhancing intervention that may reduce depressive symptomatology in mothers.

Methods

The study is a longitudinal observational study with an intervention. The observational study uses a prospective cohort design, whereas the intervention-study has a non-randomized cluster controlled design comparing a group receiving NBO with a group receiving standard care. The intervention group will receive three NBO-sessions within the first four weeks post-delivery. Between 2015 and 2018 approximately 200 families will be recruited in the municipality of Tromsø, Norway. Parents are recruited during pregnancy, and assessments will be performed during gestational week 16 – 22, 24 – 30 and 31, and at 6 weeks, 4 months and 6 months post-delivery. Predictor variables include several cognitive vulnerability factors including early maladaptive schemas, implicit attitudes and cognitive processing of emotionally valenced infant facial information.

Ethics and dissemination

The Regional Committee for Medical and Health Research Ethics in Northern Norway has approved the project. The research team has collaboration with local health services, and can assist participants who need more extensive follow-up. Results from the project will be disseminated in international and national peer-reviewed journals, and at courses and conferences.

Trials registration number: NCT0253849

Strengths and limitations of this study

- This study will provide new knowledge about cognitive vulnerability and protective

factors associated by postpartum depression, parent-infant interaction, and child development.

- This study is the first to examine the effect of Newborn Behavioral Observation (NBO), a brief and easily delivered relationship enhancing parent-infant intervention, delivered as a general preventive intervention both for postpartum depression and for parent-infant interaction difficulties.
- This study will in addition to the mothers and infants also include fathers.
- The participants will go through 6 assessments; from gestational week 16-22 until 6 months post delivery.
- A limitation of the study is that the participants are not randomly assigned to the intervention and control group, respectively.

The transition into parenthood is a period with great biological and psychosocial changes, and is associated with an elevated risk for depressed mood for both mothers and fathers (1). The prevalence of postpartum depression (PPD) is between 10 % and 15% for women (2, 3), and between 5 % and 10 % for men (1, 4-9). However, a meta-analysis suggested the rate in men may be as high as 25 % in the period between 3- and 6-months postpartum (9).

Important risk factors for developing maternal PPD include antenatal depression and anxiety, previous psychiatric illness, a poor marital relationship, life stressors, a negative attitude towards pregnancy and lack of social support (10). Adverse childhood experiences are in general considered a risk for depression (11) and stress (12) in adulthood. In addition, an insecure adult attachment style is shown to be related to maternal PPD (13). Paternal PPD shares many of the same risk factors as maternal PPD (5, 6). However, the most common correlate for paternal postpartum depression is having a depressed partner (8, 14). Thus, depression in one parent increases the risk for couple comorbidity where both parents become depressed.

Cognition in PPD

Parents' ability to cope with and relate to this transitional period can be assessed by measuring their cognitive schemas and information processing. Cognition may have an important role in the development of maternal PPD and may affect the quality of mother-

infant interactions. In fact, cognitive factors such as antenatal self-devaluating tendencies, a lack of specificity in autobiographical retrieval (15), brooding rumination and negative inferential styles (16) have been found to be predictive of depressive symptoms eight weeks after childbirth.

Further, depression is characterized by impairments and deviations from normal functioning across a broad range of cognitive domains, e.g., attention, attitudes, memory (17, 18). For instance, there is support for a depression related bias for processing of facial information (19-23). Research suggests that mothers with symptoms of PPD judge neutral infant faces as less neutral (24) and rate negative infant faces more negatively (25) compared to non-depressed mothers. Also, mothers with PPD may less accurately identify happy infant faces compared to healthy controls (26), and lower accuracy may be associated with higher levels of maternal depression (27). Still, research on cognitive biases for facial information in PPD is limited.

The cognitive mechanisms that may mediate the effect of PPD on parenting are not well understood. Rumination in depressed mothers is associated with difficulties in the mother-infant relationship, probably because the depressed mother's focus is mostly on herself and not on the needs of the child (28). Müller et al. (29) also found that maternal rumination in pregnancy was related to an impaired mother-infant relationship postpartum. In addition, parents processing of infants facial expression is indicated to have an important role for attunement, emotional attachment, and emotional regulation (30).

Impact of PPD on parent-infant interaction

Maternal depression interferes with healthy interactions with the infant by reducing the mother's ability to be sensitively attuned and responsive to her infant's signals and needs (31-34). Depressed mothers may also show a more negative (hostile and intrusive) and less responsive parenting style (35). Furthermore, they may touch and talk less with their infant and may show more negative facial expressions during face-to-face-interaction (36).

Studies also indicate that mothers with depression tend to have poorer mentalization skills (37). Mentalization can be defined as the capacity to understand the behavior of oneself and others in terms of underlying mental states and intentions (38), whereas reflective functioning is described as an overt manifestation of the capacity to mentalize (39). Depressed

mothers have difficulty reading the affective communication of the infant and responding appropriately (36). Accordingly, the ability for affect regulation and interactive coordination is impaired (40, 41). The capacity to mentalize develops through a child's social interaction with a caregiver who has the ability to understand the child as an individual with a mind (42). Thus, a parent's own unresolved adverse childhood experiences may both increase the risk of psychopathology, as well as impact on their own capacity for reflective functioning and ability to bond (39, 43, 44). Parental reflective functioning is further related to infant attachment (45). Studies suggest that this may be one important factor in the intergenerational transmission of attachment patterns (46).

Consequences for the child

It is well-documented that maternal depression has an adverse effect on the child's development (36, 47). Children of depressed mothers are more likely to have cognitive, behavioural, emotional, and attachment difficulties in childhood (48, 49). Disrupted maternal affective communication is linked with attachment disorganization (50). Disorganized attachment is overrepresented in children of depressed mothers (48), and is associated with internalizing and externalizing behavior problems (51, 52). The risk for adverse outcomes such as poorer school adjustment, lower peer social competence, and an increased risk for depression persist into later childhood and adolescence (53-55).

Maternal insensitivity can also influence infant stress-related physiology, as shown by greater activation of the autonomic nervous system (56, 57). Infants of more sensitive mothers show higher resting heart rate variability (HRV) compared to infants of less sensitive mothers (57). Heart rate variability is proposed as a marker for stress and health (58). Higher HRV is associated with more adaptive coping and emotion regulation, and lower HRV is related to negative outcomes such as depression and anxiety implicating emotional dysregulation (59).

Paternal PPD also has important implications. Studies show that even after controlling for maternal depression, depression in fathers in the pre- and postnatal period is related to negative social, emotional and behavioral outcomes for the child up to 7 years of age (4, 60-62). Some studies suggest that postpartum depression in fathers may be especially associated with an increased risk for oppositional defiant and conduct disorders in boys (4, 60).

Prevention and Treatment of PPD

PPD in mothers can be conceptualized as a mother-infant relationship disorder (63). Thus, interventions improving parent-infant interactions can potentially improve and prevent maternal PPD, as well as improve the trajectories for the children (64, 65). Such preventive efforts could have important societal implications. A recent report listed the high level of costs associated with maternal perinatal health problems (66), and concludes that even modest improvements in outcomes as a result of better services would benefit society.

One such relationship-enhancing intervention is The Newborn Behavioral Observation (NBO; 67). The NBO is a brief, low-cost intervention that can be used in a range of settings (68). It is compatible with the regular practice of public health nurses in Norway, and has been implemented as standard care in several regions. The goal of NBO is to sensitize parents to their infant´s competencies and to how the newborn baby communicates through body signs, movements, state regulation, and responsivity (67). Enhanced understanding of how to "read the baby" can contribute to the development of a positive parent-infant relationship. In addition, results from a pilot study indicated that delivering NBO as a universal preventive intervention may reduce depressive symptomatology (69). By increasing parental sensitivity, the intervention also has the potential to positively affect biomarkers related to infant stress, as indicated by previous studies of attachment-based interventions (70). However, research on the effect of NBO as a preventive intervention is scarce, and there is a need for more studies.

Aims

The present study has three broad aims:

1) *Examine key predictors related to parental functioning*: a) parental postpartum depression, anxiety, and stress, b) parental reflective functioning in relation to the infant, and c) parent-infant attachment style.
2) *Examine key predictors related to interaction and developmental problems in the child*: a) difficulties in parent-infant interaction in the first 4 months post-delivery, and b) infant's cognitive, communicative and motor development, signs of sustained withdrawal behaviour, and heart-rate variability at 6 months post-delivery.
3) *Evaluate the effectiveness of the NBO as a universal preventive intervention* delivered in routine practice as compared to standard care, on:

- Parental (depressive symptoms, parenting stress, reflective functioning, attachment to the infant),

- Relational (emotional availability in parent-child interaction), and

- Infant outcomes (cognitive, communicative and motor development at 6 months post-delivery, heart-rate variability).

Predictor variables include some well-known vulnerability factors for developing PPD (e.g., depression symptoms in pregnancy, adult attachment style, relationship satisfaction and life stress), but the main focus in the observational part of the research project is on cognitive vulnerability factors such as early maladaptive schemas, repetitive negative thinking, rumination, implicit attitudes and cognitive processing of emotionally valenced infant facial information.

Methods

Study design

This is a longitudinal observational study with an intervention. The observational part of the study will use a prospective cohort design. The effect of the intervention will be evaluated using a non-randomized cluster controlled design, since neither cluster nor individual randomization is feasible in this routine practice setting. An intervention group receiving NBO (families belonging to two well-baby clinics in Tromsø municipality) will be compared with a control group (families at the remaining four well-baby clinics in Tromsø) receiving care as usual.

Recruitment

All pregnant women and expecting fathers who speak Norwegian are eligible for inclusion in the study. Between autumn 2015 and autumn 2018 approximately 200 families will be recruited by midwifes and by general practitioners (GPs) in the municipality of Tromsø, which is the 9th largest municipality in Norway (~73000 inhabitants; 71). The participants will be recruited in (approximately) week 16 of gestation. At recruitment, women will be given written information about the study and a flyer with an inquiry to be contacted by the research team. The health worker informs the research team who contacts the women

to plan a meeting preferable between week 16 and 22 of gestation. In this meeting, the prospective parents are given detailed information about the study and are invited to sign an informed consent to participate. In addition, at 4 months post-delivery the parents will be asked to sign an informed consent to obtain birth related information from the birth record.

Power calculations/statistical analysis

The sample size is calculated on the basis of differences between intervention group and standard care group on the *Edinburgh Postnatal Depression Scale* (EPDS) maternal score, the *Parenting Stress Scale* (PSI-PD), the *Reflective Functioning Scale* (PRFQ) and the *Parent Infant-Attachment Scale* (MPAS) 6 weeks post-delivery. Based on the pilotstudy by Nugent et al. (69) and some regression to the mean, we expect a small to medium effect size ($f^2 = .07$). A MANOVA with the four aforementioned outcome variables can detect a difference between the groups with a power of .80 given a group sizes of N = 176. With an estimated dropout of 10 %, a group size of 200 will be recruited. The estimation is based on an α-level of .05.

Procedure

For the observational part of the study, assessments will be performed at six time points (see Figure 1): During gestational week 16 – 22 (Step 1), 24 – 30 (Step 2) and 31 (Step 3), and at 6 weeks (Step 4), 4 months (Step 5) and 6 months (Step 6) post-delivery. For the intervention study, pre-intervention measures will be collected at Step 3, post-intervention measures at Step 4 and follow-up measures at Step 5 and 6. Since the families will receive the first NBO already two-days post-delivery, no pre-test assessment can be obtained for the interaction and infant measures. Hence, analyses of intervention effects will be based on differences between groups at 4 and 6 months post-delivery controlling for relevant covariates. The data is collected using online questionnaires, computerized cognitive tests, video-filmed observations of parent-infant interactions, and a standardised test of the child's cognitive, communicative and motor development (Bayley Scales of Infant and Toddler Development; 72).

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T1: 16 – 22 weeks gestation

- Demographic information
- Depressive symptoms (EPDS + BDI
- Pregnancy related anxiety (PRAQ-R
- Adverse childhood experiences (ACE)
- Risk drinking during pregnancy (TWEAK)
- Repetitive negative thinking (PTQ)
- Life stress (LSS)
- Implicit associations (IAT)
- Selective attention (EDP)

T2: 24 – 30 weeks gestation

- Depressive symptoms (EPDS)
- Pregnancy related anxiety (PRAQ-R)
- Maladaptive core beliefs (YSQ)
- The face recognition task

T3 / pre-intervention measures: about 31 week gestation

- Depressive symptoms (EPDS)
- Pregnancy related anxiety (PRAQ-R)
- Rumination (RRS)
- Prenatal attachment (MAAS / PAAS)
- Adult attachment style (ECR-R)
- Quality of life (SWLS)

Birth (obstetric information)

Routine care plus 3 NBO consultations: within 2 days, 7-10 days and about 4 weeks post-delivery	**Routine care**

T4 / post-intervention measures: 6 weeks postpartum

- Depressive symptoms (EPDS)
- Repetitive negative thinking (PTQ)
- Parent infant-attachment (MPAS / PPAS)
- The face recognition task
- Quality of life (SWLS)
- Reflective functioning (PRFQ)
- Parenting stress (PSI-PD)
- Sleep, wakefulness and distress diary (The diurnal clock)

T5 / follow-up measures: 4 months postpartum

- Depressive symptoms (EPDS + BDI-II)
- Parent infant-attachment (MPAS / PPAS)
- Parent-child interaction (EAS)
- Implicit associations (IAT)
- Selective attention (EDP)
- Reflective functioning (PRFQ)
- Parenting stress (PSI)

Follow-up measures: 6 months postpartum

- Depressive symptoms (EPDS)
- Quality of life (SWLS)
- Infant temperament (CRTQ)
- Heart rate variability
- Infant withdrawal behavior (ADBB)
- Infant development (BSITD – screening version)

Figure 1. Study protocol and assessments at different time points during the study.

The intervention

The NBO is designed to strengthen the parent-infant relationship and foster a positive alliance between the family and the health-care provider. It takes 20 to 40 minutes to administer and consists of 18 neurobehavioral observations which give a profile of the infant's behavioural repertoire along the dimensions: attentional-interactional, autonomic, motor and state organization (67). The parents are invited to actively participate in the shared observation of the infant's unique behavioural expressions. Together with the clinician, they can identify techniques for meeting the infant's responses, as well as ventilate feelings and thoughts, and ask questions.

The intervention group will receive three NBO consultations: 1) Routine care plus NBO at the maternity ward in hospital within two days post-delivery; 2) Routine home visit plus the NBO by a public health nurse when the infant is 7-10 days old; and 3) NBO at the well-baby clinic when the infant is 4 weeks old. The intervention will be conducted by midwifes at the University Hospital of North Norway (UNN), and public health nurses in Tromsø municipality. Both the midwives and health nurses are certified in using the NBO. The control group will receive care as usual. Between 7 and 10 days after birth a public health nurse routinely visits the family at home to evaluate the baby's weight gain and provide guidance on topics such as feeding, crying, sleeping patterns and handling the baby. The parents can also ask questions and voice concerns. Six weeks after birth, the mother and the infant visit the well-baby clinic. Participants in both groups have equal possibilities to seek out other health care interventions for their own or their baby's health during the project period.

Instruments

Predictor variables / independent variables.

Socio-demographics. This includes questions about gender, age, education, marital status, work situation, income, ethnicity, social support, whether pregnancy is wanted, number of pregnancies and children, medication, smoking, and questions about current and previous mental and physical health, as well as help seeking for mental health issues.

Parental cognition and maladaptive schemas. *The Rumination Response Scale* (RRS; 73) is a 22-item self-report measure designed to assess responses to depressed mood that are

focused on the self, the symptoms, and on possible causes and consequences. *The Perseverative Thinking Questionnaire* (PTQ; 74) is a 15-item self-report measure developed as a content independent measure of repetitive negative thinking. *The Young Schema Questionnaire* (YSQ; 75) consists of 90 items measuring maladaptive core beliefs about the self and others that are rooted in adverse relational experiences in childhood and adolescence.

Parental relationship measures. *Adverse Childhood Experiences* (ACE; 76) is a 10-item measure of emotional, physical, and sexual maltreatment and abuse in childhood. *The Experiences in Close Relationships-Revised Questionnaire* (ECR-R; 77) is a 36-item measure of adult attachment style. The ECR-R includes two attachment subscales: avoidance and anxiety. *The Maternal Antenatal Attachment Scale* (MAAS; 78) is a 19-item self-report used to assess maternal antenatal bonding to the foetus. *The Paternal Antenatal Attachment Scale* (PAAS; 79) is a 16-item self-report measure used to assess paternal behaviours, attitudes and feelings towards the foetus.

Measures of parental stress and alcohol abuse. *The Life stress scale* (LSS) is a subscale of the Parenting Stress Index (PSI; 80) consisting of 19 items measuring stress factors over the last 12 months. *The Pregnancy-Related Anxiety Questionnaire* (PRAQ-R; 81) is a 10-item self-report inventory that assesses three subscales of anxiety that are specific to pregnancy: fear of giving birth, fear of bearing a handicapped child, and pregnancy-related concerns about one's appearance. *The Tolerance, Worried, Eye-opener, Amnesia, Kut down* (TWEAK; 82) is a 5-item self-report scale developed to screen for risk drinking during pregnancy.

Experimental tests. Parental cognition and a potential depression related negative bias to infant signals (83) will be measured with a) a face recognition task (84, 85) b) a single category Implicit Associations Test (86) and c) a modified Emotional Dot-Probe (EDP) Task (19, 87). The tests will be administered pre- and postpartum. A) *The face recognition task* measures bias towards memory of facial expressions. Pilot data yielded that patients with major depression were better in recognizing faces of negative valence than a matched control group (85). B) *The IAT* is a well-established measure of implicit attitudes towards the tested categories, e.g., objects or persons (including the self). By associating the category of interest with positive and negative words, the resulting difference in reaction times sheds light on a person's attitude. We will use a single-category IAT to investigate attitudes towards infants, using neutral infant images. C) *The EDP* is a test used to assess selective attention. The presentation of emotional stimuli interferes with a spatial task to respond as quickly as

possible to the location of a seen target (e.g. a dot or cross). In this exogenous cueing task, emotional infant faces are presented either on the left or right side of the screen. Immediately after a probe is shown. The task is to respond as quickly as possible to the location of the probe. The valence of the stimulus and the mood of the subject biases attention either towards or away from the probe location (88, 89).

Outcome measures.

Parental measures of depression, stress and quality of life. *The Edinburgh Postnatal Depression Scale* (EPDS; 90) is a 10-item self-report inventory designed to identify women at risk for postnatal depression. The scale is also validated for use in men (91). Depression severity will be assessed with *the Beck Depression Inventory-II* (92). Depressive symptoms during pregnancy assessed with these scales will also be used as predictor variables. *The Parenting Stress Index* (PSI-FF, third edition; 80) is a parent self-report measure consisting of 120 items. It is designed to identify potentially dysfunctional parent-child systems and parental stress. The PSI yields a total stress score, and scores for two general domains: Child Domain and Parent Domain and the LSS (previously described). Quality of life will be assessed with *the Satisfaction With Life Scale (SWLS)* which is a 5-item scale measuring global life satisfaction according to the individual's own criteria (93). In addition, one item asking participants to rate how happy they feel will be included (94).

Parent-infant measures. In order to assess parent-child interaction, we will employ *the Emotional Availability Scale (*Infancy to Early Childhood Version up to 4 years) (EAS; 95). The EAS is rated on the basis of 15-30 minutes videotaped episodes of parent-infant play interaction. *The Parental Reflective Functioning Questionnaire* (PRFQ; 96) is an 18-item self-report questionnaire. It consists of three subscales: pre-mentalizing, certainty in mental states and interest and curiosity in mental states. *The Maternal Postnatal Attachment Scale* (MPAS; 97) and *The Paternal Postnatal Attachment Scale* (PPAS; 98) are 19-item self-report questionnaires for measuring mother- / father-infant attachment.

Infant measures. *The Cameron-Rice Temperament Questionnaire* (CRTQ; 99) is a 45-item inventory in which parents are asked to rate their infant's sensitivity, general activity, general intensity, frustration tolerance, adaptability, regularity, and soothability. *The diurnal clock* (DC; 100) is a sleep diary with quantifiable information about sleep, wakefulness and distress over a 24-h period. Prior to the meeting at 6-weeks post-delivery the parents are sent two copies of this registration chart and are instructed to complete them over a 48 h period.

The screening test version of Bayley Scales of Infant and Toddler Development (BSITD - Screening version; 72) is a short version of the Bayley-III full-scale version. Bayley is a test of cognitive, communicative and motor development, widely used for research and clinical purposes. *The Alarm Distress Baby Scale* (ADBB; 101) is completed based on child behavior during administration of the Bayley at 6 months. This scale is designed to detect signs of sustained withdrawal behavior in infants 2–24 months of age.

Biological measures. Heart rate variability will be measured in parents and infants during child cognitive testing using wireless unobtrusive electrocardiogram (ECG)-equipment (102).

Fidelity measure. After each NBO consultation the interventionist fills out a fidelity form developed for the current study that indicates which NBO-items were performed, who participated (mother, father etc.), intervention duration and which themes that were discussed. The health workers also rate how they performed the intervention, e.g., to which degree they interpreted the baby's signals together with the parents, validated the parents' observations and skills, summed up their observations of the baby's strengths and need for support, and how much they counselled the parents.

Ethical considerations and dissemination

The project follows the standards of the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, and the project has been approved by the Regional Committee for Medical and Health Research Ethics in Northern Norway (2015/614). All participants receive both oral and written information about the project. Parents give informed consent for themselves and their infant's participation. Participants receive unique IDs, which they use for questionnaires, cognitive tests and observations. The sheet connecting IDs with names will be securely stored separately from the data. Only authorized personnel from the project will have access to this sheet. We are using a university survey system to ensure secure data storage. All investigators will have access to a data set cleaned of all personal identifiable information. Data sets will be password protected.

During the data collection, it will be emphasized that the participant is free to decline the researcher's involvement. None of the assessments or interventions involves any health

risks. As we cooperate with both primary health care in Tromsø municipality and the specialist mental health care services and they are well informed about the study, participants who are in need of more extensive services will be helped to get in touch with the health services for further treatment.

Results from the project will be disseminated in international and national peer-reviewed journals. The results will also be communicated at courses and conferences. In addition, results will be disseminated to the public in various media outlets, and study participants will be informed of the results through the study website: http://site.uit.no/SIN

Discussion

PPD is common among mothers and fathers. There is accumulating evidence that PPD interferes with a healthy interaction between parents and infants, as well as negative developmental outcomes for the child up to several years later. This study aims to increase the knowledge of cognitive risk factors for postpartum depression, interaction difficulties with the child and child development. Such knowledge will be of help in identifying risk families as early as pregnancy. In addition, we aim to investigate if NBO can be effective in preventing PPD and parent-infant interaction problems.

The main focus of the observation part of the study is to investigate cognitive risk factors for PPD and parent-infant relationship difficulties. Cognition is a predictor that has received relatively little attention in this field of research. Several researchers have suggested that cognitive processing and interpretation of infant signals is central for the parents´ attunement to their child. To explore this assumption we have set up three cognitive tests using pictures of emotional infant faces to measure parents´ attention, memory and implicit associations towards infants.

Furthermore, the study expands on the transgenerational perspective by looking at parent´s own adverse childhood experiences as background and reflective functioning for their coping with the postpartum period and relating to their infant. Further, we will study how this influences infant stress-related physiology, as measured with heart rate variability, which is proposed as a marker for emotion regulation.

There is a need for interventions with a potential for preventing PPD and improving the parent- infant relationship. This may further promote a healthy development of the child.

The NBO is a brief intervention that aims to sensitize parents to their infant's competencies. In the present study, one group of parents will receive three NBO-sessions as a universal preventive intervention during the first four weeks after birth, while the control group will receive standard health care. We will examine the NBO´s potential positive effects on the parent-infant relationship, as well as in reducing depressive symptoms in the parents.

Finally, although fathers have become more active caregivers for infants in many societies, they are to a lesser degree included in research in this field compared to women. Accordingly, we also include fathers to explore their experiences in this period of transition, and examine factors associated with their relationship with the infant.

Contributors

Study concept and design: Høifødt, Nordahl, Pfuhl, Landsem, Thimm, Ilstad, and Wang have all contributed equally to study concept and design. Drafting the manuscript: Høifødt, Nordahl, Pfuhl and Wang. Critical revision of the manuscript for important intellectual content: Høifødt, Nordahl, Pfuhl, Landsem, Thimm, Ilstad, and Wang.

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Competing interests None declared.

Ethics approval The project has been approved by the Regional Committee for Medical and Health Research Ethics in Northern Norway (2015/614).

Data sharing statement The data will be presented through peer-reviewed journals and conference presentation.

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Contributor statement

Høifødt, R. S., Nordahl, D., Pfuhl, G., Landsem, I. P., Thimm, J., Ilstad, L. K. K., and Wang, C. E. A have all contributed to study concept and design.

Drafting the manuscript were done by Høifødt, R. S., Nordahl, D., Pfuhl, G., and Wang, C. E. A.

Høifødt, R. S., Nordahl, D., Pfuhl, G., Landsem, I. P., Thimm, J., Ilstad, L. K. K., and Wang, C. E. A., have all critically revised the manuscript for important intellectual content.

Reporting guidelines

Dear editor,

since our manuscript presents both an observation study and an intervention study we found no reporting guidelines that satisfy both studies. Therefore we have tried to use both the SPIRIT guideline and the STROBE guideline.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym - Information about study population is missing from the title
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry. - Page 2 in the manuscript
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier - date found in header, version identifier is missing.
Funding	4	Sources and types of financial, material, and other support - Page 15 in the manuscript
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors - Page 15 in the manuscript
	5b	Name and contact information for the trial sponsor - Page 15 in the manuscript.

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities - The study sponsor had no role in the study concept, design and implementation of the study; collection, management, preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) - not relevant
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention - Page 3 to 7 in the manuscript
	6b	Explanation for choice of comparators - Missing in the manuscript
Objectives	7	Specific objectives or hypotheses - Page 6 and 7 in the manuscript
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) - Page 7 in the manuscript
Methods: Participants, interventions, and outcomes		

	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained - Page 7 to 10 in the manuscript. Reference to where a list of study sites can be obtained is missing.
	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) - inclusion and exclusion criteria for participants found on page 7.
	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered - information about the intervention and the administration of the intervention is found on page 10. Not sure if this is presented in sufficient detail to allow replication.
		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) - not relevant
		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) - missing from the manuscript
		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial - not relevant
	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended - page 12 and 13 of the manuscript, in addition see Figure 1 in page 9, for time point for each measure.

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) - time schedule of enrolment presented on page 7. A figure for assessments at different time points is found on page 9.
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations - see page 8 for power calculations.
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size - Yes, see page 7 in the manuscript.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions - not relevant
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned - not relevant
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions - not relevant
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how - not relevant

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial - not relevant
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol - See figure page 9 for plans for assessment and collection of data. For further informasjon about study instruments see page 10 to 13. Information about reliability and validity of study instruments is missing, as are reference to where data collection forms can be found.
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols - missing from the protocol
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol - se page 13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol - missing
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) - missing
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) - missing

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed - not relevant
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial - missing from the protocol
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct - see page 13 and 14 for information about plan for managing participants who are in need of more extensive services.
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor - not relevant

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval - The Regional Committee for Medical Research Ethics in Northern Norway have approved the project, see page 13.
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) - missing from the manuscript
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) - see page 7 and 8

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable - not relevant
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial - Yes, see page 13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site - yes, see page 15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators - see page 15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation - not relevant
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions - yes, see page 14
	31b	Authorship eligibility guidelines and any intended use of professional writers - missing
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code - missing
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates - missing

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable - not relevant

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract - Yes, page 1 in the manuscript
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found - The abstract provides an informative summary of what we plan to do. The abstract is found in page 2 of the manuscript.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported - Page 3 to 6 in the manuscript
Objectives	3	State specific objectives, including any prespecified hypotheses - Page 6 and 7 in the manuscript
Methods		
Study design	4	Present key elements of study design early in the paper - Yes, key elements of study design are presented early in the method section. Page 7.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection - Yes, found in pages 7 to 10 of the manuscript.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up - Eligibility criteria, and sources and methods of selection of participants are found in pages 7 and 8 of the manuscript
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed - not relevant *Case-control study*—For matched studies, give matching criteria and the number of controls per case -not relevant
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable - Partly missing, but see page 10 to 13 for information about outcomes and predicors.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias - Missing in the manuscript
Study size	10	Explain how the study size was arrived at - Page 8 in the manuscript
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why - Not relevant, since this is a study protocol article

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding - Missing in the manuscript
		(*b*) Describe any methods used to examine subgroups and interactions - Missing in the manuscript
		(*c*) Explain how missing data were addressed - Missing in the manuscript
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed - Missing in the manuscript *Case-control study*—If applicable, explain how matching of cases and controls was addressed - not relevant *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy - not relevant
		(*e*) Describe any sensitivity analyses - missing

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed - not relevant
		(b) Give reasons for non-participation at each stage - not relevant
		(c) Consider use of a flow diagram - not relevant
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders - Not relevant
		(b) Indicate number of participants with missing data for each variable of interest - Not relevant
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) - Not relevant
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time - Not relevant
		Case-control study—Report numbers in each exposure category, or summary measures of exposure - not relevant
		Cross-sectional study—Report numbers of outcome events or summary measures - not relevant
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included - Not relevant
		(*b*) Report category boundaries when continuous variables were categorized - Not relevant
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period - Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses - Not relevant.
Discussion		
Key results	18	Summarise key results with reference to study objectives - not relevant
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias -not relevant
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence -not relevant
Generalisability	21	Discuss the generalisability (external validity) of the study results - not relevant

Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based - Yes, found in page 15 in the manuscript

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Northern Babies: Predicting postpartum depression and improving parent-infant interaction with The Newborn Behavioral Observation Intervention: A non-randomized cluster controlled design nested in a longitudinal observational study

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Title:

Northern Babies: Predicting postpartum depression and improving parent-infant interaction with The Newborn Behavioral Observation Intervention: A non-randomized cluster controlled design nested in a longitudinal observational study

Research protocol of

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Abstract

Introduction

Postpartum depression (PPD) is a prevalent disorder. Studying the factors related to PPD will help to identify families at risk and provide preventive interventions. This can in turn improve the developmental trajectories for the children. Several previous studies have investigated risk factors for PPD. However, few studies have focused on cognitive vulnerability factors. The first aim of the present study is to explore a range of protective and risk factors, including cognitive factors, for PPD, parent-infant interactions and child development. The second aim of the study is to evaluate the effectiveness of The Newborn Behavioral Observation (NBO) as a universal preventive intervention delivered in routine practice. The NBO is a brief relationship-enhancing intervention that may reduce depressive symptomatology in mothers.

Methods

The study is a longitudinal observational study with an intervention. The observational study uses a prospective cohort design, whereas the intervention-study has a non-randomized cluster controlled design comparing a group receiving NBO with a group receiving standard care. The intervention group will receive three NBO-sessions within the first four weeks post-delivery. Between 2015 and 2018 approximately 200 families will be recruited in the municipality of Tromsø, Norway. Parents are recruited during pregnancy, and assessments will be performed during gestational week 16 – 22, 24 – 30 and 31, and at 6 weeks, 4 months and 6 months post-delivery. Predictor variables include several cognitive vulnerability factors including early maladaptive schemas, implicit attitudes and cognitive processing of emotionally valenced infant facial information.

Ethics and dissemination

The Regional Committee for Medical and Health Research Ethics in Northern Norway has approved the project. The research team has collaboration with local health services, and can assist participants who need more extensive follow-up. Results from the project will be disseminated in international and national peer-reviewed journals, and at courses and conferences.

Trials registration number: NCT02538497

Strengths and limitations of this study

- This study will provide new knowledge about cognitive vulnerability and protective factors associated by postpartum depression, parent-infant interaction, and child development.
- The study is the first to examine the effect of Newborn Behavioral Observation (NBO), a brief relationship enhancing parent-infant intervention, delivered as a universal preventive intervention both for postpartum depression and for parent-infant interaction difficulties.
- Mothers, infants and fathers are followed through 6 assessments; from gestational week 16-22 until 6 months post-delivery.
- A limitation of the study is that the participants are not randomly assigned to the intervention and control group, respectively.
- Further limitations are that depression is measured by self-report questionnaires only, and that potentially important factors such as parental personality and other mental health variables, e.g., anxiety and PTSD symptoms, are not included.

The transition into parenthood is a period with great biological and psychosocial changes, and is associated with an elevated risk for depressed mood for both mothers and fathers (1). The prevalence of postpartum depression (PPD) is between 10 % and 15% for women (2, 3), and between 5 % and 10 % for men (1, 4-9). However, a meta-analysis suggested the rate in men may be as high as 25 % in the period between 3- and 6-months postpartum (9).

Important risk factors for developing maternal PPD include antenatal depression and anxiety, previous psychiatric illness, a poor marital relationship, life stressors, a negative attitude towards pregnancy and lack of social support (10). Adverse childhood experiences are in general considered a risk for depression (11) and stress (12) in adulthood. In addition, an insecure adult attachment style is shown to be related to maternal PPD (13). Paternal PPD shares many of the same risk factors as maternal PPD (5, 6). However, the most common correlate for paternal postpartum depression is having a depressed partner (8, 14). Thus, depression in one parent increases the risk for couple comorbidity where both parents become depressed.

Cognition in PPD

Parents' ability to cope with and relate to this transitional period can be assessed by measuring their cognitive schemas and information processing. Cognition may have an important role in the development of maternal PPD and may affect the quality of mother-infant interactions. In fact, cognitive factors such as negative self-schemas (15), antenatal self-devaluating tendencies, a lack of specificity in autobiographical retrieval (16), brooding rumination and negative inferential styles (17) have been found to be predictive of depressive symptoms after childbirth.

Further, depression is characterized by impairments and deviations from normal functioning across a broad range of cognitive domains, e.g., attention, attitudes, memory (18, 19). For instance, there is support for a depression related bias for processing of facial information (20-24). Research suggests that mothers with symptoms of PPD rate negative infant faces more negatively compared to non-depressed mothers (25). Also, mothers with PPD may less accurately identify happy infant faces compared to healthy controls (26), and lower accuracy may be associated with higher levels of maternal depression (27). Gil, Teissèdre, Chambres and Droit-Voilet (28) found that judgment of facial expressions depended largely on anxiety, but intensity of depressed mood was correlated to judging infant faces as less neutral. Still, research on cognitive biases for facial information in PPD is limited.

The cognitive mechanisms that may mediate the effect of PPD on parenting are not well understood. Rumination in depressed mothers is associated with difficulties in the mother-infant relationship, probably because the depressed mother's focus is mostly on herself and not on the needs of the child (29). Müller, Teismann, Havemann, Michalak and Seehagen (30) also found that maternal rumination in pregnancy was related to an impaired mother-infant relationship postpartum. In addition, parents processing of infants facial expression is indicated to have an important role for attunement, emotional attachment, and emotional regulation (31).

Impact of PPD on parent-infant interaction

Parental psychopathology such as depression and anxiety may interfere with the parent-infant relationship (32, 33). This pertains not only to postnatal mental health, but also psychopathology in the antenatal period. In fact, a study by Parfitt, Pike and Ayers (34) indicated that prenatal mental health, especially anxiety, was related to parent-infant interaction to a greater extent than postnatal measures.

Although a range of mental health issues are related to parental-child outcomes, the focus of this study will mainly be on depression. Maternal depression may interfere with healthy interactions with the infant by reducing the mother's ability to be sensitively attuned and responsive to her infant's signals and needs (35-38). Depressed mothers may also show a more negative (hostile and intrusive) and less responsive parenting style (39). Furthermore, they may touch and talk less with their infant and may show more negative facial expressions during face-to-face-interaction (40).

Emerging research on the maternal brain and hormones shows that processes underlying parent-infant relationships and parental sensitivity are complex and include markers related to PPD and exposure to childhood adversity (see 41 for a review). There is indication that mothers with depression tend to have poorer mentalization skills (42). Mentalization can be defined as the capacity to understand the behavior of oneself and others in terms of underlying mental states and intentions (43), whereas reflective functioning is described as an overt manifestation of the capacity to mentalize (44). Depressed mothers may have difficulty reading the affective communication of the infant and responding appropriately (40). Accordingly, the ability for affect regulation and interactive coordination is impaired (45, 46). The capacity to mentalize develops through a child's social interaction with a caregiver who has the ability to understand the child as an individual with a mind (47). Thus, a parent's own unresolved adverse childhood experiences might both increase the risk of psychopathology, as well as impact on their own capacity for reflective functioning and ability to bond (44, 48, 49). Parental reflective functioning may further be related to infant attachment (50). A recent meta-analysis (51) supports the existence of an intergenerational transmission of attachment patterns, but concludes that caregiver sensitivity cannot fully explain the transmission and that other moderators are not fully understood. This picture is further complicated by studies suggesting that insecure ambivalent infants often have insecure avoidant

mothers and the other way around (52). Studies suggest that parental reflective functioning may be one factor in the intergenerational transmission of attachment patterns (53).

Consequences for the child

It is well-documented that maternal depression has an adverse effect on the child's development (40, 54). Children of depressed mothers are more likely to have cognitive, behavioural, emotional, and attachment difficulties in childhood (55, 56). Disrupted maternal affective communication is linked with attachment disorganization (57). Disorganized attachment is overrepresented in children of depressed mothers (55), and is associated with internalizing and externalizing behavior problems (58, 59). The risk for adverse outcomes such as poorer school adjustment, lower peer social competence, and an increased risk for depression persist into later childhood and adolescence (60-62).

Maternal insensitivity can also influence infant stress-related physiology, as shown by greater activation of the autonomic nervous system (63, 64). Infants of more sensitive mothers show higher resting heart rate variability (HRV) compared to infants of less sensitive mothers (64). Heart rate variability is proposed as a marker for stress and health (65). Higher HRV is associated with more adaptive coping and emotion regulation, and lower HRV is related to negative outcomes such as depression and anxiety implicating emotional dysregulation (66).

Paternal PPD also has important implications. Studies show that even after controlling for maternal depression, depression in fathers in the pre- and postnatal period is related to negative social, emotional and behavioral outcomes for the child up to 7 years of age (4, 67-69). Some studies suggest that postpartum depression in fathers may be especially associated with an increased risk for oppositional defiant and conduct disorders in boys (4, 67).

Prevention and Treatment of PPD

PPD in mothers can be conceptualized as a mother-infant relationship disorder (70). Thus, interventions improving parent-infant interactions can potentially improve and prevent maternal PPD, as well as improve the trajectories for the children (71,

72). Such preventive efforts could have important societal implications. A recent report lists the high level of costs associated with maternal perinatal health problems (73), and concludes that even modest improvements in outcomes as a result of better services would benefit society.

One such relationship-enhancing intervention is The Newborn Behavioral Observation (NBO; 74). The NBO is a brief, low-cost intervention that can be used in a range of settings (75). The intervention can be delivered from around the time of birth, and it is compatible with the regular practice of public health nurses in Norway, and has been implemented as standard care in several regions. The goal of NBO is to sensitize parents to their infant´s competencies and to how the newborn baby communicates through body signs, movements, state regulation, and responsivity (74). Enhanced understanding of how to "read the baby" can contribute to the development of a positive parent-infant relationship. Compared to usual care NBO has been found to be related to higher perceived parent- infant interaction quality among parents of high-risk infants (76). In addition, results from a pilot study indicated that delivering NBO as a universal preventive intervention can be related to lower depressive symptomatology in first-time mothers (77). By increasing parental sensitivity, the intervention also has the potential to positively affect biomarkers related to infant stress, as indicated by previous studies of attachment-based interventions (78). However, research on the effect of NBO as a preventive intervention is scarce, and there is a need for more studies.

Aims

The present study has three broad aims:

1) *Examine key pre- and postnatal predictors related to parental functioning*: a) parental depression, anxiety, and stress, b) parental reflective functioning in relation to the infant, and c) parent-infant attachment style.
2) *Examine key pre- and postnatal predictors related to interaction and developmental problems in the child*: a) difficulties in parent-infant interaction in the first 4 months post-delivery, and b) infant's cognitive, communicative and motor development, signs of sustained withdrawal behaviour, and heart-rate variability at 6 months post-delivery.

3) *Evaluate the effectiveness of the NBO as a universal preventive intervention* delivered in routine practice as compared to standard care, on:

- Parental outcomes (depressive symptoms, parenting stress, reflective functioning, attachment to the infant),

- Relational outcomes (emotional availability in parent-child interaction), and

- Infant outcomes (cognitive, communicative and motor development at 6 months post-delivery, heart-rate variability).

Predictor variables include some well-known vulnerability factors for developing PPD (e.g., depression symptoms in pregnancy, adult attachment style, relationship satisfaction and life stress), but the main focus in the observational part of the research project is on cognitive vulnerability factors such as early maladaptive schemas, repetitive negative thinking, rumination, implicit attitudes and cognitive processing of emotionally valenced infant facial information.

Methods

Study design

This is a longitudinal observational study with an intervention. The observational part of the study will use a prospective cohort design. The effect of the intervention will be evaluated using a non-randomized cluster controlled design, since neither cluster nor individual randomization is feasible in this routine practice setting. An intervention group receiving NBO (families belonging to two well-baby clinics in Tromsø municipality) will be compared with a control group (families at the remaining four well-baby clinics in Tromsø) receiving care as usual.

Recruitment

All pregnant women and expecting fathers who speak Norwegian are eligible for inclusion in the study. Between autumn 2015 and autumn 2018 approximately 200 families will be recruited by midwifes and by general practitioners (GPs) in the municipality of Tromsø, which is the 9th largest municipality in Norway (~73000

inhabitants; 79). There are approximately 1000 births a year in Tromsø municipality. Based on the experiences from a comparable study, "Little in Norway" (80), the recruitment of 200 families within the project period is considered feasible.

The participants will be recruited in (approximately) week 16 of gestation. At recruitment, women will be given written information about the study and a flyer with an inquiry to be contacted by the research team. If the child`s father is not present, the mother is encouraged to inform him about the study. The health worker informs the research team who contacts the women to plan a meeting with them and their partners, preferable between week 16 and 22 of gestation. In this meeting, the prospective parents are given detailed information about the study and are invited to sign an informed consent to participate. In addition, at 4 months post-delivery the parents will be asked to sign an informed consent to obtain birth related information from the birth record.

Power calculations/statistical analysis

The sample size is calculated on the basis of differences between intervention group and standard care group on the Edinburgh Postnatal Depression Scale (EPDS) maternal score, the *Parenting Stress Index* (PSI-PD), the *Parental Reflective Functioning Scale* (PRFQ) and the *Maternal Postnatal Attachment Scale* (MPAS) 6 weeks post-delivery. Based on the pilot study by Nugent et al. (77) and some regression to the mean, we expect a small to medium effect size (f2 = .07). A MANOVA with the four aforementioned outcome variables can detect a difference between the groups with a power of .80 given a group sizes of N = 176. With an estimated dropout of 10 %, a group size of 200 will be recruited. The estimation is based on an α-level of .05.

Procedure

For the observational part of the study, assessments will be performed at six time points (see Table 1): During gestational week 16 – 22 (Step 1), 24 – 30 (Step 2) and 31 (Step 3), and at 6 weeks (Step 4), 4 months (Step 5) and 6 months (Step 6) post-delivery. For the intervention study, pre-intervention measures will be collected

at Step 3, post-intervention measures at Step 4 and follow-up measures at Step 5 and 6. Since the families will receive the first NBO already two-days post-delivery, no pre-test assessment can be obtained for the interaction and infant measures. Hence, analyses of intervention effects will be based on differences between groups at 4 and 6 months post-delivery controlling for relevant covariates. The data is collected using online questionnaires, computerized cognitive tests, video-filmed observations of mother-infant interactions, and a standardised test of the child's cognitive, communicative and motor development (Bayley Scales of Infant and Toddler Development; 81).

Table 1 Study protocol and data collection at different time points during the study

Data collection	T1[1]	T2[2]	T3[3]	Birth		T4[4]	T5[5]	T6[6]
Women/mothers and men/fathers								
Demographic information	•							
EPDS (Depressive symptoms)	•	•	•			•	•	•
BDI-II (Depressive symptoms)	•						•	
PRAQ-R (Pregnancy related anxiety)	•	•	•					
ACE (Adverse childhood experiences)	•							
TWEAK (Risk drinking during pregnancy)	•							
PTQ (Repetitive negative thinking)	•					•		
LSS (Life stress)	•						•	
IAT (Implicit associations)	•						•	
EDP (Selective attention)	•						•	
YSQ (Maladaptive core beliefs)		•						
The face recognition task		•				•		
RRS (Rumination)			•					
MAAS / PAAS (Prenatal self reported attachment)			•					
ECR-R (Adult attachment style)			•					
SWLS (Quality of life)			•			•		
MPAS / PPAS (Parent-infant self reported			•			•		

Routine care plus 3 NBO consultations vs. **Routine care**

attachment)					
PRFQ (Reflective functioning)			•	•	
PSI-PD (Parenting stress)			•		
PSI (Parenting stress)				•	
Heart rate variability					•
Parents - infants					
Obstetric information	•				
The diurnal clock (Sleep wakefulness and distress diary)			•		
EAS (Parent-child interaction)				•	
CRTQ (Infant temperament)					•
Heart rate variability					•
ADBB (Infant withdrawal behavior)					•
BSITD – screening version (Infant development)					•

Note. [1]T1: 16-22 weeks gestation.

[2]T2: 24-30 weeks gestation.

[3]T3 / pre-intervention measures: about 31 week gestation.

[4]T4 / post-intervention measures: 6 weeks postpartum.

[5]T5 / follow-up measures: 4 months postpartum.

[6]T6 / follow-up measures: 6 months postpartum.

The intervention

The NBO is designed to strengthen the parent-infant relationship and foster a positive alliance between the family and the health-care provider. It takes 20 to 40 minutes to administer and consists of 18 neurobehavioral observations which give a profile of the infant's behavioural repertoire along the dimensions: attentional-interactional, autonomic, motor and state organization (74). How many items that are used in each NBO session depends on the child's state (e.g., asleep, awake and calm, or crying). This is in line with the recommendations for use of NBO in Norway (82) The parents are invited to actively participate in the shared observation of the infant's unique behavioural expressions. Together with the clinician, they can identify techniques for meeting the infant's responses, as well as ventilate feelings and thoughts, and ask questions.

The intervention group will receive three NBO consultations: 1) Routine care plus NBO at the maternity ward in hospital within two days post-delivery; 2) Routine home visit plus the NBO by a public health nurse when the infant is 7-10 days old; and 3) NBO at the well-baby clinic when the infant is 4 weeks old. The intervention will be conducted by midwifes at the University Hospital of North Norway (UNN), and public health nurses in Tromsø municipality. Both the midwives and health nurses are certified in using the NBO. The control group will receive care as usual. Between 7 and 10 days after birth a public health nurse routinely visits the family at home to evaluate the baby's weight gain and provide guidance on topics such as feeding, crying, sleeping patterns and handling the baby. The parents can also ask questions and voice concerns. Six weeks after birth, the mother and the infant visit the well-baby clinic. Participants in both groups have equal possibilities to seek out other health care interventions for their own or their baby's health during the project period.

Instruments

Predictor variables / independent variables.

Socio-demographics. This includes questions about gender, age, education, marital status, work situation, income, ethnicity, social support, whether pregnancy is wanted, number of pregnancies and children, medication, smoking, and questions about current and previous mental and physical health, as well as help seeking for mental health issues.

Parental cognition and maladaptive schemas. *The Rumination Response Scale* (RRS; 83) is a 22-item self-report measure designed to assess responses to depressed mood that are focused on the self, the symptoms, and on possible causes and consequences. *The Perseverative Thinking Questionnaire* (PTQ; 84) is a 15-item self-report measure developed as a content independent measure of repetitive negative thinking. *The Young Schema Questionnaire* (YSQ; 85) consists of 90 items measuring maladaptive core beliefs about the self and others that are rooted in adverse relational experiences in childhood and adolescence.

Parental relationship measures. *Adverse Childhood Experiences* (ACE; 86) is a 10-item measure of emotional, physical, and sexual maltreatment and abuse in childhood. *The Experiences in Close Relationships-Revised Questionnaire* (ECR-R;

87) is a 36-item measure of adult attachment style. The ECR-R includes two attachment subscales: avoidance and anxiety. *The Maternal Antenatal Attachment Scale* (MAAS; 88) is a 19-item self-report used to assess maternal antenatal bonding to the foetus. *The Paternal Antenatal Attachment Scale* (PAAS; 89) is a 16-item self-report measure used to assess paternal behaviours, attitudes and feelings towards the foetus.

Measures of parental stress and alcohol abuse. *The Life stress scale* (LSS) is a subscale of the Parenting Stress Index (PSI; 90) consisting of 19 items measuring stress factors over the last 12 months. *The Pregnancy-Related Anxiety Questionnaire* (PRAQ-R; 91) is a 10-item self-report inventory that assesses three subscales of anxiety that are specific to pregnancy: fear of giving birth, fear of bearing a handicapped child, and pregnancy-related concerns about one's appearance. *The Tolerance, Worried, Eye-opener, Amnesia, Kut down* (TWEAK; 92) is a 5-item self-report scale developed to screen for risk drinking during pregnancy.

Experimental tests. Parental cognition and a potential depression related negative bias to infant signals (93) will be measured with a) a face recognition task (94, 95) b) a single category Implicit Associations Test (IAT) (96) and c) a modified Emotional Dot-Probe (EDP) Task (20, 97). The tests will be administered pre- and postpartum. A) *The face recognition task* measures bias towards memory of facial expressions. Pilot data yielded that patients with major depression were better in recognizing faces of negative valence than a matched control group (95). B) *The IAT* is a well-established measure of implicit attitudes towards the tested categories, e.g., objects or persons (including the self). By associating the category of interest with positive and negative words, the resulting difference in reaction times sheds light on a person's attitude. We will use a single-category IAT to investigate attitudes towards infants, using neutral infant images (98). C) *The EDP* is a test used to assess selective attention. The presentation of emotional stimuli interferes with a spatial task to respond as quickly as possible to the location of a seen target (e.g. a dot or cross). In this exogenous cueing task, emotional infant faces (98) are presented either on the left or right side of the screen. Immediately after a probe is shown. The task is to respond as quickly as possible to the location of the probe. The valence of the stimulus and the mood of the subject biases attention either towards or away from the probe location (99, 100).

Outcome measures.

Parental measures of depression, stress and quality of life. *The Edinburgh Postnatal Depression Scale* (EPDS; 101) is a 10-item self-report inventory designed to identify women at risk for postnatal depression. Scores on the EPDS range from 0 - 30, and we use a threshold of 10 or more to define at least probable minor depression (102, 103). The scale is also validated for use in men (104). Depression severity will be assessed with *the Beck Depression Inventory-II* (BDI-II) (105). BDI-II is a 21-item self-report inventory, and scores on the inventory range from 0-63. Total scores will be categorized as follows: 0-13 minimal, 14-19 mild, 20-28 moderate and 29-63 severe. Depressive symptoms during pregnancy assessed with these scales will also be used as predictor variables. *The Parenting Stress Index* (PSI-FF, third edition; 90) is a parent self-report measure consisting of 120 items. It is designed to identify potentially dysfunctional parent-child systems and parental stress. The PSI yields a total stress score, and scores for two general domains: Child Domain and Parent Domain and the LSS (previously described). Quality of life will be assessed with *the Satisfaction With Life Scale (SWLS)* which is a 5-item scale measuring global life satisfaction according to the individual's own criteria (106). In addition, one item asking participants to rate how happy they feel will be included (107).

Parent-infant measures. In order to assess parent-child interaction, we will employ *the Emotional Availability Scale (*Infancy to Early Childhood Version up to 4 years) (EAS; 108). The EAS is rated on the basis of 15-30 minutes videotaped episodes of mother-infant play interaction. *The Parental Reflective Functioning Questionnaire* (PRFQ; 109) is an 18-item self-report questionnaire. It consists of three subscales: pre-mentalizing, certainty in mental states and interest and curiosity in mental states. *The Maternal Postnatal Attachment Scale* (MPAS; 110) and *The Paternal Postnatal Attachment Scale* (PPAS; 111) are 19-item self-report questionnaires for measuring mother- / father-infant attachment.

Infant measures. *The Cameron-Rice Temperament Questionnaire* (CRTQ; 112) is a 45-item inventory in which parents are asked to rate their infant's sensitivity, general activity, general intensity, frustration tolerance, adaptability, regularity, and soothability. *The diurnal clock* (DC; 113) is a sleep diary with quantifiable information about sleep, wakefulness and distress over a 24-h period. Prior to the

meeting at 6-weeks post-delivery the parents are sent two copies of this registration chart and are instructed to complete them over a 48 h period. *The screening test version of Bayley Scales of Infant and Toddler Development* (BSITD - Screening version; 81) is a short version of the Bayley-III full-scale version. Bayley is a test of cognitive, communicative and motor development, widely used for research and clinical purposes. *The Alarm Distress Baby Scale* (ADBB; 114) is completed based on child behavior during administration of the Bayley at 6 months. This scale is designed to detect signs of sustained withdrawal behavior in infants 2–24 months of age.

Biological measures. Heart rate variability will be measured in parents and infants during child cognitive testing using wireless unobtrusive electrocardiogram (ECG)-equipment (115).

Fidelity measure. After each NBO consultation the interventionist fills out a fidelity form developed for the current study that indicates which NBO-items were performed, who participated (mother, father etc.), intervention duration and which themes were discussed. The health workers also rate how they performed the intervention, e.g., to which degree they interpreted the baby's signals together with the parents, validated the parents' observations and skills, summed up their observations of the baby's strengths and need for support, and how much they counselled the parents.

Ethical considerations and dissemination

The project follows the standards of the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, and the project has been approved by the Regional Committee for Medical and Health Research Ethics in Northern Norway (2015/614). All participants receive both oral and written information about the project. Parents give informed consent for themselves and their infant's participation. Participants receive unique IDs, which they use for questionnaires, cognitive tests and observations. The sheet connecting IDs with names will be securely stored separately from the data. Only authorized personnel from the project will have access to this sheet. We are using a university survey system to ensure secure data storage. All investigators will have access to a data set cleaned of all personal identifiable information. Data sets will be password protected.

During the data collection, it will be emphasized that the participant is free to decline the researcher's involvement. None of the assessments or interventions involves any health risks. As we cooperate with both primary health care in Tromsø municipality and the specialist mental health care services and they are well informed about the study, participants who are in need of more extensive services will be helped to get in touch with the health services for further treatment.

Results from the project will be disseminated in international and national peer-reviewed journals. The results will also be communicated at courses and conferences. In addition, results will be disseminated to the public in various media outlets, and study participants will be informed of the results through the study website: http://site.uit.no/SIN

Discussion

PPD is common among mothers and fathers. There is accumulating evidence that PPD interferes with a healthy interaction between parents and infants, as well as negative developmental outcomes for the child up to several years later. This study aims to increase the knowledge of cognitive risk factors for postpartum depression, interaction difficulties with the child and child development. Such knowledge will be of help in identifying risk families as early as pregnancy. In addition, we aim to investigate if NBO can be effective in preventing PPD and parent-infant interaction problems.

The main focus of the observation part of the study is to investigate cognitive risk factors for PPD and parent-infant relationship difficulties. Cognition is a predictor that has received relatively little attention in this field of research. Several researchers have suggested that cognitive processing and interpretation of infant signals is central for the parents´ attunement to their child. To explore this assumption we have set up three cognitive tests using pictures of emotional infant faces to measure parents´ attention, memory and implicit associations towards infants.

Furthermore, the study expands on the transgenerational perspective by looking at parent´s own adverse childhood experiences as background and reflective functioning for their coping with the postpartum period and relating to their infant.

Further, we will study how this influences infant stress-related physiology, as measured with heart rate variability, which is proposed as a marker for emotion regulation.

There is a need for interventions with a potential for preventing PPD and improving the parent- infant relationship. This may further promote a healthy development of the child. The NBO is a brief intervention that aims to sensitize parents to their infant's competencies. In the present study, one group of parents will receive three NBO-sessions as a universal preventive intervention during the first four weeks after birth, while the control group will receive standard health care. We will examine the NBO´s potential positive effects on the parent-infant relationship, as well as in reducing depressive symptoms in the parents.

Finally, although fathers have become more active caregivers for infants in many societies, they are to a lesser degree included in research in this field compared to women. Accordingly, we also include fathers to explore their experiences in this period of transition, and examine factors associated with their relationship with the infant.

Contributors

Study concept and design: Høifødt, Nordahl, Pfuhl, Landsem, Thimm, Ilstad, and Wang have all contributed equally to study concept and design. Drafting the manuscript: Høifødt, Nordahl, Pfuhl and Wang. Critical revision of the manuscript for important intellectual content: Høifødt, Nordahl, Pfuhl, Landsem, Thimm, Ilstad, and Wang.

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Competing interests None declared.

Ethics approval The project has been approved by the Regional Committee for Medical and Health Research Ethics in Northern Norway (2015/614).

Data sharing statement The data will be presented through peer-reviewed journals and conference presentation.

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Reporting guidelines

Dear editor,

since our manuscript presents both an observation study and an intervention study we found no reporting guidelines that satisfy both studies. Therefore we have tried to use both the SPIRIT guideline and the STROBE guideline.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym - Information about study population is missing from the title
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry. - Page 2 in the manuscript
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier - date found in header, version identifier is missing.
Funding	4	Sources and types of financial, material, and other support - Page 15 in the manuscript
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors - Page 15 in the manuscript
	5b	Name and contact information for the trial sponsor - Page 15 in the manuscript.

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities - The study sponsor had no role in the study concept, design and implementation of the study; collection, management, preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) - not relevant
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention - Page 3 to 7 in the manuscript
	6b	Explanation for choice of comparators - Missing in the manuscript
Objectives	7	Specific objectives or hypotheses - Page 6 and 7 in the manuscript
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) - Page 7 in the manuscript
Methods: Participants, interventions, and outcomes		

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained - Page 7 to 10 in the manuscript. Reference to where a list of study sites can be obtained is missing.
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) - inclusion and exclusion criteria for participants found on page 7.
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered - information about the intervention and the administration of the intervention is found on page 10. Not sure if this is presented in sufficient detail to allow replication.
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) - not relevant
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) - missing from the manuscript
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial - not relevant
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended - page 12 and 13 of the manuscript, in addition see Figure 1 in page 9, for time point for each measure.

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) - time schedule of enrolment presented on page 7. A figure for assessments at different time points is found on page 9.
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations - see page 8 for power calculations.
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size - Yes, see page 7 in the manuscript.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions - not relevant
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned - not relevant
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions - not relevant
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how - not relevant

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial - not relevant
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol - See figure page 9 for plans for assessment and collection of data. For further informasjon about study instruments see page 10 to 13. Information about reliability and validity of study instruments is missing, as are reference to where data collection forms can be found.
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols - missing from the protocol
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol - se page 13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol - missing
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) - missing
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) - missing

Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed - not relevant
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial - missing from the protocol
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct - see page 13 and 14 for information about plan for managing participants who are in need of more extensive services.
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor - not relevant
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval - The Regional Committee for Medical Research Ethics in Northern Norway have approved the project, see page 13.
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) - missing from the manuscript
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) - see page 7 and 8

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable - not relevant
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial - Yes, see page 13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site - yes, see page 15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators - see page 15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation - not relevant
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions - yes, see page 14
	31b	Authorship eligibility guidelines and any intended use of professional writers - missing
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code - missing
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates - missing

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable - not relevant

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract - Yes, page 1 in the manuscript
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found - The abstract provides an informative summary of what we plan to do. The abstract is found in page 2 of the manuscript.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported - Page 3 to 6 in the manuscript
Objectives	3	State specific objectives, including any prespecified hypotheses - Page 6 and 7 in the manuscript
Methods		
Study design	4	Present key elements of study design early in the paper - Yes, key elements of study design are presented early in the method section. Page 7.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection - Yes, found in pages 7 to 10 of the manuscript.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up - Eligibility criteria, and sources and methods of selection of participants are found in pages 7 and 8 of the manuscript
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed - not relevant *Case-control study*—For matched studies, give matching criteria and the number of controls per case -not relevant
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable - Partly missing, but see page 10 to 13 for information about outcomes and predicors.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias - Missing in the manuscript
Study size	10	Explain how the study size was arrived at - Page 8 in the manuscript
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why - Not relevant, since this is a study protocol article

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding - Missing in the manuscript
		(*b*) Describe any methods used to examine subgroups and interactions - Missing in the manuscript
		(*c*) Explain how missing data were addressed - Missing in the manuscript
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed - Missing in the manuscript *Case-control study*—If applicable, explain how matching of cases and controls was addressed - not relevant *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy - not relevant
		(*e*) Describe any sensitivity analyses - missing

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed - not relevant
		(b) Give reasons for non-participation at each stage - not relevant
		(c) Consider use of a flow diagram - not relevant
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders - Not relevant
		(b) Indicate number of participants with missing data for each variable of interest - Not relevant
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) - Not relevant
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time - Not relevant
		Case-control study—Report numbers in each exposure category, or summary measures of exposure - not relevant
		Cross-sectional study—Report numbers of outcome events or summary measures - not relevant
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included - Not relevant
		(*b*) Report category boundaries when continuous variables were categorized - Not relevant
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period - Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses - Not relevant.
Discussion		
Key results	18	Summarise key results with reference to study objectives - not relevant
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias -not relevant
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence -not relevant
Generalisability	21	Discuss the generalisability (external validity) of the study results - not relevant

Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based - Yes, found in page 15 in the manuscript

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Protocol for the Northern Babies longitudinal study: Predicting postpartum depression and improving parent-infant interaction with The Newborn Behavioral Observation

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Title:

Protocol for the Northern Babies longitudinal study: Predicting postpartum depression and improving parent-infant interaction with The Newborn Behavioral Observation

Research protocol of

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Word count: 4375

Abstract

Introduction

Postpartum depression (PPD) is a prevalent disorder. Studying the factors related to PPD will help to identify families at risk and provide preventive interventions. This can in turn improve the developmental trajectories for the children. Several previous studies have investigated risk factors for PPD. However, few studies have focused on cognitive vulnerability factors. The first aim of the present study is to explore a range of protective and risk factors, including cognitive factors, for PPD, parent-infant interactions and child development. The second aim of the study is to evaluate the effectiveness of The Newborn Behavioral Observation (NBO) as a universal preventive intervention delivered in routine practice. The NBO is a brief relationship-enhancing intervention that may reduce depressive symptomatology in mothers.

Methods

The study is a longitudinal observational study with an intervention. The observational study uses a prospective cohort design, whereas the intervention-study has a non-randomized cluster controlled design comparing a group receiving NBO with a group receiving standard care. The intervention group will receive three NBO-sessions within the first four weeks post-delivery. Between 2015 and 2018 approximately 200 families will be recruited in the municipality of Tromsø, Norway. Parents are recruited during pregnancy, and assessments will be performed during gestational week 16 – 22, 24 – 30 and 31, and at 6 weeks, 4 months and 6 months post-delivery. Predictor variables include several cognitive vulnerability factors including early maladaptive schemas, implicit attitudes and cognitive processing of emotionally valenced infant facial information.

Ethics and dissemination

The Regional Committee for Medical and Health Research Ethics in Northern Norway has approved the project. The research team has collaboration with local health services, and can assist participants who need more extensive follow-up. Results from the project will be disseminated in international and national peer-reviewed journals, and at courses and conferences.

Trials registration number: NCT02538497

Strengths and limitations of this study

- This study will provide new knowledge about cognitive vulnerability and protective factors associated by postpartum depression, parent-infant interaction, and child development.
- The study is the first to examine the effect of Newborn Behavioral Observation (NBO), a brief relationship enhancing parent-infant intervention, delivered as a universal preventive intervention both for postpartum depression and for parent-infant interaction difficulties.
- Mothers, infants and fathers are followed through 6 assessments; from gestational week 16-22 until 6 months post-delivery.
- A limitation of the study is that the participants are not randomly assigned to the intervention and control group, respectively.
- Further limitations are that depression is measured by self-report questionnaires only, and that potentially important factors such as parental personality and other mental health variables, e.g., anxiety and Post Traumatic Stress Disorder (PTSD) symptoms, are not included.

The transition into parenthood is a period with great biological and psychosocial changes, and is associated with an elevated risk for depressed mood for both mothers and fathers (1). The prevalence of postpartum depression (PPD) is between 10 % and 15% for women (2, 3), and between 5 % and 10 % for men (1, 4-9). However, a meta-analysis suggested the rate in men may be as high as 25 % in the period between 3- and 6-months postpartum (9).

Important risk factors for developing maternal PPD include antenatal depression and anxiety, previous psychiatric illness, a poor marital relationship, life stressors, a negative attitude towards pregnancy and lack of social support (10). Adverse childhood experiences are in general considered a risk for depression (11) and stress (12) in adulthood. In addition, an insecure adult attachment style is shown to be related to maternal PPD (13). Paternal PPD shares many of the same risk factors as maternal PPD (5, 6). However, the most common correlate for paternal postpartum depression is having a depressed partner (8, 14). Thus, depression in one parent increases the risk for couple comorbidity where both parents become depressed.

Cognition in PPD

Parents' ability to cope with and relate to this transitional period can be assessed by measuring their cognitive schemas and information processing. Cognition may have an important role in the development of maternal PPD and may affect the quality of mother-infant interactions. In fact, cognitive factors such as negative self-schemas (15), antenatal self-devaluating tendencies, a lack of specificity in autobiographical retrieval (16), brooding rumination and negative inferential styles (17) have been found to be predictive of depressive symptoms after childbirth.

Further, depression is characterized by impairments and deviations from normal functioning across a broad range of cognitive domains, e.g., attention, attitudes, memory (18, 19). For instance, there is support for a depression related bias for processing of facial information (20-24). Research suggests that mothers with symptoms of PPD rate negative infant faces more negatively compared to non-depressed mothers (25). Also, mothers with PPD may less accurately identify happy infant faces compared to healthy controls (26), and lower accuracy may be associated with higher levels of maternal depression (27). Gil, Teissèdre, Chambres and Droit-Voilet (28) found that judgment of facial expressions depended largely on anxiety, but intensity of depressed mood was correlated to judging infant faces as less neutral. Still, research on cognitive biases for facial information in PPD is limited.

The cognitive mechanisms that may mediate the effect of PPD on parenting are not well understood. Rumination in depressed mothers is associated with difficulties in the mother-infant relationship, probably because the depressed mother's focus is mostly on herself and not on the needs of the child (29). Müller, Teismann, Havemann, Michalak and Seehagen (30) also found that maternal rumination in pregnancy was related to an impaired mother-infant relationship postpartum. In addition, parents processing of infants facial expression is indicated to have an important role for attunement, emotional attachment, and emotional regulation (31).

Impact of PPD on parent-infant interaction

Parental psychopathology such as depression and anxiety may interfere with the parent-infant relationship (32, 33). This pertains not only to postnatal mental health, but also psychopathology in the antenatal period. In fact, a study by Parfitt, Pike and Ayers (34) indicated that prenatal mental health, especially anxiety, was related to parent-infant interaction to a greater extent than postnatal measures.

Although a range of mental health issues are related to parental-child outcomes, the focus of this study will mainly be on depression. Maternal depression may interfere with healthy interactions with the infant by reducing the mother's ability to be sensitively attuned and responsive to her infant's signals and needs (35-38). Depressed mothers may also show a more negative (hostile and intrusive) and less responsive parenting style (39). Furthermore, they may touch and talk less with their infant and may show more negative facial expressions during face-to-face-interaction (40).

Emerging research on the maternal brain and hormones shows that processes underlying parent-infant relationships and parental sensitivity are complex and include markers related to PPD and exposure to childhood adversity (see 41 for a review). There is indication that mothers with depression tend to have poorer mentalization skills (42). Mentalization can be defined as the capacity to understand the behavior of oneself and others in terms of underlying mental states and intentions (43), whereas reflective functioning is described as an overt manifestation of the capacity to mentalize (44). Depressed mothers may have difficulty reading the affective communication of the infant and responding appropriately (40). Accordingly, the ability for affect regulation and interactive coordination is impaired (45, 46). The capacity to mentalize develops through a child's social interaction with a caregiver who has the ability to understand the child as an individual with a mind (47). Thus, a parent's own unresolved adverse childhood experiences might both increase the risk of psychopathology, as well as impact on their own capacity for reflective functioning and ability to bond (44, 48, 49). Parental reflective functioning may further be related to infant attachment (50). A recent meta-analysis (51) supports the existence of an intergenerational transmission of attachment patterns, but concludes that caregiver sensitivity cannot fully explain the transmission and that other moderators are not fully understood. This picture is further complicated by studies suggesting that insecure ambivalent infants often have insecure avoidant

mothers and the other way around (52). Studies suggest that parental reflective functioning may be one factor in the intergenerational transmission of attachment patterns (53).

Consequences for the child

It is well-documented that maternal depression has an adverse effect on the child's development (40, 54). Children of depressed mothers are more likely to have cognitive, behavioural, emotional, and attachment difficulties in childhood (55, 56). Disrupted maternal affective communication is linked with attachment disorganization (57). Disorganized attachment is overrepresented in children of depressed mothers (55), and is associated with internalizing and externalizing behavior problems (58, 59). The risk for adverse outcomes such as poorer school adjustment, lower peer social competence, and an increased risk for depression persist into later childhood and adolescence (60-62).

Maternal insensitivity can also influence infant stress-related physiology, as shown by greater activation of the autonomic nervous system (63, 64). Infants of more sensitive mothers show higher resting heart rate variability (HRV) compared to infants of less sensitive mothers (64). Heart rate variability is proposed as a marker for stress and health (65). Higher HRV is associated with more adaptive coping and emotion regulation, and lower HRV is related to negative outcomes such as depression and anxiety implicating emotional dysregulation (66).

Paternal PPD also has important implications. Studies show that even after controlling for maternal depression, depression in fathers in the pre- and postnatal period is related to negative social, emotional and behavioral outcomes for the child up to 7 years of age (4, 67-69). Some studies suggest that postpartum depression in fathers may be especially associated with an increased risk for oppositional defiant and conduct disorders in boys (4, 67).

Prevention and Treatment of PPD

PPD in mothers can be conceptualized as a mother-infant relationship disorder (70). Thus, interventions improving parent-infant interactions can potentially improve and prevent maternal PPD, as well as improve the trajectories for the children (71,

72). Such preventive efforts could have important societal implications. A recent report lists the high level of costs associated with maternal perinatal health problems (73), and concludes that even modest improvements in outcomes as a result of better services would benefit society.

One such relationship-enhancing intervention is The Newborn Behavioral Observation (NBO; 74). The NBO is a brief, low-cost intervention that can be used in a range of settings (75). The intervention can be delivered from around the time of birth, and it is compatible with the regular practice of public health nurses in Norway, and has been implemented as standard care in several regions. The goal of NBO is to sensitize parents to their infant´s competencies and to how the newborn baby communicates through body signs, movements, state regulation, and responsivity (74). Enhanced understanding of how to "read the baby" can contribute to the development of a positive parent-infant relationship. Compared to usual care NBO has been found to be related to higher perceived parent- infant interaction quality among parents of high-risk infants (76). In addition, results from a pilot study indicated that delivering NBO as a universal preventive intervention can be related to lower depressive symptomatology in first-time mothers (77). By increasing parental sensitivity, the intervention also has the potential to positively affect biomarkers related to infant stress, as indicated by previous studies of attachment-based interventions (78). However, research on the effect of NBO as a preventive intervention is scarce, and there is a need for more studies.

Aims

The present study has three broad aims:

1) *Examine key pre- and postnatal predictors related to parental functioning*: a) parental depression, anxiety, and stress, b) parental reflective functioning in relation to the infant, and c) parent-infant attachment style.
2) *Examine key pre- and postnatal predictors related to interaction and developmental problems in the child*: a) difficulties in mother-infant interaction in the first 4 months post-delivery, and b) infant's cognitive, communicative and motor development, signs of sustained withdrawal behaviour, and heart-rate variability at 6 months post-delivery.

3) *Evaluate the effectiveness of the NBO as a universal preventive intervention* delivered in routine practice as compared to standard care, on:

- Parental outcomes (depressive symptoms, parenting stress, reflective functioning, attachment to the infant),

- Relational outcomes (emotional availability in mother-child interaction), and

- Infant outcomes (cognitive, communicative and motor development at 6 months post-delivery, heart-rate variability).

Predictor variables include some well-known vulnerability factors for developing PPD (e.g., depression symptoms in pregnancy, adult attachment style, relationship satisfaction and life stress), but the main focus in the observational part of the research project is on cognitive vulnerability factors such as early maladaptive schemas, repetitive negative thinking, rumination, implicit attitudes and cognitive processing of emotionally valenced infant facial information.

Methods

Study design

This is a longitudinal observational study with an intervention. The observational part of the study will use a prospective cohort design. The effect of the intervention will be evaluated using a non-randomized cluster controlled design, since neither cluster nor individual randomization is feasible in this routine practice setting. An intervention group receiving NBO (families belonging to two well-baby clinics in Tromsø municipality) will be compared with a control group (families at the remaining four well-baby clinics in Tromsø) receiving care as usual.

Recruitment

All pregnant women and expecting fathers who speak Norwegian are eligible for inclusion in the study. Between autumn 2015 and autumn 2018 approximately 200 families will be recruited by midwifes and by general practitioners (GPs) in the municipality of Tromsø, which is the 9th largest municipality in Norway (~73000

inhabitants; 79). There are approximately 1000 births a year in Tromsø municipality. Based on the experiences from a comparable study, "Little in Norway" (80), the recruitment of 200 families within the project period is considered feasible.

The participants will be recruited in (approximately) week 16 of gestation. At recruitment, women will be given written information about the study and a flyer with an inquiry to be contacted by the research team. If the child`s father is not present, the mother is encouraged to inform him about the study. The health worker informs the research team who contacts the women to plan a meeting with them and their partners, preferable between week 16 and 22 of gestation. In this meeting, the prospective parents are given detailed information about the study and are invited to sign an informed consent to participate. In addition, at 4 months post-delivery the parents will be asked to sign an informed consent to obtain birth related information from the birth record.

Power calculations/statistical analysis

The sample size is calculated on the basis of differences between intervention group and standard care group on the Edinburgh Postnatal Depression Scale (EPDS) maternal score, the *Parenting Stress Index* (PSI-PD), the *Parental Reflective Functioning Scale* (PRFQ) and the *Maternal Postnatal Attachment Scale* (MPAS) 6 weeks post-delivery. Based on the pilot study by Nugent et al. (77) and some regression to the mean, we expect a small to medium effect size ($f2 = .07$). A MANOVA with the four aforementioned outcome variables can detect a difference between the groups with a power of .80 given a group size of N = 176. With an estimated dropout of 10 %, a group size of 200 women will be recruited. Sample size is not based on the number of men recruited, as their allocation to the two groups is less predictable than for mothers. The estimation is based on an α-level of .05.

Procedure

For the observational part of the study, assessments will be performed at six time points (T; see Table 1): During gestational week 16 – 22 (T1), 24 – 30 (T2) and 31 (T3), and at 6 weeks (T4), 4 months (T5) and 6 months (T6) post-delivery. For the

intervention study, pre-intervention measures will be collected at T3, post-intervention measures at T4 and follow-up measures at T5 and T6. Since the families will receive the first NBO already two-days post-delivery, no pre-test assessment can be obtained for the interaction and infant measures. Hence, analyses of intervention effects will be based on differences between groups at 4 and 6 months post-delivery controlling for relevant covariates. The data is collected using online questionnaires, computerized cognitive tests, video-filmed observations of mother-infant interactions, and a standardised test of the child's cognitive, communicative and motor development (Bayley Scales of Infant and Toddler Development; 81).

Table 1 Study protocol and data collection at different time points during the study

Data collection	T1[1]	T2[2]	T3[3]	Birth	T4[4]	T5[5]	T6[6]
Women/mothers and men/fathers							
Demographic information	•						
EPDS (Depressive symptoms)	•	•	•		•	•	•
BDI-II (Depressive symptoms)	•					•	
PRAQ-R (Pregnancy related anxiety)	•	•	•				
ACE (Adverse childhood experiences)	•						
TWEAK (Risk drinking during pregnancy)	•						
PTQ (Repetitive negative thinking)	•				•		
LSS (Life stress)	•					•	
IAT (Implicit associations)	•					•	
EDP (Selective attention)	•					•	
YSQ (Maladaptive core beliefs)		•					
The face recognition task		•			•		
RRS (Rumination)			•				
MAAS / PAAS (Prenatal self reported attachment)			•				
ECR-R (Adult attachment style)			•				
SWLS (Quality of life)			•		•		
MPAS / PPAS (Parent-infant self reported			•		•		

Routine care plus 3 NBO consultations vs. **Routine care**

attachment)						
PRFQ (Reflective functioning)			•	•		
PSI-PD (Parenting stress)			•			
PSI (Parenting stress)				•		
Mothers – infants						
Obstetric information	•					
The diurnal clock (Sleep wakefulness and distress diary)			•			
EAS (Parent-child interaction)				•		
CRTQ (Infant temperament)					•	
Heart rate variability					•	
ADBB (Infant withdrawal behavior)					•	
BSITD – screening version (Infant development)					•	

Note. [1]T1: 16-22 weeks gestation.

[2]T2: 24-30 weeks gestation.

[3]T3 / pre-intervention measures: about 31 week gestation.

[4]T4 / post-intervention measures: 6 weeks postpartum.

[5]T5 / follow-up measures: 4 months postpartum.

[6]T6 / follow-up measures: 6 months postpartum.

The intervention

The NBO is designed to strengthen the parent-infant relationship and foster a positive alliance between the family and the health-care provider. It takes 20 to 40 minutes to administer and consists of 18 neurobehavioral observations which give a profile of the infant's behavioural repertoire along the dimensions: attentional-interactional, autonomic, motor and state organization (74). How many items that are used in each NBO session depends on the child's state (e.g., asleep, awake and calm, or crying). This is in line with the recommendations for use of NBO in Norway (82) The parents are invited to actively participate in the shared observation of the infant's unique behavioural expressions. Together with the clinician, they can identify techniques for meeting the infant's responses, as well as ventilate feelings and thoughts, and ask questions.

The intervention group will receive three NBO consultations: 1) Routine care plus NBO at the maternity ward in hospital within two days post-delivery; 2) Routine home visit plus the NBO by a public health nurse when the infant is 7-10 days old; and 3) NBO at the well-baby clinic when the infant is 4 weeks old. The intervention will be conducted by midwifes at the University Hospital of North Norway (UNN), and public health nurses in Tromsø municipality. Both the midwives and health nurses are certified in using the NBO. The control group will receive care as usual. Between 7 and 10 days after birth a public health nurse routinely visits the family at home to evaluate the baby's weight gain and provide guidance on topics such as feeding, crying, sleeping patterns and handling the baby. The parents can also ask questions and voice concerns. Six weeks after birth, the mother and the infant visit the well-baby clinic. Participants in both groups have equal possibilities to seek out other health care interventions for their own or their baby's health during the project period.

Instruments

Predictor variables / independent variables.

Socio-demographics. This includes questions about gender, age, education, marital status, work situation, income, ethnicity, social support, whether pregnancy is wanted, number of pregnancies and children, medication, smoking, and questions about current and previous mental and physical health, as well as help seeking for mental health issues.

Parental cognition and maladaptive schemas. *The Rumination Response Scale* (RRS; 83) is a 22-item self-report measure designed to assess responses to depressed mood that are focused on the self, the symptoms, and on possible causes and consequences. *The Perseverative Thinking Questionnaire* (PTQ; 84) is a 15-item self-report measure developed as a content independent measure of repetitive negative thinking. *The Young Schema Questionnaire* (YSQ; 85) consists of 90 items measuring maladaptive core beliefs about the self and others that are rooted in adverse relational experiences in childhood and adolescence.

Parental relationship measures. *Adverse Childhood Experiences* (ACE; 86) is a 10-item measure of emotional, physical, and sexual maltreatment and abuse in childhood. *The Experiences in Close Relationships-Revised Questionnaire* (ECR-R;

87) is a 36-item measure of adult attachment style. The ECR-R includes two attachment subscales: avoidance and anxiety. *The Maternal Antenatal Attachment Scale* (MAAS; 88) is a 19-item self-report used to assess maternal antenatal bonding to the foetus. *The Paternal Antenatal Attachment Scale* (PAAS; 89) is a 16-item self-report measure used to assess paternal behaviours, attitudes and feelings towards the foetus.

Measures of parental stress and alcohol abuse. *The Life stress scale* (LSS) is a subscale of the Parenting Stress Index (PSI; 90) consisting of 19 items measuring stress factors over the last 12 months. *The Pregnancy-Related Anxiety Questionnaire* (PRAQ-R; 91) is a 10-item self-report inventory that assesses three subscales of anxiety that are specific to pregnancy: fear of giving birth, fear of bearing a handicapped child, and pregnancy-related concerns about one's appearance. *The Tolerance, Worried, Eye-opener, Amnesia, Kut down* (TWEAK; 92) is a 5-item self-report scale developed to screen for risk drinking during pregnancy.

Experimental tests. Parental cognition and a potential depression related negative bias to infant signals (93) will be measured with a) a face recognition task (94, 95) b) a single category Implicit Associations Test (IAT) (96) and c) a modified Emotional Dot-Probe (EDP) Task (20, 97). The tests will be administered pre- and postpartum. A) *The face recognition task* measures bias towards memory of facial expressions. Pilot data yielded that patients with major depression were better in recognizing faces of negative valence than a matched control group (95). B) *The IAT* is a well-established measure of implicit attitudes towards the tested categories, e.g., objects or persons (including the self). By associating the category of interest with positive and negative words, the resulting difference in reaction times sheds light on a person's attitude. We will use a single-category IAT to investigate attitudes towards infants, using neutral infant images (98). C) *The EDP* is a test used to assess selective attention. The presentation of emotional stimuli interferes with a spatial task to respond as quickly as possible to the location of a seen target (e.g. a dot or cross). In this exogenous cueing task, emotional infant faces (98) are presented either on the left or right side of the screen. Immediately after a probe is shown. The task is to respond as quickly as possible to the location of the probe. The valence of the stimulus and the mood of the subject biases attention either towards or away from the probe location (99, 100).

Outcome measures.

Parental measures of depression, stress and quality of life. *The Edinburgh Postnatal Depression Scale* (EPDS; 101) is a 10-item self-report inventory designed to identify women at risk for postnatal depression. Scores on the EPDS range from 0 - 30, and we use a threshold of 10 or more to define at least probable minor depression (102, 103). The scale is also validated for use in men (104). Depression severity will be assessed with *the Beck Depression Inventory-II* (BDI-II) (105). BDI-II is a 21-item self-report inventory, and scores on the inventory range from 0-63. Total scores will be categorized as follows: 0-13 minimal, 14-19 mild, 20-28 moderate and 29-63 severe. Depressive symptoms during pregnancy assessed with these scales will also be used as predictor variables. *The Parenting Stress Index* (PSI-FF, third edition; 90) is a parent self-report measure consisting of 120 items. It is designed to identify potentially dysfunctional parent-child systems and parental stress. The PSI yields a total stress score, and scores for two general domains: Child Domain and Parent Domain and the LSS (previously described). Quality of life will be assessed with *the Satisfaction With Life Scale (SWLS)* which is a 5-item scale measuring global life satisfaction according to the individual's own criteria (106). In addition, one item asking participants to rate how happy they feel will be included (107).

Parent-infant measures. In order to assess parent-child interaction, we will employ *the Emotional Availability Scale (*Infancy to Early Childhood Version up to 4 years) (EAS; 108). The EAS is rated on the basis of 15-30 minutes videotaped episodes of mother-infant play interaction. *The Parental Reflective Functioning Questionnaire* (PRFQ; 109) is an 18-item self-report questionnaire. It consists of three subscales: pre-mentalizing, certainty in mental states and interest and curiosity in mental states. *The Maternal Postnatal Attachment Scale* (MPAS; 110) and *The Paternal Postnatal Attachment Scale* (PPAS; 111) are 19-item self-report questionnaires for measuring mother- / father-infant attachment.

Infant measures. *The Cameron-Rice Temperament Questionnaire* (CRTQ; 112) is a 45-item inventory in which parents are asked to rate their infant's sensitivity, general activity, general intensity, frustration tolerance, adaptability, regularity, and soothability. *The diurnal clock* (DC; 113) is a sleep diary with quantifiable information about sleep, wakefulness and distress over a 24-h period. Prior to the

meeting at 6-weeks post-delivery the parents are sent two copies of this registration chart and are instructed to complete them over a 48 h period. *The screening test version of Bayley Scales of Infant and Toddler Development* (BSITD - Screening version; 81) is a short version of the Bayley-III full-scale version. Bayley is a test of cognitive, communicative and motor development, widely used for research and clinical purposes. *The Alarm Distress Baby Scale* (ADBB; 114) is completed based on child behavior during administration of the Bayley at 6 months. This scale is designed to detect signs of sustained withdrawal behavior in infants 2–24 months of age.

Biological measures. Heart rate variability will be measured in mothers and infants during child cognitive testing using wireless unobtrusive electrocardiogram (ECG)-equipment (115).

Fidelity measure. After each NBO consultation the interventionist fills out a fidelity form developed for the current study that indicates which NBO-items were performed, who participated (mother, father etc.), intervention duration and which themes were discussed. The health workers also rate how they performed the intervention, e.g., to which degree they interpreted the baby's signals together with the parents, validated the parents' observations and skills, summed up their observations of the baby's strengths and need for support, and how much they counselled the parents.

Ethical considerations and dissemination

The project follows the standards of the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, and the project has been approved by the Regional Committee for Medical and Health Research Ethics in Northern Norway (2015/614). All participants receive both oral and written information about the project. Parents give informed consent for themselves and their infant's participation. Participants receive unique IDs, which they use for questionnaires, cognitive tests and observations. The sheet connecting IDs with names will be securely stored separately from the data. Only authorized personnel from the project will have access to this sheet. We are using a university survey system to ensure secure data storage. All investigators will have access to a data set cleaned of all personal identifiable information. Data sets will be password protected.

During the data collection, it will be emphasized that the participant is free to decline the researcher's involvement. None of the assessments or interventions involves any health risks. As we cooperate with both primary health care in Tromsø municipality and the specialist mental health care services and they are well informed about the study, participants who are in need of more extensive services will be helped to get in touch with the health services for further treatment.

Results from the project will be disseminated in international and national peer-reviewed journals. The results will also be communicated at courses and conferences. In addition, results will be disseminated to the public in various media outlets, and study participants will be informed of the results through the study website: http://site.uit.no/SIN

Discussion

PPD is common among mothers and fathers. There is accumulating evidence that PPD interferes with a healthy interaction between parents and infants, as well as negative developmental outcomes for the child up to several years later. This study aims to increase the knowledge of cognitive risk factors for postpartum depression, interaction difficulties with the child and child development. Such knowledge will be of help in identifying risk families as early as pregnancy. In addition, we aim to investigate if NBO can be effective in preventing PPD and parent-infant interaction problems.

The main focus of the observation part of the study is to investigate cognitive risk factors for PPD and parent-infant relationship difficulties. Cognition is a predictor that has received relatively little attention in this field of research. Several researchers have suggested that cognitive processing and interpretation of infant signals is central for the parents´ attunement to their child. To explore this assumption we have set up three cognitive tests using pictures of emotional infant faces to measure parents´ attention, memory and implicit associations towards infants.

Furthermore, the study expands on the transgenerational perspective by looking at parent´s own adverse childhood experiences as background and reflective functioning for their coping with the postpartum period and relating to their infant.

Further, we will study how this influences infant stress-related physiology, as measured with heart rate variability, which is proposed as a marker for emotion regulation.

There is a need for interventions with a potential for preventing PPD and improving the parent- infant relationship. This may further promote a healthy development of the child. The NBO is a brief intervention that aims to sensitize parents to their infant's competencies. In the present study, one group of parents will receive three NBO-sessions as a universal preventive intervention during the first four weeks after birth, while the control group will receive standard health care. We will examine the NBO´s potential positive effects on the parent-infant relationship, as well as in reducing depressive symptoms in the parents.

Finally, although fathers have become more active caregivers for infants in many societies, they are to a lesser degree included in research in this field compared to women. Accordingly, we also include fathers to explore their experiences in this period of transition, and examine factors associated with their relationship with the infant.

Contributors

Study concept and design: Høifødt, Nordahl, Pfuhl, Landsem, Thimm, Ilstad, and Wang have all contributed equally to study concept and design. Drafting the manuscript: Høifødt, Nordahl, Pfuhl and Wang. Critical revision of the manuscript for important intellectual content: Høifødt, Nordahl, Pfuhl, Landsem, Thimm, Ilstad, and Wang.

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Competing interests None declared.

Ethics approval The project has been approved by the Regional Committee for Medical and Health Research Ethics in Northern Norway (2015/614).

Data sharing statement This article is a protocol for an ongoing study. The data from the completed study will contain sensitive health information about the participants. Data cannot be made publicly

available without compromising participant confidentiality and privacy. Directives from the Research ethical committee and The Norwegian Data Protection Authority thus prohibits us from making the data set publicly available.

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Reporting guidelines

Dear editor,

since our manuscript presents both an observation study and an intervention study we found no reporting guidelines that satisfy both studies. Therefore we have tried to use both the SPIRIT guideline and the STROBE guideline.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym - Information about study population is missing from the title
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry. - Page 2 in the manuscript
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier - date found in header, version identifier is missing.
Funding	4	Sources and types of financial, material, and other support - Page 15 in the manuscript
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors - Page 15 in the manuscript
	5b	Name and contact information for the trial sponsor - Page 15 in the manuscript.

	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities - The study sponsor had no role in the study concept, design and implementation of the study; collection, management, preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) - not relevant
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention - Page 3 to 7 in the manuscript
	6b	Explanation for choice of comparators - Missing in the manuscript
Objectives	7	Specific objectives or hypotheses - Page 6 and 7 in the manuscript
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) - Page 7 in the manuscript
Methods: Participants, interventions, and outcomes		

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained - Page 7 to 10 in the manuscript. Reference to where a list of study sites can be obtained is missing.
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) - inclusion and exclusion criteria for participants found on page 7.
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered - information about the intervention and the administration of the intervention is found on page 10. Not sure if this is presented in sufficient detail to allow replication.
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) - not relevant
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) - missing from the manuscript
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial - not relevant
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended - page 12 and 13 of the manuscript, in addition see Figure 1 in page 9, for time point for each measure.

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) - time schedule of enrolment presented on page 7. A figure for assessments at different time points is found on page 9.
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations - see page 8 for power calculations.
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size - Yes, see page 7 in the manuscript.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions - not relevant
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned - not relevant
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions - not relevant
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how - not relevant

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial - not relevant
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol - See figure page 9 for plans for assessment and collection of data. For further informasjon about study instruments see page 10 to 13. Information about reliability and validity of study instruments is missing, as are reference to where data collection forms can be found.
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols - missing from the protocol
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol - se page 13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol - missing
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) - missing
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) - missing

Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed - not relevant
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial - missing from the protocol
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct - see page 13 and 14 for information about plan for managing participants who are in need of more extensive services.
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor - not relevant
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval - The Regional Committee for Medical Research Ethics in Northern Norway have approved the project, see page 13.
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) - missing from the manuscript
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) - see page 7 and 8

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable - not relevant
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial - Yes, see page 13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site - yes, see page 15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators - see page 15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation - not relevant
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions - yes, see page 14
	31b	Authorship eligibility guidelines and any intended use of professional writers - missing
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code - missing
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates - missing

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable - not relevant

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract - Yes, page 1 in the manuscript
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found - The abstract provides an informative summary of what we plan to do. The abstract is found in page 2 of the manuscript.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported - Page 3 to 6 in the manuscript
Objectives	3	State specific objectives, including any prespecified hypotheses - Page 6 and 7 in the manuscript
Methods		
Study design	4	Present key elements of study design early in the paper - Yes, key elements of study design are presented early in the method section. Page 7.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection - Yes, found in pages 7 to 10 of the manuscript.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up - Eligibility criteria, and sources and methods of selection of participants are found in pages 7 and 8 of the manuscript
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed - not relevant *Case-control study*—For matched studies, give matching criteria and the number of controls per case -not relevant
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable - Partly missing, but see page 10 to 13 for information about outcomes and predicors.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias - Missing in the manuscript
Study size	10	Explain how the study size was arrived at - Page 8 in the manuscript
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why - Not relevant, since this is a study protocol article

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding - Missing in the manuscript
		(*b*) Describe any methods used to examine subgroups and interactions - Missing in the manuscript
		(*c*) Explain how missing data were addressed - Missing in the manuscript
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed - Missing in the manuscript *Case-control study*—If applicable, explain how matching of cases and controls was addressed - not relevant *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy - not relevant
		(*e*) Describe any sensitivity analyses - missing

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed - not relevant
		(b) Give reasons for non-participation at each stage - not relevant
		(c) Consider use of a flow diagram - not relevant
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders - Not relevant
		(b) Indicate number of participants with missing data for each variable of interest - Not relevant
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) - Not relevant
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time - Not relevant
		Case-control study—Report numbers in each exposure category, or summary measures of exposure - not relevant
		Cross-sectional study—Report numbers of outcome events or summary measures - not relevant
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included - Not relevant
		(*b*) Report category boundaries when continuous variables were categorized - Not relevant
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period - Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses - Not relevant.
Discussion		
Key results	18	Summarise key results with reference to study objectives - not relevant
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias -not relevant
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence -not relevant
Generalisability	21	Discuss the generalisability (external validity) of the study results - not relevant

Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based - Yes, found in page 15 in the manuscript

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.