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Research paper

Mild-to-moderate iodine deficiency and symptoms of emotional distress and depression in pregnancy and six months postpartum – Results from a large pregnancy cohort

Anne Lise Brantsæter [a,*], Susan Garthus-Niegel [b,c,d], Ragnhild Eek Brandlistuen [b], Ida Henriette Caspersen [e], Helle Margrete Meltzer [a], Marianne Hope Abel [f]

[a] Division of Climate and Environmental Health, Norwegian Institute of Public Health, Oslo, Norway
[b] Department of Child Health and Development, Norwegian Institute of Public Health, Oslo, Norway
[c] Institute for Systems Medicine (ISM) and Faculty of Medicine, Medical School Hamburg, Hamburg, Germany
[d] Institute and Policlinic of Occupational and Social Medicine, Faculty of Medicine, Technische Universität Dresden, Dresden, Germany
[e] Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway
[f] Department of Physical Health and Ageing, Norwegian Institute of Public Health, Oslo, Norway

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ABSTRACT

Background: The relationship between iodine intake and depression is unknown. The aim of the present study was to investigate whether iodine intake was associated with symptoms of perinatal emotional distress and depression in a mild- to moderately iodine deficient population.

Methods: The study population comprised 67,812 women with 77,927 pregnancies participating in the Norwegian Mother, Father and Child Cohort Study. Self-reported emotional distress and depressive symptoms were reported in pregnancy and at six months postpartum. Iodine intake was assessed by a food frequency questionnaire in mid-pregnancy. Urinary iodine concentration (UIC) was available for 2792 pregnancies.

Results: The median iodine intake from food was 121 μg/day and the median UIC was 68 μg/L. The prevalence of high scores for emotional distress was 6.6 % in pregnancy and 5.8 % six months postpartum, and for high scores on postpartum depression it was 10.3 %. In non-users of iodine supplements (63 %), a low maternal iodine intake from food (lower than ~100–150 μg/day) was associated with increased risk of high scores of emotional distress and depression both in pregnancy and six months postpartum ($p < 0.001$). Iodine supplement use was associated with increased risk of high scores of emotional distress in pregnancy compared to no supplement use or use of supplements without iodine.

Limitations: Observational design, self-report information, and short scales to assess symptoms of emotional distress and depression.

Conclusion: A low habitual iodine intake was associated with increased prevalence of perinatal emotional distress and depression. The potential non-beneficial effect of iodine supplements may have biological explanations. More studies are needed.

1. Introduction

Perinatal depression is depression that occurs during or after pregnancy and is one of the most common complications in pregnant or postpartum populations affecting around 10–15 % of all women giving birth (Stuart-Parrigon and Stuart, 2014; Underwood et al., 2016). It includes depressive episodes occurring prenatally, i.e., during pregnancy, or postnatally in the first year after childbirth (Stuart-Parrigon and Stuart, 2014). Perinatal depression reduces maternal quality of life (Papamarkou et al., 2017), increases the risk of adverse pregnancy outcomes (Goodman et al., 2011; Grigoriadis et al., 2018), and unfavourably affects child cognitive and social-emotional development (Curry et al., 2019; Junge et al., 2017; Martini et al., 2017; Rogers et al., 2020). Risk factors of perinatal depression include psychosocial stressors e.g.,

* Corresponding author at: Division of Climate and Environmental Health, Department of Food Safety, Norwegian Institute of Public Health, PO Box 222 Nydalen, NO-0213 Oslo, Norway.
E-mail address: annelise.brantsaeter@fhi.no (A.L. Brantsæter).

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working conditions, single status, lack of support and domestic violence (Karl et al., 2020; Lancaster et al., 2010; Schaber et al., 2020; Sorbo et al., 2014) and medical and biological risk factors e.g., hormone sensitivity, history of depression and previous stillbirth (Wikman et al., 2020).

Iodine is an essential micronutrient and an integral building block of the thyroid hormones. The thyroid hormones regulate multiple metabolic processes that are important in growth, metabolism, and reproduction. They also play an important role in brain development in children, and they modulate metabolic activity in the adult brain (Bernal, 2007). Worldwide, iodine deficiency is the most common cause of all thyroid disorders, including hypothyroidism, while in iodine sufficient areas, autoimmune thyroiditis is the most common cause of thyroid failure (Chiovato et al., 2019). Patients with thyroid disorders more often report anxiety and depression than the general population (Samuels, 2014). However, the association between thyroid dysfunction and depressive symptoms is unclear as studies have generated conflicting results (Loh et al., 2019; Wildisen et al., 2020). Hypothyroidism and subclinical hypothyroidism are more prevalent in women than in men and the symptoms include fatigue, weakness, and depression (Chiovato et al., 2019). In women, thyroid dysfunction has also been linked to perinatal depression (Dama et al., 2016), though most studies have focused on postpartum depression only (Minaldi et al., 2020; Sylvén et al., 2013). While severe iodine deficiency and a depleted thyroidal hormone store have detrimental effects on foetal neurodevelopment (Pharoah et al., 2012; Zimmermann, 2016), the potential effect on maternal mental health is less known. No studies to date have examined the association between iodine intake and symptoms of perinatal emotional distress and depression in a mild-to-moderately iodine deficient population. As iodine requirements increase during pregnancy and lactation (Zimmermann, 2016), women of childbearing age are particularly vulnerable to adverse consequences of insufficient iodine intake.

In the present study, we use data from the Norwegian Mother, Father and Child Cohort Study (MoBa), which is a large pregnancy cohort with detailed information about self-reported food intake, supplement use, and mental health. We have previously shown that women in MoBa were mild-to-moderately iodine deficient according to the WHO criteria (World Health Organization et al., 2007), and that maternal iodine intake was associated with thyroid hormone concentrations (Abel et al., 2018), sub-fecundity and adverse pregnancy outcomes (Abel et al., 2020), and poorer child neurocognitive development at ages 3 and 8 years (Abel et al., 2019; Abel et al., 2017).

The aim of the current study was to examine the potential associations between iodine intake and symptoms of perinatal emotional distress and depression during pregnancy and the postpartum period in a population with mild-to-moderate iodine deficiency.

2. Methods

2.1. Subjects and study design

This study is based on MoBa, a prospective population-based pregnancy cohort conducted by the Norwegian Institute of Public Health (Magnus et al., 2016). Women pregnant in their first trimester were recruited from all over Norway during years 1999 to 2008 and were asked to answer questionnaires at regular intervals during pregnancy and after birth. Pregnancy and birth records from the Medical Birth Registry of Norway (MBRN) are linked to the MoBa database (Irgens, 2000). The women consented to participation in 41 % of the pregnancies. The cohort now includes 114,500 children, 95,200 mothers, and 75,200 fathers. The current study is based on version 12 of the quality-assured data files released for research in January 2019 and restricted to women recruited from 2002 to 2008 because the MoBa food frequency questionnaire (FFQ) was included in the data collection from March 2002.

Women were eligible for inclusion in the current study if they were registered in MBRN with a singleton birth and had responded to two questionnaires during pregnancy (gestational weeks (GW) 17 and 22). The first questionnaire assessed information about health and socio-demographic information, the second assessed of intakes of food and dietary supplements. We excluded pregnancies with reported use of thyroid medication at any time during pregnancy (1.8 %). Given the large sample size and low rates of missing values ($\leq$5 %), only pregnancies with information on all covariates were included. Approximately 15 % of women participate in MoBa with more than one pregnancy, and the final study population comprised 77,927 pregnancies (67,812 women) with data during pregnancy and data on one or more outcome measure (Fig. 1). Data on urinary iodine concentration (UIC) were available in a subsample of 2792 pregnancies and obtained from spot urine samples donated at the time of the routine ultrasound examination in GW 18.

2.2. Ethics approval and consent to participate

MoBa is conducted according to the guidelines laid down in the declaration of Helsinki and written informed consent was obtained from all participants. The establishment and data collection in MoBa were previously based on a license from the Norwegian Data protection agency and approval from The Regional Committee for Medical Research Ethics and it is now based on regulations related to the Norwegian Health Registry Act. The current study was approved by The Regional Committee for Medical Research Ethics South-East Norway (REK 2014/2211).

2.3. Exposure variables: iodine from food, iodine supplements, and urinary iodine concentration

The MoBa FFQ is semi-quantitative and specifically developed and validated for pregnant women in MoBa and was used from February 2002 and onwards (Brantsaeter et al., 2008; Meltzer et al., 2008). The FFQ included questions about intake of 255 food items in addition to meal patterns and use of dietary supplements. Participants were asked to report their average intake since becoming pregnant (GWs 0–22). We converted frequencies to food amounts using standard portion sizes and calculated iodine intake using iodine concentration data reported from Norwegian food items. The FFQ also asked about name, frequency and amount of dietary supplements. Food and nutrient intakes, including iodine intake from food and iodine-containing dietary supplements assessed by the FFQ have been validated in a subsample of 119 MoBa participants and showed good agreement with a 4-days weighed food dairy and 24-h urinary iodine excretion (Brantsaeter et al., 2008; Brantsaeter et al., 2007; Brantsaeter et al., 2009).

Dietary supplement use was also reported in the first MoBa questionnaire and we categorised initiation of supplement use in four categories (never, week 0–26 before pregnancy, GW 0–12 and GW >12). As we did not have information about supplement use after birth, we examined associations between iodine supplement use and symptoms of emotional distress or depression only for the outcome assessed in pregnancy (i.e., emotional distress).

Spot urine samples were collected at the time of the routine ultrasound examination offered free of charge to all pregnant women in Norway around GW 18. Details about analysis of urinary iodine and creatinine are reported in the Supplementary material.

2.4. Symptoms of perinatal emotional distress and depression

We calculated symptoms of emotional distress in GW 17 and six months postpartum using the five-item short version of the Hopkins Symptom Checklist (HSCL-5). This scale is designed to measure emotional distress in terms of symptoms of anxiety and depression, and the HSCL-5 correlates highly with the full 25 item HSCL (Pearson's correlation = 0.92) (Strand et al., 2003; Tambs and Moum, 1993). The

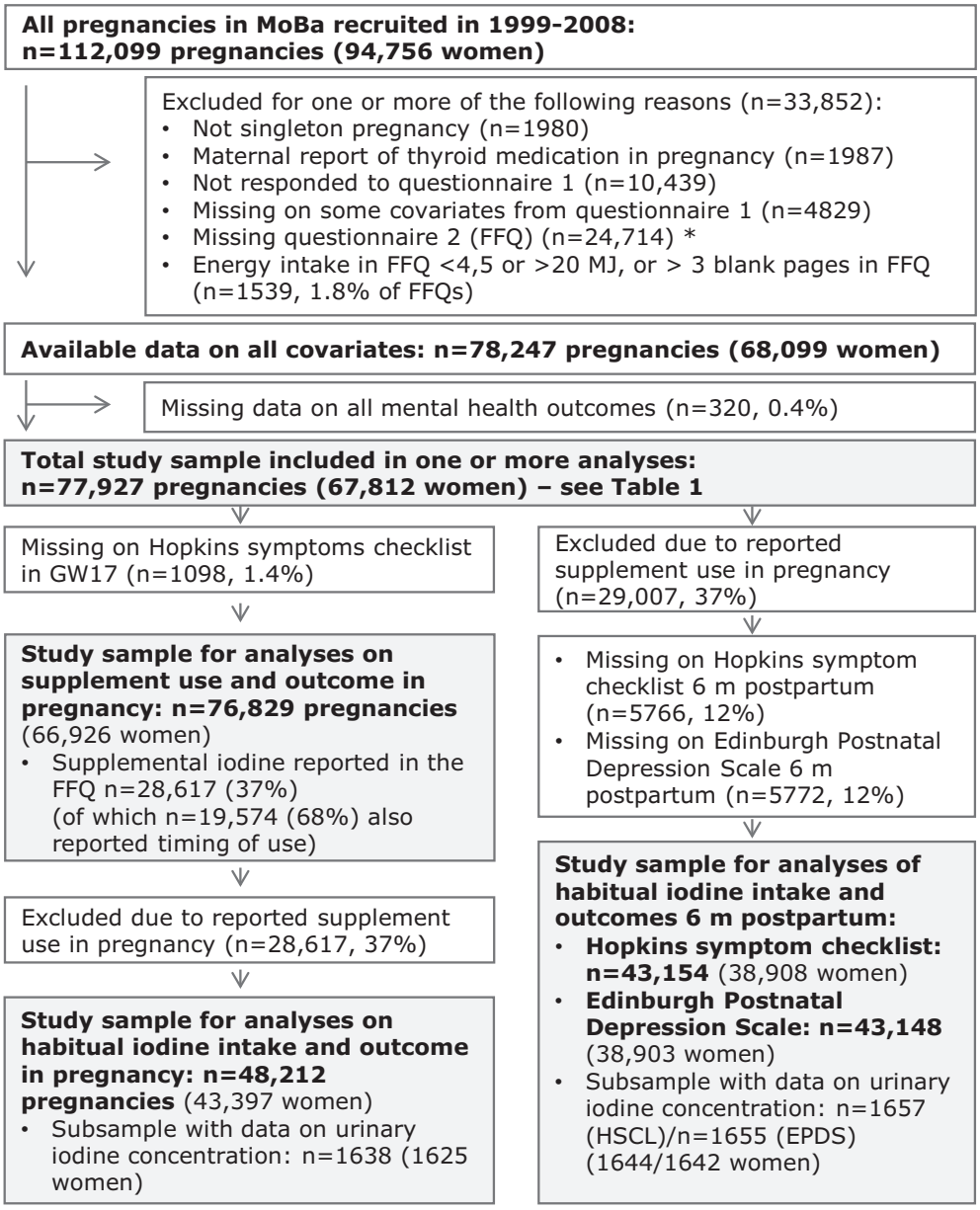

Fig. 1. Flow chart of inclusion. Only participants with complete data on covariates were included (4.8 % had missing values on one or more covariates).
* The food frequency questionnaire (FFQ) was in use from 2002.

HSCL-5 consists of five questions: "Have you been bothered by any of the following during the last two weeks?": (1) feeling fearful, (2) nervousness or shakiness inside, (3) feeling hopeless about the future, (4) feeling blue, and (5) worrying too much about things. The response options are a four-point scale with 0 = not bothered, 1 = a little bothered, 2 = quite bothered, and 3 = very bothered.

We calculated symptoms of postpartum depression at six months postpartum using six items from the Edinburgh postnatal depression scale (EPDS) (Cox et al., 1987). The MoBa questionnaire included the following six items: "Have you experienced any of the following feelings during the last week": (1) blamed yourself unnecessarily when things went wrong, (2) have been anxious or worried for no good reason, (3) have been scared or panicky for no very good reason, (4) have been so unhappy that you have had difficulty sleeping, (5) felt sad or miserable, (6) have been so unhappy that you have been crying. We recoded the answers to a scale ranging from 0 to 3 on each item, with 0 = no, never, 1 = not very often, 2 = yes, now and then, and 3 = yes, almost all of the time. The sum of the six items correlated at $r = 0.961$ with the full (ten item) version of the EDPS, and at $r = 0.963$ with a 5-item short version developed in Norway (Eberhard-Gran et al., 2007; NIPH, 2021).

We calculated mean symptom scores for HSCL-5 and EPDS. Reports with missing answers to three or more items from an instrument were recoded as missing. High emotional distress was defined as mean symptom score at 2.0 or higher on the HSCL-5 items (Strand et al., 2003). This cut-off has previously been shown to have 68 % sensitivity and 96 % specificity when using the Medical Health Index as the criterion and the HSCL-5 as the test variable (Kvalevaag et al., 2014; Strand et al., 2003). For the EPDS we used a mean symptom score with a cut-off at 1.3 or higher to define postnatal depression. This corresponds to a cut-off on the full EPDS at sum score 13 and indicates a moderate level of depression (Eberhard-Gran et al., 2007).

In the current study sample, the Cronbach's alpha for HSCL-5 was 0.80 in GW 17 and 0.84 at six months postpartum, and 0.83 for the EPDS at six months postpartum.

2.5. Depression prior to pregnancy

The MoBa baseline questionnaire included questions about a number of chronic illnesses and health problems, including separate questions about anxiety and depression at any time before pregnancy.

2.6. Covariates

Covariates were included in the statistical models based on existing literature and a directed acyclic graph (DAG) shown in Supplementary material Fig. S1. Maternal age at time of birth was obtained from the birth registry. Maternal pre-pregnancy body mass index (BMI), education (≤12, 13–16, ≥17 years), marital status (married/cohabitant: yes/no), parity (previous pregnancies ≥22 weeks: 0, 1, ≥2), history of chronic illness (asthma, diabetes, inflammatory bowel disease, rheumatic disease, epilepsy, multiple sclerosis, or cancer before or during pregnancy: yes/no), use of in vitro fertilization in current pregnancy (yes/no), and use of a folic acid supplement within the interval from 4 weeks before to 8 weeks after conception (yes/no) were obtained from questionnaire 1 (GW 17). Maternal energy intake, fibre intake (as marker of a healthy diet), and total intake of the omega-3 fatty acids EPA and DHA were calculated from the FFQ (GW 22). Also, use of dietary supplements other than the ones commonly recommended for pregnant women (i.e., other than vitamin D, folic acid, and iron) was obtained from the FFQ (yes/no). Information on smoking in pregnancy was obtained from questionnaire 1 and, if available, questionnaires 3 (GW 30) and 4 (child's age 6 months) (three categories: no reported smoking in pregnancy, reported occasional smoking or stopped smoking before GW 12, and daily smoking at any time in pregnancy and had not stopped smoking before GW 12).

2.7. Statistical analyses

Statistical analyses were performed in STATA (version 16.0; Stata Corp., College Station, TX).

Self-selection is likely to have resulted in fewer women with pre-existing depressive symptoms in MoBa than in the general population and higher loss to follow up in women with postpartum depression. To compensate for this, we used dichotomous outcome measures and estimated odds ratios from logistic regression models as the effect measures in our study which removes the potential bias from this type of outcome-dependent selection according to statistical theory (Greenland and Pearl, 2011).

Associations between iodine from food and the outcomes were modelled flexibly with restricted cubic splines with four knots at percentiles 5, 35, 65, and 95. In our study population, 14 % of the women were included with more than one pregnancy and we specified person clusters by using the option vce (cluster person ID) in models in STATA, which relaxes the assumption of independence of the observations and produces robust estimates of variance. *P*-values are reported for overall associations between continuous exposures and outcomes by testing the coefficients of all spline transformations equal to zero. In addition, tests for non-linearity were performed by testing the coefficients of the second and third spline transformations equal to zero. Covariates were included in the models based on DAGs. Continuous covariates (e.g., maternal age, BMI, energy intake etc.) were modelled flexibly by restricted cubic splines if there was evidence of non-linear associations. If not, they were modelled linearly.

The impact of iodine from supplements is likely to depend on habitual iodine intake from food, timing of introduction, dose, frequency, and duration of use (Bath, 2019). We therefore examined the associations between iodine intake from food and the outcomes exclusively in non-iodine supplement users.

The association between use of iodine-containing supplements with emotional distress was only examined in pregnancy (HSCL-5 in GW 17) and was studied in the total study population. Iodine supplement use reported in pregnancy was modelled as *any use of iodine-containing supplements* in GW 0–22 and *timing of first reported use* (never, started before conception, started in GW 0–12, started in GW 13–22). Potential interactions by iodine intake from food was explored including an interaction-term between iodine from food (modelled by restricted cubic splines) and the supplement use variable. Potential interactions were examined by testing all interaction coefficients equal to zero. If the interaction terms were not statistically significant, iodine from food was not included in the final models.

Women in the control group were all non-users of iodine-containing supplements. In a sensitivity analysis, we restricted the control group to women who had reported use of multi-vitamin-mineral supplements (without iodine) other than those routinely recommended to all pregnant women. The use of this restricted control group could control for the behaviour of taking an extra vitamin/mineral supplement and could to some extent also control for other nutrients in the multisupplements.

In sensitivity analyses, we excluded women who had reported depression or anxiety as an illness or health problem at any time before pregnancy (7.7 %) in models for iodine intake from food and supplements.

Associations between UIC and the outcomes were modelled flexibly by the use of restricted cubic splines with three knots at percentiles 10, 50, and 90, excluding iodine supplement users.

3. Results

3.1. Iodine exposures by participant background characteristics

The mean (SD) age at the time of birth in the study population was 30.2 (4.5) years. The median calculated iodine intake from food was 121 μg/day (IQR: 89–161 μg/day). Seventy four percent had an iodine intake from food lower than the estimated average requirement (EAR) of 160 μg/day for pregnant women (Food and Nutrition Board and Institute of Medicine, 2001), and only 4.6 % reached the recommended intake in pregnancy set by the WHO (i.e., ≥250 μg/day) (Andersson et al., 2007) when not including iodine from supplements. Supplemental iodine originated almost exclusively from multi-nutrient supplements, reported by 37.2 % of women.

The median UIC (measured in $n = 2792$) was 68 μg/L (IQR: 35–116 μg/L) and 37 % had UIC < 50 μg/L. The median UIC in non-users of iodine-containing supplements was 58 μg/L (IQR: 32–100 μg/L). This is well below the WHO cut-off for adequate iodine intake in groups (i.e., median UIC ≥ 150 μg/L for pregnant women and median ≥ 100 μg/L for non-pregnant) (Andersson et al., 2007).

Overall, the differences in iodine intake from food, use of iodine-containing supplements, and UIC by background characteristics were marginal (Table 1). The Spearman correlation between iodine from food (μg/d) and UIC (μg/g creatinine) in non-supplement users was $r = 0.31$ (95 % CI 0.27, 0.35). Neither iodine intake from food nor UIC was associated with use of vitamin D or folic acid supplements.

Iodine intake and UIC did not differ between the participants in the study sample and those excluded due to missing information on one or more of the independent covariates ($n = 3965$, 4.8 %), whereas use of iodine-containing supplements was slightly lower in those excluded (34.5 vs. 37.2 %, $p < 0.001$). Also, iodine intake from food did not differ significantly between the women with available UIC measurements (3.6 % of the total study population) and women without UIC measurement (median difference 0.2 μg/day, $p = 0.90$). However, iodine supplement use in GW 0–22 was marginally higher in the subgroup with available UIC than in the remaining study population (41 % vs. 37 %, $p < 0.001$).

Dietary determinants of iodine intake and urinary iodine are shown in Supplementary Table S1. Use of iodine-containing supplements and milk/yoghurt intake were important determinants of iodine intake and urinary iodine.

Table 1
Characteristics of the study population (n = 77,927) including estimated differences in iodine exposures.

	Study sample	Iodine from food, μg/day	Iodine supplement in GW 0–22	UIC[a], μg/L
	%	β (95 % CI)[b]	Odds Ratio (95 % CI)[b]	β (95 % CI)[b, c]
Maternal age at birth, years				
<25	11	1 (−1,2)	0.87 (0.83, 0.92)	1 (−10,12)
25–34	72	Ref.	Ref.	Ref.
≥35	17	0 (−2,1)	1.16 (1.12, 1,21)	6 (−2, 14)
Pre-pregnancy BMI, kg/m^2				
<18.5	2.9	0 (−2,3)	1.14 (1.04, 1.24)	4 (−12,20)
18.5–24.9	66	Ref.	Ref.	Ref.
25–30	22	−2 (−3,−1)	0.93 (0.90, 0.97)	2 (−5, 9)
>30	9.5	−5 (−6, −3)	0.95 (0.90, 1.00)	9 (−2, 19)
Parity				
0	47	Ref.	Ref.	Ref.
1	36	3 (2, 4)	0.69 (0.67, 0.72)	4 (−3,10)
2 or more	17	8 (7, 10)	0.55 (0.52, 0.57)	2 (−7, 11)
Maternal education				
≤12 y	30	Ref.	Ref.	Ref.
13–16 y	43	1 (0,2)	1.16 (1.11, 1.20)	0 (−7, 7)
>16 y	27	1 (−1, 2)	1.17 (1.12, 1.22)	1 (−7, 10)
Married/ cohabitant				
Yes	97	Ref.	Ref.	Ref.
No	3.2	2 (−1, 4)	1.02 (0.93, 1.11)	4 (−20, 28)
Smoking in pregnancy				
No	79	Ref.	Ref.	Ref.
Occasionally	16	−2 (−3, −1)	0.99 (0.95, 1.03)	−8 (−16, 1)
Daily	5.0	−1 (−3,1)	0.88 (0.82, 0.95)	−14 (−29, 1)
Chronic illness				
No	90	Ref.	Ref.	Ref.
Yes	10	−5 (−7, −4)	1.18 (1.12, 1.23)	1 (−9, 11)
Household income				
Low	26	3 (2, 4)	0.94 (0.90, 0.97)	3 (−4, 10)
Medium	41	Ref.	Ref.	Ref.
High	30	−5 (−6, −4)	1.02 (0.98, 1.05)	1 (−6, 8)
Missing	2.6	6 (3, 9)	0.91 (0.83, 1.00)	−2 (−23, 19)
		Median (95 % CI)	%	Median (95 % CI)
All participants	100	121 (121,122)	37	68 (65, 71)
Iodine from food, μg/day[d]				
<75	16	61 (60, 61)	37	51 (44, 57)
75–149.9	54	112 (111,112)	37	68 (64, 71)
≥150	31	187 (187, 188)	37	78 (73, 83)
Vitamin D supplement	77	123 (122,123)	47	70 (67, 73)
Folic acid before/ early pregnancy	73	121 (120,121)	42	70 (66, 73)

Abbreviations: UIC, Urinary Iodine Concentration; CI, Confidence interval.
[a] Urinary iodine concentration (UIC) was measured in a subsample of n = 2792 pregnant women in mean gestational week 18.5 (SD: 1.3).
[b] Estimated betas (β) or odds ratios based on regression models mutually adjusted for all covariates. Betas (β) represent estimated changes the *median* value modelled by quantile regression.
[c] Models on UIC included all covariates and, in addition, iodine supplement use.
[d] Iodine intake in the first half of pregnancy calculated from the food frequency questionnaire.

3.2. Associations between iodine exposures and perinatal emotional distress and depression

In non-users of iodine-containing supplements, a low habitual iodine intake from food was associated with increased prevalence of high scores on perinatal emotional distress and depression (high HSCL-5 scores in pregnancy and high HSCL-5 and EPDS scores at six months postpartum) in both crude and adjusted models. The associations were non-linear and iodine intakes lower than approximately 100–150 μg/day were associated with higher prevalence of all the three outcomes of perinatal emotional distress and depression ($p < 0.001$, Fig. 2 and Table 2). UIC was not associated with high scores on perinatal emotional distress and depression in GW 17 or at six months postpartum (Supplementary Fig. S2).

Finally, we examined the associations between iodine intake and a high score on HSCL-5 at six months postpartum controlling for the score on HSCL-5 in GW 17 (Supplemenatry Fig. S3). The prevalence of high HSCL-5 postpartum was still significantly higher for iodine intake in the lower end, i.e., lower than 100 μg/day, but in comparison to Fig. 2B, adjusting for emotional distress in pregnancy attenuated the association.

The results did not change in the sensitivity analysis where we applied a more restrictive filter for energy intake (range P25–P75). This indicated that the results were not influenced by potential over- or under-reporting in the FFQ. Likewise, in another sensitivity analysis, the results did not change when we excluded participants with a very low habitual iodine intake (<50 μg/day, 4 % of women). Excluding women with a self-reported history of anxiety and/or depression before pregnancy, did not change the results either (Supplementary Table S2).

Use of iodine-containing supplements was associated with a small, but significant increase in the risk of scoring high on HSCL-5 GW 17 (Table 3). The adjusted odds ratio of high HSCL-5 (scores ≥2.0) was 1.19 (95 % CI 1.12, 1.27) in iodine supplement users compared to non-users. The increased odds ratios were similar whether supplement use was initiated before the start of pregnancy or in pregnancy. Restricting the control group to participants who had reported use of at least one vitamin/mineral supplement without iodine, other than those recommended routinely in pregnancy care, resulted in only marginal attenuation of the estimates (Table 3). Excluding women with a previous history of anxiety and/or depression slightly reduced the magnitude of the effect estimates, but they were still within the confidence interval of the main analyses (Supplementary Table S3).

4. Discussion

4.1. Main finding

The main finding in this large pregnancy cohort is that a low habitual iodine intake from food (lower than ~100–150 μg/day) was associated with an increased risk of scoring high on symptoms of perinatal emotional distress and depression both in pregnancy and after childbirth. The association with symptoms of emotional distress (HSCL-5) at six months postpartum was evident also after adjusting for HSCL-5 assessed in pregnancy, suggesting that a low habitual iodine intake from food may contribute to increased symptoms of postpartum emotional distress and depression. However, the effect estimates were

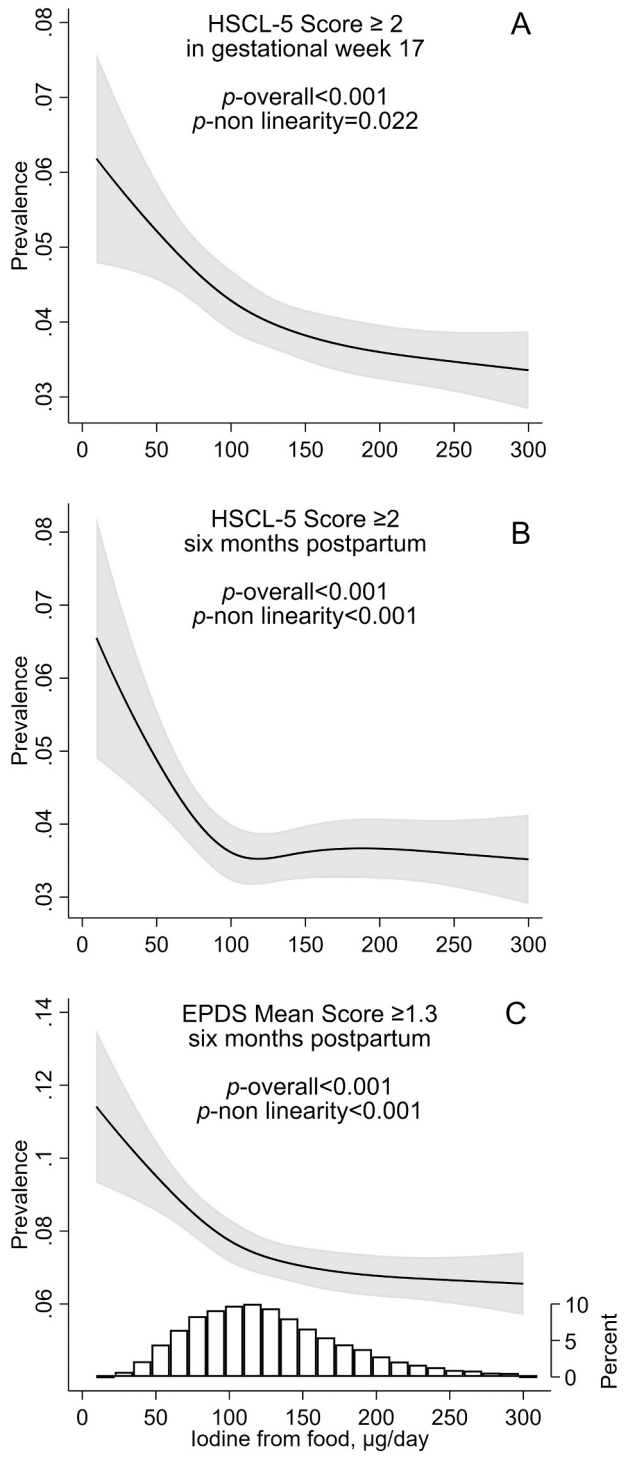

Fig. 2. Adjusted associations between habitual iodine intake and estimated prevalence of high scores for emotional distress and depression. Sample size in pregnancy was n = 48,212 (A), and six months postpartum it was n = 43,154 (B) and n = 43,148 (C). Associations were modelled in non users of iodine supplements by logistic regression adjusting for age, education, BMI, parity, smoking, energy intake, and fibre intake. Covariates were set to their mean value. For estimated odds ratios in crude and adjusted models, see Table 3. Abbreviations: BMI, body mass index; GW, gestational week; HSCL, Hopkins Symptoms Checklist; EPDS, Edinburgh Postnatal Depression Scale.

modest. Contrary to the result for iodine from food, the use of iodine-containing supplements was associated with increased prevalence of emotional distress in GW 17.

4.2. Associations of iodine exposures with perinatal emotional distress and depression

During pregnancy and breastfeeding, iodine requirements increase, and the women in MoBa had an iodine intake from food well below the recommended intake. Iodine intake was only marginally associated with socioeconomic status and not associated with a healthy dietary pattern. The results showed that having a low iodine intake from food was associated with scoring above cut-offs for emotional distress and depression, both in pregnancy and postpartum. For example, a calculated iodine intake of 75 µg/day was associated with an odds ratio 1.26 for scoring high on HSCL-5 in pregnancy compared to an intake at the estimated average requirement (160 µg/day). UIC was not significantly associated with the outcomes, but the confidence intervals were wide and thus, these analyses were not adequately powered to identify small effects. A single spot-UIC is a poor measure of iodine status at an individual level (Andersson et al., 2007), and UIC was only measured in a subsample of MoBa.

The non-consistent results for iodine from food and iodine from supplements in our study may be explained by a different effect of long-term habitual iodine intake from food versus supplemental iodine. In mild-to-moderate iodine deficiency, the body adapts to the low iodine intake, for example by increasing the size of the thyroid. When iodine intake is increased by a supplement or by salt iodization it may take months to adapt to the new intake level, and previous studies have documented a temporary inhibition of thyroid hormone production (Abel et al., 2018; Moleti et al., 2011; Rebagliato et al., 2010). Also, many supplements contain quite high amounts of iodine. Most of the supplements reported contained about 150 µg iodine per daily dose which for most women represented more than a doubling of their daily iodine intake. We included women in the supplement-group if they had reported any use of iodine-containing supplements in GW 0–22. Most of the women had used the supplements only short time or intermittently, and thus, they may not have fully adapted to a new intake level. Reverse causation could be another explanation for the non-consistent results for iodine from food and iodine from supplements in our study, as women with emotional distress might be more prone to use multivitamin/−mineral-supplements (Marques-Vidal et al., 2009). However, we tried to control for this by restricting the control group of non-users of iodine supplements to women who reported use of other multi-vitamin-mineral supplements without iodine, and the association remained largely unchanged (Table 3). Similarly, there is evidence that dietary quality is inversely associated with perinatal emotional distress and depression (Silva et al., 2019) but the long-term association may be bidirectional. Although iodine intake is independent of dietary quality, we cannot exclude the possibility that emotional distress affects iodine intake. We adjusted the analyses for many potential confounders but did not adjust for maternal history of depression in our main analyses because this may be caused by insufficient iodine intake earlier in life. However, in sensitivity analyses, excluding women with a history of anxiety and depression did not change the results significantly.

To the best of our knowledge, only two small studies have previously examined the associations between maternal iodine intake and perinatal emotional distress and depression (Bouhouch et al., 2014; Wang et al., 2020). In both studies, iodine supplement use was associated with higher EDPS scores in the postpartum period, which is consistent with our results although there are major differences in study design and iodine intakes. In a double blind randomized controlled trial in moderate-to-severely iodine deficient lactating women (median UIC: 35 µg/L), mothers supplemented with a single dose of 400 mg iodine within 8 weeks after birth had higher median EDPS scores at 12 months postpartum (9.0, 95 % CI 7, 11) than non-supplemented mothers (6.5, 95 %

Table 2
Habitual iodine intake from food and risk of scoring high on symptoms of emotional distress and depression.

	HSCL-5 score ≥ 2 in GW 17		HSCL-5 score ≥ 2 six months postpartum		EPDS score ≥ 1.3 six months postpartum	
	Crude model	Adjusted model[a]	Crude model	Adjusted model[a]	Crude model	Adjusted model[a]
N (pregnancies)	48,212	48,212	43,154	43,154	43,148	43,148
n with high score (%)	3046 (6.3)	3046 (6.3)	2358 (5.5)	2358 (5.5)	4341 (10.1)	4341 (10.1)
Iodine from food, μg/d:	Odds ratio (95 % CI)	Odds ratio (95 % CI)	Odds ratio (95 % CI)	Odds ratio (95 % CI)	Odds ratio (95 % CI)	Odds ratio (95 % CI)
25	2.22 (1.83, 2.68)	1.57 (1.30, 1.90)	2.09 (1.69, 2.59)	1.65 (1.33, 2.04)	1.96 (1.67, 2.31)	1.59 (1.35, 1.88)
50	1.77 (1.56, 2.01)	1.41 (1.24, 1.60)	1.59 (1.38, 1.84)	1.36 (1.18, 1.57)	1.61 (1.44, 1.80)	1.40 (1.26, 1.57)
75	1.42 (1.29, 1.56)	1.26 (1.14, 1.39)	1.22 (1.10, 1.36)	1.13 (1.01, 1.26)	1.33 (1.22, 1.45)	1.24 (1.14, 1.35)
100	1.19 (1.08, 1.30)	1.14 (1.04, 1.26)	1.01 (0.91, 1.12)	0.99 (0.89, 1.10)	1.14 (1.05, 1.23)	1.12 (1.03, 1.22)
125	1.07 (1.01, 1.13)	1.07 (1.01, 1.13)	0.97 (0.90, 1.03)	0.97 (0.91, 1.04)	1.05 (1.00, 1.10)	1.05 (1.00, 1.11)
150	1.01 (1.00, 1.03)	1.02 (1.00, 1.03)	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)
160 (reference[b])	1	1	1	1	1	1
175	0.99 (0.97, 1.00)	0.98 (0.97, 0.99)	1.01 (0.99, 1.03)	1.01 (0.99, 1.02)	0.99 (0.98, 1.00)	0.99 (0.97, 1.00)
200	0.98 (0.95, 1.01)	0.95 (0.92, 0.99)	1.02 (0.98, 1.06)	1.01 (0.97, 1.05)	0.98 (0.96, 1.01)	0.97 (0.94, 1.00)
225	0.98 (0.93, 1.03)	0.94 (0.88, 0.99)	1.03 (0.96, 1.10)	1.00 (0.93, 1.07)	0.99 (0.94, 1.04)	0.96 (0.91, 1.01)
250	0.99 (0.91, 1.07)	0.92 (0.84, 1.00)	1.03 (0.94, 1.14)	0.99 (0.89, 1.09)	0.99 (0.92, 1.07)	0.95 (0.88, 1.03)
300	1.00 (0.87, 1.15)	0.89 (0.76, 1.03)	1.04 (0.88, 1.23)	0.96 (0.81, 1.15)	1.00 (0.88, 1.14)	0.94 (0.82, 1.07)
p-overall	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
p-non-linearity	$p < 0.001$	$p = 0.022$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$

Iodine supplement users were not included in the sample.
Abbreviations: GW, gestational week; HSCL, Hopkins Symptoms Checklist; EPDS, Edinburgh Postnatal Depression Scale.
[a] The associations were modelled by multivariable logistic regression and adjusted for age, BMI, parity, education, smoking, energy intake, and fibre intake.
[b] 160 μg/day corresponds to the estimated average requirement for pregnant women (Food and Nutrition Board and Institute of Medicine, 2001).

Table 3
Iodine supplement use and risk of scoring high on emotional distress and depression in gestational week 17.

	n	Crude models		Adjusted models[a]		Matched controls[a, b]	
		Odds ratio (95 % CI)	*p*-value	Odds ratio (95 % CI)	*p*-value	Odds ratio (95 % CI)	*p*-value
N (pregnancies)		76,829 (100 %)		76,829 (100 %)		30,087 (100 %)	
n with high score on HSCL-5 (score ≥ 2)		5060 (6.6 %)		5060 (6.6 %)		1980 (6.6 %)	
Any iodine supplement use GW 0–20	28,617	1.12 (1.06, 1.19)	<0.001	1.19 (1.12, 1.27)	<0.001	1.17 (1.07, 1.28)	0.001
First report of iodine supplement							
Never (non-supplement user)	48,212 (13,187)	1 (ref.)		1 (ref.)		1 (ref.)	
Before pregnancy[c]	7380	1.00 (0.90, 1.10)	0.96	1.17 (1.05, 1.30)	0.003	1.14 (1.01, 1.28)	0.040
GW 0–12	7023	1.17 (1.06, 1.29)	0.001	1.20 (1.08, 1.32)	<0.001	1.17 (1.04, 1.31)	0.010
GW >12	5171	1.13 (1.01, 1.27)	0.030	1.17 (1.05, 1.31)	0.006	1.14 (1.00, 1.30)	0.046

[a] Models were adjusted for maternal age, BMI, parity, education, smoking in pregnancy, fibre intake, chronic illness, and in vitro fertilization.
[b] Restricting the reference group (non-users) to participants who reported use of one or more multivitamin/multimineral supplements in the food frequency questionnaire other than those routinely recommended in pregnancy care, but not any containing iodine.
[c] One to 26 weeks before conception.

CI: 6, 8), $p < 0.001$ (Bouhouch et al., 2014). In line with previous findings in MoBa (Abel et al., 2018) an observational study showed that pregnant women who reported daily intake of 150 μg supplemental iodine had a lower free thyroxine concentration than the non-users and reported that one month after birth, mean EDPS score was 5.0 (CI: 2.0, 8.0) in iodine supplements users, 3.5 (CI: 1.0, 7.0) and 3.0 (1.0, 7.0) in non-supplement users ($p = 0.030$) (Wang et al., 2020). Combined, these results indicate that an abrupt increase in iodine intake may trigger imbalances in the thyroid function that might affect mood.

In pregnant women, systematic reviews of longitudinal studies show that thyroid autoimmunity is associated with increased risk of developing perinatal depression (Dama et al., 2016; Minaldi et al., 2020). Thyroid autoimmunity and the presence of circulating thyroid antibodies increases in populations both when iodine intake falls below or above the recommended intake levels (Laurberg et al., 2010; Pedersen et al., 2003). Pregnancy induces increased turnover of maternal thyroxine due to metabolic changes and transplacental passage, which is why an adequate thyroidal iodine store and optimal thyroid function at the time pregnancy commences is crucial for maternal health and foetal development (Bath, 2019).

4.3. Strengths and limitations

The main strengths of this study include the large sample size including participants from all over Norway, and the extensive data collection. By including the HSCL-5, which measures both anxiety symptoms and depressive symptoms, i.e., emotional distress, and the EPDS, which primarily measures depressive symptoms, we were able to investigate possible associations with iodine intake more comprehensively. In addition, the HSCL-5 allowed us to capture both pregnancy and the postpartum period. This allowed us to cover larger portions of the perinatal period and even to consider assessment in pregnancy when examining the association between iodine intake and emotional distress in the postpartum period. Further, iodine intake from food and urinary iodine concentration did not differ much by maternal background factors including socioeconomic factors, age, BMI, and fibre as a proxy for a healthy diet, and this probably reduces the risk of residual or unmeasured confounding. Also, the pregnant women in MoBa were generally well-nourished, making confounding by other nutrient deficiencies less likely (von Ruesten et al., 2014). There was a large variation in iodine intake due to few dietary sources of iodine and the population could be defined as mild-to-moderately iodine deficient at a group level.

Iodine intake calculated by an FFQ is prone to misreporting and is a rather crude instrument for estimating intake of single nutrients. However, there was relatively good agreement between iodine intake by the FFQ and UIC, and iodine intake by the FFQ is a better marker of habitual iodine intake at the individual level than UIC in populations where salt is not an important iodine source. Although maternal iodine intake from

food was assessed in pregnancy, there is indication that it represents long-term habitual iodine intake prior to pregnancy (Abel et al., 2020).

The relatively low participation rate (41 %) in MoBa is a concern (Vejrup et al., 2021). Women participating in MoBa were older, had higher education and included fewer smokers than the general population of pregnant women (Biele et al., 2019). Since iodine intake does not differ much by education, age, and lifestyle, iodine intake is probably not a determinant of participation. On the other hand, self-selection is likely to have resulted in fewer women with pre-existing depressive symptoms in MoBa compared to the general population and higher loss to follow up in women with postpartum depression. By using odds ratios as the effect measure in our study, we removed the potential bias from this type of outcome-dependent selection as mentioned in the methods section. The presumed lower prevalence of symptoms of emotional distress and depression in our study population should thus not affect the generalizability of the results. Further limitations include the observational design and self-reported outcomes. Since MoBa assesses a multitude of constructs, symptoms of perinatal emotional distress and depression were only measured with short versions of the HSCL and EPDS, respectively. However, such short versions have previously shown to have very good psychometric properties and to correlate highly with their full versions. Hence, they have been suggested to replace the full version in large-scale questionnaire studies if necessary for the sake of parsimony (Eberhard-Gran et al., 2007; Strand et al., 2003; Tambs and Moum, 1993). Although we adjusted for potential confounding, unmeasured confounding might still exist, and no causal inferences should be made based on these results.

4.4. Clinical relevance and implications

Mild-to-moderate iodine deficiency is highly prevalent both in low- and high-income countries (Zimmermann and Andersson, 2021). In Norway, as in other countries, women of childbearing age, vegans, and vegetarians are particularly prone to inadequate iodine intake (Eveleigh et al., 2020; Garnweidner-Holme et al., 2017; Groufh-Jacobsen et al., 2020; Henjum et al., 2018). Furthermore, insufficient iodine intake is primarily a problem in countries that have not implemented universal salt iodisation as in the Nordic countries that used to rely on milk and saltwater fish as the main iodine sources (Adalsteinsdottir et al., 2020; Henjum et al., 2019; Nystrom et al., 2016). Although the potential increased prevalence of symptoms of emotional distress and depression during pregnancy and the postpartum period in mild-to-moderate iodine deficiency may be modest, it is highly relevant at the population level since iodine deficiency is so prevalent in young women and also, easily preventable.

5. Conclusions

This study is the first to indicate that insufficient maternal habitual iodine intake is associated with symptoms of perinatal emotional distress and depression. However, use of iodine supplements provided no benefit but was associated with higher prevalence of emotional distress and depression. Thus, the results must be interpreted with care. The study needs to be replicated by other well-powered studies in mild-to-moderately iodine deficient populations. Nonetheless, attention should be given to secure adequate habitual iodine intake in young girls and women of childbearing age.

CRediT authorship contribution statement

A.L.B., S.G—N., R.E.B., I.H.C., H.M.M. and M.H.A. were involved in conceptualization, planning of analyses, and writing the study protocol. M.H.A performed the statistical analysis and A.L.B. drafted the first version of the manuscript. All authors contributed to the interpretation of results, critically reviewed the manuscript, and approved the final manuscript.

Abbreviations

BMI	Body mass index
CI	Confidence interval
DAG	Directed acyclic graph
EDPS	Edinburgh Postnatal Depression Scale
FFQ	Food frequency questionnaire
GW	Gestational week
HSCL	Hopkins Symptoms Checklist
IQR	Interquartile range
MBRN	Medical Birth Registry of Norway
MoBa	Norwegian Mother, Father and Child Cohort Study
OR	Odds ratio
UIC	Urinary Iodine Concentration
TSH	Thyroid stimulating hormone
WHO	World Health Organization

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Conflict of Interest

M.H.A. was until Dec. 2019 employed by the Norwegian dairy company TINE SA, and she participated in this project as an industrial Ph.D.-student financed partly by TINE SA and partly by The Research Council of Norway. This project is designed, owned, and administered by The Norwegian Institute of Public Health (NIPH) and analysis of the data follow from protocol. All results of analysis in the project are to be published regardless of the results. TINE SA supported the project to raise awareness on the importance of iodine and to gain more knowledge about the potential health effects of milk in the Norwegian diet. Today, M.H.A. is a full-time researcher at the NIPH.

The other authors declare that they have no competing interests.

Data availability

The consent given by the participants does not open for storage of data on an individual level in repositories or journals. Researchers who want access to data sets for replication should apply to www.helsedata.no/en. Access to data sets requires approval from The Regional Committee for Medical and Health Research Ethics in Norway and an agreement with MoBa.

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Appendix A. Supplementary information

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