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Maternal selenium intake and selenium status during pregnancy in relation to preeclampsia and pregnancy-induced hypertension in a large Norwegian Pregnancy Cohort Study

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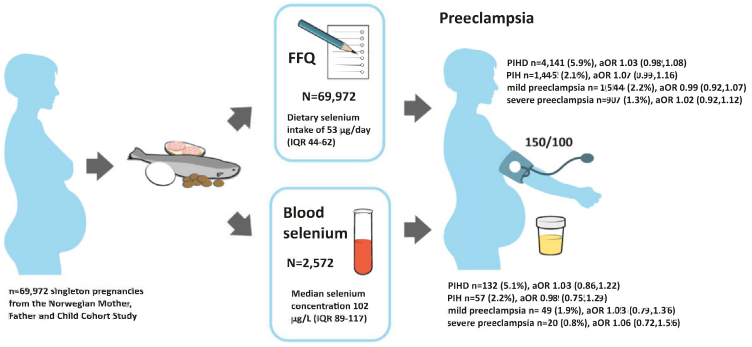
HIGHLIGHTS

- First population-based study on dietary selenium intake and preeclampsia.
- The largest study on selenium blood concentration and preeclampsia ($n = 2572$).
- Selenium intake and selenium status was not associated with preeclampsia.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Pregnancy-induced hypertensive disorders (PIHD), including preeclampsia, cause maternal and perinatal morbidity and mortality worldwide. Several studies have linked selenium supplementation and selenium status to the risk of preeclampsia, but there are no published prospective population-based studies examining associations between dietary selenium intake and preeclampsia.
Aim: To examine associations between selenium intake from diet and supplements and selenium blood status and PIHD incidence, with sub-analyses for pregnancy-induced hypertension (PIH) and preeclampsia, in a large pregnancy cohort.
Method: The study is based on 69,972 singleton pregnancies from the Norwegian Mother, Father and Child Cohort Study. Maternal dietary selenium intake was assessed with a validated, semi-quantitative food frequency questionnaire at about gestational week 22. Maternal selenium concentrations were measured in whole blood collected around gestational week 18 in a subset of 2572 women. Preeclampsia and PIH diagnosges were obtained from the Medical Birth Registry of Norway.

Abbreviations: BMI, body mass index; FFQ, food frequency questionnaire; MoBa, the Norwegian Mother, Father and Child Cohort Study; PIH, pregnancy-induced hypertension; PIHD, pregnancy-induced hypertensive disorders; RCT, randomised controlled trial; RDI, recommended daily intake; Se, selenium.

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Selenium supplementation
The Norwegian mother, father and child cohort study
MoBa

Results: Participants had a median dietary selenium intake of 53 μg/day (IQR 44–62). Dietary selenium intake was not significantly associated with PIHD (adjusted (a) OR 1.03, 95% CI 0.98, 1.08 per SD of selenium intake), pre-eclampsia or PIH. Threshold analyses for deciles of dietary selenium intake did not show any significant associations. Neither inorganic (aOR 1.01, 95% CI 0.98, 1.05) or organic selenium supplement intake (aOR 0.98, 95% CI 0.95, 1.02) or selenium blood status was significantly associated with PIHD (aOR 1.03, 95% CI 0.86, 1.22) or PIHD subgroups.

Conclusion: No significant associations were found between reported selenium intake from diet, or dietary supplements or whole-blood selenium status and PIHD in general or preeclampsia specifically. Hence, the results of this large population-based study, with selenium intake close to the recommended daily intake, do not support previous findings indicating a possible protective effect of selenium supplementation or selenium status with regard to preeclampsia incidence.

1. Introduction

Pregnancy-induced hypertensive disorders (PIHD) are the most common medical complication of pregnancy, affecting 10–15% of all pregnancies worldwide (Magee et al., 2015; Malik and Kumar, 2017; Shah and Gupta, 2019). PIHD include pregnancy-induced hypertension (PIH), defined as onset of hypertension (blood pressure > 140/90) after 20 weeks of gestation in previously normotensive women; and preeclampsia, diagnosed when hypertension and significant proteinuria develop after gestational week 20 (Shah and Gupta, 2019). Preeclampsia at the time of the current study was defined as severe when organs are significantly affected or when blood pressure exceeds 160/110 in association with proteinuria (Baha Sibai, 2005; Shah and Gupta, 2019). Preeclampsia affects 2–7% with regional differences and higher incidence in primiparous women (Baha Sibai, 2005; Burton et al., 2019). It is a major cause of maternal morbidity and mortality, as well as of perinatal death, preterm delivery and intrauterine growth restriction (Baha Sibai, 2005).

Preeclampsia is a multisystem disorder, commonly regarded as a state of oxidative stress (Mistry et al., 2008). Genetic, immunological and other factors, such as pre-existing maternal chronic diseases, are considered to interact in the modelling of inadequate spiral arterioles and abnormal placentation characterising early preeclamptic pregnancies. This leads to increased systemic vascular resistance, enhanced platelet aggregation, activation of the coagulation system and endothelial cell dysfunction (Baha Sibai, 2005; Burton et al., 2019; Mistry et al., 2008; Rana et al., 2019). Despite extensive research over the years, no breakthrough in prediction or prevention has as yet occurred, except administration of acetylsalicylic acid to women at risk (Roberge et al., 2018; Sibai, 1998). This treatment is, however, associated with increased risk of intrapartum bleeding, neonatal intracranial haemorrhage and postpartum haemorrhage (Hastie et al., 2021).

Selenium is an essential trace element for humans originating from soil (Combs, 2001). In Europe, selenium intake has declined as a consequence of collapse in import of US wheat, and suboptimal selenium intake has been documented in many European countries (Barman et al., 2020; Stoffaneller and Morse, 2015). Selenium, incorporated into seleno-proteins, has been found to influence inflammatory response and to protect against oxidative stress, both components in a pregnancy complicated by PIHD (Bizerea et al., 2018; Chamy et al., 2006; Khera et al., 2013; Rayman, 2009; Roman et al., 2014; Watson et al., 2012). Several studies have examined the potential protective role of selenium supplementation with regard to PIHD (Ghaemi et al., 2013; Han and Zhou, 1994; Mistry et al., 2015; Rayman et al., 2015; Rayman et al., 2003; Rayman et al., 2014; Tara et al., 2010). Some randomised controlled trials (RCT) have indicated beneficial effects of selenium supplementation on preeclampsia and PIH (Han and Zhou, 1994; Rayman et al., 2015; Rayman et al., 2014), while others have not (Tara et al., 2010) (see Table 1).

Studies in different global regions have found that a plasma selenium concentration ≥ 95 μg/L correlates with a lower preeclampsia incidence (Vanderlelie and Perkins, 2011). Decreased preeclampsia incidence was found in Finland and New Zeeland after introduction of routine selenium supplementation through soil enrichment (Thomson and Robinson, 1996; Vanderlelie and Perkins, 2011; Wang et al., 1998). Some case-control studies, e.g., a study from the UK and a pregnancy cohort study from Poland, reported significant associations between higher selenium levels during pregnancy and decreased incidence of preeclampsia (Atamer et al., 2005; Ghaemi et al., 2013; Lewandowska et al., 2019; Maleki et al., 2011; Rayman et al., 2003), while others did not find this association (da Silva et al., 2017; Mistry et al., 2015) (Table 2).

To the best of our knowledge, no prospective population-based study on associations between dietary selenium intake and PIHD has as yet been performed. The Norwegian Mother, Father and Child Cohort study (MoBa), comprising detailed information on dietary selenium intake based on a validated food frequency questionnaire (FFQ) and comprehensive information on lifestyle and social and medical risk factors, offers a unique possibility to study such associations. The aim of this study was to examine the associations between selenium intake from diet and supplements and the incidence of PIHD such as PIH and preeclampsia. In addition, we also examined the association between whole-blood selenium status and the incidence of these outcomes in a sub-group within the cohort.

2. Material and methods

2.1. Study population

This study is based on data from MoBa and the Medical Birth Registry of Norway (MBRN). MoBa is a prospective population-based pregnancy cohort study conducted by the 08 (Magnus et al., 2016). The MBRN is a national health registry containing information about all births in Norway. Participants were recruited from all over Norway from 1999 to 2008. Consent to participate was granted in 41% of the pregnancies in which invitations were provided. The cohort includes 114,500 children, 95,200 mothers and 75,200 fathers (Magnus et al., 2016). Pregnant women were invited by postal invitation in connection with the routine ultrasound scan offered free of charge to all women at gestational week 18. They were asked to answer three questionnaires during pregnancy and to provide blood and urine samples at the time of the scan. Participants were followed up regularly with questionnaires after delivery (Magnus et al., 2016). This study is based on information from the first questionnaire (Q1) about general health and lifestyle, filled out around gestational week 15, and the second questionnaire (Q2), a semi-quantitative food frequency questionnaire (FFQ) developed specifically for MoBa and used from 2002 onward. The FFQ was answered around gestational week 22 and asked about average intake of food and dietary supplements since the start of pregnancy (Meltzer et al., 2008).

This study is based on version 10 of the quality-assured data files released for research in 2017. Informed consent was obtained from each MoBa participant upon recruitment.

Table 1
Studies on associations between selenium supplementation and pregnancy-induced hypertensive disorders.

Ref (no)	Author, title, journal and year of publication	Study design	Mean Se status in study group at baseline[a] (gestational age at measurement)	Outcome	Country
(Han and Zhou, 1994)	*Han* et al. *Selenium supplement in the prevention of pregnancy- induced hypertension.* Chin Med J (Engl), 1994	Randomisation of women at high risk of PIH: 52 were given Se 100 μg/d (natural dietetic liquid) and 48 placebo for 6-8 weeks in late pregnancy	No information available	Incidence of PIH was 7.7% in the Se-treated group and 22.7% in the placebo group, $p < 0.05$.	China
(Tara et al., 2010)	*Tara* et al. *Selenium supplementation and the incidence of preeclampsia in pregnant Iranian women: a randomized, double-blind, placebo-controlled pilot trial.* Taiwan J Obstet Gynecol, 2010	Randomisation of 166 healthy women to 100 μg Se/day (yeast) or placebo, from first trimester to delivery	Se in serum 122.5 ± 23.2 μg/L (up to 12 weeks)	No significant difference (no incidence of preeclampsia in the Se group, compared with 4.7% ($n = 3$) in the control group, $p > 0.05$)	Iran
(Rayman et al., 2014)	*Rayman* et al. *Effect of selenium on markers of risk of pre-eclampsia in UK pregnant women: a randomised, controlled pilot trial.* Br J Nutr, 2014	230 primiparas randomised to Se 60 μg/d (Se-enriched yeast) or placebo, from 12 to 14 weeks of gestation until delivery	Se in whole blood 1.32 μmol/L (mean 12 weeks + 3 days)	Se treatment significantly reduced the odds of either preeclampsia or PIH (OR 0.350, 95% CI 0.126, 0.974; $p = 0.044$). Analyses were adjusted for baseline Se concentration and haematocrit.	UK
(Rayman et al., 2015)	*Rayman* et al. *Selenium status in U.K. pregnant women and its relationship with hypertensive conditions of pregnancy.* Br J Nutr, 2015.	Same as above (Rayman et al., 2014)	Same as above (Rayman et al., 2014)	After exclusion of non-compliers with Se treatment, Se supplementation was found to significantly reduce the OR for preeclampsia/PIH (OR 0.30, 95% CI 0.09, 1.00, $p = 0.049$)	UK

[a] Se = selenium; 1 μmol/L selenium × 79 = 1 μg/L; 80 μg/L plasma selenium equals ~100 μg/L whole blood selenium.

Table 2
Studies on associations between selenium status and pregnancy-induced hypertensive disorders.

Ref no	Author, title, journal and year of publication	Study design	Outcome	Country
(Rayman et al., 2003)	*Rayman* et al. *Low selenium status is associated with the occurrence of the pregnancy disease preeclampsia in women from the United Kingdom.* Am J Obstet Gynecol, 2003	Median toenail Se concentrations measured in 53 preeclamptic patients and 53 matched pregnant controls (toenails laid down 3-12 months previously).	Significantly lower median toenail Se concentrations in preeclamptic subjects than in controls ($p = 0.001$). Within the preeclamptic group, lower Se levels were significantly associated ($p = 0.029$) with severity of disease.	UK
(Atamer et al., 2005)	*Atamer* et al. *Lipid peroxidation, antioxidant defense, status of trace metals and leptin levels in preeclampsia.* Eur J Obstet Gynecol Reprod Biol, 2005	In a cross-sectional, prospective study serum Se levels were measured in 32 preeclamptic, 25 non-pregnant women and 28 pregnant women without PIHD, all previously healthy.	Serum levels of Se were significantly lower ($p < 0.001$) in preeclamptic women (60.68 ± 6.42 μg/L), compared to healthy women (87.50 ± 10.96 μg/L), $p < 0.001$.	Turkey
(Maleki et al., 2011)	*Maleki* et al. *The relationship between plasma level of Se and preeclampsia.* Hypertens Pregnancy, 2011	Plasma Se levels measured in 40 preeclamptic and 40 healthy pregnant women at gestational week 34-39.	Compared to the highest plasma Se tertile, women in the lowest tertile (≤47 μg/L) and in the middle tertile (≤58 μg/L) had significantly increased risk of preeclampsia (OR 4.96; 95% CI 1.56–15.6 and OR 3.94; 95% CI 1.26-12.33 respectively).	Iran
(Ghaemi et al., 2013)	*Ghaemi* et al. *A prospective study of selenium concentration and risk of preeclampsia in pregnant Iranian women: a nested case-control study.* Biol Trace Elem Res, 2013	Plasma Se concentrations were first measured at gestational week 24-28 in a group of 650 healthy primiparous women. Measured again 3 months later in 38 women presenting with preeclampsia and in nested matched controls without preeclampsia.	Se plasma concentrations were significantly lower in the case group (70.63 ± 21.41 versus 82.03 ± 15.54 μg/L, $p < 0.05$). The bottom tertile of Se concentration (less than 62.2 μg/L) was associated with higher risk of preeclampsia.	Iran
(Mistry et al., 2015)	*Mistry* et al. *Association between maternal micronutrient status, oxidative stress, and common genetic variants in antioxidant enzymes at 15 weeks' gestation in nulliparous women who subsequently develop preeclampsia.* Free Radic Biol Med, 2015	Plasma Se levels measured at gestational week 15 in 244 women who subsequently developed preeclampsia, and compared with 472 matched normotensive controls.	Mean Se in plasma [median, IQR] was 79.0 [71.8, 87.4] μg/L in cases and 79.6 [73.1, 86.8] μg/L in controls; $p > 0.05$.	UK
(Haque et al., 2016)	Haque et al. Low serum selenium concentration is associated with preeclampsia in pregnant women from Bangladesh. J Trace Elem Med Biol, 2016	Serum Se levels measured in 74 preeclampsia patients at gestational week >/=20 (52 mild and 22 severe preeclapmisa) and 118 normotensive pregnant women as controls with the same gestational age.	Mean serum concentration of selenium in preeclampsia patients was significantly lower than that of healthy pregnant women.	Bangladesh
(da Silva et al., 2017)	*da Silva* et al. *Comparison of serum selenium levels among hypertensive and normotensive pregnant women.* Hypertens Pregnancy, 2017	Serum Se levels measured at inclusion in 20 hypertensive (chronic and gestational hypertension) women, 38 preeclamptic women and 32 controls.	No significant difference in mean Se levels between controls (56.4 ± 15.3 μg/L), hypertensive women (53.2 ± 15.2 μg/L) and preeclamptic women (53.3 ± 16.8 μg/L); $p = 0.67$	Brazil
(Lewandowska et al., 2019)	*Lewandowska* et al. *Serum Selenium Level in early Healthy pregnancy as a risk marker of pregnancy induced hypertension.* Nutrients, 2019	Serum Se levels measured at gestational week 11-14. Comparison between 121 women subsequently diagnosed with PIH and 363 matched controls.	Mean Se level significantly lower in case group (57.5 μg/L vs. 62,9 μg/L), $p = 2.6 \times 10^{-10}$	Poland

Se = selenium; 1 μmol/L selenium × 79 = 1 μg/L; 80 μg/L plasma selenium equals ~100 μg/L whole blood selenium.

The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is now based on regulations related to the Norwegian Health Registry Act. The current study was approved by The Regional Committee for Medical and Health Research Ethics (2015/2425/Rek sør-øst A).

This study includes women with singleton gestations who gave birth to a live-born baby at gestational week 22–42 and who had filled in both Q1 and the FFQ ($n = 82{,}828$). Only a woman's first pregnancy enrolled in MoBa was included. Women with hypertension before pregnancy, chronic renal disease, systemic lupus erythematosus or any kind of diabetes were excluded. We also excluded women with reported energy intake less than 4500 kJ per day or more than 20,000 kJ per day, since these values were assumed to represent invalid reporting (Meltzer et al., 2008). This resulted in a study population of $n = 69{,}972$ (85% of eligible) for analysis of selenium intake. A severe form of preeclampsia might cause a woman from refraining from another pregnancy or might impact her behavior, e.g. to consume (more) supplements in order to prevent recurrence of disease, introducing a possibility of reverse causality. Therefore, analyses were performed for all women and for primiparas separately. Data on blood selenium status was available for $n = 2999$ MoBa participants in the Norwegian Environmental Biobank (Caspersen et al., 2019), resulting in a study sample of $n = 2572$ for analysis of selenium status (Fig. 1).

2.2. Selenium intake from diet and supplements

Estimated dietary selenium intake during the first half of pregnancy was based on the MoBa FFQ, designed to record dietary habits and intake of supplements during the first half of pregnancy. Women were asked to report how often per day, week, or month they consumed different food items, dishes and beverages. The PDF of the FFQ is available at the MoBa homepage (Norwegian Institute of Public Health, 2021). Food frequencies were converted into amounts (μg/day) using standard portion sizes, and energy and nutrient intakes were calculated using the Norwegian Food Composition Table and FoodCalc (Lauritsen, 1998). Registered selenium supplements contained one or more forms of selenium, including inorganic selenite or selenate, selenomethionine, *Se*-methylselenocysteine or selenised yeast, which differ in their impact on blood selenium concentration (Niedzielski et al., 2016). Therefore, intake was estimated and analysed separately for selenium originating from inorganic and organic supplements (Sigrist et al., 2012).

A validation study of the FFQ, using a four-day weighed food diary and several biological markers as reference methods, has demonstrated that the MoBa FFQ is a valid tool for assessing dietary intake of energy,

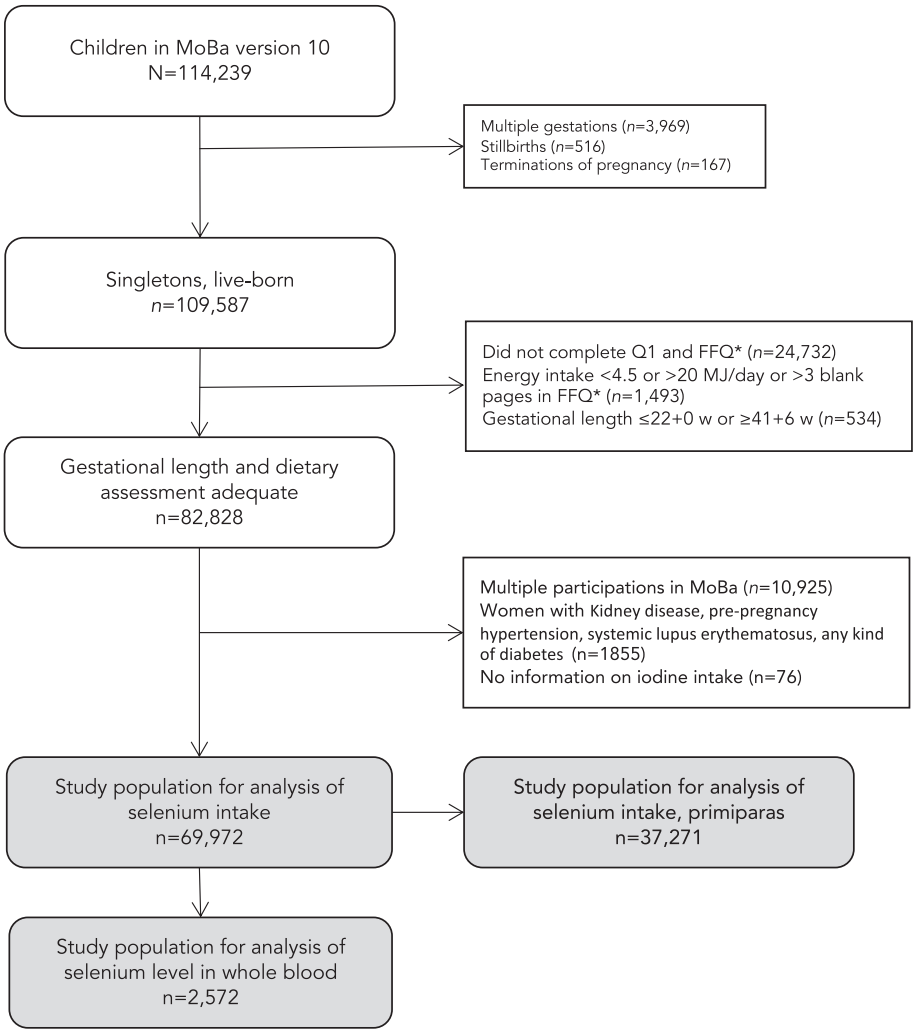

Fig. 1. Flowchart of the study population.
* The current FFQ was introduced in 2002, explaining the large drop in numbers from box 2 to 3.

nutrients and food in the first half of pregnancy (Brantsaeter et al., 2008).

2.3. Whole-blood selenium concentrations

A MoBa subgroup was included into the Norwegian Environmental Biobank, established by the Norwegian Institute of Public Health (Caspersen et al., 2019). Inclusion criteria for the Norwegian Environmental Biobank were available whole blood, urine and plasma samples, available genetic data and available data from the first six MoBa questionnaires and the fathers' questionnaire. A total of 2999 women met these criteria (Caspersen et al., 2019). Whole blood was collected in heparin tubes and shipped in a vacutainer, unrefrigerated, by ordinary mail for long-term freezing at −20 °C at a central biorepository (Paltiel et al., 2014; Ronningen et al., 2006). Selenium analyses were conducted at Lund University, Sweden, by inductive coupled plasma mass spectrometry (ICP-MS; iCAP Q, Thermo Fisher Scientific, Bremen, GmbH) equipped with a collision cell with kinetic energy discrimination and helium that served as the collision gas. The detection limit was 3.2 μg/L and the coefficient of variation was 1.5%. The analytical accuracy was verified using certified reference materials, i.e., Seronorm Trace elements Whole Blood L-1 and L-2 (SERO AS, Billingstad, Norway). The results obtained (mean ± SD) were 56.1 ± 5.7 μg/L for L-1 (Lot 1,103,128, $N = 205$), compared to the recommended level of 59 (35–83) μg/L, and 116 ± 1.5 μg/L for L-2 (Lot 1,103,129, N = 205), compared to the recommended level of 112 (66–158) μg/L (Caspersen et al., 2019). Selenium was analysed in whole blood, since this reflects both current status and uptake, while plasma/serum selenium levels only reflect short-term status (Thomson, 2004). Plasma selenium concentrations above 80 μg/L (~100 μg/L whole-blood selenium) are considered to be adequate (Thomson, 2004) while Hurst et al. found that in non-pregnant women and men a plasma selenium concentrations up to 124 μg/L still maximizes selenoprotein P concentrations (Hurst et al., 2010).

2.4. Pregnancy-induced hypertensive disorders

The main outcome was PIHD, with sub-analyses for PIH and pre-eclampsia. PIHD data were obtained from the MBRN, based on forms completed by midwives after birth. The form has tick-boxes for PIH, as follows; mild preeclampsia; severe preeclampsia; preeclampsia with onset before gestational week 34; the haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome; and eclampsia. PIHD was defined as any of these diagnoses. Sub-analyses were performed for women diagnosed with PIH, mild preeclampsia, and severe pre-eclampsia (including any of the following: severe preeclampsia, early onset preeclampsia, HELLP syndrome or eclampsia).

2.5. Covariates

Maternal age at delivery was obtained from the MBRN and categorized as <25, 25–29, 30–34 or > 34 years. Pre-pregnancy body mass index (BMI) was calculated from height and weight self-reported in Q1 and categorized according to the WHO classification as underweight (<18.5 kg/m^2), normal-weight (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2) or obese (≥30 kg/m^2). Maternal education reported in Q1 was categorized into three categories (≤ 12 years, 13–16 years, ≥ 17 years). Smoking habits during pregnancy reported in Q1 were categorized as non-smoker, occasional smoker or daily smoker. Alcohol consumption and persistent nausea reported in the FFQ were both applied as dichotomized variables (yes or no). Previous studies in MoBa and elsewhere have shown that healthy dietary patterns are associated with lower risk of preeclampsia (Brantsaeter et al., 2009); we adjusted for dietary fibre intake (g/day) as an overall marker of healthy diet. Finally, we adjusted for total energy intake. Selenium and iodine intakes from food correlate (rho = 0.57) and iodine intake has been found to be non-linearly associated with preeclampsia (Abel et al., 2020). Iodine intake, divided into quintiles, was therefore added as a confounder. Missing covariate values was treated as a category of its own, except for iodine intake, for which only 76 women had missing data. These women were excluded from the analyses.

2.6. Statistical analyses

The statistical analyses were performed using IBM SPSS Statistics version 25.0. All p-values were two-sided and values <0.003 were considered significant after Bonferroni correction (0.05 / (4 exposures * 4 outcomes)). Differences in median selenium intake from diet and selenium status according to maternal characteristics were studied with the Kruskal-Wallis test. Differences in frequency of selenium-containing supplement intake (both inorganic and organic) were studied with the Chi-Square test. Prior to analysis, selenium intake and selenium status variables were standardised. The logistic regression models with standardised selenium intake from diet and supplements as exposures were adjusted for the following pre-defined covariates: maternal age and BMI, nausea, smoking during pregnancy, alcohol consumption, total energy intake, fibre intake, iodine intake and mutual adjustment for selenium source (diet, organic supplements, inorganic supplements). Analyses were performed in the whole group as well as in primiparas only. To test for possible threshold effects and non-linear associations, a sensitivity analysis with exposure in the form of deciles of dietary selenium intake was performed. The decile closest to the recommended daily intake (RDI) of 60 μg/day, decile seven with a mean selenium intake of 62 μg/day, was used as the reference group. The threshold model was adjusted for the same covariates as the model for selenium intake as a continuous variable. The regression models with standardised selenium concentration in whole blood as exposure were adjusted for maternal age and BMI, nausea, smoking during pregnancy and alcohol consumption.

3. Results

3.1. Sources of dietary selenium intake

Fig. 2 shows dietary selenium sources. Bread, pasta, rice, cereals and grains accounted together for around one-third (34%) of the selenium

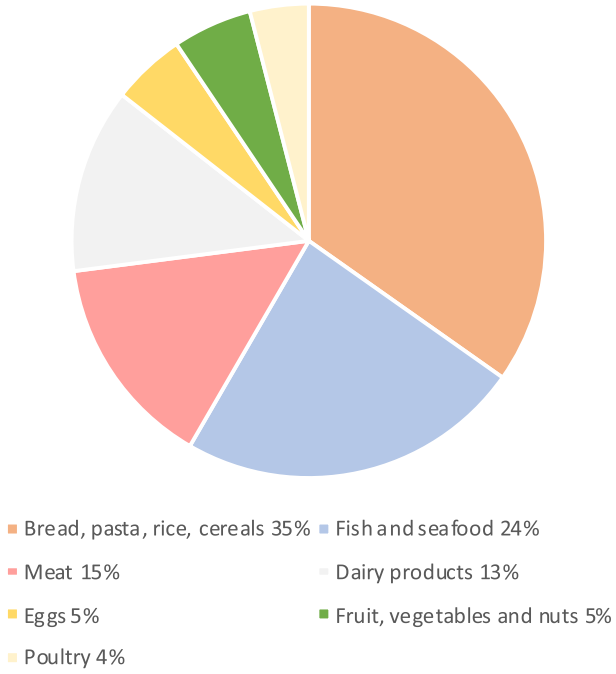

Fig. 2. Sources of selenium from food, percent of contribution.

intake. Other important sources were fish and seafood, contributing 23% of the total intake, as well as eggs and dairy products. No foods are fortified with selenium in Norway.

3.2. Maternal characteristics in relation to dietary selenium intake and selenium status

Selenium intake levels, whole-blood selenium concentrations and supplement use according to maternal characteristics are shown in Table 3. Study participants had a median dietary selenium intake of 53 (IQR 44–62) μg /day, which can be compared to the RDI of 60 μg/day for pregnant women (Nordic Council of Ministers, 2014). In total, 22,750 women (33%) reported intake of dietary supplements containing selenium. Among the 2572 women with whole-blood data, the median selenium concentration was 102 μg/L (IQR 89–117).

3.3. Selenium intake and pregnancy-induced hypertensive disorders

Among the 69,972 women included in the study, 5.9% ($n = 4141$) were diagnosed with PIHD, 2.1% (1445) with PIH, 2.2% (1544) with mild preeclampsia, and 1.3% (907) with severe preeclampsia. In the 37,271 primiparous women, the corresponding figures were: PIHD 7.6% (2846), PIH 2.5% (948), mild preeclampsia 2.8% (1059), and severe preeclampsia 1.8% (655).

Neither logistic regression analyses in all women or in the primiparas showed any significant associations between dietary (Table 4) or supplemental (Table 5) selenium intake and PIHD, PIH, mild preeclampsia or severe preeclampsia. The R-squareds were low after all three selenium sources were added to the adjusted models: PIHD 0.035, PIH 0.030, mild preeclampsia 0.035 and severe preeclampsia 0.020.

Threshold analyses on selenium intake divided into deciles were performed to examine possible non-linear associations between dietary selenium intake and PIHD. The effect estimates (ORs and 95% CIs) increased for deciles with higher dietary selenium intake than the reference group closest to the RDI, but did not reach statistical significance after Bonferroni correction (Supplementary Table 1).

3.4. Selenium status and pregnancy-induced hypertensive disorders

Among the 2572 women with whole-blood selenium concentrations, 5.1% ($n = 132$) were diagnosed with PIHD, 2.2% ($n = 57$) with PIH, 1.9% ($n = 49$) with mild preeclampsia, and 0.8% ($n = 20$) with severe preeclampsia. No significant associations were found between maternal selenium status and PIHD, PIH, mild preeclampsia or severe preeclampsia (Table 6).

Threshold analyses on whole-blood selenium concentrations divided into quintiles were performed to examine possible non-linear associations between whole-blood selenium concentrations and PIHD. The middle quintile was used as reference group (mean whole-blood selenium concentration in this group was 102 μg/L). The analyses did not show any statistically significant associations between quintiles of whole-blood selenium concentrations and PIHD suggesting that there are no threshold effects (Supplementary Table 2).

4. Discussion

To the best of our knowledge, this study is the first to examine the associations between dietary selenium intake and PIHD, PIH and preeclampsia in a population-based cohort, as well as the most comprehensive study on whole-blood selenium concentrations in relation to PIHD. We found no associations between selenium intake from diet or supplements and PIHD in this population with a median dietary selenium intake close to the RDI. Nor was selenium status, measured as selenium concentration in whole blood sampled at mid-pregnancy, associated with PIHD in this population with a median whole-blood selenium concentration close to the level considered adequate (Thomson, 2004).

Previous RCTs on selenium supplementation during pregnancy have generally been small (see Table 1). Rayman et al. (2014) studied the effect of selenium supplementation on risk markers for preeclampsia in 230 UK pregnant women, randomised to 60 μg/day of selenium (enriched yeast) or placebo from 12 to 14 weeks of pregnancy until delivery. In participants with low selenium status at baseline, the median serum concentration of soluble vascular endothelial growth factor receptor-1 (sFlt-1) was significantly lower in the selenium-treated group than in the placebo group at gestational week 35. sFlt-1 is an anti-angiogenic factor, linked to increased risk of preeclampsia. When the analyses were adjusted for baseline selenium concentration and haematocrit, selenium treatment significantly reduced the odds of either preeclampsia or PIH (OR 0.350, 95% CI 0.126, 0.974; 0 = 0.044) (Rayman et al., 2015; Rayman et al., 2014). Another RCT including 100 pregnant women in China with high risk of PIH, randomised to 100 μg selenium/day or placebo, found that selenium supplementation was significantly associated with decreased PIH incidence (Han and Zhou, 1994). Contrary to these findings, a RCT in 166 pregnant Iranian women randomised to 100 μg selenium/day or placebo did not show any difference in preeclampsia incidence between the groups (Tara et al., 2010). One hypothesis is that selenium supplementation only influences preeclampsia risk in populations with low selenium status (Rayman, 2000). In the UK, where several of the previous supplementation studies have been performed, population selenium levels are low (Ghaemi et al., 2013; Rayman et al., 2015; Tara et al., 2010), which might explain the difference in findings between those studies and the current study (Tables 1 and 2). Another explanation might be the source of dietary selenium. The availability of dietary selenium depends on the conversion of selenium within tissues to its metabolically active forms (e.g., its incorporation into GSHPx or 5′-deiodinase) and differs considerably for different selenium sources (Fairweather-Tait et al., 2010). In this study population almost a quarter of all dietary selenium was consumed in form of seafood/fish while seafood consumption is much lower in most other populations.

For adequate enzyme function, selenium concentrations need to be in the range 80–95 μg/L plasma (Thomson, 2004) corresponding to ~100–120 μg/L whole blood. Previous studies on selenium status have suggested a threshold effect at plasma selenium >95 μg/L for reducing preeclampsia incidence (Vanderlelie and Perkins, 2011). In our study, with a median whole blood selenium concentration of 102 μg/L, most women's selenium status could thus be regarded as sufficient which is also supported by the selenium intake close to the recommended intake for pregnant women (Nordic Council of Ministers, 2014). As pregnancy is a time of rapid development with well-coordinated steps of development taking place at defined time points, selenium status might be especially of interest in times of possible oxidant challenge, e.g. at initiation of intervillous blood flow around pregnancy week 8–10. Thus, the timing of selenium supplementation in different studies might impair the comparability with results from the current study.

We found no association between selenium status and risk of PIHD, which is in line with earlier studies (da Silva et al., 2017; Mistry et al., 2015). Mistry et al. analysed plasma selenium status at gestational week 15 in 244 women who subsequently developed preeclampsia, compared to 472 matched normotensive controls, finding no association (Mistry et al., 2015). Contrasting with these results, other studies have shown an association between low selenium levels before pregnancy (Rayman et al., 2003), as well as in early and mid-pregnancy, and increased risk of developing PIH and preeclampsia (Ghaemi et al., 2013; Lewandowska et al., 2019). Rayman et al. analysed selenium concentrations in toenail clippings from 106 pregnant women, reflecting pre-pregnancy selenium status, finding that almost half of the pre-eclamptic subjects, but only around one-eighth of the controls, were in the lowest tertile of toenail selenium (Rayman et al., 2003). All remaining samples were equally distributed between the middle and top tertile, suggesting a threshold effect with the lowest selenium tertile being associated with the greatest risk of preeclampsia (Rayman et al.,

Table 3
Dietary selenium intake and selenium concentrations, by maternal characteristics, in 69,972 participants in the Norwegian Mother, Father and Child Cohort Study (2002-2008).

		Selenium from food, μg/day				Selenium concentration in whole blood, μg/L				Intake frequency of selenium-containing supplements				
										Supplement users		Non-supplement users		
		n	%	Median (IQR[a])	p[b]	n	%	Median (IQR[a])	p[b]	n	%	n	%	p[b]
All women		69,972	100	53 (44-62)		2572	100	102 (89-117)		22,750	33	47,222	67	
Age at delivery, years	<25	8077	12	50 (41-62)	<0.001	216	8	98 (86-111)	0.001	2368	29	5708	71	<0.001
	25-29	23,774	34	52 (43-62)		920	36	102 (88-116)		7869	33	15,905	67	
	30-34	29,672	42	53 (45-63)		1155	45	102 (90-118)		9711	33	19,961	67	
	>34	8449	21	54 (46-64)		281	11	105 (91-121)		2801	33	5648	67	
Maternal education	<13	21,657	31	51 (42-62)	<0.001	654	25	100 (86-114)	<0.001	6143	28	15,514	72	<0.001
	13-16	29,050	42	53 (44-62)		1224	48	101 (88-116)		9845	34	19,205	66	
	>16	17,763	25	54 (46-64)		638	25	107 (94-122)		6297	36	11,466	65	
	Missing	1502	2	51 (42-62)		56	2	100 (87-116)		465	31	1037	69	
Pre-pregnancy BMI, kg/m2	<18.5	2096	3	53 (44-64)	<0.001	81	3	104 (90-116)	0.05	723	34	1373	66	<0.001
	18,6-24,9	45,217	65	53 (45-63)		1666	65	102 (91-118)		15,034	33	30,183	67	
	24,9-29,9	14,654	21	52 (43-61)		601	23	100 (88-115)		4587	31	10,067	69	
	≥30	6209	9	51 (42-61)		179	7	101 (86-116)		1898	31	4311	69	
	Missing	1796	3	53 (44-62)		45	2	101 (93-114)		508	28	1288	72	
Parity	0	37,231	53	52 (43-62)	<0.001	1475	57	104 (90-119)	<0.001	13,543	36	23,688	64	<0.001
	>0	32,684	47	52 (45-63)		1096		100 (88-114)		9187	28	23,497	71	
Nausea at FFQ response	No	61,992	89	53 (44-62)	<0.001	2291	89	102 (90-118)	0.001	20,214	33	41,778	67	0.14
	Yes	7980	11	52 (42-62)		281	11	97 (86-113)		2536	32	5444	68	
Smoking	Never	63,934	91	53 (44-62)	<0.001	2401	93	102 (89-118)	0.001	21,079	33	42,855	67	<0.001
	Occasionally	1889	3	52 (43-63)		62	2	99 (90-114)		559	30	1330	70	
	Daily	3752	5	51 (42-62)		99	4	95 (85-107)		1006	27	2746	73	
	Missing	397	1	52 (43-62)		10	0.4	97 (90-114)		106	27	291	73	
Alcohol consumption	No	62,207	89	53 (44-62)	<0.001	2267	88	102 (89-117)	0.03	20,105	32	42,102	68	0.002
	Yes	7765	11	54 (46-64)		305	12	104 (91-120)		2645	34	5120	66	
Energy intake tertiles	<8398	23,334	33	44 (37-50)	<0.001	890	35	103 (90-118)	0.26	7538	32	15,796	68	0.55
	8398-10,468	23,326	33	53 (46-60)		867	34	102 (89-117)		7621	33	15,705	67	
	>10,468	23,312	33	63 (55-73)		815	32	101 (89-116)		7591	33	15,721	67	
Fibre intake, tertiles	<25.7	23,329	33	43 (37-51)	<0.001	852	33	101 (88-116)	0.04	7350	32	15,979	68	<0.001
	25.7-33.9	23,331	33	53 (46-60)		903	36	102 (89-117)		7643	33	15,688	67	
	>33.9	23,312	33	63 (55-72)		817	32	104 (90-118)		7757	33	15,555	67	
Iodine intake, quintiles	<81.6	13,995	20	42 (35-49)	<0.001	500	19	101 (87-118)	0.46	4580	33	9415	67	0.29
	81.6-108.4	13,994	20	49 (42-56)		542	21	103 (90-118)		4568	33	9426	67	
	108.5-134.8	13,995	20	52 (45-60)		501	19	102 (90-117)		4559	33	9436	67	
	134.9-174.0	13,994	20	57 (50-65)		539	21	103 (90-117)		4545	32	9449	68	
	>174.0	13,994	20	65 (56-75)		490	19	101 (88-116)		4498	32	9496	68	
Selenium supplementation	No	47,222	67	53 (44-62)	0.002	1677	65	100 (87-115)	<0.001					
	Yes	22,750	33	53 (44-63)		895	35	106 (94-121						

Abbreviations: BMI – Body Mass Index; FFQ – Food Frequency Questionnaire.
[a] IQR = 25th–75th percentile.
[b] p-Value obtained with Mann-Whitney U test for 2 groups and with Kruskal-Wallis test for >2 groups.

Table 4
Association between maternal dietary selenium intake and pregnancy-induced hypertensive disorders (PIHD).

	n		Unadjusted		Adjusted[a]	
		% of all	OR[b] (95% CI)	p	OR[b] (95% CI)	p
All women	69,972					
PIHD	4141	5.9	0.98 (0.95,1.02)	0.30	1.03 (0.98,1.08)	0.29
PIH	1445	2.1	1.04 (0.99,1.10)	0.14	1.07 (0.99,1.16)	0.09
Mild PE	1544	2.2	0.96 (0.91,1.01)	0.08	0.99 (0.92,1.07)	0.87
Severe PE	907	1.3	0.95 (0.89,1.02)	0.13	1.02 (0.92,1.12)	0.73
Primiparas	37,271	53.3				
PIHD	2846	7.6	1.05 (0.97,1.04)	0.83	1.02 (0. 97,1.08)	0.44
PIH	948	2.5	1.07 (1.00,1.14)	0.04	1.10 (1.00,1.21)	0.046
Mild PE	1059	2.8	0.95 (0.90,1.01)	0.12	0.96 (0.87,1.05)	0.33
Severe PE	655	1.8	0.97 (0.92,1.08)	0.91	1.04 (0.93,1.16)	0.54

Daily dietary intake of selenium from food and odds ratios (OR) for any pregnancy-induced hypertensive disorders (PIHD), pregnancy-induced hypertension (PIH), mild preeclampsia (mild PE) and severe preeclampsia (severe PE) in all subjects and in primiparous women only, analysed with logistic regression.
[a] Adjusted for maternal age, education, BMI, nausea, smoking during pregnancy, alcohol consumption, total energy intake, fibre intake, iodine intake and intake of organic and inorganic selenium from supplements.
[b] OR per standard deviation, 15.6 μg, of selenium intake.

2003). Concurring with this, Lewandowska found significantly lower serum selenium levels at gestational week 11–14 in 121 women who were subsequently diagnosed with PIH, compared to 363 matched controls who remained normotensive (57.5 μg/L in cases vs. 62.9 μg/L in controls; $p = 2.6 \times 10^{-10}$) (Lewandowska et al., 2019). An Iranian nested case-control study on 650 healthy primiparous women found that women who later developed preeclampsia had significantly lower plasma selenium concentrations at gestational week 24–28, compared to matched healthy controls (70.63 μg/L vs 82.03 μg/L; $p = 0.009$) (Ghaemi et al., 2013). Moreover, being in the bottom selenium status tertile was associated with higher risk of developing preeclampsia (Ghaemi et al., 2013). While our study does not support these results, the difference in biological material, toenail clippings and plasma, compared to whole blood in our study, lowers the studies' comparability. We chose to analyse whole-blood selenium since it reflects both current status and uptake, while plasma/serum selenium only reflects short-term status (Maleki et al., 2011; Thomson, 2004).

Case-control studies have found lower serum and plasma selenium levels in preeclamptic women than in healthy women (Atamer et al., 2005; Maleki et al., 2011), suggesting a higher demand for selenium in preeclamptic pregnancies (Maleki et al., 2011). On the other hand, a

Table 5
(a) Association between maternal inorganic selenium supplement intake and pregnancy-induced hypertensive disorders (PIHD) and (b) association between maternal organic selenium supplement intake and pregnancy- induced hypertensive disorders (PIHD).

a

	Supp. users	Non-users	Unadjusted		Adjusted[a]	
	N (%)	N (%)	OR[b] (95% CI)	*p*	OR[b] (95% CI)	*p*
All women	20,213 (29)	49,759 (71)				
PIHD	1186 (5.9)	2955 (5.9)	1.01 (0.98,1.04)	0.54	1.01 (0. 98,1.05)	0.42
PIH	387 (1.9)	1058 (2.1)	0.97 (0.92,1.02)	0.22	0.97 (0.91,1.02)	0.21
Mild PE	479 (2.3)	1065 (2.1)	1.06 (1.01,1.11)	0.01	1.07 (1.02,1.12)	0.004
Severe PE	257 (1.3)	650 (1.3)	1.01 (0.95,1.08)	0.79	1.01 (0.95,1.07)	0.82
Primiparas	12,174 (33)	25,057 (67)				
PIHD	889 (7.3)	1957 (7.8)	0.99 (0.95,1.02)	0.45	0.99 (0. 96,1.03)	0.66
PIH	291 (2.4)	657 (2.6)	0.98 (0.92,1.04)	0.44	0.97 (0.91,1.04)	0.42
Mild PE	346 (2.8)	713 (2.8)	1.01 (0.96,1.07)	0.73	1.02 (0.97,1.09)	0.42
Severe PE	202 (1.7)	453 (1.8)	0.98 (0.91,1.05)	0.56	0.99 (0.92,1.07)	0.73

b

	Supp. users	Non-users	Unadjusted		Adjusted[a]	
	N (%)	N (%)	OR[b] (95% CI)	*p*	OR[b] (95% CI)	*p*
All women	3202 (5)	66,770 (95)				
PIHD	166 (5.2)	3975 (6.0)	0.98 (0.94,1.01)	0.22	0.98 (0.95,1.02)	0.37
PIH	54 (1.7)	1391 (2.1)	0.97 (0.91,1.03)	0.30	0.97 (0.91,1.04)	0.39
Mild PE	55 (1.7)	1489 (2.2)	0.95 (0.89,1.02)	0.13	0.95 (0.89,1.02)	0.13
Severe PE	47 (1.5)	860 (1.3)	1.02 (0.96,1.08)	0.3	1.02 (0.96,1.09)	0.45
Primiparas	1794 (5)	35,437 (95)				
PIHD	114 (6.4)	2732 (7.7)	0.97 (0.93,1.02)	0.22	0.98 (0.94,1.02)	0.32
PIH	37 (2.1)	911 (2.6)	0.98 (0.92,1.05)	0.64	0.99 (0.92,1.06)	0.67
Mild PE	40 (2.2)	1019 (2.9)	0.95 (0.88,1.03)	0.18	0.95 (0.88,1.03)	0.23
Severe PE	29 (1.6)	626 (1.8)	0.97 (0.89,1.06)	0.54	0.98 (0.90,1.07)	0.68

Daily intake of selenium from inorganic (a) and organic (b) supplements and odds ratios (OR) for any pregnancy-induced hypertensive disorders (PIHD), pregnancy induced hypertension (PIH), mild preeclampsia (mild PE) and severe preeclampsia (severe PE) in all subjects and in primiparous women only, analysed with logistic regression.

[a] Adjusted for maternal age, education, BMI, nausea, smoking during pregnancy, alcohol consumption, total energy intake, fibre intake, iodine intake and dietary selenium intake, and mutually adjusted for the other selenium supplement source.

[b] OR per standard deviation of the intake: 32.9 μg for inorganic selenium supplements and 10.5 μg for organic selenium supplements.

small Brazilian case-control study investigated selenium status in 58 women with preeclampsia or PIH, as well as 32 normotensive women, finding that serum selenium levels did not differ significantly in the two groups (da Silva et al., 2017).

4.1. Strengths and limitations

To the best of our knowledge, this is the most comprehensive study on selenium intake and PIHD and the first to study selenium intake from diet. It is important to note that selenium intake was only assessed once, in mid-pregnancy, and the results thus reflect intake during the first half of pregnancy. Hence, we cannot draw any conclusions on the impact of selenium intake at other stages of pregnancy. Due to the observational design of this study, residual confounding cannot be ruled out, although the comprehensive dataset allowed us to account for possible confounders.

This is also the largest study on selenium status in whole blood and PIHD. However, since one inclusion criterion for participation in the Norwegian Environmental Biobank Study was to have answered the first six MoBa questionnaires, the subgroup of women with data on whole-blood selenium concentrations is a highly selected group. The subgroup included a higher proportion of non-smokers and highly educated women, compared with the whole MoBa population (Caspersen et al., 2019), and their PIHD incidence was 5.1%, compared to 5.9% in the selenium intake study group. Thus, the generalizability of the association between blood selenium concentrations and PIHD may be limited due to selection bias.

Monitoring of selenium status in representative population groups should be encouraged.

Previous research suggests that genotype, both for seleno-proteins and related pathways, must be taken into account when assessing the impact of selenium intake or status on preeclampsia risk. Further studies combining data on selenium intake and status, seleno-protein activity and genotype are needed in order to understand the impact of selenium on PIHD risk.

Table 6
Association between maternal whole blood selenium concentration and pregnancy- induced hypertensive disorders (PIHD).

		Unadjusted		Adjusted[a]	
	n cases (%)	OR[b] (95% CI)	*p*	OR[b] (95% CI)	*p*
All women	2572				
PIHD	132 (5.1)	1.00 (0.84,1.19)	0.10	1.03 (0.86,1.22)	0.78
PIH	57 (2.2)	0.98 (0.76,1.28)	0.90	0.98 (0.75,1.29)	0.91
Mild PE	49 (1.9)	0.99 (0.74,1.31)	0.92	1.03 (0.79,1.36)	0.82
Severe PE	20 (0.8)	1.04 (0.68,1.58)	0.86	1.06 (0.72,1.56)	0.78

Selenium concentration and odds ratios for pregnancy-induced hypertensive disorders (PIHD), pregnancy-induced hypertension (PIH), mild and severe preeclampsia (mild PE and severe PE), analysed with logistic regression.

[a] Adjusted for maternal age, education, BMI, nausea, alcohol consumption, smoking during pregnancy.

[b] OR per standard deviation, 23.5 μg/L, of selenium concentration in blood.

5. Conclusions

Our results do not support a protective effect of selenium intake or status in regard to PIHD in this population with median selenium intake and levels close to those recommended for pregnant women.

Data sharing

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

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Author contributions

Conceptualization: all authors; data curation: MB; methodology: EH, MB, VS; formal analysis: MB, VS; supervision: MB, VS; funding acquisition: BJ, MB, VS; writing - original draft: EH; writing – review & editing: all authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2021.149271.

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