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Relationship between high consumption of marine fatty acids in early pregnancy and hypertensive disorders in pregnancy

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Objective To investigate whether there is a relationship between maternal intake of cod-liver oil in early and late pregnancy and hypertensive disorders in pregnancy.

Design An observational prospective study.

Setting Free-living conditions in a community with traditional fish and cod-liver oil consumption.

Population Four hundred and eighty-eight low-risk pregnant Icelandic women.

Methods Maternal use of cod-liver oil, foods and other supplements was estimated with a semiquantitative food frequency questionnaire covering food intake together with lifestyle factors for the previous 3 months. Questionnaires were filled out twice, between 11 and 15 weeks of gestation and between 34 and 37 weeks of gestation. Supplements related to hypertensive disorders in pregnancy, i.e. gestational hypertension and pre-eclampsia, were presented, with logistic regression controlling for potential confounding.

Main outcome measures Gestational hypertension, pre-eclampsia, cod-liver oil and multivitamins.

Results The odds ratio for developing hypertensive disorders in pregnancy for women consuming liquid cod-liver oil was 4.7 (95% CI 1.8–12.6, $P = 0.002$), after adjusting for confounding factors. By dividing the amount of n-3 long-chain polyunsaturated fatty acids (n-3 LCPUFA) into centiles, the odds ratio for hypertensive disorders across groups for n-3 LCPUFA suggested a u-shaped curve ($P = 0.008$). Similar results were found for gestational hypertension alone. Further, the use of multivitamin supplements without vitamins A and D in late pregnancy doubled the odds of hypertensive disorders (OR 2.4, 95% CI 1.0–5.4, $P = 0.044$).

Conclusions Consumption of high doses of n-3 LCPUFA in early pregnancy, or other nutrients found in liquid cod-liver oil, may increase the risk of developing hypertensive disorders in pregnancy.

Keywords Cod-liver oil, gestational hypertension, multivitamins, pre-eclampsia, pregnancy.

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Introduction

Hypertensive disorders in pregnancy, including gestational hypertension and pre-eclampsia, are among the most common complications associated with pregnancy, affecting 5–10% of all pregnancies worldwide.[1–3] Although the outcome for most women and their babies is good, hypertensive disorders remain the leading cause of morbidity and mortality in pregnancy.[1,4] Thus, the prevention of elevated blood pressure during pregnancy is of clinical importance.

Oxidative stress, i.e. an imbalance between maternal prooxidants and antioxidants, is thought to be involved in the pathogenesis of gestational hypertension and pre-eclampsia.[5–8] Therefore, maternal intake of polyunsaturated fatty acids as well as antioxidant nutrients is of interest.

The possible benefits and risks of the use of various dietary supplements on health have been debated.[9,10] While benefits of some dietary supplements for mother and child have been extensively investigated, e.g. folic acid[11] and iron,[12] the safety of other supplements has not been extensively studied during pregnancy. Among these are supplements containing n-3 long-chain polyunsaturated fatty acids (n-3 LCPUFA) from marine food. Iceland is a community with traditional intake of cod-liver oil as a substantial source of vitamin D during winter.[13,14]

Studies focusing on the intake of n-3 LCPUFA suggest a moderate lowering effect on blood pressure,[15,16] but studies on pregnant women have been more contradictory.[4] Some studies suggest a reduced risk of pre-eclampsia,[17–19] whereas others have found no association with either pre-eclampsia or gestational hypertension,[20–23] and still others an increased risk (total polyunsaturated fatty acids [PUFA]).[8,24] It has been suggested that pregnancy itself may be a stimulus for lipid peroxidation.[6]

Micronutrient status may play an important role in pregnancy and birth outcomes. Clinical trials have demonstrated a protective effect of multiple vitamin supplements and folic acid against malformations of the fetus,[25] but few studies have evaluated the relation between hypertensive disorders in pregnancy and multivitamin use.[26] There is a strong association between the intake of cod-liver oil and other dietary supplements.[27] Therefore, in an observational prospective study on the relationship between cod-liver oil and hypertensive disorders in pregnancy, it is of advantage to investigate other supplements as well.

The aim of this study was to investigate the relationship between intake of cod-liver oil and other supplements in early and late pregnancy and hypertensive disorders induced by pregnancy in a cohort of low-risk pregnant Icelandic women.

Subjects and methods

In this observational study, the participants were randomly selected, pregnant women, attending a routine first visit at the Center of Prenatal Care in Reykjavik, Iceland, from 1999 to 2001. Of the 549 women enrolled in the research group, 488 (89%) women who gave birth to full-term babies completed the study. The 61 women were excluded because they had essential hypertension ($n = 3$), gestational diabetes mellitus ($n = 4$), miscarriage or stillbirth ($n = 17$), twins or triplets ($n = 5$) or a preterm birth (≤259 days) ($n = 17$); their personal data could not be found; they moved abroad before giving birth ($n = 8$) or variables to be used in this study were missing ($n = 7$). The National Bioethics Committee of Iceland and the Icelandic Data Protection Commission approved the study. All women gave informed consent for participation in the study.

A semiquantitative food frequency questionnaire (FFQ) covering food intake and supplemental use for the last 3 months and a questionnaire on several lifestyle factors was mailed to the participants 2 weeks before their first visit to the clinic between 11 and 15 weeks of gestation (early pregnancy) and again 2 weeks before a visit between 34 and 37 weeks of gestation (late pregnancy). The women were asked to complete the questionnaires at home and bring them to the clinic visits or return them by mail. The semiquantitative FFQ was developed at the Icelandic Nutrition Council to assess the entire diet over the previous 3-month period. FFQs were scanned, and food and nutrient intake was calculated, using the Icelandic Nutrition Database (ISGEM) and a nutrient and food calculating program (ICEFOOD). The FFQ has been validated for some nutrients.[28,29]

Weight gain from the initial visit at 11–15 weeks of gestation until the last weighing before delivery was calculated to estimate the pregnancy weight gain. Gestational hypertension was defined as blood pressure of 140/90 mmHg or more after 20 weeks of gestation, but without proteinuria.[2,30] Clinical features of pre-eclampsia were blood pressure of 140/90 mmHg or more together with proteinuria more than 300 mg/L (≥1+ reading on dipstick).[30] Given the potential misclassification of hypertension with and without pre-eclampsia, we also presented the two diagnoses combined as hypertensive disorders in pregnancy in the analysis.

The data are described by values of mean and SD as well as percentages. Analysis of variance or Kruskal–Wallis test, depending on the distribution of the data, was used to compare maternal characteristics and intake data between healthy women and women developing gestational hypertension or pre-eclampsia. The chi-square test was used to detect differences in binary and categorised variables between groups.

Binary logistic regression models were designed for representing maternal intake of cod-liver oil and other supplements and hypertensive disorders. The odds of developing gestational hypertension, pre-eclampsia or one of these hypertensive disorders was calculated with 95% confidence intervals (95% CI), adjusting for weight gain during pregnancy, body mass index (BMI) × weight gain, smoking, parity

Table 1. n-3 LCPUFA, retinol, vitamin D and vitamin E in the mean daily dosage of liquid cod-liver oil and concentrated cod-liver oil capsules

Liquid cod-liver oil	**Total amount of nutrients in 10 ml***
n-3 LCPUFA (g)	1.8
Retinol (micrograms)	2400
Vitamin D (micrograms)	20
Vitamin E (mg)	30
Concentrated cod-liver oil capsules	**Total amount of nutrients in three capsules***
n-3 LCPUFA (g)	0.18
Retinol (micrograms)	330
Vitamin D (micrograms)	4.5
Vitamin E (mg)	0.09

*Composition at the time of the study as used for calculations from the food frequency questionnaire with the Icelandic Nutrition Database (ISGEM).

and diastolic and systolic pressure early in pregnancy. Liquid cod-liver oil intake was treated as binary data. Table 1 shows the amount of n-3 LCPUFA, retinol, and vitamins D and E in a common dosage of liquid cod-liver oil as well as in concentrated cod-liver oil capsules. The amount of n-3 LCPUFA in a 10-ml spoon of liquid cod-liver oil (1.8 g) is ten times that in the common daily dosage from three capsules (0.18 g).

Multivitamin supplements were also treated as binary data because nearly all supplement users took their tablets on a daily basis. Smoking and parity were categorised, but other variables were continuous. Stepwise backwards elimination was used for selecting the variables and other possible sources of confounding. Also, odds ratios and 95% confidence interval for hypertensive disorders in pregnancy and gestational hypertension were made by centiles of n-3 LCPUFA, retinol and vitamin D intake. Distribution into centiles was made to allow for observation of dose–response, and the reference groups were from the lowest consumption group, i.e.10th or 50th percentile. The level of significance was set at $P = 0.05$, and two-tailed P values were used. All statistical analyses were performed using the SPSS program (SPSS 11.0 for Windows; SPSS Inc., Chicago, IL, USA).

Results

Table 2 presents maternal characteristics, nutrient and food intake and birth outcome for the 488 participants included in the study. The participants were split into three groups: healthy women ($n = 439$), women developing gestational hypertension ($n = 30$), and women developing pre-eclampsia ($n = 19$). Compared with the healthy women, the women developing gestational hypertension had a higher BMI ($P < 0.001$) and higher blood pressure at the beginning and end of pregnancy ($P < 0.001$). Their consumption of liquid cod-liver oil early in pregnancy was more common (23 versus 11% of women, $P = 0.031$), and there was a trend for more vitamin D intake ($P = 0.056$). In late pregnancy, the use of multivitamin supplements without vitamins A and D was also more common among women developing gestational hypertension than among healthy women, or 40 versus 22% ($P = 0.035$).

Women developing pre-eclampsia, as compared with healthy women, gained significantly more weight during pregnancy, or 16.5 ± 5.9 kg versus 13.6 ± 4.7 kg, respectively ($P = 0.038$). They were more likely to be giving birth to their first child (79 versus 47%, respectively, $P = 0.022$) and less likely to be giving birth to their second child (11 versus 32% respectively, $P = 0.022$). Even if all pregnancies included in the study were full term, the women developing pre-eclamsia gave birth 4 days earlier than did the healthy women ($P = 0.030$), and their children tended to be smaller, although not significantly (3602 ± 526 g versus 3779 ± 479 g, respectively, $P = 0.136$).

As shown in Table 3, liquid cod-liver oil consumers got eight times more n-3 LCPUFA, and over two-fold the amount of retinol and vitamin D from their diet in early pregnancy compared with nonconsumers.

Table 4 shows logistic regression models for supplement-intake related to hypertensive disorders (gestational hypertension and pre-eclampsia combined), gestational hypertension or pre-eclampsia. According to the first model, women consuming liquid cod-liver oil in early pregnancy were almost five times as likely to develop hypertensive disorders (OR 4.7, 95% CI 1.8–12.6, $P = 0.002$), after adjusting for confounding factors. Also, the use of multivitamin supplements without vitamins A and D doubled the odds of hypertensive disorders (OR 2.4, 95% CI 1.0–5.4, $P = 0.044$). For the models wieving the diseases separately, gestational hypertension gave similar results, but there were no significant results for pre-eclampsia. Mothers included in the logistic regression models were 397, as 91 women did not fill out their food frequency and lifestyle questionnaires at the second time point, and therefore information on their smoking habits and supplement use in late pregnancy was lacking. Regarding all the other variables included in the regression model, there was no significant difference between the 91 women excluded and the women included, with the exception of maternal weight gain during pregnancy. The women included in the model gained on average 14.0 ± 4.8 kg, whereas the excluded women gained on average 12.6 ± 5.1 kg ($P = 0.011$).

Using logistic regression, the odds ratios for hypertensive disorders in pregnancy by the dose of n-3 LCPUFA, retinol and vitamin D were assessed. Adjustments were made for weight gain during pregnancy, the intercept of BMI at beginning of pregnancy and weight gain during pregnancy, smoking, parity, and diastolic and systolic blood pressure in early pregnancy. Figure 1 suggests a u-shaped curve for the odds of hypertensive disorders in pregnancy ($P = 0.008$) when maternal intake of n-3 LCPUFA early in pregnancy was divided into the lowest consumption group, i.e. 10th centile (reference ≤0.09 g/day), 11th–50th centile (0.10–0.23 g/day), 51th–90th centile (0.24–0.87 g/day) and above 90th centile (>0.87 g/day). In Figure 2 the odds ratios for hypertensive disorders in pregnancy were presented by the centiles of retinol intake in early pregnancy. Retinol intake was divided into the lowest consumption group, i.e. 50th centile (reference ≤1341 micrograms/day), 51th–90th centile (1342–2655 micrograms/day), 91th–95th centile (2656–3303 micrograms/day) and above 95th centile (> 3303 micrograms/day). There was a nonsignificant trend for increased likelihood of hypertensive disorders with higher intake of retinol ($P = 0.172$). Figure 3 presents the odds ratios for hypertensive disorders in preganncy by the centiles of vitamin D intake in early pregnancy. Division into centiles was the same as for retinol, and the values for the groups were 50th centile (reference ≤11 micrograms/day), 51th–90th centile (12–18 micrograms/day), 91th–95th centile (19–23 micrograms/day) and above 95th centile (>23 micrograms/

Table 2. Characteristics for healthy women and women developing gestational hypertension or pre-eclampsia

	Mean (SD)		
	Healthy (n = 439)	**Gestational hypertension (n = 30)**	**Pre-eclampsia (n = 19)**
Maternal anthropometry			
Age (years)	28 (5)	29 (6)	26 (4)
BMI at first visit (kg/m^2)	24.4 (4.1)	28.7 (5.2)***	26.4 (4.4)
Weight gain during pregnancy (kg)	13.6 (4.7)	13.7 (5.9)	16.5 (5.9)*
Systolic pressure at first visit (mmHg)	112 (10)	125 (10)***	116 (12)
Systolic pressure at last visit (mmHg)	116 (11)	145 (7)***	136 (12)***
Diastolic pressure at first visit (mmHg)	66 (9)	74 (9)***	69 (9)
Diastolic pressure at last visit (mmHg)	74 (9)	96 (6)***	93 (8)***
Maternal intake			
Liquid cod-liver oil, early pregnancy (yes, %)†	11	23*	16
Concentrated cod-liver oil capsules, early pregnancy (yes, %)†	31	33	37
Multivitamin supplement,‡ early pregnancy (yes, %)†	10	17	11
Multivitamin supplement,‡ late pregnancy (yes, %)†	22	40*	38
Macronutrients and vitamins in maternal diet, early pregnancy			
Energy (kJ/day)	8634 (3095)	8595 (2635)	8578 (2195)
Protein E%	15.9 (2.9)	16.6 (2.6)	15.8 (2.6)
Fat E%	32.9 (6.6)	33.6 (6.4)	32.7 (6.6)
Saturated fat E%	13.5 (3.3)	14.0 (3.1)	13.3 (2.6)
Monounsaturated fat E%	9.3 (2.1)	9.5 (1.9)	9.3 (2.2)
Polyunsaturated fat E%	4.1 (1.2)	3.8 (0.9)	4.1 (1.2)
Carbohydrate E%	51.8 (6.7)	50.5 (6.4)	52.0 (7.4)
Added sugar E%	12.5 (6.8)	13.0 (7.0)	9.9 (4.6)
Alcohol E%	0.3 (0.6)	0.2 (0.3)	0.4 (1.1)
n-3 LCPUFA§ (g/day)	0.4 (0.5)	0.5 (0.7)	0.4 (0.6)
Total n-3 PUFA (g/day)	1.7 (1.1)	1.6 (0.9)	1.7 (1.0)
Total n-6 PUFA (g/day)	6.5 (3.5)	6.3 (2.8)	6.4 (3.2)
Retinol (microgram/day)	1443 (929)	1768 (1070)	1302 (754)
Vitamin D (microgram/day)	10 (7)	13 (8)	10 (6)
Vitamin E (mg/day)	31 (50)	17 (6)	42 (64)
Smoking (n = 403, %)†			
Nonsmoker	66	65	69
Smoking only in early pregnancy	20	31	31
Smoking throughout pregnancy	14	4	0
Parity (n = 487, %)†			
First child	47	57	79*
Second child	32	30	11*
Third child or more	21	13	10
Birthoutcome¶			
Birthweight (g)	3779 (479)	3888 (562)	3602 (526)
Gestational length (days)	282 (8)	281 (8)	278 (8)*

†Chi-square statistics.
‡Multivitamin supplements without vitamins A and D.
¶Within a group of full term babies, as women were only included in the study if their gestational length was more than 259 days.
*Significant difference between healthy women and women with the disease, $P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.
§EPA = Eicosapentaenoic acid, DPA = Docosapentaenoic acid, DHA = Docosahexaenoic acid.

Table 3. n-3 LCPUFA, retinol, vitamin D and vitamin E intake in early pregnancy among consumers of liquid cod-liver oil, concentrated cod-liver oil capsules and nonconsumers

	Mean (SD)		
	Nonconsumers (*n* = 286)	Concentrated cod-liver oil capsules (*n* = 146)	Liquid cod-liver oil (*n* = 56)
n-3 LCPUFA (g)	0.2 (0.2)	0.3 (0.2)***	1.6 (0.7)***
Retinol (micrograms)	1240 (707)	1308 (712)	2954 (1102)***
Vitamin D (micrograms)	8 (5)	10 (5)*	21 (8)***
Vitamin E (mg)	29 (46)	30 (48)	42 (67)

*Significant difference between nonconsumers and the assigned groups, $P < 0.05$; ** $P < 0.01$; ***$P < 0.001$.

day). There was a significantly increased likelihood of hypertensive disorders in pregnancy with higher intake of vitamin D ($P = 0.037$). Repeating the calculations for gestational hypertension alone gave similar results for n-3 LCPUFA ($P = 0.035$) and retinol ($P = 0.090$), but vitamin D was borderline significant ($P = 0.050$).

Discussion

In the present study, high maternal consumption of n-3 LCPUFA in early pregnancy was related to the development of hypertensive disorders in pregnancy, i.e. gestational hypertension and pre-eclampsia.

The first suggestion that fish oil could prevent pre-eclampsia came from the finding of the low incidence of the disease found among Greenland Inuits.[19] Since then many interventions have been made to investigate the effect of n-3 LCPUFA on pre-eclampsia and gestational hypertension, but none has found any significant relationship.[20–23] The exact origins of pre-eclampsia are unknown but it may occur early in pregnancy.[31,32] Measurements of maternal intake early in pregnancy, as in this study, has been suggested to better relate to outcome than measurement during late pregnancy.[31] The importance of nutrients in early pregnancy and the periconceptional period has been clearly established by the recognition of the importance of folic acid intake periconceptionally.[11] We have previously found that maternal consumption of liquid cod-liver oil has an effect on birthweight prior to 15 weeks of gestation.[13] Supplement studies were begun at or beyond 16 weeks of gestation,[20–23] and in most studies, nutritional data were obtained on women already with the clinical syndromes.[33] One of the very few studies investigating maternal intake prior to disease onset found high intake of total PUFA, and both n-6 and n-3, in women who later developed pre-eclampsia.[24]

Possibly, the amount of n-3 LCPUFA may have positive effects up to a certain level, while becoming detrimental in high doses. By dividing intake of n-3 LCPUFA in centiles, the

Table 4. Logistic regression models for supplement intake related to the development of gestational hypertension, pre-eclampsia or either one of these hypertensive disorders in pregnancy*

	Gestational hypertension or pre-eclampsia, $R^2 = 34.9$; $n = 397$		Gestational hypertension, $R^2 = 38.2$; $n = 376$**		Pre-eclampsia , $R^2 = 30.2$; $n = 367$***	
	Adjusted OR**** (95% CI)	*P*	Adjusted OR**** (95% CI)	*P*	Adjusted OR**** (95% CI)	*P*
Liquid cod-liver oil in early pregnancy (yes/no)	4.7 (1.8–12.6)	0.002	5.2 (1.5–17.8)	0.009	4.2 (0.8–20.9)	0.081
Multivitamin supplement without vitamins A and D late in pregnancy (yes/no)	2.4 (1.0–5.4)	0.044	2.9 (1.0–8.5)	0.053	2.3 (1.0–5.3)	0.408

*Stepwise backwards elimination was used for selecting the variables included in the models.
**Women with pre-eclampsia were excluded for the calculation.
***Women with gestational hypertension were excluded for the calculation.
****Adjustments were made for weight gain during pregnancy, BMI × weight gain, smoking, parity and diastolic and systolic blood pressure early in pregnancy.

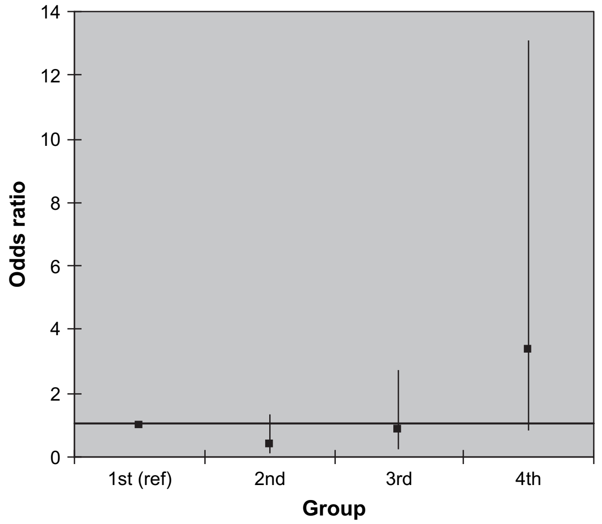

Figure 1. Odds ratios and 95% CI for hypertensive disorders in pregnancy by centiles of n-3 LCPUFA intake in early pregnancy. Groups were divided into:(1) 10th centile (reference); (2) 11th–50th centile; (3) 51th–90th centile; and (4) >90th centile. Weight gain during pregnancy, BMI × weight gain, smoking, parity and diastolic and systolic blood pressure early in pregnancy were adjusted for $P = 0.008$.

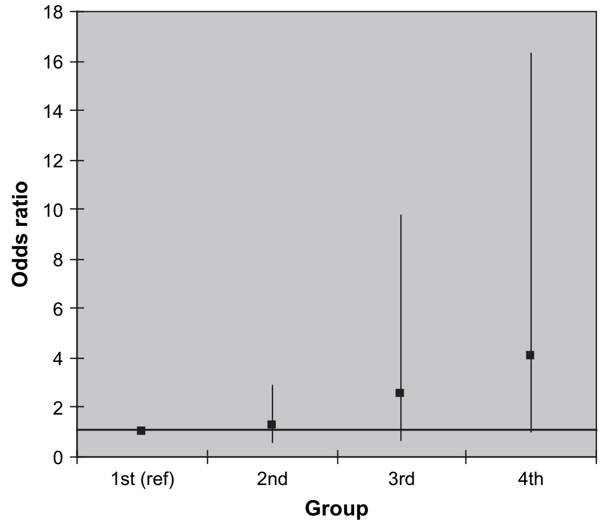

Figure 2. Odds ratios and 95% CI for hypertensive disorders in pregnancy by centiles of retinol intake in early pregnancy. Groups were divided into (1) 50th centile (reference); (2) 51th–90th centile; (3) 91th–95th centile; and (4) >95th centile. Weight gain during pregnancy, BMI × weight gain, smoking, parity and diastolic and systolic blood pressure early in pregnancy were adjusted for $P = 0.172$.

odds ratio for hypertensive disorders ($P = 0.008$) and gestational hypertension ($P = 0.035$) suggested a u-shaped curve in the present study, with the odds ratio being lowest in the second and third centiles. This corresponds to an intake of 0.1–0.9 g/day n-3 LCPUFA. The indications of a lower risk observed for pre-eclampsia after supplementation in the People's league of health study conducted in London in 1938–1939 was seen with doses of about 0.1 g/day of n-3 LCPUFA.[17]

Minimum requirements of total PUFA for adults are not known. The Nordic Nutrition Recommendations suggest a minimum intake of 5 E% including about 1 E% from n-3 fatty acids for women during pregnancy.[34] There is no differentiation made between n-3 LCPUFA and the more common linolenic acid (18:3n-3) found in vegetable oils. Prolonged intake of 1.5 E% n-3 LCPUFA has been shown to have negative consequences on bleeding and altered immune responses.[34] High intakes of total PUFA may also have untoward consequences through increased peroxidation.[34] Studies investigating the relationship between lipid peroxidation and oxidative stress in pre-eclampsia have focused not only on n-3 LCPUFA but also on total PUFA, n-6 PUFA and total n-3 PUFA.[8,24] We also considered the relationship of hypertensive disorders in pregnancy with total PUFA, n-6 PUFA and total n-3 PUFA, but did not arrive at any significant conclusions (data not shown).

Cod-liver oil is not only a rich source of n-3 LCPUFA but is also a good source of vitamins A, D and E. Cod-liver oil in Iceland is purified and controlled for dioxin and dioxin-like compounds. According to the Nordic Nutrition Recommendations, retinol intake during pregnancy should be limited to 3000 micrograms/day as it is teratogenic in high amounts.[34] Women using cod-liver oil were consuming almost this amount, or on average 2954 micrograms/day of retinol. Since the completion of the study, the retinol content of Icelandic cod-liver oil has been lowered, from 2400 to 460 micrograms in the common 10-ml dosage,[35] resulting in much lower retinol intakes.

There have only been few studies to evaluate the effect of vitamin D supplementation during pregnancy. Vitamin D supplementation seems to be well tolerated, but there is inadequate information about its safety.[36] The role of 1,25-dihydroxycholecalciferol (1,25-D), the active vitamin D, in the regulation of blood pressure is far from clear. Population studies have shown both positive and negative correlations between blood pressure and plasma levels of 1,25-D, and patients with essential hypertension have been found to have either elevated or a tendency to low plasma levels of 1,25-D.[37] We found a borderline increased likelihood of high blood pressure with high consumption of vitamin D when divided by centiles. We also tried to divide the participants into more groups separating the lowest centiles. This resulted in a u-shaped curve, but there was merely a trend for a borderline significant association ($P = 0.081$, data not shown). The number of participants limits our possibilities to investigate the dose–response further, but this would be an interesting topic for further studies.

The results indicate that large amounts of n-3 LCPUFA, rather than retinol and vitamin D, are associated with the effect on blood pressure and the related disorders in

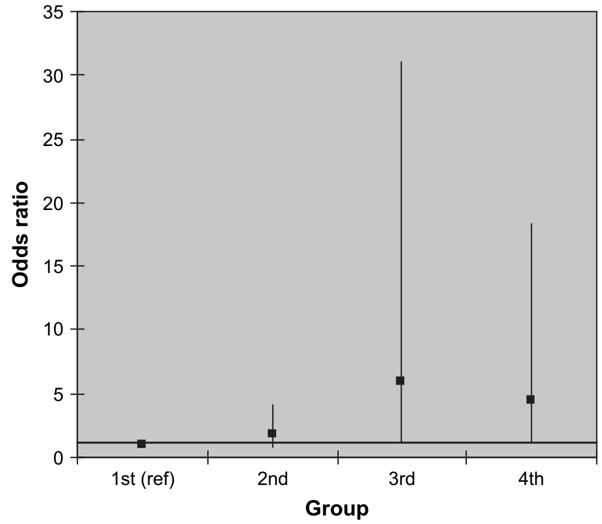

Figure 3. Odds ratios and 95% CI for hypertensive disorders in pregnancy by centiles of vitamin D intake in early pregnancy. Groups were divided into (1) 50th centile (reference); (2) 51th–90th centile; (3) 91th–95th centile; and (4) >95th centile. Weight gain during pregnancy, BMI × weight gain, smoking, parity and diastolic and systolic blood pressure early in pregnancy were adjusted for $P = 0.037$.

pregnancy. The relationship could, however, also result from some other lifestyle factor or nutrients not at all present in cod-liver oil. Many of the women who consumed liquid cod-liver oil also used vitamin supplements without vitamins A and D, and intake of these multivitamin supplements late in pregnancy was also found to be independently associated with the odds of getting hypertensive disorders in pregnancy ($P = 0.044$). However, we suspect that this association was found because of its close relationship with liquid cod-liver oil consumption. The fact that multivitamins with vitamins A and D, which are more common among women who do not consume cod-liver oil, were not found to be related to hypertensive disorders in pregnancy supports the suggestion that the higher prevalence of hypertensive disorders in pregnancy among liquid cod-liver oil consumers may as well be due to their way of living. Numerous surveys have shown that subjects with the highest nutrient intake are the most likely to take dietary supplements, and the most obvious predictor for cod-liver oil use is use of other dietary supplements.[27] Supplement use has been associated with several factors such as age, gender, BMI, socio-economic status, physical activity, alcohol consumption, smoking, education and diet. In general, their health behaviours are, however, associated with reduced risks of chronic diseases.[27]

We also considered other dietary factors that have been linked to hypertensive disorders in pregnancy.[3] These included calcium,[38,39] iron[40] and antioxiant vitamins,[41–43] and food groups containing these nutrients, i.e. milk, fruit, vegetables and fish. Several observational epidemiologic studies and some clinical trials have suggested an inverse association between dietary intake of fruits and vegetables and blood pressure.[44] Antioxidants in foods may have effects different from those of antioxidants in supplements and therefore it is important to consider consumption of both, separately and in combination. None of the above mentioned nutrients or foods could be fitted into the logistic regression models together with cod-liver oil, but we detected some associations (negative and positive) between variables on blood pressure and protein; vitamins A, C, D and E; β-carotene; iron; folic acid; calcium; milk; fruit and vegetables (data not shown). Possibly, the effect of antioxidants and other nutrients cannot be seen when liquid cod-liver oil is being used in the model because of the strong association of the latter to hypertensive disorders in pregnancy. These associations are, however, an interesting subject for further studies.

There are only limited data from well-controlled intervention studies with dietary supplements, and with few exceptions (iron, folate), the evidence is not strong that nutrient supplements confer measurable benefits in pregnancy.[45] The ability to prevent hypertensive disorders of pregnancy is limited by lack of knowledge of its underlying aetiology, including the possibility that pre-eclampsia and gestational hypertension may be two different entities.[33,41] Nevertheless, in the present study, a strong relationship was seen between maternal intake of liquid cod-liver oil and multivitamin supplements without vitamins A and D and hypertensive disorders in pregnancy as well as gestational hypertension alone. We also measured the relationship with pre-eclampsia alone, but less than 4% of the women developed pre-eclampsia in this prospective study, causing a limited power and thus an unstable model. Still a nonsignificant trend was seen for a relationship between liquid cod-liver oil intake and about four-fold increased likelihood of pre-eclampsia ($P = 0.081$).

The prospective, observational design of the present study is a strength, as it has been a major problem that virtually all studies on relationship between diet and gestational hypertension or pre-eclampsia are retrospective or they study biomarkers in women with the disease.[33] A further strength of our study is that the FFQ and questionnaires on lifestyle factors were administered both early and late in pregnancy, giving us the opportunity to investigate the relationship between diet and hypertensive disorders in pregnancy at both time points. The first FFQs were filled out between 11 and 15 weeks of gestation and assessed the entire diet over the previous 3-months. Thus, our findings on the relationship between liquid cod-liver oil and hypertensive disorders in pregnancy may as well apply periconceptionally, which is unique for studies on this topic. Adjustments were made for confounding factors that have been associated with hypertensive disorders in pregnancy in literature, i.e. weight gain during pregnancy,[46] smoking,[47,48] parity[49,50] and blood pressure early in gestation.[50] We also considered prepregnant BMI,[50,51] age[50] and several foods and nutrients.

Limitations also should be noted. We investigated a group of low-risk women, whereas most supplementation studies have investigated high-risk pregnancies.[20,23] Also, we chose not to include women who gave birth before 37 weeks of gestation. It could be suggested that this might cause bias in the data and loss of cases, as pre-eclampsia is often managed through induced labor before the disease progresses.[33] However, of the 17 women excluded because of preterm birth, there was only one woman defined with pre-eclampsia and one with gestational hypertension. The number of pregnant women consuming liquid cod-liver oil was not great. Therefore, we considered liquid cod-liver oil intake as a dichotomous variable, i.e. liquid cod-liver oil being consumed or not. Altogether, with relatively few women developing hypertensive disorders in pregnancy and a low number of liquid cod-liver oil consumers, the confidence intervals on the adjusted odds ratios are wide and accordingly the statistical power is limited. Nonetheless, the findings are statistically significant.

Hypertensive disorders remain the leading cause of morbidity and mortality in pregnancy eventhough outcome for most women and their babies is satisfactory.[1,4] Furthermore, there is a tendency to more ischaemic heart disease deaths in women who have suffered hypertensive disorders in pregnancy.[52] Thus, prevention of elevated blood pressure during pregnancy is not only a matter of prenatal health care but also important for women's health in general. High doses of n-3 LCPUFA in early pregnancy, or other nutrients found in liquid cod-liver oil, may increase the risk of developing hypertensive disorders in pregnancy. Certainly, n-3 LCPUFA may have positive health effects, but at a certain level of high amounts be detrimental, for example, for the development of hypertensive disorders in pregnancy. Maternal consumption of n-3 LCPUFA in adequate amounts is indeed important for growth and development of the fetus,[13] but the amount and proportion in which various LCPUFAs need to be provided for optimal health of the mother and fetus during the perinatal period is not known.[53] Thus, further studies investigating a safe amount would be of importance for a community with traditional cod-liver oil consumption.

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