Examining suspected dietary predictors of gestational hypertension in Iceland

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Thesis for the degree of Master of Science in Human Nutrition
Faculty of Human Nutrition and Food Science
School of Health Sciences
Thesis for the degree of Master of Science in Human Nutrition

Examining suspected dietary predictors of gestational hypertension in Iceland

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Academic Dissertation

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ABSTRACT

The aim of this study was to investigate the association between few specific dietary factors such as fish, fish liver oil, coffee and tea during pregnancy and hypertensive disorders in pregnancy. The research questions that will be addressed is whether high consumption of fish or fish liver oil during pregnancy among Icelandic women can increase the risk of gestational hypertension; and if whether coffee or tea intake during pregnancy can reduce the risk of developing preeclampsia.

A cohort of 491 pregnant Icelandic women who gave birth at landspitali National University Hospital, Reykjavik, Iceland in 1998. Women with pre-pregnant normal weight (BMI 19.5-25.5 kg/m²) were randomly selected from maternal records. The women were healthy before pregnancy, and had no history of hypertension, diabetes, cardiovascular disease, or thyroid problems. They were aged between 20-40 years old, and delivered singleton infants at 38–43 week of gestation. Information on dietary intake was collected from maternal records by a food frequency questionnaire (FFQ). Maternity records gave information on maternal age, height, marital status, pre-pregnant weight, gestational weight gain, smoking and parity. Information on gestational hypertension and preeclampsia was diagnosed at the Department of Obstetrics and Gynecology, Landspitali National University Hospital. We used gestational hypertension is defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg on two or more occasions after 20 weeks of gestation, but without proteinuria as a primary outcome measure. Systolic and diastolic, isolated systolic, and isolated diastolic hypertension were used as secondary outcome measures. Preeclampsia was diagnosed as gestational hypertension and proteinuria of ≥ 0.3 g/24h or at least 1+ on a dipstick.

In the first study we observed that the prevalence of gestational hypertension and preeclampsia was 102 (21%) and 15 (3%), respectively. Fish consumption was not associated with hypertensive disorders in pregnancy. Intake of fish liver oil was, however, positively associated with pregnancy hypertension defined as systolic blood pressure (SBP) ≥ 140 mmHg and diastolic blood pressure (DBP) ≥ 90 mmHg. Using this definition women consuming one table spoon (≈ 9g) a day or more had an adjusted odds ratio of 6.3 (95% CI 2.2; 17.9) of having pregnancy hypertension compared to those with no intake. This association appeared to be driven by a relative shift from isolated diastolic hypertension to combined systolic and diastolic hypertension as fish liver oil was not associated with hypertension defined as (SBP) ≥ 140 and/or (DBP) ≥ 90.
Our results suggest that high (≈ 9 g/day) intake of fish liver oil may affect the severity of gestational hypertension. These findings are in line with previous reports about other cohort from Iceland were high consumption of fish liver oil has been associated with hypertensive disorders in pregnancy.

In the second study we found that coffee was not associated with gestational hypertension defined as (SBP) ≥ 140 and/or (DBP) ≥ 90. Compared with non-coffee consumption, coffee consumption of the women during pregnancy was associated with a reduced risk of preeclampsia (crude odds ratio (OR) 0.16, 95% CI 0.04; 0.73). This association was also found after adjustment for covariates with adjusted OR of 0.15 (95% CI 0.03; 0.82). Tea intake, however, was not associated with hypertensive disorders in pregnancy.

Our results suggest that high intake of fish liver oil in pregnancy may be associated with an increased risk of gestational hypertension and moderate consumption of fish liver oil, thus, should be recommended. We can not rule out that substances other than n-3 LCPUFA in fish liver oil as vitamin A (retinol) and PCBs may influence gestational hypertension. Coffee consumption during pregnancy may lower risk of preeclampsia. However, reverse causality may also contribute to these findings. More research, however, is needed to confirm these findings and to investigate further elucidation of underlying pathophysiological mechanisms may indicate a role for coffee to prevent risk factors on hypertensive disorders in pregnancy.

**Key words:** Fish, fish liver oil, coffee, tea, gestational hypertension, preeclampsia and hypertensive disorders in pregnancy.
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1 INTRODUCTION

1.1 Background

Gestational hypertension and preeclampsia are common hypertensive disorders in pregnancy, associated with substantial morbidity and mortality for both mother and infants. The diagnosis of a hypertensive disorder in a pregnant woman depends, in part, upon the gestational age at presentation.

Gestational hypertension is defined as systolic blood pressure (SBP) $\geq 140$ mmHg and/or a diastolic blood pressure (DBP) $\geq 90$ mmHg, in the absence of proteinuria, in a previously normotensive pregnant woman at or after 20 weeks of gestation. Preeclampsia requires diagnosis of gestational hypertension, in addition to proteinuria. As the pregnancy progresses women diagnosed with gestational hypertension are at greater risk for developing preeclampsia.

Hypertensive disorders in pregnancy are serious maternal complications of pregnancy that affects 6% to 8% of all pregnancies in the United States. The etiology and pathogenesis of gestational hypertension and preeclampsia are mostly unknown. Preeclamptic pregnancies are characterized by endothelial dysfunction, disturbed placentation, oxidative stress, and an exaggerated inflammatory response to pregnancy. Most established risk factors for gestational hypertension or preeclampsia include maternal age, race/ethnicity, parity, and previously hypertension or preeclampsia. However, weight gain in women of normal weight before pregnancy has been associated with gestational hypertension and preeclampsia.

A number of dietary factors have been related to hypertensive disorders in pregnancy. Fish consumption, intake of fish liver oil supplements and caffeine intake such as coffee and tea consumption during pregnancy might be associated with gestational hypertension and preeclampsia.

1.2 Fish and fish liver oil consumption, and hypertensive disorders

Fish consumption and fish oil intake in pregnancy from our cohort have frequently been studied with respect to end points such as preterm delivery and size at birth, but fewer studies have addressed pregnancy complications such as gestational hypertension and preeclampsia. Some randomized controlled trials have suggested potential benefits of fish
oil intake on hypertensive disorders during pregnancy \textsuperscript{9-11}, while other studies have not found any association \textsuperscript{12, 13}. However, one cohort study reported that high intake of fish liver oil might be positively associated with pregnancy hypertension \textsuperscript{14}. As regular intakes of fish and even fish oil are frequently encouraged for pregnant women, it is important to investigate their associations with pregnancy complications.

\textbf{1.3 Coffee and tea intake, and hypertensive disorders}

Caffeine has been used for thousands of years and is one of the most widely consumed active food ingredients throughout the world \textsuperscript{15}. Caffeine is present in certain prescriptions and over the counter medications \textsuperscript{16} and beneficial health effects of caffeine on specific diseases, including insulin resistance, cancer and cardiovascular disease \textsuperscript{17}. Adverse effects of caffeine on blood pressure and risk of gestational hypertension have been reported \textsuperscript{7}.

Coffee and tea are the main sources of caffeine intake. Coffee contains 50 to 70 percent more caffeine than tea, accounting for the main source of caffeine in many populations \textsuperscript{18}. Prospective cohort studies have found coffee consumption to be associated with increased risk of hypertension \textsuperscript{19, 20}, but other studies found no association \textsuperscript{21} or even an inverse association between high coffee consumption and a lower risk of hypertension in women \textsuperscript{22}. For pregnant women, caffeine consumption through coffee and tea have been associated with reduced risk of preeclampsia \textsuperscript{23}.

In recent years, there has been a growing interest in exploring the effects of tea in various vascular diseases \textsuperscript{24}. Observational studies have reported that habitual consumption of green tea significantly reduced the risk of developing hypertension in non-pregnant women \textsuperscript{25, 26}. However, one retrospective study suggested that persistent tea consumption during pregnancy might be associated with an increased risk of preeclampsia, especially severe preeclampsia, while no association was found for coffee consumption \textsuperscript{27}.

\textbf{1.4 Dietary intake of fish, fish liver oil, coffee and tea in Iceland}

High fish and fish liver oil intake has been a characteristic of the Icelandic diet through the last decades. According to the national nutritional survey in 1990 \textsuperscript{28}, each Icelandic woman at age 20-49 consumed on average 54 g fish; fish liver oil 2 g; coffee 648 g; and tea 108 g per day, which was among the highest in Europe at that time. The Icelandic Nutrition Council published its results on the latest national nutritional survey, carried
out in 2002. The results are alarming concern the fish and fish liver oil consumption. On average each Icelandic woman in the age group 20-39 years was consuming 23 g per day of fish, 1 g per day of fish liver oil, 231 g per day of coffee and 58 g per day of tea. These are meaning that dietary intake as fish, fish liver oil, coffee and tea has decreased by 50% in 2002. The methods used for the national survey in 1990 and 2002 differ, i.e. being dietary history 1990 and 24-hour recall 2002. However, the difference in fish consumption and fish liver oil is much larger than any methodological difference could explain. Despite recent temporal decrease in intake of fish and fish liver oil in Iceland, the level of consumption observed in our study participants from 1998 should still be comparable to the level of intake in 2002, at least for some portion of the population.

1.5 Aim

Therefore, the aims of the present study were to:

- Investigate the associations between fish consumption and intake of cod liver oil supplements during pregnancy among Icelandic women with hypertensive disorders in pregnancy.
- Examine the associations between caffeine intake such as coffee and tea consumption during pregnancy and the risks of gestational hypertension and preeclampsia.
2 MATERIALS AND METHODS

2.1 Study participants
Women of pre-pregnant normal weight (N = 615) were randomly selected from maternal records of subjects giving birth at Landspitali in 1998, and fulfilled the 1-year inclusion criteria. The women were healthy before pregnancy, and had no history of hypertension, diabetes, cardiovascular disease, or thyroid problems. They were aged between 20-40 years old, had a pre-pregnancy normal weight (body mass index (BMI) of 19.5-25.5 kg/m²) and delivered singleton infants at 38-43 week of gestation, based on term assessment fetal biometry at an 18-20 week ultrasound examination. All women received early and regular antenatal care at Landspitali.

Retrospective data collection on maternal age, height, marital status, pre-pregnant weight, gestational weight gain, smoking and parity was collected from maternity records as well as information on gestational hypertension and preeclampsia diagnosis at the Department of Obstetrics and Gynecology. A focused food frequency questionnaire was sent to the women who agreed to participate and collecting information from their maternity records after the birth of their infant (n = 614), with an 80.1% response rate (n = 491). This corresponded to 11.8% of all births in the country during the study year. The study was approved by the Hospital Ethical Committee (institutional review board) at Landspitali and the Icelandic Data Protection Commission.

2.2 Outcome definitions
Information on gestational hypertension and preeclampsia were extracted from maternal records. Hypertensive disorders in pregnancy were defined as gestational hypertension and preeclampsia, according to the recommendations of the US National High Blood Pressure Education Program. Gestational hypertension was defined as a blood pressure of systolic ≥ 140 mmHg and/or diastolic ≥ 90 mmHg on at least two occasions at least six hours apart after 20 weeks of pregnancy. We also examined women with isolated systolic hypertension (SBP ≥ 140); isolated diastolic hypertension (DBP ≥ 90); and combined systolic and diastolic hypertension (SBP ≥ 140 and DBP ≥ 90). Preeclampsia was diagnosed as gestational hypertension and proteinuria with excretion (of 0.3 grams or greater in a 24-hour urine specimen (at least 1+ on dipstick value on two or more
occasions or ≥ 2+ once) in at least two random urine samples collected at least 6 hours apart) after 20 weeks of gestation in a previously normotensive women.

2.3 Exposure assessment
The Food Frequency Questionnaire contained 11 questions. The food frequency questionnaire (FFQ), a letter and an envelope with a stamp, in order to return the FFQ to the Unit for nutrition Research, was sent to 614 women after pregnancy. The FFQ collected information on both frequency of fish consumption as a main meal and as bread spread during pregnancy; as well as the amount of cod liver oil intake as capsules, teaspoons or tablespoons per day. The validation of the FFQ has been described earlier and was found to be a good measure of frequency of fish intake and intake of cod liver oil \(^8\). In our analyses, frequency of fish consumption was divided into three groups as < 4 times, 4-6 times and > 6 times per month.

Intake of cod liver oil was divided into four groups, with the lowest group reporting no intake and three groups of consuming > 0-1 g, > 1-9 g and > 9 g per day. Nutrient content of fish liver oil was calculated at the time of the study, using the Icelandic Nutrition Database (ISGEM). One tablespoon of cod liver oil is approximately 9 grams and includes around 1.8 g of n-3 LCPUFA \(^14\).

Information on consumption of coffee and tea was obtained by the food frequency questionnaire (FFQ). In our analyses, frequency (times per day) of coffee and tea intake during pregnancy was recorded. The frequency of coffee and tea consumption was divided into three intake groups of 0, < 1 and ≥ 1 times per day.

2.4 Statistical analysis
2.4.1 Fish and fish liver oil
Descriptive statistics including mean, SD (standard deviation), frequency and percentage were used for describing intakes of fish and fish liver oil and their crude associations with hypertensive disorders. Logistic regression was used to examine covariate adjusted associations between intake of fish and fish liver oil and hypertensive disorders. A priori, we identified and selected the following covariates: smoking, pre-pregnancy BMI (body mass index (kg/m\(^2\))), weight gain in pregnancy, age, parity. We also adjusted for fish when examining the separate effects of fish liver oil on hypertensive disorders and vice versa. Statistical analyses were performed in SPSS version 17 and P-value < 0.05 was considered statistically significant.
2.4.2 Coffee and tea

The data are described by values of mean and SD (standard deviation) as well as percentages. We compared mean and SD between coffee consumption groups at baseline, using ANOVA, and percentages, using Pearson chi-squared test. Multivariable logistic regression was used to examine the associations between coffee and tea consumption with gestational hypertension and preeclampsia. Adjusted models controlled for covariates: smoking, pre-pregnancy BMI (body mass index (kg/m^2)), weight gain in pregnancy, maternal age and parity. Data were analyzed using SPSS version 17 (SPSS Inc., Chicago, IL) and a P < 0.05 level was considered statistically significant.
3 RESULTS

3.1 Fish as main meal and bread spread

In the food frequency questionnaire (FFQ) the women were asked separately about fish they consumed as main meal and how much as bread spread. The results for the frequency of fish consumption as main meal are found in Table 1.

Table 1. Frequency of fish consumption

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Fish as main meal</th>
<th>Fish as bread spread</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Every day</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4-6 times a week</td>
<td>10</td>
<td>2.0</td>
</tr>
<tr>
<td>2-3 times a week</td>
<td>171</td>
<td>34.8</td>
</tr>
<tr>
<td>4-6 times a month</td>
<td>247</td>
<td>50.3</td>
</tr>
<tr>
<td>1-3 times a month</td>
<td>54</td>
<td>11.0</td>
</tr>
<tr>
<td>Rarely</td>
<td>4</td>
<td>0.8</td>
</tr>
<tr>
<td>Never</td>
<td>5</td>
<td>1.0</td>
</tr>
<tr>
<td>Total</td>
<td>491</td>
<td>100</td>
</tr>
</tbody>
</table>

When looking at the two studies, one can see how many are consuming fish less than once a week, i.e. 13%, and how many are consuming fish at least once a week, i.e. 87%.

The largest group, 32.2% claims to have fish as bread spread approximately 4-6 times a month and the second largest, 25.1%, 1-3 times per month. Around 33.6% claim that they rarely or never have fish as bread spread compared to only 1.8% of women who rarely consume fish as a main meal.

3.2 Fish and fish liver oil consumption characteristics

Table 2 shows the mean total fish and fish liver oil consumption among pregnant women. Mean total of fish consumption is 56 g/day, 52 g as main meal and 4 g as bread spread. Fish liver oil does not only contain n-3 fatty acids. It is one of the best sources for vitamin A and D known. Mean total of fish liver oil consumption is 2.3 g/day for all participants (n = 485). Mean fish liver oil consumption only for consumers is 5.1g/day (n = 218),
including 1.7 g of n-3 fatty acids, 0.6 g of EPA (eicosapentaenoic acid) and 1.0 g of DHA (docosahexaenoic acid).

Table 2. Fish and fish liver oil consumption characteristics (g/day)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fish as main meal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-3 fatty acids</td>
<td>491</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>EPA</td>
<td></td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>DHA</td>
<td></td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Fish as bread spread</strong></td>
<td>490</td>
<td>0.05</td>
<td>0.10</td>
</tr>
<tr>
<td>n-3 fatty acids</td>
<td></td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>EPA</td>
<td></td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>DHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fish liver oil (No and Yes)</strong></td>
<td>485</td>
<td>2.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Fish liver oil (yes)</td>
<td>218</td>
<td>5.1</td>
<td>5.2</td>
</tr>
<tr>
<td>n-3 fatty acids</td>
<td></td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>EPA</td>
<td></td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>DHA</td>
<td></td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Vitamin A (μg/day)</td>
<td></td>
<td>1,760</td>
<td>1,556</td>
</tr>
<tr>
<td>Vitamin D (μg/day)</td>
<td></td>
<td>14.0</td>
<td>12.1</td>
</tr>
</tbody>
</table>

EPA: Eicosapentaenoic acid  
DHA: Docosahexaenoic acid

3.3 The use of coffee, tea and energy drinks

The questions concerning coffee, tea and energy drinks in the FFQ were aimed at drinks containing caffeine. Table 3 shows the consumption of coffee, tea and energy. From the 47% of pregnant women who drank coffee 31% said that they drank coffee every day and the most common answer for amount was 2-3 cups/day (28%) or approximately 400-600 g/day. Mean coffee consumption among women who consumed coffee is 1.9 cups/day. The most common answer for tea was that it was consumed every day (17%) and the most common amount answer was 2-3 cups/day (18.5%). Mean tea consumption for consumers is 1.5 cups/day.
Table 3. Consumption of coffee, tea and energy drinks

<table>
<thead>
<tr>
<th></th>
<th>Yes (%)</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee</td>
<td>232 (47)</td>
<td>257 (53)</td>
</tr>
<tr>
<td>Tea</td>
<td>183 (37)</td>
<td>306 (63)</td>
</tr>
<tr>
<td>Energy drinks</td>
<td>16 (3)</td>
<td>473 (97)</td>
</tr>
<tr>
<td>Total</td>
<td>331 (68)</td>
<td>159 (32)</td>
</tr>
</tbody>
</table>

3.4 Fish and fish liver oil consumption and gestational hypertension

In comparison to normotensive women (Table 4), those diagnosed with gestational hypertensions, had a higher mean gestational weight gain, were less likely than to be parous and were more likely than to be non-smokers (P-values < 0.05). Overall 21% of the participants developed gestational hypertension (SBP ≥ 140 and/or DBP ≥ 90), 16% developed isolated diastolic hypertension (SBP < 140 and DBP ≥ 90); none of the participants had isolated systolic hypertension (SBP ≥ 140 and DBP < 90); 5% developed combined systolic and diastolic hypertension (SBP ≥ 140 and DBP ≥ 90), and 3% were diagnosed with preeclampsia in pregnancy (Table 4).
Table 4. Characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>Normotensive women n = 373 (76%)</th>
<th>Hypertension systolic and/or diastolic n = 103 (21%)</th>
<th>Hypertension diastolic n = 79 (16%)</th>
<th>Hypertension systolic and diastolic n = 24 (5%)</th>
<th>Preeclampsia n = 15 (3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>P</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>29.3</td>
<td>4.7</td>
<td>28.0*</td>
<td>4.9</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Height (m)</strong></td>
<td>1.68</td>
<td>0.06</td>
<td>1.68</td>
<td>0.05</td>
<td>0.97</td>
</tr>
<tr>
<td><strong>Pre-pregnancy weight (kg)</strong></td>
<td>62.7</td>
<td>6.2</td>
<td>63.3</td>
<td>5.6</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Pre-pregnancy BMI (kg/m²)</strong></td>
<td>22.2</td>
<td>1.6</td>
<td>22.4</td>
<td>1.6</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Gestational weight gain (kg)</strong></td>
<td>16.3</td>
<td>4.7</td>
<td>17.9*</td>
<td>5.1</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Smoking (%)</strong></td>
<td>18</td>
<td>9</td>
<td>9</td>
<td>5.1</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Nulliparous (%)</strong></td>
<td>34</td>
<td>58</td>
<td>58</td>
<td>58</td>
<td>0.002**</td>
</tr>
<tr>
<td><strong>Fish consumption (g/day)</strong></td>
<td>53.5</td>
<td>37.5</td>
<td>48.3</td>
<td>29.0</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Fish liver oil intake (g/day)</strong></td>
<td>2.0</td>
<td>4.1</td>
<td>4.1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

1 None is diagnosed only with systolic hypertension
SD: standard deviation
BMI: body mass index
* Comparison to normotensive women using ANOVA, LSD Post hoc test and P-value < 0.05, significant differences
** Chi-squared test and P-value < 0.05, significant differences
Mutual distribution of fish and fish liver oil is shown in (Table 5). A weak positive association was observed between daily intake of fish liver oil and frequency of monthly fish consumption ($P = 0.05$, $\chi^2$). All study participants reported consumption of fish as a main meal or as bread spread monthly during pregnancy, while 44% ($n = 215$) reported intake of fish liver oil.

Table 5. Mutual distribution of fish liver oil and fish intake among the participating mothers ($n = 491$)

<table>
<thead>
<tr>
<th>Fish liver oil (g/day)</th>
<th>Case n (%)</th>
<th>&lt; 4/month</th>
<th>4-6/month</th>
<th>&gt; 6/month</th>
<th>$P^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>63 (13%)</td>
<td>245 (50%)</td>
<td>177 (37%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>273 (56%)</td>
<td>64</td>
<td>61</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>&gt; 0-1</td>
<td>68 (14%)</td>
<td>14</td>
<td>11</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>&gt; 1-9</td>
<td>78 (16%)</td>
<td>10</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>&gt; 9</td>
<td>66 (14%)</td>
<td>12</td>
<td>11</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

$^1$Chi-squared tests

Table 6 shows the crude associations between frequency of fish consumption and fish liver oil with the risk of gestational hypertension or preeclampsia. No association was observed between either fish liver oil intake or fish intake and gestational hypertension defined as a SBP $\geq 140$ and/or DBP $\geq 90$ mmHg; nor with preeclampsia. When looking at sub-types of hypertension, there was a borderline significant inverse trend between intake of fish liver oil and reduced risk of isolated diastolic hypertension (DBP $\geq 90$, $P = 0.08$) while there was also a relatively strong positive association between high intake of fish liver oil and increased risk of combined SBP $\geq 140$ and DBP $\geq 90$ hypertension ($P = 0.006$). In contrast to these findings for fish liver oil, frequent fish consumption was modestly associated with reduced risk of systolic and diastolic hypertension ($P = 0.05$) in the crude analyses.
Table 6. Gestational hypertension and preeclampsia according to use divided by fish consumption and fish liver oil intake (n = 491)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fish consumption per month</th>
<th>Amount of fish liver oil (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases n (%)</td>
<td>&lt; 4 times</td>
</tr>
<tr>
<td></td>
<td>Percent of cases</td>
<td>63 (13)</td>
</tr>
<tr>
<td>Gestational Hypertension (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic ≥ 140 and diastolic ≥ 90</td>
<td>103 (21)</td>
<td>25.4</td>
</tr>
<tr>
<td>Systolic &lt; 140 and diastolic ≥ 90</td>
<td>79 (16)</td>
<td>14.3</td>
</tr>
<tr>
<td>Systolic ≥ 140 and diastolic ≥ 90</td>
<td>24 (5)</td>
<td>11.1</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>15 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>p<sup>1</sup> Statistical analysis using Pearson chi-squared tests for trend in proportions
In the multivariate analyses (Table 7) there was no association between intake of fish liver oil with either gestational hypertension, defined as SBP ≥ 140 and/or DBP ≥ 90; or preeclampsia. Despite an overall lack of association between cod liver oil and total gestational hypertension (SBP ≥ 140 and/or DBP ≥ 90), highest intake of fish liver oil was associated with increased risk of both systolic and diastolic hypertension defined as SBP ≥ 140 and DBP ≥ 90 with adjusted odds ratio of 6.3, (95% CI 2.22; 17.9). The risk of diastolic hypertension (DBP ≥ 90) is so much lower with adjusted odds ratio of 0.3 (95% CI 0.1; 0.89) in the highest fish liver oil consumption group compared to those not consuming. This increase in risk of both systolic and diastolic hypertension was therefore followed by a relative decrease in subjects with isolated diastolic hypertension (DBP ≥ 90). The higher risk of both systolic and diastolic hypertension (SBP≥ 140 and DBP ≥ 90) is in women, consuming 1-9 g/day, but this was not significantly different from the group consuming no cod liver oil with adjusted odds ratio of 1.27, (95% CI 0.32; 4.98). No association was, however, observed between fish consumption and gestational hypertension or preeclampsia in the covariate adjusted analyses.
Table 7. Hypertensive disorders in pregnancy according to use by frequency of fish consumption and amount of fish liver oil

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fish consumption per month</th>
<th></th>
<th>Amount of fish liver oil (g/day)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 4 times</td>
<td>4-6 times</td>
<td>&gt; 6 times</td>
<td>0</td>
<td>&gt; 0-1</td>
</tr>
<tr>
<td>OR (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gestational Hypertension (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic ≥ 140 and/or diastolic ≥ 90</td>
<td>1</td>
<td>0.89 (0.45; 1.75)</td>
<td>0.8 (0.38; 1.67)</td>
<td>1</td>
<td>0.82 (0.4; 1.6)</td>
</tr>
<tr>
<td>Systolic &lt; 140 and diastolic ≥ 90</td>
<td>1</td>
<td>1.3 (0.58; 2.9)</td>
<td>1.33 (0.55; 3.2)</td>
<td>1</td>
<td>0.78 (0.38; 1.65)</td>
</tr>
<tr>
<td>Systolic ≥ 140 and diastolic ≥ 90</td>
<td>1</td>
<td>0.37 (0.12; 1.12)</td>
<td>0.35 (0.1; 1.17)</td>
<td>1</td>
<td>0.93 (0.2; 4.5)</td>
</tr>
<tr>
<td>≤ 6 times</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 6 times</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Preeclampsia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.95 (0.3; 3)</td>
<td></td>
<td>1</td>
<td>0.6 (0.12; 2.97)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjusted for smoking, pre-pregnancy BMI (kg/m<sup>2</sup>), gestational weight gain, age, parity and fish liver oil intake

<sup>b</sup>Adjusted for smoking, pre-pregnancy BMI (kg/m<sup>2</sup>), gestational weight gain, age, parity and fish consumption

OR is odds ratio for hypertensive disorders in pregnancy by fish and fish liver oil consumption.
3.5 Coffee and tea, and preeclampsia

Characteristics of the pregnant mothers according to coffee consumption during pregnancy are shown in (Table 8). The mean maternal age increased with coffee consumption (P < 0.001). As compared to non-coffee consumers, those reporting coffee consumption, were significantly more likely to be smokers (P < 0.001), and were less likely to be nulliparous (P = 0.002).

Table 8. Descriptive and obstetric characteristics of study participants according to coffee intake (n = 487)*

<table>
<thead>
<tr>
<th>Frequency of coffee consumption (times/day)</th>
<th>0 n = 257 (53%)</th>
<th>&lt; 1 n = 77 (16%)</th>
<th>≥ 1 n = 153 (31%)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>27.6 (4.4)</td>
<td>28.7 (4.6)</td>
<td>31.4 (4.6)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.68 (0.05)</td>
<td>1.68 (0.06)</td>
<td>1.68 (0.06)</td>
<td>0.7</td>
</tr>
<tr>
<td>Pre-pregnancy weight (kg)</td>
<td>62.5 (6.1)</td>
<td>62.5 (5.6)</td>
<td>63.3 (6.3)</td>
<td>0.45</td>
</tr>
<tr>
<td>Pre-pregnancy BMI (kg/m²)</td>
<td>22.2 (1.6)</td>
<td>22.3 (1.6)</td>
<td>22.2 (1.6)</td>
<td>0.68</td>
</tr>
<tr>
<td>Gestational weight gain (kg)</td>
<td>17.0 (5.0)</td>
<td>16.0 (4.2)</td>
<td>16.6 (4.8)</td>
<td>0.14</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>7.7</td>
<td>10.8</td>
<td>32.7</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Nulliparous (%)</td>
<td>47.5</td>
<td>41.6</td>
<td>28.8</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

Abbreviations: SD standard deviation, BMI body mass index
*Values are given as mean ± SD or percentage. Using ANOVA analysis or Pearson chi-squared test in comparisons between the groups
* P-values < 0.05 shown significant differences

Mutual distribution of coffee and tea intake during pregnancy are shown in (Table 9). Coffee consumption was positively associated with frequency of daily tea intake of women during pregnancy (P = 0.002, χ²). There are 47% (n = 230) of the mothers reported coffee consumption during pregnancy and 37.5% (n = 183) tea consumption.
Table 9. Distribution of coffee consumption according to frequency of tea intake (n = 487)*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases n (%)</th>
<th>0 (304 (62.5))</th>
<th>&lt; 1 (100 (20.5))</th>
<th>≥ 1 (83 (17))</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee (times/day)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>257 (53)</td>
<td>55.3</td>
<td>59.0</td>
<td>36.1</td>
<td>0.002*</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>77 (16)</td>
<td>13.2</td>
<td>36.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>≥ 1</td>
<td>153 (31)</td>
<td>31.5</td>
<td>5.0</td>
<td>62.7</td>
<td></td>
</tr>
</tbody>
</table>

* Chi-squared analysis using Pearson chi-squared tests for trend in proportions
* Statistically significant difference at P < 0.01 level with 95% confidence interval
% within frequency of dietary consumption of mothers during pregnancy

In Table 10, results for gestational hypertension and preeclampsia are shown. Coffee consumption during pregnancy was associated with a reduced risk of preeclampsia (crude odds ratio (OR) 0.16, 95% CI 0.04; 0.73). This association was also found after adjustment for covariates with adjusted OR of 0.15 (95% CI 0.03; 0.82). No association was observed between tea intake and preeclampsia and consumption of tea and coffee were not associated with gestational hypertension.

Table 10. The association between coffee and tea consumption and risk of hypertensive disorders in pregnancy (n = 489)

<table>
<thead>
<tr>
<th>Preeclampsia (n = 15; 3%)</th>
<th>Hypertension (n = 103; 21%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases/N</td>
<td>Crude OR (95% CI)</td>
</tr>
<tr>
<td>Coffee</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13/257</td>
</tr>
<tr>
<td>Yes</td>
<td>2/232</td>
</tr>
<tr>
<td>Tea</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9/306</td>
</tr>
<tr>
<td>Yes</td>
<td>6/183</td>
</tr>
</tbody>
</table>

N value is amount of mothers in coffee and tea consumption with No or Yes
* Adjusted odds ratio (95% CI) for smoking, pre-pregnancy BMI, weight gain in pregnancy, maternal age and parity
* P-value < 0.05: statistically significant. Before and after adjustment (P = 0.018 and P = 0.03)
4 DISCUSSION

In the present study, we will discuss that mean dietary intake of pregnant women as fish, fish liver oil, coffee and tea from the FFQ, compared with the national nutrition survey 2002. Then, we become to discuss their effects on risks of hypertensive disorders in pregnancy.

4.1 Fish as main meal and bread spread

The frequency of fish consumption according to the FFQ is comparable with results for the women in the age group 20-39 from the released national nutritional survey, carried out by the Icelandic Nutrition Council in 2002. Although the categories given are not the same the FFQ and the Icelandic Nutritional Council survey they can still be compared. When looking at the two studies, one can see how many are consuming fish less than once a week, i.e. 13% according to the FFQ and 14% according to the National Nutrition Council, and how many are consuming fish more than once a week, i.e. 87% according the FFQ and 85% according to the Icelandic Nutrition Council. The FFQ gives results of higher fish consumption than the survey.

The use of fish as bread spread has never been as common in Iceland as in the other Nordic countries although now, through more availability of farmed fish, the formerly more expensive products, like smoked salmon, are accessible for the majority of people the whole year. In our study, fish consumption of pregnant women, the largest group, 32.2% claims to have fish as bread spread approximately 4-6 times a month and the second largest, 25.1%, 1-3 times per month.

4.2 Fish and fish liver oil consumption characteristics

The FFQ shows the estimated fish consumption of pregnant women in our study from 1998, but the national nutrition survey shows fish consumption of women in reproductive age regardless if they are pregnant or not in the survey 2002. The FFQ shows that consumption level reported in our study from 1998 is at least partly comparable to the national nutrition survey in 2002. The fish consumption in Iceland has been reduced in the last years. In 2002 the mean fish consumption of women in age group 20-39 (23 g/day) is about 50% less than in the survey before, carried out in 1990 with women at age
20-49 (54 g/day), and in our study 1998, pregnant women 20-40 years are 56 g/day. No one explanation is likely to be the cause of these changes. The diet of Icelanders is becoming more like the diet of other western industrialized nations, which is in some ways positive as higher consumption of vegetables and in other ways negative reflected by lower fish consumption. Reduction in fish consumption may be partly compensated with increased consumption of vegetables. In the last years the price for fish has been steadily increasing. Today fish is in some cases more expensive than meat and which is for Icelanders that fish has always been regarded as an inferior product, the daily bread so to speak.

Also the fact that the women answering the FFQ were pregnant can have influenced their diet, as fish is regarded to be healthy, rich of proteins and have less fat than meat.

The regular consumption of fish liver oil, most commonly cod liver oil, has been a strong characteristic of Icelandic diet in the last decades. In our cohort study (n = 491), almost the half of the women (44.8%, n = 218) consumed fish liver oil during their pregnancy. Most 190 women of 218, reported to have consumed fish liver oil throughout during pregnancy in 1998. In 2002 the mean fish liver oil consumption of women in age group 20-39 (1 g/day) is about 60% less than in comparison with the FFQ, carried out in our cohort study, 1998 with pregnant women at age 20-40 (2.3 g/day). It can also not explain which cause that may lead these changes. The fact that pregnant women in our study were pregnant can have influenced their fish liver oil supplementation, as fish liver oil is regarded to be healthy of the mother and infant, rich of n3-fatty acids as n-3 LCPUFA, EPA and DHA that it can reduce risk of developing gestational hypertension, and vitamin A and D supplementation.

In our study, women who took fish liver oil in full tablespoon (≥ 9 g) every day (n = 66, 14%) were receiving about 4000 μg vitamin A and 30 μg vitamin D. For the general public it is recommended that vitamin A does not exceed 7500 μg/day and that the pregnant women should avoid consuming more than 3000 μg/day because of possible adverse effects on foetus. The toxic level of vitamin D is not as well known but it is recommended that no more than 50 μg/day is consumed. So that vitamin D amount remains below any potential toxic level, although amount of vitamin A is upper intake level. In Iceland, however, there are no reports concerning vitamin A hypervitaminosis, either from fish liver oil or other sources. Fish liver oil also contains persistent pollutants such as dioxins and PCBs and although the amount of these pollutants is very high compared to most other foods it is still well below regulated levels.
4.3 The use of coffee, tea and energy drinks

In our cohort study, 232 pregnant women reported to have consumed coffee and 183 women consumed tea during pregnancy in 1998. In 2002 the mean coffee consumption (231 g/day or approximately 1 cup/day) and mean tea intake (58 g/day or ¼ cups/day) of women in age group 20-39. These are less than in comparison with the FFQ, carried out in our cohort study, 1998 with pregnant women at age 20-40, who consume mostly common amount of coffee and tea 2-3 cups/day and mean coffee consumption 1.9 cups/day and mean tea consumption 1.5 cups/day or mean both coffee and tea consumption 1-2 cups/day.

4.4 Fish and fish liver oil and risk of gestational hypertension

This observational study investigated the relationship between consumption of fish and fish liver oil in pregnancy and risk of hypertensive disorders. Fish consumption was not associated with increase in risk of gestational hypertension. No association was also observed between intake of fish liver oil and gestational hypertension; defined as SBP ≥ 140 and/or DBP ≥ 90 (including total of different types of hypertension: systolic and diastolic, isolated systolic, and isolated diastolic). Although the overall rate of gestational hypertension did not increase, high intake of fish liver oil appeared to be associated with a relative shift from isolated diastolic hypertension to the more severe combined (SBP ≥ 140 and DBP ≥ 90) gestational hypertension. No association was found between intake of fish or fish liver oil and preeclampsia in this small sample.

The prevalence of gestational hypertension (SBP ≥ 140 and/or DBP ≥ 90) and preeclampsia in our sample was 21% and 3%, respectively. This is high compared to some other studies were the prevalence of gestational hypertension has ranged between 6% to 17%; and the prevalence of preeclampsia between 2% to 7% in healthy nulliparous women. One prospective cohort study of women in 2001 was to determine the effects of nutrient intakes on hypertensive disorders in pregnancy, reported that the prevalence of gestational hypertension and preeclampsia was 17.3% and 7.6%. Similar to our findings a previous study from Iceland suggested that high intake of fish liver oil may be associated with increased risk of developing combined gestational hypertension (SBP ≥ 140 and DBP ≥ 90) in pregnancy. Given the frequent and rather high consumption of fish liver oil in our data, this could be one explaining factor for the relatively high prevalence of gestational hypertension in our study population. Furthermore, higher prevalence of gestational hypertension in our study is 21% including
systolic and diastolic (5%), isolated systolic (0%), and isolated diastolic (16%). Because as a previous study from Iceland investigated only with type of systolic and diastolic hypertension, but not with types of isolated systolic and isolated diastolic hypertension and the prevalence of gestational hypertension is 6.8% 14.

Previous studies have shown that fish oil may possess a cardio-protective effect 34, 35. Based on those studies, it has been suggested that fish oil might be protective against hypertensive disorders in pregnancy 36. Results from clinical trials have provided strong evidence for the role of fish oil containing high amount of long chain omega-3 polyunsaturated fatty acids (n-3 LCPUFA) in reducing circulating triglycerides, decreasing platelet and leukocyte reactivity for heart disease prevention 37, 38. The n-3 fatty acids decrease the production of thromboxane A2 of platelets and monocytes, and increase prostacyclin I2 synthesis and related vasodilation 2, 39. Thromboxane A2 causes blood platelets to stick together, which encourages blood clots, and increases blood pressure. As n-3 fatty acids have the potential to decrease thromboxane A2, they can decrease blood viscosity, perhaps preventing blood clots, and lower blood pressure 40. Some studies have indicated that high doses of fish oil could reduce blood pressure in individuals with primary hypertension 41, 42. However, in contrast to the suggested beneficial effect of fish oil on hypertensive disorders, some randomized controlled trials have not detected any association between intake of fish oil during pregnancy with either gestational hypertension or preeclampsia 12, 13, even at relatively high doses of n-3 PUFA (3g/day) 13.

Our findings are in accordance with a previous Icelandic study on relation between fish liver oil and hypertension defined as SBP ≥ 140 and DBP ≥ 90 in pregnancy 14. This study was conducted in a similar time period as our study. The consistency between these two cohorts and the fact that intake of fish liver oil 14 or n-3 PUFA 43 has also been associated with increased risk of preeclampsia in a larger experimental setting, does suggest that very high intake of fish liver oil may in some cases be detrimental with respect to hypertensive disorders in pregnancy.

Although positive association between high intakes of fish liver oil has been observed in two different Icelandic cohorts it is not straight forward to come up with a plausible mechanism for these findings. Fish liver oil does not only contain n-3 fatty acids. It is one of the best sources for vitamin A and D known. The recommended dietary allowance (RDA) of retinol for pregnant women is 770 μg (2600 IU) for women 19 years
and older with upper intake limit of 3000 μg (10000 IU) per day. We estimated that women with the highest intake of fish liver oil (≥ 9 g/day) in our study might have consumed up to 3600 μg/day of retinol or approximately 4000 μg/day of vitamin A. It has been hypothesized that high intakes of retinol or vitamin A might be responsible for the potential adverse effect of fish liver oil on pregnancy hypertension. There is, however, currently little evidence to support this hypothesis. A study on serum antioxidant vitamins and hypertension in the United States found that serum antioxidant vitamin levels (vitamin A, C, E and β carotene) were significantly higher in hypertensive subjects compared with normotensive. After adjusting for gender and race, serum A and E vitamins were positively and significantly associated with higher odds of both systolic and diastolic hypertension, while serum α-carotene, β-carotene and vitamin C were significantly related with lower odds of hypertension. Fish oil supplements are also a source of persistent pollutants such as polychlorinated biphenyls (PCBs) and dioxins. Levels of PCBs are often considerably higher in fish liver oil compared to conventional fish oils. Epidemiological studies have also suggested that exposures to PCBs might increase the risk of hypertension in middle aged subjects. Furthermore, modest intake of oily fish during pregnancy has been linked with substantial (≈ 50%) increase in blood PCBs levels. There is therefore some indirect evidence to suggest that exposure to vitamin A or retinol and PCBs through high intake of fish liver oil during pregnancy may explain the positive association between fish liver oil and pregnancy hypertension in our study. It could be that the beneficial effects of n-3 LCPUFA vanish in pregnant women, when vitamin A and PCBs levels reach a certain point.

Although beneficial associations between maternal fish intake and pregnancy hypertension were observed in the crude analyses in our study, they did not persist after adjustment for covariates. Our findings were comparable to previous intervention studies which did not find a reduced risk of hypertension, as combined SBP and DBP, in subjects with allocated fish consumption (providing high dose 3.65 g/day of n-3 fatty acids), compared with control group. It is also relevant to mention that the primary type of fish consumed in Iceland is lean fish, such as Cod, Plaice and Haddock. Therefore, despite relatively high fish intake in our study population, the overall intake of n-3 LCPUFA from fish should be relatively modest; at least in comparison to the amount obtained from daily use of fish liver oil supplements.
In this study we found no evidence for an association between fish or fish liver oil with risk of preeclampsia. Women who develop preeclampsia have been observed to have lower levels of biochemical markers of n-3 fatty acid intake 9, 10. Observational studies of fish consumption and randomized trials of fish oil supplementation generally have not supported a protective association with preeclampsia 12, 53. More recent observational studies have found an association between highest intakes of n-3 fatty acids, primarily from cod liver oil 14 or n-3 PUFA 43 with increased risk of preeclampsia in pregnancy. Because, our study sample was small and preeclampsia cases were few, we lacked power to detect any potential underlying associations with preeclampsia.

The study has several strengths. Gestational hypertension and preeclampsia were determined on the basis of explicit criteria, based on clinical assessment but not self-report. The women in study were healthy before pregnancy. The validation of the FFQ has been determined to be a good measure of frequency of fish and cod liver oil intake 8. Additionally, we obtained detailed information on a number of other maternal factors that have been previously shown to be important risk factor for gestational hypertension or preeclampsia. Some limitations have to be considered. The study sample was small, preeclampsia cases diagnosed were few. Furthermore we only had dichotomous values for hypertension from medical records and lacked continuous blood pressure values. Our outcome measure may therefore be prone to misclassifications. Finally, information on fish, fish liver oil intake in pregnancy was assessed retrospectively and based on maternal self-report, which may be subject to recall bias.

In conclusion, this study did not find an association between intake of fish liver oil with either gestational hypertension defined according to standard determination (systolic and/or diastolic hypertension) or preeclampsia. However, high intake of fish liver oil appeared to be associated with a relative shift from isolated diastolic hypertension to the more severe combined (SBP ≥ 140 and DBP ≥ 90) gestational hypertension. Our results are in accordance with previously published results on fish liver oil and hypertensive disorders in pregnancy 14 and suggest potential adverse effects of high intake of cod liver oil during pregnancy.

4.5 Coffee and tea, and risk of preeclampsia

In a cohort study of Icelandic pregnant women, we investigated the association between coffee and tea consumption (mean 1-2 cups/day) during pregnancy with risk of gestational hypertension and preeclampsia. We observed no association between coffee
consumption and risk of gestational hypertension. However, consumption of coffee was associated with a reduced risk of preeclampsia. No association was observed between tea intake with either gestational hypertension or preeclampsia.

Gestational hypertension and preeclampsia share many characteristics and risk factors of cardiovascular disease, including endothelial dysfunction, oxidative stress, hypertension, insulin resistance, and hypertriglyceridemia.

Caffeine increases the levels of circulating catecholamine release from the adrenal medulla, which may cause uteroplacental vasoconstriction and fetal hypoxia, all of which possibly reduce risk of preeclampsia. It is possible that the mechanisms involved in producing a reduction in fetal and placental weight, impaired fetal growth and vasoconstriction of uteroplacental circulation are similar to those involved in the protective effect against preeclampsia associated with caffeine consumption.

In one prospective study, caffeine consumption of at least 200 ml per day after 20 weeks of gestation in women with type1 diabetes was associated with a reduced risk of preeclampsia. In comparison with the other prospective cohort study have found association between high caffeine intake of 2-4 servings (1 serving = 125 ml) per day of the mothers during pregnancy and a lower risk of preeclampsia. One observational study did not find any an association between coffee consumption during pregnancy and the risk of preeclampsia.

Coffee is known to influence on risk of hypertension. One prospective cohort study has shown that high caffeine intake (5 cups/day) of medical students in the United States may increase risk of hypertension with adjusted OR of 1.6 (95% CI 1.06; 2.4). For pregnant women, the cross-sectional analyses of other prospective cohort study showed that high caffeine intake (2-4 cups/day) was not consistently associated with the risk of pregnancy hypertension (systolic and diastolic BP), compared with control group. We also found no evidence of significant adverse associations of coffee intake during pregnancy on the risk of gestational hypertension. However, risk of gestational hypertension even may be lower in coffee consumers, compared with those consumed non-coffee, although this association was not significantly in crude analyses.

A recent review article reported that caffeine, another constituent of tea may result in endothelial dysfunction through increase of intracellular oxidative stress and main constituent of tea as epigallocatechin-3-gallate (EGCG) increased production of reactive oxygen species (ROS). These might contribute to increased risk of preeclampsia based
on evidence of increased pro-oxidant activity along with decreased antioxidant protection. Therefore, one observational study has suggested that persistent tea consumption by mothers during pregnancy may be associated with an increased risk of preeclampsia, especially severe preeclampsia. However, we observed no association between tea drinking in pregnancy and the risk of preeclampsia. Because, the sample in our study was small, preeclampsia cases diagnosed were few and we lacked power to detect any potential underlying association with preeclampsia.

Several observational studies have indicated that tea consumption may have a protective effect on hypertension in non-pregnant women. However, we found no association between tea consumption of pregnant women and reduced risk of gestational hypertension. It is also relevant to mention that tea was not associated with risk of gestational hypertension.

As with previous study on fish and fish liver oil, this study has several strengths. The status of preeclampsia was determined on the basis of explicit criteria, based on standard definitions. Controls were selected from women admitted to the same hospital during pregnancy. The women in the study were healthy before pregnancy and randomly selected from maternal records. Some maternal demographic characteristics and obstetric characteristics of pregnant women were important risk factors for preeclampsia. However, some limitations have to be considered. One limitation of our study is the possibility of reverse causality. Due to the fact that consumption of coffee and tea is assessed retrospectively, it is possible that women diagnosed with gestational hypertension and preeclampsia might have reduced their coffee and tea consumption after their diagnosis. As regular coffee consumption is generally not considered healthy, it is plausible that women diagnosed with preeclampsia might have either stopped drinking coffee or reduced their intake following healthier lifestyles or falsely underestimated their intake. There is also a possibility that the preeclampsia women were not feeling good and because of that stopped drinking coffee, even before they were diagnosed with preeclampsia. These could lead to reverse causality with respect to the observed association between coffee and preeclampsia. Reduced risk of preeclampsia is also observed at a relatively low intake level (1 cups/day) and one question can whether that is biologically plausible. Another limitation of our study is that the study did not collect information regarding the type of coffee and tea that was consumed.
In conclusion, the results in our study suggest that daily coffee consumption (1-2 cups/day) of the mothers during pregnancy may be associated with a reduced risk of preeclampsia, but not associated with gestational hypertension. It appears that tea intake of pregnant mothers is not associated with the risk of gestational hypertension or preeclampsia. This observation requires further confirmation in different pregnant populations before firm recommendations can be made to mothers regarding caffeine intake in pregnancy and the risk of hypertensive disorders.
5 CONCLUSION

In summary, this study confirms previous findings from Iceland that high intake of cod liver oil during pregnancy is associated with pregnancy hypertension defined as SBP $\geq$ 140 and DBP $\geq$ 90. Furthermore the findings from this study also suggest that daily intake of coffee might be protective against preeclampsia, although this association might be caused by reverse causality.

Concerning cod liver oil, the findings from this study suggest that high ($\approx 9$ g/day) intake of fish liver oil may affect the severity of gestational hypertension. These findings are in line with previous reports from Iceland were high consumption ($\geq 5$ g/day) of fish liver oil has been associated with hypertensive disorders in pregnancy. Furthermore, add that positive association between n-3 LCPUFA and gestational hypertension is generally not observed and other substances in fish liver oil must be involved. Thus, we can not rule out that substances other than n-3 LCPUFA in fish liver oil may influence on gestational hypertension, concluded that the PCBs are most likely exposure as there is more evidence to support that mechanism than direct effect of retinol. Our findings of an inverse association between coffee and risk of preeclampsia may be due to a direct role of coffee in uteroplacental vasoconstriction and fetal hypoxia during pregnancy. However, our study is limited in size; it has not sufficient statistical power with respect to preeclampsia and reverse causality that may also contribute to these findings.

Therefore, we conclude that high (> 9 g/day) fish liver oil consumption during pregnancy should generally not be recommended for pregnant women. On the other hand, daily intake of coffee within the limit of current recommendations (1-2 cups/day) may be beneficial in preventing preeclampsia. More research, however, is needed to confirm those findings and to investigate further elucidation of underlying pathophysiological mechanisms may indicate a role for coffee to prevent risk factors on hypertensive disorders in pregnancy.
6 REFERENCES


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APPENDIX

- The Food Frequency Questionnaire (FFQ)
- Papers:
  - Fish consumption and intake of cod liver oil supplements and the risk of hypertensive disorders in pregnancy.
  - Caffeine intake during pregnancy and the risk of preeclampsia.
Appendix 1
The Food Frequency Questionnaire (FFQ)

Mataræði á meðgöngu

ATH!
Vinsamlega svarið spurningunum eins þarlega og kostur er.
Spurningarnar eiga við meðgöngu barns sem fæddist árið 1998.
Krossið við eina eða fleiri valmöguleika eftir því sem við á.

Númer þáttakanda:________

SPURING 1

1a. Hvaði þóðaðir þú oft fisk sem aðalrétta?
   Á hverjum degi  ☐
   4-6 sinnum í viku  ☐
   2-3 sinnum í viku  ☐
   4-6 sinnum í mánuði  ☐
   Annað ________

1b. Hvaða gerðir/tegundir fiska þóðaðir þú oftast?
   (Krossið við 1 eða fleiri tegundir)
   Lax  ☐
   Lúðu  ☐
   Ýsu  ☐
   Porsk  ☐
   Annað ________

1c. Hve mikilð þóðaðir þú í hverjum matmálstíma?
   grömm ______
   flak (t.d. 1 flak, 1/2 flak, 1/3 flak) ______
   Fékk mér ______ sinnum á diskinn
   Annað ________

1d. Var fiskneysla þín mjög breytileg á meðgöngutímanum?
   (t.d. í upphafi eða lok meðgöngu)
   ________
2a. Hvað bordaðir þú oft fisk sem braudálegg eða sem forrét?  
Á hverjum degi  
4-6 sinnum í viku  
2-3 sinnum í viku  
4-6 sinnum í mánuði  
Annað

2b. Hvaða gerðir/tegundir fiska bordaðir þú sem álegg eða forrét?  
Síld  
Reyktan lax  
Kavíar  
Sardínur  
Makkrið  
Rækurjúr  
Annað

2c. Hve miklø bordaðir þú í hvert sinn?  
(t.d. hve margar sneiðar, biðar eða msk á braud sneið)

2d. Var þessi fiskneysla breytilag á meðgöngutímanum?

3a. Hvaða tegund mataröðu notaðir þú oftast til matargerðar á heimilinu?  
(t.d. til steikningar, sem olli á salat eða annað)
3b. Hversu oft notaðir þú olíu?
   Á hverjum degi  ☐
   4-6 sinnum í viku ☐
   2-3 sinnum í viku ☐
   Annað __________ 

3c. Hvaða tegund af viðbiti notaðir þú á brauð?

---

### SPURNING 4

4a. Tókst þú inn lýsi á meðgöngunni?
   (Ef nei - fæðu þá beint í spurningu 5a)
   Nei  ☐
   Já  ☐

4b. Hvaða tegund?

---

4c. Hve oft?
   Á hverjum degi  ☐
   4-6 sinnum í viku ☐
   2-3 sinnum í viku ☐
   Annað __________
   Einungis ákveðinn hluta meðgöngunnar (hvaða) __________

4d. Hve miklði?
   Teskeið  ☐
   Barnaskeið  ☐
   Matskeið  ☐
   Fjöldi lýsisperla  _______
5a. Tókst þú inn omega-3 (w-3) fitusýrur á meðgöngunni?
(Ef nei - farðu þá beint í spurningu 6a)
Nei ☐
Já ☐

5b. Hvaða tegund?

5c. Hve oft?
Á hverjum degi ☐
4-6 sinnum í viku ☐
2-3 sinnum í viku ☐
Annað ☐
Einungis ákvæðinn hluta meðgöngunnar (hvaða) ☐

5d. Hve mikið?
Teskeið ☐
Barnaskeið ☐
Matskeið ☐
Fjöldi perla ☐

6a. Tókst þú inn einhver vítamín eða steinefni á meðgöngunni?
(Ef nei - farðu þá beint í spurningu 7a)
Nei ☐
Já ☐
Fjölvítamín ☐
Járntöflur eða mixtúru ☐
Kalk ☐
Fólasín ☐
Annað ☐
6b. Hvaða tegund?

6c. Hve oft?

Á hverjum degi  □
4-6 sinnum í viku  □
2-3 sinnum í viku  □
Annað  

Einungis ákveðinn hluta meðgöngunnar (hvaða)  

6d. Hve mikið?

Teskeið  □
Barnaskeið  □
Matskeið  □
Fjöldi pilla  

7a. Tókst þa í inn einhver fæðubótarefni á meðgöngunni?

(Ef nei - farðu þa í beint í spurningu 8a)

Nei  □
Já  □

Herbalife  □
Nature's Own  □
Nupo-létt  □
Gingseng  □
Sólhatt  □
Q-10  □

Annað  

7c. Hve oft?

Á hverjum degi  □
4-6 sinnum í viku  □
2-3 sinnum í viku  □
Annað  

Einungis ákveðinn hluta meðgöngunnar (hvaða)  

5
7d. Hve mikið?
   ——  bréf
   ——  skammta
   Annað

8a. Drakkst þú eiththvað af eftirfarandi á meðgöngunni?
(Ef nei - fardu þá beint í spurningu 9a)
   Nei  □
   Já   □

   Kaffi  □
   Te    □
   Orkudrykki □

8b. Hve oft?
   Á hverjum degi  □
   4-6 sinnum f viku □
   2-3 sinnum f viku □
   Annað

   Einungis ákveðinn hluta meðgöngunnar (hvaða)

8c. Hve mikið?
   ——  bolla
   ——  dl

9a. Hugsædir þú mikið um maturæði þitt á meðgöngu?
9b. Eru einhver matvæli sem þú borðar að öllu jöfnu ekki?
   Ávextir □  Hvít hveiti □
   Grænmeti □  Gos □
   Kjöt □  Sykur □
   Fiskur □  Sælgæti □
   Egg □

Annað ____________________________

SPURNING 10

10. Tókst þú sjálft eftir einhverju sérstökum vörðandi mataræði þitt á meðgöngu?
   Miklar breytingar frá því sem áður var?
   Fékkst þú "æði" fyrir einhverjum ákveðnum matvælum?
   Hættir þú að borða einhver matvæli?

__________________________
__________________________
__________________________

SPURNING 11

11. Finnst þér að það mætti auka fræðslu um mataræði á meðgöngu? Hvernig?

__________________________
__________________________
__________________________
Appendix 2
Fish consumption and intake of cod liver oil supplements and the risk of hypertensive disorders in pregnancy

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OBJECTIVE: To examine the association between fish consumption and intake of cod liver oil with hypertensive disorders in pregnancy.

METHODS: A total of 491 pregnant Icelandic women who gave birth at Landspitali National University Hospital in Reykjavik, aged 20-40, of normal weight before pregnancy were randomly selected from maternal records. Information on frequency of fish and cod liver oil consumption during pregnancy was collected from maternal records. We used gestational hypertension is defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg as a primary outcome measure. Systolic and diastolic, isolated systolic, and isolated diastolic hypertension were used as secondary outcome measures.

RESULTS: The prevalence of gestational hypertension and preeclampsia was 21% and 3%, respectively. Fish consumption was not associated with hypertensive disorders in pregnancy. Intake of fish liver oil was, however, positively associated with combined gestational hypertension (SBP) ≥ 140 and (DBP) ≥ 90. Using this definition women consuming one tablespoon (≈ 9g) a day or more had an adjusted odds ratio of 6.3 (95% confidence interval: 2.2, 17.9) of having pregnancy hypertension compared to those with
no intake. This association appeared to be driven by a relative shift from isolated diastolic hypertension to combined systolic and diastolic hypertension as overall fish liver oil was not associated with hypertension defined as (SBP) ≥ 140 and/or (DBP) ≥ 90.

**CONCLUSION:** No association was found between fish consumption and hypertensive disorders in pregnancy. Our results suggest that high (≈ 9 g/day) intake of fish liver oil may affect the severity of gestational hypertension. These findings are in line with previous reports from Iceland were high consumption of fish liver oil has been associated with hypertensive disorders in pregnancy.

**Key words:** Fish, fish liver oil, n-3 PUFA, gestational hypertension, preeclampsia and hypertensive disorders in pregnancy.

**Introduction**

Hypertensive disorders of pregnancy, including gestational hypertension and preeclampsia are associated with increased morbidity and mortality for both mother and infant. Hypertensive disorders occur in about 6-8% of all pregnancies in the United States. As the pregnancy progresses women diagnosed with gestational hypertension are at greater risk for developing preeclampsia, diagnosed as gestational hypertension and proteinuria after 20 weeks of gestation. However, the etiology and pathogenesis of gestational hypertension and preeclampsia are mostly unknown. Preeclamptic pregnancies are characterized by endothelial dysfunction, disturbed placentation, oxidative stress, and an exaggerated inflammatory response to pregnancy. Most established risk factors for gestational hypertension or preeclampsia include maternal age, ethnicity, parity, and previous hypertension or preeclampsia. Furthermore, weight gain in women of normal weight before pregnancy has been associated with gestational
hypertension and preeclampsia \(^5,^6\).

Fish consumption and fish oil intake in pregnancy have frequently been studied with respect to end points such as preterm delivery and size at birth \(^7,^8\), but fewer studies have addressed pregnancy complications such as gestational hypertension and preeclampsia. Randomized controlled trials have suggested potential benefits of fish oil intake on hypertensive disorders during pregnancy \(^9\-^{11}\), while other studies have not found any association \(^12,^13\). However, one Icelandic cohort study reported that high intake of fish liver oil might be positively associated with pregnancy hypertension \(^14\). As regular intakes of fish and even fish oil are frequently encouraged for pregnant women, it is important to investigate their associations with pregnancy complications.

The aim of this study was to examine the association between fish consumption on one hand and intake of cod liver oil supplements on the other with hypertensive disorders in pregnancy.

**Materials and methods**

**Study design**

This cohort study was conducted at Landspitali National University Hospital, Reykjavik, Iceland in 1998 \(^15\). Women with normal weight before pregnancy (N = 615) were randomly selected from maternal records. Inclusion criteria included being healthy before pregnancy with no history of hypertension, diabetes, cardiovascular disease, or thyroid disease; being 20-40 years old; and of normal weight (pre-pregnancy BMI 19.5-25.5 kg/m\(^2\)); delivering singleton term infants.

Information on maternal age, height, marital status, smoking, parity, pre-pregnant weight and gestational weight gain was collected from maternal records as well as information on gestational hypertension and preeclampsia diagnosis. A validated focused
food frequency questionnaire 6 was sent to the women who agreed to participate (N = 614), which gave 80.1% response rate (N = 491). This corresponded to 11.8% of all births in the country during the study period. Information on pregnancy complications was collected from maternity records after birth 7.

Blood pressure was registered by the midwife and gestational hypertension was recorded as dichotomous values i.e., systolic blood pressure (SBP) ≥ 140 or diastolic blood pressure (DBP) ≥ 90 in the maternal records. Continuous blood pressure measures were not available. The study was approved by the Ethical committee at Landspitali National University Hospital and by the Icelandic Data Protection Commission.

Outcome definitions

Hypertensive disorders in pregnancy were defined as gestational hypertension and preeclampsia according to the recommendations of the US National High Blood Pressure Education Program 2. Gestational hypertension was defined as elevated systolic blood pressure (SBP) ≥ 140 mmHg and/or a diastolic blood pressure (DBP) ≥ 90 mmHg (including total of different types of hypertension: systolic and diastolic, isolated systolic, and isolated diastolic) on two or more occasions after 20 weeks of gestation, but without proteinuria 2. We also examined women with three separate types of hypertension such as isolated systolic hypertension (SBP ≥ 140 and DBP < 90 mmHg); isolated diastolic hypertension (SBP < 140 and DBP ≥ 90); and combined systolic and diastolic hypertension (SBP ≥ 140 and DBP ≥ 90) 16. Preeclampsia was diagnosed as gestational hypertension and proteinuria of ≥ 0.3 g/24h (at least 1+ on a dipstick) 2.

Exposure assessment

The food frequency questionnaire (FFQ) collected information on both frequency of fish consumption as a main meal and as bread spread during pregnancy; as well as the amount
of cod liver oil intake as capsules, teaspoons or tablespoons per day. The validation of the FFQ has been described earlier and was found to be a good measure of frequency of fish intake and intake of cod liver oil. Frequency of fish consumption was divided into three groups as < 4 times, 4-6 times and > 6 times per month.

Intake of cod liver oil was divided into four groups, with the lowest group reporting no intake and three groups of consuming > 0-1 g, > 1-9 g and > 9 g per day (9 g = 1 tablespoon). Nutrient content of fish liver oil was calculated at the time of the study, using the Icelandic Nutrition Database (ISGEM).

**Statistical analysis**

Descriptive statistics including mean, SD (standard deviation), frequency and percentage were used for describing intakes of fish and fish liver oil and their crude associations with hypertensive disorders. Logistic regression was used to examine covariate adjusted associations between intake of fish and fish liver oil and hypertensive disorders. A priori, we identified and selected the following covariates: smoking, pre-pregnancy BMI (body mass index (kg/m^2)), weight gain in pregnancy, age, parity. We also adjusted for fish when examining the separate effects of fish liver oil on hypertensive disorders and vice versa. Statistical analyses were performed in SPSS version 17 and P-value < 0.05 was considered statistically significant.

**Results**

In comparison to normotensive women, those diagnosed as hypertensive, had a higher mean gestational weight gain, were less likely to be parous and were more likely to be non-smokers. Overall 21% of the participants developed gestational hypertension (SBP ≥ 140 and/or DBP ≥ 90), including 16% developed isolated diastolic hypertension (SBP <
140 and DBP ≥ 90 mmHg); none of the participants had isolated systolic hypertension (SBP ≥ 140 and DBP < 90 mmHg); and 5% developed combined systolic and diastolic hypertension (SBP ≥ 140 and DBP ≥ 90 mmHg), and 3% were diagnosed with preeclampsia in pregnancy (Table 1).

Mutual distribution of fish and fish liver oil is shown in (Table 2). A weak positive association was observed between daily intake of fish liver oil and frequency of monthly fish consumption (P = 0.05, χ²). All study subjects reported consumption of fish as a main meal or as bread spread monthly during pregnancy, while 44% (n = 215) reported intake of fish liver oil.

Table 3 shows the crude associations between frequency of fish consumption and fish liver oil with the risk of gestational hypertension or preeclampsia. No association was observed between either fish liver oil intake or fish intake and gestational hypertension defined as a SBP ≥ 140 and/or DBP ≥ 90 mmHg; nor with preeclampsia. When looking at sub-types of hypertension, there was a borderline significant inverse trend between intake of fish liver oil and reduced risk of isolated diastolic hypertension (DBP ≥ 90, P = 0.08) while there was also a relatively strong positive association between high intake of fish liver oil and increased risk of combined SBP ≥ 140 and DBP ≥ 90 hypertension (P = 0.006). In contrast to these findings for fish liver oil, frequent fish consumption was modestly associated with reduced risk of systolic and diastolic hypertension (P = 0.05) in the crude analyses.

In the multivariate analyses (Table 4) there was no association between intake of fish liver oil with either gestational hypertension, defined as SBP ≥ 140 and/or DBP ≥ 90; or preeclampsia. Despite an overall lack of association between cod liver oil and hypertension, intake of fish liver oil was associated with increased risk of hypertension defined as SBP ≥ 140 and DBP ≥ 90 with adjusted odds ratio of 6.3, (95% CI 2.22; 17.9).
This increase in risk was therefore followed by a relative decrease in subjects with isolated diastolic hypertension (DBP $\geq 90$). No association was, however, observed between fish consumption and gestational hypertension or preeclampsia in the covariate adjusted analyses.

**Discussion**

This observational study investigated the relationship between consumption of fish and fish liver oil in pregnancy and risk of hypertensive disorders. Fish consumption was not associated with increase in risk of gestational hypertension. No association was also observed between intake of fish liver oil and gestational hypertension; defined as SBP $\geq 140$ and/or DBP $\geq 90$ (including total of different types of hypertension: systolic and diastolic, isolated systolic, and isolated diastolic). Although the overall rate of gestational hypertension did not increase, high intake of fish liver oil appeared to be associated with a relative shift from isolated diastolic hypertension to the more severe combined (SBP $\geq 140$ and DBP $\geq 90$) gestational hypertension. No association was found between intake of fish or fish liver oil and preeclampsia in this small sample.

The prevalence of gestational hypertension (SBP $\geq 140$ and/or DBP $\geq 90$) and preeclampsia in our sample was 21% and 3%, respectively. This is high compared to some other studies were the prevalence of gestational hypertension has ranged between 6% to 17%; and the prevalence of preeclampsia between 2% to 7% in healthy nulliparous women $^{17, 18}$ One prospective cohort study of women in 2001 was to determine the effects of nutrient intakes on hypertensive disorders in pregnancy, reported that the prevalence of gestational hypertension and preeclampsia was 17.3% and 7.6% $^{18}$. Similar to our findings a previous study from Iceland suggested that high intake of fish liver oil may be associated with increased risk of developing combined gestational hypertension.
(SBP ≥ 140 and DBP ≥ 90) and prevalence of hypertension were present in 6.8% 14. Given the frequent and rather high consumption of fish liver oil in our data, this could be one explaining factor for the relatively high prevalence of gestational hypertension in our study population. Furthermore, higher prevalence of gestational hypertension in our study including total of different types of hypertension as systolic and diastolic (5%), isolated systolic (0%), and isolated diastolic (16%) is due to that a previous study from Iceland investigated only systolic and diastolic hypertension, but not with types of isolated hypertension.

Previous studies have shown that fish oil may posses a cardio-protective effect 19, 20. Based on those studies, it has been suggested that fish oil might be protective against hypertensive disorders in pregnancy 21. Results from clinical trials have provided strong evidence for the role of fish oil containing high amount of long chain omega-3 polyunsaturated fatty acids (n-3 LCPUFA) in reducing circulating triglycerides, decreasing platelet and leukocyte reactivity for heart disease prevention 22, 23. The n-3 fatty acids decrease the production of thromboxane A2 of platelets and monocytes, and increase prostacyclin I2 synthesis and related vasodilation 2, 24. Thromboxane A2 causes blood platelets to stick together, which encourages blood clots, and increases blood pressure. As n-3 fatty acids have the potential to decrease thromboxane A2, they can decrease blood viscosity, perhaps preventing blood clots, and lower blood pressure 25. Some studies have indicated that high doses of fish oil could reduce blood pressure in individuals with primary hypertension 26, 27. However, in contrast to the suggested beneficial effect of fish oil on hypertensive disorders, some randomized controlled trials have not detected any association between intake of fish oil during pregnancy with either gestational hypertension or preeclampsia 12, 13, even at relatively high doses of n-3 PUFA (3g/day) 13.
The Icelandic study reporting similar findings following high intakes of cod liver oil was conducted in a similar time period as our study. The consistency between these two cohorts and the fact that intake of fish liver oil has also been associated with increased risk of preeclampsia in a larger experimental setting, does suggest that very high intake of fish liver oil may in some cases be detrimental with respect to hypertensive disorders in pregnancy.

The recommended dietary allowance (RDA) of retinol for pregnant women is 770 μg (2600 IU) for women 19 years and older with upper intake limit of 3000 μg (10000 IU) per day. We estimated that women with the highest intake of fish liver oil (≥ 9 g/day) in our study might have consumed up to 3600 μg/day of retinol. It has been hypothesized that high intakes of retinol might be responsible for the potential adverse effect of fish liver oil on pregnancy hypertension. There is, however, currently little evidence to support this hypothesis. Fish oil supplements are also a source of persistent pollutants such as polychlorinated biphenyls (PCBs) and dioxins. Levels of PCBs are often considerably higher in fish liver oil compared to conventional fish oils. Epidemiological studies have also suggested that exposures to PCBs might increase the risk of hypertension in middle aged subjects. Furthermore, modest intake of oily fish during pregnancy has been linked with substantial (∼ 50%) increase in blood PCBs levels. There is therefore some indirect evidence to suggest that exposure to PCBs through high intake of fish liver oil during pregnancy may explain the positive association between fish liver oil and pregnancy hypertension in our study.

Although beneficial associations between maternal fish intake and pregnancy hypertension were observed in the crude analyses in our study, they did not persist after adjustment for covariates. Our findings were comparable to previous intervention studies which did not find a reduced risk of hypertension, as combined SBP and DBP, in
subjects with allocated fish consumption (providing high dose 3.65 g/day of n-3 fatty acids), compared with control group \(^{36}\). It is also relevant to mention that the primary type of fish consumed in Iceland is lean fish, such as Cod, Plaice and Haddock. Therefore, despite relatively high fish intake in our study population, the overall intake of n-3 LCPUFA from fish should be relatively modest; at least in comparison to the amount obtained from daily use of fish liver oil supplements.

In this study we found no evidence for an association between fish or fish liver oil with risk of preeclampsia. Women who develop preeclampsia have been observed to have lower levels of biochemical markers of n-3 fatty acid intake \(^{9, 10}\). Observational studies of fish consumption and randomized trials of fish oil supplementation generally have not supported a protective association of preeclampsia \(^{12, 37}\). More recent observational studies have found an association between highest intakes of n-3 fatty acids, primarily from cod liver oil \(^{14}\) or n-3 PUFA \(^{28}\) with increased risk of preeclampsia in pregnancy. Because, our study sample was small and preeclampsia cases were few, we lacked power to detect any potential underlying associations with preeclampsia.

The study has several strengths. Gestational hypertension and preeclampsia were determined on the basis of explicit criteria, based on clinical assessment but not self-report. The women in study were healthy before pregnancy. The validation of the FFQ has been determined to be a good measure of frequency of fish and cod liver oil intake. Additionally, we obtained detailed information on a number of other maternal factors that have been previously shown to be important risk factor for gestational hypertension or preeclampsia. Some limitations have to be considered. The study sample was small, preeclampsia cases diagnosed were few. Furthermore we only had dichotomous values for hypertension from medical records and lacked continuous blood pressure values. Our outcome measure may therefore be prone to misclassifications. Finally, information on
fish, fish liver oil intake in pregnancy was based on maternal self-report, which may be subject to recall bias.

In conclusion, this study did not find an association between intake of fish liver oil with either gestational hypertension defined according to standard determination (systolic and/or diastolic hypertension) or preeclampsia. However, high intake of fish liver oil appeared to be associated with a relative shift from isolated diastolic hypertension to the more severe combined (SBP ≥ 140 and DBP ≥ 90) gestational hypertension. Our results are in accordance with previously published results on fish liver oil and hypertensive disorders in pregnancy and suggest potential adverse effects of high intake of cod liver oil during pregnancy.
References


### Table 1. Characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>Normotensive women n = 373 (76%)</th>
<th>Hypertension systolic and/or diastolic n = 103 (21%)</th>
<th>Hypertension diastolic n = 79 (16%)</th>
<th>Hypertension systolic and diastolic n = 24 (5%)</th>
<th>Preeclampsia n = 15 (3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>Mean: 29.3, SD: 4.7</td>
<td>Mean: 28.0*, SD: 4.9, P: 0.02</td>
<td>Mean: 28.0*, SD: 4.8, P: 0.011</td>
<td>Mean: 29.0, SD: 5.3, P: 0.65</td>
<td>Mean: 28.2, SD: 4.2, P: 0.39</td>
</tr>
<tr>
<td><strong>Height (m)</strong></td>
<td>1.68, 0.06</td>
<td>1.68, 0.05, P: 0.97</td>
<td>1.68, 0.05, P: 0.76</td>
<td>1.67, 0.04, P: 0.5</td>
<td>1.67, 0.05, P: 0.2</td>
</tr>
<tr>
<td><strong>Pre-pregnancy weight (kg)</strong></td>
<td>62.7, 6.2</td>
<td>63.3, 5.6, P: 0.33</td>
<td>63.5, 5.9, P: 0.3</td>
<td>63.0, 4.3, P: 0.83</td>
<td>61.0, 5.4, P: 0.24</td>
</tr>
<tr>
<td><strong>Pre-pregnancy BMI (kg/m²)</strong></td>
<td>22.2, 1.6</td>
<td>22.4, 1.6, P: 0.16</td>
<td>22.4, 1.5, P: 0.26</td>
<td>22.5, 1.6, P: 0.3</td>
<td>22, 1.4, P: 0.68</td>
</tr>
<tr>
<td><strong>Gestational weight gain (kg)</strong></td>
<td>16.3, 4.7</td>
<td>17.9*, 5.1, P: 0.002</td>
<td>17.7*, 4.9, P: 0.017</td>
<td>18.8, 5.8, P: 0.01</td>
<td>17.7, 4.6, P: 0.25</td>
</tr>
<tr>
<td><strong>Smoking (%)</strong></td>
<td>18</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td>15, 0.18</td>
</tr>
<tr>
<td><strong>Nulliparous (%)</strong></td>
<td>34</td>
<td>58</td>
<td>58</td>
<td>73, 0.002**</td>
<td></td>
</tr>
<tr>
<td><strong>Fish consumption (g/day)</strong></td>
<td>53.5, 37.5</td>
<td>48.3, 29.0, P: 0.18</td>
<td>48.7, 27.4, P: 0.27</td>
<td>47.0, 34.0, P: 0.4</td>
<td>48.3, 27.6, P: 0.57</td>
</tr>
<tr>
<td><strong>Fish liver oil intake (g/day)</strong></td>
<td>2.4, 4.4</td>
<td>2.0, 4.1, P: 0.5</td>
<td>1.1*, 2.9, P: 0.02</td>
<td>5.0*, 5.7, P: 0.004</td>
<td>1.8, 4.5, P: 0.63</td>
</tr>
</tbody>
</table>

*None is diagnosed only with systolic hypertension*

SD: standard deviation

BMI: body mass index

* Comparison to normotensive women using ANOVA, LSD Post hoc test and P-value < 0.05, significant differences

** Chi-squared test and P-value < 0.05, significant differences
Table 2. Mutual distribution of fish liver oil and fish intake among the participating mothers (n = 491)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fish intake</th>
<th></th>
<th></th>
<th></th>
<th>P&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 4/month &lt;br&gt;63 (13%)</td>
<td>4-6/month &lt;br&gt;245 (50%)</td>
<td>&gt; 6/month &lt;br&gt;177 (37%)</td>
<td></td>
</tr>
<tr>
<td>Fish liver oil (g/day)</td>
<td></td>
<td>Case n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>273 (56%)</td>
<td>64</td>
<td>61</td>
<td>48</td>
<td>0.047</td>
</tr>
<tr>
<td>&gt; 0-1</td>
<td>68 (14%)</td>
<td>14</td>
<td>11</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>&gt; 1-9</td>
<td>78 (16%)</td>
<td>10</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>&gt; 9</td>
<td>66 (14%)</td>
<td>12</td>
<td>11</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>Chi-squared tests
Table 3. Gestational hypertension and preeclampsia according to use divided by fish consumption and fish liver oil intake (n = 491)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fish consumption per month</th>
<th>Amount of fish liver oil (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>&lt; 4 times</td>
</tr>
<tr>
<td>Gestational Hypertension (mmHg)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Systolic ≥ 140 and/or diastolic ≥ 90</td>
<td>103 (21)</td>
<td>25.4</td>
</tr>
<tr>
<td>Systolic &lt; 140 and diastolic ≥ 90</td>
<td>79 (16)</td>
<td>14.3</td>
</tr>
<tr>
<td>Systolic ≥ 140 and diastolic ≥ 90</td>
<td>24 (5)</td>
<td>11.1</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>15 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

p<sup>1</sup> Statistical analysis using Pearson chi-squared tests for trend in proportions
<table>
<thead>
<tr>
<th>Variables</th>
<th>Fish consumption per month</th>
<th>Amount of fish liver oil (g/day)</th>
<th>OR (95% CI)a</th>
<th>OR (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 4 times</td>
<td>4–6 times</td>
<td>&gt; 6 times</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational Hypertension (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic ≥ 140 and/or diastolic ≥ 90</td>
<td>1</td>
<td>0.89 (0.45; 1.75)</td>
<td>0.8 (0.38; 1.67)</td>
<td>1</td>
</tr>
<tr>
<td>Systolic &lt; 140 and diastolic ≥ 90</td>
<td>1</td>
<td>1.3 (0.58; 2.9)</td>
<td>1.33 (0.55; 3.2)</td>
<td>1</td>
</tr>
<tr>
<td>Systolic ≥ 140 and diastolic ≥ 90</td>
<td>1</td>
<td>0.37 (0.12; 1.12)</td>
<td>0.35 (0.1; 1.17)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>≤ 6 times</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 6 times</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1</td>
<td>0.95 (0.3; 3.0)</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

aAdjusted for smoking, pre-pregnancy BMI (kg/m²), gestational weight gain, age, parity and fish liver oil intake
bAdjusted for smoking, pre-pregnancy BMI (kg/m²), gestational weight gain, age, parity and fish consumption

OR is odds ratio for hypertensive disorders in pregnancy by fish and fish liver oil consumption
Appendix 3

Caffeine intake during pregnancy and risk of preeclampsia

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² Department of Obstetrics and Gynecology, Landspitali National University Hospital & Faculty of Medicine, University of Iceland, 101 Reykjavik, Iceland.

OBJECTIVE: To investigate the association between coffee and tea intake with hypertensive disorders in pregnancy.

METHODS: Healthy women (n = 491) aged 20-40, of normal weight before pregnancy (body mass index (BMI) 19.5-25.5 kg/m²) was randomly selected. Maternal records collected information on frequency of coffee and tea intake during pregnancy. Information on gestational hypertension and preeclampsia were extracted from hospital records.

RESULTS: Coffee was not associated with gestational hypertension defined as (SBP) ≥ 140 and/or (DBP) ≥ 90. Compared with non-coffee consumption, coffee consumption of women during pregnancy was negatively associated with a reduced risk of preeclampsia (crude odds ratio (OR) 0.16, 95% CI 0.04; 0.73). This association was also found after adjustment for covaristies with adjusted OR of 0.15 (95% CI 0.03; 0.82). Tea intake was also not associated with hypertensive disorders in pregnancy.

CONCLUSION: Our results suggest that coffee consumption during pregnancy may lower risk of preeclampsia. However, reverse causality may also contribute to these findings.

Key words: Coffee, tea, gestational hypertension, preeclampsia and hypertensive disorders in pregnancy.
**Introduction**

Caffeine has been used for thousands of years and is one of the most widely consumed active food ingredient throughout the world \(^1\). Caffeine is present in certain prescriptions and over the counter medications \(^2\) and beneficial health effects of caffeine on specific diseases, including insulin resistance, cancer and cardiovascular disease \(^3\). Adverse effects of caffeine on blood pressure and risk of hypertensive complications in pregnancy have been reported \(^4\).

Coffee and tea are the main sources of caffeine intake. Coffee contains 50 to 70 percent more caffeine than tea, accounting for the main source of caffeine in many populations \(^5\). Prospective cohort studies have found coffee consumption to be associated with increased risk of hypertension \(^6,\) \(^7\), but some other studies found no association \(^8\) or even an inverse association between high coffee consumption and a lower risk of hypertension in women \(^9\). For pregnant women, caffeine consumption through coffee, tea and soft drinks have been associated with reduced risk of preeclampsia \(^10\).

In recent years, there has been a growing interest in exploring the effects of tea in various vascular diseases \(^11\). Observational studies have reported that habitual consumption of green tea significantly reduced the risk of developing hypertension in non-pregnant women \(^12,\) \(^13\). However, one retrospective study suggested that persistent tea consumption during pregnancy might be associated with an increased risk of preeclampsia, especially severe preeclampsia, while no association was found for coffee consumption \(^14\).

Gestational hypertension and preeclampsia are serious maternal complications of pregnancy that affect about 8% of pregnant mothers in a Norwegian population-based study \(^15\). The etiology of gestational hypertension and preeclampsia remains largely unclear. However, hypertensive disorders in pregnancy share many characteristics and risk factors of cardiovascular disease, including endothelial dysfunction, oxidative stress,
hypertension, insulin resistance, and hypertriglyceridemia. Because coffee and tea are commonly consumed beverages even during pregnancy, the potential health effects of coffee and tea on risk of preeclampsia are an important public health issue. Less is known about the associations of caffeine intake on the risk of hypertensive disorders in pregnancy. The aim of the present study was to assess the associations between coffee and tea consumption and the risk of gestational hypertension and preeclampsia.

**Materials and methods**

*Study participants*

Women of normal pre-pregnant weight (N = 615) were randomly selected from among those who, according to birth records, fulfilled the 1-year inclusion criteria (1998) at the Landspitali National University Hospital, Reykjavik, Iceland. The women were healthy before pregnancy, and had no history of hypertension, diabetes, cardiovascular disease, or thyroid problems. They were aged between 20-40 years old, had a pre-pregnancy normal weight (body mass index (BMI) of 19.5-25.5 kg/m²) and delivered singleton infants at a 38-43.week of gestation, based on term assessment fetal biometry at an 18-20 week ultrasound examination. All women received early and regular antenatal care as described earlier.

Information on maternal age, height, marital status, pre-pregnant weight, gestational weight gain, smoking and parity was collected from maternity records as well as information on gestational hypertension and preeclampsia diagnosis at Landspitali National University Hospital of Iceland. A focused food frequency questionnaire was sent to the women who agreed to participate, collecting information from their maternity records after the birth of their infant (n = 614), with an 80.1% response rate (n = 491). This corresponded to 11.8% of all births in the country during the study year. The study
was approved by the Hospital Ethical Committee (institutional review board) at Landspitali National University Hospital and the Icelandic Data Protection Commission.

**Outcome definitions**

Information on gestational hypertension and preeclampsia were extracted from maternal records. Hypertensive disorders in pregnancy were defined as gestational hypertension and preeclampsia, according to the recommendations of the US National High Blood Pressure Education Program. Gestational hypertension was defined as a blood pressure of systolic $\geq 140$ mmHg and/or diastolic $\geq 90$ mmHg on at least two occasions at least six hours apart after 20 weeks of pregnancy. Preeclampsia was diagnosed as gestational hypertension and proteinuria with excretion (of 0.3 grams or greater in a 24-hour urine specimen [at least 1+ on dipstick value on two or more occasions or $\geq 2+$ once]) in at least two random urine samples collected at least 6 hours apart after 20 weeks of gestation in a previously normotensive women.

**Exposure assessment**

Information on consumption of coffee and tea was obtained by a food frequency questionnaire (FFQ). The frequency (times per day) of coffee and tea intake during pregnancy was recorded. The frequency of coffee and tea consumption was divided into three intake groups of 0, $< 1$ and $\geq 1$ times per day.

**Data analysis**

The data are described by values of mean and SD (standard deviation) as well as percentages. We compared mean and SD between coffee consumption groups at baseline, using ANOVA, and percentages, using Pearson chi-squared test. Multivariable logistic
regression was used to examine the associations between coffee and tea consumption with gestational hypertension and preeclampsia. Adjusted models controlled for covariates: smoking, pre-pregnancy BMI (body mass index (kg/m²)), weight gain in pregnancy, maternal age and parity. Data were analyzed using SPSS version 17 (SPSS Inc., Chicago, IL) and a P < 0.05 level was considered statistically significant.

**Results**

Characteristics of the pregnant mothers according to coffee consumption during pregnancy are shown in (Table 1). The mean maternal age increased with coffee consumption (P < 0.001). As compared to non-coffee consumers, those reporting coffee consumption, were significantly more than to be smokers (P < 0.001), and were significantly less than to be nulliparous (P = 0.002).

Mutual distribution of coffee and tea intake during pregnancy are shown in (Table 2). Coffee consumption was positively associated with frequency of daily tea intake of women during pregnancy (P = 0.002, \(\chi^2\)). There are 47% (n = 230) of the mothers reported coffee consumption during pregnancy and 37.5% (n = 183) are tea consumption.

A total of 103 (21%) developed gestational hypertension and 15 (3%) women developed preeclampsia. In Table 3, results for gestational hypertension and preeclampsia are shown. Coffee consumption during pregnancy was associated with a reduced risk of preeclampsia (crude odds ratio (OR) 0.16, 95% CI 0.04; 0.73). This association was also found after adjustment for covariates with adjusted OR of 0.15 (95% CI 0.03; 0.82). No association was observed between tea intake and preeclampsia and consumption of tea and coffee were not associated with gestational hypertension.
Discussion

In a cohort study of Icelandic pregnant women we investigated the association between coffee and tea consumption during pregnancy with risk of gestational hypertension and preeclampsia. We observed no association between coffee consumption and risk of gestational hypertension. However, consumption of coffee was associated with a reduced risk of preeclampsia. No association was observed between tea intake with either gestational hypertension or preeclampsia.

Gestational hypertension and preeclampsia share many characteristics and risk factors of cardiovascular disease, including endothelial dysfunction, oxidative stress, hypertension, insulin resistance, and hypertriglyceridemia. Caffeine increases the levels of circulating catecholamine release from the adrenal medulla, which may cause uteroplacental vasoconstriction and fetal hypoxia, all of which possibly reduce risk of preeclampsia. It is possible that the mechanisms involved in producing a reduction in fetal and placental weight, impaired fetal growth and vasoconstriction of uteroplacental circulation are similar to those involved in the protective effect against preeclampsia associated with caffeine consumption. In one prospective study, caffeine consumption of at least 200 ml per day after 20 weeks of gestation in women with type 1 diabetes was associated with a reduced risk of preeclampsia. In comparison with the other prospective cohort study have found association between high caffeine intake of 2-4 servings (1 serving = 125 ml) per day of the mothers during pregnancy and a lower risk of preeclampsia. One observational study did not find any an association between coffee consumption during pregnancy and the risk of preeclampsia.

Coffee is known to influence on risk of hypertension. One prospective cohort study has shown that high caffeine intake (5 cups/day) of medical students in the United States may increase risk of hypertension. However, for pregnant women, the cross-sectional...
analyses of the prospective cohort study showed that high caffeine intake (2-3 cups/day) was significantly associated with the risk of systolic hypertension, but not associated with pregnancy hypertension (systolic and diastolic BP), compared with control group 4. We also found no evidence of significant adverse associations of coffee intake during pregnancy on the risk of gestational hypertension. However, risk of gestational hypertension even may be lower in coffee consumers, compared with those consumed non-coffee, although this association was not significantly in crude analyses.

A recent review article reported that caffeine, another constituent of tea may result in endothelial dysfunction through increase of intracellular oxidative stress 22 and main constituent of tea as epigallocatechin-3-gallate (EGCG) increased production of reactive oxygen species (ROS) 23. These might contribute to increased risk of preeclampsia based on evidence of increased pro-oxidant activity along with decreased antioxidant protection 24. Therefore, one observational study has suggested that persistent tea consumption by mothers during pregnancy may be associated with an increased risk of preeclampsia, especially severe preeclampsia 14. However, we observed no association between tea drinking in pregnancy and the risk of preeclampsia. Because, the sample in our study was small, preeclampsia cases diagnosed were few and we lacked power to detect any potential underlying association with preeclampsia.

Several observational studies have indicated that tea consumption may have a protective effect on hypertensive disorders in non-pregnant women 12, 13. However, we found no association between tea consumption of pregnant women and reduced risk of gestational hypertension. It is also relevant to mention that tea was not associated with risk of gestational hypertension.

The study has several strengths. The status of preeclampsia was determined on the basis of explicit criteria, based on standard definitions. Controls were selected from
women admitted to the same hospital during pregnancy. The women in the study were healthy before pregnancy and randomly selected from maternal records. Some maternal demographic characteristics and obstetric characteristics of pregnant women were important risk factors for preeclampsia. However, some limitations have to be considered. One limitation of our study is the possibility of reverse causality. It is due to the fact that consumption of coffee and tea assessed retrospectively, it is possible that women diagnosed with gestational hypertension and preeclampsia might have reduced their coffee and tea consumption after their diagnosis. As regular coffee consumption is generally not considered healthy, it is plausible that women diagnosed with preeclampsia might have either reduced their intake or falsely underestimated their intake, which could lead to reverse causality with respect to the observed association between coffee and preeclampsia. Another limitation of our study is that the study did not collect information regarding the type of coffee and tea that was consumed. Although we have had sufficient power to detect moderate to strong associations between coffee and/or tea consumption with respect to pregnancy hypertension, our study was not sufficiently powered with respect to preeclampsia. Our findings on a potential inverse association between coffee and preeclampsia should therefore be interpreted cautiously.

In conclusion, the results in our study suggest that daily coffee consumption of the mothers during pregnancy may be associated with a reduced risk of preeclampsia, but not associated with gestational hypertension. It appears that tea intake of pregnant mothers is not associated with the risk of gestational hypertension or preeclampsia. This observation requires further confirmation in different pregnant populations before firm recommendations can be made to mothers regarding caffeine intake in pregnancy and the risk of hypertensive disorders.
References


### Table 1. Descriptive and obstetric characteristics of study participants according to coffee intake (n = 487)

<table>
<thead>
<tr>
<th>Frequency of coffee consumption (times/day)</th>
<th>0 ( n = 257 (53%) )</th>
<th>&lt; 1 ( n = 77 (16%) )</th>
<th>≥ 1 ( n = 153 (31%) )</th>
<th>( P ) for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>27.6 (4.4)</td>
<td>28.7 (4.6)</td>
<td>31.4 (4.6)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td><strong>Height (m)</strong></td>
<td>1.68 (0.05)</td>
<td>1.68 (0.06)</td>
<td>1.68 (0.06)</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Pre-pregnancy weight (kg)</strong></td>
<td>62.5 (6.1)</td>
<td>62.5 (5.6)</td>
<td>63.3 (6.3)</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Pre-pregnancy BMI (kg/m(^2))</strong></td>
<td>22.2 (1.6)</td>
<td>22.3 (1.6)</td>
<td>22.2 (1.6)</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Gestational weight gain (kg)</strong></td>
<td>17.0 (5.0)</td>
<td>16.0 (4.2)</td>
<td>16.6 (4.8)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Smoking (%)</strong></td>
<td>7.7</td>
<td>10.8</td>
<td>32.7</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td><strong>Nulliparous (%)</strong></td>
<td>47.5</td>
<td>41.6</td>
<td>28.8</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

**Abbreviations:** SD standard deviation, BMI body mass index

*Values are given as mean ± SD or percentage. Using ANOVA analysis or Pearson chi-squared test in comparisons between the groups

* \( P \)-values < 0.05 shown significant differences

### Table 2. Distribution of coffee consumption according to frequency of tea intake (n = 487)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases ( n (%) )</th>
<th>Frequency of tea drinking (times/day)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 ( 304 (62.5) )</td>
<td>&lt; 1 ( 100 (20.5) )</td>
</tr>
<tr>
<td>Coffee (times/day)</td>
<td>257 (53)</td>
<td>55.3</td>
<td>59.0</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>77 (16)</td>
<td>13.2</td>
<td>36.0</td>
</tr>
<tr>
<td>≥ 1</td>
<td>153 (31)</td>
<td>31.5</td>
<td>5.0</td>
</tr>
</tbody>
</table>

*Chi-squared analysis using Pearson chi-squared tests for trend in proportions

* Statistically significant difference at \( P < 0.01 \) level with 95% confidence interval

% within frequency of dietary consumption of mothers during pregnancy
Table 3. The association between coffee and tea consumption and risk of hypertensive disorders in pregnancy (n = 489)

<table>
<thead>
<tr>
<th></th>
<th>Preeclampsia (n = 15; 3%)</th>
<th>Hypertension (n = 103; 21%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases/N</td>
<td>Crude OR (95% CI)</td>
</tr>
<tr>
<td><strong>Coffee</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13/257</td>
<td>1.0 (Ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>2/232</td>
<td>0.16 (0.04; 0.73)*</td>
</tr>
<tr>
<td><strong>Tea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9/306</td>
<td>1.0 (Ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>6/183</td>
<td>1.12 (0.4; 3.2)</td>
</tr>
</tbody>
</table>

N value is amount of mothers in coffee and tea consumption with No or Yes

* Adjusted odds ratio (95% CI) for smoking, pre-pregnancy BMI, weight gain in pregnancy, maternal age and parity

* P-value < 0.05: statistically significant. Before and after adjustment (P = 0.018 and P = 0.03)