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A prospective study of *trans* fat intake and risk of preeclampsia in Denmark

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Abstract

Background and Objective—An association between biomarkers of *trans* fat intake and greater risk of preeclampsia has been reported but research in this area is scant. Thus, we examined the association of second trimester intake of *trans* fats with risk of preeclampsia and severe pre-eclampsia.

Methods—We followed 67,186 pregnancies of women participating in the Danish National Birth Cohort between 1998 and 2003. Diet was assessed with a food frequency questionnaire at gestation week 25 and preeclampsia diagnosis was obtained by linkage with the Danish National Patient Registry.

Results—There were 1,804 cases of preeclampsia and 402 cases of severe preeclampsia identified in the cohort. Intake of *trans* fats decreased during the study period as a consequence of a reduction in industrial *trans* fat intake. Second trimester intake of *trans* fats was unrelated to risk of preeclampsia or severe preeclampsia. The RR (95% CI; p, trend) of preeclampsia and severe preeclampsia comparing top to bottom quintiles of *trans* fat intake were 0.95(0.81, 1.11; 0.33) and 1.07 (0.78, 1.48; 0.92), respectively.

Conclusion—Second trimester intake of *trans* fats is unrelated to risk of preeclampsia within the intake range observed in a period of gradual reduction of industrial *trans* fats from the Danish food supply.

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Keywords

trans fat; preeclampsia; diet; Denmark

INTRODUCTION

Preeclampsia is responsible for approximately 50,000 maternal deaths per year worldwide (Duley 2009). It can also result in substantial complications and morbidity in the mother and her offspring (Duley 2009, Kuklina et al 2009). Despite its impact, relatively little is known about how modifiable factors might influence the risk of developing this condition.

It has been hypothesized that factors influencing endothelial function, inflammatory response and insulin resistance might be associated with preeclampsia (Roberts et al 2003). *Trans* fatty acids are known to negatively affect these three pathways. These fats have been associated with higher circulating levels of markers of chronic inflammation and endothelial dysfunction in observational studies (Lopez-Garcia et al 2005, Mozaffarian et al 2004). *Trans* fats also increased insulin resistance (Lefevre et al 2005, Riserus et al 2002) and circulating levels of inflammatory markers (Baer et al 2004) in randomized trials. In addition, *trans* fatty acid levels in erythrocytes have been related to a higher risk of preeclampsia (Mahomed et al 2007, Williams et al 1998).

Concern regarding the cardiovascular effects of *trans* fat intake (Mozaffarian et al 2009) has led to numerous efforts to reduce the amount of industrially produced *trans* fats in the food supply (L'Abbe et al 2009). In Denmark, massive media coverage of studies relating *trans* fat to adverse health outcomes, public response to this coverage and subsequent industry and government reaction, led to the near elimination of industrial *trans* fats from the Danish food supply between 1994 and 2004. During this same period the Danish National Birth Cohort, a study aimed at identifying risk factors for pregnancy complications and diseases in the offspring, was established. This allowed us to examine whether *trans* fats, at intake levels observed during the process of reducing industrial *trans* fats from the food supply, are associated to risk of preeclampsia.

SUBJECTS AND METHODS

Study Population

The Danish National Birth Cohort (DNBC) enrolled 91,827 women collectively accruing 101,042 pregnancies between January 1996 and October 2002, accounting for approximately 36% of all pregnancies in Denmark during this period. Study procedures have been described in detail elsewhere (Olsen et al 2001, Olsen et al 2007). Briefly, enrollment was performed by general practitioners throughout the country at the first pre-natal visit, usually in gestational week 6–12. Enrolled participants completed computer-assisted telephone interviews at study entry, gestational week 30 and at 6 and 18 months post delivery. In addition, women were mailed a Food Frequency Questionnaire (FFQ) in gestation week 25. All women gave written consent to participating in the study. The DNBC was approved by the Danish Committee of Ethics and the Danish Data Protection Agency.

The FFQ was piloted in 1996 and 1997 and its final version was introduced in 1998. There were 70,183 pregnancies with dietary data collected on or after 1998 of which 67,527 were singleton pregnancies. We restricted the study to singleton pregnancies and further excluded 341 pregnancies because the estimated total energy intake was unrealistic (defined as $<4,200\text{kJ/day}$ or $>16,700\text{kJ/day}$). After these exclusions the study population consisted of 67,186 pregnancies accrued among 63,226 women; 59,314 women contributed one pregnancy, 3,864 women contributed two pregnancies and 48 women contributed three pregnancies to the study. There were no appreciable differences in the frequency of preeclampsia or the distribution of major risk factors for preeclampsia between women included in this analysis and those excluded from it.

Assessment of diet

Dietary information was obtained from a FFQ mailed to participants at gestation week 25. More than 90% of women completed the questionnaire within one week of mailing. The FFQ included 360 food items and additional questions about dietary supplements. Women were asked to report how often they had consumed each of the foods and beverages included in the FFQ during the past four weeks. Questions had seven to eleven options for frequency of intake, ranging from never to eight or more times per day. Nutrient intakes were estimated by summing the nutrient contribution of all food items in the questionnaire, taking into consideration the brand and type fats used for cooking, as dressings or as a spread on bread. The nutrient content of each food and standard portion size (Andersen et al 1996) was obtained from a nutrient database based primarily on the Danish Food Tables (Danish Food Administration 2000). The top contributors of ruminant *trans* fat intake were dairy foods, red meats and animal fats. The top contributors of industrial *trans* fat intake were shortenings, margarines, microwave popcorn and chips. Nutrient intakes were adjusted for total energy intake using the nutrient residual method (Willett and Stampfer 1986). Intakes of multiple foods and nutrients assessed with the FFQ have been validated against 7-day weighed food diaries and blood biomarkers of intake (Mikkelsen et al 2006, Mikkelsen et al 2007).

Industrially produced *trans* fatty acids were gradually reduced from the Danish food supply during the study period as a result of voluntarily reductions by food manufacturers in response to impending legislation (effective 1 January 2004) limiting the content of industrial *trans* fats in foods to less than 2% of fats. Industrial *trans* fats intake was estimated from measurements of the *trans* fat content of Danish foods that took place in 1995 (van Poppel 1998), 1999 (Leth et al 2003) and 2002–2003 (Bysted et al 2009). Based on these measurements, *trans* fat content of most foods was assumed to decrease linearly between 1995 and 2003, margarines were known to be free of *trans* fats since 1998, and the *trans* fat content of shortenings was known to be constant between 1998 and 2003. Therefore, food items containing industrial *trans* fats in the FFQ were assigned a different *trans* fat content depending on the year the FFQ was completed. The content of *trans* fats from ruminant sources was measured in 2005 (Jakobsen et al 2005) and assumed to be constant during the study period.

Assessment of preeclampsia

Preeclampsia diagnosis was obtained through linkage with the Danish National Patient Registry. Preeclampsia was defined as elevated blood pressure ($\geq 140/90$ mmHg) and proteinuria (≥ 300 mg/24 h or $\geq 1+$ urine dipstick) with onset after 20 weeks gestation that returned to normal before 8 weeks postpartum (ICD10 diagnosis codes DO140, DO141, DO142, DO149, DO150, DO151, DO152 and DO159). Severe preeclampsia was defined as a more severe clinical presentation of preeclampsia (blood pressure $\geq 160/110$ mmHg; proteinuria ≥ 500 mg/24 h or dipstick 3+; or clinical/paraclinical manifestations of severity such as oliguria, cerebral or visual disturbance, persistent epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia, etc.), diagnosis of HELLP syndrome or eclampsia (ICD10 diagnosis codes DO141, DO142, DO150, DO151, DO152 and DO159). In a validation study comparing registry diagnosis to medical record review in a subgroup of DNBC participants, preeclampsia diagnosis was found to have a specificity of 99% and a sensitivity of 69% and severe preeclampsia was found to have a specificity of 100% and a sensitivity of 44% (Klemmensen et al 2007). The associations of traditional risk factors for preeclampsia with risk of this disease were in the same direction and of similar magnitude for registry based and medical record review based diagnosis (Klemmensen et al 2007).

Assessment of covariates

Data on important covariates was obtained from the first and second telephone interviews. Information on maternal age, pre-pregnancy body mass index, maternal height, maternal education, socio-economic status, cohabitation status and homeownership status was obtained from the first interview. Information on smoking during pregnancy was obtained from the first and second interview.

Statistical analyses

The relative risk (RR) of preeclampsia and severe preeclampsia in relation to intake of *trans* fats was estimated using logistic regression. The generalized estimating equation approach (Fitzmaurice et al 2004) with an exchangeable working correlation structure, was used to account for the within-woman correlation in outcomes on different pregnancies. We divided women into five groups according to quintiles of intake of industrial, ruminant and total *trans* fat intake. In these models, the relative risk was computed as the risk of preeclampsia in a specific quintile of intake compared to the risk in the lowest quintile. Tests for linear trend were conducted by using the median values of intake in each category as a continuous variable.

Multivariate-adjusted models were also fitted to the data to account for potential confounders. We initially fitted a covariate-only model where all suspected confounders of the association were simultaneously modeled as predictors of preeclampsia. All significant predictors of preeclampsia at $p < 0.20$ in this model were retained in the final multivariate models. In addition, we included terms for total energy intake and age in all models regardless of their statistical significance. Thus, all multivariate-adjusted models included terms for age, total energy intake, pre-pregnancy BMI, height, parity, smoking status, education and year of pregnancy.

We examined whether the associations between *trans* fat and preeclampsia were modified by participant characteristics (age, parity and BMI) or calendar year by introducing cross-product terms between *trans* fat intake and the variable of interest. Lastly, we conducted a sensitivity analysis to rule out the possibility that timing of disease diagnosis affected the results. All analyses were conducted in SAS version 9.2.

RESULTS

There were 1,804 cases of preeclampsia and 402 cases of severe preeclampsia accrued in 67,186 pregnancies among the 63,226 women included in the analysis. Women with a higher intake of *trans* fatty acids during pregnancy also had slightly higher total energy intake as well as greater intakes of saturated and mono-unsaturated fats and lower intakes of protein and carbohydrates, were less likely to engage in recreational physical activity, were less likely to be high school graduates and more likely to be single, to have ever smoked, and to have had at least 1 previous pregnancy (Table 1). Intake of *trans* fatty acids decreased slightly during the study period from a mean intake of 2.2g/day in 1998 to a mean intake of 1.8g/day in 2003 (p, trend <0.001). This reduction was due to a decrease in industrial *trans* fat intake. Intake of ruminant *trans* fats remained stable throughout the study period at approximately 1.6g/day.

We first evaluated the relationship between second trimester *trans* fat intake and preeclampsia without regard to severity of the disease (Table 2). Intake of industrial *trans* fats was unrelated to preeclampsia in all our analyses. There were inverse relations of ruminant and total *trans* fat intake with preeclampsia risk in age- and energy-adjusted analyses, but these associations disappeared after adjusting for parity.

We then restricted the case definition to severe preeclampsia. There were no significant relations between second trimester *trans* fat intake and this outcome (Table 3). Likewise, there was no evidence that the associations of second trimester *trans* fat intake with preeclampsia or severe preeclampsia differed according to a woman's age, pre-pregnancy BMI, parity or year of pregnancy (Table 4).

Because diet was assessed in gestation week 25 and a diagnosis of preeclampsia can be established starting in gestation week 20, we conducted a sensitivity analysis to exclude the possibility that timing of disease diagnosis affected our results. Among the cases whose date of FFQ completion was available (n=1,616), the median (25th, 75th percentile) time between FFQ completion and diagnosis was 68 (10, 91) days. *Trans* fat intake remained unrelated to pre-eclampsia and severe pre-eclampsia when the analyses were restricted to women whose diagnosis occurred at least 2, 4 or 6 weeks after completing the FFQ (Table 5).

DISCUSSION

We examined the relationship between second trimester intake of *trans* fats and risks of preeclampsia and severe preeclampsia in the DNBC and found no evidence of an association between *trans* fats and preeclampsia at the intake levels found in this study. Our findings are in sharp contrast with two previous reports of a strong positive association between erythrocyte levels of *trans* fatty acids, a biomarker of intake (Sun et al 2007), and risk of

preeclampsia (Mahomed et al 2007, Williams et al 1998). The difference in the results across studies raises several possibilities for interpretation. Possible interpretations include that *trans* fat intake during pregnancy is not related to preeclampsia, that this association exists but only at intake levels that could not be observed in our study due to the low intakes of industrial *trans* fats in Denmark during the study period, or that differences in study design are responsible for the differences in results.

Three studies have previously examined the relation between *trans* fats and preeclampsia. Williams and colleagues (Williams et al 1998) compared the *trans* fatty acid content of erythrocytes from blood samples obtained on the first postpartum day from 22 women diagnosed with preeclampsia and 40 normotensive controls in the United States. Women in the highest tertile of erythrocyte *trans* fatty acids had a 7.4-fold greater odds of preeclampsia compared to women in the lowest tertile (Williams et al 1998). A second study from this group (Mahomed et al 2007) used a similar methodology and enrolled 170 women diagnosed with preeclampsia and 185 normotensive controls from a maternity hospital in Zimbabwe. The odds ratio (95% confidence interval) comparing top to bottom quartile to total erythrocyte *trans* fatty acids in this study was 3.39 (1.60, 7.17) (Mahomed et al 2007). It should be noted that in both studies blood samples were drawn postpartum raising the possibility the higher erythrocyte *trans* fat levels observed in cases are a consequence of preeclampsia rather than a cause.

The third study was a prospective pregnancy cohort which examined first trimester intake of *trans* fats assessed with a FFQ in relation to subsequent risk of preeclampsia (Oken et al 2007). Intake of *trans* fats was unrelated to preeclampsia in this study as in the present study. The mean intake of *trans* fats in this study (2.1 g/day) was very similar to the average intake in the DNBC at the beginning of the recruitment period. An important limitation of this third study is its size. The cohort consisted of 1,718 women 59 of whom developed preeclampsia. This substantially limited its statistical power to detect an association between *trans* fats and preeclampsia even if it truly exists.

Our study does not completely clarify whether a relation between *trans* fats and preeclampsia truly exists. Despite the strengths of our study, there are some limitations that precluded us from settling this question. The major strengths of this study are its size and quality of data. The DNBC is the largest pregnancy and birth cohort that has collected comprehensive dietary information with a validated instrument prior to the typical onset of preeclampsia. Thus, our study is the largest one so far examining the association between *trans* fats and preeclampsia. A related strength was the availability of multiple measurements of the *trans* fat content of Danish foods during the study period which allowed us to take into account the secular changes in food content of these fats. Another major advantage was our ability to retrieve preeclampsia diagnoses from the national disease registry, and a detailed validation study indicating that this registry has a high specificity and positive predictive value for diagnosis of preeclampsia and severe preeclampsia (Klemmensen et al 2007). However, registry-based diagnosis has only a moderate sensitivity. The effect that moderate sensitivity may have on the results depends on whether the misclassification of the disease status was differential or non-differential with respect to intake of *trans* fatty acids: non-differential misclassification leads to attenuation of the

observed association whereas differential misclassification may bias effect estimates in any direction. We do not have dietary intake data among the subgroup of women who were included in the validation study. Thus, it is not possible to know whether misclassification of pre-eclampsia is differential or not with respect to *trans* fat intake. Nevertheless, we know from the validation study that misclassification of pre-eclampsia diagnosis is non-differential with respect to established risk factors for this disease (Klemmensen et al 2007), including factors strongly associated with *trans* fat intake in this study (smoking and parity). Hence, although we cannot completely rule out the possibility of differential misclassification of pre-eclampsia diagnosis, the data from our validation study suggest that the most likely scenario is that misclassification was non-differential. Therefore, that the most important consequence of the moderate sensitivity of registry diagnosis was loss of statistical power that, given the size of the study, may not have affected the results to a large extent.

A potential limitation of our study is that diet was assessed in gestation week 25. Although the pathogenesis of preeclampsia is not clear, early placentation events may be initiators of this condition (Goldman-Wohl and Yagel 2009). Therefore, it is possible that we did not assess intake at the etiologically relevant period. However, others have found that the overall composition of diet in general and intake of *trans* fats in particular, change very little between the first and second trimester of pregnancy (Rifas-Shiman et al 2006) suggesting that this weakness may not have influenced our results greatly. A related limitation is that, since preeclampsia is defined by onset of hypertension and proteinuria after gestation week 20, it is possible that some women experienced preeclampsia before completing the FFQ. Nevertheless, in the majority of cases the onset of preeclampsia symptoms is near term (Lain and Roberts 2002). Moreover, our sensitivity analysis suggested that timing of disease diagnosis relative to FFQ completion was not an important limitation of our study.

Another important limitation of our study is the narrow intake range for industrial *trans* fats in this population. This situation made it impossible to distinguish from our data whether *trans* fat intake truly is unrelated to preeclampsia or whether it is related to this condition but only at intake levels that could not be observed in our study. To resolve this question further research is necessary in populations that remain exposed to large amounts of industrial *trans* fats in their food supply. Answering this question has major public health implications. Whereas many developed nations have implemented multiple strategies to decrease or eliminate industrial *trans* fats from the food supply, the *trans* fatty acid content of cooking fats in developing regions of the world, where the burden of preeclampsia is greatest (Khan et al 2006), remains unnecessarily high (L'Abbe et al 2009). If future investigations fail to replicate the results of the biomarker-based studies it would be important to understand whether preeclampsia induces changes in fatty acid metabolism that could explain the results of these studies. Contrariwise, if future investigations find a relation between intake of *trans* fats at higher levels than those observed in this study and preeclampsia, our data would provide an additional argument for the elimination of these fats from the food supply.

In summary, we did not find evidence that, within the range of observed intake, *trans* fats are related to preeclampsia or severe preeclampsia. Our data is in conflict with two previous biomarker-based studies leaving a question open of whether these fats are truly unrelated to

preeclampsia or whether an association exists at greater intake levels. Answering this question could have important implications for the prevention of preeclampsia, a major contributor to maternal mortality worldwide.

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References

- Andersen LT, Jensen H, Haraldsdottir J. Typiske vægte for madvarer. *Scand J Nutr.* 1996; 40:S129–152.
- Baer DJ, Judd JT, Clevidence BA, Tracy RP. Dietary fatty acids affect plasma markers of inflammation in healthy men fed controlled diets: a randomized crossover study. *Am J Clin Nutr.* 2004; 79:969–973. [PubMed: 15159225]
- Bysted A, Mikkelsen AÆ, Leth T. Substitution of *trans* fatty acids in foods on the Danish market. *Eur J Lipid Sci Technol.* 2009; 111:574–583.
- Danish Food Administration. *The Composition of Foods.* 2000.
- Duley L. The Global Impact of Pre-eclampsia and Eclampsia. *Semin Perinatol.* 2009; 33:130–137. [PubMed: 19464502]
- Fitzmaurice, GM.; Laird, NM.; Ware, JH. Marginal models: generalized estimating equations (GEE). In: Fitzmaurice, GM.; Laird, NM.; Ware, JH., editors. *Applied longitudinal analysis.* Wiley & Sons; Hoboken, NJ: 2004. p. 291-321.
- Goldman-Wohl D, Yagel S. Preeclampsia--a placenta developmental biology perspective. *J Reprod Immunol.* 2009; 82:96–99. [PubMed: 19586664]
- Jakobsen MU, Bysted A, Andersen NL, Heitmann BL, Hartkopp HB, Leth T, et al. Intake of ruminant *trans* fatty acids in the Danish population aged 1–80 years. *Eur J Clin Nutr.* 2005; 60:312–318. [PubMed: 16234830]
- Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PFA. WHO analysis of causes of maternal death: a systematic review. *Lancet.* 2006; 367:1066–1074. [PubMed: 16581405]
- Klemmensen AK, Olsen SF, Osterdal ML, Tabor A. Validity of Preeclampsia-related Diagnoses Recorded in a National Hospital Registry and in a Postpartum Interview of the Women. *Am J Epidemiol.* 2007; 166:117–124. [PubMed: 17556761]
- Kuklina EV, Ayala C, Callaghan WM. Hypertensive Disorders and Severe Obstetric Morbidity in the United States. *Obstet Gynecol.* 2009; 113:1299–1306. [PubMed: 19461426]
- L'Abbe MR, Stender S, Skeaff CM, Ghafoorunissa, Tavella M. Approaches to removing *trans* fats from the food supply in industrialized and developing countries. *Eur J Clin Nutr.* 2009; 63:S50–S67. [PubMed: 19190645]
- Lain KY, Roberts JM. Contemporary Concepts of the Pathogenesis and Management of Preeclampsia. *JAMA.* 2002; 287:3183–3186. [PubMed: 12076198]
- Lefevre M, Lovejoy JC, Smith SR, DeLany JP, Champagne C, Most MM, et al. Comparison of the acute response to meals enriched with *cis*- or *trans*-fatty acids on glucose and lipids in overweight individuals with differing FABP2 genotypes. *Metabolism.* 2005; 54:1652–1658. [PubMed: 16311100]
- Leth T, Bysted A, Hansen K, Ovesen L. *Trans* FA content in Danish margarines and shortenings. *J Am Oil Chem Soc.* 2003; 80:475–478.
- Lopez-Garcia E, Schulze MB, Meigs JB, Manson JE, Rifai N, Stampfer MJ, et al. Consumption of *Trans* Fatty Acids Is Related to Plasma Biomarkers of Inflammation and Endothelial Dysfunction. *J Nutr.* 2005; 135:562–566. [PubMed: 15735094]

- Mahomed K, Williams MA, King IB, Mudzamiri S. Erythrocyte omega-3, omega-6 and trans fatty acids in relation to risk of preeclampsia among women delivering at Harare Maternity Hospital, Zimbabwe. *Physiol Res.* 2007; 56:37–50. [PubMed: 16497090]
- Mikkelsen TB, Osler M, Olsen SF. Validity of protein, retinol, folic acid and n-3 fatty acid intakes estimated from the food-frequency questionnaire used in the Danish National Birth Cohort. *Public Health Nutrition.* 2006; 9:771–778. [PubMed: 16925883]
- Mikkelsen TB, Olsen SF, Rasmussen SE, Osler M. Relative validity of fruit and vegetable intake estimated by the food frequency questionnaire used in the Danish National Birth Cohort. *Scand J Public Health.* 2007; 35:172–179. [PubMed: 17454921]
- Mozaffarian D, Pischon T, Hankinson SE, Rifai N, Joshipura K, Willett WC, et al. Dietary intake of *trans* fatty acids and systemic inflammation in women. *Am J Clin Nutr.* 2004; 79:606–612. [PubMed: 15051604]
- Mozaffarian D, Aro A, Willett WC. Health effects of trans-fatty acids: experimental and observational evidence. *Eur J Clin Nutr.* 2009; 63:S5–S21. [PubMed: 19424218]
- Oken E, Ning Y, Rifas-Shiman SL, Rich-Edwards JW, Olsen SF, Gillman MW. Diet During Pregnancy and Risk of Preeclampsia or Gestational Hypertension. *Ann Epidemiol.* 2007; 17:663–668. [PubMed: 17521921]
- Olsen J, Melbye M, Olsen SF, Sorensen TI, Aaby P, Andersen AM, et al. The Danish National Birth Cohort—its background, structure and aim. *Scand J Public Health.* 2001; 29:300–307. [PubMed: 11775787]
- Olsen SF, Mikkelsen TB, Knudsen VK, Orozova-Bekkevold I, Halldorsson TI, Strom M, et al. Data collected on maternal dietary exposures in the Danish National Birth Cohort. *Paediatric and Perinatal Epidemiology.* 2007; 21:76–86. [PubMed: 17239183]
- Rifas-Shiman SL, Rich-Edwards JW, Willett WC, Kleinman KP, Oken E, Gillman MW. Changes in dietary intake from the first to the second trimester of pregnancy. *Paediatr Perinat Epidemiol.* 2006; 20:35–42. [PubMed: 16420339]
- Riserus U, Arner P, Brismar K, Vessby B. Treatment with dietary *trans*10 *cis*12 conjugated linoleic acid causes isomer-specific insulin resistance in obese men with metabolic syndrome. *Diabetes Care.* 2002; 25:1516–1521. [PubMed: 12196420]
- Roberts JM, Balk JL, Bodnar LM, Belizan JM, Bergel E, Martinez A. Nutrient Involvement in Preeclampsia. *J Nutr.* 2003; 133:1684S–1692. [PubMed: 12730485]
- Sun Q, Ma J, Campos H, Hankinson SE, Hu FB. Comparison between plasma and erythrocyte fatty acid content as biomarkers of fatty acid intake in US women. *Am J Clin Nutr.* 2007; 86:74–81. [PubMed: 17616765]
- van Poppel G. Intake of trans fatty acids in western Europe: the TRANSFAIR study. *The Lancet.* 1998; 351:1099–1099.
- Willett WC, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol.* 1986; 124:17–27. [PubMed: 3521261]
- Williams MA, King IB, Sorensen TK, Zingheim RW, Troyer BL, Zebelman AM, et al. Risk of preeclampsia in relation to elaidic acid (*trans* fatty acid) in maternal erythrocytes. *Gynecol Obstet Invest.* 1998; 46:84–87. [PubMed: 9701685]

Table 1 Baseline characteristics according to intake of *trans* fatty acids. Danish National Birth Cohort, 1998–2003 (n = 67,186 pregnancies).

	Total <i>trans</i> fatty acids (g/day)						
	< 1.48	1.48 – 1.82	1.83 – 2.15	2.16 – 2.58	2.59		
N	13,434	13,435	13,435	13,435	13,434		
Age, years [†]	29.2 ± 4.1	29.2 ± 4.2	29.2 ± 4.2	29.1 ± 4.3	29.1 ± 4.5		
Pre-pregnancy body mass index, kg/m ² [†]	23.6 ± 4.1	23.6 ± 4.1	23.6 ± 4.1	23.6 ± 4.3	23.3 ± 4.4		
Height, m [†]	1.69 ± 0.06	1.69 ± 0.06	1.69 ± 0.06	1.69 ± 0.06	1.68 ± 0.06		
Total energy intake, kJ/d [†]	9,773 ± 2,442	9,957 ± 2,567	10,084 ± 2,607	10,217 ± 2,733	10,299 ± 3,025		
Saturated fat intake, g/d [†]	23 ± 7.8	29 ± 9.7	34 ± 11.1	39 ± 13.4	48 ± 18.1		
Mono-unsaturated fat intake, g/d [†]	20 ± 7.1	24 ± 8.1	26 ± 8.7	29 ± 9.9	33 ± 12.2		
Poly-unsaturated fat intake, g/d [†]	12 ± 4.2	12 ± 4.2	12 ± 4.2	13 ± 4.5	13 ± 4.8		
Ruminant <i>trans</i> fat intake, g/d [†]	0.9 ± 0.2	1.2 ± 0.2	1.5 ± 0.3	1.8 ± 0.3	2.2 ± 0.5		
Industrial <i>trans</i> fat intake, g/d [†]	0.3 ± 0.2	0.4 ± 0.2	0.5 ± 0.3	0.6 ± 0.3	0.8 ± 0.5		
Protein intake, g/d [†]	94.2 ± 28.2	94.3 ± 28.8	93.4 ± 28.1	91.2 ± 25.3	83.4 ± 26.6		
Carbohydrate intake, g/d [†]	358 ± 109	340 ± 93	332 ± 93	319 ± 89	294 ± 96		
Leisure time physical activity, %	48.1	41.7	35.9	32.8	27.6		
High school graduate, %	44.1	42.8	41.4	38.4	33.7		
Single, %	1.7	1.5	1.5	1.7	2.4		
Home owner, %	66.6	68.9	70.2	70.1	69.3		
Never smoker, %	82.8	79.1	75.9	73.0	64.7		
Nulliparous, %	57.3	50.0	45.9	43.3	38.1		

[†]Data presented as Mean ± SD

Second trimester intake of *trans* fatty acids in relation to risk of preeclampsia. Danish National Birth Cohort, 1998–2003 (n = 67,186 pregnancies).

Table 2

	Quintile of Intake					p, trend ¹
	1	2	3	4	5	
Industrial trans fats, range (g/day)	< 0.25	0.25 – 0.37	0.38 – 0.51	0.52 – 0.72	0.73	
Cases / Pregnancies	353 / 13,437	374 / 13,437	356 / 13,438	362 / 13,437	359 / 13,437	
Age and energy-adjusted RR	1.00	1.08 (0.93, 1.24)	1.02 (0.88, 1.19)	1.05 (0.90, 1.22)	1.03 (0.89, 1.20)	0.89
Multivariate-adjusted RR ²	1.00	1.10 (0.95, 1.27)	1.04 (0.90, 1.21)	1.09 (0.94, 1.27)	1.06 (0.91, 1.23)	0.67
Ruminant trans fats, range (g/day)	< 1.06	1.06 – 1.33	1.34 – 1.62	1.63 – 1.99	2.00	
Cases / Pregnancies	395 / 13,437	396 / 13,437	373 / 13,438	332 / 13,437	308 / 13,437	
Age and energy-adjusted RR	1.00	1.02 (0.89, 1.18)	0.96 (0.83, 1.10)	0.85 (0.74, 0.99)	0.79 (0.68, 0.92)	<0.001
Multivariate-adjusted RR ²	1.00	1.08 (0.94, 1.25)	1.02 (0.89, 1.18)	0.96 (0.82, 1.11)	0.95 (0.81, 1.11)	0.20
Total trans fats, range (g/day)	< 1.48	1.48 – 1.82	1.83 – 2.15	2.16 – 2.58	2.59	
Cases / Pregnancies	407 / 13,437	387 / 13,437	344 / 13,438	344 / 13,437	322 / 13,437	
Age and energy-adjusted RR	1.00	0.96 (0.83, 1.11)	0.87 (0.75, 1.00)	0.86 (0.74, 0.99)	0.80 (0.69, 0.93)	0.001
Multivariate-adjusted RR ²	1.00	1.02 (0.88, 1.17)	0.97 (0.84, 1.12)	0.94 (0.81, 1.10)	0.95 (0.81, 1.11)	0.33

¹ Calculated in a separate regression model where the median intake in each category was modeled as a continuous variable

² Adjusted for age, total energy intake, pre-pregnancy BMI, height, parity, smoking status, education and year of pregnancy.

Second trimester intake of *trans* fatty acids in relation to risk of severe preeclampsia Danish National Birth Cohort, 1998–2003 (n = 67,186 pregnancies).

Table 3

	Quintile of Intake					p, trend ¹
	1	2	3	4	5	
Industrial trans fats, range (g/day)	< 0.25	0.25 – 0.37	0.38 – 0.51	0.52 – 0.72	0.73	
Cases / Pregnancies	71 / 13,437	98 / 13,437	71 / 13,438	85 / 13,437	77 / 13,437	
Age and energy-adjusted RR	1.00	1.38 (1.02, 1.88)	1.01 (0.72, 1.40)	1.20 (0.88, 1.65)	1.09 (0.79, 1.51)	0.91
Multivariate-adjusted RR ²	1.00	1.43 (1.05, 1.95)	1.05 (0.75, 1.47)	1.29 (0.94, 1.79)	1.18 (0.85, 1.64)	0.69
Ruminant trans fats, range (g/day)	< 1.06	1.06 – 1.33	1.34 – 1.62	1.63 – 1.99	2.00	
Cases / Pregnancies	84 / 13,437	91 / 13,437	88 / 13,438	71 / 13,437	68 / 13,437	
Age and energy-adjusted RR	1.00	1.09 (0.81, 1.46)	1.05 (0.78, 1.41)	0.85 (0.62, 1.17)	0.82 (0.59, 1.12)	0.06
Multivariate-adjusted RR ²	1.00	1.14 (0.85, 1.54)	1.14 (0.84, 1.54)	0.98 (0.71, 1.35)	1.01 (0.73, 1.41)	0.75
Total trans fats, range (g/day)	< 1.48	1.48 – 1.82	1.83 – 2.15	2.16 – 2.58	2.59	
Cases / Pregnancies	89 / 13,437	83 / 13,437	87 / 13,438	68 / 13,437	75 / 13,437	
Age and energy-adjusted RR	1.00	0.93 (0.69, 1.25)	0.98 (0.73, 1.32)	0.77 (0.56, 1.05)	0.84 (0.62, 1.15)	0.15
Multivariate-adjusted RR ²	1.00	1.00 (0.74, 1.35)	1.11 (0.82, 1.50)	0.89 (0.64, 1.23)	1.07 (0.78, 1.48)	0.92

¹ Calculated in a separate regression model where the median intake in each category was modeled as a continuous variable

² Adjusted for age, total energy intake, pre-pregnancy BMI, height, parity, smoking status, education and year of pregnancy.

Table 4

Second trimester intake of *trans* fatty acids in relation to risk of preeclampsia and severe preeclampsia according to pre-pregnancy characteristics and year of pregnancy. Danish National Birth Cohort, 1998 – 2003 (n = 67,186 pregnancies) /

	Cases	Industrial trans fats		Ruminant trans fats	
		RR (95% CI) per 1 g/day	P, interaction	RR (95% CI) per 1g/day	P, interaction
<i>Preeclampsia</i>					
Age < 30 years	1,088	1.01 (0.84, 1.21)	0.49	0.91 (0.81, 1.02)	0.26
Age 30 years	716	1.13 (0.89, 1.40)		1.00 (0.88, 1.15)	
BMI < 25 kg/m ²	1,071	1.03 (0.86, 1.23)	0.76	0.97 (0.87, 1.08)	0.45
BMI ≥ 25 kg/m ²	733	1.08 (0.86, 1.35)		0.91 (0.79, 1.04)	
Nulliparous	1,297	1.06 (0.90, 1.24)	0.86	0.96 (0.87, 1.06)	0.61
Parous	507	1.03 (0.79, 1.35)		0.91 (0.78, 1.07)	
1998 – 1999	637	1.04 (0.84, 1.27)	0.80	1.00 (0.88, 1.14)	0.63
2000 – 2001	798	1.04 (0.83, 1.30)		0.88 (0.78, 0.99)	
2002 – 2003	369	1.14 (0.81, 1.59)		1.00 (0.82, 1.22)	
<i>Severe preeclampsia</i>					
Age < 30 years	238	0.98 (0.65, 1.47)	0.24	0.90 (0.70, 1.16)	0.33
Age 30 years	164	1.39 (0.91, 2.12)		1.07 (0.84, 1.36)	
BMI < 25 kg/m ²	266	1.06 (0.74, 1.51)	0.59	0.95 (0.76, 1.19)	0.77
BMI ≥ 25 kg/m ²	136	1.25 (0.74, 2.13)		1.01 (0.75, 1.35)	
Nulliparous	310	1.03 (0.72, 1.48)	0.34	1.02 (0.82, 1.26)	0.26
Parous	92	1.40 (0.83, 2.36)		0.81 (0.57, 1.16)	
1998 – 1999	136	1.23 (0.82, 1.86)	0.45	0.97 (0.73, 1.28)	0.81
2000 – 2001	186	1.11 (0.66, 1.86)		0.95 (0.72, 1.24)	
2002 – 2003	80	0.80 (0.38, 1.68)		1.03 (0.68, 1.57)	

/ All models are adjusted for age, total energy intake, pre-pregnancy BMI, height, parity, smoking status, education and year of pregnancy.

Table 5

Sensitivity analysis for the association of second trimester intake of *trans* fatty acids with risk of preeclampsia and severe preeclampsia. Danish National Birth Cohort, 1998 – 2003. (n = 67,186 pregnancies) ¹.

	Cases	Industrial trans fats	Ruminant trans fats
		RR (95% CI) per 1 g/day	RR (95% CI) per 1g/day
<i>Preeclampsia</i>			
All cases	1,804	1.05 (0.91 – 1.21)	0.95 (0.87 – 1.03)
Diagnosis 2 or more weeks after FFQ	1,203	0.98 (0.82 – 1.18)	1.00 (0.90 – 1.11)
Diagnosis 4 or more weeks after FFQ	1,157	0.96 (0.80 – 1.15)	0.98 (0.88 – 1.08)
Diagnosis 6 or more weeks after FFQ	1,086	0.89 (0.73 – 1.08)	0.95 (0.86 – 1.06)
<i>Severe preeclampsia</i>			
All cases	402	1.12 (0.83 – 1.51)	0.97 (0.81 – 1.16)
Diagnosis 2 or more weeks after FFQ	270	0.98 (0.66 – 1.45)	1.00 (0.80 – 1.23)
Diagnosis 4 or more weeks after FFQ	248	1.02 (0.68 – 1.53)	0.99 (0.79 – 1.24)
Diagnosis 6 or more weeks after FFQ	212	0.84 (0.53 – 1.34)	0.92 (0.72 – 1.18)

¹ All models are adjusted for age, total energy intake, pre-pregnancy BMI, height, parity, smoking status, education and year of pregnancy.