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Original article

Maternal intake of fat in pregnancy and offspring metabolic health – A prospective study with 20 years of follow-up

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SUMMARY

Background: Maternal fat intake during pregnancy in relation to offspring metabolic outcomes has been studied primarily in animal models, yet little is known about the association in humans. The aim of this study was to examine the association of total and subtype of fat consumption in pregnancy with anthropometric measures and biomarkers of adiposity and glucose metabolism in the offspring.
Methods: A source population was 965 Danish pregnant women recruited in 1988–1989 with offspring follow-up at 20 years. Information on fat intake was collected in the 30th week of gestation, and we subdivided fat according to saturated (SFA), monounsaturated (MUFA), and polyunsaturated (PUFA) fat. Offspring body mass index (BMI) and waist circumference (WC) were recorded at follow-up (n = 670–678), and biomarkers were quantified in a subset (n = 443) of participants. Multivariable linear and log-binomial regression were used to calculate effect estimates and 95% CI for a 1:1%energy substitution of carbohydrates for fat.
Results: The mean (standard deviation) BMI was 22.1 (3.3) and 22.8 (2.9) kg/m^2 in female and male offspring, respectively. The median (10th to 90th percentile) of maternal fat intake was 31% of energy [23,39]. We found no overall associations for maternal fat intake with female offspring anthropometry. However, for male offspring higher intake of MUFA during pregnancy was associated with higher insulin levels at 20 years (Q4 vs. Q1: %Δ: 37, 95% CI: 1, 86) accompanied by a non-significant 3.6 (95% CI: −1.1, 8.2) cm increase in WC. High maternal total fat intake (>=35% energy) was also associated with higher BMI (0.9, 95% CI: 0.2, 1.6) and WC (4.0, 95% CI: 1.6, 2.3) among male offspring.
Conclusions: A high fat diet during pregnancy may increase adiposity in adult male offspring. We surmise that maternal MUFA intake during this time included both MUFA and *trans* fat misclassified as MUFA, and that the associations observed may be more reflective of the latter exposure.

1. Introduction

Since the birth of the fetal origins hypothesis, there has been significant interest in the effect of macronutrient in pregnancy on the development of offspring metabolic health [1]. The role of fat intake has been considered relevant largely due to its relationship with metabolic and cardiovascular outcomes in adults [2,3]. Studies in animals have shown that maternal consumption of a diet high in saturated fat during gestation resulted in increased body fat, and elevated circulating glucose, insulin, and triglyceride concentrations in the offspring [4,5]; other have noted a decreased beta-cell mass and reduced insulin sensitivity in the offspring [6,7]. Also human studies have implicated maternal fat intake during pregnancy in reduced insulin secretion in the offspring [8]. Many studies have focused specifically on gestational high fat

Abbreviations: BMI, Body Mass Index; GDM, gestational diabetes mellitus; HOMA-IR, homeostatic model assessment for insulin resistance; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; RR, relative risk; SFA, saturated fatty acids; TFA, trans fatty acids.

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programming of insulin sensitivity and secretion, while less is known about programming effects of fat and types of fat on offspring adiposity. While it has long been thought that higher fat intake leads to increased body fat, we now know that the issue is far more complex and depends not only on the quantity but also the quality of fat [9]. The implications of high fat intake and subtypes of fat in pregnancy on offspring adiposity have been less studied. A study of 174 pregnant women in Australia showed an increased percentage of fetal mid-thigh fat with higher intake of maternal saturated fat, while the opposite was true for polyunsaturated fat [10]. This study could not conclude what, if any, effects this may have beyond the womb. Maternal n-3 fatty acid intake was also inversely related to obesity at age 3 years in a US cohort [11]. A UK study found that maternal postnatal, but not prenatal, fat intake was weakly associated with lower child adiposity and lean mass at age 9 after adjusting for parental underreporting [12]. However, the study did not evaluate subtypes of maternal fat intake. A previous study in the present cohort examining the relation between maternal marine n-3 fatty acid intake in pregnancy, and offspring anthropometry and cardiometabolic biomarkers, did not show any association [13]. A randomized clinical trial of fish oil (versus olive oil) in pregnancy similarly did not find any association with offspring BMI and waist circumference 19 years later [14]. No information was provided on saturated and monounsaturated fat.

Given a general lack of understanding of maternal fat intake in pregnancy in relation to offspring adiposity, especially as it pertains to subtypes of fat, we decided to examine this association in a unique research setting with follow-up data 20 years post-pregnancy on offspring body mass index (BMI), waist circumference, and biomarkers of adiposity, and glucose and lipid homeostasis.

2. Methods

2.1. Study population

We recruited 965 women with singleton pregnancies April 1988 to January 1989 for a birth cohort study in Aarhus, Denmark [15]. These women constituted 80% of a consecutive sample of 1212 women attending prenatal care in the city. Prior to a routine antenatal visit in gestational week 30, a dietary questionnaire and a questionnaire on lifestyle and health were mailed to the women, which were returned at the visit. We extracted other information on the women's health, birth outcomes, and medical history from hospital records and the Danish Medical Birth Registry.

A follow-up study on the offspring was conducted in 2008–2009 when mothers were contacted and informed about the study. We then asked the offspring to fill out an online questionnaire and to participate in a clinical visit. Approximately 95% ($n = 915$) mother-child dyads were identified in the central registration registry. Out of these, 690 of the offspring filled out the questionnaire and 443 attended the clinical examination. The online questionnaire asked about lifestyle and health, including anthropometry. During the clinical visit, we performed standardized anthropometric measures and drew a fasting blood sample. We used body mass index (BMI) and waist circumference measures from the clinical examination when available ($n = 443$). Self-reported measures of BMI ($n = 252$) and waist circumference ($n = 254$) from the web-based questionnaire were employed for the remaining subjects. Out of these 695-697 subjects, $n = 10$ were missing maternal dietary data and one offspring was excluded due to an implausible BMI value (<10 kg/m^2), leaving a total of 684–686 mother-offspring pairs.

The study was approved by the Danish Data Protection Agency and the Danish Council of Ethics (Reference No. 20070157).

2.2. Exposure assessment

In gestational week 30, the women filled out a self-administered dietary questionnaire covering the previous 3 months and participated in a face-to-face interview. The objective of the interview was to quantify main ingredients of cooked meals and to complement the information from the questionnaire with quantitative estimates for commonly consumed food items. Photographs modelling portion sizes were used in the quantification procedure. Our emphasis was on obtaining an accurate assessment of macronutrient and energy intake, which we quantified using the 1996 Danish food composition table v. 4. The questionnaire has been well validated against erythrocyte measurements of marine fatty acids, but not any other fatty acids or nutrients [15].

Total fat intake was divided into saturated, monounsaturated, and polyunsaturated fatty acids to distinguish between potentially differential biological roles and effects. All nutrients were energy–adjusted using the residual method [16]. Residuals were scaled to intake at mean energy and converted from grams to kcal.

2.3. Outcome assessment

Standardized anthropometric measures were used to measure offspring BMI and waist circumference during the clinical visit. To measure their waist circumference, all offspring received a tape measure by mail with instructions on how to carry out the measurement. It is known that subjects tend to underestimate their weight by self-report (on average 0.4 kg/m^2 lower based on $n = 400$ with both measurements). However, relative rank of subjects was retained in our cohort with the correlation (Spearman rho) between measured and self-reported BMI and waist circumference being 0.91 and 0.78, respectively. We defined overweight as $\geq$ 25 kg/m^2 and high waist circumference as >88 cm for females and >102 cm for males [17]. Birth weight was retrieved from the Danish Medical Birth Registry and linked to the cohort data using the participants' unique national identity number.

2.4. Offspring biomarkers

Quantification of biomarker levels has been described in an earlier publication [13]. In brief, serum triglycerides and cholesterol were measured according to standard methods on a Modular P (Roche Diagnostics). We used a time-resolved immunofluorometric assay based on two antibodies and recombinant human adiponectin (R&D Systems, Abingdon, United Kingdom) to quantify adiponectin levels; the analysis was similarly carried out for leptin [18]. Plasma insulin concentrations were determined by a commercial ELISA kit (DAKO). Blood glucose was measured using bedside equipment (Accu-chek; Roche Diagnostics) following blood sampling and HbA1c was quantified using an HPLC assay (Bio-Rad Laboratories) on a Variant II Turbo. The homeostatic model assessment for insulin resistance (HOMA-IR) was calculated as previously described [19].

2.5. Covariate assessment

The following covariates were included in the multivariable model: maternal age (continuous), maternal education (elementary schooling, high-school or technical schooling, university education, higher academic education, other education), maternal smoking (never, <10 and ≥10 cigarettes/day), pre-pregnancy body mass index (BMI, continuous), parity (0, 1, 2+), and sibling overweight (binary). Covariate missing data ranged from 0 to 7% for most covariates with at most 6% missing data on two covariates. Sibling overweight had the largest proportion of missing data