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Organic Food Consumption during Pregnancy and Hypospadias and Cryptorchidism at Birth: The Norwegian Mother and Child Cohort Study (MoBa)

Anne Lise Brantsæter,[1,§] Hanne Torjusen,[1,2,§,] Helle Margrete Meltzer,[1] Eleni Papadopoulou,[1] Jane A. Hoppin,[3] Jan Alexander,[4] Geir Lieblein,[5] Gun Roos,[2] Jon Magne Holten,[6] Jackie Swartz,[7,8] and Margaretha Haugen[1]

[1]Division of Environmental Medicine, Department of Exposure and Risk Assessment, Norwegian Institute of Public Health, Oslo, Norway; [2]National Institute for Consumer Research (SIFO), Oslo, Norway; [3]Center for Human Health and the Environment, Department of Biological Sciences, North Carolina State University, Raleigh, North Carolina, USA; [4]Office of the Director-General, Norwegian Institute of Public Health, Oslo, Norway; [5]Department of Plant Sciences, Norwegian University of Life Sciences, Ås, Norway; [6]Oikos – Organic Norway, Oslo, Norway; [7]Department of Neuroscience, Child and Adolescent Psychiatry, Uppsala University, Uppsala, Sweden; [8]Vidarkliniken, Järna, Sweden. [§]The first two authors should be regarded as joint first authors.

Address correspondence to Anne Lise Brantsæter, Division of Environmental Medicine, Norwegian Institute of Public Health, P.O. Box 4404, Nydalen, NO-0403 Oslo, Norway. Telephone: +47 21076326. E-mail: anne.lise.brantsaeter@fhi.no

Running title: Organic food consumption and hypospadias

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Abstract

Background: The etiologies of the male urogenital anomalies hypospadias and cryptorchidism remain unclear. It has been suggested that maternal diet and environmental contaminants may affect the risk of these anomalies via placental or hormonal disturbances.

Objectives: To examine associations between organic food consumption during pregnancy and prevalence of hypospadias and cryptorchidism at birth.

Methods: Our study includes 35,107 women participating in the Norwegian Mother and Child Cohort Study (MoBa) who delivered a singleton male infant. Information about use of six groups of organically produced food (vegetables, fruit, bread/cereal, milk/dairy products, eggs and meat) during pregnancy was collected by a food frequency questionnaire. Women who indicated that they sometimes, often, or mostly consumed organic foods in at least one of the six food groups were classified as organic food consumers in analyses. Hypospadias and cryptorchidism diagnoses were retrieved from the Medical Birth Registry of Norway. We estimated odds ratios (ORs) and 95 percent confidence intervals (95% CIs) using multiple logistic regression.

Results: Seventy-four male newborns were diagnosed with hypospadias (0.2%) and 151 with cryptorchidism (0.4%). Women who consumed any organic food during pregnancy were less likely to give birth to a boy with hypospadias (OR=0.42; 95% CI: 0.25, 0.70 based on 21 exposed cases) than women who reported they never or seldom consumed organic food. Associations with specific organic foods were strongest for vegetable (OR=0.36; 95% CI: 0.15, 0.85; 10 exposed cases) and milk/dairy (OR=0.43; 95% CI: 0.17, 1.07; 7 exposed cases) consumption. No substantial association was observed for consumption of organic food and cryptorchidism.

Conclusions: Consumption of organically produced foods during pregnancy was associated with a lower prevalence of hypospadias in our study population. These findings were based on small numbers of cases and require replication in other study populations.

Introduction

Hypospadias and cryptorchidism are genital birth defects in male neonates. Hypospadias is a condition defined by the penile meatus not being at the tip of the penis as a result of failure of the urethral fold to unite over and cover the urethral groove. Cryptorchidism is diagnosed when one or both testicles have not descended into the scrotum (Paulozzi 1999). The incidence of hypospadias and cryptorchidism diagnosed in Norway is 0.2% and 0.3%, respectively (Aschim et al. 2004a; Aschim et al. 2006).

The etiology of these disorders remains largely unknown but existing evidence suggests both genetic and environmental contributors (Aschim et al. 2004b; Thorup et al. 2014). Fetal growth restriction and preeclampsia have been consistently associated with hypospadias, a finding that may implicate placental insufficiency as an underlying cause (Thorup et al. 2014). Maternal diet composition strongly influences placental function, level of inflammation and fetal nutrient supply (Thornburg et al. 2010). Other in-utero exposures of interest in relation to anomalies of sexual maturation are substances in the environment, e.g. organochlorine pesticides and other endocrine-active chemicals. There is evidence from animal studies that environmental xenohormones interfere with male genital development (WHO 2013), but the evidence from human studies is not conclusive (Carmichael et al. 2013; Rocheleau et al. 2009; Trabert et al. 2012; Virtanen and Adamsson 2012). Heavy metals, such as cadmium, have also been associated with hypospadias (Sharma et al. 2014).

The principles of organic farming as formulated by the International Federation of Organic Agriculture Movements (IFOAM) imply no use of agrochemicals (artificial pesticides, growth regulators, veterinary medicines and synthetic soluble fertilizers) as well as no use of genetically modified organisms (Luttikholt 2007). The definitions of organic used for labeling purposes may vary among different countries and according to the specific terms used. All food sold as organic in Norway must be certified by the non-profit organization Debio and labelled with Debio's Ø-label (Debio 2015). This is based on an agreement with the Norwegian Food Safety Authority and ensures that regulations for organic production are met (EU Council Regulation 2092-1991). Debio is accredited by Norwegian Accreditation according to the quality standard ISO 65/EN 45011 and by IFOAM (IFOAM 2015).

Organically produced food has been shown in some cases to have higher concentrations of naturally occurring plant constituents, e.g. secondary plant metabolites and lower levels of cadmium and nitrate, and lower incidence of detectable pesticide residues than conventionally produced food (Baranski et al. 2014; Brandt et al. 2013; Forman and Silverstein 2012; Smith-Spangler et al. 2012). Organic dairy products have been shown to contain higher levels of beneficial fatty acids and fat soluble antioxidants compared with conventional dairy products (Benbrook et al. 2013; Huber et al. 2011). However, findings with regard to nutritional content have not been consistent among all studies, and may be partly influenced by factors that are not a consequence of organic production practices specifically. In Norway, reports from the surveillance program for pesticide residues in plant foods have shown that although the levels of detected residues were low, pesticide residues are detected almost exclusively in conventional food samples (Mattilsynet 2013).

Few studies have investigated the potential health effects of eating organic compared to conventional foods. A Danish case-control study with mothers of boys who were operated for hypospadias and mothers of healthy boys suggested a protective association between hypospadias in the offspring and mother choosing the organic alternatives for butter and cheese (Christensen et al. 2013). We recently reported a modest, but significantly lower prevalence of preeclampsia associated with frequent consumption of organic vegetables, which was observed in addition to the reduced prevalence of preeclampsia associated with a healthy diet (Torjusen et al. 2014).

The aim of this study was to examine associations between consumption of organically produced food during pregnancy and prevalence of hypospadias and cryptorchidism at birth.

Material and Methods

Study population

The dataset in this study is part of the Norwegian Mother and Child Cohort Study (MoBa), a population-based prospective pregnancy cohort study conducted by the Norwegian Institute of Public Health (Magnus et al. 2006). Participants were recruited from across Norway from 1999-2008 and 40.6% of the invited women participated. The cohort now includes 114,500 children, 95,200 mothers and 75,200 fathers. Women were recruited to the study by postal invitation prior to the routine ultrasound examination in gestational weeks 17-19. The women were asked to provide biological samples at baseline and to answer questionnaires at regular intervals during pregnancy and after birth. The data included in this study were from two questionnaires answered in gestational weeks 15 (questionnaire 1) and 22 (questionnaire 2). Questionnaire 1 was a general questionnaire covering lifestyle, background, illness and health related factors. Questionnaire 2 was a food frequency questionnaire asking the women to report average dietary intakes since the start of pregnancy. The cohort database is linked to the Medical Birth Registry of Norway (MBRN) which was established in 1967 and contains information about pregnancy, delivery and health of the mother and the neonate for every birth or abortion after 12th week of gestation (Irgens 2000).

The source population eligible for inclusion in the current study (n=74,774) were women participating in MoBa who had responded to questionnaire 1 and questionnaire 2 and were registered in MBRN with a singleton delivery, including stillbirths. Furthermore, they had to have answered at least one of the six questions about consumption of organic food groups in questionnaire 2 (excluding 750) and they had to have reported a daily energy intake between 4.5 and 20 MJ, excluding 1131 (Meltzer et al. 2008). A total of 72,893 (97.5%) women fulfilled these criteria, of which 37,299 delivered a male neonate. Of these, women who were included in the cohort with more than one pregnancy were only included in the present study with their first enrollment. This resulted in a final study population of 35,107 mother-infant pairs. Of these, 34,986 were live born, 92 were dead before delivery, 10 died during delivery and 19 were registered with unknown time of death. There were no cases of hypospadias or cryptorchidism among the 121 not live born babies. The current study is based on version 4 of the quality-assured data files released for research in January 2009. All MoBa participants provided written informed consent prior to enrollment into the study.

Ethical approval

MoBa was approved by the Regional Committee for Ethics in Medical Research (S-95113 and S-97045) and the Norwegian Data Inspectorate (Magnus et al. 2006).

Data Collection

Dietary variables: Information on organic food consumption was collected by a semi-quantitative food frequency questionnaire which was designed specifically for assessing diet during the first four months of pregnancy (NIPH 2002). The FFQ included questions about the frequency of use of organic food specified in six food groups: 1) milk and dairy products, 2) bread and cereal products, 3) eggs, 4) vegetables, 5) fruit and 6) meat. There were four response categories for organic food consumption: 'never/seldom', 'sometimes', 'often', or 'mostly'. Missing responses on all six group-specific questions resulted in exclusion from the study population, while missing responses on one to five questions were coded as 'never/seldom'. In the present study we examined the specific organic food groups in two categories, i.e. 'never/seldom' versus 'sometimes', 'often' and 'mostly'), with the exception of a descriptive table with three categories ('never/seldom', 'sometimes' and 'often/mostly'). The organic food groups were examined both as separate variables and as a combined variable denoting consumption of 'any organic' food. The 'any organic' variable was a dichotomous variable (no or yes) with yes defined as having answered 'sometimes', 'often' or 'mostly' on at least one of the six organic food groups. The FFQ has been extensively validated in 119 women using a four day weighed food record and biological markers as reference methods. The results showed acceptable agreement (less than 10% grossly misclassified and correlation coefficients ranging from 0.3 – 0.6) between the FFQ estimates and the reference methods with regard to nutrients, dietary supplements and food groups including fruit and vegetables (Brantsaeter et al. 2007a; Brantsaeter et al. 2007b; Brantsaeter et al. 2008). The validity of the questions about organic food consumption has not been evaluated. We did not have information about quantity (g/day) for organic foods, only frequency. From the FFQ we included the daily intakes (g/day) of vegetables, fruit, cereals, milk/dairy, eggs and meat, and variables denoting a vegetarian diet (vegans, lacto-vegetarians or lacto-ovo-vegetarians, no/yes), alcohol consumption (no/yes), dietary supplement use (no/yes). To take the total diet into account we previously used principal component analysis to extract dietary patterns based on the quantitative intakes of 58 major food groups. The first principal component was interpreted as a healthy dietary pattern, with high positive loadings for vegetables, fruit and berries, plant oils and whole grain cereals (Torjusen et al. 2012); those in the highest tertile were deemed 'high scores'.

Outcome variables: Information about hypospadias and cryptorchidism was retrieved from MBRN. MBRN includes all live births and stillbirths with a gestational age greater than 16 weeks. The main objective of the registry is the surveillance and detection of changes in perinatal health. Notification is compulsory and is carried out by midwives or physicians attending the birth within 7 days after delivery. The standardized form contains detailed information about the parents and the child, e.g. maternal health before and during index pregnancy, procedures and complications during delivery, and condition of the child at birth. Medical coding is classified according to the International Classification of Diseases, 10th revision (ICD-10 codes). Hypospadias was classified with ICD-10 codes Q54.0, Q54.1, Q54.2, Q54.3, Q54.4, Q54.8, or Q54.9 and cryptorchidism was classified with ICD-10 codes Q53.0, Q53.1, Q53.2, or Q53.9 (WHO 2010). MBRN is a national birth registry that since its establishment in 1967 has been an important source for epidemiological surveillance and research (Irgens 2000). A comparison of prevalence rates of hypospadias diagnoses in MBRN and the number of surgical procedures for hypospadias performed during a year and registered in the Norwegian Patient Registry showed approximately 25% underreporting in MBRN. The authors concluded that mild hypospadias cases are likely to be underreported in MBRN (Aschim et al. 2004a). No information is available on the performance of the registry with regard to cryptorchidism.

Other variables: In the baseline questionnaire women provided information about socio-demographic and lifestyle variables including: maternal pre-pregnancy weight and height for calculation of body mass index (BMI), parity, level of education, household income, leisure exercise activity and maternal as well as paternal smoking habits, use of oral contraceptives, and handling of 'disinfectants or vermin poisons' or 'weed killers, insecticides or fungicides' at work or at home during the last six months. BMI was categorized according to the WHO classification as normal (18.5-24.9 kg/m^2), underweight (<18.5 kg/m^2), overweight (25.0-29.9kg/m^2) and obese (≥30.0 kg/m^2). In addition, we included a missing category comprising those who had missing information on weight or height (n=924). Parity was divided into two categories (nulliparous and parous). Education was divided into the following categories: high school or less (≤12years), 3-4 years of college/university (13-16 years), four or more years of college/university education (17+ years) and other/missing information (n=924). Household income was measured as a combination of the participant's and her partner's income (both <300,000 NOK [Norwegian kroner; 1 NOK ~0.12 GBP], one > 300,000 NOK, or both > 300,000 NOK). In addition, we included a missing category (n=1025). Maternal and paternal smoking habits during pregnancy were divided into two categories, non-smokers vs. smokers.

Information about singleton or plural delivery, infant sex, maternal age at delivery, paternal age, infant birth weight, gestational length, in vitro fertilization (IVF) and previous stillbirths was retrieved from the MBRN. Gestational length was calculated from expected date of delivery on the basis of first trimester ultrasound. In event of missing an ultrasound measure, gestational length was calculated from last menstrual period. Preterm delivery was defined as gestational length <37 weeks. Small for gestational age (SGA) was defined as infant birth weight lower than the 10th percentile for nulliparous and multiparous births for each week of gestation based on the distribution in all singleton pregnancies in MoBa. Missing information on birth weight or gestational length and observations with birth weight less than 600 g and gestational length less than 25 weeks resulted in 204 infants with missing data on SGA. These were excluded in the adjusted analyses for hypospadias. Likewise, there were 123 missing data on paternal age excluded in the adjusted analyses for cryptorchidism.

Statistical analyses

All *P* values were two-sided and values <0.05 were considered statistically significant. Pearson Chi-square test was used to test for group difference in categorical data.

Crude and adjusted odd ratios (OR) with 95% confidence intervals (CIs) were estimated for the association between consumption of 1) any organic food expressed in a combined variable of all organic food groups and the outcomes, 2) individual organic food groups and the outcomes, and 3) individual food groups and the outcomes with additional adjustment for use of any organic food.

Characteristics and dietary quality associated with organic food consumption in MoBa have been described in detail previously (Torjusen et al. 2010; Torjusen et al. 2012). Variables considered as potential confounding variables in the current study were maternal age, paternal age, maternal pre-pregnancy BMI, parity, maternal education, leisure exercise activity, being a student, household income, dietary supplement use, having a vegetarian diet, healthy diet scores, energy intake, use of alcohol, maternal smoking, paternal smoking, handling of 'disinfectants or vermin poisons' or 'weed killers, insecticides or fungicides' at work or at home during the last six months, IVF, oral contraceptives any time during the previous year, previous stillbirths, preterm delivery and SGA. From these, variables were selected on the basis of their association with both the exposure and the outcome ($p<0.10$) using the any organic variable as the exposure. Variables fulfilling this criterion with hypospadias as outcome were: pre-pregnancy BMI, maternal education, leisure exercise activity and household income. Variables fulfilling this criterion with cryptorchidism as outcome were: paternal age, maternal education, mother being a student and household income. In addition, we included known risk factors for hypospadias or cryptorchidism (IVF, preterm delivery and SGA). Adjustment variables were assessed using the change in estimate method, starting with all variables in the models with deletion of one by one in a stepwise manner (backward regression). None of the variables resulted in a change in estimate >10% and all variables with $p<0.10$ were retained in the final models. The variables retained in the analyses of hypospadias were: maternal education, household income, pre-pregnant BMI, SGA and preterm delivery. The variables retained in the analyses of cryptorchidism were: maternal education, household income and paternal age. In addition, the calculated amount of vegetables, fruit, cereals, milk/dairy, eggs, and meat was included in the model for each organic food group to adjust for quantity although these did not meet the criterion of $p<0.10$.

All analyses were performed using the statistical package for social sciences version 20.0 (IBM SPSS Statistics 20) for Windows (SPSS, Chicago, IL, USA).

Results

Of the 35,107 mothers in this study, 17,996 (51.3%) reported ‘never/seldom’ use of all the organic food, 11,370 (32.4%) reported ‘sometimes’ as the highest frequency for at least one organic group, and 5741 (16.4%) reported ‘often or mostly’ for at least one of the six organic food groups. The number of neonates with hypospadias was 74 (0.2%) and the number with cryptorchidism was 151 (0.4%) diagnosed within 7 days of birth. Only one boy had both anomalies. Use of any organic food was associated with higher education and household income, and with lower BMI, nulliparity, non-smoking, being a student, use of dietary supplements, drinking alcohol, adhering to vegetarian diet, and having a healthy diet (Table 1). In general the percentages reporting “never/seldom” consumption of organic food were higher in hypospadias cases than in the total study population, while this was not seen for cryptorchidism (Table 2).The most widely consumed organic food group was vegetables, with 35.2% of women reporting this ‘sometimes’, ‘often’ or ‘mostly’, followed by eggs (34.1%), fruit (28.8%), milk/dairy products (26.0%), cereals (20.3%) and meat (12.2%). The highest proportion of organic consumers was found for the vegetable group (72.2%), but there were substantial overlap among the organic food groups (Table 3).

In unadjusted models, a lower prevalence of hypospadias was seen for women who reported use of organic vegetables and organic milk/dairy products (Table 4). Adjusted ORs were similar to crude ORs (Table 4). The adjusted OR for hypospadias in association with consumption of any organic food was 0.42 (95% CI: 0.25, 0.70) based on 21 exposed cases, and significant negative associations were also estimated for consumption of organic vegetables (10 exposed cases), organic fruit (13 exposed cases), organic milk/dairy products (7 exposed cases), and organic eggs

(16 exposed cases) (Table 4). Excluding observations with missing information on SGA (n=204) led to exclusion of two boys with hypospadias. A total of 2,582 (7.3%) women had missing values on maternal pre-pregnant BMI, educational attainment and/or household income. When these were excluded rather than modelled as "missing" categories, the number of hypospadias cases were 68 but the associations did not change (OR=0.42 (95% CI: 0.25, 0.71) based on 20 exposed cases). Additional adjustment for the estimated total daily intake (organic and non-organic) of food items (g/day) within each organic food group had no influence on the ORs.

Due to the large overlap between consumption of organic food in the various food groups, the separate food groups could not be included in the same model. However, we added to the model for each of the food groups the variable 'any organic use' to control for whether being an 'organic consumer' influenced the results. As expected, this largely removed the associations between the organic food groups and hypospadias, with the exception of the ORs for organic vegetables and organic milk. The association remained significant for consumption of organic vegetables, with adjusted OR=0.36 (95%CI; 0.15, 0.85) based on10 exposed cases). For organic milk/dairy products the adjusted OR was borderline significant with OR=0.43 (95%CI; 0.17, 1.07) based on 7 exposed cases, *p* value 0.070.

Consumption of organic food was not associated with the prevalence of cryptorchidism for any of the food groups (Table 5). However, a borderline negative association with cryptorchidism was found for organic milk/dairy products with OR=0.65 (95%CI; 0.40, 1.04), *p*=0.071 and 31 exposed cases.

Finally, we repeated the analyses for any organic food consumption and hypospadias adjusting for preeclampsia (n=1387). The adjusted OR remained unchanged (OR=0.42 (95%CI: 0.25, 0.69) based on 21 exposed cases). When mothers with preeclampsia were excluded from the analysis, the adjusted OR was 0.35 (95%CI: 0.20, 0.62) based on 16 exposed cases.

Discussion

The main finding of this study was that women who reported “sometimes, often or mostly” eating organically produced food during pregnancy, were less likely to give birth to a boy with hypospadias than women who reported never or seldom consuming organic foods. Of the six individual organic food groups queried, the negative association was strongest for consumption of organic vegetables, based on 10 cases classified as consumers and 62 cases classified as non-consumers. The associations were consistent and marginally influenced by adjusting for food intakes, lifestyle factors and socio-demographic variables. However, in most cases there were substantial changes with adjustment for “any organic consumption” although the estimates are difficult to interpret due to probable collinearity. We found no association between organic food consumption and cryptorchidism, with the exception of a borderline significant association for use of organic milk/dairy products (OR=0.65 (95%CI: 0.40, 1.04), p=0.071 based on 31 exposed cases).

To the best of our knowledge, this is the first prospective study to report a significant association between consumption of organic food and hypospadias. There are limited data to explain this finding. Properties of organic food, particularly vegetables, which could possibly contribute to explain the finding of a reduced prevalence of hypospadias at birth in our study population, include compositional differences with regard to bioactive substances including nutrients and pesticide residues (Baranski et al. 2014; Brandt et al. 2013; Forman and Silverstein 2012; Smith-Spangler et al. 2012). However, findings with regard to nutritional content have not been consistent among all studies. Given differences in bacterial communities on the surfaces on organic and conventional fresh fruits and vegetables (Leff and Fierer 2013) one might speculate that this could impact the gut microbiota and thereby the proneness to inflammation (Bengmark 2013), but this is largely hypothetical.

Exposure to pesticides in the general population, with the exception of occupational and accidental exposure, is mainly via residues on food (Lu et al. 2008). Consumption of organic food has been associated with lower urinary concentrations of pesticide metabolites in children and adults (Curl et al. 2003; Lu et al. 2006; Oates et al. 2014). Pesticide exposure could hypothetically lead to hypospadias via hormonal or placental disturbances. Hypospadias and cryptorchidism are both related to androgen receptor function (Toppari et al. 2010), and the role of fetal androgens is especially important during the first trimester when organogenesis takes place (Kalfa et al. 2009). Numerous pesticides are known to be endocrine-active substances with estrogenic or anti-androgenic activity (WHO 2013). Despite restriction for use in most developed countries, organochlorine pesticides are persistent and remain in the environment together with their breakdown products (Clarke et al. 2010; Kannan et al. 1997). However, use still remains in other parts of the world. As the Norwegian food supply is global, residents may be exposed to banned pesticides through consumption of imported fruits and vegetables. Metabolites of the banned pesticides DDT, hexachlorobenzene, β-hexachlorocyclohexane and oxychlordane, have been detected and quantified in Norwegian breast milk sampled in years 2002 to 2006 (Polder et al. 2009).

Placental insufficiency may play an important role in hypospadias etiology as fetal growth restriction and preeclampsia both are risk factors for hypospadias (Akre et al. 1999; Thorup et al. 2014; van der Zanden et al. 2012). Placental function may link the lower prevalence of hypospadias with organic vegetable consumption in the present study with our previous finding of lower prevalence of preeclampsia associated with consumption of organic vegetables (Torjusen et al. 2014). In the present study, the significant association between any organic food and lower prevalence of hypospadias remained both when adjusting for and when excluding women with preeclampsia.

We found lower prevalence of hypospadias associated with consumption of organic food, and in particular organic vegetables, but it was not possible to distinguish clearly between the organic food groups. We had no data to evaluate the quantitative amount of organic food consumption as the estimated intake within the food groups comprised both organic and non-organic items. The weak association between consumption of organic milk/dairy products and hypospadias in our study (p=0.07 based on 7 exposed cases) is in line with the results from a case-control study in Denmark. The study included 306 boys with hypospadias and 306 controls and showed an association between hypospadias in the offspring and the mother not choosing the organic alternative, and having a high intake (>=daily) of nonorganic butter and cheese in comparison with mothers regularly choosing the organic alternative and having a low intake of butter and cheese (<daily) (Christensen et al. 2013). The authors explained their finding by suggesting that conventionally produced butter and cheese contain more traces of pesticide residues than organic food (Christensen et al. 2013).

The strengths of this study include the prospective design and the large study population comprising pregnant women from all regions of Norway, representing all age groups and all socioeconomic groups. Information about maternal diet and use of organically produced food covered the first half of pregnancy and was assessed using a validated FFQ (Brantsaeter et al. 2008). While many women adopt healthier lifestyle and dietary habits during pregnancy (Meltzer et al. 2008), use of organic food is likely to reflect a more long-term practice (Codron et al. 2006). The participation rate in MoBa is 40.6% and MoBa participants are older, have higher educational attainment and comprise fewer smokers than the general population of pregnant women. However, evaluation of this non-representativeness in MoBa showed that it did not affect exposure-outcome associations, including prenatal smoking and birth outcomes (low birthweight, placental abruption, stillbirth), chronic hypertension and gestational diabetes, maternal vitamin use and placental abruption, parity and preeclampsia, marital status and preterm birth (Nilsen et al. 2009), and perinatal and prenatal exposures (primipara pregnancy (no, yes), prenatal folic acid use (no, yes), prenatal smoking (no, yes), low birthweight (no, yes), preterm birth (no, yes), offspring sex (female, male), and cesarean section history (no, yes)) and specialist-confirmed diagnosis of autism spectrum disorders (Nilsen et al. 2013).

While our study benefits from a large cohort design, it is limited with the lack of detail regarding specific aspects of our hypothesis. We had no biological or environmental measurements to assess whether women who consumed organically produced food had different exposure to adverse or favorable substances than those who did not have organic diets. Additionally we lacked detail on the extent of organic consumption of an individual, so women who ate exclusively organic were combined with those who ate mostly conventional diets. We had no family data on genital malformations, which are known to have a hereditary component. Furthermore, use of medical registry data is likely to result in under- reporting of mild forms, i.e. cryptorchidism with spontaneous descent and mild hypospadias with normal foreskin. The prevalence of hypospadias in our study is similar to the prevalence rate in MBRN (0.2%) (Veiby et al. 2014), while the prevalence of cryptorchidism (0.4%) was slightly higher than previously reported in Norway (0.3%) (Aschim et al. 2006). Although case-diagnoses were based on international case definitions, misclassification or misreporting may occur. Ideally, case-diagnoses should be ascertained through the patient registry using both diagnoses at birth and surgical operations for the condition as criteria of being a case. For the present study we did not have access to the patient registry, but a previous study that evaluated the prevalence rates for hypospadias in MBRN and the patient registry indicated misclassification primarily of mild hypospadias (Aschim et al. 2004a). Our study included 74 mothers of boys with hypospadias of which 22 were consumers of any organic food, and although misclassification might be random with regard to exposure, the consequences of bias cannot be predicted with certainty when the numbers of observations are small. The diagnosis of cryptorchidism is less certain because mild cases descend spontaneously after birth. It is possible that misclassification of cryptorchidism might have contributed to the finding of no associations between organic foods and this outcome.

We were able to adjust for many potential confounding variables and adjustment had little influence on the results. However, use of organic food was self-reported and residual confounding cannot be excluded. Use of organic food may reflect other lifestyle factors such as differences in use and sources of cosmetics, household cleaning products, cleaning frequency, home interior materials, clothing material and home cooking practices (e.g. use of plastic storage containers).

In conclusion, mothers who reported "sometimes, often, or mostly" consuming organic foods during pregnancy were less likely to give birth to a boy with hypospadias than women who reported never or seldom consuming organic foods. The association between organic food consumption and lower prevalence of hypospadias were strongest for organic vegetables and organic milk and dairy products, though findings were based on small numbers of cases. We did not find evidence of an association between organic food consumption and cryptorchidism at birth in our study population. To improve public health, pregnant women are encouraged to eat more vegetables regardless of how they are produced, and choosing the organic alternative might give additional benefits. However, the replication of our findings in other cohorts is warranted.

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Table 1. Organic food consumption[a] by maternal characteristics

Characteristic	All	Never/seldom organic	Sometimes, often or mostly organic	*P*-value [b]
N (%)	35,107 (100)	17,996 (51.3)	17,111 (48.7)	
Maternal age				<0.001
<20 years	667 (1.9)	310 (46.5)	357 (53.5)	
20-29 years	18,041 (51.4)	9624 (53.3)	8417 (46.7)	
≥30 years	16,399 (46.7)	8062 (49.2)	8337 (50.8)	
Paternal age				<0.001
<20 years	184 (0.5)	79 (42.9)	105 (57.1)	
20-29 years	12,223 (34.8)	6492 (53.1)	5731 (46.9)	
≥30 years	22,577 (64.3)	11,375 (50.4)	11,202 (49.6)	
Missing information	123 (0.4)	50 (40.7)	73 (59.3)	
Maternal BMI				<0.001
<18.5 kg/m^2	1017 (2.9)	516 (50.7)	501 (49.3)	
18.5 – 24.9 kg/m^2	22,336 (63.6)	11,123 (49.8)	11,213 (50.2)	
25 – 29.9 kg/m^2	7500 (21.4)	4055 (54.1)	3445 (45.9)	
≥30 kg/m^2	3330 (9.5)	1826 (54.8)	1504 (45.2)	
Missing information	924 (2.6)	476 (51.5)	448 (48.5)	
Parity				<0.001
Nulliparous	16,919 (48.2)	8502 (50.3)	8417 (49.7)	
Parous	17,699 (50.3)	9211 (52.1)	8458 (47.9)	
Maternal education				<0.001
≤ 12 years	11,099 (31.6)	6235 (56.2)	4464 (43.8)	
13 – 16 years	17,793 (42.1)	7741 (52.3)	7052 (47.7)	
≥17 years	8448 (24.1)	3605 (42.7)	4843 (57.3)	
Missing information	767 (2.2)	415 (54.1)	352 (45.9)	
Mother student				<0.001
No	31,707 (90.3)	16,433 (51.8)	15,274 (48.2)	
Yes	3400 (9.7)	1563 (46.0)	1837 (54.0)	
Household income				<0.001
Both partners <300,000 NOK	10,143 (28.9)	5399 (53.2)	4744 (46.8)	
One partner ≥300,000 NOK	14,832 (42.2)	7788 (52.5)	7044 (47.5)	
Both partners ≥300,000 NOK	9107 (25.9)	4311 (47.3)	4796 (52.7)	
Missing information	1025 (2.9)	498 (48.6)	527 (51.4)	
Dietary supplement use				<0.001
No	7170 (20.4)	4123 (57.5)	3047 (42.5)	
Yes	27,937 (79.6)	13,873 (49.7)	14,064 (50.3)	
Vegetarian diet				<0.001
No	35,044 (99.8)	17,982 (51.3)	17,062 (48.7)	
Yes	63 (0.2)	14 (22.2)	49 (77.8)	
Healthy diet scores				<0.001
Lowest tertiles	23,405 (66.7)	13,713 (58.6)	9692 (41.4)	
Upper tertile	11,702 (33.3)	4283 (36.6)	7419 (63.4)	
Alcohol in pregnancy				<0.001
No	31,106 (88.6)	16,146 (51.9)	14,960 (48.1)	
Yes	4001 (11.4)	1850 (46.2)	2151 (53.8)	

Smoking in pregnancy				<0.001
No	32,194 (91.7)	16,332 (50.7)	15,862 (49.3)	
Yes	2913 (8.3)	1664 (57.1)	1249 (42.9)	

[a] Consumption of organic food defined as having answered ‘sometimes’, ‘often’ or ‘mostly’ for at least one of the six organic food groups (vegetables, fruits, cereals, milk/dairy, eggs, meat). Non-consumption defined as having answered ‘Never/seldom’ for all organic food groups. No missing data on use of organic food

[b] P-value obtained by Pearson's chi-square test

Table 2. Prevalence of hypospadias and cryptorchidism diagnosed within 7 days of birth, by organic food consumption[a]

Organic food consumption	Total n (%)	Hypospadias n (%)	Cryptorchidism n (%)
	35,107	74	151
Organic Vegetables			
Never/seldom	22,759 (64.8)	63 (85.1)	98 (64.9)
Sometimes	9785 (27.9)	8 (10.8)	44 (29.1)
Often or mostly	2563 (7.3)	3 (4.1)	9 (6.0)
Organic Fruit			
Never/seldom	25006 (71.2)	61 (82.4)	107 (70.9)
Sometimes	7802 (22.2)	9 (12.2)	36 (23.8)
Often or mostly	2299 (6.5)	4 (5.4)	8 (5.3)
Organic Cereals			
Never/seldom	27,980 (79.7)	64 (86.5)	123 (81.5)
Sometimes	4915 (14.0)	6 (8.1)	18 (11.9)
Often or mostly	2212 (6.3)	4 (5.4)	10 (6.6)
Organic Milk/dairy products			
Never/seldom	25,992 (74.0)	67 (90.5)	120 (79.5)
Sometimes	6582 (18.7)	5 (6.8)	18 (11.9)
Often or mostly	2533 (7.2)	2 (2.7)	13 (8.6)
Organic Eggs			
Never/seldom	23,144 (65.9)	58 (78.4)	99 (65.6)
Sometimes	8749 (24.9)	8 (10.8)	38 (25.2)
Often or mostly	3214 (9.2)	8 (10.8)	14 (9.3)
Organic Meat			
Never/seldom	30,814 (87.8)	70 (94.6)	136 (90.1)
Sometimes	2793 (8.0)	2 (2.71)	13 (8.6)
Often or mostly	1500 (4.2)	2 (2.7)	2 (1.3)

[a] No missing data on use of organic food

Table 3. Pattern of organic food consumption within the six organic food groups as reported by 35,107 pregnant women in the Norwegian Mother and Child Cohort Study (MoBa) who delivered a singleton male infant in years 2002 to 2008

		Any Organic [a]	
Organic Food group	n (%)	Never/seldom	Sometimes, often or mostly
Organic Vegetables			
Never/seldom	22,759 (64.8)	17,996	4763 (27.8)
Sometimes, often or mostly	12,348 (35.2)	0	12,348 (72.2)
Organic Fruit			
Never/seldom	25,006 (71.2)	17,996	7010 (41.0)
Sometimes, often or mostly	10,101 (28.8)	0	10,101 (59.0)
Organic Cereals			
Never/seldom	27,980 (79.7)	17,996	9015 (58.3)
Sometimes, often or mostly	7127 (20.3)	0	7127 (41.7)
Organic Milk/dairy products			
Never/seldom	25,992 (74.0)	17,996	7996 (46.7)
Sometimes, often or mostly	9115 (26.0)	0	9115 (53.3)
Organic Eggs			
Never/seldom	23,144 (65.9)	17,996	5148 (30.1)
Sometimes, often or mostly	11,963 (34.1)	0	11,963 (69.9)
Organic Meat			
Never/seldom	30,814 (87.8)	17,996	12,818 (74.9)
Sometimes, often or mostly	4293 (12.2)	0	4293 (25.1)

[a] Any organic defined as having answered ‘sometimes’, ‘often’ or ‘mostly’ for any of the six organic food groups (vegetables, fruits, cereals, milk/dairy, eggs, meat). Non-consumption defined as having answered ‘Never/seldom’ for all organic food groups. No missing data on use of organic food

Table 4. Associations between organic food consumption and hypospadias [a]

Exposure to organic food	Total n	Hypospadias n	(%)	Crude	Adjusted [b]	Adjusted [c]
	35,107	n	(%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Any organic food [d]						
Never/seldom	17,996	52	0.3	1	1	NA
Sometimes, often or mostly	17,111	22	0.1	0.44 (0.27, 0.73)	0.42 (0.25, 0.70)	
Organic Vegetables						
Never/seldom	22,759	63	0.3	1	1	1
Sometimes, often or mostly	12,348	11	0.1	0.32 (0.17, 0.61)	0.30 (0.15, 0.58)	0.36 (0.15, 0.85)
Organic Fruit						
Never/seldom	25,006	61	0.2	1	1	1
Sometimes, often or mostly	10,101	13	0.1	0.53 (0.29, 0.96)	0.54 (0.30, 0.99)	1.15 (0.48, 2.79)
Organic Cereals						
Never/seldom	27,980	64	0.2	1	1	1
Sometimes, often or mostly	7127	10	0.1	0.61 (0.32, 1.19)	0.62 (0.32, 1.22)	1.27 (0.54, 3.00)
Organic Milk/dairy products						
Never/seldom	25,992	67	0.3	1	1	1
Sometimes, often or mostly	9115	7	0.1	0.30 (0.14, 0.65)	0.30 (0.14, 0.65)	0.43 (0.17, 1.07)
Organic Eggs						
Never/seldom	23,144	58	0.3	1	1	1
Sometimes, often or mostly	11,963	16	0.1	0.53 (0.31, 0.93)	0.54 (0.31, 0.94)	1.40 (0.51, 3.82)
Organic Meat						
Never/seldom	30,814	70	0.2	1	1	1
Sometimes, often or mostly	4293	4	0.1	0.41 (0.15, 1.22)	0.42 (0.15, 1.17)	0.72 (0.23, 2.15)

[a] Numbers of observations (total and cases) do not account for observations with missing covariate data (204 missing including 2 cases)

[b] Results from logistic regression models adjusted for maternal education, household income, maternal pre-pregnancy body mass index, small for gestational age baby, preterm delivery. In addition, the model for each organic food group was adjusted for the total daily intake of food items (organic and non-organic) in the respective group

[c] Additional adjustment for consumption of any organic food

[d] Reported use of at least one of the organic food groups. No missing data on use of organic food

NA = not applicable

Table 5. Associations between organic food consumption and cryptorchidism[a]

Exposure to organic food	Total n	Cryptorchidism		Crude	Adjusted [b]	Adjusted [c]
	35,1077	n	(%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Any organic food [d]						
Never/seldom	17,996	79	0.4	1	1	NA
Sometimes, often or mostly	17,111	72	0.4	0.96 (0.70, 1.32)	0.91 (0.66, 1.26)	
Organic Vegetables						
Never/seldom	22,759	98	0.4	1	1	1
Sometimes, often or mostly	12,348	53	0.4	0.99 (0.71, 1.39)	0.92 (0.66, 1.30)	1.03 (0.61, 1.74)
Organic Fruit						
Never/seldom	25,006	107	0.4	1	1	1
Sometimes, often or mostly	10,101	44	0.5	1.02 (0.72, 1.45)	1.04 (0.73, 1.44)	1.17 (0.73, 1.90)
Organic Cereals						
Never/seldom	27,980	123	0.4	1	1	1
Sometimes, often or mostly	7127	28	0.4	0.89 (0.59, 1.35)	0.86 (0.57, 1.30)	0.88 (0.55, 1.42)
Organic Milk/dairy products						
Never/seldom	25,992	120	0.5	1	1	1
Sometimes, often or mostly	9115	31	0.3	0.74 (0.50, 1.09)	0.70 (0.47, 1.05)	0.65 (0.40, 1.04)
Organic Eggs						
Never/seldom	23,144	99	0.4	1	1	1
Sometimes, often or mostly	11,963	52	0.5	1.02 (0.73, 1.42)	0.97 (0.69, 1.36)	1.09 (0.65, 1.82)
Organic Meat						
Never/seldom	30,814	136	0.4	1	1	1
Sometimes, often or mostly	4293	15	0.4	0.79 (0.46, 1.35)	0.78 (0.45, 1.33)	0.78 (0.44, 1.38)

[a] Numbers of observations (total and cases) do not account for observations with missing covariate data (123 missing including 1case).

[b] Results from logistic regression models adjusted for maternal education, household income, and paternal age. In addition, the model for each organic food group was adjusted for the total daily intake of food items (organic and non-organic) in the respective group

[c] Additional adjustment for any organic food

[d] Reported use of at least one of the organic food groups. No missing data on use of organic food

NA = not applicable