Organic food, pregnancy and health

Associations between consumption of organic food in pregnancy, maternal characteristics and pregnancy health outcomes in the Norwegian Mother, Father and Child Cohort Study (MoBa)

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Abstract

The aims of this thesis were to characterise women who included organic food in their diets during pregnancy and investigate the potential impact of organic food consumption on the risk of pre-eclampsia in the mothers and of hypospadias and cryptorchidism in male babies.

Analyses are based on data from the Norwegian Mother, Father and Child Cohort Study (MoBa) and data from the Medical Birth Registry of Norway. The study population included pregnant women recruited to MoBa in years 2002 to 2008 who had answered MoBa's food frequency questionnaire (FFQ) and a general health questionnaire, and their male babies.

The MoBa FFQ included a question about frequency of organic consumption within six food groups: i) milk and dairy products, ii) bread and cereal products; iii) eggs, iv) vegetables, v) fruit and vi) meat. For each of these food groups, four alternative response categories were given: 'never/seldom', 'sometimes', 'often', or 'mostly'.

Frequent consumption defined as eating organic food 'sometimes' or 'mostly' was reported by 9.1% of the study population. Results in the first two papers showed that frequent organic food consumption was associated with various personal, socio-economic- and lifestyle characteristics. Several, but not all of these characteristics were in line with traditional markers of good health. Frequent organic food consumers reported higher intake of vegetables and lower intake of meat and had an overall healthier and more sustainable dietary pattern. The personal, socio-demographic- and lifestyle characteristics, including dietary quality, were used to control for confounding in our subsequent analyses of possible associations between organic food consumption and the studied health outcomes.

Results in the third paper showed that frequent consumption of organic vegetables, but not organic fruit, cereals, eggs, milk, or meat, was associated with lower risk of pre-eclampsia compared with less frequent organic vegetable consumption. The result was significant also when taking dietary quality into account by adjusting for the healthy and sustainable dietary pattern score.

In the fourth paper, the results showed that women who reported any organic food consumption during pregnancy, defined as 'sometimes', 'often', or 'mostly' for any of the organic food groups, were less likely to give birth to a boy with hypospadias than women who reported 'never/seldom' consuming organic food. Results for individual food groups showed

that associations were strongest for consumption of organic vegetables and milk/dairy products. However, the findings were based on small numbers of cases and require replication in other study populations. No substantial association was observed for consumption of organic food and cryptorchidism.

Dietary guidelines recommend frequent consumption of plant food, including vegetables, to all pregnant women. Results from the studies in this thesis indicate that choosing organically grown vegetables may yield additional benefits.

Contextual knowledge about relevant characteristics and dietary practices associated with consumption of organic food is important to include in future investigations of organic food and health.

List of papers

Paper I

Torjusen H, Brantsæter AL, Haugen M, Lieblein G, Stigum H, Roos G, Holmboe-Ottesen G, Meltzer MH. Characteristics associated with organic food consumption during pregnancy; data from a large cohort of pregnant women in Norway. *BMC Public Health* 2010; 10:775.

Paper II

Torjusen H, Lieblein G, Næs T, Haugen M, Meltzer HM, Brantsæter AL. Food patterns and dietary quality associated with organic food consumption during pregnancy; data from a large cohort of pregnant women in Norway. *BMC Public Health* 2012; 12:612.

Paper III

Torjusen H, Brantsæter AL, Haugen M, Alexander J, Bakketeig LS, Lieblein G, Stigum H, Næs T, Swartz J, Holmboe-Ottesen G, Roos G, Meltzer HM. Reduced risk of pre-eclampsia with organic vegetable consumption: results from the prospective Norwegian Mother and Child Cohort Study. *BMJ Open* 2014; 4(9):e006143.

Paper IV

Brantsæter AL, Torjusen H, Meltzer MH, Papadopoulou E, Hoppin JA, Alexander A, Lieblein G, Roos G, Holten JM, Swartz J, Haugen M. Organic Food Consumption during Pregnancy and Hypospadias and Cryptorchidism at Birth: The Norwegian Mother and Child Cohort Study (MoBa). *Environmental Health Perspectives* 2016;124(3):357-64.

Abbreviations and definitions

Abbreviations

FFQ: Food frequency questionnaire

MoBa: The Norwegian Mother, Father [1] and Child Cohort Study

DNBC: The Danish National Birth Cohort

MBRN: The Medical Birth Registry of Norway

NIPH: Norwegian Institute of Public Health

OR: Odds ratio

CI: Confidence interval

OP pesticides: Organophosphorous pesticides

DAP metabolites: Dialkylphosphate metabolites

REC: the Regional Committees for Medical and Health Research Ethics (In Norwegian: Regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK))

Definitions

Prenatal (=antenatal): relating to or denoting the period before birth.

Postnatal: relating to or denoting the period after birth.

Perinatal: relating to the period comprising both the pregnancy and up to a year after giving birth.

Neonate: an infant less than four weeks old.

In utero: in the uterus; before birth.

[1] From July 2019, 'Father' has been included in the study name.

Fetal development/Gestation: Gestation is the period of time between conception and birth when a baby grows and develops inside the mother's womb.

Gestational age, gestational weeks: Because it is impossible to know exactly when conception occurs, gestational age is measured from the first day of the mother's last menstrual cycle to the current date. It is measured in weeks. This means that during weeks 1 and 2 of pregnancy, a woman is not yet pregnant. A normal gestation lasts anywhere from 37 to 42 weeks [2].

Nullipara: A woman who has never borne a child.

Primipara: A woman who has had one pregnancy.

Singleton: A child born as a singe birth, in contrast to one that is part of a multiple birth (e.g. twins).

Aetiology: the science and study of the causes of disease and their mode of operation.

Pre-eclampsia: A syndrome of high blood pressure, fluid accumulation in tissue, and protein in the urine that becomes apparent in the second half of pregnancy. Pre-eclampsia is primarily a placental disorder with damage to the inner lining of placental blood vessels.

Hypospadias: Hypospadias is a genital birth defect in male neonates. It is a condition where the opening of the urethra is located under the penis rather than at the tip of the penis as a result of failure of the urethral fold to unite over and cover the urethral groove. The aetiology of hypospadias is poorly understood, but existing evidence suggest both genetic and environmental factors.

Cryptorchidism: Cryptorchidism is a genital birth defect in male neonates. It is diagnosed when one or both testicles have not descended into the scrotum.

Epigenetic modifications: persistant and heritable changes made to the DNA, which regulate how genes are expressed, but do not affect the nucleotide sequence itself. Epigenetic modifications include DNA methylation, histone modification, and microRNA regulation.

[2] Fetal development: MedlinePlus Medical Encyclopedia

Metabolomics: broadly defined as the comprehensive measurement of all metabolites and low-molecular-weight molecules in a biological sample.

Gut microbiome: The gut microbiome, as defined by molecular biologist Joshua Lederberg, is the totality of microorganisms, bacteria, viruses, protozoa, and fungi, and their collective genetic material present in the gastrointestinal tract.

Gut microbiota: The gut microbiota is comprised of all the bacteria, commensal, and pathogenic, residing in the gastrointestinal tract.

Organic Agriculture: In organic agriculture, food is produced without the use of synthetic fertilisers and pesticides, although some natural substances are approved for use, and no use of genetically modified organisms (GMOs). The international organisation for organic agriculture provides the following definition: "Organic Agriculture is a production system that sustains the health of soils, ecosystems, and people. It relies on ecological processes, biodiversity and cycles adapted to local conditions, rather than the use of inputs with adverse effects. Organic Agriculture combines tradition, innovation and science to benefit the shared environment and promote fair relationships and a good quality of life for all involved." (IFOAM General Assembly, 2008) [3].

Organic food: In the present text, the term 'organic food' is used, for simplicity, as a short-hand for food produced according to regulations for organic agriculture.

Conventional farming: In the present text, conventional farming and conventional products include all which are not defined as certified organic.

Debio: The Norwegian certification organisation for organic products. Debio [4] inspects organic production in accordance with the Norwegian "Regulations on the Production and Labelling of Organic Agricultural Products". The inspection services are founded on an agreement with the Norwegian Food Safety Authority, and the regulation is based on the EU Council Regulation 834/2007 [5]. It covers farming, processing, import and marketing of organic agricultural products.

[3] Definition of Organic Agriculture | IFOAM
[4] Information in English - Debio
[5] EU Council. COUNCIL REGULATION (EC) No 834/2007 Brussels, Belgium 2007.

Table of contents

1 Introduction

When the current research project was initiated around 2005, few studies had described characteristics of organic food consumers or directly addressed the potential effects of organic food consumption on human health. However, the belief that organic food is better for human health and the environment than conventionally produced food was, and continues to be, a main motivation for the interest in organic food worldwide. This introductory chapter describes the principles of organic food production, the importance of diet during pregnancy, assessment of diet and organic food consumption, and gives a brief summary of current knowledge with regard to organic food consumption and health in mothers and babies. Finally, the introduction will provide information about the setting of the studies included in this thesis.

1.1 Organically produced food

1.1.1 Definition of organic food production

Inherent in organic agriculture is a principle of interrelatedness of the health of soil, plants, animals and humans [6] (1). Organic agriculture is a production system that relies on ecological processes, biodiversity and cycles adapted to local conditions, aiming at sustaining the health of soils, ecosystems and people (2,3). It is based on principles of health, ecology, fairness and care, and involves restricted use of agrochemicals (pesticides, herbicides, growth regulators, synthetic soluble fertilisers and veterinary medicines) as well as no use of genetically modified organisms (GMO) (4,5).

To describe the different phases of the development of organic farming, IFOAM Organics International has in recent years used the terms Organic 1.0 (piloting organic agriculture), Organic 2.0 (codification of organic practices), and Organic 3.0 (contributing to sustainable development) (5,6). Organic 3.0 aims at "bringing organic out of its current niche into the mainstream and positioning organic systems as part of the multiple solutions needed to solve the tremendous challenges faced by our planet and our species" (5). Although traditional organic farming practices have prevailed for thousands of years, the modern organic

[6] "The health of soil, plant, animal and man is one and indivisible. " is a central quote from Lady Eve Balfour, founder of the UK Soil Association and one of the pioneers of organic farming.

movement began in Europe in the 1920s. The main motivations were to preserve and develop the fertility of the soil and to counteract the industrialisation of agriculture. Later, Rachel Carson's book "Silent spring" published in 1962 (7) started a new era of environmental awareness and was instrumental for the present-day organic movement (8). There has been a significant growth in organic farming in many European countries since EU regulations for organic production was first established in 1991. During these 30 years, organic farming in Europe has grown from a small niche to major industry, covering more than 15 million hectares (9). In EU's Farm to Fork strategy presented in May 2020, one of many ambitions is to transform 25 % of EU farming to organic practises by 2030 (10).

In Norway, organic production is inspected by Debio in accordance with the Norwegian "Regulations on the Production and Labelling of Organic Agricultural Products". The inspection services are founded on an agreement with the Norwegian Food Safety Authority, and the regulation is based on the EU Council Regulation 834/2007 (4,11). It covers farming, processing, import and marketing of organic agricultural products.

Products which meet these regulations may be sold under Debio's Ø-label. In addition, the Demeter-label is used specifically for products from Bio-dynamic agriculture. The EU-label (green leaf) is also used in the Norwegian food market [7] (12) (Figure 1).

Figure 1. Labels used in Norway on products fulfilling the criteria for organic food

1.1.2 Determinants of organic food consumption in Norway

The Norwegian food system is characterised by a high degree of government regulation, a dominant role of a few, large market actors both in the processing industry and in the retail business, and generally high levels of trust in food among consumers (13,14). Initiatives aimed at promoting alternative food consumption have been marginal in terms of both

[7] The EU-logo may be used in Norway on a voluntary basis, while it is mandatory with certification by Debio for all products, which are produced, processed etc. in Norway

practices and public discourses (13). Compared to other European countries, the development of the organic food market in Norway has been slow (15,16).

After the initial pioneer phase, with the first bio-dynamic farm coming into operation in the 1930's and the first bio-dynamic food shop being established in Oslo in 1969, a phase of institutionalisation began in the mid-1980s, when different organic producer organisations started to collaborate, and the national certification scheme for organic food, Debio, was established in 1986 (17,18). Gradually, organic food started to be included in the conventional food system. With an increasing focus on environmental challenges in the agricultural sector, support grants for organic production were introduced in the 1990s, and the authorities regarded organic farming as an important spearhead in the environmental efforts within the agricultural sector (19-21). Following this, production increased fairly rapidly, while availability of organic food to the consumers continued to be low. There were relatively few organic specialty shops and alternative distribution channels, and organic food was largely unavailable in mainstream stores (22). Getting hold of even the most common food products was perceived as difficult and time consuming, as organic products were often placed in shelves not immediately visible in the stores, sometimes among specialty products such as dietetic products rather than together with the main food category (20,23).

Consumer surveys from around 2000 confirmed that structural difficulties, such as availability, were the main barriers for buying organic food rather than negative perceptions or poor interest among consumers (24,25). In a national survey from 2000, 71% of respondents agreed that '*I seldom see organic alternatives where I shop*', while only 28% agreed in the statement '*I see no advantages in organic food*' (25). Since the beginning of 2000, the alternative food market in Norway gradually changed, providing consumers with a wider selection of food with different qualities, including locally and organically produced food. Specialty foods from local or small-scale producers entered the market, and new sales channels for direct sales of local food were established (17). In a representative survey conducted in 2019, 32% of participants reported to do most of their organic food shopping in smaller supermarkets and shops, making these the main types of market channels for organic food. Specialty shops were reported by 18% to be where they do some or most of their organic food shopping, while 13% reported that they use direct purchase from farmers, and 5% for shopping on the internet. As such, organic food shopping largely follows the same trends as food shopping in general (26,27).

There has been a considerable increase in sales numbers for organic food during the time-frame of this study (2002-2008), especially in the last part of this period; from 2007 to 2008 sales of organic food increased by 25% (28).

From 2000 to 2015 consumers have become increasingly content with the availability of organic food; from being the most important barrier in 2000, it was ranged as number 4 in 2015 (29). There has also been a tendency towards fewer consumers saying they never or seldom buy organic food, and more consumers saying that they sometimes or often buy organic food. In 2006, the share of consumers stating that they had bought organic food during the last four weeks was 46% , while 58% did the same in 2013 (29). In a representative survey conducted in 2019, 30% of Norwegian respondents reported that they had eaten organic food once a week or more often, 4% of these on a daily basis. While 23% reported to eat organic food once a month or less often, 13% reported to never eat organic food (26). Nevertheless, both price and availability remain important barriers and organic food still constitutes only a marginal part of the total food market, having been relatively stable around 1% (30). In 2019, 19% responded that they rarely find organic alternatives when buying food (26).

With regard to gender differences in organic food shopping in Norway, findings have varied over the years, and it appears not to be any consistent major differences. A higher interest in buying organic food among women compared with men was reported by Berg (31), while in 2008 it was reported that equally many men and women, about one in four, came out of food stores having bought organic food (32). Results from the SIFO-survey conducted in 2000 showed that women purchased organically produced food more often than men, while there was no significant effect of gender in 2013 (30). In a representative survey from 2019, slightly more women than men reported to buy organic food 'often' (19% of the women vs. 12% of the men), while more men than women reported that they 'never' (18% of the men vs. 8% of the women) bought organic food (26). As far as could be established at the time of the studies included in this thesis, there were no data available about organic food consumption specifically during pregnancy.

Motivations for including organic food in the diet have been the subject of numerous studies from various disciplines and perspectives. Such motivations are personal, complex and varied, and reflect cultural, structural and practical matters (33-36). Consumer conceptions may combine short- and long-term perspectives of sustaining health, such as minimising exposure to pesticides, food additives or GMO, sustaining the environment, and providing for the health and well-being of future generations. The issue of the precautionary principle seems also to be at the core of consumer perceptions and motivations for eating organic food (33).

Given the complex and embedded nature of practices related to organic food consumption, it is not surprising that results of studies aiming at pin-pointing consumer motivations, also reflect the presumptions and set-up of the research, including how 'the consumer' is conceptualised (33-35). Health is, however, consistently found to be an important reason why people buy and eat organic food, reported across a variety of studies conducted in Norway as well as in other countries (24,33,35-42).

It can be concluded that conceptions about health related to organic food may span a whole continuum from concrete issues, such as the presence or absence of substances in particular foods, to overarching issues, including relations between the ecosystems in which food production takes place, the quality of food, and human health – in all its aspects. When the potential healthfulness of organic food is seen from this broader view, where care for food quality, human health, animal welfare and the natural environment come together in a systems perspective, consumer conceptions about organic food resonate well with the basic principles of organic agriculture. The image of a "feeding web"[8] is illustrative of these vital relations. Such interlinkages between organic principles and practices in food production systems and public health are acknowledged by major institutions, such as FAO, WHO and the European Parliament (43,44).

[8] Joan Dye Gussow published the book 'The Feeding Web' in 1978 and established the pioneering course 'Nutritional Ecology' at Columbia University, Department of Nutrition in 1988.

1.1.3 Compositional differences and biomarkers of exposure

Compositional differences between organically and conventionally produced food have been documented. Organically produced food has been shown in some cases to have higher concentrations of naturally occurring plant constituents, e.g. secondary plant metabolites, and some vitamins, as well as lower levels of cadmium and nitrate, and lower incidence of detectable pesticide residues than conventionally produced food (45-50). Organic dairy products have been shown to contain higher levels of beneficial fatty acids and fat-soluble antioxidants than conventional dairy products (51-53). It is also shown that organic production methods leave a significant imprint in the plant metabolome, indicating that metabolomics may be useful for organic food authentication and as a quality indicator (54,55). Whether these differences have nutritional and health relevance in a generally well-nourished society like the Norwegian remains an open question (8,43,56-58). A review by Johansson et al. suggested that synergistic effects of several constituents might be the background for potential beneficial health effects of organic food, as well as absence of pesticide residues (59). With regard to health effects of pesticide residues, negative effects have been documented in a number of studies, warning e.g. about severe implications for child health, including impact on endocrine- and respiratory systems as well as neurodevelopment (60,61), estimates indicating that organophosphorus pesticides (OP), among other environmental chemicals, contribute to neurodevelopmental morbidity exceeding those of many nonchemical risk factors (62). An overview of studies examining organic food and pesticide residues in urine is given in Appendix 2. In Norway, reports from the surveillance program for pesticide residues in plant foods show that although detection levels of pesticide residues were very low, they were almost exclusively found in conventionally produced food samples (63).

Performing long-term randomized controlled studies with organic food as the intervention and conventional food as placebo is virtually impossible due to methodological difficulties and costs. However, some clinical or controlled trials have investigated the differences between organic versus conventional food consumption on health-related intermediate biomarkers which respond more quickly (43,64).

Most studies that have investigated the potential health effects of eating organic compared to conventional foods are observational and rely on self-reported organic food consumption. An overview of studies is given in Appendix 1. The only study encompassing pregnancy and child outcome, published at the time of our studies, was a Danish case-control study with mothers of boys who were operated for hypospadias and mothers of healthy boys. The study suggested a protective association between mothers choosing the organic alternatives for butter and cheese and hypospadias in the offspring (65). Later, two more prospective cohort studies have been published, one from the French PELAGIE-study, reporting decreased risk of parent-reported otitis media in children before 2 years old with organic food consumption during pregnancy (66), and one from the Dutch KOALA-study, reporting lower prevalence of diabetes in pregnancy among the women with organic food consumption (67).

1.2 Fetal development

Four decades ago, the concensus was that the fetus was protected and lived more or less as a parasite on the mother, only being affected by maternal nutrition if this was extremely insufficient. It was believed that the mother would pay the nutritional price of a pregnancy, rarely the child (68). Gradually, our knowledge has been extended and today it is well established that diet is one of the major environmental factors influencing pregnancy outcome and growth trajectories with both immediate and long-lasting effects on child health (69).

The ‘fetal origins’ hypothesis, proposed by Barker in the 1980s, suggests that alterations in fetal nutrition and endocrine status result in developmental adaptations that permanently change structure, physiology and metabolism, thereby predisposing to cardiovscular, metabolic and endocrine diseases in adult life (70,71). Although there are relatively small differences in the concentrations of nutrients, secondary plant metabolites and contaminants between organic and conventional food, these and other differences, e.g. differences in microflora, may be relevant for later health of the children.

Barker and his colleagues used birth weight as a surrogate marker for poor intrauterine nutrition and could show correlations between birth weight and the mortality risks for cardiovascular disease, insulin resistance and hypertention (72-75). Early contributions to insight into this field of research also include Anders Forsdahl’s report from Finnmark, Norway in 1977, that poor living conditions in childhood was linked to subsequent adult mortality (76). Another important early contribution to the ‘fetal origins’ hypothesis came from Dörner, who, according to Koletzko et al., first introduced the term *programming* into the scientific literature in a publication from 1975 (77).

Barker et al. reported an inverse relationship between death risk from cardiovascular disease and birthweight among English men and women. Term babies born at the 5 pound end of the birthweight scale had 3-5 times greater risk for cardiovascular disease compared with babies born at the 9 pound end (78). The seminal observations by Barker and his colleagues were followed by many epidemiologic studies demonstrating that perinatal and early postnatal environmental challenges influence the risk of developing cardiovascular disease, diabetes, obesity, cancer and even some behavioural disorders (79,80). Among environmental factors that program adult metabolic disorders, poor intrauterine nutrition is the most extensively studied (81,82). Inadequate prenatal nutrition usually results in intrauterine growth restriction and, ultimately, low birth weight (83).

The theoretical explanation put forward by Barker and colleagues is that chronic disease ‘originates in developmental plasticity, in response to under-nutrition during fetal life and infancy’ (79). The unborn baby responds physiologically to under-nutrition in ways that are adaptive in the short term but, according to this theory, these adaptations have sequelae that are potentially disadvantageous in the long term. Reduced growth *in utero*, culminating in reduced birth-weight, is an overt sign of such physiological adaptation, but the more fundamental changes could include limitations on cell numbers in key organs and altered hormonal regulation. In fact, relevant changes to organ structure and physiological function could occur in the absence of a discernable impact on newborn size (84).

Barker and colleagues have emphasised the concept of adaptation to an early environment that is different from the environment encountered subsequently. It is suggested that a woman provides her unborn baby with a ‘nutritional forecast’ that guides metabolic development. Such developmental plasticity becomes adverse for health if conditions experienced later in life do not match this forecast (85).

When do environmental and dietary factors influence the epigenome, thus leading to long-term changes in gene expression? The current evidence linking diet to epigenetic modifications can be narrowed down to two specific scenarios: First, during ‘critical windows’ of early deveopment, in particular during fetal deveopment and/or early neonatal growth (Figure 2), and, second: in adult individuals, during ‘Dietary Transitions’, such as high fat feeding, caloric restriction, etc. occurring over a relatively long period of time (86).

The association between perinatal nutrition and late-onset disease has been conceptualised into the Developmental Origins of Health and Disease Hypothesis (DOHaD). The most abundant evidence linking diet and epigenetic modifications is based on studies relating early nutritional imbalances with later onset of chronic diseases in the context of DOHaD (86).

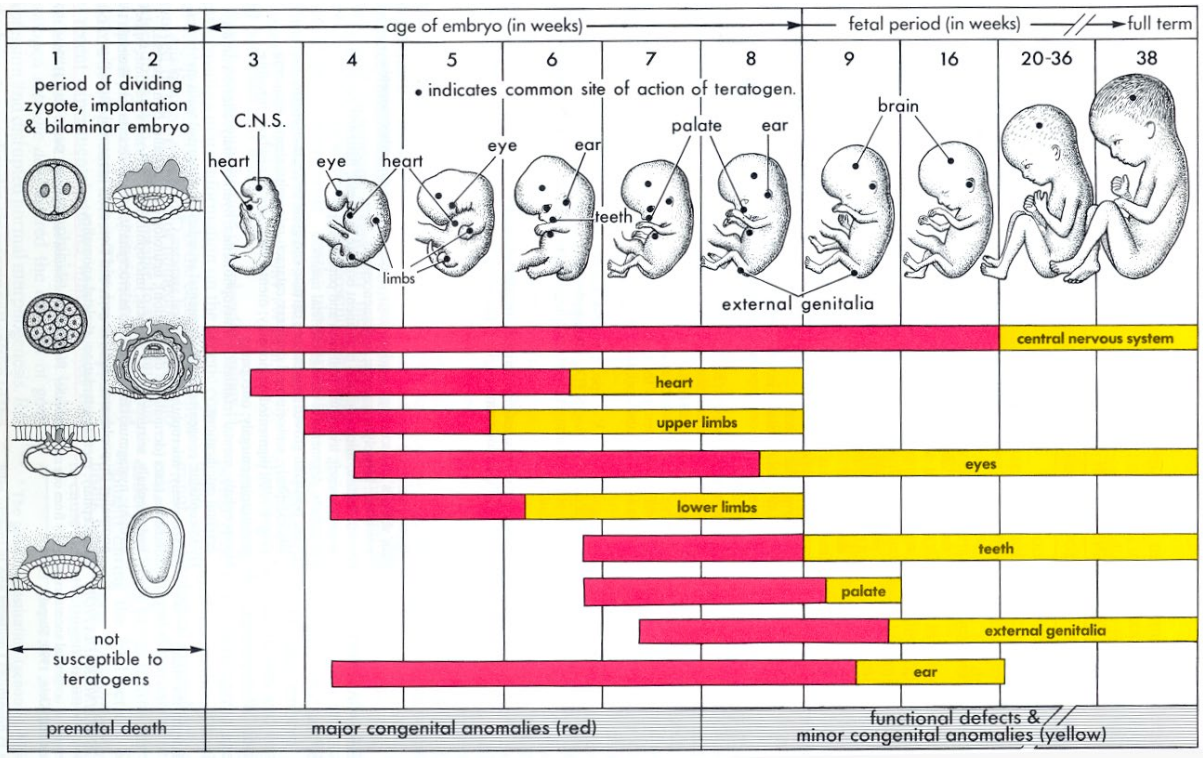

Figure 2. Crucial periods in prenatal development. Dots on the developing fetus show common sites of action of teratogens (agents that can disturb the development of an embryo or fetus). Horizontal bars indicate fetal development during a highly sensitive period (red) and less sensitive period (yellow). From http://www.c2law.com/links/cerebral-palsy-information/critical-periods-of-fetal-development/

We are ony beginning to appreciate the generation-spanning effects of poor environmental conditions during early life. Furthermore, the possibilities of promoting health by positively affecting conditions during fetal life may be of great importance. Compared with the diverse challenges associated with succeeding in public health interventions later in life (to change dietary habits etc.), the benefits of tilting a newborn's phenotype in a robust rather than vulnerable direction by positive effects of maternal diet during pregnancy, is hard to overestimate. It is therefore crucial to continue to better understand the potential benefits for public health by "early prevention of disease" as well as "early promotion of health" (87,88).

There are far-reaching perspectives and potentially huge impacts of successful intervention aimed at improved maternal nutrition (89). Targeting this life-phase may have the potential of large public health benefits in the long term - the effects possibly not being apparent for decades - as it may provide a means of promoting cardiovascular and metabolic health (90). Althogh the current evicende is not fully conclusive, an increasing body of research substantiate the importance of pre-pregnancy and prenatal diet on health and well-being of women and their offspring with regard to prevention of non-communicable dieseases (91-95).

In a global perspective, such effects may be particularly relevant to populations in transition between traditional and western lifestyles, where the prevalences of diabetes, obesity and cardiovascular diseases are rapidly expanding (96).

The relevance of organic food consumption in research related to health outcomes in mothers and children is based on the hypothesis that organic food is healthier for humans and the environment than conventionally produced food. There is a clear need for more human studies of the relationship between organic food consumption and health, not least in pregnancy and early life. This will be elaborated in the discussion.

1.2.1 Pre-eclampsia

Pre-eclampsia is a pregnancy induced hypertensive disorder characterised by reduced perfusion of the placenta, oxidative stress and endothelial dysfunction (97). It is more prevalent in nulliparity and is one of the major causes of maternal and perinatal morbidity and mortality worldwide, with an estimated prevalence of approximately 2-8% (98,99). One estimate, derived from global data of nearly 39 million pregnancies, suggests an incidence of 4.6% (100). Even after the resolution of pre-eclamptic pregnancy, women face increased risk of cardiovascular events later in life (101). The aetiology is largely unknown, but numerous targets for nutritional intervention have been suggested (102). In observational studies, dietary components and qualities associated with pre-eclampsia risk in observational studies include macronutrients, micronutrients, dietary fibre, and individual foods as well as overall food patterns (103). Furthermore, observational studies have also linked exposure to environmental contaminants in air, water, food and consumer products to adverse pregnancy outcomes, with proposed mechanisms including disrupted placental blood flow, up-regulated proinflammation and other changes that contribute to disrupted regulation of endocrine and immune system signalling (104,105).

Because other ongoing studies in MoBa examined associations between dietary factors and pre-eclampsia (106,107), we considered pre-eclampsia as a highly relevant health outcome in the current project.

1.2.2 Hypospadias and cryptorchidism

Hypospadias and cryptorchidism are genital birth defects in male neonates. The prevalence of both conditions in Norway is around 0.3% (108,109). Hypospadias is a condition where the opening of the urethra is located under the penis rather than at the tip of the penis as a result of failure of the urethral fold to unite over and cover the urethral groove (Figure 3). The aetiology of hypospadias is poorly understood, but existing evidence suggest both genetic and environmental factors (110). Fetal growth restriction and pre-eclampsia have been consistently associated with hypospadias, a finding that may implicate placental insufficiency as an underlying cause (65). Prenatal exposure to environmental chemicals such as organophosphate pesticides has been linked to hypospadias (111), but findings are inconsistent (112-116).

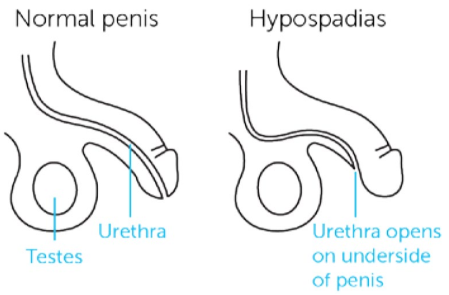

Figure 3. A normal penis and hypospadias (Source: Boston Children's Hospital family education sheet; https://thriving.childrenshospital.org/wp-content/uploads/2018/08/fe_hc_hypospadias_repair_160015.pdf)

Cryptorchidism is diagnosed when one or both testicles have not descended into the scrotum (117). Endocrine disrupting chemicals have been suggested as potential risk factors also for cryptorchidism (118,119). Based on the hypothesis of endocrine disruption as a biological pathway for both hypospadias and cryptorchidism, the two outcomes are often included in the same studies and sometimes also studied as a combined outcome, as done in a recent case-control study on occupational exposure to endocrine disrupting chemicals and other parental risk factors in hypospadias and cryptorchidism development (115).

1.3 Dietary assessment

Accurate assessment of the diet in free-living populations is very challenging because there is no existing method to capture an individual's habitual food intake without errors (120). Diet is also a time-varying exposure, with individual dietary habits and food composition changing over time (121). Dietary assessment during pregnancy is even more complicated than in non-pregnant adults due to the physiological changes which affect energy and nutrient demands, appetite and meal patterns (122). Assessment of organic foods in the diet is an additional challenge and makes the dietary methodology more complex and time consuming.

Pregnancy is a period when most women are highly motivated for healthier food choices, such as increasing intakes of fruit and vegetables and reducing intakes of alcoholic beverages, coffee and unhealthy foods, or risks related to environmental contaminants (123,124). However, overall, women's diets change little from before to during pregnancy and diet assessed in pregnancy will to a large degree reflect longer-term dietary habits (125,126).

There are several ways to assess dietary intake in individuals, such as retrospective recalls (e.g. 24-h recalls and food frequency questionnaires) and prospective recording which requires consecutive recording of all food, drink and dietary supplements consumed for a given period of time. Assessment of organic food consumption should ideally cover both the frequency and amount (quantity) of organic food in the diet and within specific food groups. However, few existing cohort studies that have included questions about organic food consumption have captured the quantitative share (in grams) of organic items relative to the total food amount, and assessments have usually been restricted to frequency (127-129). The French NutriNet-Santé study introduced an organic food frequency questionnaire to quantify the amount of organic food in the diet in the 2014-follow-up (129).

All dietary assessment methods have some components of error, which could be random day-to-day, diurnal, and seasonal variation in an individual's diet over time, or because of systematic mechanisms, such as errors in estimating portion sizes, and misreporting of or omission of foods when collecting data (130). A food frequency questionnaire (FFQ) consists of a structured food list and a frequency response section in which participants indicate their usual frequency of intake of each food over a certain period of time in the past. The FFQ method has been extensively criticised (131-133), but in spite of the known limitations, using an FFQ is the most common choice for dietary assessment in large epidemiological studies because it has low participant burden, is cost-effective and has the ability to simultaneously measure the usual intake of multiple dietary components (134). Validation of FFQ data using other methods, including biological markers of food intake as reference methods, has shown that FFQs have reasonable validity and are able to rank participants according to high and low intakes of food groups, food items and nutrients, e.g. less than 5% grossly misclassified in the extreme quintile when comparing intakes calculated by FFQ and diet recall or consecutive records. However, misclassification is unavoidable and imprecision in dietary assessment is a serious issue in nutrition epidemiology and reduces the power to detect diet-disease associations (121,131,135,136).

Issues related to measurement error are not isolated to dietary assessment methods to quantify food intakes, but extend to assessment of most behavioural exposures, including use of organic food, physical activity, smoking and alcohol intake. These issues are discussed further in the discussion (Chapter 5).

1.4 Nutritional epidemiology

The role of diet in the prevention of disease is the focus of nutritional epidemiology. Nutritional epidemiology is based on an understanding of human nutrition and on the principles of epidemiology, which provide methodological tools for investigating diet-disease relationships in a population (137).

Nutritional epidemiology has advanced considerably over the last decades with respect to understanding types and sources of measurement error in dietary intake data. The underestimation of energy intake from self-reported data in all populations groups, including pregnant women, has long been known to nutrition researchers (138,139) and different ways to take this into account have been suggested (121,140,141).

Nutritional epidemiology relies predominantly on observational data, which are deemed to be inferior to experimental data in determining causality. Carrying out randomised intervention trials with "normal diets' as the exposure and hard endpoints (e.g. coronary heart disease or cancer) is virtually impossible to answer questions regarding long-term effects of dietary intake, unless for specific dietary components that can be packaged in a pill. However, shorter-term studies where intermediary endpoints are used, like changes in blood lipid profiles, have been conducted with e.g. fish (142,143). Therefore, prospective cohort studies are considered the strongest observational study design in terms of scientific evidence. Results from prospective studies have contributed valuable knowledge and constitute a major basis for dietary guidelines worldwide (144-146).

Confounding is a major challenge in all observational data. A confounder is a variable that is associated with both the exposure and outcome but is not caused by either, and when unaccounted for, introduces bias into the exposure-disease relation (147). To account for this type of bias in a prospective cohort study, it is critical to identify and adjust for all relevant confounders. Once data have been collected on these variables, it is possible to statistically adjust for confounders in a regression model or restrict the data to a specific subgroup to minimise residual confounding (148). However, although there are several ways in which confounding can be accounted for in prospective cohort studies, such studies are seen as providing statistical associations but not causations, as residual or unmeasured confounding cannot be ruled out (148). The Bradford Hill criteria, published in 1965 by Sir Austin Bradford Hill, are useful when evaluating the scientific value and possible causality of associations found in epidemiological studies (149). The key criteria comprise strength, consistency, temporality, biological gradient (dose-response), plausibility, coherence, and experimental evidence, and are discussed in more detail in chapter 5.

1.5 Setting

1.5.1 The Norwegian Mother, Father and Child Cohort Study (MoBa)

This thesis is based on data from the Norwegian Mother, Father and Child Cohort Study (MoBa), a large pregnancy cohort initiated and conducted by the Norwegian Institute of Public Health (NIPH) (150). MoBa is population-based and one of the largest pregnancy cohorts world-wide. The overall aim of MoBa is to identify early life environmental exposures and genetic factors associated with diseases in pregnancy and childhood, aiming at prevention (150,151).

Participants were recruited from all over Norway from 1999 to 2008, and 40.6% of the invited women consented to participate. The cohort now includes 114,500 children, 95,200 mothers and 75,200 fathers. Women were recruited through a postal invitation prior to the routine ultrasound examination around gestation week 18, which is part of the free antenatal care for all pregnant women in Norway. The women were asked to provide biological samples at the time of the ultrasound examination and to answer three questionnaires during pregnancy and several after birth (Figure 4).

The study is ongoing and follow-up is continuing through questionnaires throughout childhood and adolescence, through sub-studies where participating families are invited to more in-depth clinical examination, and through linkage to National Health Registries. For more detail, see the protocol of the study including the consent (152). Data from the Medical Birth Registry of Norway (MBRN), which comprises data on all pregnancies and births in Norway, is linked to the MoBa database (153).

Figure 4: Overview of data collection in MoBa in the first fourteen years.

Data collection in MoBa was set up to assess as many data as possible on exposures, mediators, effect-modifying variables and outcomes, so that data would be in place to answer as many research questions as possible (151). Maternal diet during pregnancy was regarded as an important environmental exposure and a new food frequency questionnaire was developed and validated specifically for pregnant women in MoBa (123,154). This MoBa FFQ was used from early 2002 and throughout the remaining recruitment period.

As of April 1st, 2021, more than 830 scientific articles have been published using MoBa data as a basis, and approximately 160 of these (20 percent) have included the use of the FFQ.

Apart from more descriptive studies, a number of diet – health relationships have been explored, including the impact of mother's diet during pregnancy and the child growth trajectories, the child's cognitive development and the child's risk of developing ADHD symptoms. For an overview of major findings published before 2016, see Magnus *et al*. (151).

1.5.2 Data included in this thesis

The MoBa FFQ, which was developed to collect dietary data on as many relevant aspects as possible, included a question about use of organic food in six major food groups (123). This question provides data to explore and describe the characteristics of women who reported use of organic food during pregnancy (Paper I), to describe dietary patterns and qualities related to use of organic food (Paper II), and to examine the potential associations between use of organic food and pregnancy outcomes (Paper III-IV). Data on the pregnancy outcomes were retrieved from MBRN. (A detailed presentation of the variables included in the studies is given in Methods, chapter 3)

The pregnancy outcomes studied as part of this thesis are pre-eclampsia in mothers and hypospadias and cryptorchidism in male infants. There were several reasons for choosing these particular outcomes. Firstly, for pre-eclampsia, previous studies in MoBa showed that dietary factors were associated with the prevalence of this condition (106,107). The causes of pre-eclampsia are multifactorial and largely unknown, but the condition is linked to an excessive maternal inflammatory response to pregnancy. Established risk factors include primiparity, previous pre-eclampsia, maternal obesity, diabetes and other underlying medical conditions (155). Previous literature suggest that organic food might modulate immune responses and hence this was a highly relevant outcome (Paper III). Secondly, hypospadias and cryptorchidism are male malformations with unknown aetiologies, but with indications from animal and some human studies (65) that environmental exposures, particularly substances that differ between organic and conventional food, might play a role (Paper IV).

2 Aims of the study

The overall aims of this research project were first to identify personal and socio-demographic characteristics as well as dietary habits of pregnant women who reported organic food consumption during pregnancy, and secondly, to investigate potential associations between organic food consumption and pregnancy outcomes.

More specifically, the aims of the individual parts of the study were:

1. To describe socio-economic, personal and lifestyle characteristics associated with consumption of organically produced food among pregnant women participating in the Norwegian Mother, Father and Child Cohort Study (Paper I).

2. To describe dietary patterns, food intake and nutrient density associated with consumption of organically produced food among pregnant women participating in the Norwegian Mother, Father and Child Cohort Study (Paper II).

3. To investigate whether consumption of organically produced food during pregnancy was associated with the prevalence of pre-eclampsia in the Norwegian Mother, Father and Child Cohort Study, taking the overall food pattern into account (Paper III).

4. To examine whether consumption of organically produced food during pregnancy was associated with the prevalence of hypospadias and cryptorchidism at birth in the Norwegian Mother, Father and Child Cohort Study (Paper IV).

3 Methods

3.1 Study design

The two first papers have a cross-sectional design and describe personal, socio-economic and lifestyle characteristics (Paper I) and dietary quality (Paper II) associated with consumption of organic food during pregnancy. The two last papers have a prospective design, investigating associations between use of organic food and pre-eclampsia in mothers (Paper III) and hypospadias and cryptorchidism in male children (Paper IV).

The principles outlined in STROBE for observational studies were used as a guide for papers III and IV (137) (Appendix 3: STROBE checklist for Paper III).

3.2 Study population

Information used in this thesis was obtained from the two first MoBa-questionnaires answered during pregnancy and from MBRN. The first (baseline) questionnaire (Q1: 16 pages) was sent to the women in week 15 of pregnancy and included questions covering a broad range of personal, medical, lifestyle and socio-demographic information. The second questionnaire (Q2: 14 pages) was the food frequency questionnaire (FFQ) developed for MoBa and sent to participants in weeks 17-22 of pregnancy. In the latter part of the inclusion period, the questionnaires could also be filled out electronically. English translations of the questionnaires and instrument documentation for each questionnaire are available at the NIPH website (156).

Access to data were given only to the principal investigator based on an application to the MoBa steering committee. Data for delivery to the research project were prepared at the MoBa data unit and all data delivered to the research-project were de-identified. Data were stored in a password-protected safe server at NIPH with access only for project members.

3.2.1 Selection of participants

The current thesis is based on information in the fourth version of the quality-assured data files released for research in January 2009. The source population for all four papers was

76,591 MoBa participants who had responded to questionnaire 1 and questionnaire 2, were included in the study between 2002 and 2008, and were registered in MBRN (Figure 4).

In paper I, we excluded 13,030 pregnancies due to missing information and mothers participating in the cohort with more than one pregnancy, resulting in a study sample of n=63,561 (83% of the source population). In paper II, we applied nearly the same exclusion criteria except the exclusion due to missing data on covariates (=247), resulting in a study sample of n=63,808 (83%). In paper III, we restricted the study population to nulliparous women who delivered a singleton baby and had no missing data on maternal weight, height and gestational weight gain, resulting in a study sample of n=28,192. In paper IV, the study population was restricted to mothers who gave birth to male infants, resulting in a study sample of n=35,107 (Figure 5).

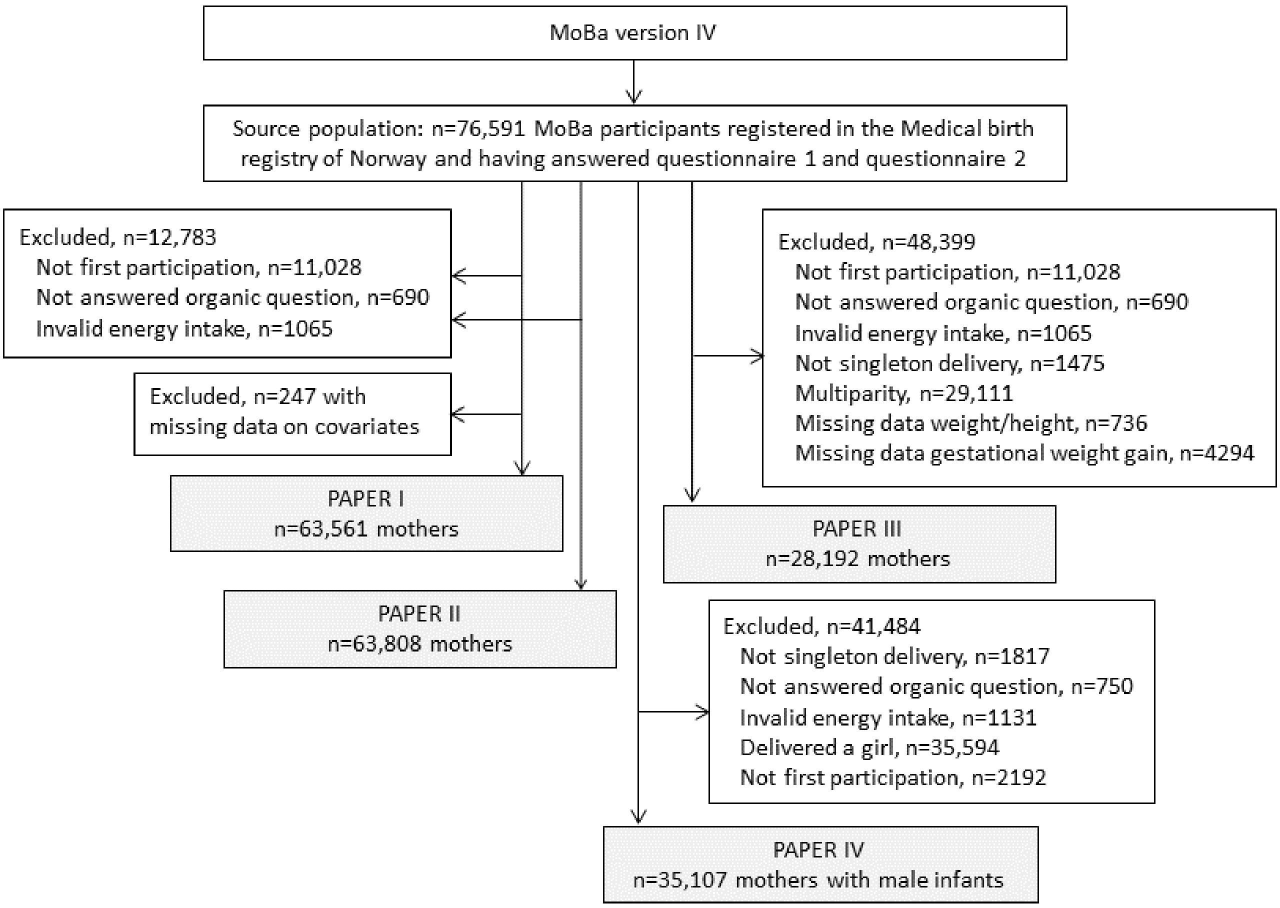

Figure 5. Flow diagram for selection of participants in papers I-IV. The MoBa FFQ used in the present project (questionnaire 2) was introduced in March 2002.

3.3 Dietary information

3.3.1 Food, nutrients and dietary supplements

The basic planning of MoBa was not made on the basis of any single hypothesis or any set of hypotheses because specific research questions that may emerge 10-50 years in the future cannot be foreseen. Therefore, the strategy was to collect data on as many relevant exposures and health outcomes as feasible (69,123). With regard to diet, this implied covering as many known aspects of the diet as possible on an individual level over a restricted time-period during the pregnancy.

The FFQ is semi-quantitative and designed to capture dietary habits and intake of dietary supplements during the first four to five months of pregnancy. Participants were asked to respond to the FFQ in gestational weeks 17- 22. The FFQ included 340 questions on the frequency of intake of 255 food items (157). Food frequencies were converted to amounts using portion sizes for women, and food and nutrient calculations were performed with the use of FoodCalc (158) and the Norwegian food composition table (159).

The FFQ has been thoroughly validated in 119 women using a four-day weighed food record and biological markers in blood and 24-hour urine 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 (154,160-162). The validity of the questions about organic food consumption has not been evaluated as we did not have information about quantity (g/day) for organic foods, only frequency.

3.3.2 Organic food consumption

The assessment of organic food consumption in the MoBa FFQ included separate questions about the frequency of organic consumption within six food groups: i) milk and dairy products, ii) bread and cereal products, iii) eggs, iv) vegetables, v) fruit and vi) meat. For each of these food groups, four alternative response categories were given: ‘never/seldom’, ‘sometimes’, ‘often’, or ‘mostly’ (Figure 6).

Have you consumed organic food products since you became pregnant? (Mark only one box per line).

Organic food group	Seldom/never	Sometimes	Often	Mostly
1. Milk, dairy products, cheese	☐	☐	☐	☐
2. Bread and cereals	☐	☐	☐	☐
3. Eggs	☐	☐	☐	☐
4. Vegetables	☐	☐	☐	☐
5. Fruit	☐	☐	☐	☐
6. Meat	☐	☐	☐	☐

Figure 6. The questions about use of organic food in the MoBa FFQ.

Missing responses in all six group-specific questions resulted in exclusion from the study population, while missing responses in one to five questions were coded as 'never/seldom'.

The responses to the questions about consumption of organically produced food were operationalised as follows:

1. A sum index combining the six organic food groups. As a measure of total organic food consumption, a 'sum index' variable was computed by combining the answers. For each question, the answer alternatives were given the following scores and then summed: never/seldom=0, sometimes=1, often=2 and mostly=3. The sum index reflects organic food consumption on a scale ranging from 0 to 18, with 0 representing no use of organic food and 18 representing 'mostly' organic for all six food groups. For respondents who had no reported intake of meat, eggs, milk/dairy or vegetables (i.e. the calculated intakes of these foods were zero), and who had not reported organic consumption of the corresponding food group, we upscaled the sum index by multiplying with 6/5 for each omitted food category.
2. 'Frequent' versus 'no or low' organic consumption. Frequent was defined as having a sum index of >6, which corresponds to having reported eating organic food 'often' for at least one of the six food categories (Paper I, Paper II, Paper III).
3. 'High' versus 'low' for each of organic food groups. 'High' corresponds to having answered 'often' or 'mostly' and 'low' corresponds to having answered 'never/seldom' or 'sometimes' to the question for the respective food group (Paper II, Paper III).
4. 'Any organic food', yes versus no. This corresponds to having answered 'sometimes', 'often' or 'mostly' to at least one of the six food groups, and 'no' corresponds to having answered 'never/seldom' to all (Paper IV).

5. ‘Any use’ of organic within each food group, yes or no: ‘Yes’ corresponds to having eaten organic within the specific food group ‘sometimes’, ‘often’ or ‘mostly’ and ‘no’ corresponds to ‘never/seldom’ having eaten organic within this food group (Paper IV).

3.4 Outcome variables

The outcome variables in papers III and IV were obtained from MBRN. The cohort database is linked to pregnancy and birth records in the MBRN. This registry was established in 1967 and contains information about pregnancy, delivery and health of the mother and the neonate. The registry is based on notification of all live births and stillbirths from 16 weeks (since 2002, from 12 weeks) of gestation. A standardised notification form is completed by midwifes or obstetricians shortly after delivery. Notification is compulsory and is carried out by midwives or physicians attending the birth within 7 days after delivery. The standardised form contains detailed information about the parents and the child, e.g. maternal health before and during pregnancy, procedures and complications during delivery, and condition of the child at birth (163).

The main outcome in Paper III was pre-eclampsia as registered in the MBRN (153). The form has 5 check-off boxes relevant to pre-eclampsia: haemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome); eclampsia; early pre-eclampsia (diagnosed before 34 weeks); mild pre-eclampsia; and severe pre-eclampsia. The diagnostic criteria for pre-eclampsia were given if any of the above-mentioned diagnoses were present. Women with chronic hypertension were included in the case group only if they also developed proteinuria. The diagnostic criteria for pre-eclampsia in Norway, according to guidelines issued by the Society for Gynaecology, are blood pressure > 140/90 after 20 weeks of gestation, combined with proteinuria >+1 dipstick on at least 2 occasions. Pre-eclampsia is diagnosed as severe pre-eclampsia if blood pressure is ≥160/110 (164). In Norway, all pregnant women receive free antenatal care. Blood pressure measurement and urinalysis for protein are carried out at each antenatal visit.

The outcome variables in Paper IV, hypospadias and cryptorchidism, were also obtained from MBRN. 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.

3.5 Other variables

In all four papers we used information obtained from the baseline questionnaire (Q1), which included questions about health, socio-demographic and lifestyle variables such as maternal pre-pregnancy weight and height for calculation of body mass index (BMI), parity, level of education, household income, leisure exercise activity, and smoking habits. The details of all variables and how they were treated (continuous or categorical) are explained in detail in each of the papers. Potential confounding variables differed for the outcomes examined in papers III and IV, and in addition to information about outcomes, we also obtained information from MBRN, such as hypertension prior to pregnancy, singleton or plural delivery, infant sex, maternal age at delivery, infant birth weight, gestational length, in vitro fertilisation (IVF) and previous stillbirths.

3.6 Statistical methods

The statistical package for social sciences (SPSS) was used in all papers (IBM SPSS Statistics versions 17-20, Chicago, IL, USA). In addition, we used Stata (version 11, Stata Corp, Texas 77845, USA) in Paper I for calculating polychoric correlations and the Unscrambler (X version 10.1, CAMO Software AS, Oslo, Norway) in paper II to identify dietary patterns.

In all analyses $p<0.05$ was considered significant. An overview of the statistics in the respective papers is shown in Table 3.1.

Table 3.1. Overview of statistical methods used in the four papers.

Statistics	Paper I	Paper II	Paper III	Paper IV
Polychoric correlation	x			
Pearson Chi-square test	x		x	x
Linear binomial regression	x			
Principal component analyses (PCA)		x		
ANOVA analyses		x		
Bonferroni p-value		x		
Cross-validation		x		
Multiple logistic regression			x	x
Independent samples T test			x	
P-trend			x	
Sensitivity analyses, stratification	x	x	x	x

Paper I

We used Polychoric correlation to examine organic consumption among all food groups. The differences in organic food consumption between categories of maternal characteristics were tested with Pearson Chi-square test.

We used linear binomial regression with frequent versus rare use of organic food as outcome variable and characteristics of the respondent as independent variable. This analysis provides information about the risk difference (RD) between being in the frequent organic consumption group or not, given as various personal, socio-economic and lifestyle characteristics as covariates. The analyses were repeated using linear regression with the sum index (indicating/as a measure of organic consumption) as a continuous variable, and comparable results were obtained (results not shown in the paper).

Paper II

Food patterns were explored by Principal component analyses (PCA). PCA were also used to describe the variation in dietary patterns among participants. From the scores plot we can interpret relations between respondents, e.g. those who eat similar diets and those who eat very differently, as well as which food groups that dominate the diet of a particular respondent. A respondent's score denotes the position in the scores plot, and the position in the scores plot is directly related to the loadings plot: The diet of a respondent who is positioned to the left in the plot is characterised by consumption of food groups to the left in the loadings plot and so on.

ANOVA analyses were used to investigate how food patterns and intake of selected food groups and nutrients were associated with consumption of organic food. The method of first using PCA on the original food consumption data with the sub-sequent ANOVA of the scores to test the effects of the design factors, here: consumption of organic food, on the scores (PC-ANOVA) is described by Luciano and Næs (165).

We used cross-validation to assess the importance of each component (166). Since there are many tests in the paper, one should be careful about interpreting each of the values as exact values of significance. This corresponds to the explorative character of the paper with many possibilities tested simultaneously. We looked at the Bonferroni p-values, and found that in for instance Table 1 in Paper II, with 14 different tests in each column, the Bonferroni p-value is equal to 0.0035. There were several values even below that threshold.

Paper III

Relative risks were estimated as odds ratios (OR) by performing multiple logistic regression with pre-eclampsia as the outcome variable and organic food consumption as the exposure.

Co-variates which were included in the final analysis were confounders i.e. variables associated with both the exposure and the outcome variable ($p<0.100$), and some known risk factors for the outcome.

Independent t test was used (to test significance) for continuous variables, and chi-square was used to test categorical variables.

P-trend was calculated for the association between reported consumption of organic vegetables and pre-eclampsia.

Variables were modelled as continuous or categorical, depending on how they related to organic food consumption. For instance, maternal height, total energy intake, and BMI were used as continuous variables in the model because the associations between these variables and the outcome were linear and the results were similar whether the variables were modelled as continuous or categorical. Maternal age was, however, modelled as categories due to a nonlinear association with organic food consumption.

We tested for interaction between reported consumption of organic food and the confounders.

Paper IV

Pearson Chi-square test was used to test for group difference in categorical data. Multiple logistic regression was performed, and crude and adjusted odd ratios (OR) with 95% confidence intervals (CIs) were estimated for the association between consumption of organic food and the outcomes.

We conducted sensitivity analyses to examine whether the associations were strongly influenced by other variables. Because placental insufficiency has been indicated to be an underlying cause for pre-eclampsia as well as for hypospadias, we repeated the analyses for any organic food consumption and hypospadias adjusting for pre-eclampsia and found that the adjusted OR remained unchanged. Likewise, excluding women with pre-eclampsia did not change the association. Analyses were also repeated excluding mothers on antiepileptic drugs, finding that this did not change the results.

3.7 Ethical issues

The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency (01-4325) and approval from The Regional Committees for Medical and Health Research Ethics Southern Norway (REK S-97045, S-95113). All MoBa participants provided a broad written informed consent prior to enrolment. The research project which is the basis for this PhD was based on the existing MoBa contract with the Norwegian Data Protection Agency and REK. The MoBa cohort is now based on regulations related to the Norwegian Health Registry Act and all research projects using data from MoBa are now required to obtain a project specific ethical approval.

All studies included in this thesis have been conducted according to the guidelines laid down in the Declaration of Helsinki (167).

4 Summary of results

In this chapter, an overview of the reported use of organic foods will be presented followed by a summary of the main results in each paper.

The sum index reflects organic food consumption on a scale ranging from 0 to 18, where 0 corresponds to having answered never or seldom to organic food consumption in all food categories and 18 represents 'mostly' organic for all six food groups (Table 4.1). Sum Index > 6 corresponds to having reported to eat organic food 'often' for at least one food category and is denoted as 'frequent' organic food consumption in the analyses. This was reported by 9.1% of respondents. (See section 3.3.2 for more detail on the sum index).

Table 4.1. Overview of reported organic food consumption, total of six food groups, used in paper I, II and III

Sum Index	0	1-6	7-12	13-18
(numbers from Paper I *n*=63,561)	51.7%	39.2%	7.2%	1.9%

Approximately 7% of respondents had reported to have eaten organic food in at least one food category 'mostly'. Eggs and vegetables were the food groups that most respondents answered that they used 'often' or 'mostly' organic, while organic meat was the least often used food category. Across all food categories, the 'never/seldom' organic was the most dominant answer, ranging from 65.4% for vegetables to 88.7% for meat. Around 93% reported to have eaten organic food 'never or seldom' for at least one food category.

There was a high correlation between consumption of organic food in the different food categories, with fruit and vegetables being most strongly correlated with each other and with the sum index (shown in Table 2 in Paper I).

In some of the analyses in Paper II and III, organic food consumption in each of the six food categories was used, divided into 'low' or 'high' consumption (Table 4.2).

Table 4.2. Frequency (percent) organic food consumption within the food categories used in Paper II and III

Organic food	Vege-tables	Fruit	Bread/cereal	Milk/dairy	Eggs	Meat
'low' (never/seldom or sometimes)	91.2%	93.1%	93.7%	92.8%	90.8%	96.0%
'high' (often or mostly)	8.8%	6.9%%	6.3%	7.2%	9.2%	4.0%

Numbers from Paper III (*n*=28,192)

In Paper IV, the prevalence of outcomes was so low that the categorisation used in previous papers with 'low' and 'high' for specific organic food groups resulted in less than 5 cases in the 'high' organic group. Therefore, a less detailed categorisation was needed and use of organic food was categorised by combining 'sometimes', 'often' and 'mostly' and examined against 'never/seldom' (Table 4.3). Of the 35,107 women who gave birth to a male infant, 48.7% reported using at least one organic food group 'sometimes, often or mostly', and 51.3% reported never/seldom use of all organic foods. Vegetables and eggs were the food groups with the highest reported use (Table 4.3).

Table 4.3. Frequency (percent) organic food consumption for any organic and within the food categories used in paper IV.

Organic food	Any organic	Vege-tables	Fruit	Bread/cereal	Milk/dairy	Eggs	Meat
Never/seldom	51.3%	64.8%	71.2 %	79.7%	74.0%	65.9%	87.8%
Sometimes, often, or mostly	48.7%	35.2%	28.8 %	20.3%	26.0%	34.1%	12.2%

Numbers from Paper IV (*n*=35,107)

4.1 Paper I

Title: Characteristics associated with organic food consumption during pregnancy; data from a large cohort of pregnant women in Norway

In this paper, 'frequent' organic food consumption, which was reported by 9.1% (n=5754) of the participants, was compared with less frequent organic food consumption with regard to socio-economic characteristics. Participants included 63,561 pregnant women recruited to the Norwegian Mother, Father and Child Cohort Study during the years 2002–2007.

Participants reporting frequent organic food consumption included more women in the lower (<25 years) and higher (>40 years) age-groups, more women with normal or low body mass index, more vegetarians, more who exercised regularly (3+times weekly), consumed alcohol and smoked cigarettes during pregnancy than those who reported less frequent organic consumption ($p<0.001$ for all, except alcohol: $p=0.044$). Further, participants who reported frequent organic consumption included more women in the lower (≤12 years) or higher (17 years +) categories of educational attainment, women who were students or had a partner being a student, who belonged to the lowest household income group (both respondent and her partner earned < 300 000 NOK), who entered the study 2005-2007, and who lived in an urban area ($p<0.001$ for all).

The main finding was that frequent organic food consumption during pregnancy was associated with various personal, lifestyle- and socio-demographic variables. These characteristics were not limited to those commonly associated with a healthy lifestyle, such as higher income and higher education. Although frequent consumption of organic food was less common than no or low consumption of organic food, the results indicate that organic food consumption was quite widely distributed among MoBa participants across the characteristics investigated in this paper.

4.2 Paper II

Title: Food patterns and dietary quality associated with organic food consumption during pregnancy; data from a large cohort of pregnant women in Norway

The paper describes the dietary patterns and qualities associated with organic food consumption in 63,808 pregnant women recruited to the Norwegian Mother, Father and Child Cohort Study during the years 2002–2007.

Food patterns were identified using principal component analyses, identifying two main principal components. The first component (PC1), which accounted for 12% of the variation, was interpreted as a ‘health and sustainability component’, with high loadings for vegetables, fruits and berries, cooking oil, whole grain bread and cereal products and negative loadings for meat, including processed meat, white bread, and cakes and sweets. Frequent consumption of organic food was associated with an increase in score on the ‘health and sustainability component’ of 0.73 units in the scores plot, ($p < 0001$), which represented approximately 1/10 of the total variation. This association was independent of sociodemographic and lifestyle characteristics. Participants with frequent consumption of organic food had a diet with higher density of fibre and most nutrients such as folate, beta-carotene and vitamin C, and lower density of sodium compared to participants with no or low consumption of organic food.

The study showed that pregnant Norwegian women who reported frequent consumption of organically produced food had a dietary pattern and quality more in line with public advice for healthy diets. Among the traits of participants eating organic food that were investigated in paper I and II, diet came out as the most significant distinction between this group and those who did not eat organic food frequently.

4.3 Paper III

Title: Reduced risk of pre-eclampsia with organic vegetable consumption: results from the prospective Norwegian Mother and Child Cohort Study

The paper investigates whether consumption of organic food during pregnancy was associated with the risk of pre-eclampsia, taking the overall food pattern into account.

In this study, relative risk for pre-eclampsia was estimated as Odds Ratio (OR) by performing binary logistic regression with pre-eclampsia as the outcome variable and organic food consumption as the exposure. The prevalence of pre-eclampsia in the study sample was 5.3% (n=1 491).

The study showed that women who reported having eaten organic vegetables ‘often’ or ‘mostly’ (n=1 951, 6.9 %) had lower risk of pre-eclampsia compared with those who reported to consume organic vegetables ‘never’ or ’rarely’ (crude OR=0.76, 95% CI 0.61 to 0.96; adjusted OR=0.79, 95% CI 0.62 to 0.99). The lower risk of pre-eclampsia associated with high organic vegetable consumption was evident also when adjusting for overall dietary quality, assessed as scores on a healthy food pattern derived by principal component analysis. No associations with pre-eclampsia were found for high intake of organic fruit, cereals, eggs or milk, or a combined index reflecting organic consumption across food categories.

4.4 Paper IV

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

The paper investigates associations between organic food consumption during pregnancy and prevalence of hypospadias and cryptorchidism at birth among 35,107 male infants born to women who were recruited to the Norwegian Mother and Child Cohort Study during the years 2002–2008 and who delivered a singleton male infant.

Among those who reported 'sometimes', 'often' or 'mostly' organic, the food group most widely consumed as organic was vegetables (n=35.2%), followed by eggs (n=34.1%), fruit (28.8%) and milk/dairy products (26.0%). Seventy-four male newborns were diagnosed with hypospadias (0.2%) and 151 with cryptorchidism (0.4%).

The study showed that women who consumed organic food during pregnancy were less likely to give birth to a boy with hypospadias than women who reported never or seldom consuming organic food. Results for individual food groups showed that associations were strongest for consumption of organic vegetables and milk/dairy products. No substantial association was observed for consumption of organic food and cryptorchidism. The findings were based on small numbers of cases and the results require replication in other large pregnancy cohorts.

5 Discussion

In this chapter, I will first discuss methodological issues that might have influenced the findings in the thesis. I will then discuss the findings, interpretation of the findings, and strengths and limitations of the specific studies.

5.1 Methodological considerations

The results presented in this thesis are based on data from one of the largest pregnancy cohorts in the world. Prospective cohort studies are considered to have the strongest observational study design (131). Nevertheless, there are limitations associated with this study design and with the specific studies in this thesis, and the most important of these will be addressed in the following discussion.

5.1.1 Validity of variables

With the exception of information obtained from the MBRN, all variables used in the studies included in this thesis are based on self-reported answers. The use of self-reported FFQs is considered the preferred method in most population studies because administration is easy, intake can be assessed over a long period of time, and the cost is low (136). However, self-reported data on variables such as e.g. smoking, food intake and weight are particularly vulnerable to misreporting, and the usefulness of self-reported data, particularly the use FFQs to assess food and nutrient intakes has been debated (133,168,169). Evaluation of the validity and reliability of self-reported data generally shows that personal characteristics, including sex, age and weight status, do influence the data, but that overall, self-reported data are the only feasible option in large epidemiological studies. Repeated measurement is a method to evaluate the reliability of data by evaluating the consistency and stability of self-reported information. Inclusion of objective markers, such as e.g. plasma cotinine as a marker of smoking and metabolites in blood and/or urine as markers of specific foods and nutrients in a subsample of the source population, may provide information about the relative validity of the data. In MoBa, self-reported smoking in pregnancy showed good agreement with plasma cotinine in a sub-study and the results suggest that self-reported tobacco use is a valid marker for tobacco exposure in pregnant women in the cohort (170). Likewise, the MoBa FFQ was extensively validated in a subsample of 119 MoBa participants, using four-days weighed food records, four days motions sensor registration of energy expenditure, and biomarkers in 24-hour urine and blood as reference methods. The results from the validation study of the MoBa FFQ showed that the FFQ was a useful tool to rank women according to high and low intakes of energy, nutrients and foods, and that major food groups like vegetables, fruits, fish and dairy were reflected by biological markers measured in blood or urine (154,160-162). On average, energy intake estimated by the FFQ was higher than energy intake estimated by four-day weighed food records. Still, the energy intake calculated by the FFQ ranged from unrealistic low to unrealistic high intakes and differed with participant characteristics.

The health outcomes used in Paper III and IV were obtained from MBRN. With regard to pre-eclampsia, a validation study was carried out using hypertension and proteinuria on the antenatal charts and/or hospital discharge codes indicating pre-eclampsia as gold standard. The results showed that pre-eclampsia registration in MBRN in years 1999 to 2010 had satisfactory positive predictive value and sensitivity (171). With regard to the validity hypospadias and cryptorchidism, milder forms are more likely to be underreported. This was shown for hypospadias in a study of risk factors for hypospadias in Norwegian boys. The study included an evaluation of hypospadias registration in MBRN against diagnoses in the national patient registry, which showed misclassification primarily of mild hypospadias (109). The diagnosis of cryptorchidism has not been validated and is less certain because in mild cases the testes descend spontaneously after birth.

Information about organic food consumption

The MoBa FFQ provided information about frequency of consumption of organic foods in six food categories, but no information about quantity (g/day) for organic foods. Ideally, more precise information about the consumption of organic food could have been desirable, e.g. frequency categories referring to the total food intake within each food category. It could also be argued that it would have been preferable to be able to operationalise the exposure variable in finer distinctions within the food categories, e.g. fruits and vegetables with/without peel, which would likely be removed before eating, with potentially corresponding differences in risk for exposure to pesticide residues. This has not been possible within the present study. As described in the methods chapter, the MoBa FFQ was developed for a broad range of issues envisaged to be of future importance, and detail about specific issues had to be balanced against the length of the questionnaire (69).

Validation of the specific question about organic food consumption would also have been an advantage so that we could have confirmed compliance between reported and actual consumption of organic food. We had no biological or environmental measurements available at the time of the studies to assess whether women who reported organic food consumption had different exposure to either adverse or favourable substances than those who did not report organic food in their diets. This is a limitation of the studies. However, a later European collaboration study including n=272 children from MoBa and five other cohorts (in total 818 mothers and 1,288 children) used a cruder measure of child organic food consumption (no organic consumption, once a week or less, and more than once a week) and examined food intakes and environmental contaminants in blood and urine from the children. The results showed that organic food consumption was negatively associated with OP pesticide metabolites in the child urine (172). The concentrations of OP specific metabolites were up to 38% lower in those with organic consumption more than once a week than in those with no organic consumption. This indicates that self-reported organic food consumption in observational studies corresponds quite well with actual consumption and that even crude questions about use of organic food are able to detect differences in OP metabolites. This is in line with the results from experimental studies which consistently have found that intake of conventionally produced food is a major source of urinary OP metabolites (173). Although differences between organically and conventionally produced food may be small, the annual plant-food surveillance program of pesticide metabolites in Norway detect pesticide residues predominantly in conventionally produced items and rarely in organic items. For both conventionally and organically produced items, pesticide metabolites are more often detected in imported items than in those of local origin (63) (The report by the Norwegian Food Safety Authority is published yearly, here I use the same reference as in Paper IV, the report for 2012).

Some of the food categories that the organic food questions refer to were validated (fruit and vegetables), finding less than 10% grossly misclassified (correlation coefficients ranging from 0.3 – 0.6) between the FFQ estimates and the reference food groups including fruit and vegetables (154). This means that reported intake of fruit and vegetables has been found to be good enough to categorise in right quartiles.

With regard to the question about organic food consumption, the frequencies categories used when answering could have been interpreted differently among respondents (e.g. the meaning of 'often' etc.). Although validation studies of the FFQ conveyed less than 10% grossly misclassified respondents/answers for fruit and vegetable consumption (154), we have no specific information about whether the same applies to the question about consumption of organic fruit and vegetables.

Interpretation of the term 'organic food' in the FFQ is another issue. The relatively high level of knowledge about the national label for organically produced food in the general population at the time of the studies (2002-2008) speaks for the likelihood of correct reporting; according to a yearly survey among supermarket shoppers in 2008, 88% recognised and knew the meaning of Debio's Ø label (32). This is similar to the findings in a national representative survey conducted in 2019, where 87% did the same (26).

5.1.2 Bias in observational studies

Selection bias

Selection bias refers to differences between the study-population and the target population that results in differences in effect estimates for the exposure-outcome association between those included in the study and the target population. The participation rate in MoBa is 41%, and selection bias is an issue of concern. MoBa-participants differed from the general pregnant population at the time of recruitment by being of average older age, having higher educational attainment, comprising fewer smokers and being healthier. Furthermore, the proportion of ethnic minorities is much smaller in MoBa than in the general pregnant population in Norway because the information to participants was available only in Norwegian language. A prospective study in multi-ethnic pregnant women require other methods for data collection and one such study started in Oslo at the same time as participants were recruited to MoBa (174). A study of potential self-selection bias in MoBa showed that there were no significant differences in eight evaluated exposure-outcome associations between cohort participants and a representative sample of the total pregnant population in Norway during the same period (175).

One method that could have been applied to check for possible effects of selection bias is inverse probability weighting (IPW) of participant participation, described in Biele, et al. (176) and applied in studies using MoBa-data to examine associations between prenatal diet quality and child neurodevelopment up to 5 years of age (177) and ADHD at 8 years of age (178). The authors used meta-data for the target population on maternal education, maternal age and parity (obtained from Statistics Norway) to calculate weights used in analyses. These weights where then included directly in the model estimations. By doing this, data points for underrepresented and overrepresented sub-groups in MoBa were weighted up and down, respectively; producing results that are more generalisable to the target population (176). However, this is only correct given that self-reported educational attainment is not over-reported. Although loss to follow-up as the child grows older contributes to further decrease the participation rate, application of IPW did not substantially change the results.

Information bias

Information bias refers to the systematic error relating to aspects of data collection, which might lead to biased results. In MoBa, recall bias is a type of information bias that may impact the data. This bias relates to the ability of participants to accurately recall the information they are asked to report in the questionnaires and depends on the complexity and time frame of the question. In the MoBa FFQ, respondents were asked to report their average intake of food items since the start of pregnancy, which is a rather complex cognitive task. The choice of time frame, number of questions, when in pregnancy to answer the FFQ and other methodological issues were considered when the MoBa FFQ was designed (123). In MoBa, study-specific cut-offs were established to exclude participants with implausible energy intakes (<4.5 MJ or >20 MJ) (123), but misreporting within the accepted range of energy intake is still inevitable.

Dietary practices and patterns are likely less vulnerable to respondent misreporting than estimated intake of a specific nutrient. Nutrition epidemiology is therefore moving more towards studying overall dietary indices rather than single foods and nutrients when examining diet-disease relationships (179).

Social desirability bias is another type of information bias which is commonly seen in health-related questions. It refers to intentionally or unintentionally under-reporting of behaviours or food intakes perceived as “unhealthy” and over-reporting of behaviours perceived as “healthy” (180,181).

5.1.3 Confounding

Confounding is a major challenge in all observational studies. We designed the sequence of studies with the aim of increasing our possibilities of handling confounding and provide robustness to results in the health outcome studies. In MoBa, a wide range of information has been collected from the participants, making it possible to identify and adjust for many relevant confounders. Results from papers I-II were used to account for as many potentially confounding factors as possible in papers III and IV.

Confounding and interaction between independent variables can be examined by sensitivity analyses, which restrict the study sample by e.g. excluding participants with potential large influence on the association of interest, such as excluding smokers when studying the impact of diet on birth weight. Stratification is another additional analysis commonly used, i.e. repeat the analyses within subgroups of the study population to minimise residual confounding (148) and compare results between the strata to see if they are comparable or substantially changed. Sensitivity analyses that were performed are further discussed in section 5.2.

Treatment of missing data on covariates is also an issue that can affect the results when examining exposure-health associations. Missing data occurs in almost all research. Whether individuals with missing information are excluded or included as a separate “missing group” may influence the results. Ideally, missing data should be imputed, e.g. estimated based on other characteristics, but this requires advanced statistical skills. In this thesis, missing information on covariates was generally treated as a missing category, but we checked that handling of those with missing values on one or more variables did not have substantial effects on results, by performing analyses both with and without the cases who had missing on one or more co-variates. We found that it did not substantially change the results. (For more detail, please see descriptions in the papers).

In conclusion, many types of bias were present in our studies, and although we were able to account for some of these, observational studies using self-reported data can only provide statistical associations but not causations. Regardless of the approaches to account for bias and confounding, it is very likely that some bias remain, e.g. social desirability bias, recall bias and residual confounding (148).

5.2 Discussion of results

5.2.1 Characteristics and dietary quality associated with organic food consumption (paper I and II)

In the context of this thesis, a characterisation of MoBa-participants who consumed organic food compared with those who did not, was crucial as a preparatory phase for studying potential associations between organic food consumption and health outcomes. Beyond this methodological aspect, knowledge about organic food consumption in pregnancy and related practices and characteristics adds to the general knowledge about organic food practices among pregnant women, an important sub-group of the population.

Reported frequency of organic food consumption

The finding that 9.1% of the study population reported frequent consumption of organic food is within the expected range. Market information shows a trend of steady increase in sales of organically produced foods in the retail sector throughout the study period 2002-2008, and in particular during the last years (2005-2008) (182). Nevertheless, the total share of the market was low; there was an increase from 0.43% in the first half of 2005 to 1.08% in the second half of 2007 and between 2006 and 2008 sales of organic food accounted for around 1% of the total food market (30,183). It is therefore not surprising that the level of organic food consumption within the time-frame of this study was not higher. It is also in line with market development that frequent organic consumption increased during the last part of the study period, as described in Paper I.

A comparison between participants in the Danish national birth cohort (DNBC) in the years 1996-2002 and MoBa in the years 2002-2008 showed that the proportion of participants with the highest frequency of organic food consumption was considerably higher in Denmark (7%) than in Norway (1.9%) (128,184). In a study from the PELAGIE mother-child cohort, with participants recruited from April 2002 through February 2006 in the French region of Brittany, 55% of the women reported an organic diet (from sometimes to frequent) during pregnancy (66). In the French Nutrinet-Santé Cohort Study, of French adults, 14% were classified as ‘regular organic food consumers’ among participants enrolled in the study from it was launched in 2009 (185) to the end of 2011 (42). These differences are not surprising, given the differences in the market and general consumption levels of organic food.

Characteristics associated with organic food consumption (paper I and II)

The results of Paper I and II reflect complexities associated with organic food consumption, rather than clear-cut profiles of typical consumers of organic food. This was more so with regard to socio-economic and lifestyle characteristics in general, than with regard to overall dietary habits, which were found to be more clearly associated with a 'healthy' and more sustainable dietary pattern. Similar findings of a diet with more vegetables and less meat among consumers of organic food have been described in other studies, e.g. Great Britain, Australia, Germany, France, Denmark and Norway (24,42,186-190).

Studies from other birth cohorts have also found that organic food consumption during pregnancy is associated with different characteristics, food patterns and intake (67,128,191).

A joint, multivariate analysis comparing characteristics of the participants with the lowest vs. the highest frequency of organic food consumption in the Danish and Norwegian birth cohort studies respectively (DNBC in the years 1996-2002 and MoBa in the years 2002-2008) showed that the Danish organic food consumers had higher age, higher educational attainment, and comprised more occasional smokers and urban residents compared with the respective Norwegian group. Similarities between frequent consumers of organic food in DNBC and MoBa included a higher degree of adherence to a healthy diet ('healthy'/'prudent' pattern); engagement in physical activity; they had lower BMI and higher total energy intake compared with non-consumers of organic food (128,184,192).

The latter finding in MoBa and DNBC with regard to lower BMI and higher levels of leisure physical activity among frequent organic food consumers, is also reported in the Dutch KOALA Birth Cohort Study, and in the French NutriNet-Santé study (42,191). In the KOALA-study, similar differences in food patterns as reported from MoBa and DNBC were found, while the corresponding energy intakes were similar. In MoBa and DNBC, there was a higher total energy intake among frequent organic food consumers, while nevertheless, in all these three studies, BMI levels were lower in the organic consumer groups. This may indicate a better balance between energy intake and energy expenditure, and likely a more active lifestyle.

Both in the KOALA-study and in MoBa, organic food consumption was associated with higher probability of adhering to a vegetarian diet, indicating a close connection to overall dietary intake. Vegetarian diets, particularly lacto-ovo-vegetarian diets, have been linked to lower mortality and morbidity and better health in adult populations (193,194), and the association between vegetarianism and use of organic food makes it more difficult to disentangle the potential health impact of either.

In the KOALA-study, consumption of organic food was associated with higher levels of a biomarker of dairy products intake and trans-fatty acids from natural origin and lower levels of a marker for industrially hydrogenated fats compared with participants consuming no organic food (67). These differences were explained in part by food patterns accompanying the consumption of organic food.

Our finding that frequent organic food consumption was not associated with the highest income classes, and not only the highest level of educational attainment, but also the lowest, as well as being a student, could be interpreted as an indication of a value-based orientation. In both DNBC and the NutriNet-Santé study, organic food consumption was more clearly associated with higher socio-economic status. Other studies, however, have pointed to the shortcomings of socio-demographic variables in explaining organic food consumption, while attitudes and behavioural variables as well as value-orientations seem to be better predictors (195).

A methodological implication of results from paper I and II is that socio-economic and lifestyle characteristics, including the overall diet, within the relevant contexts, need to be included in future studies of potential health outcomes related to consumption of organic food during pregnancy. However, in spite of adjusting for multiple socio-economic and lifestyle characteristics, unmeasured confounding cannot be excluded.

The comparison between DNBC and MoBa showed that despite the differences, there seemed to be a trend towards more similarities with higher frequency of organic food consumption. Within MoBa, we observed that some characteristics of participants, such as age and cigarette smoking, varied with 'intensity' of organic food consumption. Changes in dietary pattern, e.g. increased vegetable consumption and decreased meat consumption, were observed even at the lowest frequency of organic food consumption, continuing to become more pronounced with increased frequency of organic consumption (showed in Figure 2 in Paper II). Consequently, interpretations of results with regard to generalisability should preferably take degree of organic consumption into account.

Despite methodological challenges with regard to organic food consumption being embedded in local (and temporal) contexts, and the challenges arising from the characteristics associated with organic food consumption, it is important to use the possibilities available (such as large cohort studies) to investigate potential health-effects.

5.2.2 Consumption of organic food and pre-eclampsia (Paper III) and hypospadias and cryptorchidism (Paper IV)

Large knowledge gaps remain in our understanding of how consumption of organic foods in pregnancy and related lifestyle practices influence the health of mother and child. To the best of our knowledge, our studies are the first to report associations between consumption of organically grown vegetables during pregnancy and reduced risk of pre-eclampsia as well as reduced risk of giving birth to a boy with hypospadias, based on a large cohort study. In the papers, we suggest three possible explanations of the results based on the following characteristics of a diet including organically produced vegetables rather than conventional vegetables: (1) higher intake of secondary plant metabolites; (2) lower dietary pesticide exposure and (3) possibly a different microflora on organic vegetables, which could affect human (maternal) intestinal microbiota in a beneficial way. Furthermore, pesticides, or the absence of them, might impact the composition of the gut microbiota. These hypotheses will be discussed in the following section, but first some methodological and statistical issues regarding the robustness and interpretations of results in paper III and IV will be addressed.

Statistical considerations

A major finding was that frequent organic consumption was associated with more vegetables, fruit and berries, and whole grain bread and cereals, and less meat and highly processed food such as e.g. processed meat, white bread and cornflakes, cakes and sweets. This could arguably have introduced bias into the results if unadjusted for. We thoroughly explored possible confounding by these variables in our subsequent analyses in Papers III and IV. The inclusion of the total calculated food intake within each food group, including vegetables, in the analyses had no influence on the ORs.

With regard to dietary intake, some additional analyses were also carried out, in addition to what had been found to vary with organic food consumption. For example, coffee intake (quartiles of reported intake) was included in the analyses and was found not to change the effect estimate for the association between frequent use of organic vegetables and the prevalence of pre-eclampsia. In addition, all known risk factors for pre-eclampsia, hypospadias and cryptorchidism of which we had available data were controlled for.

In Paper IV, we included a variable denoting 'any organic use' in order to account for the fact that those eating organic food also may differ from those with no organic food consumption with regard to other lifestyle factors. Examples of factors which we had no information about, and which could be hypothesised to be related to use of organic food, include the use and sources of cosmetics and hygiene products, household cleaning products, home interior materials, clothing materials/textiles (e.g. frequency of buying new clothes, use of second-hand clothes) and home cooking practices (e.g. use of plastic storage). All of these could be of relevance, for example, in relation to exposure to endocrine-disruptive chemicals, and introduce bias into the analyses if un-evenly distributed among consumers/non-consumers of organic food (196). It could be argued that adjusting for the 'any organic' variable in the models for each organic food group is an over-adjustment because it entails adjusting also for the exposure variable. These analyses showed that including the variable 'any organic' indeed attenuated the results, but association for organic vegetables and lower prevalence of hypospadias remained highly significant and the association for dairy was borderline significant (Figure 7).

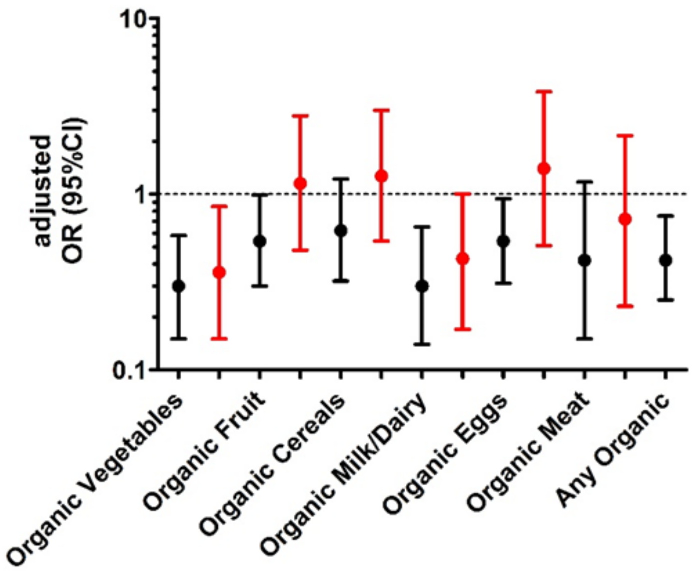

Figure 7. The association between organic food groups and use of any organic food and hypospadias. The black bars show models adjusted for maternal education, household income, pre-pregnancy BMI, infant being born small for gestational age, preterm delivery, and total daily intake of food items (organic and nonorganic) in the respective group. The red bars show models with additional adjustment for 'any organic'.

In some cases, where we lacked detailed information regarding specific aspects of our hypotheses, we searched for an appropriate proxy in the data material. For example, we had no family data on genital malformations, which are known to have a hereditary component. The solution we found for this was using the variable 'Urdu as second language' as a proxy for higher prevalence of consanguineous marriages. The rationale for this was that hypospadias is more prevalent in settings where consanguineous marriages are common (197), and in Norway, the Pakistani immigrant population is the largest group where marriage between relatives (cousins) is known to occur. We found that there were no one with Urdu as second language in the case group.

When analysing large data sets and doing several tests and comparisons, inherently, there is a risk of chance findings. Basing analyses on biologically plausible research questions and hypotheses as well as previous findings is one way of counteracting chance findings. It is also important with caution when interpreting statistical significance.

In the case of paper IV, when studying cryptorchidism, we observed a trend towards a lower prevalence of cryptorchidism associated with maternal consumption of organic milk/dairy products with OR = 0.65 (95% CI 0.40, 1.04, $p = 0.071$; $n = 31$ exposed cases). However, we chose not to emphasise these borderline significant associations. In the case of hypospadias, there was a previously published study indicating a possible protective effect of organic dairy products, suggesting that there may be a true association in this case (65). The results were also clearer for hypospadias, as compared with those for cryptorchidism. Therefore, we came to different conclusions with regard to the robustness of the results and how to report them; even though the risk of chance findings could be equally relevant in the two cases, the evidence was stronger in the first case.

Evaluations according to the Bradford Hill criteria

The associations found in paper III and IV are based on observational data and residual or unmeasured confounding can never be ruled out. The British epidemiologist Augustin Bradford Hill described criteria for evaluating causality, including the key criteria strength, consistency, temporality, biological gradient (dose-response), plausibility, coherence, and experimental evidence (198).

In observational studies such as in paper III and IV, applying the Bradford Hill criteria for assessing disease causation can help gain further insight into the nature of the observed associations. The magnitude (strength criteria) of the association between frequent organic vegetable consumption and pre-eclampsia was consistent in sub-strata of maternal characteristics (paper III), and the same was seen for the association between any organic consumption and hypospadias (paper IV). Information about organic food consumption preceded delivery (temporality criteria). A biological mechanism (plausibility criteria) underlying the observed associations is not obvious, but different potential explanations exist.

In the following, results presented in this thesis will be evaluated in light of these criteria.

1. The criterion about *strength*: Strong associations are more likely to be causal associations than weak associations. (At the same time, it is worth keeping in mind that strong associations are neither necessary nor sufficient for causality, and weak associations are neither necessary nor sufficient for lack of causality.)

The effect estimates for the association between eating organic food (of any of the six food groups) 'sometimes', or 'often or mostly' and prevalence of giving birth to a boy with hypospadias can be considered to be quite strong: OR=0.42 (95% CI: 0.25, 0.70.). This result implies that women who reported that they 'never or seldom' ate organic foods were 2.4 times more likely to give birth to a boy with hypospadias. The association was strongest for consumption of organic vegetables and lower prevalence of hypospadias (OR=0.36; 95% CI: 0.15, 0.85). The association between consumption of organic vegetables and pre-eclampsia is arguably not particularly strong: OR=0.79 (95% CI: 0.62-0.99). However, the p-value is 0.04, and the estimate is robust in all adjusted analyses.

Both effect estimates are within what could be expected, given the complexity of diet as the exposure in general, and the fact that information about consumption of organic food was based on a relatively crude set of questions. The questions about use of organic foods (specified in six food categories) had four answer categories: 'seldom/never', 'sometimes', 'often', and 'mostly', and these may have been perceived and interpreted differently among participants, leading to misclassification.

2. The criterion about *consistency*: the associations should be possible to demonstrate in different populations under different conditions and in different contexts. This is an important criterion, which we aimed to fulfil by performing the analyses in different sub-groups of the study population. The association between use of organic vegetables and pre-eclampsia was

consistent also when we explored it separately in groups based on high/low education, high/low age, high/low age, high/low BMI, high/low score on 'healthy' dietary pattern etc.

3. The criterion about *specificity* implies that one causal factor gives only one effect, not many different effects. This criterion is not considered relevant today, because several exposures (e.g. smoking) are contributing causal factors to a large number of diseases.

4. The criterion about *relation in time* requires that the exposure (possible cause) must take place before the outcome. This is an absolute requirement. One of the strengths with MoBa being a prospective study is that participants report about dietary habits and other lifestyle factors in mid-pregnancy, while the outcomes appear later in time, and is based on data from MBRN.

5. The criterion about *biological gradient* implies a dose-response curve which goes in one direction. A tendency towards a dose-response trend is shown in both paper III and IV (Table 2 in both papers). However, such an association is neither necessary nor sufficient for a causal relation.

6. The criterion about *plausibility* implies that the finding must be regarded as biologically credible based on current knowledge. In paper III and IV we present three suggestions of possible explanations of our findings, based on current knowledge.

7. The criterion about *coherence* implies that the interpretation of the association should not be in conflict with current knowledge about the aetiology and biology of the disease/outcome. This is related to the criterion about plausibility and is met in these studies.

8. The criterion about *experiments*, implies that controlled experiments, e.g. randomised, controlled dietary interventions, give the same result as the actual finding strengthens the credibility of the causal effect. Long-time controlled studies with organic food as the exposure are virtually impossible to conduct, but some short-time studies exist.

9. The criterion about *analogy* implies that the demonstration of associations with similar exposures and similar health outcomes strengthens the hypothesis about causal effect.

Evaluation of causality in epidemiology has developed since the time of Bradford Hill, but the criteria are still considered fundamental in causal assessment (199). Prospective cohort studies are considered the strongest observational study design in terms of scientific evidence. The evaluation above indicates that our findings are reasonably strong. However, prospective cohort studies are seen as providing statistical associations and not causations, residual or unmeasured confounding cannot be ruled out, and results must be interpreted with caution and should be replicated in other studies (148).

On the other hand, it is important to balance scientific rigor and possible public benefit, as pointed out by Schwartz and Susser, citing Bradford Hill: '*All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time*.' (200)

Hypotheses and possible explanations of the results

In the following, the three hypotheses put forward in the health-outcome papers will be briefly discusses.

1. The secondary plant metabolite hypothesis

Meta-analyses have indicated that low-dose aspirin initiated in early pregnancy may be a promising method of reducing the incidence of pre-eclampsia in high and moderate risk women (201-203). As the effects of eating organically vs. conventionally grown produce with regard to higher contents of salicylic acid is compared with the effects of taking low-dose aspirin (204), this may represent a possible explanation to our findings of lower prevalence of pre-eclampsia with consumption of organic vegetables. It is not established whether salicylic acid derived from dietary sources is beneficial to health, but concentrations of salicylic acid in the serum of vegetarians who were not taking aspirin overlap with those in the serum of patients who had taken low doses of aspirin over a longer period of time (205).

A second plant metabolite of interest is reservatrol, a naturally occurring polyphenol found in a number of plants. Reservatrol is among the defence-related secondary plant metabolites found by Brandt et al. to be in higher concentrations in organically produced fruit and vegetables; on average 16% higher than in corresponding conventional products (206). Reservatrol has been shown to induce relaxation of uterine arteries *in vivo* (animal models) as well as improve many pathological conditions associated with pre-eclampsia and fetal growth restriction (207). The beneficial effects of reservatrol appear to be mediated via several pathways including enhanced nitric oxide (NO) bioavailability through endothelial NO synthase expression, as well as a reduction in oxidative stress, improvement of mitochondrial oxidative capacity and a decrease in ischemia reperfusion injury (208). In a double-blind study on humans, reservatrol was shown to increase cerebral blood flow (209), and increased blood flow to the kidney and in coronary arteries has been demonstrated in animal models (207).

Since intrauterine growth restriction and fetal growth restriction is a common risk factor for both pre-eclampsia and hypospadias, higher contribution of secondary plant metabolites in organically grown produce may offer a relevant possible explanatory factor for results regarding both health outcomes. The fact that we adjusted for total intake of vegetables in the analyses, strengthens the robustness of the interpretation of results being related to differences in consumption of organic vs. conventional vegetables.

2. The gut microbiota hypothesis

The polyphenols are discussed above with regard to antioxidant effects, and this group of compounds is also of interest because they may contribute to a healthy gut microbiota (210). Polyphenols are known to exert prebiotic effects, as they arrive intact to a great extent in the colon (are *non-digestible*), they are *fermentable*, and they stimulate in a selective way growth and/or metabolic activity of the intestinal bacteria that are associated with health and wellbeing (they are metabolised by the microbiota in the colon) – thereby polyphenols meet the criteria of being defined as 'prebiotic' (211). By a reciprocal relationship with the gut microbiota, polyphenols are shown to maintain the intestinal barrier as well as the community of the gut microbiota in normal status, and in turn, the gut microbiota can improve the bioavailability of polyphenols (212). A higher content of polyphenols in organic food may therefore serve to reduce overall systemic inflammation levels through two different mechanisms; by antioxidant effect, as discussed above, and by contributing to a beneficial gut microbiota (210,213).

In addition to providing secondary plant metabolites, organic plant food may provide a different exposure to microorganisms compared to conventional food. High biological diversity in the soil is characteristic of organic agriculture, and the microbial diversity in soil varies between organic and conventional farming systems (214). It may be hypothesised that a distinct and more diverse microflora is not only found in the soil, but also on the fresh produce of organic agriculture. Differences in bacterial community diversity on the surface of fresh fruits and vegetables are reported depending on production types, and such differences may in turn influence the dietary intake of probiotic substances (215-217).

The gut is a major immune organ, and the gut microbiota shapes intestinal immune response during health and disease (218-220). It is becoming increasingly clear that the effect of the gut goes beyond the local gut immune system and is implicated in immune-related disorders, such as type-2 diabetes and obesity (220-222). A lower general, systemic inflammatory level may be protective against pre-eclampsia. Evidence supporting the relevance of the intestinal microbiota for the prevention of pre-eclampsia include studies finding protective effects of probiotics (223,224), and evidence supporting the hypothesis that plant foods may protect against pre-eclampsia through intestinal anti-inflammatory mechanisms (225). Brantsæter and colleagues found that regular intake of probiotic milk (containing *Lactobacillus* bacteria) is associated with reduced risk of pre-eclampsia, and it is hypothesised that the *Lactobacillus* probiotics may have supressed the Gram-negative bacterial lipopolysaccharide (LPS) expression to reduce inflammation (223). This mechanism would be in agreement with other studies which found that lactobacilli influenced the LPS response to reduce overall systemic inflammation levels (226).

Besides a possible different exposure to microorganisms with organic plant food, reduced risk of exposure to pesticides is an additional way that consumption of organic food may beneficially affect gut microbiota, as pesticides are shown to selectively influence its composition (227). This will be further addressed in the section below, together with other possible effects of reduced exposure to pesticides.

3. Lower exposure to pesticides

With regard to dietary exposure to pesticides, it is well established that consumption of organic food is associated with lower exposure to pesticide residues (45). Intervention studies with organic food have shown significant reduction in urinary excretion of various pesticide metabolites in adults and children, in urban as well as rural areas, indicating reduced exposure to common agricultural pesticides with consumption of organic compared with conventional food (228-233). The body of evidence also includes a study in pregnant women: An intervention study among 20 pregnant women found lower urinary concentration of a biomarker of pyrethroid pesticide exposure, suggesting that the addition of organic produce to an individual's diet, as compared to conventional produce, significantly reduces exposure to pyrethroid insecticides (234).

As mentioned above, one way in which pesticides may affect human health is by affecting the gut microbiome (227). A recent study on glyphosate, the most common broad-spectrum herbicide, investigated impacts on the biodiversity and composition of microbial communities, including the human gut biome. This study concluded that a conservative estimate indicates that 54% of species in the core human gut microbiome are sensitive to glyphosate (235). Other studies have investigated the pesticide Chlorpyrifos in a model of the human intestinal microbial ecosystem, as well as in rat studies, finding that perinatal exposure to Chlorpyrifos delayed the maturation of the digestive tract in rats (236), and that chronic exposure selectively altered the intestinal microbiota by enhancing the growth of some species, including the *Enterococcus* spp and *Bacteroides* spp, and decreasing the number of beneficial bacteria, such as bifidobacteria and lactobacilli (237). Chlorpyrifos has further been shown to increase permeability of the intestine in an *in vitro* model based on an enterocyte cell line (238), and increased permeability of the intestine ('leaky gut') may induce inflammation (239).

An endocrine-disrupting chemical has been defined by the World Health Organization (WHO) as 'an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations' (240). Numerous pesticides are known to be 'endocrine disrupting' or 'endocrine-active' substances with estrogenic or anti-androgenic activity (241).

Lower exposure to pesticides with organic vs. conventional food, and thereby lower exposure to substances with endocrine-disruptive effects, may be of relevance in explaining both the findings of lower prevalence of pre-eclampsia and lower prevalence of hypospadias. Exposure to pesticides have been associated with intrauterine growth restriction (242), which is a common risk factor for pre-eclampsia and hypospadias (243,244). Exposure to pesticides during pregnancy may increase the risk of hypertensive disorders of pregnancy (105), and emerging evidence suggests that environmental exposure to some pesticides may be associated with the risk of pre-eclampsia, although more research is needed (245).

The use of pesticides and other endocrine-disrupting (or endocrine-active) chemicals have been proposed to contribute to the observed increase in incidence of hypospadias (243-247). Endocrine-disruptive chemicals are highly relevant for the prevention or risk of hypospadias, as its aetiology is related to androgen-receptor function. Vinclozolin is a well-characterised anti-androgenic pesticide (248), and prenatal exposure has been shown in animal (rodent) models to be associated with decreased adult sperm concentration and motility as well as increased risk of hypercholesterolemia, kidney and prostate disease, abnormalities in immune system function, and cancer in male offspring (248).

Pesticide exposure is linked to obesity and type-2 diabetes through obesogenic endocrine disrupting effects (249-252). Hence, lower exposure to pesticides may be protective against pre-eclampsia, since obesity and dyslipidaemia (hypertriglyceridemia) are associated with the development of pre-eclampsia (253,254).

As pregnancy is a time period when biological changes can increase sensitivity to chemical exposures, it is of particular importance to understand how such exposures, including dietary exposure to pesticide residues, may impact health outcomes of mother and child. A recent review concluded that there is a relative paucity of such studies, and recommend further research on women's health and the pregnancy exposome, defined as the totality of external and internal exposure during the pregnancy period, which can alter the course of pregnancy and influence maternal and perinatal health outcomes (255). The health outcomes studied in this thesis should be followed up by other studies, and it would further be important to investigate other health outcomes, especially those which potentially share some aetiological factors.

The beneficial health effects of vegetables and fruits and other foods recommended in a balanced diet are well documented, but the jury is still out and not ready to conclude whether choosing the organic alternatives would provide additional benefits (8,57). The current dietary guidelines, which recommend more fruit, vegetables, and plant foods and less meat, are based on a large number of studies and are valid regardless of whether the produce is organic.

6 Conclusions

The conclusions from the four papers can be summarised as follows:

From Paper I, we conclude that frequent organic food consumption during pregnancy was associated with personal, lifestyle- and socio-demographic variables. These characteristics were not limited to those commonly associated with a healthy lifestyle, such as higher income and higher education. Although the largest share of respondents were those who reported to never or seldom eat organic food, we conclude that organic food consumption was quite widely distributed among MoBa participants across the characteristics investigated in this paper.

Paper II concludes that MoBa-participants who reported frequent organic food consumption had a dietary pattern and quality more in line with public advice for healthy diets.

A methodological implication from Paper I and II is that personal, socio-demographic-, and lifestyle characteristics, including information about the overall diet, need to be included in future studies of potential health outcomes related to consumption of organic food during pregnancy.

Paper III concludes that frequent consumption of organically produced vegetables during pregnancy was associated with reduced risk of pre-eclampsia. Consumption of plant foods, including vegetables, is recommended to all pregnant women, and this study shows that choosing organically grown vegetables may yield additional benefits.

In Paper IV it is concluded that consumption of organically produced foods, particularly organically produced vegetables, during pregnancy was associated with a lower prevalence of hypospadias. No substantial association was observed for organic food and cryptorchidism. These findings were based on small numbers of cases and require replication in other studies.

The overall conclusion with regard to the studied health outcomes is that although beneficial associations were indicated for consumption of organic food, particularly organic vegetables, the results must be interpreted with care and no causal inference can be drawn.

7 Implications and future perspectives

There is a clear need for studies addressing the relationship between organic food consumption and health, particularly in life phases such as pregnancy and fetal development, with its critical windows for ‘early prevention of disease’ and not least, ‘early promotion of health’ (88).

A methodological implication of the present studies is that personal, socio-economic and dietary characteristics should be included in future studies of possible associations between organic food consumption during pregnancy and health outcomes. Although similarities in characteristics associated with organic food consumption are reported in various studies, caution should be taken to account for differences arising from the embeddedness of food practices in local, structural and cultural contexts.

With about 107 000 mother-infant pairs, MoBa is the largest and most costly cohort study ever conducted in Norway, and it is one of the largest of its kind, internationally. This large number of participants makes it possible to study even rare outcomes. Still, we observed that when we study an exposure such as frequent consumption of organic food – which comprises a smaller share of the total study population (9.1%, Paper I), and associations with health-outcomes, which are also quite rare (such as hypospadias, with the prevalence of around 0.3%, Paper IV), we come close to the limit for sufficient statistical power. Therefore, it is promising that it is feasible to combine the datasets of the world’s two largest birth cohorts; DNBC and MoBa (256). The benefits of replicating analyses in the combined data-set would be twofold: 1) possibilities of replicating analyses in a different setting and broader context, and 2) to expand the size of the population study, thereby increasing the statistical power. Today we see even larger merging of data from different studies, exemplified by the LifeCycle Project where nineteen European pregnancy and children cohorts are brought together (257).

Studies of diet and health are in general challenging, and it applies to studies of organic food as well – with the added layer of complexity represented by including the origin of food. With the exception of short-term experimental studies with conventional versus organic food, the impact of organic food consumption for long-term health rely on large prospective cohort studies. Further, carefully designed studies to investigate potential effects of organic food consumption on human health are needed, particularly during critical periods such as during pregnancy. Questions about the origin of foods (organic vs. conventional) have rarely been included in birth cohort studies investigating dietary habits. If future cohort studies to a larger extent would include such questions, this would further increase opportunities to investigate possible associations between organic food consumption and health outcomes.

A point of potential improvement for future studies in this field would be to develop and apply more detailed measures of organic food consumption. As was the case in the present studies, there is a balance to be made between the detail in individual questions and the appropriate length of questionnaires in large cohort studies investigating dietary impact (diet inherently being a broad and complex subject). In order to further advance investigations about potential health effects of organic food consumption, it would be beneficial with more detail in the exposure variable, e.g. including information about amounts or shares of organic food within the general food group, as has already been done in some cohort studies (129).

For the present studies, there were no biological or environmental measurements available to assess whether women who consumed organic foods had different exposure to adverse or favourable substances than those who did not consume organic foods. Such measures will be important to seek in future studies, although there probably is a large border zone between participants with organic and conventional exposures due to the fact that absence of markers of pesticides or other chemical use is not exclusive to consumers of organic food (8). The potential of including biomarkers for consumption of organic food, encompasses biomarkers for potentially harmful substances, (such as toxic environmental contaminants, pesticide residues, etc.), as well as potentially beneficial qualities of organic food (e.g. traits enhancing beneficial gut microbiota, or naturally occurring antioxidants, etc.). In addition to validation of information about organic food consumption by the use of biomarkers, improvements of questions could be sought in the design phase by use of methods such as pilot studies with qualitative interviews with respondents when they answer the questionnaire, and testing and re-testing in smaller groups with measurement of internal consistency (258).

There is ongoing European research to advance methods in organic food production to make organic agriculture ‘more true to organic principles’ and phase out the use of contentious inputs [9], and further enhance compliance with sustainability goals in line with the EU Bio-economy strategy for a sustainable Europe (259). Also, in the United States, there are initiatives to move certified organic food production closer to core principles and values, for example by advocating the centrality of healthy soil and opposing allowance of aquaponics within U.S. organic certification [10]. Such developments within research, policy and practices, may lead to clearer differences between organically produced foods and conventionally produced food and a larger degree of unity around central principles of organic food within the community of organic food producers. Another possible trajectory of development would be a greater implementation of organic principles and practices in all food production, which would be in line with the 'spear-head role' assigned to organic agriculture (260).

A deeper understanding of the diverse aspects of the healthfulness of food – spanning the whole web of connections in which food systems are embedded and the qualities of foods are dependent on – would serve us well in a public health perspective. The interrelated nature of human health and the health of ecosystems is acknowledged by e.g. FAO and WHO in their united definition of sustainable diets (44); in strategies for future sustainable food systems by the European Commission as well as the International Panel of Experts on sustainable Food Systems (10,261) and by the European Parliament, commissioning a review of human health implications of organic food and organic agriculture (43).

"*When do you start raising a child*?" This question is posed in the book 'The Third Plate', by Dan Barber. The answer reads, citing a conversation with a Mennonite bishop; "*child rearing begins not at birth, or even conception, but one hundred years before a child is born, because that's when you start building the environment they're going to live in."* (262) (p.32).

Such a perspective may prove fruitful when aiming at achieving human health as well as ecological sustainability through food in all its aspects.

[9] See the EU-funded project 'Organic-PLUS Pathways to phase-out contentious inputs from organic agriculture in Europe' (European Horizon 2020, grant agreement 774340) (organic-plus.net)
[10] See the Real Organic Project; https://www.realorganicproject.org/

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Paper I

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ERRATA Paper I

Numbers given in the text on page 4 differ slightly from numbers given in Table 1, and the percentage in Table 1 for consumption of organic eggs ‘Sometimes’ should be 24.7, not 24.2.

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RESEARCH ARTICLE Open Access

Characteristics associated with organic food consumption during pregnancy; data from a large cohort of pregnant women in Norway

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Abstract

Background: Little is known about the use of organic food during pregnancy. The aim of this study was to describe characteristics associated with the use of organic food among pregnant women participating in the Norwegian Mother and Child Cohort Study (MoBa).

Methods: The present study includes 63,561 women who during the years 2002-2007 answered two questionnaires, a general health questionnaire at gestational week 15 and a food frequency questionnaire at weeks 17-22. We used linear binomial regression with frequent versus rare use of organic food as outcome variable and characteristics of the respondent as independent variables. The outcome variable was derived from self-reported frequency of organic food use in six main food groups (milk/dairy, bread/cereal, eggs, vegetables, fruit and meat).

Results: Organic eggs and vegetables were the food items which were most frequently reported to be used "often" or "mostly". The proportion of women reporting frequent intake of organic food was 9.1% (n = 5754). This group included more women in the lower (<25 years) and higher (>40 years) age-groups, with normal or low body mass index, who were vegetarians, exercised regularly (3+times weekly), consumed alcohol and smoked cigarettes during pregnancy (p < 0.001 for all, except alcohol: p=0.044). Further, participants with frequent organic consumption included more women in the lower (≤12 years) or higher (17 years +) category of educational attainment, women who were students or had a partner being a student, who belonged to the lowest household income group (both respondent and her partner earned <300 000 NOK), who entered the study 2005-2007, and who lived in an urban area (p < 0.001 for all).

Conclusions: The socio-economic characteristics of pregnant Norwegian women with frequent organic consumption did not unambiguously follow those typically associated with better health, such as higher levels of education and income. Rather, lower household income, and both lowest and highest levels of education were associated with a higher prevalence of frequent organic consumption. The results indicate that personal and socio-economic characteristics are important covariates and need to be included in future studies of potential health outcomes related to organic food consumption during pregnancy.

Background

Dietary quality is especially critical during pregnancy, as adequate nutrition is essential for both maternal and foetal health. There is growing evidence that maternal diet may influence longer-term health of the offspring even within relatively well-nourished populations [1-3]. Dietary intake and food patterns have been described among pregnant women in many populations including Norway [4-6], but little is known about pregnant women who go against mainstream food culture and choose to eat vegetarian diets or organically grown food. In Norway, the generic term for 'organic food' includes food produced at farms following the basic certification requirements as well as farms practicing biological

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dynamic agriculture. Debio is the Norwegian certification body administering the label 'Ø' for organic food, which is combined with the international label 'Demeter' in the case of bio-dynamic food [7]. The interest for and reported use of organically grown food in the diet has increased in the general public in Norway during the last decade, with women reporting a higher interest than men (25%, as compared to 16%) [8]. It is known from a number of previous studies that health is a main motivation for choosing organic food [9,10]. The expected beneficial health effects of eating organic food during pregnancy include avoiding the possible risks of exposing the developing foetus to synthetic pesticides [11]. On the other hand, higher risks of contamination from mycotoxins, heavy metals and enteric pathogens that could complicate pregnancy have frequently been ascribed to organic production methods, although studies have shown less fusarium mycotoxin contamination [12,13] and lower risk of salmonella and E. coli [14,15] in organic than in conventional foods. Furthermore, higher levels of beneficial substances such as bioactive compounds in plant foods [16,17] and polyunsaturated fatty acids, such as omega-3 and CLA [18] in milk - also found in higher levels in breast milk of lactating women who had eaten organic dairy and/or meat products [19] may be associated with health benefits. A review of literature published in the period from 1958 to 2008 concluded, based on 55 studies, that there is no evidence of a difference in nutrient quality between organically and conventionally produced foodstuffs of relevance to health [20]. Another review by the same authors concluded, based on 12 studies from the same time period, that there is currently no evidence of a health benefit from consuming organic compared to conventionally produced foodstuffs [21]. While the first of these reviews has been criticised for omitting relevant research due to inaccurate selection criteria [22], there seem to be consensus that there is need for further and more detailed studies to investigate possible health effects of eating organic food.

The possible associations between eating organic food and other lifestyle factors and health behavior are not well-described. Information about the prevalence of use of organically grown food within sub-groups of the population is lacking. Such knowledge is important to obtain, especially in critical life phases such as pregnancy, as maternal diet, and possibly also organic food consumption, may have long-term implications for health of the offspring [1,2]. Very few investigations have been conducted concerning the health effects or safety of organic food and no studies have evaluated this in a pregnant human population. The Norwegian Mother and Child Cohort Study (MoBa), a nation wide prospective pregnancy cohort that since 2002 has asked pregnant women about their frequency of organic food use, provides a unique possibility to explore background characteristics and lifestyle behaviors associated with the consumption of organic food during pregnancy. In MoBa we also plan to investigate dietary habits among organic food consumers and to examine potential diet-health relationships related to organic food consumption during pregnancy. To the best of our knowledge, this is the first study to report the use of organic food among pregnant women in relation to a wide range of personal and socio-demographic characteristics.

Compared to other European countries, the development of the organic food market in Norway has been slow [23] and for several decades, organic food had a marginal position outside of the conventional food market [24]. During the last 10-15 years, however, organic products have slowly been introduced into the Norwegian general food market, and sales have grown rapidly in the last few years parallel with an increase in the number of food items certified as organic, particularly since 2005 [25].

Given the close relation between consumers' choice of organic food and their focus on health, as well as the particular relevance of health during pregnancy, the aim of this study was to examine associations between frequent consumption of organic food during pregnancy and health behaviors, socio-economic and demographic characteristics. Could it be that women eating organic food during pregnancy live particularly healthy? Or, on the other hand, could it be that the choice of organic food during pregnancy is associated with lifestyle patterns which are contrary to public advice and knowledge about diet and health relationships?

Methods

Subjects and Methods

The data set is part of the MoBa study, initiated by and maintained at the Norwegian Institute of Public Health, and this study is presently the largest pregnancy cohort in the world with 107 000 pregnancies included since 1999 [26]. Pregnant women were recruited to the study by postal invitation after they had signed up for the routine ultrasound examination in their local hospital. The participation rate was about 43% [26]. The women were asked to provide biological samples and to answer questionnaires covering a wide range of information. The cohort database is linked to the Medical Birth Registry of Norway and other national health registries. The MoBa study has been approved by the Regional Committee for Ethics in Medical Research and the Data Inspectorate in Norway.

Subjects

This study uses version 4 of the data files made available for research in January 2009. To be included in the present study, the women had to have responded to the general questionnaire at gestational week 15 and to the MoBa food frequency questionnaire (FFQ) at weeks 17-22. In addition, participants had to have answered at least one of the 6 questions about organic food, and have a reported daily energy intake >4.5MJ or <20 MJ [27]. We only used data from the first time participation for women who had been included in the MoBa more than once because of multiple pregnancies. This resulted in a sample of 63,808 women. From this sample, we excluded 250 women who had missing values on age (n = 4) or urban/rural living (n = 246) due to the small numbers, resulting in a final study sample of 63,561.

The MoBa food frequency questionnaire

The MoBa FFQ http://www.fhi.no/dokumenter/011fbd699d.pdf is a semi-quantitative food frequency questionnaire designed specifically for assessing diet during the first four months of pregnancy, when the fetus is most vulnerable [3]. The FFQ is described in detail elsewhere [27]. Data has been collected from February 2002 and onwards. The questionnaire has 40 categories of questions covering the daily intake of 255 specific food items and dietary profile such as vegetarian, vegan or partly vegetarian and use of organic food in six main food groups (milk/dairy, bread/cereal, eggs, vegetables, fruit and meat).

Outcome variable

The use of organic food was calculated as a sum index based on the question about the frequency of use of organic food specified in six food groups: milk and dairy products, bread and cereal products, eggs, vegetables, fruit and meat. The alternative answers for use of organic food were: 'never or seldom', 'sometimes', 'often', or 'mostly' and were given values from 0-3. For those who had answered at least one of the questions about organic food, missing values for one or more of the other questions were interpreted as 'seldom or never'. The sum index reflects organic food consumption on a scale ranging from 0 to 18, with 0 representing no use of organic food and 18 representing "mostly" organic for all six food groups. Due to inconstancy between the reported dietary profile (vegetarian) and food intakes in the FFQ, we defined 'vegetarian' as having no intake of meat and fish based on the actual food intake. All respondents reported consumption of bread/cereal products and fruit. However, for respondents who had no reported intake of meat (n = 361), eggs (n = 1462), milk/dairy (n = 718) or vegetables (7) and who had not reported organic consumption of the corresponding food group, we upscaled the sum index by multiplying with 6/5 for each omitted food category. This resulted in the upscaling of 817 subjects and included not only vegetarians, but also individuals who avoided relevant food groups due to for instance allergy.

We defined frequent organic consumption as having a sum index of >6, which corresponds to at least one organic food answer in the "often" category. The upscaling resulted in allocation of 48 respondents into the 'frequent organic' consumption group, of which three were vegetarians.

Other variables

From the MoBa FFQ, we included the following dietary variables: The inclusion of meat or fish in the diet or a vegetarian diet, and alcohol consumption (yes/no). The variable for vegetarian diet in this study comprises vegans, lacto-vegetarians and lacto-ovo-vegetarians.

From the general questionnaire we included the participant's age, pre-pregnancy body mass index (BMI), smoking, exercise, level of education, the participant or her partner being a student, household income, and year of participation in MoBa. Age was divided into six categories (<20, 20-24, 25-29, 30-34, 35-39, 40+ years). BMI was calculated from self-reported height and pre-pregnant weight and categorized according to the WHO classification as normal (18.5-24.9 kg/m^2), underweight (≤18.5 kg/m^2), overweight (25.0-29.9 kg/m^2), obese grade 1 (30.0 - 34.9 kg/m^2) or obese grade 2 (≥35.0 kg/m^2). Smoking during pregnancy was divided into three categories (daily smokers, occasional smokers and non-smokers). Exercise during pregnancy was based on respondents' reports of their participation in 13 different types of recreational exercise and divided into four categories (no exercise, less than once weekly, 1-2 times weekly and 3+ times weekly). Education was divided into three categories: high school or less (≤12 years), 3-4 years of college/university (13-16 years) or four or more years of college/university education (17+ years). Being a student (yes/no) was included for both the participant and her partner. Household income was measured as a combination of the participant's and her partner's income (both <300 000 NOK, one ≥300 000 NOK, or both ≥300 000 NOK). Urban or rural living area was explored using several variables: 1) an urban/rural variable based on 35 selected urban municipalities with >20,000 inhabitants and city status, 2) a variable based on 32 selected rural municipalities with a special focus on organic food, and 3) a variable indicating geographic location of a municipality in relation to urban settlements of various sizes, according to definitions obtained from Statistics Norway [28].

Statistical analyses

We used polychoric correlation to examine organic consumption among all food groups. The differences in organic food consumption between categories of maternal characteristics were tested using chi-square, and p value of <0.05 were considered to indicate statistical significance. We used linear binomial regression, with frequent use of organic food (sum index >6) as the binomial outcome variable. This analysis provides information about the risk difference (RD) between being in the frequent organic intake group or not, given various personal, socio-economic and lifestyle characteristics as covariates. Linear rather than logistic regression was preferred because the risk estimates for various constellations of covariates may be directly interpreted from the adjusted model as prevalence at reference category +/- the risk difference for any given characteristic/covariate, e.g. year 2005, age 35-39 etc. The model was checked by repeating the analysis using linear regression with the sum index as a continuous outcome variable, and comparable results were obtained (not shown).

A total of 13,174 (20.7%) women had missing values on one or more of the covariates. Participants with missing data on a variable are often categorized in a "missing" category to avoid exclusion of incomplete cases. This may, however, introduce bias. We therefore performed the linear binomial analysis in the full sample (n = 63,561) as well as in complete cases only (50,387) to examine the influence of including incomplete cases. The results were almost identical and we chose to present results for the full sample.

All analyses were performed using the statistical software PASW statistics 17 (SPSS Inc., IBM Company, Chicago, Ill., USA), except the polychoric correlation analysis which was performed in Stata version 11 (Stata Corp, Texas 77845 USA).

Results

Eggs and vegetables were the food categories that most respondents reported to use 'often' or 'mostly' organic, while few women reported consumption of organic meat. Across all food categories, the 'never/seldom' organic was the dominant answer, ranging from 65.4% for vegetables to 88.7% for meat, while the most frequent organic user group was small, ranging from 1.0% for meat to 3.5% for eggs. A total of 3376 (6.7%) women reported 'mostly' organic consumption for at least one of the six food groups (Table 1). There was a high correlation between organic food consumption across the food groups, with vegetables and fruits being most strongly correlated with each other and with the sum index (Table 2).

When summing the reported use of organic food across the six food groups, 1.9% of the women reached a sum index of 13 to 18, 7.2% had a sum index of 7 to 12, 39.2% had a sum index of 1 to 6 and 51.7% a sum index of 0, indicating that they had answered never or seldom to all organic food categories. In the further analysis we chose to define frequent organic consumption as having a sum index >6, which corresponds to reported consumption of at least one organic food group in the 'often' category. This resulted in 5754 (9.1%) frequent organic consumers (Table 3). There was a strong effect of age on frequent organic food consumption; among 30-34 year old there were 8.1% frequent consumers, compared to 28% among <20 year old, a crude difference of 20 percentage points (pp). The adjusted difference from the model was 15.6 pp (Table 3).

Higher prevalence of frequent organic use was also found among women in the underweight and normal weight BMI categories. The largest difference in use of organic food was found for eating a vegetarian diet (RD = 23.1 pp.), while only a very low share of participants were vegetarians (0.2%) (Table 3).

Overall, 91.6% of the women in this study were non smokers and 88.4% abandoned alcohol completely during pregnancy. However, among smokers and among women who consumed alcohol during pregnancy, there was a higher prevalence of frequent organic use. Further, physical activity three times a week or more was associated with a higher prevalence of organic food consumption (Table 3).

With regard to education, there was a two-sided trend with more frequent organic food consumption among those with 12 years or less or 17 years or more, while it

Table 1 Self reported organic consumption of six main food categories§.

	'Never/ seldom' (Value 0) % answered	'Sometimes' (Value 1) % answered	'Often' (Value 2) % answered	'Mostly' (Value 3) % answered
Milk/dairy	74.5	18.3	4.6	2.5
Bread/ cereal	80.0	13.7	3.7	2.6
Eggs	66.2	24.2	5.7	3.4
Vegetables	65.4	27.2	5.6	1.7
Fruit	71.7	21.7	4.7	1.8
Meat	88.0	7.8	3.1	1.1
Any	92.8	44.9	13.6	7.0

§Percentage reported use within each food category. N = 63,561 pregnant women in the Norwegian Mother and Child Cohort Study 2002-2007

Table 2 Polychoric correlation between the reported use of organic food categories (n = 63,561)

	Milk/ dairy	Bread/ cereal	Eggs	Vegetables	Fruits	Meat	Sum index§
Milk/dairy	1	0.79	0.68	0.73	0.72	0.74	0.76
Bread/ cereal		1	0.65	0.75	0.79	0.81	0.78
Eggs			1	0.74	0.70	0.65	0.73
Vegetables				1	0.92	0.78	0.82
Fruit					1	0.82	0.82
Meat						1	0.73

§Sum index is the summation of reported use across all food categories

Table 3 Association between socio-economic, personal and lifestyle factors and frequent consumption of organic food.

		Unadjusted model				Adjusted model§
			SumIndex >6	*P-value**	RD*100	(95% CI)
	Total n 63,561	**n**	**%**			
Total			9.1			
Prevalence at ref. category					7.8	
Age				*<0.001*		
<20	854	239	28		**15.6**	**(12.6,18.7)**
20-24	7745	996	12.9		**3.0**	**(2.1, 3.8)**
25-29	22689	1820	8.0		-0.5	(0.9, 0.0)
30-34	22925	1866	8.1		0	
35-39	8306	715	8.6		0.3	(-0.4, 0.9)
40 +	1042	118	11.3		**2.6**	**(0.7, 4.5)**
Prepregnant BMI				*<0.001*		
<18.5	1825	226	12.4		**1.8**	**(0.4, 3.3)**
18.5-24.9	40519	3795	9.4		0	
25-29.9	13547	1102	8.1		**-0.9**	**(-1.4, -0.4)**
30-34.9	4355	314	7.2		**-1.8**	**(-2.5, -1.1)**
35+	1645	128	7.8		**-1.5**	**(-2.7, -0.3)**
Missing	1670	189	11.3		**1.0**	(-0.5, 2.5)
Dietary habits				*<0.001*		
Meat/fish	63449	5716	9.0		0	
Vegetarian	112	38	33.9		**23.1**	**(14.4, 31.8)**
Alcohol in pregnancy				*0.59*		
No	56182	5072	9.0		0	
Yes	7379	682	9.2		**0.7**	**(0.0, 1.4)**
Smoking in pregnancy				*<0.001*		
No smoking	58241	5116	8.8		0	
Occasionally	1812	218	12.0		**2.0**	**(0.6, 3.4)**
Daily	3508	420	12.0		**1.5**	**(0.5, 2.6)**
Exercise in pregnancy				*<0.001*		
No	9166	756	8.2		0	
Less than weekly	12317	888	7.2		-0.5	(-1.1, 0.2)
1-2 times weekly	18734	1538	8.2		0.4	(-0.3, 1.0)
3+ times weekly	17992	1956	10.9		**2.5**	**(1.8, 3.2)**
Missing	5352	616	11.5		**2.6**	**(1.7, 3.6)**
Education				*<0.001*		
<10 y-12 y	20398	2252	11.0		**0**	
13-16 y	26462	1822	6.9		**-2.5**	**(-3.0, -1.9)**
17+	15319	1534	10.0		-0.1	(-0.7, 0.6)
Missing	1382	146	10.6		-0.2	(-1.8, 1.4)
Student, participant				*<0.001*		
No	57279	4928	8.6		0	
Yes	6282	826	13.1		**1.9**	**(1.1, 2.8)**
Student, participant's partner				*<0.001*		
No	60296	5342	8.9		0	
Yes	3265	412	12.6		**1.7**	**(0.6, 2.9)**
Household income				*<0.001*		
Low (both <NOK 300 000)	17324	1861	10.7		0	
Medium (one ≥NOK 300 000)	24357	1947	8.0		**-1.6**	**(-2.1, -1.0)**
High (both ≥NOK 300 000)	16561	1268	7.7		**-2.3**	**(-2.9, -1.6)**
Missing	5319	677	12.7		**1.0**	(-0.0, 1.9)

Table 3 Association between socio-economic, personal and lifestyle factors and frequent consumption of organic food. *(Continued)*

Year of participation				*<0.001*		
2002	8768	679	7.7		0	
2003	10834	855	7.9		0.3	(-0.4, 1.0)
2004	10717	834	7.8		0.4	(-0.3, 1.1)
2005	12369	1135	9.2		**1.5**	**(0.8, 2.2)**
2006	11030	1097	9.9		**2.3**	**(1.6, 3.1)**
2007	8562	993	11.6		**4.1**	**(3.3, 5.0)**
Missing	1281	161	12.6		**3.6**	**(1.7, 5.4)**
Living area				*<0.001*		
Rural	31070	2675	8.6		0	
Urban	32491	3079	9.5		0.6	**(0.1, 1.0)**

§ Linear binomial model. Prevalence at reference category shows the constant term which equals expected use of organic food with medium or high frequency (Sum index >6) when all covariates are zero.

The table shows risk differences × 100 (with 95% confidence interval) for frequent consumption of organic food. Zero values are the reference categories.

*P for trend across characteristic categories (Chi square).

was lower in the middle category. There was a higher likelihood of frequent organic consumption in households where the participant and/or her partner were students, and in households with low income. The likelihood of frequent organic consumption was in fact inversely correlated with higher income (Table 3).

Participation in MoBa at later years (2005 or later) was associated with frequent use of organic food. This was also the case for those living in urban areas. When using a four-level variable for living area, based on traveling distance to nearest town or city, the largest share of women with frequent use of organic food was found in the most central areas (9.4%), followed by the least central municipalities (8.6%). The lowest prevalence of frequent organic consumption was in the middle-category municipalities (8.0% and 8.4% in less or quite central municipalities respectively) (data not shown in table).

By combining the risk differences for the variables in the model we theoretically estimated that the group with the highest propensity to have a frequent intake of organic food were women <20 years of age, having BMI < 18.5, adhering to a vegetarian diet, consuming alcohol and smoking occasionally during pregnancy, exercising three times a week or more, having attained less than 13 years of education, being a student and having a partner who is a student, having low household income (both the participant and her partner earned <300 000 NOK), participating in MoBa in year 2007, and living in an urban area. The estimated prevalence of a frequent intake of organic food for this group was 61.8% (prevalence at reference category + risk difference for the relevant values of all the variables in the model). In the same way we estimated the prevalence in the group with the lowest propensity to have frequent intake of organic food to be 0.2%.

Discussion

The main finding of this study was that no single "healthy lifestyle" orientation could be identified among the women who reported frequent use of organic food. The frequent use of organic food was associated with lower and higher age groups, lower BMI, a vegetarian diet, cigarette smoking and use of alcohol during pregnancy, regular exercise, lower and higher levels of education, the participant and/or her partner being a student, low household income, urban living area, and participation in MoBa between 2005 and 2007. The associations between socio-demographic and lifestyle variables and eating organic food reflect complexity and indicate that no quick label like "young and idealistic" or "well educated and wealthy" can be applied to describe women who report frequent intake of organic food during pregnancy. Some previous studies also reported that use of organic food is quite widely distributed across socio-economic groups and associated with various types of motivation [10,29], while others, particularly within the marketing tradition, have identified consumer segments in the market with a high likelihood to buy organic food such as "the engaged", "the eco-healthy", or "the practical green" etc. [30].

The strength of this study is the large sample of pregnant women with participants from both urban and rural regions, representing all age groups and all socioeconomic groups. The participation rate in MoBa is 43% and the prevalence of organic consumption may not be representative for all pregnant women in Norway [26]. However, this is not likely to influence the associations between reported use of organic food and characteristics of the respondents. The potential bias due to self-selection in MoBa was recently evaluated by Nilsen et al., 2009. No statistically relative differences in association measures were found between participants and the total population regarding eight exposure-outcome associations evaluated [31].

In the present study we examined the associations between participant characteristics and frequent organic consumption with and without women having missing data on participant characteristics. Covariates with missing data were BMI (2.6%), exercise (8.4%), education (2.2%), income (8.4%), and year of participation (2.0%). The numbers of missing values were higher in year 2002, in the youngest age group, among women with low education, among smokers, and among frequent organic food consumers. Including missing as separate categories in a regression is a simple method of dealing with missing values compared to the more correct but also more complex method of multiple imputations. Including missing in a regression will, contrary to popular belief, increase bias from confounding, but will reduce bias from possible heterogeneity of effects (interaction) between responders and non-responders/missing. It will also increase sample size and thereby power. The results from models with and without missing included were similar in our data, indicating that neither confounding nor heterogeneous effects played a strong role here.

The sum index provides a robust indicator of the consumption of a variety of the main organic food groups in the diet, appropriate for the explorative aim in this study. The sum index attributes equal importance to each food category and thus some detail may have been lost. The categories are dissimilar with regard to number of items within the category (e.g. 'eggs' containing only one item while 'fruit' and 'vegetables' contain numerous items). Eating 'mostly organic' vegetables is a more extensive practice than eating 'mostly organic' eggs. A related, but different challenge is that we do not know a respondents total variety of consumption within each category, e.g. whether 'mostly organic fruit' refers to only apples - or a whole range of different fruits. However, the high correlation between organic consumption within the six food groups supports the viability of using a sum index in this study (Table 2).

Eating a vegetarian diet was the characteristic which was most strongly associated with frequent consumption of organic food during pregnancy. Even though the total number of vegetarians among the MoBa-participants was low (0.2%), this was the single most predictive factor among all variables in the analysis, with 23.1 percentage points higher prevalence of frequent organic use among vegetarians than among non-vegetarians (Table 3). This reinforces earlier findings of an association between eating organic food and a vegetarian diet [32,33]. Frequent use of organic food and eating a vegetarian diet may well be part of a healthy lifestyle, as a vegetarian diet has been associated with many health benefits such as lower risk of heart disease and type 2 diabetes [34-37]. Further associations between eating a vegetarian diet and the general dietary quality among the women with a frequent consumption of organic food will be published in a separate paper. Well-planned vegetarian diets are considered appropriate for individuals in all life-phases, including pregnancy [34]. Lower levels of BMI have been reported among vegetarians in various populations [35,37], and also among consumers of organic food in a study of soy consumers and non-soy consumers in Minnesota, USA [38].

Participation in regular exercise and being underweight or normal weight were also associated with being a frequent organic consumer. Being physically active is an important contributor to a healthy lifestyle in the general population as well as among pregnant women, and is strongly inversely related to excessive body mass [39-41].

Entering pregnancy with a normal weight is beneficial with regard to pregnancy complications and health outcomes for both the mother and the child. Maternal obesity is a risk factor for all major pregnancy complications, which have increased in prevalence in later years [42], including gestational diabetes, pre-eclampsia, foetal overgrowth, preterm births, and cesarean delivery [42-45]. Being underweight, on the other hand, is also associated with unfavorable birth outcomes such as preterm birth and low birth weight, while overall, the outcome is favorable and several adverse outcomes are less common in this group of women [46]. We plan to further investigate dietary habits among organic food consumers and to examine potential diet-health relationships related to organic food consumption during pregnancy. It would also be interesting to further investigate subgroups within the population, as the characteristics associated with frequent organic consumption in the present study have also been related to a higher prevalence of eating disorders, such as adhering to a vegetarian diet [47], exercising more than three times per week, older age and being a student [48].

It is well established that both cigarette smoking and alcohol consumption during pregnancy is associated with increased risk of adverse health outcomes for the fetus, and consequently health authorities in many countries, including Norway recommend that pregnant women and those trying for a baby should totally avoid alcohol and smoking [49]. In this study we found a higher prevalence of smokers among women with frequent consumption of organic food. If the use of organic food is motivated by perceived health benefits, this finding may appear surprising. However, sociological studies of health behavior have indicated that the associations between them are complex. In a Finish study, an attempt to construct 'health indices' based on all relevant factors associated with good health proved difficult, and even though there were clear associations between health behaviors, their distribution into different combinations were quite diverse [50,51]. Smoking has been shown to be central in the interplay between health behaviors, and the majority of smokers had either only smoked or had one additional unhealthy habit [51].

Our finding of a higher prevalence of cigarette smoking among women with a frequent consumption of organic food is contrary to a European multi-country study that reported less maternal smoking during pregnancy and current smoking in families with anthroposophic lifestyle (having children at Waldorf schools, eating organic/biodynamic food and/or living at farms practicing Biodynamic farming) compared to reference families [52,53], while a Swedish study reported equal prevalence of parental smoking in families with anthroposophic lifestyle vs. reference families [54]. In the present study, however, consumers of all types of organic food are included, and we have not looked at respondents adhering to an anthroposophic lifestyle in particular.

We found a two-sided trend between frequent use of organic food both in regard to age and education, with the highest and lowest age and education groups being more likely to be frequent organic consumers than the middle groups. Next to eating a vegetarian diet, being in the lowest age group (<20 years) represented the highest likelihood for being a frequent organic consumer, with 15.6 percentage points higher prevalence than in the reference group (30-34 years). The present study has a smaller age range than studies in the general population as only pregnant women were included. Studies in the general population have also reported diverging results related to age, some finding that younger age (see for example [55-58]) and others that older age [59] was associated with a higher propensity to buy organic food, while some reported no difference with regard to age [29]. It has been suggested that there may be a pattern whereby there are higher shares of younger consumers among early adopters in developing markets, while older consumers are in higher numbers in more mature markets [60]. In Denmark and Great Britain, both being mature markets for organic food, the highest likelihood of buying organic food was found in households with middle-aged. In Great Britain the likelihood was lower in both the younger and older groups, while in Denmark it generally increased with age, but with a peak for the age group 40-49 years [61]. The Norwegian market for organic food is not by far as mature as the British or Danish, even though it has developed quite rapidly during the last decade. It might be that we see a combination of young new-comers and women who have longer experience with eating organic food.

Household economy could be expected to be crucial for the level of organic consumption given the fact that these products generally are more expensive. However, our finding of an inverse relation between household income and frequency of organic consumption indicate a complexity beyond economic ability alone, and that other factors are more decisive for the likelihood of eating organic food. Higher levels of education, on the other hand, were associated with a higher likelihood of eating organic food compared with middle-levels of education, and so was being a student - even in the older age groups. Both education and income are strongly associated with better health in population studies. Our finding of lower household income may therefore be interpreted as an indicator of vulnerability with regard to health, while higher levels of education - particularly with increasing age, provides for robustness. The combination of higher education and lower income among the frequent consumers of organic food may point to a different value-orientation in this group.

Previous Norwegian surveys have reported higher levels of education among consumers with more frequent use of organic food and food produced without use of pesticides [29,59,62], while a regional survey did not find any association between length of education and likelihood of buying organic food [63]. Studies from other countries have also reported differing results regarding respondents' level of education and use of organic food [30,57,64,65]. Higher income was associated with a higher likelihood of buying organic food in one Norwegian study [63], while no difference with regard to income was reported in another [29]. A study of consumption of organic food in Denmark and Great Britain reported an increased propensity to buy organic food with higher 'social group', a composite indicator of educational level and income. However, in both countries, the highest propensity to buy organic food was found for the middle class households, while it was actually lower for the upper middle class [61]. Another Danish study also found that income explained very little of the purchasing behavior related to organic food [30].

Taken together, the lifestyle- and socio-economic characteristics of the frequent organic food consumers in the present study point to a complex phenomenon, involving diverse groups of women which go beyond narrowly defined 'consumer segments'. Some of the characteristics, such as regular exercise, lower BMI, and - in part - higher education indicate robustness with regard to a healthy lifestyle, while other characteristics, such as cigarette smoking and use of alcohol, and - in part - lower levels of education, may indicate vulnerability with regard to health of mother and child.

Our finding of a higher prevalence of frequent organic users in urban areas, is contrary to previous Norwegian studies that reported no difference between urban and rural areas [29,63], but in line with results from Denmark and Great Britain [60,66]. Further, our more nuanced finding that the highest level of organic consumption in the urban areas was followed by the most rural areas, with the lowest consumption in the two middle categories, is supported by other findings [67], and may be related to the possible 'idealistic' nature of organic consumption. Codron et al (2006) describe that a typical development for radical movements, such as those associated with organic food, is that when these products first enter the market, buyers are typically either local rural consumers, or urban consumers with higher income levels, including members of consumer associations and politically active movements sharing these values. In later phases, the constellations may change. These suggested lines of development may be relevant for Norway, where the market situation may still be described as not having reached maturity with regard to organic food - and we do find the highest levels of consumption among the contrasting groups: either urban or rural.

Conclusions

Our results indicated that frequent use of organic food is a practice that is adopted among pregnant women across various 'groups' referring to the personal, lifestyle and socio-demographic variables investigated. This fits well with earlier observations that the consumption of organic food in the general Norwegian population has not been limited to special sub-groups, but rather quite widely distributed across socio-economic groups.

We did find certain characteristics to be more common among the frequent organic food consumers, but these characteristics were diverse and not necessarily associated with a healthy lifestyle. Lower levels of education and income as well as smoking and use of alcohol in pregnancy were less favorable factors in relation to health in our cohort. On the other hand, being lean and doing regular exercise are in line with health recommendations. A vegetarian diet may well be part of a healthy lifestyle. In conclusion, we found that in our material associations between socio-demographic and lifestyle variables and eating organic food were complex and could not be reduced to one single 'healthy lifestyle' orientation. However, given the relatively short period of time that organic food has been available to the majority of people in Norway, patterns of organic food consumption may keep changing as the market grows more mature. Characteristics of pregnant women who eat organic food may then change, possibly making differences between socio-demographic groups and the association to the different lifestyle factors more easily discernable. A methodological implication of the results is that personal and socio-economic characteristics should be regarded as important covariates in future studies of potential health outcomes related to organic food consumption during pregnancy.

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Authors' contributions

HMM initiated and was PI of the study. HT and HMM designed the study. HT performed the statistical analysis assisted by HS, ALB and MH. HT wrote the manuscript. ALB, GL, GR, MH and GHO participated in the design of the study and contributed to the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Paper II

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Some of the numbers used in the text to refer to tables are incorrect:

Page 5: References to Table 2 should be Table 1.

Page 6, 7, and 10: References to Table 3 should be Table 2.

Page 3, 8 and 10: References to Table 1 should be Table 3.

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RESEARCH ARTICLE Open Access

Food patterns and dietary quality associated with organic food consumption during pregnancy; data from a large cohort of pregnant women in Norway

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Abstract

Background: Little is known about the consumption of organic food during pregnancy. The aim of this study was to describe dietary characteristics associated with frequent consumption of organic food among pregnant women participating in the Norwegian Mother and Child Cohort Study (MoBa).

Methods: The present study includes 63 808 women who during the years 2002–2007 answered two questionnaires, a general health questionnaire at gestational weeks 15 and a food frequency questionnaire at weeks 17-22. The exploration of food patterns by Principal component analyses (PCA) was followed by ANOVA analyses investigating how these food patterns as well as intake of selected food groups were associated with consumption of organic food.

Results: The first principal component (PC1) identified by PCA, accounting for 12% of the variation, was interpreted as a 'health and sustainability component', with high positive loadings for vegetables, fruit and berries, cooking oil, whole grain bread and cereal products and negative loadings for meat, including processed meat, white bread, and cakes and sweets. Frequent consumption of organic food, which was reported among 9.1% of participants ($n = 5786$), was associated with increased scores on the 'health and sustainability component' ($p < 0.001$). The increase in score represented approximately 1/10 of the total variation and was independent of sociodemographic and lifestyle characteristics. Participants with frequent consumption of organic food had a diet with higher density of fiber and most nutrients such as folate, beta-carotene and vitamin C, and lower density of sodium compared to participants with no or low organic consumption.

Conclusion: The present study showed that pregnant Norwegian women reporting frequent consumption of organically produced food had dietary pattern and quality more in line with public advice for healthy and sustainable diets. A methodological implication is that the overall diet needs to be included in future studies of potential health outcomes related to consumption of organic food during pregnancy.

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Background

The essential importance of dietary quality during pregnancy for the health of mother and child is continuously becoming clearer, and there is growing evidence that maternal diet may influence longer-term health of their children even within relatively well-nourished populations [1-3].

Dietary composition, the kinds of foods that are eaten and their relative amounts, is together with the nutritional quality of food decisive for the impact of the diet on health. Organic production methods are generally claimed to enhance food quality, and research indicating superior quality of organically produced food include findings of higher levels of vitamins, antioxidants [4,5], poly-unsaturated fatty acids [6], and lower levels of heavy metals [7], mycotoxins [8] and pesticide residues [9,10] in a range of crops and/or milk. This matter is far from settled, however, and Dangour et al. [11] suggest, based on a review, that there is not sufficient evidence to draw conclusions about major differences in nutritional quality between organically and conventionally produced food.

In studies from Great Britain, Denmark and Norway, Denver et al. [12], Holt [13] and Torjusen et al. [14] have found associations between the choice of organically produced food and dietary patterns high in fruit and vegetables and low in meat compared to intake levels among consumers who did not buy organic food. It is known from a number of studies that health is a main motivation for choosing organic foods, together with ethical and environmental considerations [15,16]. Since there is a considerable overlap between dietary recommendations aiming for good health and those aiming for environmental sustainability [17], it is possible to theorize that the choice of organic food for both of these reasons may be accompanied by dietary patterns more in line with health recommendations.

Variation in dietary patterns has been described among pregnant women in several populations, including Norway [18-20]. However, there is little knowledge about the diets of women who choose organically grown food during pregnancy. Given the possibility that the choice of organic food may be related to dietary characteristics of relevance to health, and the particular importance of health during pregnancy, it is important to gain more knowledge about this issue. The Norwegian Mother and Child Cohort Study (MoBa), which is a nation-wide pregnancy cohort [21], includes questions about the frequency of organic food consumption, and thus provides an opportunity to explore possible associations between consumption of organically produced food and dietary composition. We have previously reported socio-economic and lifestyle characteristics associated with frequent consumption of organic food among the MoBa participants. The socioeconomic characteristics of pregnant women with frequent organic consumption did not unambiguously follow those typically associated with better health, such as higher education and income [22]. We also plan to investigate potential diet-health relationships related to consumption of organic food.

The aim of the present study was to examine associations between frequent consumption of organically produced food and the overall dietary patterns, food intake and nutrient density of pregnant women in MoBa. In particular, we wanted to investigate whether there were significant differences in dietary patterns between women who frequently ate organic food during pregnancy and those who seldom or never ate organic food. Furthermore, we wanted to investigate whether there were significant differences between consumption of organic food of different food categories (milk/dairy, bread/cereal, eggs, vegetables, fruit and meat) and diet in general.

Methods

Subjects and methods

The data set is part of the MoBa study, which is initiated by and maintained at the Norwegian Institute of Public Health. The cohort now includes 108 000 children, 90 700 mothers and 71 500 fathers [21]. Pregnant women were recruited to the study by postal invitation after they had signed up for the routine ultrasound examination in their local hospital [21]. A total of 38.5% of invited women participated in the study. The women were asked to provide biological samples and to answer questionnaires covering a wide range of information. The cohort database is linked to the Medical Birth Registry of Norway [23]. The MoBa study has been approved by the Regional Committee for Ethics in Medical Research and the Data Inspectorate in Norway, and informed written consent was obtained from all participants.

Subjects

This study uses version 4 of the data files made available for research in January 2009. We only included the first participation for women who were in MoBa with more than one pregnancy. The source population for the present study comprised 65,563 women who had responded to the general questionnaire asking about socio-demographic, health and lifestyle information (week 15) and the MoBa food frequency questionnaire (FFQ) (weeks 17-22). In addition, participants had to have answered at least one of the 6 questions about organic food (n = 690 excluded), and they had to have reported a credible daily energy intake (>4.5 MJ or <20 MJ) (n = 1065 excluded). This resulted in a sample of 63 808 women (97.3%).

The MoBa food frequency questionnaire

The MoBa FFQ (http://www.fhi.no/dokumenter/011fbd699d.pdf) is a semi-quantitative food frequency questionnaire designed to capture dietary habits during the first four to five months of pregnancy and has been described in detail elsewhere [24]. Data were collected from February 2002 and onwards. The questionnaire has 40 groups of questions covering the daily intake of 255 specific food items as well as use of organic food in six main food groups (milk/dairy, bread/cereal, eggs, vegetables, fruit and meat).

Food groups

Based on reported daily intake of 255 specific food items, we selected 58 as well as 28 more aggregated food groups (non-overlapping) for identification of dietary patterns. The interrelations between food groups in the PCA plots were more or less similar independent of which set of food groups that was used as input variables, and the PCA plot with 58 food groups, providing more detail, is only shown in supplemental material. Additional file 1: Table S1 shows the relation between the two sets of food groups, and Additional file 2: Table S2 gives further details of the food items included in the food groups.

Food groups were selected based on significance regarding the quantity and quality of food as well as ability to distinguish between different types of diets. Some food items were not included for their nutritional relevance, but rather as a marker of certain types of foods/diets, for example ketchup as a marker for fast food, soy products as a marker for alternative diets and rice porridge as a marker of traditional foods. Not all of the 225 food items were included in the food groups used in this study, only those judged as relevant according to the above mentioned criteria (186 food groups).

Consumption of organic food

As in the previous study of organic food consumption in MoBa, the use of organic food was calculated as a sum index based on the question about the frequency of use of organic food specified in six food groups: milk and dairy products, bread and cereal products, egg, vegetables, fruit and meat [22]. The response alternatives for use of organic food were:’never or seldom’,’sometimes’,’often’, or’mostly’ and were given values from 0-3. For those who had answered at least one of the questions about organic food, missing values for one or more of the other questions were interpreted as ‘seldom or never’. The sum index reflects organic food use on a scale ranging from 0 to 18, with 0 representing no use of organic food and 18 representing ‘mostly’ organic for all six food groups. For respondents who had no reported intake of meat (n = 450), eggs (n = 1976), milk/dairy (n = 979) or vegetables (n = 11) and who had not reported organic consumption of the corresponding food group, we upscaled the sum index by multiplying with 6/5 for each omitted food category (additively). This resulted in the upscaling of 1066 subjects, and the re-allocation of 63 respondents into a ‘frequent organic’ consumption group. We defined frequent organic consumption as having a sum index of >6, which corresponds to having reported eating organic food ‘often’ for at least one of the six food categories, given that the answer to all other categories was "sometimes". Consumption of organic food was operationalised in the analyses as ‘no or low’ vs. ‘frequent’ total consumption of organic food (sum index ≤6 vs. >6) and as ‘low’ vs. ‘high’ consumption of the individual six food groups: milk and dairy products, bread and cereal products, egg, vegetables, fruit and meat. The reported frequencies of the six main organic food groups as well as correlations between them have been reported in detail previously [22].

Statistical analyses

Principal Component Analyses (PCA) were performed to describe the variation in dietary patterns among participants, followed by ANOVA analyses to explore associations between consumption of organic food and dietary patterns (described by the two first principal components) as well as selected foods, beverages and nutrients. The method of first using PCA on the original food consumption data with subsequent ANOVA of the scores to test the effects of the design factors, here: use of organic food, on the scores (PC-ANOVA) is described by Luciano and Næs [25]. We used cross-validation to assess the importance of each component [26]. Since there are many tests in the paper, one should be careful about interpreting each of the values as exact values of significance. This corresponds to the explorative character of the paper with many possibilities tested simultaneously. If wanted, one can look at the Bonferroni p-values, and in for instance Table 1 with 14 different tests for each column, the Bonferroni p-value is equal to 0.0035. As can be seen, there are several values even below that threshold.

In this study we wanted to explore the relative amount of the daily intake of the different food groups reported, and they were therefore transformed into shares (g/day of each food group was divided by total g/day eaten for each respondent). This was done in order to eliminate the effect of some participants eating a lot while others eating less. In other words we concentrate on the pattern of the food categories relative to each other. In this process we decided to eliminate the beverages. The main reason for doing so was that the beverages were very dominating in weight as compared to the other food categories. A person with a high intake of beverages and a

Table 1 Personal, socioeconomic and lifestyle characteristics of the study participants and associations with frequent organic consumption and mean dietary patterns scores (n = 63808)

	All total n	Frequent organic consumption		Mean score PC1[§]	Mean score PC2[§§]
		n	%		
Frequent organic consumption					
No		58022	90.9	-0.07	0.01
Yes		5785	9.1	0.66	0.14
Age					
<20	860	242	28.1	-1.28	-0.24
20-24	7758	998	12.9	-0.73	-0.08
25-29	22760	1829	8.0	-0.11	0.01
30-34	23015	1875	8.1	0.21	0.05
35-39	8358	723	8.7	0.42	-0.04
40 +	1053	118	11.2	0.77	-0.21
Missing data	4				
Prepregnant BMI					
<18.5	1834	226	12.3	0.01	0.02
18.5-24.9	40674	3819	9.4	0.16	0.01
25-29.9	13606	1107	8.1	-0.24	-0.002
30-34.9	4368	315	7.2	-0.48	-0.03
35+	1651	129	7.8	-0.55	0.03
Missing data	1675	190	11.3	0.04	-0.04
Dietary habits					
Meat/fish	63696	5748	9.0	0.00	0.00
Vegetarian	112	38	33.9	2.15	0.93
Alcohol in pregnancy					
No	56391	5101	9.0	-0.04	-0.04
Yes	7417	685	9.2	0.32	0.28
Smoking in pregnancy					
No smoking	58462	5144	8.8	0.09	0.01
Occasionally	1815	219	12.1	-0.54	-0.01
Daily	3531	426	12.0	-1.21	-0.13
Education					
<10y-12 y	20460	2260	11.0	-0.64	-0.13
13-16y	26559	1931	6.9	0.01	-0.03
17+	15401	1548	10.1	0.84	0.22
Missing data	1388	147	10.6	0.01	0.12
Student					
No	57499	4956	8.6	-0.01	0.00
Yes	6309	830	13.2	0.08	0.04
Household income					
Low (both<NOK300 000)	18850	2073	11.0	-0.40	-0.13
Medium (one ≥NOK 300 000)	26456	2137	8.1	-0.05	-0.06
High (both ≥NOK 300 000)	16625	1277	7.7	0.56	0.26
Missing data	1887	299	15.9	-0.25	-0.17

Table 1 Personal, socioeconomic and lifestyle characteristics of the study participants and associations with frequent organic consumption and mean dietary patterns scores (n = 63808) *(Continued)*

Living area					
Rural	31070	2675	8.6	-0.37	-0.22
Urban	32492	3079	9.5	0.35	0.21
Missing data	246	32	13.0	0.52	0.27

§ High scores on PC1 indicate high intake of vegetables, fruit and berries, wholegrain cereal products and cooking oil, low scores on PC1 indicate high intake of meat, white bread, cakes and sweets.
§§ High scores on PC2 indicate high intake of pasta, rice, poultry, olive/cooking oil and vegetables, low scores on PC2 indicate high intake of potatoes, lean fish, margarine, fruit and berries.

person who drink very little, but with a similar intake of the other food categories, would then come out as completely different in the data set. This would be an unwanted effect in our study. In addition we wanted to emphasise the relative importance of each food group rather than emphasising those foods which were eaten in larger amount. We therefore used a standardised analysis (we divided each variable by its standard deviation). It is then important to emphasize that we later on when analysing the different food groups, also incorporated the beverages. In this way the beverages are taken care of, but not in such a way that they damage the overall interpretation of the general food intake pattern.

PCA is a method suitable for explorative aims as it is based on few assumptions. The analysis finds the directions with most variability, and projects the information down onto these dimensions. Results from the PCA are presented in two types of interrelated plots: scores plot and loadings plot. From the loadings plot, relations between variables are interpreted: variables (in our case food groups) which are positioned close to each other are highly correlated, while variables on opposite side of the plot are negatively correlated to each other. From the scores plot we can interpret relations between respondents, e.g. those who eat similar diets and those who eat very differently, as well as which food groups that dominate the diet of a particular respondent. A respondent's score denotes the position in the scores plot, and the position in the scores plot is directly related to the loadings plot: The diet of a respondent who is positioned to the left in the plot is characterised by consumption of food groups to the left in the loadings plot and so on.

Finally, we also performed two sensitivity analyses. First we evaluated the influence of upscaling the sum index of participants who reported no intake of meat, eggs and/or milk/dairy (n = 1066), and second we evaluated the influence of vegetarians (n = 112). Repeating the analysis without these groups resulted in only marginal differences.

PCA analyses were performed using the Unscrambler X version 10.1 (CAMO Software AS, Oslo, Norway). All other analyses were performed using the statistical software PASW statistics 17 (SPSS Inc., IBM Company, Chicago, Ill., USA).

Results

Principal component analyses uncovered relatively large variation in reported dietary behavior among the 63808 pregnant women in this study. The first principal component (PC1), accounting for 12% of the variation in food intake among the women (Figure 1), was characterized by high positive loadings for vegetables, fruit and berries, cooking oil, olive oil, whole grain products and negative loadings for meat, including processed meat, white bread, salty snacks, Pommes frites and cakes and sweets. This principal component was denoted a 'health and sustainability component'. The second principal component (PC2), accounting for 7% of the variation in food intake (Figure 1), was characterized by high positive loadings for pasta and rice, poultry, olive oil, cooking oil, and vegetables and negative loadings for yoghurt, potatoes and fruit. This component did not add significantly to the illumination of dietary variation relevant for health, but rather displayed variation in culinary preferences. A cross-validation based on three segments [26] indicates that more than two components in principle could be assessed as significant. There is, however, a clear indication from the scree plot (i.e explained variance plot, in particular for cross-validation) that the first component is clearly dominating with only relatively minor contributions given by the rest of the components. The third and subsequent principal components were not considered because they were not readily interpretable and added less to explained variation in food intake.

Frequent consumption of organically produced food, which was reported by 9.1% of the participants, was associated with higher scores on both principal components. While frequent organic consumption did not unambiguously increase with increasing age, education, income and abstinence from alcohol and smoke, the scores for the 'health and sustainability component' increased with all of these characteristics (Table 2). When adjusting for all potential confounding variables shown in Table 2, the differences in score between the

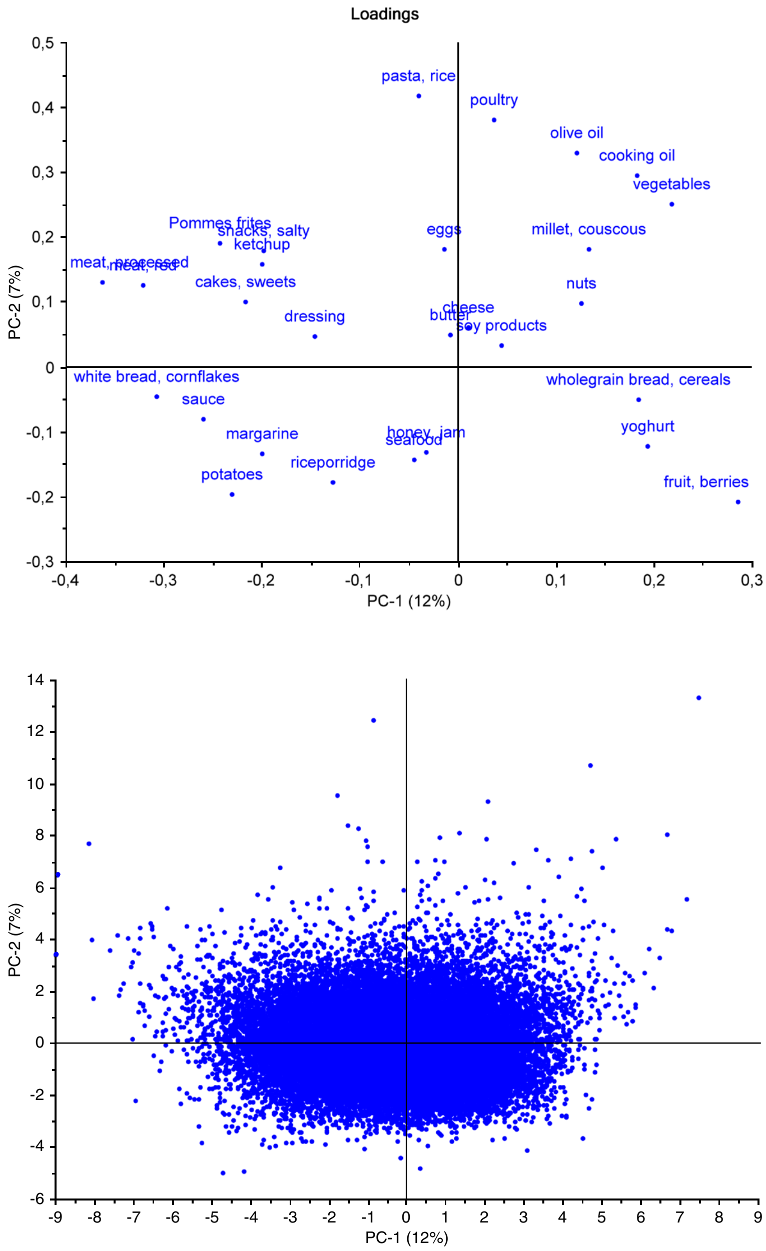

Figure 1 Loadings and scores plot from PCA (N = 63808). Names of overlapping food groups in the loadings plot, upper left: processed meat, red meat. Standard deviations for the scores are 1.82 for PC1 and 1.35 for PC2. The explained variance for component 1, 2, 3 and 4 are 12%, 7%, 5% and 5% respectively.

frequent organic consumers and non-frequent consumers increased from 0.73 to 0.80 for PC1 and from 0.16 to 0.17 for PC2. While the difference between the groups in score on the ‘health and sustainability component’ (PC1) was considerable (0.73 units in the scores plot), and represented approximately 1/10 of the total variation in scores, the difference between the groups in scores on the second principal component was smaller (0.16 units in the scores plot) and in practice insignificant (Table 3). We therefore primarily focus on variation according to the first principal component in the following. Organic consumption of all the six food groups was statistically associated with both principal components, except organic fruit and meat, which were only significantly associated with PC1 (Table 3).

These findings were corroborated in the analyses which showed increases in daily intake of food groups characterizing the components, e.g. vegetables (+29 g/d), fruit and berries (+44 g/d), whole grain products (+9.4 g/d), pasta and rice (+4.5 g/d), and decreases in

Table 2 Differences in food patterns and intake of selected food groups by reported frequency of organic consumption among 63 808 women in the Norwegian Mother and Child Cohort Study 2002-2007

	Total organic consumption (all food groups combined)		Organic consumption by food groups					
	Low = sum index≤6	**Frequent = sum index>6**	**Organic vegetables**	**Organic fruit**	**Organic bread & cereal**	**Organic milk & dairy**	**Organic eggs**	**Organic meat**
Dietary pattern	Mean score (SE)		*Difference in patterns scores*					
		Frequent vs. low (SE)	High vs. low organic consumption by food groups (SE)					
PC1('health-component')	-0.07 (0.007)	0.73 (0.03)***	0.82 (0.03)***	0.63 (0.03)***	0.56 (0.03)***	0.59 (0.03)***	0.97 (0.03)***	-0.12 (0.04)**
PC2	0.01 (0.006)	0.16 (0.02)***	0.11 (0.02)***	ns	0.15 (0.02)***	0.13 (0.02)***	0.23 (0.02)***	ns
Food groups	Mean intake g/10MJ (SE)		*Difference in intake (g/10MJ)*					
		Frequent vs. low (SE)	High vs. low organic consumption by food groups (SE)					
Vegetables (total)	156 (0.4)	29 (1.4)***	38 (1.5)***	25 (1.6)***	21 (1.6)***	18 (1.5)***	35 (1.4)***	ns
Vegetables (raw)	91 (0.3)	9.0 (1.0)***	16 (1.0)***	8.5 (1.1)***	4.5 (1.1)***	3.6 (1.1)**	15 (1.0)***	-6.2 (1.4)***
Fruit & berries	279 (0.8)	44 (2.6)***	55 (2.9)***	61 (3.1)***	31 (3.1)***	21 (2.9)***	43 (2.6)***	10 (3.8)**
Nuts	2.3 (0.02)	1.1 (0.1)***	0.9 (0.1)***	0.6 (0.1)***	1.1 (0.1)***	0.7 (0.1)***	1.5 (0.1)***	-0.2 (0.1)*
Pasta & rice	51 (0.1)	4.5 (0.5)***	5.4 (0.5)***	5.3 (0.6)***	3.9 (0.6)***	2.9 (0.5)***	2.7 (0.5)***	4.0 (0.7)***
White bread & cornflakes	118 (0.4)	-15 (1.3)***	-16 (1.5)***	-9.8 (1.6)***	-14 (1.6)***	-12 (1.5)***	-23 (1.3)***	ns
Wholegrain bread/cereal	131 (0.4)	9.4 (1.5)***	9.5 (1.6)***	ns	101 (1.8)***	8.2 (1.7)***	21 (1.5)***	15 (2.1)***
Cakes and sweets	104 (0.2)	-7.7 (0.7)***	-7.5 (0.7)***	-8.2 (0.8)***	-8.5 (0.8)***	-7.0 (0.7)***	-6.1 (0.7)***	-6.6 (0.9)***
Meat (total)	169 (0.2)	-24 (0.8)***	-22 (0.9)***	-20 (0.9)***	-21 (0.9)***	-23 (0.9)***	-22 (0.8)***	-8.1 (1.1)***
Red meat	102 (0.2)	-15 (0.6)***	-14 (0.7)***	-13 (0.7)***	-14 (0.7)***	-15 (0. 7)***	-15 (0.6)***	-1.8 (0.9)*
Processed meat	41 (0.1)	-7.2 (0.3)***	-7.7 (0.3)***	-6.4 (0.3)***	-5.9 (0.3)***	-6.1 (0.3)***	-7.5 (0.3)***	-2.7 (0.4)***
Eggs	112 (0.1)	1.7 (0.2)***	1.5 (0.2)***	1.2 (0.2)***	1.2 (0.2)***	1.1 (0.2)***	4.1 (0.2)***	1.0 (0.3)***
Yoghurt	80 (0.5)	14 (1.6)***	16 (1.7)***	15 (1.8)***	11 (1.8)***	12 (1.7)***	18 (1.6)***	ns
Lowfat milk	312 (1.2)	-37 (4.4)***	-39 (4.6)***	-28 (4.8)***	-42 (4.9)***	ns	-42 (4.1)***	-17 (5.9)**
Softdrinks	156 (1.0)	ns	-11 (3.6)**	ns	ns	ns	-28 (3.3)***	44 (4.7)***
Softdrinks diet	156 (1.3)	-43 (4.6)***	-36 (5.1)***	-35 (5.3)***	-35 (5.4)***	-54 (5.1)***	-47 (4.6)***	ns
Tea	183 (1.1)	35 (3.7)***	39 (4.1)***	27 (4.3)***	34 (4.4)***	24 (4.1)***	52 (3.7)***	ns

* p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001. One-way ANOVA analyses.

intake of meat (-24 g/d), processed meat (-7.2 g/d), white bread (-15 g/d) and cakes and sweets (-7.7 g/d) among women with frequent consumption of organic food (Table 3). In addition to a higher total vegetable intake, women with frequent organic food consumption ate a larger proportion of raw vegetables (+9 g/day). Regarding beverages, frequent organic consumption was associated with less artificially sweetened soft drinks (-43 g/10 MJ), (but not sugar sweetened soft drinks), less low fat and skimmed milk (-37 g/10 MJ), and more tea (+35 g/10 MJ).

We observed some variations in dietary patterns associated with consumption of the six different groups of organically produced foods (Table 3). The increase in vegetable consumption was particularly high for high consumption of organic vegetables, and the highest increase in consumption of fruit and berries was found among participants with high consumption of organic fruit and berries. High consumption of organic meat represented an exception from the overall associations between frequent organic consumption and dietary patterns: no increase in vegetable consumption, only a small increase in fruit and berries, no decrease in intake of white bread and highly processed breakfast cereals, and only a small reduction in meat intake. Consumption of organic meat was also associated with consumption of more sugar-sweetened soft drinks, and no difference in intake of artificially sweetened soft drinks, contrary to organic consumption of the other five food groups.

A gradual increase in vegetable consumption and a corresponding decrease in meat consumption were evident across increasing frequencies of reported organic consumption (Figure 2). The graphs depict a significant difference in consumption of both meat and vegetables already at the lowest frequency of organic consumption, and that these differences become more pronounced with increasing consumption of organically produced food. Even among women with high scores on PC1

Table 3 Differences in intake of selected nutrients by reported frequency of organic consumption among 63 808 women in the Norwegian Mother and Child Cohort Study 2002-2007

	Total organic consumption (all food groups combined)		**Organic consumption by food groups**					
	Low = sum index≤6	**Frequent = sum index>6**	**Organic vegetables**	**Organic fruit**	**Organic bread & cereal**	**Organic milk & dairy**	**Organic eggs**	**Organic meat**
Nutrients	Mean intake (SE)	*Difference in intake*						
		Frequent vs. low (SE)	High vs. low organic consumption by food groups (SE)					
Energy kJ/day	9686 (11)	592 (36)***	577 (39)***	681 (42)***	556 (42)***	560 (40)***	361 (36)***	646 (51)***
E% from protein	15.5 (0.009)	-0.3 (0.03)***	-0.2 (0.03)***	-0.3 (0.03)***	-0.3 (0.03)***	-0.2 (0.03)***	-0.1 (0.03)***	-0.4 (0.04)***
E% from fat	30.4 (0.02)	0.2 (0.1)**	ns	-0.3 (0.1)***	0.3 (0.1)**	0.4 (0.1)***	0.3 (0.1)***	ns
E% from carbohydrate	53.9 (0.02)	ns	0.2 (0.1)**	0.5 (0.1)***	ns	-0.2 (0.1)**	-0.2 (0.1)**	ns
E% from added sugar	10.6 (0.02)	ns	-0.3 (0.1)**	ns	ns	ns	-0.5 (0.1)***	0.8 (0.1)***
Dietary fiber g/10MJ	31.8 (0.03)	1.5 (0.1)***	2.0 (0.1)***	1.4 (0.1)***	1.3 (0.1)***	0.5 (0.1)***	2.0 (0.1)***	0.7 (0.2)***
β-carotene μg/10MJ	2702 (7.7)	293 (26)***	520 (28)***	294 (30)***	230 (30)***	150 (29)***	316 (26)***	ns
Vitamin D, μg/10MJ	3.56 (0.009)	0.2 (0.03)***	0.2 (0.03)***	0.1 (0.03)**	0.1 (0.04)**	ns	0.2 (0.03)***	ns
Vitamin C mg/10MJ	171 (0.3)	16 (1.2)***	21 (1.3)***	21 (1.3)***	9.4 (1.4)***	7.2 (1.3)***	17 (1.2)***	6.1 (1.7)***
Folate, μg/10MJ	284 (0.3)	21 (1.0)***	26 (1.1)***	23 (1.1)***	15 (1.2)***	13 (1.1)***	25 (1.0)***	4.5 (1.4)**
Calcium, mg/10MJ	1075 (1.3)	ns	ns	ns	-13. (5.0)**	30 (4.7)***	ns	-20 (6.1)**
Magnesium, mg/10MJ	414 (0.2)	7.4 (0.8)***	11 (0.9)***	6.6 (0.9)***	4.8 (1.0)***	3.9 (0.9)***	14 (0.8)***	9.2 (1.2)***
Potassium, mg/10MJ	4169 (2.9)	90.6 (9.7)***	162 (11)***	135 (11)***	42 (12)***	36 (11)**	128 (9.7)***	41 (14)**
Sodium, mg/10MJ	3190 (2.3)	-127 (6.8)***	-118 (7.5)***	-140 (7.9)***	-119 (8.0)***	-118 (7.6)***	-100 (6.8)***	-97 (9.7)***

* p-value < 0.05, ** p-value < 0.01, *** p-value < 0.001. One-way ANOVA analyses.

(e.g. high vegetable consumption and low meat consumption), frequent consumption of organic food was associated with higher vegetable consumption and reduced meat consumption compared with women within the same pattern score but with low organic consumption (data not shown).

The results show that rather than a mere ‘substitution’ of conventionally produced foods with organically produced foods of similar types (substituting conventional minced meat with organic minced meat, for example), we see qualitative differences in dietary composition. These qualitative differences include the relative amounts of main food groups (such as less meat and more vegetables), as well as emphasis on different types of products (if meat: rather lamb than sausages,) and food preparation and degree of processing (more vegetables eaten raw, more whole foods rather than highly processed) (see Table 3, Figure 1 and Additional file 3: Figure S1).

Frequent organic consumption and high consumption of all organic food groups were associated with higher energy intake (Table 1). The same was found for the relative contribution of energy from protein. However, the differences in energy contributed by the other macronutrients were small. Furthermore, higher intakes of vegetables, wholegrain products, fruit and berries and lower intakes of processed foods among the frequent organic consumers were reflected in higher relative (energy adjusted) intakes of beta-carotene, ascorbic acid, folate, fiber and magnesium and lower intakes of sodium (Table 1). There were only marginal differences in intake of zinc, selenium and iron between the groups (results not shown).

Discussion

The main finding of this study was that frequent consumption of organic food among the pregnant women in the MoBa study was strongly associated with higher scores on the ‘health and sustainability component’ (PC1), i.e. a diet characterized by more vegetables, fruit and berries, and whole grain cereal products and less meat, including processed meat, white bread, refined cereal products, cakes and sweets, compared with participants with no or low consumption of organic food. Diets of the pregnant women with frequent organic consumption, consequently, were more in line with dietary recommendations for health as well as ecological sustainability.

In the multivariate part of the present study we have considered data based on first adjusting for amount of food eaten in order to highlight pattern rather than amount. We also decided to exclude beverages when extracting underlying dietary components (patterns) since they had strong dominance on the results. Thirdly we used standardization in order to give all the foods equal opportunity to contribute meaning which means that we consider relative differences in each of the foods rather than the dominating effect of those with the largest variance. This analysis revealed clear differences between

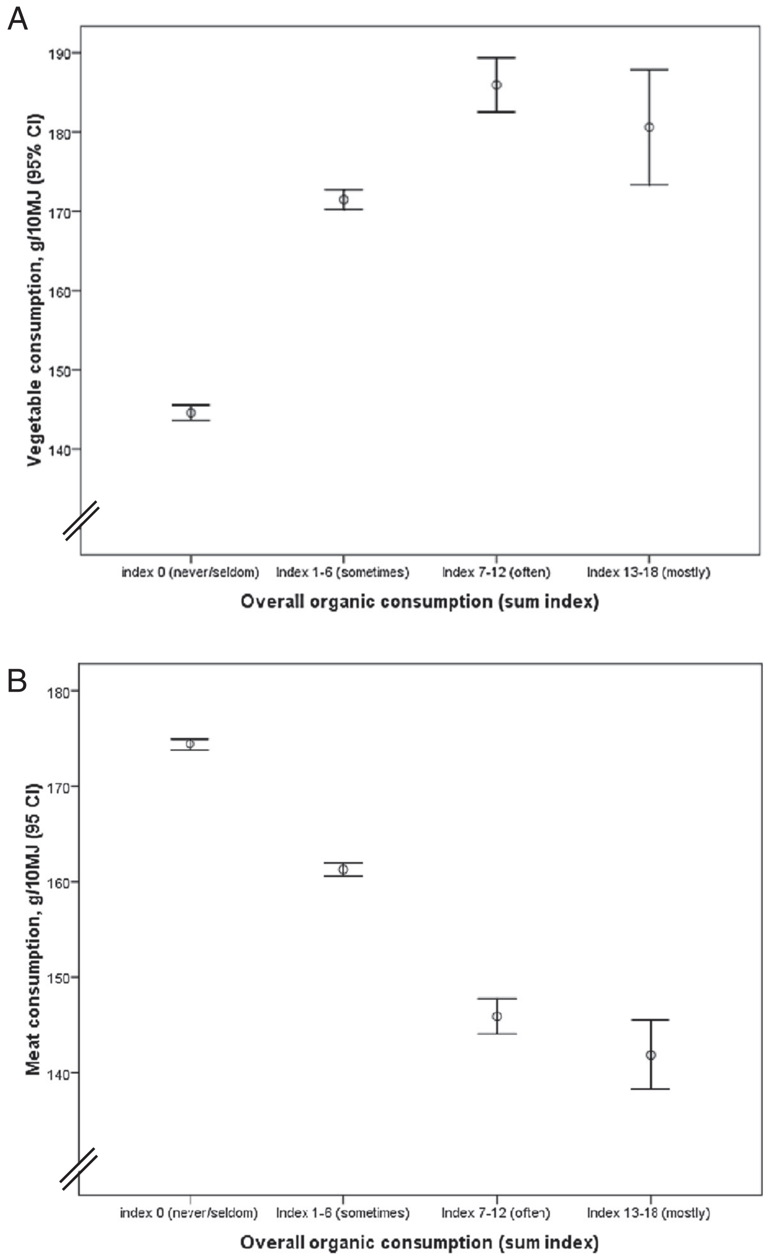

Figure 2 A and B. Amount of vegetables and meat in the diet according to consumption of organic food.

'healthy' and 'unhealthy' diets represented in particular by the score along the first principal component. In other studies of dietary patterns, contrasting patterns are often found, the first two typically being 'prudent' and 'western' (or denoted with similar names) [18,27-29]. In the present study, however, both 'healthy' and 'unhealthy' diets are covered by the first principal component, represented by high and low scores, respectively. This dual dimension within the first component was also seen in a large cohort of pregnant women in Southampton [30,31]. The first principal component extracted in that study was characterized by high intakes of healthy food items vs. unhealthy food items.

In the present study, two types of food issues were brought together: *How* food is produced and *what kinds of* foods that are eaten. The findings confirm that in the dietary practices of the pregnant women in this study, there was an association between these two food dimensions. We have no means of knowing the order in which choices were made and practices established: Did the choice of buying organically produced food form the choice of diet, or did more people who preferred certain types of diets choose organically produced foods – or did reflection about both these aspects of food mutually influence each other? Regardless of how these practices have developed, the significant differences in dietary characteristics are of relevance with regard to their ability to contribute to good health and ecological sustainability. Dietary recommendations aiming at both these goals are to a large extent overlapping. Central to ecological sustainability is eating lower in the biological food chain (i.e. more plant foods and less meat), because it maximizes the amount of high quality food for human nutrition relative to the ecological costs of production, and this also fits well with health advice.

We have previously reported a large difference in prevalence of vegetarians (+23 percentage points) among the pregnant women in MoBa who frequently ate organic food compared to those who did not [22]. Since the total number of vegetarians was very low, however, (0.2%, ibid) the practical significance of the change in dietary pattern expressed as a shift of the whole group of frequent organic consumers from lower to higher scores on the 'health and sustainability component' (PC1) is by far much larger. An implication of this was that on average, the frequent organic consumers in the MoBa-study had a reported intake of over half a kilo more vegetables, fruit and berries weekly than those with low organic consumption, and they reached the Norwegian recommendations of '5 a day' (500 g vegetables, fruit and berries a day), while those with no or little organic food in their diets were 65 g short of doing so.

In addition to a higher total consumption of vegetables, women with frequent organic consumption also ate a larger proportion of these vegetables raw. Higher intakes of 'whole foods' such as raw vegetables, fruit and berries, nuts, wholegrain bread and cereal products among the frequent consumers of organic food in the present study are in line with preferences for less processed and refined foods as reported by both Holt [32] and Torjusen [33], as well as consumers' associations of organic food with characteristics such as 'natural' and 'home made' [16,34]. Similarly, lower consumption of refined and processed foods such as processed meat, highly refined cereal products, potato chips ('salty snacks') and Pommes frites further confirms such trends. Characteristic in this respect is also the negative correlation between tomato ketchup and fresh tomatoes, as representatives of diets with 'fast food' or processed food vs. diets based on fresh produce and whole foods (see details in Additional file 3: Figure S1).

There was large variation in use of different types of fat in the diet (Figure 1), and the association between frequent consumption of organic food and more use of olive oil and cooking oil, which is in line with previous findings [33], may be related to a larger emphasize on health among those who choose organic food.

The observed negative correlation between processed meat and meat from intensive production systems (such as pork) with negative loadings and meat from extensive production (lamb), with positive loadings on the 'health and sustainability component' (Additional file 3: Figure S1), may be interpreted in light of ecological consciousness or a preference for what is perceived as more 'natural' or 'closer to nature'.

In her study of dietary habits among organic consumers in the UK, Holt reported a shift away from a diet focused on meat, potato and bread, towards increased consumption of vegetable foods and in particular, the incorporation of non-traditional plant foods, such as nuts, pulses and grains into the diet, resulting in a greater diversity of protein and staple foods among consumers of organic foods [13]. In the present study, frequent consumers of organic food had slightly lower percentage of energy derived from protein (Table 1), as well as a higher relative proportion of proteins from plant foods rather than animal foods, but still a protein intake well within (and in the upper levels of) dietary recommendations for pregnant women [35]. Higher intakes of foods such as nuts, pulses and legumes and soy products represent alternative sources of proteins in diets with less meat. We also recognize more diversity in 'staple foods': higher intake of less traditional grains such as millet, as well as higher intake of pasta and rice (Figure 1 and Table 3).

Our finding of higher average energy intake among frequent organic consumers (about 600 kJ/day more, Table 1) is likely to be related to higher levels of physical activity, as we have previously found that a larger proportion of the frequent organic consumers in the MoBa-study exercised regularly and were normal or low weight compared to those with no or low organic consumption [22]. Their food intake therefore seems to be more in balance with their energy expenditure.

The large sample size including women from both urban and rural regions, representing all age groups and socio-economic groups is a major strength in the present study. The large sample size ensures large variation in dietary composition and use of organically produced food. However, only 38.5% of those who were invited participate in MoBa, which imply that the prevalence of organic consumption may not be representative for all pregnant women in Norway. The potential influence of self-selection in MoBa has been evaluated, and no statistically relative differences in association measures were found between participants and the total population regarding eight exposure-outcome associations [36]. Hence, the selection bias in MoBa is not likely to influence the associations between reported use of organic food and dietary behavior among the frequent organic consumers. The sum index is a relatively crude measure, but in spite of this we observed important associations between overall frequent organic consumption and dietary quality. We also observed differences in food and nutrient intakes between frequent consumers of the various organic food groups. When designing a new FFQ, as was done for the MoBa cohort, there is a trade-off between the number of questions and the burden imposed on respondents. If questionnaires ask in too much detail there is an increased risk of participant drop-out [37,38]. We do not know how the MoBa FFQ influenced the participation rate, but 93% of the women participating in MoBa did answer the FFQ [21].

Misreporting is a serious error in all dietary assessment methods [39], and it has been shown that foods perceived as 'unhealthy' are underreported to a larger degree than foods perceived as 'healthy' [40]. The food frequency methods challenges participants with complex cognitive tasks and is particularly difficult to answer early in pregnancy when many women are experiencing nausea and changes in appetite and eating patterns. However, the MoBa FFQ was developed and validated for use in pregnancy [24] and the validation study demonstrated that relative to a dietary reference method and several biological markers, it produces a realistic estimate of the habitual intake and is a valid tool for ranking pregnant women according to high and low intakes of energy, nutrients, and food [41].

We have previously reported that frequent consumption of organic food among pregnant women in the MoBa-study was not solely associated with socio-economic and lifestyle factors that are normally associated with good health [22]. While women who consumed organic food exercised more frequently, a larger proportion of them also consumed alcohol and smoked during pregnancy (although total prevalences were low). Lower household income and lower as well as higher levels of education were associated with frequent organic food consumption. While the consumption of organic food was not typically associated with high socio-economic status and healthy lifestyle factors, the association between frequent organic consumption and diet quality appeared to be clearer: pregnant women who chose organically produced food also ate diets that were more in line with health recommendations. Dietary quality is especially critical in pregnancy and PCA-derived dietary patterns in pregnancy have been associated with various health outcomes in well-nourished populations, including gestational weight gain [42]), preeclampsia [18], foetal growth [43] and post-partum depression [44]. There are, however, few previous studies addressing the combination of organic food consumption and the general dietary patterns and quality among pregnant women.

A methodological implication of the present study is that information about the diet in general needs to be included in future studies of possible health outcomes related to organic food consumption. It will further be advantageous to have specific information about consumption of organic food of different food groups, since high consumption of organic meat was associated with a somewhat different dietary pattern than that of organic vegetables, fruit, cereal products, dairy products and eggs.

Large knowledge gaps remain in our understanding of the consumption of organic food, related food practices and possible implications for health of mother and child. It remains an unsettled question whether there are systematic differences in the absolute content of nutrients and other substances of importance for health in foods that are organically or conventionally produced. The food analyses in the present study are based on the same food tables for both organically and conventionally produced foods, because at present there are no separate data on organically produced foods in the form of systematic food tables. If such differences are present, estimates of nutrient intakes would be imprecise or wrong. There are knowledge gaps in our understanding of how the consumption of organic food may be related to health, both in short and long term. Findings that indicate possible associations between consumption of organic food and health, such as prevalence of allergic diseases among children in families with organic consumption [45,46], will be addressed in future studies.

Conclusions

The present study showed that pregnant Norwegian women reporting frequent consumption of organically produced food had a dietary pattern and quality more in line with public advice for healthy and sustainable diets. A methodological implication is that the overall diet needs to be included in future studies of potential health outcomes related to consumption of organic food during pregnancy.

Additional files

Additional file 1: Table S1. Overview of food groups in PCA (Figure 1 and 2).

Additional file 2: Table S2. Overview of food items from the FFQ included in food groups.

Additional file 3: Figure S1. Loadings plot from PCA with 58 food groups (N=63808).

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
HMM took the initiative and was PI of the study. HT and HMM designed the study. HT performed the statistical analyses and wrote the manuscript. TN,

GL, ALB and MH assisted in the statistical analyses. All authors contributed to the interpretation of results and read and approved the final manuscript.

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SUPPLEMENTAL Table 1. Overview of food groups in PCA (Figure 1 and 2)

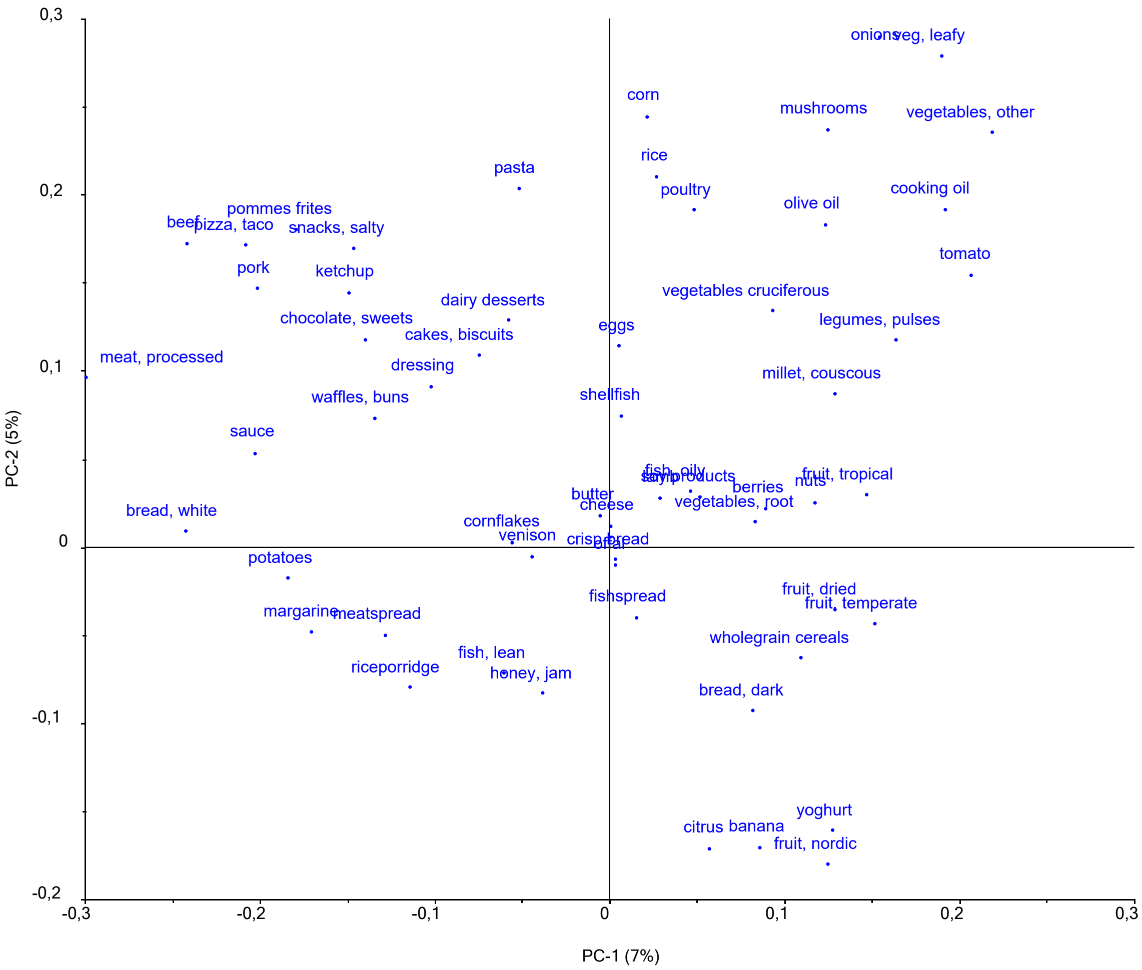
	58 Food groups (Figure 1)	28 Food groups (Figure 2)
1	Cruciferous vegetables, onions, tomatoes, mushrooms, corn, green leafy vegetables, root vegetables, legumes and pulses, other vegetables	Vegetables
2	Potatoes (boiled, baked, mashed), creamed potatoes, potato casserole	Potatoes
3	Pommes frites	Pommes Frites
4	Citrus, Nordic fruit, temperate fruit, tropical fruit, banana, dried fruit, berries	Fruit and berries
5	Nuts	Nuts
6	Dark bread, crisp bread, wholegrain cereals	Wholegrain bread and cereals
7	White bread, cornflakes	White bread and cornflakes
8	Pasta and rice	Pasta, rice and millet
9	Millet and couscous	Millet and couscous
10	Rice porridge	Rice porridge
11	Waffles and buns, cakes and biscuits, dairy desserts, chocolate and sweets	Cakes and sweets
12	Salty snacks	Salty snacks
13	Cheese	Cheese
14	yoghurt	Yoghurt
15	Eggs	Eggs
16	Lean fish, oily fish, shellfish, fish spread	Seafood
17	Poultry	Poultry
18	Pork, beef, lamb, venison, offal, meat spread	Red meat and pork
19	Processed meat, Pizza and taco	Processed meat
20	Honey and jam	Honey and jam
21	Olive oil	Olive oil
22	Cooking oil	Cooking oil
23	Butter	Butter
24	Margarine	Margarine
25	Ketchup	Ketchup
26	Dressing	Dressing
27	Sauce	Sauce
28	Soy products	Soy products

SUPPLEMENTAL Table 2. Overview of food items from the FFQ included in food groups

	Foods or food groups	Food items in the FFQ
1	Cruciferous vegetables	Cauliflower, broccoli, cabbage, brussels sprouts
2	Onions	Garlic, onion, leek, spring onion
3	Tomatoes	Tomatoes
4	Mushrooms	Mushrooms (champignon, wild mushrooms)
5	Corn	Corn
6	Green leafy vegetables	Green salad (lettuce, ruccula, endives, spinach, chicory),
7	Root vegetables	Carrot, swede
8	Legumes and pulses	Green beans, green peas, dish with lentils/beans
9	Other vegetables	Frozen vegetables, aubergine, zucchini, bell peppers, celery, avocado
10	Potatoes	Potatoes (boiled, baked, mashed), Creamed potatoes, potato casserole
11	Pommes frites	French fries, fried potatoes
12	Citrus	Orange, mandarin, grapefruit
13	Fruit, Nordic	Apple, pear, plum
14	Fruit, temperate	Grapes, peach/nectarine, melon, other (kiwi)
15	Fruit, tropical	Papaya, mango
16	Banana	Banana
17	Fruit, dried	Dried apricot, raisin, prune, fig, date
18	Berries	Strawberries, other berries (blueberries)
19	Nuts	Peanuts, other nuts (almonds, hazel nuts, cashew nuts)
20	Dark bread	Fibre bread, whole-grain bread
21	Crisp bread	Crisp bread, rye crisp, rusk
22	Wholegrain cereals	High grain cereals (müsli), oat flakes, oat flake porridge
23	White bread	White bread, low fibre bread, baguettes, ciabatta
24	Corn flakes	Corn flakes
25	Pasta	Spaghetti, macaroni, noodles
26	Rice	Rice (normal, whole)
27	Millet and couscous	Millet, couscous
28	Rice porridge	Rice porridge/rice pudding
29	Waffles and buns	Waffles and pancakes, sweet buns and rolls
30	Cakes and biscuits	Danish pastry, doughnut, sponge cake, chocolate cake, cream layer cake, sweet biscuits,
31	Dairy desserts	Ice-cream, yoghurt ice-cream, chocolate pudding, custard
32	Chocolate and sweets	Plain chocolate, fancy and filled chocolate, caramel, candies, liquorice, jelly sweets, marshmallow, marzipan, pastille with sugar, pastille sugar free
33	Salty snacks	Potato chips, popcorn
34	Cheese	Whey cheese goat milk, hard cheese, cream cheese, blue cheese, other kinds of cheese, regular and low fat
35	Yoghurt	Yoghurt full-fat and low-fat
36	Eggs	Eggs, raw, cooked, scrambled
37	Lean fish	Cod, saithe, haddock, Pollock, plaice, flounder, tuna, perch, pike, cat fish, fish burger, fish soufflé
38	Fatty Fish	Mackerel, herring, salmon, trout
39	Shellfish	Shrimps, crab, mussels
40	Fish spread	Liver and roe spread, mackerel/sardine in tomato sauce, sardine in oil, herring, pickled, shrimp, crab,
41	Poultry	Chicken and turkey fillet, chicken and/or turkey sausage, pan fried/ baked/boiled chicken or turkey, chicken schnitzel,

		nuggets, other poultry (duck, goose, ostrich)
42	Pork	Pork
43	Beef	Beef, veal
44	Lamb	Lamb, mutton
45	Venison	Venison
46	Offal	Liver, kidney, other offal, hashed lungs
47	Meat spread	Ham, roast beef, cold cuts of lamb, calf, salami, Swedish sausage, liver pâté,
48	Processed meat	Meat sauce for pasta dishes, sausages, hot-dogs, meat balls, meat loaf, hamburger, meat patty, minced meat, beef/pork/lamb stew
49	Pizza and taco	Pizza, frozen and homemade, taco
50	Honey and jam	Jam, honey
51	Olive oil	Olive oil
52	Cooking oil	Soya oil, sunflower oil, rape seed oil, corn oil
53	Butter	Butter, low-fat butter, melted butter
54	Margarine	Normal margarine, low-fat margarine
55	Dressing	Spread with mayonnaise (Italian etc.), Mayonnaise, remoulade, dressing, regular and low-fat (Thousand-island etc.)
56	Sauce	Sauce (béchamel or gravy, Bearnaise)
57	Ketchup	Tomato ketchup
58	Soy products	Soy products (dinner)

SUPPLEMENTAL Figure 1. Loadings plot from PCA with 58 food groups (N=63808)



Names of overlapping food groups in the loadings plot:
Upper left: beef, pizza, pommes frites, salty snacks
Upper right: onions, leafy vegetables
Central right: oily fish, lamb, soy products
Central: crisp bread, offal
Lower left: citrus, banana
Lower left: margarine, meat spread

Paper III

III

ERRATA Paper III

In the abstract, the numbers for ‘frequent’ organic consumption is given in the place of the numbers for ‘often’ or ‘mostly’ organic vegetables.

The correct numbers for women who reported having eaten organic vegetables ‘often’ or ‘mostly’ is: n=1 951, 6.9 %.

BMJ Open

Reduced risk of pre-eclampsia with organic vegetable consumption: results from the prospective Norwegian Mother and Child Cohort Study

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ABSTRACT

Objective: Little is known about the potential health effects of eating organic food either in the general population or during pregnancy. The aim of this study was to examine associations between organic food consumption during pregnancy and the risk of pre-eclampsia among nulliparous Norwegian women.

Design: Prospective cohort study.

Setting: Norway, years 2002–2008.

Participants: 28 192 pregnant women (nulliparous, answered food frequency questionnaire and general health questionnaire in mid-pregnancy and no missing information on height, body weight or gestational weight gain).

Main outcome measure: Relative risk was estimated as ORs by performing binary logistic regression with pre-eclampsia as the outcome and organic food consumption as the exposure.

Results: The prevalence of pre-eclampsia in the study sample was 5.3% (n=1491). Women who reported to have eaten organic vegetables 'often' or 'mostly' (n=2493, 8.8%) had lower risk of pre-eclampsia than those who reported 'never/rarely' or 'sometimes' (crude OR=0.76, 95% CI 0.61 to 0.96; adjusted OR=0.79, 95% CI 0.62 to 0.99). The lower risk associated with high organic vegetable consumption was evident also when adjusting for overall dietary quality, assessed as scores on a healthy food pattern derived by principal component analysis. No associations with pre-eclampsia were found for high intake of organic fruit, cereals, eggs or milk, or a combined index reflecting organic consumption.

Conclusions: These results show that choosing organically grown vegetables during pregnancy was associated with reduced risk of pre-eclampsia. Possible explanations for an association between pre-eclampsia and use of organic vegetables could be that organic vegetables may change the exposure to pesticides, secondary plant metabolites and/or influence the composition of the gut microbiota.

Strengths and limitations of this study

- This is the first study to report an association between use of organically grown vegetables during pregnancy and reduced risk of pre-eclampsia. Consumption of plant food, including vegetables, is recommended to all pregnant women, and this study shows that choosing organically grown vegetables may yield additional benefits.
- The lower risk of pre-eclampsia among women who consumed organic vegetables was observed independently of a healthy food pattern including a generally higher vegetable intake.
- Major strengths of this study include the prospective design; the large sample of women from all regions of Norway, including all age and socioeconomic groups; and detailed information on diet and potential confounding factors.
- Since this study is observational, no causal implications can be drawn, and although confounding by other variables was carefully considered, residual confounding cannot be excluded.

INTRODUCTION

Pre-eclampsia is one of the major causes of maternal and perinatal morbidity and mortality worldwide, affecting 2–8% of pregnancies.[1 2] The aetiology of pre-eclampsia is largely unknown, but increasing evidence suggests an excessive maternal systematic inflammatory response to pregnancy.[3–7] Pre-eclamptic pregnancies are characterised by endothelial dysfunction, disturbed placentation, oxidative stress and an exaggerated inflammatory response to pregnancy.[8] Known risk factors include first pregnancy, obesity and other cardiovascular risk factors.[2 9]

The maternal diet is one of many factors suggested to play a role in the aetiology of pre-eclampsia.[10 11] In a previous study in the Norwegian Mother and Child Cohort Study (MoBa), we found that high scores on a healthy diet characterised by high intake of vegetables, fruits and vegetable oils was associated with reduced risk of pre-eclampsia in nulliparous women.[12] Dietary components and qualities associated with pre-eclampsia risk in observational studies include macronutrients, micronutrients, dietary fibre, and individual foods as well as overall food patterns.[10–16] Trials aiming at pre-eclampsia prevention have yielded mixed results. Some evidence has been indicated for calcium supplementation,[17 18] while a review of 15 studies concluded that available evidence does not support the use of antioxidants, e.g. vitamin C and E, for the prevention of pre-eclampsia.[19]

Organic agriculture is a production system that relies on ecological processes, biodiversity and cycles adapted to local conditions, aiming at sustaining the health of soils, ecosystems and people.[20] Organically produced food is produced without the application of synthetic pesticides, synthetic fertilisers or genetically modified organisms. All food sold as organic in Norway must, in agreement with the Norwegian Food Safety Authorities, be certified by Debio and labelled with Debio's Ø-label, which ensures that regulations for organic production are met, following the EU Council Regulation 2092/91.[21]

Several reviews have concluded that organic foods have been convincingly demonstrated to expose consumers to fewer and lower levels of pesticide residues.[22–25] Lower urinary excretion of pesticide metabolites have been found in children eating a predominantly organic diet compared with children eating conventional diets.[26 27] Little difference is reported for most nutrients, except a higher content of phosphorus in organic foods,[22] while higher levels of secondary plant metabolites as well as differences in the microflora on organically compared with conventionally grown plant food have been described.[28 29] Sales of organic food has increased in recent years,[30] and one of the main reasons for consumers to choose organic food is that they perceive it as healthier, as well as better for the environment and animal health.[31]

Little is known about potential health effects of eating organic food either in general or during pregnancy. In the Norwegian Mother and Child Cohort Study, the dietary questionnaire administered in mid-pregnancy included a question about consumption of organic food in six food groups (vegetables, fruits, cereals, milk/dairy, eggs and meat). We have previously reported that frequent consumption of organic food during pregnancy was not solely associated with socioeconomic and lifestyle factors that are normally associated with good health.[32] However, the women who chose organically produced food had a healthier dietary pattern with more vegetables, fruit and berries, cooking oil, whole grain and cereal products, and less meat, including processed meat, white bread, and cakes and sweets than women with no or low organic consumption.[33]

The aim of the present study was to investigate whether consumption of organic food during pregnancy was associated with the risk of pre-eclampsia, taking the overall food pattern into account.

METHODS

Population and study design

The data set is part of the Norwegian Mother and Child Cohort Study, which is initiated by and maintained by the Norwegian Institute of Public Health.[34] Participants were recruited from all over Norway in the years 1999–2008. The women consented to participation in 40.6% of the pregnancies. The cohort now includes 114 500 children, 95 200 mothers and 75 200 fathers. Pregnant women were recruited to the study by postal invitation after they had signed up for the routine ultrasound examination in their local hospital.[34] The women were asked to provide biological samples and to answer questionnaires covering a wide range of information. The cohort database is linked to the Medical Birth Registry of Norway.[35] The Norwegian Mother and Child Cohort study has been approved by the Regional Committee for Ethics in Medical Research and the Data Inspectorate in Norway.

This study uses V.4 of the data files made available for research in January 2009. To be included in the present study, the women had to have responded to the baseline questionnaire in the Norwegian Mother and Child Cohort Study as well as the food frequency questionnaire in gestational weeks 17–22. In addition, participants had to have answered at least one of the 6 questions about organic food, and they had to have reported a credible daily energy intake (>4.5 or <20 MJ). In total, 63 808 pregnancies fulfilled these criteria and this population has been described in detail previously.[33] From the eligible population of n=63 808, we excluded pregnancies not registered in the Medical Birth Registry of Norway with a singleton delivery (n=1475). We further excluded multiparous women (n=29 111) due to the special importance of parity for the prevalence and aetiology of pre-eclampsia. We also excluded participants with missing data on height or weight (n=736) and gestational weight gain (n=4294). This resulted in a final sample of 28 192 nulliparous women for studying associations between organic food and pre-eclampsia (figure 1). The prevalence of pre-eclampsia was higher in the study population than in the 35 616 excluded pregnancies (5.3% (1491 cases) vs 3.1% (1068 cases)). Women in the study sample were younger (29 vs 31 years), had higher levels of education (27.2% vs 21.5% with 17 years or more of educational attainment), fewer who smoked cigarettes in pregnancy (6.9% vs 9.6%) and fewer with high consumption of organic vegetables (6.9% vs 7.7%).

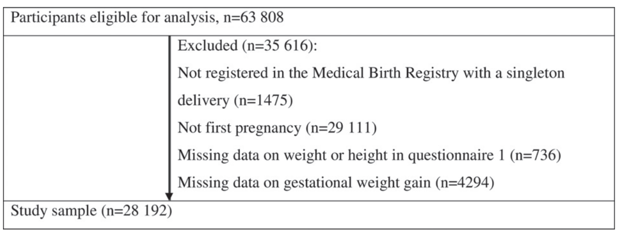

Figure 1 Flow chart showing selection of study participants from the Norwegian Mother and Child Cohort Study.

Consumption of organic food

Information about consumption of organic food is based on 6 questions about specified organic food groups included in the food frequency questionnaire of the Norwegian Mother and Child Cohort Study (http://www.fhi.no/dokumenter/011fbd699d.pdf). This is a semiquantitative food frequency questionnaire designed to capture dietary habits during the first 4–5 months of pregnancy, described in detail elsewhere.[36] The mean ±SD gestational age when answering the food frequency questionnaire was 20.7±3.7 weeks. The response alternatives for consumption of organic food were: 'never or seldom', 'sometimes', 'often' or 'mostly' and were given values from 0–3. For those who had answered at least one of the questions about organic food, missing values for one or more of the other questions were interpreted as 'seldom or never'. In addition to data on the frequency of consumption of organic food in each of the six food categories, we calculated a 'sum index' variable as a measure of total organic food consumption. The sum index reflects organic food consumption on a scale ranging from 0 to 18, with 0 representing no use of organic food and 18 representing 'mostly' organic for all six food groups. For respondents who had no reported intake of meat (n=450), eggs (n=1976), milk/dairy (n=979) or vegetables (n=11) and who had not reported organic consumption of the corresponding food group, we upscaled the sum index by multiplying with 6/5 for each omitted food category. For more details about the combined index, see Torjusen *et al*.[33] We defined frequent organic consumption as having a sum index of >6, which corresponds to having reported eating organic food 'often' for at least one of the six food categories. Consumption of organic food was operationalised in the analyses as 'no or low' vs 'frequent' consumption of organic food (sum index ≤6 vs >6) and as 'low' ('never/seldom' or 'sometimes') vs 'high' ('often' or 'mostly)' consumption of the individual six food groups: milk and dairy products, bread and cereal products, egg, vegetables, fruit and meat. The reported frequencies of the six main organic food groups as well as correlations between them have been reported in detail previously.[32]

Pre-eclampsia

The main outcome was pre-eclampsia as registered in the Medical Birth Registry of Norway.[35] Information provided to the registry is based on the forms completed by the midwives after birth. The form has 5 check-off boxes relevant to pre-eclampsia: haemolysis, elevated liver enzymes and low platelet count (HELLP syndrome); eclampsia; early pre-eclampsia (diagnosed before 34 weeks); mild pre-eclampsia and severe pre-eclampsia. The diagnostic criteria for pre-eclampsia were given if any of the aforementioned diagnoses were present. Women with chronic hypertension were included in the case group only if they also developed proteinuria. The diagnostic criteria for pre-eclampsia in Norway, according to the guidelines issued by the Society for Gynecology, are blood pressure >140/90 after 20 weeks of gestation, combined with proteinuria >+1 dipstick on at least 2 occasions. Pre-eclampsia is diagnosed as severe pre-eclampsia if blood pressure is ≥160/110.[37] In Norway, all pregnant women receive free antenatal care. Blood pressure measurement and urinalysis for protein are carried out at each antenatal visit.

Covariates

Hypertension prior to pregnancy (yes/no) was based on diagnoses by a physician reported in the Medical Birth Registry of Norway. Information about parity was retrieved both from the Medical Birth Registry of Norway and from the baseline questionnaire and combined into one variable. Self-reported pre-pregnancy height and weight were used to calculate body mass index (BMI; kg/m^2). Gestational weight gain was calculated from self-reported pre-pregnancy weight (baseline questionnaire) and self-reported weight at the end of pregnancy (reported in the questionnaire answered 6 months postpartum). Information about educational attainment was retrieved from the baseline questionnaire and divided into four categories (high school or less (≤12 years), 3–4 years of college/university (13–16 years), 4 years or more of college/university (17+years), or other/missing values (n=584)). Maternal age at delivery was retrieved from the Medical Birth Registry of Norway and divided into four categories (14–20, 20–29, 30–40 and 40–46 years). Smoking in pregnancy was divided into three categories (non-smokers, occasional smokers and daily smokers) based on information from the baseline questionnaire. Household income was expressed as a combination of the participant's and her partner's income, as reported in the baseline questionnaire (both <300 000 NOK, one ≥300 000 NOK, both ≥ 300 000 NOK or missing values (n=632)). The food frequency questionnaire provided dietary information in this study. Overall food pattern was described as scores on a principal component denoted as a 'health and sustainability component', derived by principal component analysis and ranked into tertiles.[33] Dietary supplement use reported in the food frequency questionnaire was computed as a categorical variable with three categories: no supplement use, use of any supplement without vitamin D and use of a vitamin D containing supplement.

In the Norwegian Mother and Child Cohort Study, >99% of the participants is of Caucasian ethnicity, so ethnicity is not a relevant confounder.

Statistical methods

Frequencies and descriptive statistics were expressed as n (%) and as means and SDs. For testing group differences, we used independent samples t test for continuous variables and χ^2 test for categorical variables.

For one analysis (figure 2), organic food consumption was modelled according to the four ordered alternative answer (never/rarely, sometimes, often, mostly) while

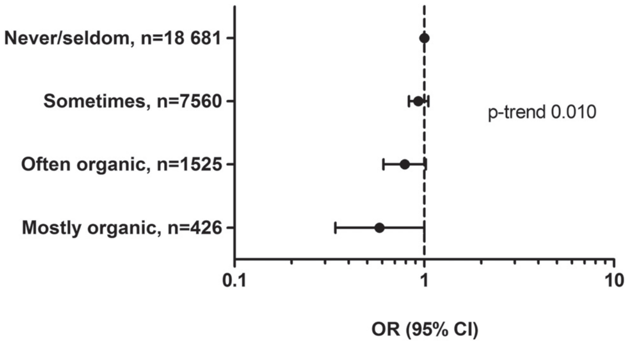

Figure 2 Associations (ORs and 95% CIs) between reported consumption of organic vegetables and pre-eclampsia among 28 192 pregnant women in the Norwegian Mother and Child Cohort Study 2002–2008.

for the remaining analyses it was modelled as a dichotomous variable with the two lowest frequencies combined into 'low' and the two highest frequencies combined into 'high' organic consumption.

We estimated relative risks as ORs by performing binary logistic regression with pre-eclampsia as the outcome and organic food consumption as the exposure.

We examined, as potential confounders, the following variables based on previous knowledge from the literature and our knowledge about characteristics associated with organic food consumption: maternal pre-pregnant BMI, maternal age, educational attainment, household income, gestational weight gain, cigarette smoking, alcohol consumption, exercise, total energy intake, overall food pattern and/or intake of main food groups and beverages (including sugar-sweetened beverages), intake of probiotic milk, and dietary supplement use. Covariates which were included in the final analysis were associated with both the exposure and the outcome (p<0.100): maternal pre-pregnant BMI, maternal age, educational attainment, gestational weight gain, cigarette smoking, total energy intake and overall food pattern. In addition, known risk factors were included (hypertension prior to pregnancy and maternal height). Maternal height, total energy intake, and BMI were used as continuous variables in the model because the associations between these variables and the outcome were linear and the results were similar whether the variables were modelled as continuous or categorical. Maternal age was, however, modelled as categories due to a non-linear association with organic food consumption.

To take into account that frequent consumers of organic food often report use of more than one of the six organic food groups, we additionally adjusted for 'any consumption' of organic food groups, defined by having a sum index above 6, which corresponds to having reported eating organic food 'often' for at least one of the six food categories. This will, to some degree, overadjust the model, as consumption of organic vegetables is also included in the sum index. We tested for interaction between reported consumption of organic food and the confounders. Participants with missing data on potential confounding variables were categorised in a 'missing' category. In total, 1216 (4.3%) had missing data on education and income, and excluding these in the adjusted models did not substantially change the results. Statistical analyses were performed using the statistical software PASW statistics V.17 (SPSS Inc, IBM Company, Chicago, Illinois, USA).

RESULTS

Participant characteristics and organic food consumption

Among the 28 192 women in this study, the majority (14 566) reported that they never/rarely ate organic food, 11 133 (39.8%) had a combined scores reflecting use of at least one organic food 'sometimes', 1987 (7%) had scores reflecting use of at least one organic food 'often' and 506 (1.8%) had scores reflecting use of any organic food 'mostly'. Women who reported higher frequency of organic food differed from those who reported low consumption. The frequent organic users were younger, had lower BMI and reported higher energy intake than women with low organic consumption. There were also differences with regard to smoking and education, but the most significant difference was seen for higher adherence to a healthy food pattern (table 1).

Table 1 Maternal characteristics associated with consumption of organic food among 28 192 pregnant women in the Norwegian Mother and Child Cohort Study 2002–2008

	Consumption of any organic food group, (sum index)	
n (%)	**Low 25 699 (91.2)**	**Frequent 2493 (8.8)**
	Mean±SD	Mean±SD
Maternal age, years	28.6±4.3	27.6±4.9**
Maternal body mass index	23.8±4.1	23.3±3.9**
Gestational weight gain, kg	15.2±6.0	15.5±6.5†
Energy intake, MJ/day	9.51±2.5	10.0±2.9**
	Per cent	Per cent
Maternal education ≤12 years	25.5	37.7**
Maternal education 17+years	27.1	28.6*
Smoking in pregnancy‡	6.6	11.0**
High household income§	29.7	23.1**
Alcohol in pregnancy (yes/no)	9.3	9.3
Hypertension prior to pregnancy (yes/no)	0.5	0.2*
High score 'healthy' food pattern¶ (yes/no)	36.0	50.2**

Independent samples t test (continuous variables), χ^2 (categorical variables): *p<0.05, **p<0.001, †0.05>p<0.01.
‡Comprise occasional and daily smoking.
§High income denotes that both participant and her partner have annual income ≥300 000 NOK.
¶High score denotes upper third on pattern scores. The food pattern is described in detail in Torjusen *et al*.[33]

Consumption of organic food and risk of pre-eclampsia

The number of participants diagnosed with pre-eclampsia was 1491 (5.3%). We found no associations with pre-eclampsia for high intake of organic fruit, cereals, milk/dairy, eggs or milk, or the combined index reflecting total organic consumption. However, lower risk was indicated for high intake of organic vegetables (table 2). Adjusting for any consumption of the organic food groups (sum index low/frequent) strengthened the association between organic vegetables and pre-eclampsia, in spite of organic vegetables also being included in the 'any organic' variable (table 2). The association between consumption of organic vegetables and pre-eclampsia did not reach statistical significance when examined according to the four alternative answers, but a dose–response relationship was indicated (p trend 0.010; figure 2). However, when the 'often' and 'mostly' groups were combined into 'high' and the 'never/rarely' and 'sometimes' groups were combined into 'low' consumption of organic vegetables, the association with pre-eclampsia reached statistical significance (adjusted OR=0.75, 95% CI 0.60 to 0.95; model 1, table 3). Higher scores on the 'healthy' food pattern was also associated with lower risk of pre-eclampsia (OR tertile 2 vs tertile 1 0.80, 95% CI 0.70 to 0.91, and OR tertile 3 vs tertile 1 0.73, 95% CI 0.64 to 0.84; model 1, table 3). Because women who report use of organic food also have higher adherence to the 'healthy' diet, the 'healthy' food scores were included among the confounding variables (model 2, table 3). This resulted in wider CIs for both organic vegetables and the 'healthy' diet, but the associations remained statistically significant for organic vegetable consumption, with OR=0.79 (95% CI 0.62 to 0.99), and for the food pattern, with OR tertile 3 vs tertile 1 0.74 (95% CI 0.64 to 0.85). Additional adjustment for any consumption of the organic food groups (sum index low/frequent) strengthened the association between organic vegetables and pre-eclampsia (data not shown). As previously reported, women who consumed organic vegetables had higher intakes of seafood, milk, iodine, calcium and several other foods and nutrients than those with no or low organic vegetable consumption.[33]

However, no food or nutrient intake attenuated the association of interest. Adjusting for single food groups, e.g. fish or milk, or for specific nutrients, e.g. iodine or calcium, did not change the association between consumption of organic vegetables and pre-eclampsia. This supports that adjusting for the overall dietary pattern accounts for the observed differences in food and nutrient intakes between women with high and low intake of organic vegetables.

No interactions were observed between use of organic vegetables and the food pattern, maternal age, education, BMI or smoking. Rerunning the association between organic vegetable consumption and pre-

Table 2 Associations between consumption of organic food groups and risk of pre-eclampsia among 28 192 pregnant women in the Norwegian Mother and Child Cohort Study 2002–2008

Organic food group	Total n	Pre-eclampsia n (%)	Unadjusted OR (95% CI)	Adjusted for consumption of any organic food group, (sum index low/frequent) OR (95% CI)
	28 192	1491 (5.3)		
Organic consumption in any food group (sum index)				
Low	25 699	1368 (5.3)	1	
Frequent	2493	123 (4.9)	0.92 (0.76 to 1.12)	
Vegetables				
Low	26 241	1410 (5.4)	1	1
High	1951	81 (4.2)	*0.76 (0.61 to 0.96)*	*0.68 (0.50 to 0.92)*
Fruit				
Low	26 416	1404 (5.3)	1	1
High	1776	87 (4.9)	0.92 (0.73 to 1.15)	0.96 (0.70 to 1.32)
Cereals				
Low	26 403	1395 (5.3)	1	1
High	1789	96 (5.4)	1.02 (0.82 to 1.26)	1.18 (0.87 to 1.61)
Milk/dairy				
Low	26 155	1383 (5.3)	1	1
High	2037	109 (5.4)	1.03 (0.83 to 1.24)	1.14 (0.87 to 1.50)
Eggs				
Low	25 602	1363 (5.3)	1	1
High	2590	128 (4.9)	0.93 (0.77 to 1.11)	0.95 (0.76 to 1.18)
Meat				
Low	27 037	1425 (5.3)	1	1
High	1155	66 (5.7)	1.09 (0.84 to 1.40)	1.28 (0.92 to 1.79)

Table 3 Associations between consumption of organic vegetables and risk of pre-eclampsia among 28 192 pregnant women in the Norwegian Mother and Child Cohort Study 2002–2008

	Total n	Pre-eclampsia N (%)	Crude model OR (95% CI)	Adjusted model 1* OR (95% CI)	p Value	Adjusted model 2† OR (95% CI)	p Value
	28 192	1491 (5.3)					
Organic vegetables							
Low	26 241	1410 (5.4)	1	1		1	
High	1951	81 (4.2)	0.76 (0.61 to 0.96)	0.75 (0.60 to 0.95)	0.017	0.79 (0.62 to 0.99)	0.043
Scores on a 'healthy' food pattern‡							
Tertile 1	8369	556 (6.6)	1	1		1	
Tertile 2	9320	480 (5.2)	0.76 (0.67 to 0.87)	0.80 (0.70 to 0.91)		0.81 (0.71 to 0.92)	0.001
Tertile 3	10 503	455 (4.3)	0.64 (0.56 to 0.72)	0.73 (0.64 to 0.84)	0.001	0.74 (0.64 to 0.85)	<0.001
p Trend			<0.001	<0.001	<0.001	<0.001	

*Model adjusted for hypertension prior to pregnancy, pre-pregnant body mass index, maternal height, maternal age, maternal education, household income, maternal smoking in pregnancy, total energy intake and gestational weight gain.
†Model adjusted for all of the above and mutual adjustment for organic vegetable consumption and 'healthy' food scores.
‡Food pattern described in detail in Torjusen *et al*.[33]

eclampsia separately in each stratum (tertiles) of food pattern scores resulted in risk estimates of 0.87, 0.77 and 0.79 for tertiles 1, 2 and 3. Likewise, when stratifying women by BMI ≥25 and <25 the risk estimates were 0.76 and 0.82, respectively.

When dividing pre-eclampsia in subgroups by time of onset or severity, the risk estimates were lower than 1 for all, but borderline significantly lower risk was indicated for use of organic vegetables only for the subtypes late-onset pre-eclampsia and mild pre-eclampsia, which were the subgroups with the highest number of cases (table 4).

DISCUSSION

The main finding of this study was that women who reported eating organically grown vegetables 'often' or 'mostly' had lower risk of developing pre-eclampsia than women who reported not consuming organic vegetables or to do so less frequently. This association was observed

Table 4 Associations between consumption of organic vegetables and subgroups of pre-eclampsia among 28 192 pregnant women in the Norwegian Mother and Child Cohort Study 2002–2008

	N	Per cent	High consumption, organic vegetables (%)	Adjusted model* OR (95% CI)	p Value	Adjusted model† OR (95% CI)	p Value
Subtypes by time of onset							
Early-onset pre-eclampsia‡							
Yes	142	0.5	0.4	0.69 (0.32 to 1.48)	0.34	0.75 (0.35 to 1.62)	0.46
No	26 701	94.7	95.8				
Late-onset pre-eclampsia							
Yes	1349	4.8	3.8	0.76 (0.60 to 0.97)	0.030	0.79 (0.62 to 1.01)	0.063
No	26 701	94.7	95.8				
Subtypes by clinical severity							
Mild pre-eclampsia							
Yes	841	3.0	2.2	0.70 (0.51 to 0.96)	0.029	0.73 (0.53 to 1.00)	0.051
No	26 701	94.7	95.8				
Severe pre-eclampsia§							
Yes	434	1.5	1.4	0.91 (0.61 to 1.34)	0.62	0.97 (0.65 to 1.43)	0.86
No	26 701	94.7	95.8				
Unspecified pre-eclampsia							
Yes	216	0.8	0.5	0.66 (0.35 to 1.24)	0.20	0.67 (0.35 to 1.27)	0.22
No	26 701	94.7	95.8				

*Model adjusted for hypertension prior to pregnancy, pre-pregnant body mass index, maternal height, maternal age, maternal education, household income, maternal smoking in pregnancy, total energy intake and gestational weight gain.
†Model adjusted for all of the above and additional adjustment for 'healthy' food scores.
‡Diagnosed before 34 weeks.
§Severe pre-eclampsia including eclampsia and HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count).

independently of a healthy food pattern including a generally higher vegetable intake.

Strengths

The major strengths of this study are the large sample of women from all regions of Norway, the prospective design and the detailed information on a wide range of potential confounding factors. All age and socio-economic groups are represented in the study group. Validated pre-eclampsia diagnosis was obtained from the Medical Birth Registry of Norway.[37] Women were unaware of the outcome of pregnancy when dietary data and information about consumption of organic food was collected, which reduces the likelihood of misreporting as a consequence of the disease.

The food frequency questionnaire used in our study has been extensively validated and shown to be a valuable tool for ranking pregnant women according to high and low intakes of energy, nutrients and foods.[36 38–40] The smoking variable, as used in the present study (non-smokers, occasional smokers and daily smokers), has been validated against plasma cotinine in a sub-sample of 2997 women in the Norwegian Mother and Child Cohort Study.[41] A study of potential self-selection bias in the Norwegian Mother and Child Cohort Study found no significant differences between the eight evaluated exposure–outcome associations in the cohort and the total pregnant population in Norway during the same period,[42] nor does it appear to compromise validity of exposure–outcome associations related to autism in a substudy of the Norwegian Mother and Child Cohort Study.[43] Our findings are likely to be generalisable outside of Norway, because although consumption of organic food is embedded in specific structural and cultural features of the food system in any particular country, there are similarities in characteristics and motivations among consumers of organic food across Europe.[31]

Limitations

The exposure variable is based on 6 questions about specified organic food groups, with four alternative frequency categories given as the answer options. These frequency categories may have been interpreted differently among participants as the distinction between 'sometimes' and 'often' or between 'often' and 'mostly' might not be clear. A potential misclassification resulting from this should however be equally distributed among women who did and did not develop pre-eclampsia. Furthermore, imprecision in the exposure variable is likely to cause attenuation in the risk estimation, in this case attenuation towards the null of the estimated associations between organic food practices and pre-eclampsia.[44]

Although the food frequency questionnaire of the Norwegian Mother and Child Cohort Study has been validated, the question about use of organic food was not evaluated. It would have strengthened the study if we had had access to biological material and could have assessed pesticide and secondary plant metabolite levels in the participants' urine.

In spite of a large study population, the number of frequent organic vegetable consumers (1951) was relatively low (6.9%), which was a limitation in the analysis of pre-eclampsia subgroups, e.g. late vs early onset. The risk estimates in subgroup analyses were indicative of lower risk, but the low numbers resulted in wide CIs. A further limitation of this study is that the data available do not allow the assessment of impact of pre-pregnancy nutritional status, which may be a confounder of the relationship shown.

Since the study is observational, no causal implications can be drawn, and although confounding by other variables was carefully considered, residual confounding cannot be excluded.

Possible explanations for findings

We will, in the following, outline some properties of organic vegetables that could possibly contribute to explain our findings of a reduced risk of pre-eclampsia, emphasising that these are purely hypothetical suggestions since we only have associations from epidemiological data. Our suggestions of possible explanations are based on the following characteristics of a diet including organically produced vegetables rather than conventional vegetables: (1) lower dietary pesticide exposure; (2) higher intake of secondary plant metabolites and (3) possibly a different microflora on organic vegetables, which could affect human (maternal) intestinal microbiota in a beneficial way. Furthermore, pesticides, or the absence of them, might impact the composition of the gut microbiota.

Lower pesticide exposure

Although the most persistent pesticides have been banned in most countries, they may still be present at trace levels in foods due to their long environmental and biological half-lives. It is well established that a diet consisting of predominantly organically produced foods significantly reduces the exposure to organophosphorous pesticides.[26 45] Chlorpyrifos (CPF) has been shown to increase permeability of the intestine in an *in vitro* model based on an enterocyte cell line.[46] Increased permeability of the intestine ('leaky gut') may induce inflammation.[47]

Some recent studies have reported an association between pesticide exposure or residues in the body and obesity and type 2 diabetes.[48–50] In a prospective study, exposure to organochlorine pesticides was shown to increase the risk of obesity, dyslipidaemia and insulin resistance among participants without diabetes.[49] Organochlorine pesticides, particularly chlordane, predicted incidents of type 2 diabetes in a nested case–control study.[51] Chemicals, such as organochlorine pesticides, may cause obesity by altering homoeostatic metabolic set points, disrupting appetite controls, perturbing lipid homoeostasis to promote adipocyte hypertrophy or stimulating adipogenic pathways that enhance adipocyte hyperplasia during development or in adults.[47 52 53] Since obesity and dyslipidaemia (hypertriglyceridaemia) are also associated with the development of pre-eclampsia,[54] lower exposure of pesticide residues may provide a possible explanation of lower risk of pre-eclampsia with the inclusion of organically produced vegetables in the diet.

Furthermore, a diet with lower levels of pesticide residues may reduce proneness to inflammations by affecting the composition of the gut microbiota in a beneficial way. In a model of the human intestinal microbial ecosystem, as well as in rat studies, it has been shown that chronic exposure of CPF selectively altered the intestinal microflora.[55] Proliferation of the total intestinal flora was observed, mainly due to an increase in certain subpopulations such as the *Enterococcus* spp and *Bacteroides* spp, while there was a decrease in the numbers of beneficial bacteria such as bifidobacteria and lactobacilli.[55]

Higher intake of secondary plant metabolites

A majority of studies comparing the contents of secondary plant metabolites in organically vs conventionally grown fruits and vegetables report higher contents of these compounds in organic products.[28 56 57] Brandt *et al*[28] reported substantially higher contents of defence-related secondary metabolites, represented by phenolic acids; other defence compounds (tannins, alkaloids, chalcones, stilbenes, flavanones and flavanols, hop acids, coumarins and aurones), and total phenolics. The authors estimate, based on a meta-analysis of 65 papers, that if a person changes from consuming exclusively conventional fruit and vegetables to consuming the organic alternatives of the same products in the same amounts, the intake of all secondary metabolites would increase by approximately 12%, and the intake of more specifically defence-related secondary metabolites would increase by approximately 16%.[28] Whether such a difference has health-related implications remains to be shown. Baxter *et al*[57] showed that soups based on organically grown plants had higher content of salicylic acid than those made from non-organic plants.

In terms of human health, many of these compounds, such as salicylic acid and polyphenols, have anti-inflammatory properties.[58] Furthermore, polyphenols are a class of dietary substances that act as a 'prebiotic', influencing the intestinal microflora in a beneficial way.[59]

In our study, adjusting for single foods or nutrients did not attenuate the association between consumption of organic vegetables and pre-eclampsia. Furthermore, the association between consumption of organic vegetables and pre-eclampsia was independent of the reduced risk also indicated by an overall healthy diet, supporting the hypothesis that organic vegetables may provide higher amount or different composition of non-nutrients. By providing higher dietary intakes of secondary plant metabolites, organically grown vegetables may contribute to a less inflammation-prone milieu in the maternal gut, as well as an improved antioxidant status, thereby possibly reducing the risk of pre-eclampsia.

Different microflora on organically grown vegetables compared with conventionally grown

The gut is a major immune organ, and the gut microbiota shapes intestinal immune response during health and disease.[59–61] It has been shown that the human gut microbiome can rapidly respond to altered diet,[62] and it is becoming increasingly clear that the effect of the microbial ecology of the gut goes beyond the local gut immune system and is implicated in immune-related disorders, such as type 2 diabetes and obesity.[63–65]

It has been reported that children growing up in families with an anthroposophical lifestyle, including consumption of organic/biodynamic food and fermented vegetables, have lower risk of developing atopic diseases, and this is associated with development of a more beneficial intestinal microflora compared with children not living in families with anthroposophical lifestyles.[66–68] It is, however, unclear whether these observed effects are related to the consumption of organic food as such, or the additional consumption of fermented vegetables. It may be hypothesised that organic farming practices not only enhance a richer, more diverse microflora in the soil but also on fresh produce such as vegetables and that this in turn may influence the dietary intake of probiotic substances.[29 69 70] A possible explanation why the results in this study showed an association between organic vegetables but not with organic fruits and pre-eclampsia might be that people are more likely to peel fruit, resulting in lower exposure to microbes than for raw vegetables.

The relevance of the integrity of the intestinal microflora for the development of pre-eclampsia is supported by the evidence from studies finding protective effects of probiotics,[14 71] and evidence supporting the hypothesis that plant foods may influence pre-eclampsia through intestinal anti-inflammatory mechanisms.[72] Brantsæter and colleagues found that probiotic milk (containing *Lactobacillus* bacteria) is associated with reduced risk of pre-eclampsia, and it is hypothesised that the *Lactobacillus* probiotics in this study may have suppressed the Gram-negative bacterial lipopolysaccharide (LPS) expression to reduce inflammation.[14] This mechanism would be in agreement with other studies which found that lactobacilli influenced the LPS response to reduce overall systemic inflammation levels.[73]

Comparison with other studies

To the best of our knowledge, this is the first study investigating a potential association between consumption of organically grown food during pregnancy and lower risk of pre-eclampsia. To date, only a limited number of studies have examined possible human health outcomes associated with consumption of organic foods. A case–control study from Denmark examined maternal use of organic food and hypospadias in male neonates. They found a higher likelihood of hypospadias in the offspring among women who never used organic high fat dairy foods compared with those who often used organic high fat dairy products.[74] Reduced risk of allergic (IgE) sensitisation in infancy, lower prevalences of atopic diseases, differences in the intestinal microflora and lower levels of salivatory cortisol have been shown in children living in families with an anthroposophic lifestyle, in which consumption of organic/biodynamic food is one of several characteristics.[66 67 75–78] Kummeling *et al*[67] found that children who consumed dairy products of which more than 90% were organically produced had a lower risk of eczema at age 2 than children who consumed dairy products of which less than 50% were organically produced.

CONCLUSIONS AND POLICY IMPLICATIONS

Large knowledge gaps remain in our understanding of how the consumption of organic foods and related lifestyle practices influence the health of mother and child. It is important that questions about organic food choices are incorporated into large new and ongoing studies. The present study suggests a lower risk of pre-eclampsia in pregnant Norwegian women who reported frequent consumption of organically produced vegetables compared with those with no or low consumption of such foods. Increased consumption of plant food, including vegetables, is recommended to all pregnant women, and this study shows that choosing organically grown vegetables may yield additional benefits. Future studies need to confirm the observed association and if so further address possible causal relationships.

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Paper IV

IV

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

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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: We examined 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% confidence intervals (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.

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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 prevalence of both hypospadias and cryptorchidism in Norway is around 0.3% (Aschim et al. 2004a, 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, for example, organochlorine pesticides and other endocrine-active chemicals. There is evidence from animal studies that environmental xenohormones interfere with male genital development (Bergman et al. 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 nonprofit organization Debio and labeled 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 (European Union) Council Regulation 2092-91 (EU 1991)]. Debio is accredited by Norwegian Accreditation according to the quality standard ISO 65/EN 45011 and by IFOAM (2015).

Organically produced food has been shown in some cases to have higher concentrations of naturally occurring plant constituents—for example, secondary plant metabolites and lower levels of cadmium and nitrate—and lower incidence of detectable pesticide residues than conventionally produced food (Barański et al. 2014; Brandt et al. 2011; 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

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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 on 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 the prevalence of hypospadias and cryptorchidism at birth.

Material and Methods

Study population. The data set 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 through 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 before 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 (FFQ) 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 the 12th week of gestation (Irgens 2000).

The source population eligible for inclusion in the present 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, participants had to have answered at least one of the six questions about consumption of organic food groups in questionnaire 2 (excluding 750 participants), and they had to have reported a daily energy intake between 4.5 and 20 MJ (megajoules), excluding 1,131 participants (Meltzer et al. 2008). A total of 72,893 (97.5%) women fulfilled these criteria, of whom 37,299 delivered a male neonate. Of these, women who were included in the cohort with more than one pregnancy were included in the present study only with their first enrollment. This resulted in a final study population of 35,107 mother–infant pairs. Of these infants, 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 babies who were not live born. The present study is based on version 4 of the quality-assured data files released for research in January 2009 (unpublished data). All MoBa participants provided written informed consent before enrollment into the study.

Ethics 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 semiquantitative FFQ which was designed specifically for assessing diet during the first 4 months of pregnancy (Norwegian Institute of Public Health 2002). The FFQ included questions about the frequency of use of organic food specified in six food groups: *a*) milk and dairy products, *b*) bread and cereal products, *c*) eggs, *d*) vegetables, *e*) fruit, and *f*) 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, and 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" vs. "sometimes," "often," and "mostly"), except for 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/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 4-day weighed food record and biological markers as reference methods. The results showed acceptable agreement (< 10% grossly misclassified and correlation coefficients ranging from 0.3 to 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, 2007b, 2008). The validity of the questions about organic food consumption has not been evaluated. We did not have information about quantity (grams/day) for organic foods, only frequency. From the FFQ we included the daily intakes (grams/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 > 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—for example, 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. 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 (Aschim et al. 2004a) concluded that mild hypospadias cases are likely to be underreported in MBRN. No information is available on the performance of the registry with regard to cryptorchidism.

Other variables. In the baseline questionnaire women provided information about sociodemographic and lifestyle variables including maternal prepregnancy 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 preceding 6 months. BMI was categorized according to the World Health Organization classification as normal (18.5–24.9 kg/m^2), underweight (< 18.5 kg/m^2), overweight (25.0–29.9 kg/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 (≤ 12 years), 3–4 years of college/university (13–16 years), ≥ 4 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 ($n = 1,025$). Maternal and paternal smoking habits during pregnancy were divided into two categories, nonsmokers versus smokers.

Information about singleton or plural delivery, infant sex, maternal age at delivery, paternal age, infant birth weight, gestational age, *in vitro* fertilization (IVF), and previous stillbirths was retrieved from the MBRN. Gestational age was calculated from expected date of delivery on the basis of first-trimester ultrasound. In the event of missing an ultrasound measure, gestational age was calculated from last menstrual period. Preterm delivery was defined as gestational age < 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 age and observations with birth weight < 600 g and gestational age < 25 weeks resulted in 204 infants with missing data on SGA. These were excluded in the adjusted analyses for hypospadias. Likewise, 123 missing data on paternal age were excluded in the adjusted analyses for cryptorchidism.

Statistical analyses. All p-values were two-sided, and values < 0.05 were considered statistically significant. The 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 *a*) any organic food expressed in a combined variable of all organic food groups and the outcomes, *b*) individual organic food groups and the outcomes, and *c*) 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, 2012). Variables considered as potential confounding variables in the current study were maternal age, paternal age, maternal prepregnancy 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 previous 6 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 any organic variable as the exposure. Variables fulfilling this criterion with hypospadias as outcome were prepregnancy 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, prepregnancy 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 5,741 (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, nonsmoking, 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, whereas 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 prepregnancy BMI, educational attainment, and/or household income. When these were excluded rather than modeled as "missing" categories, the number of hypospadias cases was 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 nonorganic) of food items (grams/day) within each organic food group had no influence on the ORs.

Because of 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, except for 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; n = 10 exposed cases). For organic milk/dairy products, the adjusted OR was borderline significant with OR = 0.43 (95% CI: 0.17, 1.07, p = 0.070; n = 7 exposed cases).

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; n = 31 exposed cases).

Finally, we repeated the analyses for any organic food consumption and hypospadias adjusting for preeclampsia (n = 1,387). The adjusted OR remained unchanged (OR = 0.42; 95% CI: 0.25, 0.69; n = 21 exposed cases). When mothers with preeclampsia were excluded from the analysis, the adjusted OR was 0.35 (95% CI: 0.20, 0.62; n = 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 nonconsumers. The associations were consistent and marginally influenced by adjusting for food intakes, lifestyle factors, and sociodemographic 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; n = 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 explaining 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 (Barański et al. 2014; Brandt et al. 2011; 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 affect the gut microbiota and thereby the proneness to inflammation (Bengmark 2013), but this is largely hypothetical.

Exposure to pesticides in the general population, except for 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

Table 1. Organic food consumption,[a] by maternal characteristics [n (%)].

Characteristic	All [35,107 (100)]	Never/seldom organic [17,996 (51.3)]	Sometimes, often, or mostly organic [17,111 (48.7)]	p-Value[b]
Maternal age (years)				< 0.001
< 20	667 (1.9)	310 (46.5)	357 (53.5)	
20–29	18,041 (51.4)	9,624 (53.3)	8,417 (46.7)	
≥ 30	16,399 (46.7)	8,062 (49.2)	8,337 (50.8)	
Paternal age (years)				< 0.001
< 20	184 (0.5)	79 (42.9)	105 (57.1)	
20–29	12,223 (34.8)	6,492 (53.1)	5,731 (46.9)	
≥ 30	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 (kg/m^2)				< 0.001
< 18.5	1,017 (2.9)	516 (50.7)	501 (49.3)	
18.5–24.9	22,336 (63.6)	11,123 (49.8)	11,213 (50.2)	
25–29.9	7,500 (21.4)	4,055 (54.1)	3,445 (45.9)	
≥ 30	3,330 (9.5)	1,826 (54.8)	1,504 (45.2)	
Missing information	924 (2.6)	476 (51.5)	448 (48.5)	
Parity				< 0.001
Nulliparous	16,919 (48.2)	8,502 (50.3)	8,417 (49.7)	
Parous	17,669 (50.3)	9,211 (52.1)	8,458 (47.9)	
Missing information	519 (1.5)	283 (54.5)	236 (45.5)	
Maternal education (years)				< 0.001
≤ 12	11,099 (31.6)	6,235 (56.2)	4,464 (43.8)	
13–16	17,793 (42.1)	7,741 (52.3)	7,052 (47.7)	
≥ 17	8,448 (24.1)	3,605 (42.7)	4,843 (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	3,400 (9.7)	1,563 (46.0)	1,837 (54.0)	
Household income (NOK)				< 0.001
Both partners < 300,000	10,143 (28.9)	5,399 (53.2)	4,744 (46.8)	
One partner ≥ 300,000	14,832 (42.2)	7,788 (52.5)	7,044 (47.5)	
Both partners ≥ 300,000	9,107 (25.9)	4,311 (47.3)	4,796 (52.7)	
Missing information	1,025 (2.9)	498 (48.6)	527 (51.4)	
Dietary supplement use				< 0.001
No	7,170 (20.4)	4,123 (57.5)	3,047 (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)	9,692 (41.4)	
Upper tertile	11,702 (33.3)	4,283 (36.6)	7,419 (63.4)	
Alcohol in pregnancy				< 0.001
No	31,106 (88.6)	16,146 (51.9)	14,960 (48.1)	
Yes	4,001 (11.4)	1,850 (46.2)	2,151 (53.8)	
Smoking in pregnancy				< 0.001
No	32,194 (91.7)	16,332 (50.7)	15,862 (49.3)	
Yes	2,913 (8.3)	1,664 (57.1)	1,249 (42.9)	

[a]Consumption of organic food was 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). Nonconsumption was defined as having answered "never/seldom" for all organic food groups. No data were missing on use of organic food. [b]p-Value obtained by Pearson's chi-square test.

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 (Bergman et al. 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. Because the Norwegian food supply has global sources, 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 2002–2006 (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, particularly 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 because the estimated intake within the food groups comprised both organic and nonorganic items. The weak association between consumption of organic milk/dairy products and hypospadias in our study ($p = 0.07$, $n = 7$ 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). Although 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 nonrepresentativeness in MoBa showed that it did not affect exposure–outcome associations, including

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

Organic food consumption	Total (*n* = 35,107)	Hypospadias (*n* = 74)	Cryptorchidism (*n* = 151)
Organic vegetables			
Never/seldom	22,759 (64.8)	63 (85.1)	98 (64.9)
Sometimes	9,785 (27.9)	8 (10.8)	44 (29.1)
Often or mostly	2,563 (7.3)	3 (4.1)	9 (6.0)
Organic fruit			
Never/seldom	25,006 (71.2)	61 (82.4)	107 (70.9)
Sometimes	7,802 (22.2)	9 (12.2)	36 (23.8)
Often or mostly	2,299 (6.6)	4 (5.4)	8 (5.3)
Organic cereals			
Never/seldom	27,980 (79.7)	64 (86.5)	123 (81.5)
Sometimes	4,915 (14.0)	6 (8.1)	18 (11.9)
Often or mostly	2,212 (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	6,582 (18.8)	5 (6.8)	18 (11.9)
Often or mostly	2,533 (7.2)	2 (2.7)	13 (8.6)
Organic eggs			
Never/seldom	23,144 (65.9)	58 (78.4)	99 (65.6)
Sometimes	8,749 (24.9)	8 (10.8)	38 (25.2)
Often or mostly	3,214 (9.2)	8 (10.8)	14 (9.3)
Organic meat			
Never/seldom	30,814 (87.8)	70 (94.6)	136 (90.1)
Sometimes	2,793 (8.0)	2 (2.7)	13 (8.6)
Often or mostly	1,500 (4.2)	2 (2.7)	2 (1.3)

[a]No data were missing 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	4,763 (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	7,010 (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	9,015 (58.3)
Sometimes, often, or mostly	7,127 (20.3)	0	7,127 (41.7)
Organic milk/dairy products			
Never/seldom	25,992 (74.0)	17,996	7,996 (46.7)
Sometimes, often, or mostly	9,115 (26.0)	0	9,115 (53.3)
Organic eggs			
Never/seldom	23,144 (65.9)	17,996	5,148 (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	4,293 (12.2)	0	4,293 (25.1)

[a]Any organic was defined as having answered "sometimes," "often," or "mostly" for any of the six organic food groups (vegetables, fruits, cereals, milk/dairy, eggs, meat). Nonconsumption was defined as having answered "never/seldom" for all organic food groups. No data were missing on use of organic food.

prenatal smoking and birth outcomes (low birth weight, 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).

Although our study benefits from a large cohort design, it is somewhat limited by 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 underreporting of mild forms—that is, cryptorchidism with spontaneous descent and mild hypospadias with normal foreskin. The prevalence of hypospadias in our study is similar to the prevalence in MBRN (0.2%) in mothers not exposed to anti-epileptic drugs (Veiby et al. 2014), whereas 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 whom 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 in mild cases testes 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

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

Exposure to organic food	Total (*n* = 35,107)	Hypospadias *n* (%)	Crude OR (95% CI)	Adjusted[b] OR (95% CI)	Adjusted[c] 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	7,127	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	9,115	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	4,293	4 (0.1)	0.41 (0.15, 1.22)	0.42 (0.15, 1.17)	0.72 (0.23, 2.15)

NA, not applicable.
[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 prepregnancy BMI, SGA baby, preterm delivery. In addition, the model for each organic food group was adjusted for the total daily intake of food items (organic and nonorganic) 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 data were missing on use of organic food.

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

Exposure to organic food	Total (*n* = 35,107)	Cryptorchidism *n* (%)	Crude OR (95% CI)	Adjusted[b] OR (95% CI)	Adjusted[c] 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	7,127	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	9,115	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	4,293	15 (0.4)	0.79 (0.46, 1.35)	0.78 (0.45, 1.33)	0.78 (0.44, 1.38)

NA, not applicable.
[a]Numbers of observations (total and cases) do not account for observations with missing covariate data (123 missing including 1 case). [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 nonorganic) in the respective group. [c]Additional adjustment for any organic food. [d]Reported use of at least one of the organic food groups. No data were missing on use of organic food.

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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Appendices

Appendix 1

Overview of studies investigating organic food consumption and human health[1]

Studies in pregnant women (including two studies from the present thesis, Paper III and Paper IV) are presented first, followed by studies in other population groups.

Appendix 1 - Table 1. Studies investigating organic food consumption and human health in pregnant women

Main endpoint	Study population and design	Exposure	Main findings	Authors/ reference
Hypospadias	Case-control study in mothers of 306 boys who are operated on for hypospadias and 306 mothers of healthy boys in Denmark 2003-2005	Retrospective recall of organic consumption in six food groups during pregnancy	No difference with any organic food consumption but higher prevalence with nonorganic milk/dairy combined with frequent consumption of high fat dairy products	Christensen *et al.* 2013 (65)
Hypospadias and cryptorchidism	Prospective study in 35,107 mothers of singleton male infants in Norway 2002-2008	Organic food consumption in six food groups assessed by FFQ grouped into any vs. seldom/never	Lower prevalence of hypospadias with any organic food consumption, and in particular organic vegetables. No difference for cryptorchidism	Brantsaeter *et al.* 2016 (263) The MoBa study
Pre-eclampsia	Prospective study in 28,192 first time singleton pregnant women in Norway 2002-2008	Organic food in six food groups assessed by FFQ grouped into frequent versus sometimes	Lower prevalence of preeclampsia with frequent organic vegetables, no difference for other food groups or any organic consumption	Torjusen *et al.* 2014 (264) The MoBa study

[1] In the present overview, the studies included have investigated organic foods in relation to various health outcomes, be it altered incidence of some health condition or effects on biomarkers of health and disease. In this context, "human health" in relation to organic food is defined as "the organic diet's or diet constituent's ability to influence indicators of health or disease".

Otitis media	Prospective study with 1,461 mother-child pairs. Women were recruited from April 2002 through February 2006 in the Brittany region, France. Metabolites of triazine herbicides and organophosphate insecticides measured in urine collected before the 19th week of gestation in a subgroup analysis (248 mothers)	Organic food consumption during pregnancy and domestic use of pesticides	Lower risk of parent-reported otitis media (at least one episode) in children before 2 years old of mothers who had eaten organic food during pregnancy	Buscail *et al.* 2015 (66) The PELAGIE study
Gestational diabetes, maternal pre-pregnancy BMI, and hypertension	Prospective study with 1,339 pregnant women in the Netherlands, 2000- 2002, who filled in FFQ and donated a blood sample	Organic food consumption during pregnancy	Organic food consumption was associated with lower prevalence of gestational diabetes and a more favourable pre-pregnancy BMI	Simões-Wüst *et al.* 2017 (67) The KOALA study

Appendix 1 - Table 2. Studies investigating organic food consumption and human health in children

Main endpoint	Study population and design	Exposure	Main findings	Authors/ reference
Atopy	Cross-sectional study in 295 children from families with anthropo-sophic life-style and 380 children from control families in Sweden	Organic/bio-dynamic food consumption as part of an anthroposophicl ifestyle	Less atopy in the children in families with anthroposophic lifestyle	Alm *et al.* 1999 (265)
Allergies and atopic sensitization	Cross-sectional study including 14,893 children aged 5-13 years from families with anthroposophic lifestyle in Sweden, Austria, Germany, Netherlands, and Switzerland	Organic/bio-dynamic food consumption as part of an anthroposophic Lifestyle	Less allergy in families with anthroposophic lifestyle	Alfvén *et al.* 2006 (266) The PARSIFAL study

Allergies and atopic sensitization	Cross-sectional multicenter study including 6630 children age 5 to 13 years (4606 from Steiner schools and 2024 from reference schools) in Sweden, Austria, Germany, Netherlands, and Switzerland	Organic/bio-dynamic food consumption as part of an anthroposophic Lifestyle	Certain features of the anthroposophic lifestyle, such as restrictive use of antibiotics and antipyretics, are associated with a reduced risk of allergic disease in children	Flöistrup *et al*. 2006 (267) The PARSIFAL study
Eczema and/or wheeze occurrence	Prospective follow-up with 2,764 children in the Netherlands. Blood samples from 815 infants at 2 years of age were analysed for total and specific immunoglobulin-E	Organic consumption in six food groups and proportion of organic within the total diet, from week 34 in pregnancy until child age 2	Less eczema at 2 years with consumption of organic dairy products, but not with other foods. No effect on wheeze or atopic sensitization	Kummeling *et al.* 2008 (268) The KOALA study
Allergic sensitization	Prospective study of 330 children from families with an anthroposophic, partly anthroposophic, or nonanthroposophic lifestyle in Sweden. Allergen-specific immunoglobulin-E sensitization measured in blood	Organic/bio-dynamic food consumption as part of an anthroposophic lifestyle	Immunoglobulin-E sensitization to common allergens was lower among children of families with an anthroposophic lifestyle	Stenius *et al.* 2011 (269) The ALADDIN study
Salivatory cortisol levels	Prospective study with children from families with anthroposophic, partly anthroposophic, or non-anthroposophic lifestyles in Sweden. Salivatory samples of the child was collected at age 12 months (n=178) and 24 months (n=149)	Organic/bio-dynamic food consumption as part of an anthroposophic lifestyle	An anthroposophic lifestyle is associated with low cortisol levels in the evening at age 12 and 24 months, at age 24 months, also in the afternoon	Swartz *et al.* 2012 (270) The ALADDIN study

Sense of Coherence (SOC) scores, and salivatory cortisol scores	Prospective study with children from families with anthroposophic, partly anthroposophic, or non-anthroposophic lifestyles in Sweden. Salivatory samples of the whole family when the child was 6 months (n=210), 12 months (n=178) and 24 months of age (n=149)	Organic/bio-dynamic food consumption as part of an anthroposophic lifestyle	Sense of Coherence (SOC) scores did not vary in parents with different lifestyles and were not associated with salivatory cortisol levels in parents or children	Swartz *et al.* 2013 (271) The ALADDIN study
Salivatory cortisol levels, and allergic sensitization	Prospective study with children from 507 families with anthroposophic, partly anthroposophic, or non-anthroposophic lifestyles in Sweden. Salivatory cortisol levels, measured at 6 months. Blood samples for analyses of sensitization were obtained from parents at inclusion and from children at 6, 12, 24, and 60 months	Organic/bio-dynamic food consumption as part of an anthroposophic lifestyle	Lower risk of developing sensitization up to 5 years in children from families with an anthroposophic life-style. This risk is partially explained by low cortisol levels during infancy	Swartz *et al.* 2015 (272) The ALADDIN study

Appendix 1- Table 3. Studies investigating organic food consumption and human health in adults

Main endpoint	Study population and design	Exposure	Main findings	Authors/ reference
Hay fever and asthma-like symptoms	Cross-sectional study in 593 organic and 1,205 conventional farmers in the Netherlands	Organic vs. conventional farming practice	No difference in respiratory disease associated with organic consumption/ farming practice	Smit *et al.* 2007 (273)
Sperm quality	Cross-sectional study in 30 members of organic farming organisations and 73 blue-collar workers as controls in Denmark in 1994	Organic farmers had a high proportion of organic food in their diets	Higher sperm density in organic farmers	Abell *et al.* 1994 (274)
Sperm quality	Cross-sectional study in 55 members of organic farming organisations (age 20-45 years) and 141 controls working in an airline company (age 23-43 years) in Denmark in 1996	The organic farmers had at least 25% organic food in their diets	Higher semen quality in organic food consumers	Jensen *et al.* 1996 (275)
Sperm quality	Cross-sectional study in 85 organic (mean age 40 years) and 171 conventional farmers (mean age 38 years) in Denmark in 1995/1996	Organic food consumption assessed by FFQ and grouped into 0%, 1- 49%, and 50 -100% organic fruits and vegetables	Lower concentration of morphologically normal spermatozoa in the group with no organic food intake. No difference in 14 other parameters	Juhler *et al.* 1999 (276)
Sperm quality	Cross-sectional study in 85 organic (mean age 40 years) and 171 conventional farmers (mean age 38 years) in Denmark in 1995/1996	Comparison of pesticide exposure and sperm quality between organic and conventional farmers	No difference in sperm quality between organic and conventional farmers	Larsen *et al.* 1999 (277)

Risk factors for cardiovascular disease	Intervention study, cross-over design with 150 Italian men (100 healthy and 50 patients with chronic liver disease) in 2006-2008. Outcomes: BMI by dexa scan and blood parameters	14 days intervention with Mediterranean conventional diet (T1) and Mediterranean organic diet (T2)	Significant reduction in risk factors for cardiovascular disease after the T2 period	De Lorenzo *et al.* 2010 (278)
Perceived health effects experienced by consumers	Cross-sectional study among 566 adults who consumed organic food, in the Netherlands. Online questionnaire, May-December 2009	Organic food consumption	No health effects were reported by 30% of participants, while 70% reported general health benefits, including e.g. better resistance to illness, improved mental wellbeing, better stomach and bowel-function, fewer allergic complaints, and improved satiety	Van de Vijver and van Vliet 2012 (279)
Relative risks for cancer incidence, overall and for 17 individual cancer sites	Prospective study in 623,080 British middle-aged women with follow-up for 9.3 years from 2002 to 2011	Organic food consumption (any food group) in four categories; never, sometimes, usually, or always	No difference for all cancer incidence between usually/ always consume vs. never organic food, but a significant reduction in the risk of non-Hodgkin lymphoma was observed. A marginal increase in the risk of breast cancer was also detected	Bradbury *et al.* 2014 (127) The Million Women Study
Overall risk of cancer	Prospective study of 68,946 French adults (78.0% female; mean age at baseline, 44.2 years). Follow-up dates were May 10, 2009, to November 30, 2016	Organic food score, modelled as quartiles, was computed based on reported frequency of consumption of 16 products, (never, occasionally, or most of the time)	High organic food scores were linearly and negatively associated with the overall risk of cancer	Baudry *et al.* 2018 (280) The NutriNet-Santé study

Diabetes Mellitus	Cross-sectional study with 8199 participants aged ≥20 years from the National Health and Nutrition Examination Survey 2007–2008 and 2009–2010, in USA	Organic food purchase and frequency, ascertained by questionnaire, as a proxy of organic food consumption	Inverse association between organic food purchase and diabetes mellitus	Sun *et al.* 2018 (281) NHANES
Risk of type 2 diabetes	Prospective (internet-based) study with 33,256 participants (76% women, mean age: 53 years) in France, 2014–2019. Organic FFQ	Organic food consumption. Organic score calculated based on frequency of 264 food and drink items	Organic food consumption was inversely associated with the risk of type 2 diabetes	Kesse-Guyot *et al.* 2020 (282) The NutriNet-Santé study
Risk of overweight and obesity	Prospective (internet-based) study with 62,224 participants (78% women, mean age: 45 years) in France, 2009–2015. Measures of body weight change or obesity	Organic food consumption based on FFQ. Organic score calculated based on frequency of 264 food and drink items	Lower BMI increase with higher score for organic food consumption	Kesse-Guyot *et al.* 2017 (283) The NutriNet-Santé study
Metabolic syndrome	Cross-sectional study with 8,174 participants from the NutriNetSanté study who attended a clinical visit and completed an organic FFQ	Proportion of organic food in the diet (overall and by food group)	Higher organic food consumption was negatively associated with the prevalence of metabolic syndrome	Baudry *et al.* 2018 (284) The NutriNet-Santé study

Full name of the studies using acronyms

The PARSIFAL study: Prevention of Allergy Risk factors for Sensitization In children related to Farming and Anthroposophic Lifestyle

The ALADDIN study: Assessment of Lifestyle and Allergic Diseases During Infancy

The KOALA Birth Cohort Study: Kind, Ouders en gezondheid: Aandacht voor Leefstijl en Aanleg (Child, parents, and health: addressing lifestyle and constitution)

The MoBa study: The Norwegian Mother, Father and Child Cohort Study

The PELAGIE study: Perturbateurs endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance

NHANES: National Health and Nutrition Examination Survey

Appendix 2

Overview of studies in humans examining organic food consumption and related bio-markers

Studies investigating organic food consumption and pesticide residues in urine are presented first, according to type of study-population; pregnant women, children, families and adults, followed by studies of other types of biomarkers related to organic food.

Appendix 2 - Table 1. Studies examining organic food consumption and pesticide residues in urine in pregnant women

Main endpoint	**Study population and design**	**Exposure**	**Main findings**	**Authors/ reference**
Pesticide exposure among pregnant women	24-week organic produce intervention study with 20 women, aged 18-35 years, who reported eating exclusively conventionally grown food, recruited from the Idaho Women, Infants, and Children (WIC) program during their first trimester of pregnancy. Weekly spot urine samples were collected, combined to yield monthly composites and analysed for biomarkers of organophosphate (OP) and pyrethroid insecticides	Organic or conventional fruits and vegetables, randomly assigned, delivered weekly throughout their second or third trimesters. Food diary data demonstrated that 66% of all servings of fruits and vegetables consumed by participants in the 'organic produce' group were organic, compared to <3% in the 'conventional produce' group	Significant reduction in exposure to pyrethroid insecticides. No statistically significant differences were observed in detection frequency or concentrations for the four biomarkers of OP exposure quantified in this trial	Curl *et al.* 2019 (234)

Appendix 2 – Table 2. Studies examining organic food consumption and pesticide residues in urine in children

Main endpoint	**Study population and design**	**Exposure**	**Main findings**	**Authors/ Reference (Study)**
Urinary excretion of pesticide metabolites	Cross-sectional study (biological monitoring survey) of 110 children aged 2–5 years, from 96 urban and suburban households in Seattle, Washington, USA. Two spot urine samples from each child were collected in spring and fall 1998. Possible exposure risk factors were identified through a parental interview	General OP pesticide exposure	Measurable levels of OP pesticide metabolites was found in the urine of all children sampled, except for one child whose parents reported buying exclusively organic produce	Lu *et al.* 2001 (285)
Urinary excretion of OP pesticide metabolites (5 DAP)	Cross-sectional study of 18 children with organic diets and 21 children with conventional diets (aged 2-5 years) in Seattle, Washington, in 2001. Food diaries (3 days) before24-hr urine collection to assess OP pesticide exposure from diet	Diets with 'nearly all juice, fresh fruit, and fresh vegetable organic' vs. 'nearly all juice, fresh fruit, and fresh vegetable conventional'	Children with primarily organic diets had lower OP pesticide exposure than did children with primarily conventional diets Dose estimates suggest that organic diets can reduce children's exposure levels from above to below the U.S. EPA's chronic reference doses, thereby shifting exposures from a range of uncertain risk to a range of negligible risk	Curl *et al.* 2003 (286)

Urinary excretion of 5 common pyrethroid pesticide metabolites	Dietary intervention study during 15 consecutive days with 23 children 3–11 years of age, in the Seattle, Washington, area, USA, from July 2003 to May 2004. Most of the children's conventional diets were substituted with organic food items for 5 consecutive days and two daily spot urine samples were collected	Organic food for most of the diet during 5 consecutive days	The median urinary concentrations of malathion and chlorpyrifos decreased to the non-detectable levels immediately after the introduction of organic diet and remained nondetectable until the reintroduction of the conventional diets. Dietary intake of OP pesticides represents the major source of exposure in young children	Lu *et al.* 2006, 2008, 2009 (228,229, 287) The Children's Pesticide Exposure Study
Urinary excretion of pesticide metabolites. 23 metabolites measured	Dietary intervention study in 40 low-income Mexican-American children, 3-6 years of age, living in urban and agricultural communities in California, USA. Urinary samples collected over 16 consecutive days: 4 days of conventional food, 7 days with organic food, 5 days with conventional food	Organic diet were provided to the entire families for 7 days. Parents were instructed to request food items that were normally consumed by the participating child. Organic foods provided included fruits, breads, cereals, vegetables, dairy, eggs, juices, and snack foods	Reduced urinary concentrations of nonspecific dimethyl OP insecticide metabolites and the herbicide 2,4-D was associated with an organic diet	Bradman *et al.* 2015 (231)

Appendix 2 - Table 3. Studies examining organic food consumption and pesticide residues in urine in families

Main endpoint	Study population and design	Exposure	Main findings	Authors/reference
Insecticides, herbicides, and fungicides or their metabolites in urine	6-day dietary intervention study in adults and children (n=16 participants and a total of 158 urine samples) in four racially and geographically diverse families in USA	Organic food was provided to all family members for 6 days while at home, work, school, or day-care, including all beverages, all food categories, and oils, condiments, and spices	Significant reductions in urinary levels of thirteen pesticide metabolites and parent compounds representing OP, neonicotinoid, and pyrethroid insecticides and the herbicide 2,4-D following the introduction of an organic diet	Hyland *et al.* 2019 (233)

Appendix 2 - Table 4. Studies examining organic food consumption and pesticide residues in urine in adults

Main endpoint	Study population and design	Exposure	Main findings	Authors/reference
Urinary excretion of pesticide metabolites	7-day randomized, single-blinded, cross-over dietary intervention study with 13 adults (18-65 years of age) in Melbourne, Australia. Organic food intake diary. Urinary levels of six dialkylphosphate metabolites were analysed in first-morning voids collected on day 8 of each phase	Organic vs. conventional diets (> 80% of the diet)	Consumption of an organic diet for one week significantly reduced OP pesticide exposure	Oates *et al.* 2014 (230)

Urinary DAP measurements. Long-term dietary exposure to 14 OPs	Long-term dietary OP exposure was studied in a cohort of 4,466 participants in six metropolitan areas, in USA. Urinary DAP levels were analysed among 'conventional consumers' across tertiles of estimated exposure (N=480). Association between self-reported organic produce consumption habits and urinary DAP levels was studied in a subset of participants (n = 240)	Organic produce consumption	Frequent consumption of organic produce was associated with lower DAPs. Long-term dietary exposure to OPs estimated from dietary intake data were consistent with DAP measurements	Curl *et al.* 2015 (288) The MESA study
Urinary pesticide concentrations	Observational study of 300 participants (70% women, mean age 58.5 years), in France. Dietary information based on FFQ	'Low' (>10% organic food, in g/day in the whole diet) vs. 'high' (>50%) organic food) organic consumers. Comparison of a subset (n=150) based on a propensity score matching procedure to obtain two similar subsets mostly by the organic valence of their diet	Significantly lower urinary levels of diethylthiophosphate, dimethylthiophosphate, dialkylphosphates, and free 3-phenoxybenzoic acid were observed among organic consumers compared to conventional consumers	Baudry *et al.* 2019 (289) The NutriNet-Santé study

Appendix 2 - Table 5. Studies examining organic food consumption and various biomarkers

Main endpoint	**Study population and design**	**Exposure**	**Main findings**	**Authors/ Reference (Study)**
Flavonoids and biomarkers of antioxidant defence in blood and urine	Double-blinded, randomized crossover intervention study with 16 adults (six males and 10 females, 21-35 years of age) in Denmark. Two intervention periods, each lasting 22 days with a strict control of dietary intake, separated by a washout period of 3 weeks with habitual diet. 24-hour hour urine samples were collected on days 0 and 22. Biomarker analyses were performed on duplicate blood samples (taken on two successive days) before and after each intervention period	Organically produced vs. conventionally produced diets (no foods or drinks other than those provided in the study were allowed)	Higher content of flavonoids and biomarkers of antioxidant defence in blood and urine among those receiving the organic diet	Grinder-Pedersen *et al.* 2003 (50)
Physiological biomarkers, eating behaviour, and indicators of psychological well-being	Eight-week dietary intervention study with 17 women (aged 59-80) living in a cloister in Germany. Participants received a 2+4+2 weeks of conventional / bio-dynamic /conventional diet, respectively. Food diary, questionnaire about well-being	Organic (bio-dynamic) diet (all foods)	Lower blood pressure and enhanced well-being in the weeks with biodynamic diet compared with the weeks with the conventional diet	Huber *et al.* 2004 (290)
Antioxidant capacity	Clinical cross-over study in 10 Italian men aged 30-65 years. 14 days conventional diet, 14 days similar but organic diet	Organic vs. conventional diet	Increased antioxidant capacity after the 14 days with organic diet	Di Renzo *et al.* 2007 (291)

Conjugated linoleic acids in breast milk	Study of 312 breastfeeding mothers in the Netherlands. Breast milk was sampled December 2002 to May 2003, and June 2003 to September 2003 and analysed for contents of the conjugated linoleic acid isomers (CLA) and trans-vaccenic acid (TVA). Dietary information from FFQ	Organic dairy and meat products in the maternal diet	Higher levels of CLA in the breastmilk of women in the group with strict organic dairy consumption (analyses adjusted for co-variables)	Rist *et al.* 2007 (292) The KOALA study
Fatty acid composition in breast milk	Cross-sectional study of breastmilk among 310 mothers with different coherence to organic diet, 1 month postpartum, in the Netherlands	Mostly organic vs. mostly conventional diets	Higher concentrations of several trans fatty acids with organic diet, reflecting the fatty acid intake of the mothers	Mueller *et al.* 2010 (293) The KOALA study
Plasma status of carotenoids	A double-blinded, cross-over, human intervention trial on adult Danish men (n=18) was performed for two consecutive years (2007 and 2008) from January to April with diets prepared from the crop study	Effects of organic and conventional growth systems on the content of carotenoids in carrot roots, and on intake and plasma status of carotenoids in humans	The plasma status of carotenoids increased significantly after consumption of the organic and conventional diets, but no systematic differences between the agricultural production systems were observed	Søltoft *et al.* 2011 (294) The OrgTrace project
Bioavailability of Cu and Zn	Two double-blinded, cross-over trials with n=17 (2008) and n=16 (2009) adult Danish men. Three dietary periods of 12 days. On day 8 isotope labelled breakfast, lunch and dinner were given	Organic and conventional diets. Foods for the organic diet intervention was provided from a cultivation trial	No difference in intake or bioavailability of zinc or copper between the organic and conventional diets	Mark *et al.* 2013 (295) The OrgTrace project

Blood biomarkers (Fe, homocysteine, 25-hydroxy-vitamin D, plasma lipids)	Prospective cohort study among pregnant women (n 1339) in the Netherlands, years 2000 - 2002. FFQ and blood samples	Organic food consumption participant-groups defined based on the share of consumed organic products. Healthy diet indicators were considered in some statistical models	Higher levels of a marker of dairy products intake (pentadecanoic acid) and trans-fatty acids from natural origin (vaccenic acids) among participants consuming organic food, and lower plasma levels of homocysteine and 25-hydroxyvitamin D in the organic group than in the reference group. Corrected for indicators of the healthy diet pattern associated with organic food consumption	Simões-Wüst *et al.* 2017 (67) The KOALA study

Full name of the studies using acronyms

The MESA study: The Multi-Ethnic Study of Atherosclerosis study

The KOALA Birth Cohort Study: Kind, Ouders en gezondheid: Aandacht voor Leefstijl en Aanleg (Child, parents, and health: addressing lifestyle and constitution)

The Children Pesticide Exposure Study – Washington (CPES-WA)

The OrgTrace project: Content, bioavailability and health effects of trace elements and bioactive components of food products cultivated in organic and conventional agricultural systems

Appendix 3: STROBE check-list

Overview of how the items in the STROBE checklist were accounted for in Paper III

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

Please find below our account of how our work complies with the items in the STROBE checklist.

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Please see the title: "Reduced risk of preeclampsia with organic vegetable consumption; results from the prospective Norwegian Mother and Child Cohort Study", which includes the study design with commonly used terms. The study's design is also stated in the abstract: **Design** Prospective cohort study.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found This is what we have aimed at providing in the abstract.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Because dietary factors are among the factors which may affect risk of preeclampsia, and because a diet comprised of organically grown food differs qualitatively from a diet with conventionally grown food, the present study aimed at investigating possible association between organically grown food during pregnancy and the risk of preeclampsia. This rationale is outlined in the introduction.
Objectives	3	State specific objectives, including any prespecified hypotheses The objective of the study is stated on page 5.
Methods		
Study design	4	Present key elements of study design early in the paper This prospective study, within the Norwegian Mother and Child Cohort study, is presented early in the methods section, including description of the exposure variable (organic food consumption reported in mid-pregnancy), the outcome variable (preeclampsia as registered in the Medical Birth Registry of Norway), the relevant covariates, and the statistical methods used.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection The setting of the study is given first in the abstract, and further in the methods section (page 5). Time of data collection is stated on page 6.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Recruitment and methods of selection of participants are described in the methods section on page 5, and selection of the final study sample from the initially eligible women is described on page 6. Selection of participants is also described in Figure 1 (flow chart).
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed: Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Exposure, outcome, and potential confounders are described in the methods section, page 6-9. Diagnostic criteria for the outcome, preeclampsia, is stated in the methods section, page 7.

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Sources of the data in the present study are specified in the methods section, page 6 to page8. Please see an overview below: **The Baseline questionnaire in the MoBa-Study:** - Parity - Self-reported pre-pregnancy height - Self-reported pre-pregnancy weight - Self-reported weight at the end of pregnancy - Educational attainment (four categories: high school or less (≤12 years), 3-4 years of college/university (13-16 years), four years or more of college/university (17+ years), or other/missing values (n=584)). - Smoking in pregnancy (non-smokers, occasional smokers, and daily smokers) - Household income was expressed as a combination of the participant's and her partner's income (both <300 000 NOK, one ≥ 300 000 NOK, both ≥ 300 000 NOK, or missing values (n=632)). **The questionnaire answered six months postpartum:** - Self-reported weight at the end of pregnancy **The Food frequency questionnaire in the MoBa-Study:** - Organic food consumption in six specified food categories - Intake of individual food groups used to derive food patterns by principal component analysis. - Dietary supplement use (no supplement use, use of any supplement without vitamin D, and use of a vitamin D containing supplement) **The Medical Birth Registry of Norway:** Information about preeclampsia provided to the registry based on forms completed by the midwives after birth: - HELLP-syndrome (haemolysis, elevated liver enzymes and low platelet count); - Early onset preeclampsia - Late onset preeclampsia - Mild preeclampsia - Severe preeclampsia - Hypertension prior to pregnancy (yes/no) - Parity - Maternal age at delivery (four categories (14-20, 20-29, 30-40, and 40-46 years). The following variables have been validated: - Preeclampsia diagnosis in the Medical Birth Registry of Norway is validated (see reference page 7, methods, preeclampsia). - Food and nutrient intakes - The smoking variable
Bias	9	Describe any efforts to address potential sources of bias In the Norwegian Mother and Child Cohort Study as well as in similar studies, differences in socio-economic status and selection bias are the most serious concerns. These were addressed by adjusting for maternal education and total household income. In addition, we adjusted for known risk factors, e.g. smoking, body mass index, gestational weight gain, maternal age, and food pattern. (Statistical methods, page 8 -9 and discussion, page 11-13).
Study size	10	Explain how the study size was arrived at: The selection of the final study sample from the initially eligible women is described on page 6. Selection of participants is also described in Figure 1 (flow chart).

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why The way in which quantitative variables were divided into groups and why are described on page 7 (covariates), and page 8-9 (statistical methods). It is specified which variables were used as continuous variables, and which ones that were used as categorical variables in the statistical analyses. (Page 9 statistical methods)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Statistical methods are described on page 8. Relative risks were estimated as odds ratios (OR) by performing binary logistic regression with preeclampsia as the outcome and organic food consumption as the exposure. Examination of and controlling for confounding is described in the methods section on page 8 and 9.
		(*b*) Describe any methods used to examine subgroups and interactions Subgroups of the outcome (preeclampsia) is examined and reported in table 4, and in the text in the results section on page 11. Examination of interaction is described in the methods section on page 9, line 43, and in the results section on page 11.
		(*c*) Explain how missing data were addressed Exclusion due to missing data is described in the methods section, page 6 as well as in Figure 1. Variables with missing values were included in the analyses as categorical variables with missing values as one of the categories. This only applied to Educational attainment (n=584 with missing values) and Household income (n=632 with missing values). These variables are described in the methods section (under covariates), page 8.
		(*d*) If applicable, explain how loss to follow-up was addressed Not applicable.
		(*e*) Describe any sensitivity analyses Sensitivity analysis (with *v* without participants with missing values on any covariates) is described on page 9.
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed The numbers of individuals potentially eligible, excluded at each stage, and finally included in the study population are given on page on page 6.
		(b) Give reasons for non-participation at each stage Reason for exclusion is given on page 6.
		(c) Consider use of a flow diagram Please see Fig 1 for a flow diagram showing inclusion to the study population.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders The characteristics of study participants are given in Table 1. It is described in the text in the results section, page 10.

		(b) Indicate number of participants with missing data for each variable of interest The number of participants with missing values are given for each variable with a missing values category: Educational attainment: other/missing values (n=584). Page8. Household income: missing values (n=632). Page 8.
		(c) Summarise follow-up time (eg, average and total amount) Not applicable.
Outcome data	15*	Report numbers of outcome events or summary measures over time The number of participants diagnosed with preeclampsia is presented in Table 2 and Table 3, and in the text in the results section on page 10. It is also given in the abstract.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included In Table 2, unadjusted estimates for the association between consumption of organically produced food in six individual food groups and preeclampsia are given, as well as estimates adjusted only for total organic food consumption. In Table 3, estimates for the association between consumption of organic vegetables consumption and preeclampsia are given: 1) unadjusted (crude model), 2) confounder-adjusted excluding adjustment for dietary pattern, and 3) confounder-adjusted including adjustment for dietary pattern. All confounders are listed in the Tables, and their inclusion is described in the text in the methods section on page 9. For all estimates their precision is reported in the form of 95% confidence intervals.
		(*b*) Report category boundaries when continuous variables were categorized The only continuous variable categorised was maternal age at delivery (range 14 – 46 years), and the categories were: First category: 14-19 years Second category: 20-29 years Third category: 30-39 years Fourth category: 40-46 years This is described in the text on page 8 (covariates).
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period In the present study relative risk is calculated as odds ratio, and this is considered valid because of the low prevalence of the outcome (5.3%).
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses - Characteristics of participants *v* non-participants are given on page 6. - Sensitivity analysis (with *v* without participants with missing values on any covariates) is described on page 9. - Analyses with additional adjustment for total organic consumption are described on page 11. - Examinations of interaction are described on page 11. - Analyses of the outcome (preeclampsia) divided into sub-groups 1) by time of onset and 2) by severity are presented in Table 4, and described in the text on page 11.

Discussion		
Key results	18	Summarise key results with reference to study objectives The main result is stated in the beginning of the discussion section, page 11.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Limitations of the study are discussed on page 12-13.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Interpretation of the results is presented on pages 11 to page 16. Our interpretation is cautious, in the form of possible, hypothetical explanations, recognising the limitations of associations based on epidemiological data. Nevertheless, the hypotheses suggested are biologically plausible.
Generalisability	21	Discuss the generalisability (external validity) of the study results The generalizability of the study results is discussed on page 12.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based The funding of the present project as well as the funding for the Norwegian Mother and Child Cohort Study is described on page 17.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.