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Department of Landscape Architecture and Spatial Planning
Section of Public Health Science

Effect of dietary patterns on pregnancy outcomes in women with inflammatory bowel disease

Results from The Norwegian Mother- and Child Cohort Study (MoBa)

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Acknowledgements

This study was conducted in collaboration with the Institute of Clinical Molecular Biology (EpiGen) at Akershus University Hospital. The data in this study is collected from The Norwegian Mother- and Child Cohort Study (MoBa), owned by the National Institute of Public Health.

A project similar to this, was first presented to me on the master thesis presentation day for the Public Health students at NMBU, in 2015. I was, for several reasons, immediately drawn to this project in particular.

Firstly, I have a bachelor degree in nutrition, and I have come across inflammatory bowel disease in several occasions. I find the disease very interesting, as it has a large impact on nutrition. Secondly, this study was of an epidemiologic character, and included data from the largest pregnancy cohort in the world; MoBa. Epidemiology has been one of my favorite courses through this master program, and I am intrigued by the "detective work" one may find oneself doing when working within an epidemiological design. In addition, it did not hurt that the main supervisor in this project was Geir Aamodt, professor II at Norwegian University of Life Sciences (NMBU). His help has been invaluable, and he has done a great job in optimistically (and patiently!) guiding me through this thesis, in which I am very grateful for. Thank you, Geir.

I also want to thank my second supervisor MD, PhD May-Bente Bengtson, for discussing my article with me. I want to thank the MoBa-participants, The National Institute of Public Health, EpiGen and project manager Morten H. Vatn for the data access.

In addition, I want to add a special thanks to my fiancé Hans Joakim, for his invaluable support through this writing process, and through my entire education. There have been a lot of flash cards and pretend-censorship on your behalf through the years, and I am not sure where you found the patience. In addition, I want to thank my wonderful classmates for their optimism, and a special thanks to Bjørnar for sharing his knowledge and technical skills.

The original aim of the project was to investigate drinking quality in relation to pregnancy outcomes in women with IBD. However, the data never showed up from the extern source. Although there was some stress related to the change of topic, I am very happy with the result. When examining dietary patterns in this epidemiological study, I feel that my bachelor degree and master degree unite.

Thea L. Myklebust
Ås, Mai 2016

Summary

This Master thesis in Public Health Science aims at examining the relationship between dietary patterns and pregnancy outcomes in women with inflammatory bowel syndrome.

The thesis is divided into two parts. The first part includes a comprehensive presentation of relevant background information regarding the problem under interest. A wider presentation of inflammatory bowel disease will be given, in addition to the public health relevance of this study. This is followed by a method section, which comprises methodological considerations not accounted for in the article, and finally a wider theoretical and methodological discussion. The second part is a scientific article. The article gives detailed information regarding methods and results in particular. We will try to publish this article in an international journal.

The article describes our cohort study, conducted with data from The Norwegian Mother- and Child Cohort study (MoBa)(1999-2008). Our total sample included 104.996 singleton births. Of these, 489 children were born by mothers with inflammatory bowel disease and available for analysis. Information regarding dietary habits was obtained through a food frequency questionnaire, in MoBa. Three dietary patterns were extracted through factor analysis and entered into two logistic regression analyses. The models were adjusted for a set of confounders.

A significant protective effect was found in the highest third in one of the dietary patterns in relation to an adverse pregnancy outcome defined as small for gestational age, in women with inflammatory bowel disease compared to controls.

The discussion in the main thesis proposes several potential mechanisms explaining this observed effect. It is possible that both nutritional requirements and disease activity may play an important role in the relationship between dietary patterns and pregnancy outcomes.

Sammendrag

Denne masteroppgaven i folkehelsevitenskap søker å utforske forholdet mellom kostholdsmønstre og fødselsutfall, hos kvinner med inflammatorisk tarmsykdom.

Oppgaven består av to deler. Den første delen er en kappe som inneholder en utvidet presentasjon av relevant bakgrunnsinformasjon, samt en redegjørelse for oppgavens folkehelserelevans. I tillegg inneholder den en metodedel med informasjon som ikke finnes i artikkelen, samt en diskusjonsdel med utvidet diskusjon vedrørende teori og metode.

Den andre delen er en vitenskapelig artikkel, som vil bli forsøkt publisert i et internasjonalt tidsskrift. Artikkelen inneholder detaljert informasjon, spesielt i forhold til metode og resultater.

Artikkelen omhandler vår kohortstudie basert på data fra Den norske mor- og barnundersøkelsen (MoBa)(1999-2008). Det totale utvalget i vår studie bestod av 104.996 fødsler. Av disse var 489 barn født av kvinner med inflammatorisk tarmsykdom. Informasjon vedrørende kostholdsvaner ble innhentet fra et eget spørreskjema rettet mot kosthold (food frequency questionnaire) i MoBa. Tre forskjellige kostholdsmønstre ble identifisert gjennom faktoranalyse. Kostholdsmønsterne ble videre undersøkt i to logistisk regresjonsmodeller, justert for konfunderende variabler.

En signifikant, beskyttende effekt ble observert for et av kostholdsmønsterne på negativt fødselsutfall definert som liten for alder, hos kvinner med inflammatorisk tarmsykdom sammenlignet med kontroller.

I diskusjonsdelen vil potensielle mekanismer for denne observerte effekten bli grundig gjennomgått. Det er sannsynlig at både næringsstoffbehov og sykdomsaktivitet kan påvirke effekten mellom kostholdsmønstre og fødselsutfall.

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List of abbreviations

CD	Crohn’s disease
FD	Food diary
FFQ	Food frequency questionnaire
HL	Health literacy
IBD	Inflammatory bowel disease
LBW	Low birth weight
MBRN	Medical Birth Registry of Norway
MoBA	The Norwegian Mother- and Child Cohort Study
NIPH	Norwegian Institute of Public Health
NPH	New Public Health
NPR	Norwegian Patient Registry
PCA	Principal component analysis
SGA	Small for gestational age
UC	Ulcerative colitis

1. Introduction

Nature and nurture in beautiful harmony is the strongest force behind our existence. Through billions of years, series of random events in the form of spontaneous mutations and the environment's ruthless influence, have lead to adaptations resulting in life as we know it. The partition of nature versus nurture is not as apparent today, as new knowledge has risen. It is now clear that the environment has an even bigger influence on our phenotype than what was assumed in the Mendelian era. The field of epigenetics has contributed to this new knowledge in a great manner, and it is now widely accepted that factors in the environment can influence the transcription and translation of our genes; by determining whether our genes should be turned on or off.

In the following chapters we will investigate how exposures in the womb may affect the pregnancy outcome, and thereby somewhat determine the future life course of the offspring.

1.1 Public Health in a modern world

Public health, as stated by the World Health Organization (WHO), entails health and wellbeing on a population level, and aims at preventing disease, promoting health and prolonging the life in the entire population as a whole (1). The activities of public health aim at the total environment surrounding individuals; both on an individual level such as providing vaccines and health education, but also on a global and political level; making policies that promotes health and prevents poverty and infirmity.

The World Health Organization (WHO)(1) states three main functions of public health: 1) Assessment and monitoring of health, 2) Formulation of public policies designed for health promotion, both on a local and national level, and 3) Ensuring access to appropriate and cost-effective health services.

Much progress has been made in the field of public health since the days of John Snow, and his discovery of the source of the cholera outbreak in London in 1854 (2). In the early 20th century, public health underwent a transformation, changing its main perspective from a traditional biomedical model to a social model (3). This new approach was called the New Public Health (NPH). The magnitude and effect of health determinants change over time, and with the NPH the main focus in public health shifted as well. Public health activities became multidimensional, targeting both the individual and determinants in the environment likely to affect the health behavior of the individual, which in turn is linked to health outcomes (3). The importance of this focus became evident alongside the increasing industrialization. Communicable diseases were on retreat due to large-scale immunization programs, better housing, sanitation and nutrition. However, at this point the incidence of non-communicable (chronic) diseases were on the rise (4).

Chronic illnesses are of great concern for the public health. Such diseases lead to great health costs directly and indirectly, and deprivation of quality of life. As for many of these diseases, the pathology is fully understood, but the etiology remains unclear. Inflammatory bowel disease (IBD) is a chronic illness, where we know little about the cause, despite heavily investigated over the last decade (5). Results from large epidemiological studies suggest that environmental factors play an important role in the pathogenesis in genetic susceptible individuals (6). There are, however, no general agreement on what kind of environmental factors these are. However, what we do know, is that women with IBD have a higher incidence of complications during pregnancy and adverse pregnancy outcomes than women from the general population (7-15). IBD is a disease affecting the gastrointestinal system, and nutrition and dietary patterns are of interest in investigating possible preventive strategies for pregnant IBD-women.

1.2 Adverse pregnancy outcomes in a Public Health Perspective

1.2.1 The Fetal Programming hypothesis

Research has shown that malnutrition in pregnancy may affect the epigenome of the fetus and thus be a risk factor for developing chronic diseases in adult life (16-19). This hypothesis is known as the fetal programming hypothesis (20). The hypothesis is strongly influenced by Dr. David Barker, a physician and epidemiologist developing the programming idea in the early 1990s. Barker hypothesized that coronary disease and stroke, and associated conditions such as hypertension and diabetes type 2, originates from growth restrictions during fetal life and infancy (20). Further support was offered by the research reported by the Norwegian doctor, Anders Forsdahl (21). Through his geographical research, he found that past infant mortality correlated with later coronary heart disease in 20 counties in Norway. The programming hypothesis is closely related to epigenetics, and proposes the theory of adverse intrauterine conditions in early fetal development may result in long-term changes in the physiology and metabolism of the offspring (20, 22). Malnutrition has been particularly studied, and research findings indicate that individuals exposed to malnutrition in fetal life where more likely to become overweight or obese in adult life, due to "programming"- and alterations in the metabolism of the fetus.

The fetus undergoes so called ”critical” periods of development (20). In these periods, often characterized by rapid cell division, the fetus will adapt to a potential lack of nutrients by slowing down the cell division rate in tissues undergoing ”critical” periods of development. This may lead to serious effects on the function of the organs, and a ”programming” of the body. A large body of evidence suggests that this programming may contribute in explaining several of the major chronic diseases of today, such as coronary heart disease and diabetes, and associated conditions such as hypertension, high levels of cholesterol and abnormal glucose-insulin metabolism (17, 18, 20). A Finnish study with a follow up of 350.000 person-years, found that low birth weight and short length at birth, predicted premature death in adulthood (<55 years) (23). This may be as a consequence to fetal adaption to malnutrition that is beneficial for short-term survival.

Those nine (or less!) months *in utero* may set the life course for the offspring, not only by altering physiological processes, but also through socioeconomic disadvantages. Research suggests an association between birth weight and later socioeconomic disadvantage in childhood and adolescence (24, 25). An association has been found between low birth weight and housing inadequacy, lower social class, overcrowding in the household and financial difficulties. Socioeconomic status has been identified as an important health determinant, and may be a risk factor for an overwhelming number of diseases (4).

In addition to harmful programming, preterm and low birth weight infants are at increased risk of neonatal mortality and morbidity. Preterm birth is considered the leading cause of neonatal death worldwide, and is a risk factor for infections, respiratory- and gastrointestinal diagnosis, cerebral palsy and other neurodevelopmental disabilities (26-28).

Although more research is required, these findings suggests that adverse pregnancy outcomes may influence the future life course of the offspring, lead to significant health costs, and increase social inequalities in health, and thus influence the public health of tomorrow.

1.3 Acting on the matter: Prevention and health promotion

With the slightly increasing incidence of IBD in Europe, and the disease being a risk factor for adverse pregnancy outcomes, it is important to understand factors that may interact with the disease and thus increase the risk. Optimized care for IBD-patients in pregnancy will be an investment in public health and health costs in the future.

1.3.1 Health promotion

Public health entails health promotion and prevention (29). The term "prevention" is often used interchangeably with "disease prevention", according to a biomedical model of health. However, in the NPH approach, prevention may entail both prevention and health promotion. The latter terminology will be used throughout this thesis.

Health promotion is, in contrast to disease prevention, aiming at improving factors that contributes to good health rather than focusing on factors which negatively influences the health (4). This is in accordance with the NPH-perspective. Factors that influences our health (in either direction) are called health determinants. A wide range of health determinants have been identified through the years, and we may find them interacting in several pathways and levels. On a personal and individual level, such determinants may be sex, genetics, age and lifestyle factors. In the light of epigenetics, one may even add our parents and grandparents' lifestyle factors into this category. On a social level, we may determinants to be social networks, living conditions and psychosocial work environment. On a community- or global scale, important determinants may be access to food and healthcare, general socioeconomic conditions, warfare and unemployment rates. These are factors the individual cannot readily influence. In public health, we may thus on different levels of determinants. In this study, the focus is primarily at the individual health determinants.

1.3.2 Prevention strategies

The primary goal of prevention is to avoid, reduce or delay the onset of disease (29). This is known as primary prevention. Secondary prevention aims at preventing worsening of already existing disease, while tertiary prevention aims at reducing pain and complications in disease.

The Norwegian Public Health Act (30) states that the aim of the public health is to promote the health, wellbeing, social and environmental conditions, and prevent physical and psychological sickness, illness or disease in the public. In the Law of Specialized Health Care (31), prevention is also explicitly mentioned as an aim in the specialized health care units, and both private and public hospitals are to promote the public health. This is in particular importance regarding our study, as the clinical care of pregnant women with IBD is set to the hospitals.

In relation to the public health relevance of this study, the prevention focus is not on maternal IBD, but on preventing adverse pregnancy outcomes. This may thus be looked at both as a primary and a secondary prevention strategy. We wish to produce knowledge to prevent adverse pregnancy outcomes as a result of the disease (secondary prevention), and we wish to do so because of the potential influence of the adverse pregnancy outcome on the health of the neonate and future life course (primary prevention).

Pregnancies in women with IBD are considered high-risk pregnancies, and may need extra care and support at the hospital during the pregnancy (32). Our results may be of interest in the clinical care and follow-up of pregnant women with IBD in the hospital or general practitioner. This prevention strategy may be considered as a high-risk prevention strategy (29). High-risk prevention is often set in the clinic, and requires a diagnosis on an individual level. We wish to inform those at high risk of the outcome, rather than the whole population of pregnant women. This would not be very cost-effective, given that IBD is a rather rare disease. In the high-risk prevention approach, the probability of changing the outcome for one individual is higher than in mass strategy.

1.3.3 Knowledge as an important health determinant

In relation to dietary patterns and pregnancy in women with IBD, prevention would be an appropriate approach considering the fact that nutrition in pregnancy is a modifiable risk factor, and may be altered through sufficient guidance and health education.

Knowledge is an important determinant in health behavior (3). In health promotion, one seek to encourage people to adopt healthy behaviors, or healthy lifestyles, in which health can be improved (4). Behavior change may be modeled as a spiral, as in the Transtheoretical model, developed by Prochazka and DiClemente (Figure 2)(3). This model is also often referred to as the “Stages of Change”. In the first stages, knowledge is considered a key factor for initiating change through consciousness raising. Such knowledge may be provided by health professionals in educational programs or brochures, or through personal feedback from family and friends.

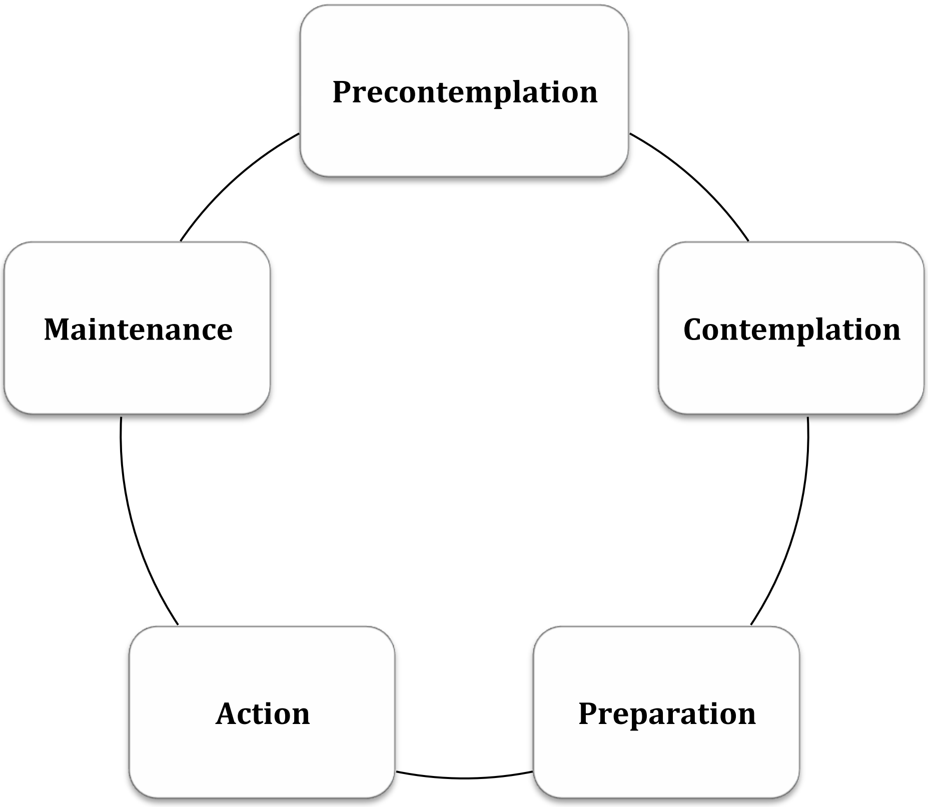

Figure 2. The Transtheoretical model. Modified after the model developed by Prochaska and DiClemente in 1983 (3).

Health education has been a formalized activity within the public health since the 1980's, with the emergence of various campaigns (4). Health education is defined as providing information, raise awareness, motivating and equipping people with skills needed to make lifestyle changes. Guidance may be both theoretical and practical, and should be evidence-based. This approach has been criticized for victim blaming and not acknowledging the fact that humans do not exist in a vacuum. It is important to underline the fact that health education needs to be addressed alongside other individual- or structural health determinants. Health education is closely related to empowerment. Empowerment is a way of enabling people to gain control and power over their own lives through development of skills and resources, such as knowledge (29).

When choosing a communication strategy, several important factors need to be considered before tailoring a suitable program. Social characteristics such as previous experiences, age, culture and educational level may influence the health behavior and health literacy of the individual (29). Health literacy (HL) is defined as an cognitive and intellectual asset in which enables the individual to obtain, evaluate, understand and apply health information (33). HL serves as both a premise and a goal in health education. The HL-level in the target population should be considered before initiating health education programs, and may be considered a tool in choosing effective means of communication.

Nutrition guidance in an educational way may increase knowledge and motivation in changing inappropriate dietary habits. Research has found pregnant women in general to be more motivated for lifestyle changes than non-pregnant women (34, 35).
Health education and alterations in the diet may thus be a very cost-effective strategy in preventing adverse pregnancy outcomes in IBD. Better care and nutritional guidance may prevent adverse pregnancy outcomes and give the offspring a better chance in life, while reducing social inequalities in health, and health costs related to chronic illnesses in which the offspring may be at increased risk of in adult life.

1.4 Inflammatory bowel disease; epidemiology and risk factors

Inflammatory bowel disease (IBD) comprises diseases characterized by an inappropriate, relapsing inflammatory response of the intestinal mucosa in genetic susceptible individuals (5). The most prevalent forms of the disease are Crohn's disease (CD) and ulcerative colitis (UC). Despite some phenotypic overlap, it is widely accepted that the two are separate entities. However, in 10% of cases there are impossible to separate the two diagnoses (36).

1.4.1 Epidemiology

The peak onset of the disease is in adolescence and early adulthood; 15 to 30 years of age (37). The prevalence in Europe is estimated to be around 2,5 – 3 million people. This has a direct health cost of 4,6 – 5,6 billions euro per year (38). Epidemiological studies indicate that both CD and UC have a high prevalence in industrialized countries, such as countries in Western Europe and North America (36, 38).

The incidence is rather stable worldwide, but seems to increase in some areas (6). This is thought to be a result of the population growth, and due to the fact that IBD-patients do not have a higher mortality rate than the general population (38). The lowest incidence rates are reported from South America, southeast Asia, Africa (except South Africa) and Australia (39). These findings suggest a North-South gradient, and may reflect geographical variations in environmental exposures, health services, industrialization, sanitation and hygiene, in addition to genetic and ethnic variation. This hypothesis is supported by research showing an increased incidence rate of IBD in immigrants moving to developed countries, and a correlation between industrialization and IBD in Hong Kong and Mainland China (39).

Scandinavia and UK have the highest incidence in Europe. South and Eastern Europe have the lowest incidence (38). Given the high incidence in western countries, and the increase in incidence in developing countries, a hypothesis has been formed, stating that the western lifestyle and modernization may play a causal role in the etiology (6).

Although we have a high prevalence in Scandinavia compared to other regions of the world, the disease is still considered a rare disease. In the Norwegian IBSEN-study from 1996, researchers estimated the incidence of CD in Norway to be 5.8 per 100.000 person years, and 13.6 per 100.000 person years for UC (40, 41). In comparison, the incidence rate for breast cancer in women in Norway in 2014, was 126.5 per 100.000 person-years (42).

1.4.2 Etiology

The cause of IBD remains unclear. Research indicates that the etiology involves an interaction between the immune system of the intestine, intestinal microbes, genetic- and environmental factors (37). Inflammation is caused by an abnormal immune response in genetic susceptible individuals.

As the field of genetics advances, knowledge has been produced regarding specific genes and risk of developing IBD (37). Multiple genes have been associated with both conditions of IBD. The NOD2 (also called CARD15) gene is identified as a risk factor for CD. The gene codes for a peptide that recognizes bacteria in the intestine (43). In CD-patients this gene may be affected. When the body fails to produce this peptide, it may result in an abnormal immune response such as seen in IBD, with fibrosis and tissue damaging. Variation in the gene encoding interleukin-23 receptor subunits and the IL12B, STAT3 and NKX2-3 gene regions have been associated with both UC and CD (44).

There is a familial clustering in 6-8% of UC-patients and 20% of CD-patients (36). Having a first relative with IBD increases the risk of developing IBD. A familial history of the disease is considered to be the largest independent risk factor for IBD (39).

Ethnicity is identified as a potential risk factor (39). CD is more prevalent in Jewish people than in any other ethnic group, and UC has a three- to fivefold increase in prevalence in Jewish people.

Microorganisms are thought to play a role in the etiology, and animal studies have found that mice without a normal intestinal bacterial flora does not develop the IBD (36). Research indicates that a form of dysregulation of the normally controlled immune response and mucosal barrier to commensal bacteria in the gut drives the inflammation (44).

A large number of environmental factors have been identified as potential predictors of the disease. The variation in prevalence of the disease across geographical areas and time has lead to hypotheses regarding factors found in the environment (6). However, despite the increasing number of studies on the matter, no consensus has been made around single environmental factors – except for smoking. Smoking is found to be a risk factor in CD. However smoking is found to be somewhat protective in UC.

Dietary patterns have been investigated as potential risk factors, supported by the theory of the increase in incidence of IBD with westernization and the western lifestyle. While somewhat inconclusive, research on dietary patterns and risk of IBD has shown some association between large consumption of meat, fatty acids and sugar-containing foods and development of IBD, and a protective effect of a diet rich in fiber, fruits and vegetables (45-48).

1.4.3 Symptoms

Both conditions of IBD affect the gastrointestinal tract, and thus share similar symptoms. Both of the diseases are characterized by intermittent inflammation of the intestine followed by symptoms like chronic diarrhea, abdominal pain, fever, food intolerance, weight loss, anemia and other extra intestinal symptoms (43).

CD primarily affects the ileum and colon, although it may affect any part of the intestine. UC is exclusive to the colon, and rectum is always affected (37). As for CD, the inflammation is transmural and separated by healthy segments, while in UC the inflammation is of a continuous pattern and confined to the mucosa. CD is associated with intestinal granulomas, strictures and fistulas, while these are not typical in UC (37). Location of the inflammation may have a great impact on the absorption of nutrients, and thus the nutritional status (43).

1.4.4 Complications

There are a number of serious complications related to the disease, such as obstruction and perforation of the intestine (36). In CD, common complications are strictures that may obstruct the intestines, and fistulas and lesions in the rectum. UC is a risk factor for colorectal cancer. However, there are no increased mortality in IBD-patients compared to the general population (49).

IBD may have a large influence on the nutritional status of the individual. In active state of the disease (especially in CD) it is normally a loss of epithelium cells in the mucosa, affecting the absorption of nutrients in the small intestine (5). Drug-nutrient interaction may impair the absorption as well (50). An increased loss of nutrients and fluids may occur in chronic diarrhea (43). In addition, IBD-patients may have increased nutritional requirements. Inflammation may impair the secretion of enzymes important to digestion, such as lactase. In CD, a transient lactose intolerance may be observed in active state of the disease (51). Food intolerance is more prevalent in IBD-patients than in the general population, and weight loss is a common complication. In general, IBD-patients have a lower BMI than healthy individuals (36).

Extra intestinal complications such as affection of the eyes, joints (rheumatic diseases), skin, liver and anemia is rather prevalent in IBD-patients (36). In addition, the disease exposes the individual to several physical and psychosocial challenges that may impair the life quality (49, 52, 53). In UC, there may be an acute and urgent need of using the toilet that may be unpractical and challenging in everyday life. The fear of incontinence may lead to inactivity and isolation of the patient. This may hinder the patient from engaging in work- and social life (36).

1.4.5 Diagnosis

The diagnosis depends on clinical history, physical findings such as endoscopic or histological features, as well as laboratory tests (54). These findings usually permit a firm diagnosis. However, in 10% of patients there are impossible to distinguish UC from CD – this is caller indeterminate colitis. In this study, none of the women participating in this study had this IBD-subtype.

1.4.6 Treatment and prognosis

Treatment is primarily palliative and secondary preventive. Type of treatment depends on type of disease and complications. Both forms of IBD can be treated with anti-inflammatory drugs such as 5-ASA and corticosteroids (5). Immunosuppressive drugs may be used in CD. Supportive treatment such as anti-diarrheal drugs and carefully regulated diet may be needed in active state of the disease (50). In some cases nutritional treatment may be considered as primary treatment. There are no well-established dietary guidelines for IBD-patients.

It is estimated that around 70% of all CD-patients will need a form of surgery at one point in life. Acute complications such as perforation of the intestine may require surgery. In UC resection of the colon may be curative (43).

1.5 Pregnancy in inflammatory bowel disease

IBD is usually onset in early adulthood, coinciding with the peak reproductive years of women (37). However, research indicates that neither women nor men have reduced fertility compared to the general population (7, 55). Tavernier et al. found in a review from 2013 that childlessness observed in IBD-patients may be by choice due to concerns and impairment of everyday life due to the disease (55).

Pregnancies in women with IBD are considered as high-risk pregnancies (32). Research indicates that IBD is a risk factor for negative pregnancy outcomes such as preterm birth, low birth weight, small for gestational age, caesarean section, and congenital abnormalities (7-15). Pregnancy outcome is found to be dependent both on IBD-subtype and state of the disease (7, 9, 56). Both maternal and paternal IBD are risk factors for preterm birth, and the risk is increased if a first degree relative has IBD (10). These findings may be explained by the genetic component in IBD.

Disease activity at conception is considered to be an important predictor of disease activity through pregnancy (7, 56, 57). Long disease duration and immunosuppressive therapy was found to be a risk factor for active disease in women with CD during pregnancy, in a study by Pedersen et al. (58). Active disease at time of conception and in pregnancy is considered a potential risk factor for both complications during pregnancy and adverse pregnancy outcomes; such as preterm birth (7, 56, 59, 60).

1.6 Nutritional considerations in IBD and in pregnancy

A high proportion of IBD-patients have a restricted diet due to various subjective dietary beliefs (61-64). Many patients report symptom relief when excluding certain foods from their diet. There is not sufficient data to support a single diet in IBD, neither for CD nor UC (65). Although there are no firm dietary recommendations for IBD, some exclusion diets may benefit subgroups (50, 62, 63). A large proportion of IBD-patients report exclusion of dairy products from their diet, although research is inconclusive on the matter of dairy being a risk factor for IBD or worsening of symptoms (51, 64).

Although symptom relief is of great importance in pregnancy, exclusion of food groups may lead to nutrition deficiencies of both micro- and macro nutrients (50). The importance of a healthy diet with few restrictions should be stressed. IBD-patients are already vulnerable to nutrition deficiencies, in clinical remission as well as in active state of the disease (66). The severity of malnutrition in IBD-patients is dependent on duration, activity and location of the disease (67). CD patients are generally more exposed to protein-energy malnutrition and micro-nutrient deficiency, given the location of the disease (50). IBD patients are found to be especially at risk of energy-, calcium-, vitamin D, folic acid-, vitamin B12- and zinc deficiencies (50, 68). An appropriate nutritional status in the mother is of great importance for fetal development and health (16, 18-20). The fetus requires an adequate amount of macro- and micronutrient to develop organ systems (43). Ensuring optimal nutrition is important for a safe pregnancy and healthy birth outcome, and may also decrease the risk of chronic diseases in adults through epigenetic alterations (16, 18-20).

1.6.1 Dietary patterns

Dietary patterns may be defined as a collection of correlating foods and food groups, often extracted by factor analysis (69). For example, foods rich in fat and/or sugar often correlate in a typical western diet. Dietary patterns are often heavily influenced by culture, ethnicity, geography, age, family structure and educational status (70-73). Dietary patterns have been investigated as potential risk factors for adverse pregnancy outcomes in a general pregnant population (74-82). A "prudent" or Mediterranean dietary pattern rich in dairy, fish, vegetable oils, fruit and vegetables has been found to lower the risk of preterm delivery and LBW in healthy women (74-79, 81, 82). A dietary pattern based on foods and beverages rich on sugar is found to be a risk factor for SGA (78).

1.7 Aim of the study

Nutrition is of unquestionable importance in pregnancy. Pregnant women with IBD are at increased risk of adverse pregnancy outcomes. With IBD being a gastrointestinal disorder, putting patients at an increased risk of nutritional deficiencies, it is of great interest to investigate whether dietary patterns could interact with the disease and thus have a greater impact on pregnancy outcomes. Research exists on the relationship between dietary patterns and pregnancy outcomes in a general, pregnant population. To the best of our knowledge, dietary patterns in relation to pregnancy outcomes in women with IBD, has yet to be investigated.

The aim of this study was to investigate the association between dietary patterns in women with IBD and risk of adverse pregnancy outcomes, using data from the Norwegian MoBa-study. Findings may be important in developing sufficient clinical care and health education of pregnant women with IBD, and thus prevent adverse pregnancy outcomes, which may impair the public health.

2. Material and method

2.1 Summary of the method

Our study is a sub-cohort in the MoBa-study, which is a prospective, population based cohort based on questionnaires and national health registries (83, 84). Women with IBD (CD or UC) were identified in MoBa from The Norwegian patient registry (NPR).

The aim of this study was to examine the relationship between various dietary patterns and risk of adverse pregnancy outcomes in women with IBD. Adverse pregnancy outcomes were defined as preterm birth (delivery < 37 weeks of gestation), low birth weight (LBW)(< 2500 g) and small for gestational age (SGA); defined as birth weight below the 10th percentile of the Norwegian weight curve (85).

Birth outcomes were obtained from MoBa from The Medical Birth Registry of Norway (MBRN)(84). Personal information such as age, educational status and medical history was collected from the first questionnaire submitted in MoBa. Information on dietary habits was collected from a food frequency questionnaire.

Dietary patterns were extracted using principal component factor analysis, and three patterns were identified; a ”Prudent”, ”Western” and ”Traditional” dietary pattern.

We used logistic regression to estimate the relationship between dietary patterns and pregnancy outcomes. The analysis was performed in two steps; 1) a logistic regression analysis within a IBD sub-set in MoBa; to analyze the effect of dietary patterns on pregnancy outcomes in women with IBD, and 2) a logistic regression within MoBa; entering dietary patterns as interaction terms with IBD, to investigate whether the effect of dietary patterns on pregnancy outcomes is increased in women with IBD compared to

controls. Estimates of risk are presented in odds ratios (OR) with corresponding 95% confidence intervals. The statistical analysis was restricted to singleton births.
A sensitivity analysis was performed on the IBD-subset, testing disease activity as a potential effect modifier.

2.2 Study design

2.2.1 The Norwegian Mother and Child Cohort Study

Producing knowledge on the matter of dietary patterns and pregnancy outcomes in women with IBD is a premise for the development of educational programs. In order to do so, we need to conduct both exploratory and explanatory research. Epidemiology is the main research tool in public health science (86). Using information from population data may provide samples sizes that yields trustworthy risk estimates, rather than mere coincidences. Fortunately, health registries in Norwegian and the Scandinavian countries are of high quality, and may thus be used in epidemiological studies. The Norwegian Mother- and child cohort study (MoBa) is such a study, based on national registries and surveys (83, 84).

MoBa is an open, prospective cohort conducted by the Norwegian Institute of Public Health (NIPH)(83). The study is considered to be the largest pregnancy cohort in the world, including 114.500 pregnancies in total.

The main objective in MoBa is to estimate the association between various exposures and diseases, to develop effective prevention strategies (83). The study has no exclusion criteria. The target population is all women who give birth in Norway, and women can participate in the study with several pregnancies. All hospitals and maternity units in Norway are included in the study.

The recruitment period lasted from 1999 to 2008 (83). Invitations were sent out to all pregnant women in Norway before their appointment for the routine ultrasound, around pregnancy week 17. The postal invitation included information, first questionnaire (Q1) and consent form. The mother and father received a total of three questionnaires during the pregnancy, including a food frequency questionnaire (FFQ)(83). Biological samples such as blood and urine samples were collected at ultrasound examination at the hospitals, after the woman has consented. A blood sample was drawn from the father, given his consent.

Q1 addresses outcome of previous pregnancies, mother's medical history before and during pregnancy, medication use, lifestyle habits, mental health, occupational status and exposures in the workplace and home (83). The paternal questionnaire addresses the medical history of the father, lifestyle, occupation and exposures at the workplace and home. The second questionnaire (Q2) was a FFQ sent out around week 22 of pregnancy, addressing various aspects of the mother's dietary habits. Q3 was submitted in week 30 and addresses the health status of the mother during pregnancy, and changes in work and lifestyle. In our primary study we analyze data from Q1 and Q2.

The data from the questionnaires and biological samples are linked to the national health registries; Medical Birth Registry, National Patient Registry, Cause of Death Registry, Prescription Database, Vaccination Registry and Cancer Registry (87).

2.3 Literature

Relevant literature for our study was collected through strategic searching in PubMed (Medline) and Web of Science (Web of Knowledge).

In PubMed, MeSH-terms were used to find literature on the different topics addressed in the article and thesis. Articles in the initial search were selected with respect to relevance, journal and citations.

In Web of Science, articles may be ranked after number of citations, and articles with the highest number of citations were preferred. This method may be heavily affected by publication bias, and was primarily used on topics with a lot of search results, such as general information regarding IBD. Reviews were preferred in the initial search.

Search words used in the initial search (either as MeSH-terms or as free text):

- Dietary patterns + inflammatory bowel disease
- Dietary patterns + pregnancy outcome
- Dietary patterns + inflammatory bowel disease + pregnancy outcome
- Etiology + inflammatory bowel disease
- MoBa cohort study
- Nutrition + fetal programming
- Nutrition + inflammatory bowel disease
- Nutrition + pregnancy outcomes
- Nutrition + inflammatory bowel disease + pregnancy outcome
- Nutrition deficiencies + inflammatory bowel disease
- Pathology + inflammatory bowel disease

After the literature from the initial search was reviewed, snowball sampling was used as the primary method for collecting additional information (88). Reference lists of articles with an appropriate study design and quality, were examined. Relevant references found in the articles were retrieved from PubMed.

2.4 Covariates

Potential confounding variables were identified through existing literature and knowledge regarding the nature of IBD, dietary patterns and pregnancy outcomes.
We controlled for maternal body mass index (BMI) as a continuous variable, age divided into three groups (<18, 18-34, >34 years), educational status divided into the following categories (high school or less, 3 years of college/university, or master degree or higher), total energy intake in quartiles (<1870, 1871-2224, 2225-2657, and > 2658 kcal), and smoking (dichotomous variable). Diabetes mellitus and chronic hypertension were considered as important confounders, but was excluded from the model due to low prevalence in the IBD group.

2.5 Dietary information

Data regarding dietary habits and consumption of specific foods and beverages were obtained from the FFQ. The FFQ is a semi-quantitative questionnaire where the women are to report the consumption frequencies of different foods and beverages, and other nutrition related questions such as nutrient supplement use (83). The questionnaire is designed to give an estimation of both quantity and quality of the dietary habits of the mother during pregnancy. From March 2002 to the spring of 2004, the FFQ was sent out alongside the Q1 and postal invitation. However from May 2004, it was sent out as the Q2 in week 22 of pregnancy, hoping this would increase the participation rate of the study (76).

The FFQ was especially developed for MoBa, and has been validated in a study by Brantsæter et al. (89, 90). The FFQ from 2004 (12 pages long) consist of 340 questions organized into 40 groups according to the Norwegian meal pattern (76). Three of these groups included questions regarding dietary patterns, and 23 regarding the consumption of 255 specific food items. The aim was to cover energy intake, nutrients, non-nutrients, foods and food-groups.

2.6 Extracting dietary patterns

Research shows that extraction of dietary patterns is a valid tool in assessing association between diets and health outcomes, and gives a good characterization of diet on a nutrient level (91). Factor analysis is a way of extracting patterns in a dataset from correlating variables (69).

We conducted a principal component analysis (PCA), using an orthogonal (varimax) rotation in SPSS. Prior to the analysis, we tested the suitability of the data by conducting a correlation matrix, Bartlett's Test of Sphericity ($p< 0,001$) and Kaiser-Meyer-Olkin test (KMO = 0,721). The Bartlett's Test of Sphericity tests the null hypothesis; that there are no relationships between the food variables in the correlation matrix (69). The Kaiser-

Meyer-Olkin test also tests the strength of the relationship between the food variables, by comparing calculated correlation coefficients to the partial correlation coefficients. The KMO measure ranges between 0 and 1, with smaller values indicating a weak relationship between food variables.

We entered 98 continuous food group variables from the MoBa-dataset in the PCA. These variables are recoded into food groups from the FFQ-answers, by researchers in the MoBa research team. An eigenvalue over 1 was set as an initial criterion, and the analysis extracted 29 components in which none of the food groups had factor loadings below the absolute value of 0.25. This was due to interpretability issues; if many food variables with low loadings had appeared in a pattern in would be difficult to label and describe the dietary pattern. A component may be regarded as a cluster of related food variables representing an underlying pattern (69).

After the extraction, we needed to reduce the data into a smaller number of components. Three dietary patterns were retained after examining the scree plot and the nature of the variables in the components with the highest eigenvalues. A fourth dietary pattern was considered, as it appeared over the “elbow” in the scree plot, but after examining the factor loadings of the food groups we found this pattern too hard to label due to few factor loadings over absolute value 0,25 (Figure 2).

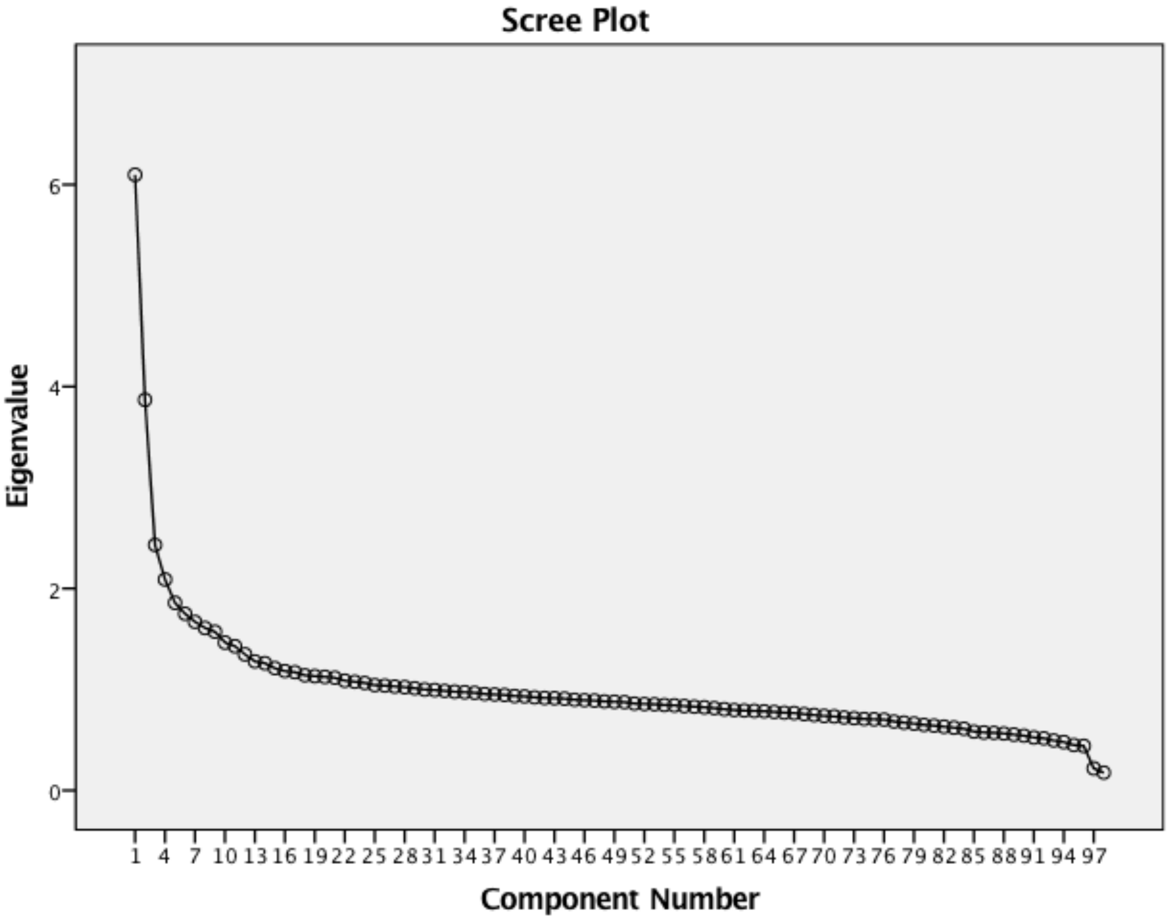

Figure 2. Scree plot obtained from the PCA, using SPSS, version 23.

The three components were labeled based on the factor loadings and nature of variables, and identified as a "Prudent"-, "Western"-, and "Traditional" dietary pattern. The three variables were entered in the logistic regression models as independent variables. All variables were entered into the same model, controlling for each other.

Each food group within a given dietary pattern is assigned a factor loading in the factor analysis. This factor loading is a loading coefficient that is multiplied with the consumption of a given food group in each pregnancy. The sum of these loadings forms a factor score that reflects the adherence to a given dietary pattern for each woman. As an example, the "Prudent" dietary pattern scores negatively in processed meat products. If a woman has consumed a high proportion of such products, her factor score for the

"Prudent" dietary pattern will be reduced, and she will thus be likely to be categorized in the lowest third of the dietary pattern. The mean factor score across the whole MoBa population is zero. A negative factor score indicates a lower consumption of the dietary patterns, and a positive factor score indicates a higher consumption.

2.7 Statistical analysis

In this study, we wanted to investigate whether there was a synergy effect between dietary patterns and IBD on pregnancy outcomes. Synergy, or biological interaction, is a concept within epidemiology, relating to the fact that two or more causes are necessary to develop disease (92). It assumed that most diseases occur from an interaction between two or more causes or exposures.

The pregnancy outcomes were denoted as dichotomous variables, and the relationship between dietary patterns and pregnancy outcomes was estimated in a logistic regression analysis, using SPSS version 23. We performed two logistic regression analyses; one on the whole MoBa-population and one in the IBD sub-population.

In the first logistic regression model, we created three interaction terms from the IBD-variable in MoBa and the three new dietary pattern variables created from the factor analysis. The model also included the confounders maternal age, BMI, education level, total energy consumption and smoking status. In the second logistic regression model, dietary patterns were entered as regular exposure variables alongside the confounders. All three pregnancy outcomes were tested. Results are presented as odds ratios (OR) with corresponding 95% confidence intervals.

Distribution of dietary patterns in relation to sample population characteristics was obtained in SPSS using the compare means function. The statistical significance was tested for categorical variables with more than two categories using the One-way ANOVA analysis with the Dunnett's post-hoc analysis, comparing the mean factor score for a given dietary pattern in a given level of the characteristic to the lowest level. Dichotomous variables were tested using an Independent samples t-test. The distribution is for IBD, CD and UC respectively, as we cannot present results on the general MoBa-population in our study. Distributions of mean factor score for a given dietary pattern in relation to pregnancy outcomes were obtained using the compare mean function. Statistical significance was tested using an Independent samples t-test.

Multiple births were excluded from the analysis. About 1900 pairs of twins have been born in MoBa (87). Even though they are twin births, each pregnancy is registered as a separate unite in MoBa. Multiple births are considered a risk factor for low birth weight, and was thus excluded from the analysis (93).

We were *a priori* interested in testing disease activity as a potential effect modifier on the relationship between dietary patterns and pregnancy outcomes. Information regarding disease activity was obtained from a separate questionnaire sent out to women with IBD in MoBa, in the IBD sub-cohort. We divided the disease activity variables from the IBD-questionnaire into dichotomous variables (yes or no) and combined the variables reflecting disease activity in pregnancy week 0-4, 5-12 and 13-24 using the "compute variable"-function in SPSS. The new variable regarding disease activity reflected whether the women had active disease in the total period from week 0 to 24 in pregnancy, which is approximately the same period as covered by the FFQ (83). We used logistic regression analysis to test disease activity as a potential effect modifier on the effect between dietary patterns and pregnancy outcomes in women with IBD, using the "split file"-function in SPSS. We included the same confounders as listed above. Results are presented in OR with corresponding confidence intervals.

2.8 Ethical considerations

This study is in accordance with the Declaration of Helsinki, adopted by the World Medical Association in 1964 (94). The Helsinki declaration serves as a basis for medical research ethics, and provides a set of morally justified guidelines to be used when conducting research on human subjects or identifiable human material and data.

Research should be conducted in accordance with existing legal rules and norms in the society (94). The Helsinki declaration provides a framework in which such practice may be carried out. The declaration states that the researcher should carry out the research in a way that minimizes possible harm to the participants as well as the environment. In public health, the individual good and the good of society ("the greater good") may be in conflict. The objective of the study should justify the individual risks and harms of the participant. However, the declaration states that the objective may never take precedence over the rights and integrity of the participants (95).

Any study should be designed in a way that provides valid results (95). MoBa is an observational study, and not an intervention study where an exposure is induced on the participants. However, some labor is involved in the data sampling. The questionnaires may be time consuming to fill out, but they are designed in a way that should minimize the labor and thus increase the participation rate (89). However, the participation rate was not very high in MoBa, which may be an indicator of unsatisfactory study design (83). Biometric measurements of mother, father and fetus during pregnancy are set to routine examinations in the hospital.

A central point in the Declaration of Helsinki, is the one of informed consent. Satisfactory information regarding the research and study design must be provided to the participants before the data sampling (94). Participation must be voluntary, and the participants may withdraw their consent at any time without reprisal. In the MoBa-study, participants were given the informed consent form alongside the invitation and first questionnaire (83). Data from participants are not to be used in the study without informed consent from the mother and father. The consent states that MoBa may access health registries if the purpose is in accordance with the general objective of the study. The participants may withdraw their consent at any time, and they will thus not receive any more questionnaires. They may also at any time ask to be deleted from the study. In this case, all data on the participant will be deleted. The women are assigned a pregnancy ID in MoBa, and thus disidentified. In our study results, the women are anonymised.

Sub-populations underrepresented in research should be enabled appropriate access to participation in research (94). There are no exclusion criteria in MoBa, and the sampling is conducted in a way that in theory gives all pregnant women the chance to participate. However, the questionnaires are only provided in Norwegian (83, 89).

The MoBa-study is approved by the Regional Ethic Medical Research committee. The project in which our study is a subject, was approved by the committee in 2011 (Appendix 1). Morten H. Vatn is project manager and Akershus university hospital is responsible for the research.

3. Results

This chapter includes an extended description of the extracted dietary patterns, and the sensitivity analysis. Please see the article for results from the unadjusted and adjusted analysis described in detail. Given the fact that this study is based on the IBD-sub cohort in MoBa, we cannot present results regarding the general MoBa-population.

3.1 Summary

Three distinct dietary patterns were extracted from the PCA, explaining 12.65% of the total variance. The adjusted logistic regression in the complete dataset revealed a significant protective effect of the highest tertile in the "Traditional" dietary pattern on SGA in women with IBD, compared to non-IBD women and women with IBD adhering to the lowest tertile (OR for tertile 3 vs. tertile 1: 0.33 (95% CI: 0.13 – 0.86)). In the adjusted analysis in the IBD-subsample, we found a significant protective effect of preterm birth in the IBD-group from the same dietary pattern. The dietary pattern was found to significantly increase the risk of LBW in the IBD- and CD-group.

3.2 Dietary patterns

Three dietary patterns were extracted from the PCA. The first dietary pattern (eigenvalue 6.1, explaining 6,2% of the variance) had positive factor loadings for fruit, berries, vegetables (cooked and raw), beans, vegetable oils, rice, corn, poultry, nuts, tuna fish, yoghurt, probiotic foods and water as beverage. The dietary pattern had negative factor loadings for processed meats (hamburgers, hot dogs) and casseroles. This dietary pattern was considered as a prudent diet, given the high proportion of fiber, protein, unsaturated fatty acids, fruit and vegetables, and the negative association with processed red meats. We found the most appropriate label to be "Prudent", given the fact that the loaded term "Healthy" is something quite relative and must not be misused.

“Mediterranean” was considered as a label, but the dietary pattern was considered to be too inconsistent due to the low factor loadings on lean fish and fish products, which is an important part of the Mediterranean diet.

The second dietary pattern (eigenvalue 3.9, explaining 3,95% of the variance) had high factor loadings for foods and beverages rich in sugar (such as sodas, waffles, pancakes, pastries, chocolate, dairy desserts and white bread) and fat (such as chocolate, mayonnaise, high-fat dairy products, gravy, salty snacks, processed meats and fried potatoes), but also cooked vegetables, potatoes, berries and corn. However, the highest factor loadings were found in food products with a high proportion of added sugar, saturated fatty acids and salt. A diet consisting of such nutrients is consistent with the current Western dietary pattern, and “Western” was thus considered the most appropriate label.

The third pattern (eigenvalue 2.4, explaining 2,48% of the variance) was the most difficult to interpret and label because it did not include many factor loadings with an absolute value over 0.25. This pattern scored positively in lean fish and fish products, gravy, potatoes and rice porridge, and negatively in poultry, casseroles, pizza and tacos. It is rather difficult to give a consistent nutritional evaluation of this dietary pattern, given the sparse information. We were a bit reluctant at first in naming this pattern “Traditional”, given the low factor loadings for vegetables (especially cooked vegetables). However, based on the factor loadings above 0.25 we found the “Traditional” label to be the most appropriate, due to high consumption of fish, potatoes, rice porridge and gravy, and negative factor loadings on modern foods such as pizza and tacos. The dietary patterns are presented in Table 1 in the article.

3.3 Dietary patterns in relation to characteristics

Distributions of dietary patterns in relation to characteristics are presented in Table 3 in the article. In this unadjusted analysis, we found a significant difference in mean factor score for the “Traditional” dietary pattern in relation to age in the IBD- and UC-group.

Consumption was found to increase with age. Similar findings were found for the "Western" dietary pattern in the UC-group.

The "Prudent" dietary pattern was found to be significantly lower in the middle educational level compared to the lowest, and was found to be significantly higher in the highest educational level in the CD-group. In the UC-group, the "Western" dietary pattern was found to be significantly lower in the middle- and highest educational level compared to the lowest.

Dietary patterns were found to vary with total energy consumption in the mother. The "Western" dietary pattern was found to increase with total energy consumption in all three groups. The consumption of the "Traditional" dietary pattern was found to be higher in the highest level of energy consumption compared to the lowest, in the CD-group.

3.4 Sensitivity analysis

Disease activity was included in our dataset as a dichotomous variable, denoting disease activity in pregnancy week 0-24. We found no significant differences in the effect of the dietary patterns on pregnancy outcomes between the two groups of disease activity (active or not active), in the logistic regression analysis. We also included disease activity as an interaction term with each dietary pattern and as a confounder in the adjusted logistic regression model in the IBD subset. The interaction terms failed to reach statistical significance on any of the three pregnancy outcomes. When including disease activity as a confounder, we found no significant effect of dietary patterns on the three pregnancy outcomes. However, we found no effect of disease activity on pregnancy outcomes, either.

4.0 Discussion

4.1 Summary

Three distinct dietary patterns were extracted from the factor analysis. These were named "Prudent, "Western" and "Traditional" dietary pattern after examining the nature and factor loadings of food groups within each pattern. In general, women with IBD were found to have a lower adherence to the "Traditional" and "Prudent" dietary pattern than controls, while a higher adherence to the "Western" dietary pattern.

In the adjusted analysis, we found a significant protective effect of the "Traditional" dietary pattern on SGA in women with IBD compared to controls. In this analysis we controlled for maternal age, education status, diabetes mellitus, smoking status and total energy consumption. In the adjusted logistic analysis in the IBD-subset we found a significant protective effect of the "Traditional" dietary pattern on preterm birth in the total IBD sample. However, confidence intervals were wide.

4.2 Previous findings

To the best of our knowledge, dietary patterns in relation to pregnancy outcomes in IBD have not been investigated in previous research. However, several studies have examined the relationship in a general pregnant population (74, 75, 77-82).

In general, previous results indicate a protective effect from dietary patterns with high factor loadings in fruit and vegetables (a prudent or Mediterranean diet,) on preterm birth and birth weight (74, 75, 78, 81, 82). Similar results were found in a study by Brantsæter et al., investigating the relationship between dietary patterns and preeclampsia in the general MoBa-population (76). However, in a study by Haugen et al., a Mediterranean diet failed to reach statistical significance as a protector of preterm birth in the same sample (77). In our unadjusted analysis, we found that women with IBD who gave birth to babies who were small for gestational age, had a significantly lower adherence to the “Prudent” dietary pattern than controls. We found no effect of the “Prudent” dietary pattern in our adjusted analysis.

A western diet consisting of refined carbohydrates, saturated fatty acids, sugared foods and beverages, processed meat products, and low levels of fiber, has been found to be a risk factor for IBD, in addition to increasing the risk of SGA in a general pregnant population (45-48, 78). We found no significant results regarding adherence to a “Western” dietary pattern and adverse pregnancy outcomes in our adjusted analysis. Dietary patterns are often influenced by other health determinants, such as age, family structure, level of physical activity, smoking and educational status (70-73). In the study by Brantsæter et al., results indicated that adherence to a dietary pattern similar to our “Western” dietary pattern was more frequent in younger women, smokers, women with less education and women with previous preterm delivery (74). We found a higher adherence to the “Western” dietary pattern in women with lower education and higher total energy consumption, and in smokers.

Most studies investigating dietary patterns, focuses on somewhat mutual exclusive diets, such as a vegetarian- and a western dietary pattern (74, 75, 77-82). Englund-Ögge et al. investigated a traditional dietary pattern similar to ours, in a study based on the general MoBa-population (74). However, we found no other study with a traditional dietary pattern that was readily comparable to our “Traditional” dietary pattern. The results from the study by Englund-Ögge et al. indicated that a traditional dietary pattern reduced the risk of preterm birth when comparing the upper third of the factor scores to the lower third. When stratifying on pre-pregnancy BMI, researchers found a significantly reduced risk for preterm birth in the “Traditional” dietary pattern. In our adjusted analysis, we did not find an increased protective effect of the “Traditional” dietary pattern in relation to preterm birth in women with IBD. However, results indicated a significant protective effect on SGA.

Previous research has found women with IBD to have specific beliefs regarding their diet (61-64). Foods rich in fiber are often excluded from the diet, due to worsening of symptoms (50, 63). Dairy products are also frequently excluded, which may be due to transient lactose intolerance, which is rather prevalent in IBD patients with active disease (51, 64). In addition, IBD patients are found to have a higher consumption of carbohydrates and sugar compared to the general population (67, 96, 97). This is in accordance with the results from our unadjusted analyses, showing a higher adherence to the "Western" dietary pattern in women with IBD, compared to controls, and a lower adherence to the "Prudent" and "Traditional" dietary pattern.

4.3 Theoretical considerations

Diet has been suggested to play an important role in IBD (45-48, 50, 63). Previous research indicates an effect of dietary pattern on pregnancy outcomes in a general pregnant population (74-82). We wanted to investigate whether this relationship was stronger in women with IBD, suggesting IBD as an effect modifier on the relationship between dietary patterns and pregnancy outcome. It is possible that diet may interact with the disease and thus enhance the effect compared to controls, either through disease activity or due to nutritional deficiencies; which is a common complication in IBD (5, 43, 50).

4.3.1 Nutritional deficiencies

Pregnant women with IBD are vulnerable to nutritional deficiencies (5, 43, 50). A large proportion of IBD patients report exclusion of different foods or food groups from their diet, although no pathological mechanisms have been identified between specific foods and disease activity (61-67). When excluding whole food groups, such as dairy products, one may be at an increased risk of nutritional deficiencies if the nutrient requirements are not met in the remaining diet.

Malnutrition in the mother may impair fetal growth, and is a risk factor for adverse pregnancy outcomes (19, 74-82). Women with IBD are more likely to have nutritional deficiencies than the general pregnant population, both in remission and active state of the disease (50). In addition, requirements of certain nutrients are increased in pregnancy (32). Nutrition may thus be of greater importance in pregnant women with

IBD, compared to women without IBD. A dietary pattern with a nutrient profile that meets the increased requirements of the mother may have a protective effect on the pregnancy outcome, acting as a modifier of the disease.

We found the "Traditional" dietary pattern to have a significant protective effect on SGA in women with IBD. Adherence to the highest third decreased the odds of SGA with 66%, compared to controls and women with IBD adhering to the lower third. This may reflect the protective effect of specific nutrients in the dietary pattern, or several nutrients interacting. In this scenario, controlling for supplement use would be appropriate.

There are at least two ways that the nutrient profile of the dietary pattern may affect pregnancy outcome in IBD. It may act as a mediator on the effect of dietary patterns on pregnancy outcome (Figure 3), or it can be an effect-modifier in the causal pathway between the dietary pattern and pregnancy outcome (Figure 4).

Figure 3. Causal graph suggesting that the nutritional profile of a dietary pattern will act as a mediator of the effect of dietary patterns on pregnancy outcomes, by meeting certain nutritional requirements in the mother (and fetus).

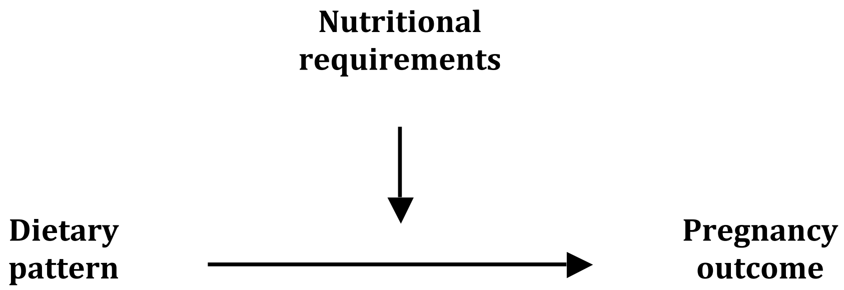

Figure 4. Causal graph suggesting that increased nutritional requirements in women with IBD may act as an effect modifier on the effect of dietary patterns on pregnancy outcomes.

The "Traditional" dietary pattern had high factor loadings for lean fish, fish products, boiled potatoes, rice porridge and gravy. Fish is an excellent source of protein, vitamin D and omega-3 (43). However, this dietary pattern scored high in lean fish and fish products, which are rich in neither vitamin D nor omega-3. Englund-Ögge et al. found a traditional dietary pattern based on MoBa-data and similar to ours, to correlate with protein, potassium, magnesium and dietary fibre (74). IBD patients have a higher prevalence of deficiencies in energy-, protein-, zinc, folic acid, calcium, iron, vitamin D, and vitamin B12 than the general population (50, 68). It is possible that the "Traditional" dietary pattern is a good source to all-, or some, of these nutrients. If the increase requirements of the women with IBD are met through the dietary pattern, it is likely to believe that this will affect the pregnancy outcome in a positive manner. Research exists on the effect of different nutrients and pregnancy outcome in general pregnant populations, such as zinc and risk of preterm birth, iron and LBW and folic acid on SGA (98-100). We did not perform a correlation test on dietary patterns in relation to nutrients, as it is beyond the scope of this study. A correlation test could have uncovered nutrients with a potential effect on pregnancy outcomes, and should be performed in future studies. Until then, theoretical considerations regarding specific nutrients will be mere speculations, as our study is somewhat explorative.

Given that our hypothesis regarding nutrient requirements holds true, this may explain why we did not find any significant effects from the dietary patterns in the UC group, as malnutrition is not as common in UC (50).

4.3.2 Genetic variations

We found that the ”Traditional” dietary pattern had a protective effect on SGA when comparing to controls, while acting as a risk factor when analysing the IBD and CD subgroups alone. Although the confidence intervals were wide due to a low sample size in the latter analysis, these differences may be explained by the genetic variation in IBD. Triggs et al., investigated disease activity and food groups in CD patients, and found food groups to be well tolerated by some, and not tolerated by others (101). Several genes have been identified as risk factors for developing IBD, some genes are only found in CD, some in UC and some are found in both the diseases, partially explaining the similarity between the phenotypes. One may hypothesize that different genes interact with different risk factors, such as components in the diet. However, substantial research is required to confirm this hypothesis.

4.3.3 Disease activity

Active disease is considered a risk factor for adverse pregnancy outcomes in women with IBD (56, 59, 60). In addition, disease activity influences the nutritional status of the mother (50). Active disease (especially in CD) may lead to increased nutrient- and energy requirements due to an increased loss and decreased absorption in the intestine. In addition, IBD patients often exclude certain types of food from their diet (61-64).
In a study by Cohen et al., fruits, nuts and vegetables was found to worsen symptoms (63). Foods rich in fibre may be hard to digest during active inflammation (50). Many patients experience a transient lactose intolerance in active disease, and may thus exclude dairy products from their diet (51, 64).

This suggests several pathways that disease activity may influence the effect of diet on pregnancy outcomes. Firstly, disease activity may act as a confounder in our analysis (Figure 5). Although somewhat sparse, research suggests that active disease may be a risk factor for adverse pregnancy outcomes (7, 56, 57). Disease activity may in addition influence the dietary habits of the women, given the fact that there exist strong dietary beliefs regarding symptom relief among IBD patients (61-64).

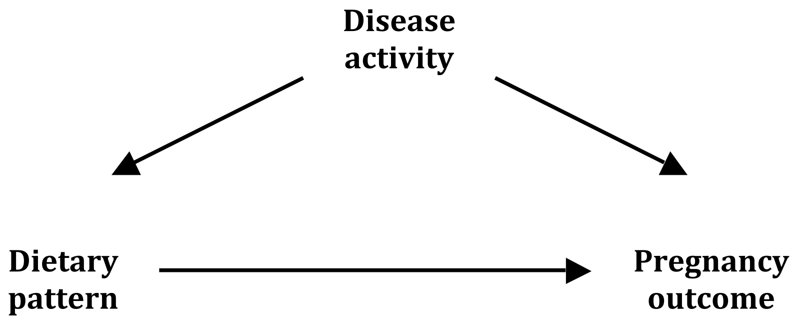

Figure 5. Causal graph suggesting how disease activity may confounder the relationship between dietary patterns and pregnancy outcomes.

A given dietary pattern may have a nutrient profile appropriate for women with active disease, and thereby reduce the risk of adverse pregnancy outcomes due to nutritional deficiencies in the fetus. This is in accordance with our previously stated nutrient theory. In this scenario the dietary pattern will act as an effect modifier on the effect of active disease on pregnancy outcomes (Figure 6). Exactly how disease activity will modify the effect will be mere speculations, but it may be through absorption or metabolism of nutrients.

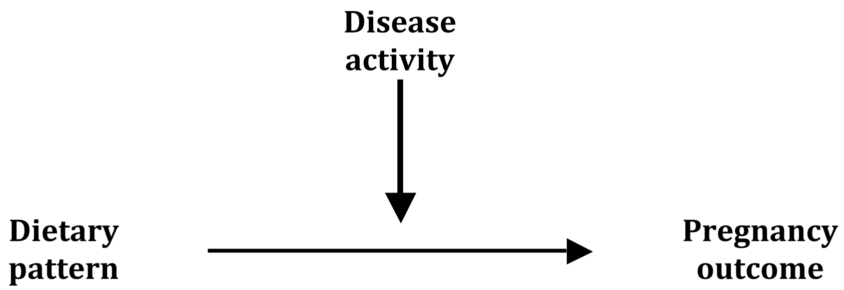

Figure 6. Causal graph suggesting disease activity as an effect modifier on the relationship between dietary patterns and pregnancy outcomes.

We tested this potential interaction effect in a sensitivity analysis. Women with IBD were grouped by disease activity. Information regarding disease activity was collected from a questionnaire sent out to all women in the IBD sub-cohort, and included in our analysis as a dichotomous variable. We included information on disease activity from pregnancy week 0 to 24, which is approximately the same period covered by the FFQ. We found no significant differences in OR in any of the dietary patterns between groups (data not shown). However, the sample was small due to missing cases (n = 275), and confidence intervals extremely wide.

Disease activity may interact with dietary patterns as a mediator in the causal pathway between dietary patterns and pregnancy outcomes (Figure 7). Research suggests that diet may play a central role in the development, symptoms and treatment of IBD (45-48). It is likely to believe a given dietary pattern could affect disease activity, either preventive or as a risk factor.

Figure 7. Causal graph suggesting disease activity as a mediator on the effect of dietary patterns on pregnancy outcomes.

In addition, it might be likely to believe that disease activity may influence the dietary habits of the woman (Figure 8). In active disease, fibre may be hard to digest, in addition to dairy products (50, 51, 63, 64). An increased loss of nutrients may give energy deficiencies, and women may thus be likely to adhere to dietary patterns with high factor loadings for food groups with high energy density, such as found in the "Western" dietary pattern. Further studies should investigate the distribution of dietary patterns in relation to disease activity.

Figure 8. Causal graph suggesting dietary patterns as a mediator on the effect of disease activity on pregnancy outcomes.

As a part of our sensitivity analysis, we included disease activity as an interaction term with the "Traditional" dietary pattern in an adjusted logistic regression model. We found no significant effect of the interaction term on SGA. In addition, disease activity was included as a confounder in the adjusted logistic regression in the IBD group. In this analysis, there was no significant effect of the "Traditional" dietary pattern on SGA, we found no significant effect of disease activity on SGA either. These findings may be due to a low sample size.

As we have seen, there are several potential pathways in which IBD may interact with diet on pregnancy outcomes. Analyses cannot readily separate between these, and we may not be able to find out exactly which pathway is the correct one. However, it is likely that there might be several pathways interacting. Further research is required to investigate the importance of disease activity in relation to diet and pregnancy outcomes.

4.4 Methodological considerations

4.4.1 Study design

This study is a sub-cohort in the prospective cohort study MoBa, which is based on questionnaires and national health registries (83). The recruitment period lasted from 1999 to 2008, and the follow-up period is still running.

There are several strengths in this study design. One of the main strengths is the large sample size derived from MoBa. Our dataset included 104.996 singleton births. A large sample size is necessary to give the statistical analysis enough strength to produce valid estimates regarding the relationship between the exposure and outcome (86). A large cohort with a long follow-up period may be suitable for investigating rare diseases, such as IBD. MoBa is an open cohort, which allows recruitment of participants over several years and enables a large sample. However, the participation rate in MoBa was rather low, only 41% of the pregnant women in Norway at the given time, attended the study (87).

In the cohort design, the exposure is measured prior to the outcome. This gives us the opportunity to examine the temporality regarding exposure and disease. This design will also reduce the chance of information bias due to the outcome (86). In addition, the cohort design enables investigation of different outcomes in relation to one exposure variable. This made it possible to investigate three pregnancy outcomes for each dietary pattern, which may give a wider understanding of the relationship between diet and pregnancy outcomes.

Although considered the primary design within epidemiology, there are some limitations to the study design: Great resources are required to conduct such a study. However, we were lucky to be provided ready-to-use data from MoBa. An important limitation to a cohort design, is the fact that we cannot establish causality (102). Causality is related to cause and effect, whether the exposure under observation is a determinant of the observed outcome (86). Causality has been established for a number of diseases, while remaining unclear for others, such as numerous cancer types and chronic diseases such as IBD. When initiating an investigation of an outcome in which we know nothing about the cause, epidemiology is a valuable tool. Observational studies such as case-control studies, cross-sectional studies, and cohort studies are suitable designs for such exploration. In these observational designs, we may increase internal validity by controlling for confounders, but we cannot readily control all determinants surrounding the subjects in their daily life. However, in this inductive approach, we may generate hypotheses that may be confirmed through controlled experiments.

4.4.2 Information bias

Information bias is also known as misclassification, and relates to information regarding the sample population (86). This type of error is considered to be the most important bias in a cohort design, posing serious threats to the internal validity of the study.

Recall-bias is a type of information bias, and especially evident within the nutrition sciences (102). When participants are to answer questions regarding lifestyle habits, such as dietary habits in the FFQ, many fail to remember what they have eaten and thus over- or underreport their consumption of various foods. However, this is most apparent in case-control studies were the participants are to answer questions regarding lifestyle habits a long time ago.

In our study, the participants are to fill out a FFQ comprising dietary habits since they got pregnant (83). Although the time frame is not very wide, it may be hard to remember exactly what has been eaten. How well one remembers depends on different factors. If such a factor is related to the outcome or other variables under study, the error is considered to be differential misclassification (86, 102). In this scenario, a misclassification of the women into a wrong dietary pattern tertile may occur. This may impair the internal validity of the study. Patients with IBD often have alterations in their diet due to various beliefs regarding symptom relief (61-64). It is likely to believe that the women with IBD may be more aware of their dietary habits than women without IBD. In this case, the fact that the controls do not have IBD may lead to a misclassification of dietary patterns in controls. This is a type of recall-bias and differential misclassification. We do not know whether the controls are over- or underestimating in relation to their true consumption.

Maternal recall-bias is related to recall-bias in the mother, due to an outcome in her child (102). If the child has a given disease, the mother may remember the dietary habits prior to the disease differently than controls. This is especially evident within case-control studies. Participants in MoBa send in the FFQ prior to birth, and the outcome can thus not influence the reporting of dietary habits. However, women may participate with several pregnancies in MoBa. If a woman has experienced a negative pregnancy outcome in a previous pregnancy, this may affect how she answers the FFQ. However, the FFQ is about nutrition in the current pregnancy, and although previous experience may influence dietary beliefs, this will not affect our estimates, as the pregnancies are registered as two separate entities. Misclassification of outcome as a result of the exposure is thus not likely in this setting. In addition, when MoBa was initiated no study outcomes were set (83).

In non-differential misclassification the misclassification of the exposure is independent of the outcome or any other variable under study (102). Misclassification will thus be equally distributed in women with IBD and controls. However, this may lead to an underestimation of the effect between the exposure and outcome. The potential challenges related to the FFQ as mention above, may fall under this category. However, the MoBa FFQ has been validated and considered an appropriate tool for assessing dietary habits and low versus high intake of nutrients in a MoBa sub sample (90).

Both self-reported and registry based diagnosis of IBD (and UC or CD) are included in the MoBa database. The self-reported number of cases did not match the numbers of cases from NPR. This may lead to information bias, when regarding IBD as an exposure. Differences may be due to misunderstandings, time gaps (maybe the woman was not diagnosed with IBD when filling out the form), or typing errors. A misinterpretation of the question may be possible as the diagnosis “inflammatory bowel disease (IBD)” is very similar to “irritable bowel syndrome (IBS)” in Norwegian. Such errors will be non-differential. Misclassification of IBD as an exposure due to the outcome is not possible in this cohort study. We decided to only include NPR cases in our study.

Adverse pregnancy outcomes defined as preterm birth, LBW or SGA were included as dichotomous variables in our analysis. When dichotomizing a variable one may exclude potential misclassification in relation to typing errors for instance, because the variable only have two categories. However, if the error is in the borderline area between the two categories, there is a risk of misclassification. The pregnancy outcomes are obtained from The Medical Birth Registry of Norway (MBRN)(83). The validity of MBRN has been tested for various pregnancy complications and –outcomes, in a validation study recently published (103). MBRN was considered to give valid information regarding preterm birth and birth weight. The positive predictive value (PPV) was 90% for preterm birth, and 100% for low birth weight.

4.4.3 Selection bias

Selection bias is related to whether our sample is representative of the background population in wish we would like to generalize our results (86, 102). Selection bias will thus affect the external validity of our study, but also the internal validity of the study, given the fact that there may be characteristics in the sample population that is not found in the background population, and thus serves as confounders.

Any cohort study strives for a high participation rate, as a large sample will have an increased variability and may cover all exposures of interest. A small sample size on the other hand, may not represent the background population. In the MoBa study, the total participation rate was in total 41%, and the sampling method was opportunistic due to limited funding (87). This participation rate is rather low. The participants were found to be of higher age, have a higher level of education, and have a lower prevalence of smokers and those living alone, than in the general pregnant population. This is in accordance with the phenomenon named volunteer bias (104). People participating in medical research often tend to be more health conscious and have a healthier lifestyle than the general population. Those with less appropriate health behaviors are often less interested in studies investigating health outcomes. This potential self-selection bias may influence our results. It is likely that there exist several confounding variables related to health behavior that may affect the outcomes under study. In addition, the kind of self-selection bias found in MoBa, may create a socioeconomic partition from the general population, and thus affect the generalizability. The participants in MoBa were also found to have a higher prevalence of supplement use than the general pregnant population. This may influence our results, and may lower the actual effect of dietary patterns on pregnancy outcomes, given that our hypothesis regarding nutritional deficiencies in IBD holds true.

Although the prevalence of the outcomes under study may be different than the general population due to selection bias, estimated associations may be valid. However, it is important to carefully consider the potential bias when discussing the application of results. In a methodological study investigating the potential self-selection bias in MoBa, Nilsen et al. found no significant differences between eight exposure-outcome associations comparing MoBa-participants with the general pregnant population (105). Preterm birth was one of the outcomes evaluated. Similar results was found in a study investigating self-selection bias in The Autism Birth Cohort study, a sub-cohort in MoBa (106).

Due to limited resources, the questionnaires in MoBa were only conducted in Norwegian language (89). This may thus exclude pregnant women with a migration background, who has not learned the Norwegian language. If the questionnaires were translated into English or other non-Norwegian language, a broader range of characteristics could be reflected in the sample. This would make the MoBa sample an even better representation of the general pregnant population, and thus give the study a better external validity.

Not all women participating MoBa answered the FFQ (87). The FFQ was first sent out from 2002, resulting in missing data on a large proportion of existing participants. Missing data may reduce our sample size, and thus be a weakness in our data. Losses to follow-up were not especially evident in MoBa before the women where to answer Q3 and onwards (83). It is thus not very likely that our results are biased by losses to follow-up and response-bias.

4.4.4 Confounding

Within epidemiology, a confounding variable is a variable that has an effect both on the assumed exposure and the outcome (102). However, in traditional medical research a confounder is regarded as a “hidden” variable affecting the outcome. We reduced potential confounding by controlling for several relevant factors. Maternal age, BMI, educational level, and smoking are important risk factors for adverse pregnancy outcomes, and may also affect dietary habits. Hypertension and diabetes mellitus are also considered risk factors for adverse pregnancy outcomes, but were excluded from the statistical analysis due to low prevalence.

BMI has been found to be a risk factor of adverse pregnancy outcomes. Patients with IBD have been found to have a lower BMI than the general population, and pregnant women with IBD may thus be at risk of insufficient weight during pregnancy (36). Total energy consumption is closely related to BMI and weight gain during pregnancy, and was included as a potential confounder. Energy consumption correlates with the energy density of food and beverages, and a “Western” dietary pattern is considered a dietary pattern with high energy density. This was confirmed by Englund-Ögge et al. in their study (74). A prudent dietary pattern was found to correlate inversely with energy density, while the traditional dietary pattern was not associated with energy density.

Level of education is a frequently used proxy-measure of socioeconomic status, and has been found to correlate with both pregnancy outcomes and dietary habits (70). Smoking is an important risk factor for preterm birth, and may also affect the disease activity in IBD (107-109). Maternal age is an important predictor for pregnancy outcomes, and may also influence dietary habits (71, 72).

Women may have had a food consumption relating to several dietary patterns. All dietary patterns were thus included in the same model in our analysis, controlling for each other. A strength in our study is that we investigated dietary patterns as a group of several foods and beverages. Foods or nutrients are rarely eaten alone, and if we were to investigate a certain nutrient or food group independently of the diet, we would have to control for several other components in the diet. When examining dietary patterns we examine the diet as a whole, and we may cover possible interactions between nutrients. However, (in a somewhat paradoxical manner), our results require verification through studies examining certain foods or nutrients.

Supplement use was found to correlate with certain dietary patterns in the study by Brantsæter et al., and could also be included as a confounder (76). Disease activity should, as previously discussed, be considered as a potential confounder in future research. In addition, there are several other factors that could affect the pregnancy outcome if untreated, such as anemia, which is prevalent in women with IBD (110). However, a model that is too big may give wrongful estimates.

Even tough we adjusted for several confounders in our analysis, we cannot completely exclude residual confounding when observing the participants in their natural environment (104).

4.4.5 Reliability and validity of the FFQ

Reliability relates especially to the consistent of measurements in a study, and our study the primary measuring instrument is the FFQ (111). A high quality FFQ should aim at high accuracy and precision, in order to produce reliable and valid results. Precision relates to random errors in our study. Random errors lead to variation in our data, and will be evenly spread out and not systematically under- or overestimating our results. The precision will decrease with increased random errors. Random errors may occur in the FFQ, for instance when the participants read the questions (reads wrong word or misses a question) or when filling (misspelling), or when the answers are being read optically (wrong coding).

Accuracy relates to systematic errors (104). The ability of the FFQ to produce the same results if a participant is tested at two different occasions, is reflected in accuracy. This may relate to the formulation of questions, as it is a cognitive process to both remember what has been eaten and to remember how much has been eaten. In addition, it is important to test whether the FFQ measures what it is meant to measure in relation to nutrients and dietary habits.

The FFQ has been validated using a sub-sample (n=119) from MoBa (89, 90). The method in the validation study was four-day weighed food diary (FD), a motion sensor measuring total energy expenditure, a 24 hour urine and a venous blood sample for analysis of various nutrients (90). The agreement between the FFQ and FD was considered appropriate, with significant correlations for all major food groups and all nutrients, except vitamin E. The biological markers confirmed the FFQ as suitable for distinguishing between high and low intakes of nutrients.

When the FFQ in MoBa was designed, researchers were relying on research indicating that the dietary pattern of the mother was somewhat stabile throughout the pregnancy (89). However, results from recent studies indicate that dietary habits and health behavior may change through pregnancy (35). Research indicates that pregnant women are more motivated for lifestyle changes and healthy behaviors than the general non-pregnant population. However, it is likely to believe that such changes occur early in pregnancy, and in the FFQ the women are asked about dietary habits since they got pregnant. This will thus cover the present diet of the woman, in gestational week 22. However, if the woman changes her diet later on in pregnancy, this may affect our results.

4.4.6 Statistical considerations

The large sample size in MoBa is, as previously stated, a strength in our study. However, when including all confounders in the model, there were some missing cases. There are several reasons for this. Firstly, the FFQ was not sent out until 2002. Secondly, participants may withdrawn their consent. Thirdly, the participants may have answered the questions wrongfully or missed questions (either on purpose or not) and therefore been treated as missing cases by SPSS. The risk of this increases with confounders added in the model, because information regarding several of the confounding variables were obtained from Q1 (such as smoking and educational level). In addition, the IBD sub-sample was rather small.

A small sample size may reduce the power of our study, the ability to detect an actual relationship. Our results may be biased by type 2-error; an underestimation of an actual effect (86). In the IBD sub-sample the confidence intervals were wide due to few participants with IBD. Wide confidence intervals lower our precision in estimating the true effect between dietary patterns and pregnancy outcomes. A small sample size may also result in an overestimation of the effect, and result in a type 1-error. The results from the logistic regression in the IBD-subset were somewhat conflicting. In addition, we did not find an effect of the "Traditional" dietary pattern on SGA, which we observed in the first logistic regression when IBD was included as an interaction term. The estimated effects from this analysis may be biased due to the low sample size, and should be interpreted with caution.

As for the PCA, statisticians have argued that a component from a PCA may over-estimate the relationships between sets of variables (69). The authors of the book "Measurement, design and analysis: an integrated approach", Pedhazur and Schmelkin, argues that unless the first few components extracted from the PCA accounts for ≥ 50% of the variance, the results from the PCA will have little value (111). The three dietary patterns included in our analysis only explained 12,65% of the variance in food intakes. This may be regarded as a weakness in our study. Even though dietary patterns are in fact shown to be good indicators of nutrient intake, we only cover a small part of the dietary habits of the women in our analysis. However, the variance explained by the dietary patterns is not as high as 50% in previous studies. In the study by Englund-Ögge et al., three dietary patterns were extracted, explaining 16% of the total variation (74). In the study by Brantsæter et al., the cumulative variance explained from the four dietary patterns included was 18% (76). In a study by Cúco et al., investigating dietary patterns in preconception, pregnancy and postpartum, the two dietary patterns included explained 20-25% of the total variance (70).

In the factor analysis we aimed at extracting dietary patterns that could serve as exposure variables, reflecting the diet of the mother. Dietary patterns may be a valid tool in assessing dietary habits, and is found to be a good indicator of consumption of nutrients (91). However, the dietary patterns do not explain the total dietary consumption of the participants. There are food groups that are not denoted in any of the three dietary patterns, such as low-fat dairy products which was a variable entered into the factor analysis. This is not necessarily due to a low consumption of such products (which would have given a negative factor loading), but could reflect an even distribution of low-fat dairy products across all dietary patterns. A food group must have an especially strong correlation (negative or positive) to the other food groups in a given dietary pattern to be included in the component (pattern). In addition, we must stress the fact that we only included food groups with factor loadings above the absolute value of 0.25 in the dietary patterns, due to interpretability issues. This may result in certain foods being excluded from a dietary pattern, although the women may have had an adequate consumption of these foods, - but not in comparison with the other foods in the pattern. Further research should investigate what level of consumption the factor scores reflect, and whether it is within nutritional guidelines.

4.4.7 External validity

External validity relates to the extent in which the study results can be generalized (102). In our study, the question is whether our findings can be generalized to pregnant women with IBD outside the cohort. Potential threats to the external validity, such as selection bias, have been discussed in previous sections in this chapter.

MoBa is an open cohort with many participants from all over the country, which gives us the opportunity to collect a large sample with a broad range of characteristics. This may increase the external validity of the study. However, there are only 489 participants with IBD in the MoBa dataset. IBD is a relatively rare disease, and it is likely that the prevalence of IBD is similar in the general population. Although we must not forget the potential self-selection bias in the MoBa-sample, there are good reasons to believe that our results may apply for pregnant women with IBD in the general, Norwegian population. However, given the fact that the MoBa questionnaires are only provided in Norwegian language, migrating women may not be covered adequately in this study.

5. Conclusion and implications

Adverse pregnancy outcomes are found to be of higher prevalence in women with IBD than the general population. IBD is a disorder affecting the gastrointestinal tract, and nutrition play an important role in the management of the disease. Previous studies have investigated the relationship between dietary patterns and pregnancy outcomes in a general population. However, diet in relation to pregnancy outcomes in women with IBD has, to the best of our knowledge, not previously been investigated.

In this study, we aimed at examining the potential interaction between IBD and dietary patterns in relation to the adverse pregnancy outcomes low birth weight, preterm birth and small for gestational age. We found a significant protective effect of the highest tertile in the "Traditional" dietary pattern on SGA in women with IBD, compared to controls. This protective effect may be explained by several potential mechanisms, and both nutritional deficiencies and disease activity may play an important role as effect modifiers, mediators or confounders. However, we found no significant results on disease activity as an effect modifier in our sensitivity analysis.

Although we cannot draw causal conclusions from our study, our results may set a basis for further research on this matter. Information regarding diet and dietary patterns may be of great importance in the clinical care of pregnant women with IBD. Future studies should investigate the nutritional profile of dietary patterns in relation to nutrition status in women with IBD. Disease activity should be included in the study.

Adverse pregnancy outcomes may pose both immediate- and long-term threats to the newborn child. In addition, malnutrition in pregnancy may affect the health of the offspring in adult life through fetal programming. Appropriate nutritional care for the women with IBD may reduce the risk of adverse pregnancy outcomes, and thus promote the public health of tomorrow.

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Dietary Patterns in women with Inflammatory Bowel Disease and Risk of Adverse Pregnancy Outcomes: Results from The Norwegian Mother and Child Cohort Study (MoBa)

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Abstract

Background: Women with inflammatory bowel disease (IBD) have increased risk of adverse pregnancy outcomes. Previous studies have shown associations between dietary patterns and pregnancy outcomes in healthy women. IBD women are vulnerable to nutritional deficiencies, which may have an impact on pregnancy outcome and life course of the offspring through the concept of fetal programming. The aim of this study was to examine dietary patterns and risk of preterm birth, low birth weight (LBW) and small for gestational age (SGA) in women with IBD in the Norwegian population-based Mother and Child cohort study (MoBa).

Method: The MoBa cohort includes 95.200 mothers recruited from all over Norway in the period 1999 to 2008. The cohort comprises 815 mothers with CD and 287 mothers with UC. Women participating in MoBa answered questionnaires at gestational weeks 15 (general health questionnaire) and 17-22 (Food frequency questionnaire). IBD history, medication, complications and disease activity during pregnancy and at delivery were ascertained. Factor analysis identified three dietary patterns, labeled as a "Prudent", "Western" and "Traditional" dietary pattern. We used logistic regression analysis to model the relationship between dietary patterns and pregnancy outcomes, controlling for potential confounders. We were a priori interested in effect-modification of disease activity.

Results: We found a significant protective effect of the interaction between IBD and the "Traditional" dietary pattern on SGA (OR tertile 3 vs. tertile 1: 0,33 (95% CI: 0.13-0.86)). When performing a logistic regression in the IBD-subset we found a significant increase in odds for LBW in the middle tertile of the "Traditional" dietary pattern (OR tertile 2 vs. tertile 1: 6.25 (95% CI: 1.23 – 31.82)), and a protective effect for preterm birth (OR tertile 2 vs. tertile 1: 0.30 (95% CI: 0.09 – 0.97)). However, confidence intervals were wide. In the CD-subset we found a significant increase in risk of LBW in the highest third of the "Traditional" dietary pattern compared to the lowest (OR tertile 3. vs tertile 1: 29.81 (95% CI: 1.73 – 515.14).

Conclusion: Although inconclusive, our results indicate a significant effect of a "Traditional" dietary pattern characterized by high consumption of lean fish, fish products, potatoes, rice porridge and gravy, on SGA, LBW and preterm birth. Our findings may serve as a basis for further research on dietary patterns in women with IBD and risk of adverse pregnancy outcomes.

Introduction

Inflammatory bowel disease (IBD) represents chronic complex disorders of the gastrointestinal tract, and is characterized by an inappropriate inflammatory response of the gastrointestinal mucosa in genetic susceptible individuals (1). Crohn's disease and ulcerative colitis are the most prevalent forms of IBD. While accepted as two separate entities, the diseases share genetic and environmental similarities.

The etiology of the disease remains unclear. Part of the pathology is explained by defects in the barrier function of the intestinal epithelium and the mucosal immune system (1).

IBD is most prevalent in North America and Northern Europe, suggesting a north-south gradient in incident rates (2-4). This geographical variation suggests that environmental factors are important modifying factors of the disease. Temperature has been suggested as a potential explanation for the spatial variability, which was found to apply also within countries (5). The incidence rate of the disease is increasing in the developing world, indicating that westernization is a potential risk factor. While somewhat inconclusive, research on dietary patterns and risk of IBD have shown an association between a western diet with a high proportion of fatty acids and sugar-containing foods and beverages, and IBD (6-8). The results indicate a protective effect in diets rich in fiber, fruits and vegetables.

IBD is early onset and usually diagnosed in late adolescence and early adulthood, coinciding with the peak reproductive years of women (1). A large body of evidence suggests that pregnant women with IBD have an overall increased risk for adverse pregnancy outcomes, than those of the general population (9-14). Active disease, malnutrition and insufficient weight gain are considered to be important risk factors for adverse pregnancy outcomes such as preterm birth (<week 37), cesarean section, low birth weight (<2500 grams) (LBW) and small for gestational age (SGA) (15-17).

IBD-patients are at risk of nutrition deficiencies due to an increased loss, impaired absorption of nutrients from the intestine, drug-nutrient interactions and increased nutritional requirements (1, 18). Prevalent deficiencies include protein-, calcium-, vitamin D-, folic acid-, iron-, vitamin B12-, and zinc deficiencies (18, 19).

In pregnancy, the fetus receives all required nutrients through the placenta, solely dependent on the transfer of nutrients from the mother. Maternal dietary habits may thus heavily influence the fetal development and pregnancy outcome, as well as the long-term health of the child, through the concept of fetal programming (20-22).

Previous studies have investigated the relationship between dietary patterns and pregnancy outcomes in healthy women (23-31). While somewhat inconsistent, the studies found that diets characterized by high consumption of dairy products, fish, vegetable oils, fruits and vegetables were protective of adverse pregnancy outcomes.

The role of dietary patterns in pregnant women with IBD has, to the best of our knowledge, not yet been investigated. The aim of this study was to investigate the relationship between dietary patterns and risk of adverse pregnancy outcomes in women with IBD.

Materials and methods

Population and study design

Participants were recruited from the Norwegian mother and Child Cohort Study (MoBa) (32). MoBa is a population-based, prospective cohort conducted by the Norwegian Institute of Public Health (NIPH). The recruitment period lasted from 1999 to 2008, and pregnant women nationwide were invited by postal invitation, with no exclusion criteria. The total participation rate was 41% (33).

Follow-ups were conducted through questionnaires and by linkage to national health registries (32, 34). A total of three questionnaires were sent out during the pregnancy period. The present study includes data from the two first questionnaires; Q1 and Q2. Q1 was submitted at gestational week 15, and covered the mother's medical history before and during pregnancy, including lifestyle habits and various environmental exposures. Q2 was a food frequency questionnaire (FFQ), submitted at gestational weeks 17 to 22.

Of the 739 mothers who claimed to suffer from IBD in the basic questionnaire (Q1), 655 mothers were available for the present study. We mailed out an additional questionnaire in 2013 including questions regarding sub-classification of IBD, medication use, surgery and disease activity during pregnancy. Disease activity was defined as change of medication, IBD-related surgery or hospital admissions during pregnancy. Non-responders were recorded as CD or UC by The Norwegian Patient Registry (NPR), which left the study with 502 patients, 215 CD and 287 UC, for for further analyses reflecting the association between dietary patterns and pregnancy outcomes in women with IBD. The cohort was linked to The Medical Birth Registry (MBRN)(34).

Dietary information

Dietary information was collected in the FFQ, which was sent out to the participants from 2002 and onwards (32). The FFQ was a semi-quantitative questionnaire, designed to obtain information on dietary habits and intake of nutrient supplements during the first four to five months of the pregnancy.

The FFQ is developed especially for the MoBa study, and has been validated in a subsample of the cohort participants (35). This study found the questionnaire to give realistic estimates on dietary habits and high vs. low intake of energy, nutrients and foods.

Extraction of dietary patterns

We conducted a principal component factor analysis to extract dietary patterns. Factor analysis is a way of identifying variables that correlate and form a pattern across the sample population.

Food- and beverage variables (n = 98) were included in the principal component analysis (PCA). Suitability of the data prior to the analysis was tested using correlation matrix, Bartlett's Test of Sphericity ($p < 0{,}001$) and Kaiser-Meyer-Olkin test (KMO = 0,721).

A total of 29 components were extracted from the PCA. Coefficients with absolute value below 0.25 were suppressed due to interpretability of the patterns. We used scree plot to determine the number of components to retain, and orthogonal (varimax) rotation to obtain optimal interpretability of the extracted components (dietary patterns).

Food items are denoted with a positive or negative coefficient within the dietary pattern, called factor loadings. Participants are assigned factors scores based on their consumption of the given food item (from the FFQ) multiplied with the factor loading produced from the given dietary pattern. The factors scores, which are approximately normally distributed, were divided into tertiles, indicating low, medium or high intake of food items associated with the score.

Pregnancy outcomes

Pregnancy outcomes are defined as the dichotomous variables preterm birth (delivery < 37 weeks of gestation), low birth weight (LBW)(defined as birth weight below 2500 g) and small for gestational age (SGA); defined as birth weight below the 10^{th} percentile of the mean Norwegian weight curve (36).

Expected date of birth is estimated (in MoBa) based on ultrasound scan, or the recorded date of last menstrual period, if ultrasound scan is missing (32). The information regarding birth outcomes was collected from the Norwegian Medical Birth Registry (MBRN) in MoBa (34).

Covariates

We adjusted for a set of potential confounders: maternal body mass index (BMI) as a continuous variable; age divided into the following groups: <18, 18-34, >34 years; educational status divided into high school or less, 3 years of college/university, or master degree or higher; total energy intake in quartiles: <1870, 1871-2224, 2225-2657, and > 2658 kcal; and smoking as a dichotomous variable. These variables are all known as important predictors on pregnancy outcomes.

Hypertension and diabetes mellitus were considered as potential confounders, but was excluded from the model due to low prevalence in the IBD-subsample.

Statistical analysis

One-way ANOVA and Independent samples t-tests were performed to analyze the distribution of dietary patterns in relation to characteristics and pregnancy outcomes.

Logistic regression analysis was used to model the relationship between the exposure variables and the outcome variables. The models were adjusted for potential confounding by maternal BMI, age, educational status, total energy intake, diabetes mellitus and smoking. All dietary patterns were entered into the same model, controlling for each other.

We estimated the relationship between dietary pattern and pregnancy outcomes in women with IBD, by entering dietary patterns as three distinct interaction terms with IBD in the same model. Non-IBD women and women with IBD adhering to the lowest third in the dietary pattern was used as reference category. The parameters reported shows excess risk of outcome for women with IBD in the second and third tertiles compared to the women in the reference category.

A second logistic regression analysis was conducted in the IBD-subset, excluding controls. We estimated the relationship between dietary pattern and pregnancy outcome in women with IBD. In this analysis all three dietary patterns were included in the same model as single variables divided into tertiles. The analysis was performed on participants with IBD, CD and UC respectively.

Risks of the stated adverse pregnancy outcomes are presented in odds ratios (OR) with corresponding p-value and confidence intervals (CI).

The statistical analyses were performed using SPSS version 23. Statistical significance was considered for p-values < 0.05.

Ethics

MoBa is approved by The Regional Committee for Medical Research Ethics (REK). This study is a part of a project administered by Akershus University hospital, and was approved by the REK and the owners of the registries and databases, in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants before the study (32).

Results

This study comprises 218 CD- and 287 UC mothers, of whom 489 births were available for the analysis reflecting the association between dietary patterns and pregnancy outcomes in women with IBD compared to controls. We only included singletons in the analysis (n = 104.996).

Dietary patterns

Three distinct dietary patterns were extracted from the PCA, explaining 12.65% of the total variance (Table 1).

The first dietary pattern (eigenvalue 6.1 explaining 6.22% of the variance), labeled "Prudent", had positive factor loadings for fruit, berries, vegetables (cooked and raw), beans, vegetable oils, rice, corn, poultry, nuts, tuna fish, yoghurt, probiotic foods and water as beverage. The "Prudent" dietary pattern had negative factor loadings for processed meats (hamburgers, hot dogs) and casseroles. The second dietary pattern (eigenvalue 3.9, explaining 3,95% of the variance), labeled "Western", had high factor loadings for foods and beverages rich in sugar (such as sodas, waffles, pancakes, pastries, chocolate, dairy desserts and white bread) and fat (such as chocolate, dairy desserts, gravy, salty snacks, processed meats and fried potatoes), but also cooked vegetables, potatoes, berries and corn. The third pattern (eigenvalue 2.4, explaining 2.48% of the variance) labeled "Traditional", scored positively in fish (lean) and fish products, gravy, potatoes and rice porridge, and negatively in poultry, casseroles, pizza and tacos.

[Table 1]

The distribution of IBD, CD and UC in relation to characteristics, dietary patterns and pregnancy outcomes are presented in Table 2.

Mean factor scores for dietary pattern tertiles in relation to characteristics for IBD, CD and UC are presented in Table 3. The mean factor score was negative for almost all characteristics in the "Prudent" and "Traditional" dietary pattern. The mean factor score in the complete dataset is around zero. This indicates that women with IBD have, in general, a lower consumption of the “Prudent” dietary pattern and the “Traditional dietary pattern”, and a higher consumption of the “Western” dietary pattern, compared to controls, and across all characteristics.

[Table 2]

[Table 3]

Dietary patterns in relation to pregnancy outcomes

The unadjusted analysis revealed that women with IBD had, in general, a lower mean factor score for the “Prudent” and “Traditional” dietary pattern than controls for all pregnancy outcomes (Table 4). We found no significant differences in mean factor score for the different dietary patterns in relation to pregnancy outcome, in the IBD- CD- or UC-subsample. Women with CD giving birth to preterm babies, was found to have a significant lower adherence to the “Traditional” dietary pattern than non-IBD women. Women with CD who gave birth to SGA-babies, was found to have a significant higher adherence to the “Western” dietary pattern, than non-IBD women. Women with UC giving birth to SGA-babies, were found to a have a significant lower adherence to the “Prudent” dietary pattern.

[Table 4]

In the adjusted logistic regression analysis, including IBD and dietary patterns as interaction terms, women with IBD in the highest third of the “Traditional” dietary pattern had a significant lower risk of giving birth to babies with SGA compared to controls and women with IBD in the lower third of the dietary pattern, for the same pregnancy outcome (OR for tertile 3 vs. tertile 1: 0.33 (95% CI: 0.13 – 0.86))(Table 4). This finding suggests a protective effect of the “Traditional” dietary pattern, reducing the risk of SGA with 66%. Significant results were not found for any of the other dietary patterns and pregnancy outcomes.

[Table 5]

In the adjusted logistic regression analysis in the IBD-subset, significant effects were observed in the middle tertile of the "Traditional" dietary pattern in the LBW group (OR for tertile 2 vs. tertile 1: 6.25 (95% CI: 1.23 – 31.82)), and in the preterm group (OR tertile 2 vs. tertile 1: 0.30 (95% CI: 0.09 – 0.97)) in women with IBD (Table 5).

In the CD subgroup, the highest tertile of the "Traditional" dietary pattern was found to significantly increase the risk of LBW (OR tertile 3 vs. tertile 1: 29.81 (1.73 – 515.14)).

No significant differences between dietary patterns and pregnancy outcomes where found in the UC subgroup.

[Table 6A-C]

Sensitivity analysis

We performed a sensitivity analysis, testing the effect of a potential interaction of the "Traditional" dietary pattern with disease activity on SGA (data not shown). We found no interaction or effect-modification of disease activity.

When entering disease activity as a confounder, we found no significant effects of dietary patterns or disease activity on pregnancy outcomes. This may be due to a high proportion of missing values.

Discussion

Summary

The aim of this study was to investigate the effect of dietary patterns on pregnancy outcomes in women with IBD, and in relation to controls.

Three dietary patterns ("Prudent", "Western" and "Traditional") were extracted from the principal component analysis. The "Traditional" dietary pattern was associated with LBW, SGA and preterm birth. This dietary pattern is characterized by lean fish, fish products, potatoes, gravy and porridge, and negatively associated with pizza, tacos and casseroles. Women with IBD had a lower adherence to the "Prudent" and "Traditional" dietary pattern, and a higher adherence to the "Western" dietary pattern than controls.

We found a significant protective effect on SGA among women with IBD with the highest tertile in the "Traditional" dietary pattern, compared to controls and IBD women in the lowest dietary group. In the adjusted analysis in the IBD subgroup we found a significant protective effect of the "Traditional" dietary pattern on preterm birth. Surprisingly, we found the same dietary pattern to increase the risk of LBW in the IBD- and CD group. However, the sample size was small in this analysis, and confidence intervals were wide.

Previous findings

To the best of our knowledge, dietary patterns in relation to pregnancy outcomes in women with IBD has not been investigated in previous research. However, several studies have examined the relationship between dietary patterns and pregnancy outcomes in a general pregnant population (24-31).

The results from these studies indicate a protective effect of a dietary pattern characterized by high consumption of fruit and vegetables (a prudent- or Mediterranean diet) on preterm birth and birth weight (24, 27, 28, 30, 31). However, a large study based on the MoBa cohort did not find any protective effect of a "Mediterranean diet" on preterm birth (25). Brantsæter et al. found that a "Prudent" dietary pattern reduced the risk for preeclampsia in the same sample, which in turn may be a risk factor for adverse pregnancy outcomes (23). We found no effect of the "Prudent" dietary pattern on pregnancy outcomes in women with IBD.

Previous studies have primarily investigated somewhat mutually exclusive dietary patterns, such as a prudent or vegetarian dietary pattern and a western dietary pattern. Results indicate that a "Western" dietary pattern characterized by a high consumption of saturated fatty acids, sugar and salt may increase the risk of SGA in a general pregnant population (27). We found a higher mean factor score for the "Western" dietary pattern in women with lower education and higher total energy consumption, and in smokers. However, we found no significant effect of the dietary pattern on pregnancy outcomes.

As for the "Traditional" dietary pattern, Englund-Ögge et al. investigated a traditional dietary pattern similar to ours, in a study based on the general MoBa-population (24). The results indicated that a traditional dietary pattern reduced the risk for preterm birth when comparing the upper third of the factor score with the lower third. When stratifying on pre-pregnancy BMI, researchers found a significantly reduced risk for the preterm birth in the "Traditional" dietary pattern.

Potential mechanisms explaining the effect

Diet has been suggested to play a role in the etiology of IBD, and as a modifier of disease activity (6-8, 37). IBD patients are vulnerable to nutrition deficiencies due to an increased loss, drug-nutrient interaction, decreased absorption from the ileum, and increased requirements (1, 18). A large proportion of IBD patients report exclusion of certain foods or food groups from their diet, although no pathological mechanisms have been identified between specific foods and disease activity (37-43). Such deficiencies and alterations in diet may be of great importance in pregnancy, with nutrition being an important predictor for adverse pregnancy outcomes and future life course in the offspring (20-31, 44). In addition, the nutrient requirement is increased in pregnancy (45). This suggests several mechanisms for biological effects of dietary patterns on pregnancy.

It is likely to believe that certain dietary patterns have a better nutrient profile in relation to women with IBD than other dietary patterns. The "Traditional" dietary pattern was found to lower the risk of SGA significantly in IBD women compared to controls, indicating an interaction between IBD and the "Traditional" dietary pattern.

It is possible that the "Traditional" dietary pattern correlates with nutrients especially important in IBD and in fetal development. Such nutrients may be protein, calcium, sink or folic acid, in which IBD patients have been found to have deficiencies (18). In the study by Englund-Ögge et al., potassium, magnesium, protein and dietary fibre were found to correlate with a traditional dietary pattern similar to the one in our study (24). Research exists on several nutrients and their effect on pregnancy outcomes (46-48). We did not perform a correlations test on nutrients in relation to dietary patterns. However, this should be done in further research. When meeting the nutritional requirements of the mother and fetus through the diet, it is plausible that this may enhance sufficient intrauterine growth. Further investigation is required to confirm this hypothesis.

Active disease in pregnancy has been found to be a potential risk factor for adverse pregnancy outcomes in maternal IBD (16, 49, 50). Disease activity is an important determinant on the nutritional status of the mother, as active disease may impair absorption and lead to an increased loss of nutrients through diarrhea (18). The requirement of nutrients may be increased in active state of the disease. However, in the present study, we found no significant results indicating disease activity as an effect-modifier on the stated pregnancy outcomes.

Many IBD patients report specific dietary beliefs regarding symptom relief (37-39, 41). Foods rich in fibre, such as fruit and vegetables are frequently reported as worsening symptoms (37). Foods rich in fibre may be hard to digest during active inflammation. Dairy products are also frequently excluded during active disease, due to a transient lactose intolerance (39, 51). In addition, medicament use during active inflammation may impair the nutritional status further, due to various drug-nutrient interactions (18). Medicament use could be included as a potential confounder in further studies.

It is possible that disease activity may act as a confounder on the effect of dietary patterns on pregnancy outcomes, having an effect both on adherence to dietary patterns and pregnancy outcomes. It is likely to believe that mothers with IBD may adhere to a certain diet due to disease activity. The "Traditional" dietary pattern has low factor loadings for fruit and vegetables, except potatoes. A study by Cohen et al. found that IBD patients considered fruit, vegetable and nuts to worsen symptoms, and women with active disease may thus adhere to a dietary pattern low in such food groups (37). This may explain why we observed a negative factor score for the IBD subgroups in the

"Prudent" dietary pattern compared to controls. In this scenario, dietary patterns may be regarded as a mediator of the effect of disease activity on pregnancy outcomes.

Diet has been linked to the etiology of IBD (6-8). It is likely to believe that dietary patterns may have an influence on disease activity (18, 37). It is possible that disease activity may act as a mediator on the effect of dietary patterns on pregnancy outcomes.

We found no significant effect of disease activity in our sensitivity analysis. We tested disease activity both as a confounder and an effect modifier. However, the sample size was rather small in this analysis, probably explaining why the results failed to reach statistical significance.

Methodological considerations

MoBa is an open cohort with no exclusion criteria, and the large sample size is a strength in our study. However, there are losses to follow up in the study, and the FFQ was first sent out from 2002 and onwards (32).

IBD is a rather rare disease, and relatively few births were registered with the maternal condition (n = 739). This sample is rather vulnerable to missing cases, and in the logistic regression analysis, confidence intervals were wide. However the total number of women with IBD included in the analysis (0,67 %) is in accordance with the prevalence rates in the general population (approximately 0,80 %) (52, 53)

The MoBa study is a nationwide study including women with a broad range of characteristics (32). Participants are from all parts of the country, and represent all age- and socioeconomic groups. However, the total participation rate in MoBa was only 41% and the participants have been found to have higher age and higher education level than the general pregnant population (32, 54). In addition, smokers, younger women (<25 yrs) and those living alone were underrepresented. Multivitamin- and folic acid supplement users were overrepresented. This may introduce selection bias to our study and impair internal and external validity of the results. However, in a study focusing on potential self-selection bias in MoBa, researchers found no significant differences between eight exposure-outcome associations comparing MoBa participants with the total pregnant population in the same time frame (54). Preterm birth was one of the outcomes evaluated. Similar results were found in a study analyzing self-selection bias in The Autism Birth cohort study, a sub-cohort in MoBa (55).

The prospective cohort design in this study minimizes the potential differential misclassification errors, because dietary habits were measured before pregnancy outcomes. The pregnancy outcome had not yet occurred when the mothers were to fill out the FFQ, and the outcome could thus not influence the classification of exposures. Differential misclassification of pregnancy outcome in relation to the exposure is very unlikely given the fact that outcome information is attained from MBRN, which has no direct linkage to the FFQ (34).

Non-differential misclassification error may occur in nutritional studies due to recall bias, and may present itself as over- or under estimation of dietary intake. However, such errors are assumed to have an equal distribution in cases and controls. This may underestimate a potential effect. However, if this under- or overestimation is related to a variable under study, the misclassification will be differential. In this case, it is likely to believe that women with IBD may be more conscious of what they eat, than controls. Women without IBD may under- or overestimate their consumption due to recall bias, and thus be misclassified into a wrong tertile of a given dietary pattern.

The FFQ was especially developed for the MoBa study, and has been validated in a study of a MoBa sub sample (35, 56). The method in the validation study was a four-day weighed food diary (FD) and analysis of nutrients in urine- and venous blood samples (35). The agreement between the FFQ and FD was considered appropriate, with significant correlations for all major food groups and all nutrients, except vitamin E. The biological markers confirmed the FFQ as suitable for distinguishing between high and low intakes of nutrients.

We only included cases with a confirmed IBD diagnosis from the NPR registry, reducing non-differential misclassification of the disease due to errors in self-reported diagnosis. In relation to the pregnancy outcomes, misclassification may occur, but we lowered this probability by including the outcomes as dichotomous variables.

We reduced potential confounding by controlling for several relevant factors. Information regarding medical history, lifestyle factors and work exposures were attained from Q1 and national health registries. We controlled for the variables maternal age, BMI, educational level and smoking. These are all considered to be important risk factors for adverse pregnancy outcomes, and may also affect dietary habits. Diabetes and hypertension was initially included in the model, but was excluded due to low prevalence in the IBD subgroup. Although controlling for several potential confounders, we cannot exclude potential residual confounding in such an observational design.

Dietary patterns is considered a valuable tool in assessing associations between diet and health outcomes in pregnant populations (57). However, dietary patterns extracted from factor analysis will only explain a small part of the variation in diet in the pregnant women in MoBa. The three dietary patterns extracted from the PCA only accounted for 12,65% of the total variance in food intakes in MoBa. However, the variance explained by the dietary patterns is similar in previous studies. In the study by Englund-Ögge et al., the three dietary patterns extracted explained 16% of the total variation (24). In the study by Brantsæter et al., the cumulative variance explained from the four dietary patterns included was 18% (23). In the study by Cuco et al., investigating dietary patterns in preconception, pregnancy and postpartum, the two dietary patterns included explained 20-25% of the total variance (58).

There are food groups that are not denoted in any of the three dietary patterns, such as low-fat dairy products which was a variable entered into the factor analysis. This is not necessarily due to a low consumption of such products, but could reflect an even distribution of low-fat dairy products across all dietary patterns. In addition, we only included food groups with a factor loading above the absolute value of 0.25. This may result in certain foods being excluded from a dietary pattern, although the women may have had an adequate consumption of these foods, - but not in comparison with the other foods in the pattern. Further research should investigate what level of consumption the factor scores reflect, and whether it is within nutritional guidelines.

Analysis of dietary patterns are considered a valid tool for assessing associations between diet and diseases (57). Analysis of dietary patterns may give a wider perspective on the importance of nutrition in pregnancy in women with IBD, and may provide more relevant and applicable information than investigation of single nutrients or food groups alone. Nutrients and foods are not consumed independently of each other, and may interact in different ways.

Conclusion

This study revealed that women with IBD had lower adherence to the “Prudent” and “Traditional” dietart pattern, and a higher adherence to the “Western” dietary pattern, than controls. Furthermore, we demonstrated that high intake of a “Traditional” dietary pattern, characterized by a high consumption of lean fish and fish products, potatoes, rice porridge and gravy, was protective for SGA in women with IBD compared to controls.

Disease activity was tested as a potential effect-modifier, but failed to reach statistical significance in our sensitivity analysis.

As far as we know, this is the first study examining the relationship between dietary patterns and pregnancy outcomes in women with IBD. Further studies are required to confirm our findings. An interventional approach examining nutritional deficiencies, fetal development and nutritional profile of dietary patterns in women with IBD would be of interest. However, such studies may be of great economic costs.

Although inconclusive, our findings may serve as a basis for further research and indicates that adherence to certain dietary patterns may be of importance in the pregnant IBD patient. Research indicates that pregnant women may be more motivated for lifestyle changes than the general female population, and proper nutritional guidance in the clinical care may prevent adverse pregnancy outcomes (59).

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TABLE 1 – Structures of the three rotated components identified by PCA in 104.996 singleton births, from MoBa 1999-2008

Dietary Pattern	Food group	Loading coefficient	Variance explained, %
"Prudent"	Green salads	0.611	6.22
	Raw vegetables	0.590	
	Cooked vegetables	0.545	
	Onions, leek, garlic	0.532	
	Cooking oils	0.524	
	Mushroom	0.480	
	Green beans	0.479	
	Tomato, cucumber	0.445	
	Fruit, traditional	0.432	
	Vegetables as main course	0.429	
	Fruit, exotic	0.422	
	Olive oil	0.421	
	Rice, millet, coscous	0.363	
	Dried fruits	0.358	
	Almonds, nuts	0.338	
	Berries	0.331	
	Porridge	0.327	
	Green-, herbal-, rose hip tea	0.316	
	Water, bottled or tap	0.297	
	Corn	0.295	
	Poultry	0.286	
	Tuna fish	0.276	
	Yoghurt	0.265	
	Probiotic drinks	0.256	
	White bread	-0.279	
	Casseroles, meat	-0.312	
	Processed meat products	-0.471	
"Western"	Salty snacks	0.57	3.95
	Cakes	0.52	
	Dairy desserts	0.474	
	Chocolates	0.456	

	Potatoes, fried	0.454	
	Caramels, pastilles, candies	0.445	
	Waffles, pancakes	0.440	
	Sugared sodas	0.379	
	Buns	0.378	
	Gravy	0.377	
	Cooked tomato	0.364	
	Mayonnaise, mayonnaise salads	0.352	
	White bread	0.341	
	Marzipan	0.331	
	Cookies	0.305	
	High-fat dairy products	0.299	
	Potetatoes, cooked or mashed	0.293	
	Processed meat products	0.287	
	Cooked vegetables	0.269	
	Sugared squash drinks	0.265	
	Corn	0.261	
	Berries	0.256	
"Traditional"	Processed fish products	0.583	2.48
	Potetatoes, cooked or mashed	0.521	
	Lean fish	0.508	
	Rice porridge	0.318	
	Gravy	0.29	
	Casseroles, meat	-0.295	
	Pizza, tacos	-0.306	
	Poultry	-0.308	

TABLE 2 – Distribution of 489 singleton births with maternal IBD, from MoBa 1999-2008, in relation to characteristics.

	IBD (n = 489)	**CD** (n= 209)	**UC** (= 280)
Age (yrs)			
<18	1	1	N/A
18-34	294	130	164
>35	71	28	43
Body mass index			
<25	326	139	187
≥25	163	70	93
Diabetes mellitus			
Yes	6	1	5
No	483	208	275
Education (completed level)			
High school or less	121	61	60
3 years of college/university	167	68	99
Master degree or higher	78	30	48
Energy (kcal)			
<1870	97	45	52
1871-2224	81	27	54
2225-2657	95	43	52
>2658	93	44	49
Chronic hypertension			
Yes	1	N/A	1
No	488	209	279
Smoking			
Yes	34	23	11
No	332	136	196
”Prudent dietary pattern			
Low	126	49	77
Middle	140	68	72
High	100	42	58
Western dietary pattern			
Low	107	45	62
Middle	122	44	78
High	137	70	67
Traditional dietary pattern			
Low	144	75	69
Middle	121	40	81
High	101	44	57
Low birth weight			
<2500 g	16	10	6
> 2500 g	350	149	201
Preterm birth			
<week 37	24	12	5
>week 37	342	147	200
Small for gestational age			
Below 10th percentile	36	17	18
Above 10th percentile	330	142	188

TABLE 3 - Mean factor scores in relation to maternal characteristics in 489 births, from MoBa 1999-2008. Dietary patterns are extracted through PCA.

	IBD (n = 489)			CD (n= 209)			UC (= 280)		
	Prudent	Western	Traditional	Prudent	Western	Traditional	Prudent	Western	Traditional
Age (yrs)[1]									
≤34	-0.09	0.07	-0.18	-0.04	0.21	-0.21	-0.13	-0.03	-0.16
>35	-0.08	0.13	**0.18**	-0.14	-0.05	0.03	-0.05	**0.25**	**0.28**
Body mass index[1]									
<24,9	-0.12	0.13	-0.19	-0.12	0.11	-0.29	-0.12	0.14	-0.12
≥25	-0.07	0.06	-0.72	-0.03	0.19	-0.11	-0.1	-0.03	-0.04
Diabetes mellitus[1]									
Yes	-0.69	-0.39	-0.58	-1.16	0.17	0.24	-0.57	-0.53	-0.78
No	-0.08	0.09	-0.11	-0.05	0.16	-0.17	-0.10	0.04	-0.06
Education (completed level)[2]									
High school or less	-0.38	0.35	-0.06	-0.38	0.48	-0.09	-0.38	0.24	-0.03
3 years of college/uni.	-0.07	0.04	-0.05	**-0.01**	0.03	-0.10	-0.11	**0.04**	-0.01
Master degree or higher	0.31	-0.19	-0.29	**0.42**	-0.03	-0.59	0.24	**-0.30**	-0.11
Energy (kcal)[2]									
<1870	-0.26	-0.39	-0.26	-0.28	-0.44	-0.39	-0.24	-0.50	-0.40
1871-2224	-0.17	**-0.39**	-0.17	-0.13	-0.20	-0.42	-0.19	**-0.18**	-0.20
2225-2657	-0.17	**1.08**	**-0.39**	0.03	**0.14**	-0.14	-0.07	**0.13**	-0.07
>2658	-0.09	**-0.39**	**-0.11**	0.13	**1.09**	**0.20**	0.07	**0.68**	**0.40**
Chronic hypertension[1]									
Yes	5.79	0.97	1.12	N/A	N/A	N/A	5.80	0.97	1.12
No	-0.1	0.08	-0.12	-0.06	0.16	-0.17	-0.13	0.02	-0.07
Smoking[1]									
Yes	-0.19	0.51	-0.15	-0.34	0.44	-0.10	0.08	0.63	-0.25
No	-0.05	**0.05**	-0.14	-0.01	0.15	-0.21	-0.08	**-0.02**	-0.08

[1] Differences between categories were tested using Independent samples T-test

[2] Differences between categories were tested using One-way ANOVA, with Dunnett's post-hoc analysis, comparing the different levels to the lowest level. Results were considered statistical significant for P<0,05

TABLE 4 – Mean factor scores in relation to pregnancy outcomes in 489 singleton births with maternal IBD, from MoBa 1999-2008

		LBW			Preterm			SGA		
		Yes	No	P-value[1]	Yes	No	P-value	Yes	No	P-value
IBD	Prudent	-0.11 (-0.49 - 0.26)	**-0.09 (-0.18 - 0)**	0.90	-0.21 (-0.48 - 0.06)	-0.08 (-0.17 - 0.01)	0.43	**-0.27 (-0.49 - -0.05)**	-0.07 (-0.16 - 0.03)	0.20
	Western	0.23 (-0.18 - 0.65)	**0.08 (0 - 0.16)**	0.46	0.14 (-0.13 - 0.41)	**0.08 (0 - 0.17)**	0.75	0.22 (-0.04 - 0.49)	0.07 (-0.01 - 0.16)	0.28
	Traditional	-0.32 (-0.75 - 0.11)	**-0.1 (-0.2 - -0.01)**	0.34	-0.4 (-0.8 - 0.01)	**-0.09 (-0.19 - 0)**	0.11	-0.08 (-0.37 - 0.22)	**-0.12 (-0.21 - -0.02)**	0.80
CD	Prudent	-0.01 (-0.53 - 0.5)	-0.06 (-0.2 - 0.08)	0.87	-0.18 (-0.63 - 0.27)	-0.05 (-0.19 - 0.09)	0.63	-0.27 (-0.64 - 0.1)	-0.04 (-0.18 - 0.11)	0.31
	Western	0.17 (-0.32 - 0.65)	**0.16 (0.02 - 0.3)**	0.99	0.33 (-0.12 - 0.77)	**0.15 (0.01 - 0.29)**	0.50	**0.45 (0.04 - 0.86)**	0.13 (-0.01 - 0.27)	0.17
	Traditional	-0.43 (-0.91 - 0.04)	**-0.15 (-0.3 - -0.01)**	0.33	**-0.55 (-1.08 - -0.01)**	**-0.14 (-0.28 - 0)**	0.13	-0.24 (-0.61 - 0.14)	**-0.16 (-0.31 - -0.01)**	0.75
UC	Prudent	-0.31 (-0.76 - 0.13)	-0.1 (-0.22 - 0.02)	0.59	-0.24 (-0.55 - 0.07)	-0.1 (-0.22 - 0.02)	0.60	**-0.27 (-0.53 - -0.02)**	-0.09 (-0.22 - 0.03)	0.40
	Western	0.36 (-0.47 - 1.2)	0.02 (-0.08 - 0.12)	0.29	-0.07 (-0.34 - 0.21)	0.03 (-0.07 - 0.14)	0.66	0.02 (-0.31 - 0.36)	0.03 (-0.08 - 0.13)	0.98
	Traditional	-0.11 (-1.02 - 0.81)	-0.07 (-0.19 - 0.05)	0.92	-0.24 (-0.85 - 0.38)	-0.06 (-0.18 - 0.06)	0.52	0.07 (-0.38 - 0.52)	-0.08 (-0.21 - 0.04)	0.50

[1] Independent samples T-test

TABLE 5 – Associations between the highest and middle tertile of dietary pattern scores and risk of adverse pregnancy outcomes in women with IBD compared to controls and women with IBD in the lowest tertile.

		LBW		SGA		Preterm	
	Pregnancies (n = 431)	Pregnancy outcome n (%)	Model OR[1] (95% KI)	Pregnancy outcome n (%)	Model OR (95% KI)	Pregnancy outcome n (%)	Model OR (95% KI)
Prudent							
Low (controls + IBD)	152	7 (4.6)	1 (ref.)	18 (11.8)	1 (ref.)	10 (6.6)	1 (ref.)
Middle (IBD)	162	5 (3.1)	0.85 (0.24 - 2.99)	12 (7.4)	1.73 (0.70 - 4.29)	10 (6.2)	1.22 (0.39-3.82)
High (IBD)	117	6 (5.1)	1.72 (0.44 - 6.81)	10 (8.5)	0.91 (0.35 - 2.37)	7 (6.0)	1.17 (0.39-3.49)
Western							
Low (controls + IBD)	126	5 (4.0)	1 (ref.)	9 (7.1)	1 (ref.)	8 (6.3)	1 (ref.)
Middle (IBD)	143	5 (3.5)	1.34 (0.36 - 4.98)	14 (9.8)	0.62 (0.24 - 1.59)	6 (4.2)	0.85 (0.30-2.40)
High (IBD)	162	8 (4.9)	1.35 (0.38 - 4.72)	17 (10.5)	0.88 (0.39 - 1.98)	13 (8.0)	0.51 (0.17-1.52)
Traditional							
Low (controls + IBD)	165	11 (6.7)	1 (ref.)	17 (10.3)	1 (ref.)	15 (9.1)	1 (ref.)
Middle (IBD)	141	3 (2.1)	0.43 (0.12 - 1.61)	8 (5.7)	0.56 (0.25 - 1.24)	5 (3.5)	1.98 (0.69-5.72)
High (IBD)	125	4 (3.2)	1.90 (0.31-11.71)	15 (12.0)	**0.33 (0.13-0.86)**	7 (5.6)	0.63 (0.16-2.42)

[1] Adjusted for maternal age, BMI, educational level, total energy consumption and smoking

TABLE 6A - Associations between tertiles of dietary pattern scores and risk of adverse pregnancy outcomes in women with IBD

		LBW		SGA		Preterm	
	Pregnancies (n = 431)	Pregnancy outcome n (%)	Model OR[1] (95% KI)	Pregnancy outcome n (%)	Model OR (95% KI)	Pregnancy outcome n (%)	Model OR (95% KI)
Prudent							
Low	152	7 (4.6)	1 (ref.)	18 (11.8)	1 (ref.)	10 (6.6)	1 (ref.)
Medium	162	5 (3.1)	1.97 (0.48 - 8.05)	12 (7.4)	0.59 (0.25-1.44)	10 (6.2)	0.78 (0.26-2.30)
High	117	6 (5.1)	1.44 (0.30 - 6.82)	10 (8.5)	0.73 (0.26-2.03)	7 (6.0)	0.51 (0.13-1.98)
Western							
Low	126	5 (4.0)	1 (ref.)	9 (7.1)	1 (ref.)	8 (6.3)	1 (ref.)
Medium	143	5 (3.5)	1.33 (0.27 - 6.68)	14 (9.8)	1.37 (0.49-3.88)	6 (4.2)	0.49 (0.13-1.84)
High	162	8 (4.9)	1.24 (0.17 - 8.88)	17 (10.5)	1.90 (0.55-6.53)	13 (8.0)	0.64 (0.15-2.74)
Tradiditional							
Low	165	11 (6.7)	1 (ref.)	17 (10.3)	1 (ref.)	15 (9.1)	1 (ref.)
Medium	141	3 (2.1)	**6.25 (1.23-31.82)**	8 (5.7)	0.51 (0.19-1.35)	5 (3.5)	**0.30 (0.09-0.97)**
High	125	4 (3.2)	4.17 (0.84 - 20.70)	15 (12.0)	1.67 (0.67-4.20)	7 (5.6)	0.47 (0.14-1.56)

[1] Adjusted for maternal age, BMI, educational level, total energy consumption and smoking

TABLE 6B - Associations between tertiles of dietary pattern scores and risk of adverse pregnancy outcomes in women with CD

		LBW		SGA		Preterm	
	Pregnancies (n = 431)	Pregnancy outcome n (%)	Model OR[1] (95% KI)	Pregnancy outcome n (%)	Model OR (95% KI)	Pregnancy outcome n (%)	Model OR (95% KI)
Prudent							
Low	58	3 (5.2)	1 (ref.)	6 (10.3)	1 (ref.)	5 (8.6)	1 (ref.)
Medium	77	4 (5.2)	1.50 (0.19 - 11.68)	9 (11.7)	1.18 (0.33 - 4.20)	5 (6.5)	0.29 (0.04 - 1.86)
High	51	5 (9.8)	0.91 (0.09 - 9.52)	4 (7.8)	1.12 (0.24 - 5.31)	4 (7.8)	0.24 (0.03 - 2.25)
Western							
Low	58	4 (6.9)	1 (ref.)	4 (6.9)	1 (ref.)	4 (6.9)	1 (ref.)
Medium	51	3 (5.9)	5.53 (0.27 - 112.40)	4 (7.8)	1.14 (0.19 - 6.87)	3 (5.9)	0.19 (0.02 - 2.35)
High	77	5 (6.6)	17.00 (0.70 - 414.92)	11 (14.3)	2.63 (0.40 - 17.25)	7 (9.1)	0.13 (0.01 - 1.93)
Tradiditional							
Low	81	8 (9.9)	1 (ref.)	11 (13.6)	1 (ref.)	9 (11.1)	1 (ref.)
Medium	51	2 (3.9)	9.79 (0.77 - 125.19)	2 (3.9)	0.16 (0.02 - 1.36)	2 (3.9)	0.13 (0.01 - 1.56)
High	54	2 (3.7)	**29.81 (1.73-515.14)**	6 (11.1)	1.07 (0.29 - 3.94)	3 (5.6)	0.13 (0.02 - 1.12)

[1] Adjusted for maternal age, BMI, educational level, total energy consumption and smoking

TABLE 6C - Associations between tertiles of dietary pattern scores and risk of adverse pregnancy outcomes in women with UC

		LBW		SGA		Preterm	
	Pregnancies (n = 431)	Pregnancy outcome n (%)	Model OR[1] (95% KI)	Pregnancy outcome n (%)	Model OR (95% KI)	Pregnancy outcome n (%)	Model OR (95% KI)
Prudent							
Low	94	4 (4.3)	1 (ref.)	12 (12.8)	1 (ref.)	5 (5.3)	1 (ref.)
Medium	85	1 (1.2)	1.59 (0.12 - 21.47)	3 (3.5)	0.29 (0.07 - 1.30)	5 (5.9)	1.99 (0.38 - 10.43)
High	66	1 (1.5)	1.80 (0.09 - 35.40)	6 (9.1)	0.58 (0.13 - 2.52)	3 (4.5)	1.40 (0.19 - 10.12)
Western							
Low	68	1 (1.5)	1 (ref.)	5 (7.4)	1 (ref.)	4 (5.9)	1 (ref.)
Medium	92	2 (2.2)	0.34 (0.01 - 8.40)	10 (10.9)	1.63 (0.39 - 6.90)	3 (3.3)	0.56 (0.09 - 3.46)
High	85	3 (3.5)	0.02 (0.00 - 1.64)	6 (7.1)	1.23 (0.19 - 8.05)	6 (7.1)	1.55 (0.21 - 11.48)
Tradiditional							
Low	84	3 (3.6)	1 (ref.)	6 (7.1)	1 (ref.)	6 (7.1)	1 (ref.)
Medium	90	1 (1.1)	7.18 (0.36 - 141.76)	6 (6.7)	1.04 (0.27 - 4.02)	3 (3.3)	0.32 (0.06 - 1.73)
High	71	2 (2.8)	0.25 (0.01 - 5.23)	9 (12.7)	3.02 (0.71 - 12.87)	4 (5.6)	1.61 (0.30 - 8.68)

[1] Adjusted for maternal age, BMI, educational level, total energy consumption and smoking

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Ingrid Middelthon	22845515	07.09.11	2011/1317
			Deres dato:	**Deres referanse:**
			15.06.11	

Morten H. Vatn
EpiGen-instituttet
1478 Lørenskog

IBD hos gravide og miljømessige risikofaktorer

Vi viser til søknad av 15.06.11 for det ovenfor nevnte forskningsprosjekt. Søknaden ble behandlet i komiteens møte 18.08.11.

Prosjektleder professor Morten H. Vatn.

Forskningsansvarlig er Akershus universitetssykehus ved øverste administrative ledelse.

Prosjekttema:
Målsetningen med studien er å undersøke svangerskapskomplikasjoner hos IBD (Inflammatorisk tarmsykdom)- pasienter og betydningen av miljøfaktorer som kosthold, kvalitet på drikkevann og luftforurensning. Studien baserer seg hovedsakelig på allerede avgitte blodprøver, pasientjournaler og registerdata. Det skal inkluderes 6 deltakere i Norge. Samtykke innhentes for utvalgte data.

Vedtak:
Komiteen har vurdert søknaden og godkjenner prosjektet med hjemmel i helseforskningsloven § 10. Det knytter seg imidlertid vilkår til godkjenningen som må oppfylles før prosjektet settes i gang.

I tillegg til vilkår som fremkommer av dette vedtaket er tillatelsen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, protokollen og de bestemmelser som følger av helseforskningsloven med forskrifter.

Vilkår vedrørende overføring av forskningsdata til utlandet:
Det må fremkomme av informasjonsskrivet at forskningsdata skal overføres til utlandet.

REK godkjenner at det biologiske materialet kan overføres til utlandet dersom prosjektdeltakerne samtykker til dette.

Personidentifiserbare helseopplysninger som blir behandlet som en del av prosjektet kan bare overføres til et land utenfor EØS-området dersom:

- Den utenlandske databehandlingsansvarlige skriftlig forsikrer overfor den forskningsansvarlige at behandlingen vil skje i samsvar med direktiv 95/46/EF
- Det er gitt samtykke til dette fra den opplysningene gjelder.

- Den registrerte ikke har reservert seg og det har blitt gitt informasjon om at opplysningene vil bli overført til et land utenfor EØS.

Helseopplysninger som er avidentifiserte eller pseudonyme kan overføres til land utenfor EØS dersom kopling til personidentifikasjoner ikke kan skje så lenge opplysningene befinner seg i vedkommende land.

Vilkår vedrørende informasjonssikkerhet:
Komiteen forutsetter at data lagres på et nettverk som er godkjent for dette og under kontroll av prosjektets forskningsansvarlige institusjon. Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren», http://www.norsk-helsenett.no/informasjonssikkerhet/bransjenormen/Personvern%20og%20informasjonssikkerhet%20i%20forskningsprosjekter%20v1.pdf

Tillatelsen gjelder til 31.12.2017. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 31.12.2022. Opplysningene skal lagres avidentifisert, dvs. adskilt i en nøkkel- og en opplysningsfil. Opplysningene skal deretter anonymiseres eller slettes.

Prosjektet skal sende sluttmelding til REK Sør-Øst D senest 31.06.2018.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. forvaltningsloven 28 flg. En eventuell klage sendes til REK Sør-Øst D. Klagefristen er tre uker fra mottak av dette brevet.

Med vennlig hilsen

Stein Evensen(sign.)
professor dr. med.
leder

Ingrid Middelthon(sign.)
seniorrådgiver

Kopi:
Akershus universitetssykehus