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Associations between intake of dairy products and colorectal lesions in the Norwegian CRCbiome study: a cross-sectional study

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Abstract

Background: Intake of dairy is associated with lower risk of CRC. It is, however, unclear whether this risk reduction applies to all types of dairy products and whether it also applies to precancerous lesions.

Aim/objective: To examine the association between intake of dairy products and CRC screening findings (non-advanced lesions and advanced colorectal lesions (ACN)) in participants with a positive fecal immunochemical test (FIT). Further, to investigate the association between types of dairy products and screening findings. Lastly, to investigate the association between total dairy intake and alpha diversity in the gut microbiome.

Methods: Data from the ongoing prospective cohort study CRCbiome were utilized for this master's thesis. The thesis includes baseline data of 1,659 CRC screening participants with a positive FIT and is of cross-sectional design. Information on dietary intake was collected using a food frequency questionnaire and a lifestyle and demographic questionnaire. Screening findings were assessed through colonoscopy. Alpha diversity in the gut microbiome was analyzed by metagenome sequencing of fecal samples. Multinomial logistic regression and ANOVA were used to analyze the associations.

Results: The master's thesis included 1,466 participants eligible for the aim regarding CRC screening findings while 933 participants were eligible for the aim regarding alpha diversity in the gut microbiome. Each increment of daily servings of total dairy products was associated with 7% lower odds for ACN. Each increment of daily servings of fermented dairy products was associated with 27% lower odds of ACN. No associations were shown for low-fat dairy, high-fat dairy, or cheese, and CRC screening findings. Furthermore, no association was observed between intake of dairy products and alpha diversity in the gut microbiome.

Conclusion: Dairy intake was associated with the risk of ACN detected in CRC screening participants with a positive FIT. The results indicated that a higher intake of total dairy and fermented dairy is associated with lower odds of ACN.

Sammendrag

Bakgrunn: Inntak av meieriprodukter er assosiert med lavere risiko for tarmkreft. Det er imidlertid uklart om denne assosiasjonen også gjelder forstadier til tarmkreft, og om den varierer mellom ulike typer meieriprodukter.

Hensikt: Undersøke sammenhengen mellom inntak av meieriprodukter og funn i tarmkreftscreening (ikke-avanserte lesjoner og avansert kolorektal neoplasi (ACN)) hos deltakere med positiv screeningprøve (FIT). Videre var hensikten å undersøke om inntak av ulike typer meieriprodukter er assosiert med funn i tarmkreftscreening og om inntak av meieriprodukter er assosiert med alfadiversiteten i tarmens mikrobiom.

Metode: Data i denne masteroppgaven er hentet fra den pågående prospektive kohortstudien CRCbiome. Masteroppgaven inkluderer baselinedata fra 1,659 screeningdeltakere med positiv FIT, og har tverrsnittdesign. Kostholdsdata ble samlet inn med et matfrekvensskjema og et livsstils- og demografisspørreskjema. Funn i tarmscreening ble gjort via koloskopi. Alfadiversitet i tarmens mikrobiom ble analysert ved metagenomsekvensering av avføringsprøver. Multinomial logistisk regresjon og ANOVA ble brukt for å analysere disse assosiasjonene.

Resultat: Det ble inkludert 1,466 deltakere i analysene om inntak av meieriprodukter og funn i tarmscreening og 933 deltakere i analysene om alfadiversitet i tarmens mikrobiom. En daglig porsjons økning av meieriprodukter samlet var assosiert med 7% lavere odds for å ha ACN, og en daglig porsjons økning av fermenterte meieriprodukter var assosiert med 27% lavere odds for å ha ACN. Det ble ikke funnet noen signifikante assosiasjoner mellom magre meieriprodukter, fete meieriprodukter eller ost og funn i tarmscreening. Det ble heller ikke funnet noen assosiasjon mellom inntak av meieriprodukter og alfadiversitet i tarmens mikrobiom.

Konklusjon: Våre funn indikerte en sammenheng mellom totalt meieriinntak og ACN hos deltakere i tarmscreening med positiv FIT. Resultatene viste at høyere inntak av meieriprodukter samlet og fermenterte meieriprodukter er assosiert med lavere odds for ACN.

Abbreviations

ACN	Advanced colorectal neoplasia
APC	Adenomatous polyposis coli
BCSN	Bowel cancer screening in Norway
BMI	Body mass index
CI	Confidence interval
CIN	Chromosome instability
CRC	Colorectal cancer
DCA	Deoxycholic acid
FAO	Food and Agriculture Organization
FAP	Familial adenomatous polyposis
FFQ	Food frequency questionnaire
FIT	Fecal immunochemical test
HDI	Human development index
HP	Hyperplastic polyp
IBD	Irritable bowel syndrome
KBS	Kostberegningssystem (Dietary calculation system)
LAB	Lactic acid bacteria
LDQ	Lifestyle and demographics questionnaire
MSI	Microsatellite instability
MSS	Microsatellite stable
OR	Odds ratio
RCT	Randomized controlled trial
SCFA	Short-chained fatty acid

SSL	Sessile serrated lesion
TSA	Traditional serrated adenoma
TSD	Tjenester for sensitive data (services for sensitive data)
UiO	University of Oslo
WCRF	World Cancer Research Fund
WHO	World Health Organization

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1 Background

In 2020, about 1,9 million people worldwide got the diagnosis of colorectal cancer (CRC) (1). This accosts for around 10 percent of all new cancer cases and is the third most common type of cancer globally. The incidence rate is higher among men than women. This applies to all countries around the world (2). Globally, Norway has the third highest incidence rate, with women having the highest, while men are not among the top ten countries (3).

The number of risk factors for CRC is associated with the human development index (HDI), affecting both incidence and mortality. Countries with a high or very high HDI have a four times higher CRC incidence rate than countries with low HDI (1). The CRC mortality rate is highest in highly developed countries, and according to World Cancer Research Fund (WCRF), CRC causes 9% of all cancer deaths worldwide. Late-stage diagnosis of CRC is associated with a lower survival rate (2). Moreover, about 40% of individuals diagnosed with CRC have a comorbid disease, which may affect the treatment and survival of CRC (4). Despite the potential harmful effects of high HDI, late-stage diagnosis and comorbid diseases on CRC incidence and mortality, there are several factors that are associated with decreased risk of CRC, including intake of dairy products.

In 2012, WCRF estimated that there will be a 60% increase in CRC incidence and mortality over the next 15 years (2). We have already seen a global increase in incidence by approximately 34% between 2012 to 2020, from 1,4 to 1,9 million new cases per year. Simultaneously, the mortality rate has also increased by 32% from 694,000 to 916,000 CRC deaths (1, 2). However, Norway has the past five years had a decreasing trend of CRC, as well as an increased survival rate for both males and females (5).

1.1 Colorectal cancer

CRC is cancer in any part of the colon or rectum (**Figure 1**) (2). Approximately 95% of CRCs are adenocarcinomas. These are malignant lesions characterized as cancer in glandular epithelial cells of the bowel mucosa (2, 6). The location of the tumor in the colorectum shows different molecular and histological features. Right-sided (proximal) tumors tend to have lower overall survival compared to left-sided (distal) tumors (7, 8). In average, it takes 10-15 years for colorectal lesions to progress into cancer, this through different neoplastic pathways. The different pathways are the adenoma-carcinoma pathway and the serrated neoplasia pathway, each of which represents 60-90% and 10-30% of CRC cases, respectively (8, 9). Both the adenoma-carcinoma pathway and the serrated neoplasia pathway can develop precursor lesions for adenocarcinomas (6, 10). A small disruption in any part of the signaling pathways can affect the transcription of genes to promote tumorigenesis (11).

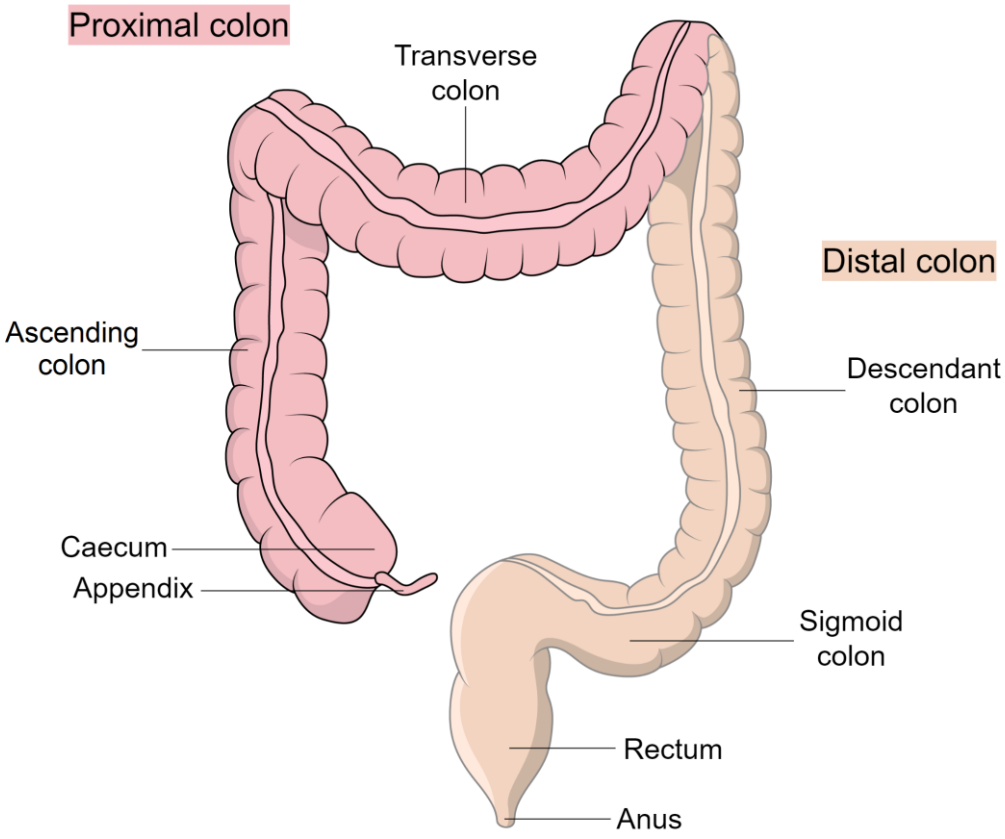

Figure 1 *- Anatomy of the colon and rectum.*

This figure is created by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under Creative Commons Attribution 3.0. Unported License (https://creativecommons.org/licenses/by/3.0/) (12).

Approximately one-third of all CRC is related to genetic factors, with recognized hereditary syndromes representing 5-10% (2, 8, 13). The two major conditions of hereditary colorectal conditions are familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (also referred to as Lynch syndrome) (2, 13). Both FAP and Lynch syndrome leads to mutations in genes involved in cancer development and people with these dispositions have a substantially increased risk of developing CRC (2). Features of FAP are hundreds to thousands of adenomatous lesions in the colorectal tract and are easy to detect during colonoscopy (9, 11). If FAP is left untreated, the majority will develop CRC before the age of 40 (2). Identification of Lynch syndrome is largely dependent on family history and represents approximately 3% of all CRC cases (9).

1.1.1 Colorectal lesions

Most CRCs start with a crypt in the epithelium of the colorectum, which evolves into a lesion of either an adenomatous polyp (referred to as adenomas) or a serrated lesion. These are the major types of precursor lesions for adenocarcinoma and further, CRC (8-11). Adenomas are characterized by an elevation of the epithelium with a stalk or pedicle (9), and depending on their level of dysplasia and histology, they are categorized as tubular, villous, or both (6). If the adenoma grows to ≥10 mm or has villous histology it is considered a high-risk, or advanced, lesion. Further, tubular adenomas sized <10 mm are considered low-risk, or non-advanced, lesions (14). Adenomas occur through the adenoma-carcinoma pathway due to cell proliferation and altered mechanisms of DNA repair, like inactivation of the tumor suppressor gene adenomatous polyposis coli (APC) and activation of the KRAS gene (8, 9, 11). When differentiation and apoptosis of cells are disrupted, the adenoma grows and can over time develop into a dysplastic lesion. This development can take over 10 years. Mutation of APC is also a causative gene mutation for FAP (11).

The World Health Organization (WHO) classifies the group of serrated lesions into hyperplastic polyp (HP), sessile serrated lesion (SSL), SSL with dysplasia, and traditional serrated adenoma (TSA) (15). Serrated lesions share many overlapping characteristics, with slight variations in appearance. However, they are all believed to develop more rapidly than adenomas. HPs are the most frequently occurring serrated lesion, representing over two-thirds of the cases. These tend to be small (<5 mm), pale, and sessile and are most commonly found

in the distal colon along with TSAs. TSAs are protuberant lesions with a pine-cone appearance and villous pattern (16, 17). They tend to be large, with an average size of 15 mm, and account for a smaller portion of serrated lesions (17) SSLs account for approximately one-third of serrated lesions (11). These lesions tend to occur in the proximal colon and are featured by a flat or sessile structure, with prominent folds, indistinct borders, and a mucus cap (16). These features make them easier to miss during endoscopy compared to adenomas (9). What sets them apart from HPs is the presence of a distorted crypt, which is considered a diagnostic criterion for SSL (17). SSLs without dysplasia sized <10 mm are considered non-advanced, while SSLs with dysplasia or ≥10 mm are considered advanced, which is considered predictive for CRC (14). Identifying and removal of precancerous lesions is essential for a reduction in CRC incidence and mortality (9).

The molecular features of colorectal lesions (**Figure 2**) are also key events in carcinogenesis. Chromosome instability (CIN) is present in up to 70% of sporadic CRC cases which can cause mutation in APC. CIN tumors have abnormal karyotypes with a lack of base-pair mutation in the coding sequence and do not have microsatellite instability. Microsatellite instability (MSI), however, is observed in approximately 15% of sporadic CRC cases and is characterized by frequent DNA base-pair mutations, which can result in dysfunctional proteins and initiate tumorigenesis. While CIN tumors can develop over 10 years or more, MSI tumors can occur in a few years (11). MSI is observed in all tumors that develop within Lynch syndrome and the majority of SSLs with dysplasia. Dysplasia in SSL usually initiates by BRAF gene mutation, which leads to inactivation tumor suppressor genes through a cascade of events (17). This is what separates SSL from SSL with dysplasia. Microscopic analyzing is necessary to confirm malignancy in these lesions. HPs, which are normally considered benign, have potential to progress to SSLs by BRAF gene mutation, which can result in inactivation of tumor suppressor genes and development to CRC (16). TSAs, however, have less clear molecular distinctions. They include mutations of either BRAF (usually associated with MSI) or KRAS (usually associated with CIN) genes and are microsatellite stable (MSS). MSS tumors with BRAF mutation are associated with higher disease-specific mortality (9, 11).

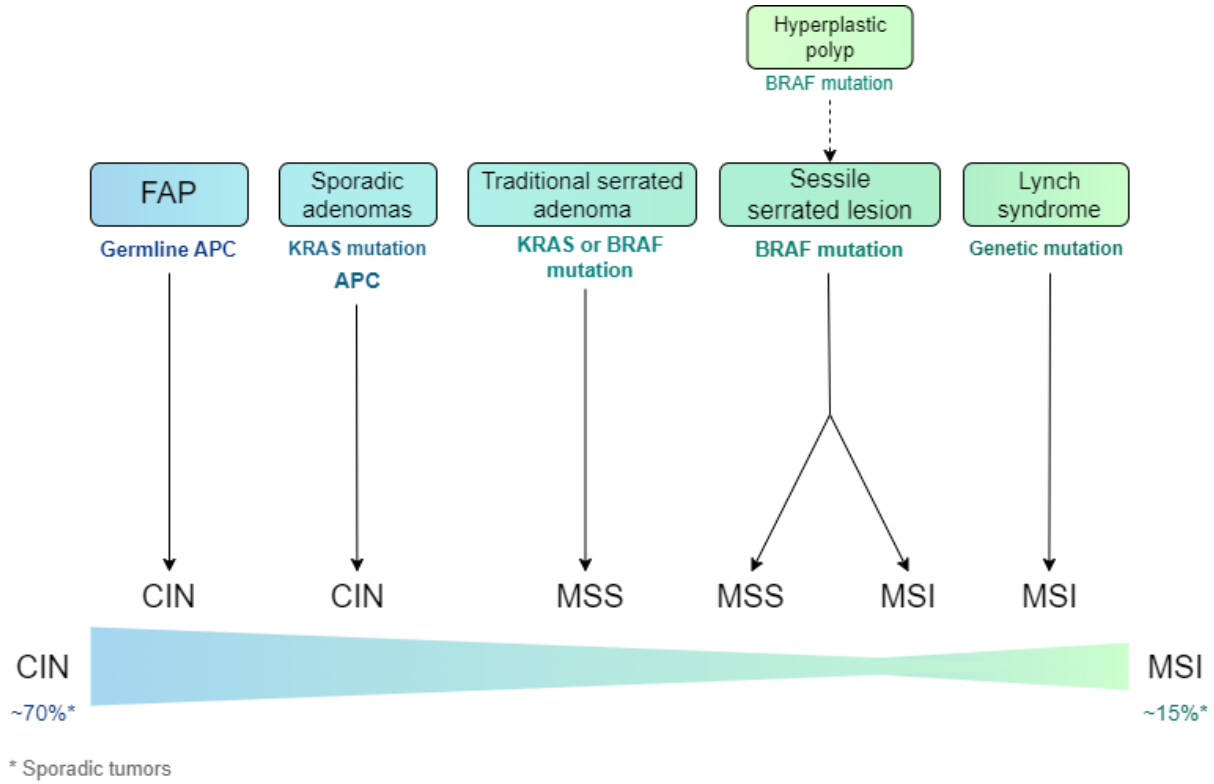

Figure 2 *– Simplified overview of molecular pathways for colorectal cancer development.*

The development of colorectal cancer is complex and involves various molecular changes. The chromosome instability pathway is present in approximately 70% of all sporadic tumors. Most conventional adenomas follow this pathway. Approximately 15% of all sporadic tumors exhibit microsatellite instability, which is strongly associated with Lynch syndrome and is also present in most sessile serrated lesions. It is worth noting that these percentages do not include hereditary syndromes. Hyperplastic polyps are initially benign, but they can, in some cases, progress to sessile serrated lesions due to mutations in the BRAF gene. This gene is also linked to sessile serrated lesions and some traditional serrated adenomas, which also are associated with mutations in the KRAS gene. KRAS mutation is also associated with the development of conventional adenomas. It is important to note that these mechanisms have a gradual transition, making colorectal cancer development a complex and multifaceted process.
Abbreviations: FAP: Familial Adenomatous Polyposis, APC: Adenomatous Polyposis Coli, CIN: Chromosomal Instability, MSS: Microsatellite Stable, MSI: Microsatellite Instability.

1.1.1.1 Screening for colorectal lesions

International guidelines recommend screening for CRC (18). According to a meta-analysis from 2016 based on observational studies, screening for colorectal lesions reduces both the incidence and mortality of CRC, even though extent of reduction differ between screening methods (19). However, a Randomized Controlled Trial (RCT) from 2022 only found a reduction in CRC incidence, but not CRC mortality (20). The most common CRC screening tools are home-based stool tests and hospital-based endoscopy (sigmoidoscopy and colonoscopy), while other tests are being developed (9). In countries where CRC screening is established, it is most common to recommend screening from age 50 (18). Individuals with first-degree relatives with CRC are at increased risk of CRC and are recommended to start

screening 10 years earlier (9). Norway is currently implementing a national CRC screening program that uses stool-based testing with a fecal immunochemical test (FIT) (21). While there is ongoing debate about the best CRC screening method, population-based programs often prefer FIT (18).

1.2 Role of lifestyle and diet in CRC

Family history is estimated to play a role in 10-20% of CRC cases (8). CRC is a multifactorial disease and several of the known risk factors are modifiable lifestyle factors (**Figure 3**). This makes lifestyle a key factor for preventing CRC, as this may be targeted (2). An optimal reduction of the CRC burden includes targeting lifestyle, dietary risk factors for CRC, and CRC screening (2, 9). A major modifiable risk factor for CRC is a western lifestyle, which represents the lifestyle of countries with a high HDI (9, 22).

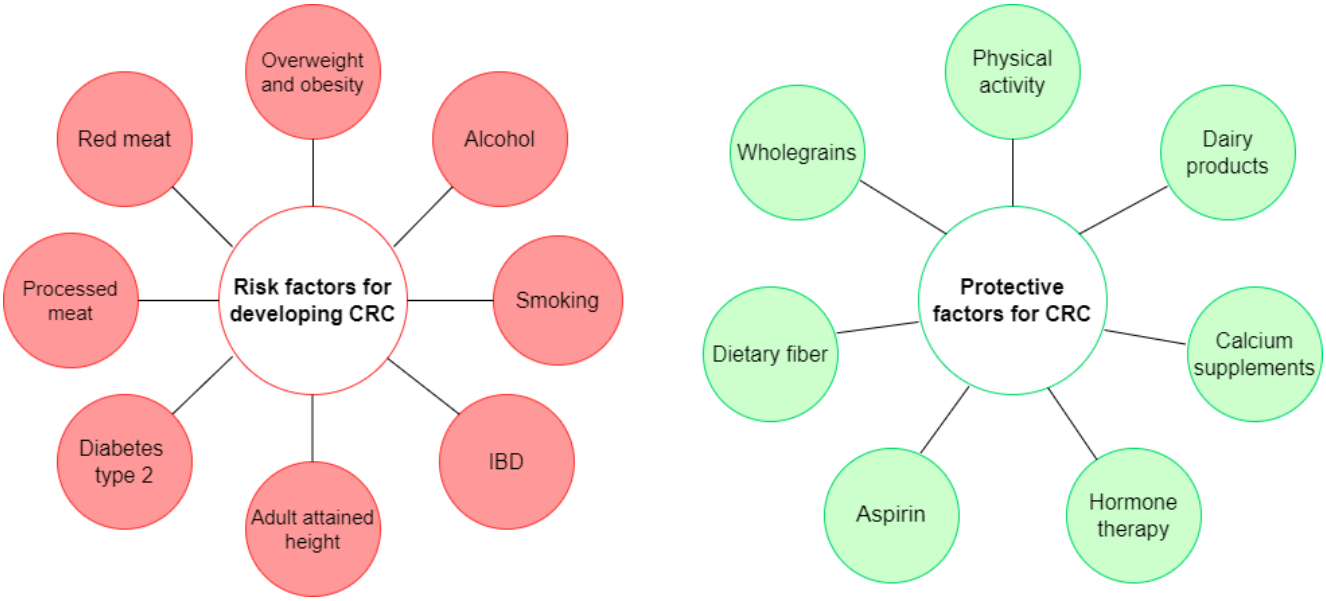

Figure 3 *- Risk factors and protective factors for colorectal cancer.*

Aspirin is protective in case of long-term use in amounts of ≥75 mg per day. Hormone therapy is protective in postmenopausal women. Abbreviations: CRC: colorectal cancer, IBD: inflammatory bowel disease.

1.2.1 Risk factors for CRC

Risk factors for CRC include environmental, hereditary, and lifestyle-related factors, as well as increasing age, male sex, and height (2, 8). Established lifestyle risk factors are overweight and obesity, physical inactivity, and smoking (2). Duration of smoking and number of cigarettes are of importance for the increased risk of CRC (23). In addition, some diseases

predispose to develop CRC, like IBD and type 2 diabetes, as well as a family history of CRC and hereditary CRC syndromes (8). As for medication, both hormone therapy in postmenopausal women and long-term (≥5 years) daily use of the NSAID aspirin in amounts of ≥75 mg per day decreases the risk of CRC (2). Additionally, some evidence suggests that specific bacterial infections in the intestine can affect the risk of CRC (8).

Colorectal lesions are also considered risk factors for CRC. Some report an equal risk of CRC in patients with serrated lesions or adenomas, while others report a higher risk of SSLs and TSAs compared to adenomas (16). Whether all risk factors for CRC also apply to colorectal lesions is uncertain. However, some evidence reports a protective effect of non-steroidal anti-inflammatory drugs (NSAIDs) on adenomas (11) and an increased risk by smoking, high BMI, and intake of alcohol on SSLs (9, 17). Additionally, increasing age and male sex seems not to be equally important risk factors for SSLs and adenomas (17).

Dietary risk factors for CRC are high intake of processed meat, red meat, and alcohol, as well as a low intake of whole grains, dietary fiber, dairy products, and calcium supplements (2). Additionally, dietary calcium has in one meta-analysis been inversely associated with colorectal adenomas (24), but other findings in dietary risk factors for colorectal lesions are inconclusive (17).

1.3 Dairy

Dairy products are one of several protective dietary factors against CRC. WCRF strongly concluded with a probable protective effect of dairy consumption on reduced risk of CRC (2). The main known mechanism of dairy for protecting against CRC is the content of calcium. The 2018 WCRF report and multiple meta-analyses also show decreased risk of CRC with intake of dietary calcium and calcium supplements (2, 25-28). A recent meta-analysis from 2022 also showed an inverse association between both dietary and dairy calcium, and incidence of colorectal adenomas (24). Yet, dairy products contain several other bioactive compounds which also can contribute to the protection against CRC, such as lactic acid-producing bacteria, lactose, casein, lactoferrin, butyrate, linoleic acid, and vitamin D in fortified products (2, 25, 26).

The main source of calcium in Europe and North America is dairy products (25, 29). Most dietary guidelines in countries worldwide, including Norway, recommends having dairy products daily to reach the recommended daily intake of calcium (30, 31). Other dietary sources of calcium are dark green vegetables, some nuts and seeds, canned fish with bones, and tofu (29). Dairy products have a higher calcium content than other sources of calcium, which affects the observed protective effect of calcium in different continents (25). Calcium can bind bile acids and free fatty acids (32, 33). Secondary bile acids promotes carcinogenic factors in both laboratory and animal studies and a higher presence of calcium in the intestinal lumen reduces the exposure of these carcinogens in the colon mucosa (32, 34). The promotion of colorectal carcinogenesis from bile acids is associated with dietary factors, as they play a significant role in fat metabolism and promote the absorption of fat in the small intestine. A diet high in fat leads to more excretion of fat and bile acids through the feces compared to a diet low in fat, and research shows a higher CRC incidence in patients with a higher concentration of bile acids in the feces. There are several types of bile acids, but the most carcinogenic one is deoxycholic acid (DCA). A high-fat diet is known to increase levels of DCA, which can induce genomic instability over long-term exposure by damaging DNA and cell organelles. The damage of cell organelles produces an excessive amount of reactive oxygen species, which promotes a cascade of events that results in the destruction of epithelial cells in the colon. DCA also alters genetic stability of the colon cells by affecting the numbers of chromosomes, gene mutations, and cell proliferation (34).

Another antitumor mechanism is that calcium can inhibit cell proliferation and promote cell differentiation in the colon cells. By binding to calcium-sensing receptors in the colonic epithelium, a cascade of intracellular events activates protein kinase C and releases intracellular calcium. This is believed to induce cell differentiation and apoptosis to prevent precancerous cells from further development (33).

Several meta-analyses and reviews support an inverse association between the intake of dairy products and the risk of CRC (26, 35-39). The association mainly applies to total dairy, with no distinction between different subgroups of dairy products, like low-fat dairy, high-fat dairy, fermented dairy, or cheese (2). Research investigating the association between subgroups of dairy products and CRC is limited, and most studies did not find any association (35, 36, 39) with some exceptions that are further explained in the following chapters (26, 37). The same holds for studies on the association between dairy products and colorectal lesions.

1.3.1 Low-fat dairy

Limited studies have investigated the separate associations between low-fat and high-fat dairy intake and the risk of CRC. However, it is desirable to understand if there are any differences in the risk of CRC between low-fat and high-fat dairy since the majority of dietary recommendations in the world encourage intake of low-fat and fat-free dairy products over high-fat dairy products (37). Theoretically, low-fat dairy should for the risk of CRC be preferred to high-fat dairy, as high-fat dairy has a high level of saturated fatty acids, which increases the level of secondary bile acids (30).

Even though the research on CRC is limited for low-fat dairy intake, there might be a trend toward an association between intake of low-fat dairy and reduced CRC risk. A meta-analysis from 2019 investigated the association between intake of low-fat dairy products and CRC risk but found no significant association (37). However, a systematic review from 2020 found suggestive evidence supporting an inverse association between a diet high in low-fat milk and CRC incidence. They also investigated intake of high-fat milk, but the results were nonsignificant (35). A case-control study from 2021 found an inverse association between intake of low-fat dairy and overall mortality, as well as association between high intake of high-fat dairy and increased overall mortality, but no significantly associations for CRC mortality in particular (40). This provides a hypothesis for an association between dairy sorted by fat content and colorectal lesions, due to few studies on CRC and none on colorectal lesions, as well as varying results in the existing studies.

1.3.2 Fermented dairy

Fermented foods are defined by the International Scientific Association for Probiotics and Prebiotics as “foods made through desired microbial growth and enzymatic conversions of food components” (41). Fermented foods have historically been used to improve the quality and taste of raw foods with preservation, production of antimicrobial products, and for nutritional properties, like enrichment or removal of components that affect the nutritional composition of the product (41). Fermentation generally increases the bioavailability of nutrients in foods (42). It is still used globally for extending shelf life and removal of harmful compounds and is particularly important for public health in countries with low food security (41).

Fermented dairy, like non-fermented dairy, is a good source of protein and calcium (39). Dairy products produced by fermentation are yogurt, kefir, sour cream, and most cheeses. In the fermentation of dairy, microorganisms reduce the concentrations of monosaccharides and disaccharides by hydrolysis during the fermentation process (41). The microorganisms will continue hydrolyzation during digestion, which contributes to reducing the content of lactose (39). This makes fermented dairy more favorable to people with lactose malabsorption (39, 41).

One of the most common and widely used microorganisms in fermented dairy is lactic acid bacteria (LAB). Multiple studies in humans have shown that intake of LAB in food can survive the gastric transit until the colon. When it reaches the colon, it has the potential to affect the gut microbiome, depending on the physiology and dietary habits of the host (41). A small RCT from 2021 showed an increased gut microbiome diversity when having a diet high in fermented foods (43). However, it is uncertain whether this effect is long- or short-term, as well as if it is proportional to the amount of intake. The evidence suggests that even an increased intake for a limited period is sufficient to affect the gut microbiome by producing favorable bioactive metabolites which further can contribute to the immune system and inhibit pathogens. This effect is related to all fermented foods, and not only fermented dairy products, which argues that more studies are necessary to both investigate fermented dairy more specifically, and whether this modulation of the gut microbiome is permanent (41, 43). Despite these uncertainties, the physiological differences in digestion between fermented and non-fermented dairy suggest different protective effects against CRC (39).

There is still limited evidence in humans for whether there is an association between intake of fermented dairy and colorectal lesions. However, Kim et al (2022) reported an inverse association between intake of yogurt and lower incidence of colorectal neoplasia (44), and two meta-analyses from 2021 and 2022 found evidence suggesting an inverse association between yogurt and cheese consumption and the risk of CRC (26, 45). A possible mechanism for the protective effect of yogurt is the effect of probiotic bacteria, *Lactobacillus bulgaricus* and *Streptococcus thermophilus*, present in most yogurts (41, 46). Probiotics are defined by WHO and the Food and Agriculture Organization (FAO) as “live microorganisms that which when administered in adequate amounts confer a health benefit on the host” (47). These may lower levels of carcinogens in the colorectal tract, such as fecal bile acids (26, 46).

A recent cohort study investigated the association between intake of dairy products during adolescence and the incidence of colorectal adenomas and found an inverse association between dairy and risk of advanced adenomas (48). In a 2014 meta-analysis, dairy intake was divided into three categories: non-fermented milk, fermented milk, and cheese. The results showed an inverse association between intake of non-fermented milk and CRC, but this was not observed for either fermented milk or cheese. One possible explanation is that the three dairy categories led to differences in mean calcium intake, with non-fermented milk providing a greater calcium source than fermented milk and cheese (39). As dietary calcium is associated with reduction in CRC risk, this could make a difference in the protective effect of dairy products (2). Another possible explanation is that non-fermented milk contains more lactose. Considering that about 75% of the world population has trouble digesting lactose, many people will experience that the lactose goes undigested to the colon, which makes the lactose function as a prebiotic (39). Prebiotics are non-digestible dietary fibers that are transported undigested to the colon and used to feed the gut bacteria. These fibers have in multiple cases shown to have bioactive effects considered anti-carcinogenic (6, 39). Short-chained fatty acids (SCFA) are the end product of prebiotics in the colon. These have several physiological functions and affect the gut barrier, as well as metabolic and immunological functions (30).

One of the SCFAs that are produced by the prebiotic is butyrate, which also is a bioactive component in dairy products (26, 30). Butyrate has been shown to have a variety of beneficial health effects in humans, such as maintaining gastrointestinal function, reducing intestinal inflammation improving insulin sensitivity, as well as inducing cell apoptosis and differentiation in tumor cells (33, 49, 50). In vitro, studies also show prevented adherence of pathogenic bacteria (49). However, the evidence in humans is mixed and the amount reaching the colon when administered orally is limited, which makes it questionable if butyrate from dairy products is involved in carcinogenesis (33, 49, 51).

1.3.2.1 Cheese

Solid cheese is produced when the milk protein casein is coagulated, and the whey protein is removed. Whey protein has a high content of amino acids with sulfur, which can produce precursors to a cellular antioxidant called “glutathione”. This antioxidant can be beneficial in cancer prevention, which gives cheese the absence of a potential cancer-preventative effect

(39). Furthermore, cheese is a fermented dairy product with a lower lactose content compared to non-fermented dairy, which may reduce the bioavailability of calcium (33). While casein and lactose are thought to increase the bioavailability of calcium (52), the intestinal absorption of calcium from solid cheese has been found to be adequate, despite its low lactose content (53). However, due to the high content of fat in cheese, bile acids in the colonic lumen may increase, which could limit the potential benefits (26). Despite this, there is limited research investigating the association between intake of cheese and CRC, and the existing studies show conflicting associations (2, 37, 39).

1.4 Gut microbiome and alpha diversity

All humans have a normal flora consisting of microbes living in the body. The microbes form an ecosystem in symbiosis with the host, which is favorable for both parties. The composition and abundance of microbes differ in each part of the body and between each individual, even though the metabolic function of the microbes and the stability of the composition are similar. The normal flora of the colon consists of over a thousand different bacteria species, as well as several other microbes like viruses, fungi, and non-pathogen parasites (54).

The gut microbiome includes both the composition of the microbes and the belonging genetic material (54). The composition of these microbes is influenced by the characteristics of the host, environmental factors, and the diet (6). Quality of the diet can affect the gastrointestinal function and microbial community of the gut (6, 50, 54), which again is of importance to the immune system and cell proliferation (50). Dysbiosis of the normal flora and abundance of certain bacteria can affect the development and progress of diseases, like IBD and type 2 diabetes, which both increase the risk of CRC (6, 8, 54).

To investigate microbial flora, diversity is measured. This is divided into two measures: alpha and beta diversity. The alpha diversity determines the richness, evenness, or both within a sample (55, 56). The richness measures the number of different species present in the sample, while the evenness expresses the relative abundance of the present species (55, 57). Beta diversity measures the diversity between samples based on the abundance of the species in each sample (56).

Evidence supports the theory of an association between the gut microbiome and CRC. Some studies have shown differences in microbial community between healthy parts of the colon compared to areas with precancerous polyps (58-60), as well as the different abundance of certain bacteria strains in the colon of patients with colon cancer compared to healthy individuals (61). A case-control study from 2013 comparing feces from CRC patients and non-cancer subjects found that subjects with CRC had an overall decreased richness in the gut microbiome. Because of the potential to enhance the beneficial impact and minimize adverse effects of the gut microbiome by diet, these type of findings indicate a possibility to impact CRC risk and prevention (60).

1.4.1 Alpha diversity and dairy products

There are theories proposing a link between dairy intake, gut microbiome composition, and colorectal adenomas (6). A recent cross-over study conducted on middle-aged overweight individuals found significant changes in the gut microbiome within those who had a high intake of dairy products, although no significant changes in total diversity were observed. The dairy products consumed consisted of a combination of fermented and non-fermented dairy. Furthermore, fermented dairy appears to be more effective than non-fermented dairy in modifying the gut microbiome by altering evenness in diversity (62). Another study suggests that fermented foods may increase the alpha diversity of the gut microbiome (43).

In mice, there is observed an association between fatty acids from milk and the growth of microbes which promotes colitis, gut barrier dysfunction, and metabolic syndrome. These findings suggest that high-fat dairy may have potentially harmful effects in gut microbiome, although research on the impact of high-fat dairy on the microbiome is currently limited in humans (30). Both animal and human studies have demonstrated the potential association between dairy products and the gut microbiome, which points out the relevance of more research, given the limited existing evidence.

2 Aims of the thesis

This study is conducted by data analysis from the sub-study CRCbiome in the CRC screening pilot trial. The main aim of this master's thesis is to examine the association between the intake of dairy products and colorectal lesions in a selection of CRC screening participants with a positive FIT.

The specific aims are:

- Is intake of total dairy products associated with colorectal lesions?
- Is there a different association between intake of low-fat and high-fat dairy products and colorectal lesions?
- Is intake of fermented dairy products associated with colorectal lesions?
- Does the alpha diversity in the gut microbiome differ between persons who have a high and a low intake of total dairy products?

3 Materials and methods

3.1 The Bowel Cancer Screening in Norway

The Bowel Cancer Screening in Norway (BCSN) study is a randomized pilot trial for a national CRC screening program, coordinated by the Cancer Registry of Norway and initiated in 2012. The trial compares two screening methods: once only sigmoidoscopy and four repeated FIT rounds. All men and women aged 50-74 years old in the two geographical areas in the southeast of Norway, earlier Østfold county and selected municipalities in Vestre Viken Hospital Trust, were invited to the BCSN pilot trial. These were randomly assigned to sigmoidoscopy or FIT with a computer-based algorithm adjusted for age, sex, and localization. A total of 70,096 were assigned to the FIT screening and 47,532 (68%) chose to participate in at least one of the four rounds of testing (63).

FIT-based CRC screening is a home-based method, where the participant collects a stool sample in a pre-sent collection tube with 2 ml buffer. The tube is mailed to the laboratory at Oslo University Hospital (OUS) for analysis of occult blood by immunochemical testing. The analysis is performed by using OC-sensor Diana (Eiken Chemical) mainly on the same day as the sample is received. If not analyzed the same day, the sample is stored at 4°C until analyzed. The FIT is considered positive at a threshold of 15 µg hemoglobin per g of feces. Participants with a positive FIT are scheduled for a follow-up colonoscopy in one of the screening centers. Participants with negative FIT/non-attenders get continuous invitations every second year until a maximum of four rounds of testing/invitations or upper age limit of 76 years is reached (63, 64). The last round for FIT will be completed by the end of 2023.

Before the follow-up colonoscopy, the participants are interviewed by phone to assess their medical history. Bowel cleansing prior to the colonoscopy is conducted at home using PicoPrep (Ferring Pharmaceuticals), provided free of charge for the participants. During the examination, sedation or analgesia is given on demand. Information about the lesion’s size, localization, appearance, technique of removal, and completeness of removal is registered during the colonoscopy. All precancerous lesions detected are removed and the histopathological subtype of each lesion is established. Ten years after the screening, a long-term follow-up will obtain data about CRC mortality and incidence (63).

3.2 The CRCbiome study

The CRCbiome study is a prospective cohort derived from the BCSN on participants who tested positive in the second, third, or fourth round of FIT screening (**Figure 4**). Recruitment for the CRCbiome study went on continuously until 2,700 were invited. Of those, 1,659 participants agreed to participate. The invitation (**Appendix 1**) was sent out between the date of positive FIT registration and the date of the follow-up colonoscopy. The invitation included an information letter about CRCbiome and two questionnaires about diet and lifestyle. Information about diet and lifestyle was collected one time only. Returning one or both questionnaires was considered consent for participating in the CRCbiome study. Consent for participation covered allowance for the use of the fecal sample in metagenome sequencing analysis and the data from the questionnaires, as well as linkage to the Norwegian Prescription Database and the Cancer Registry of Norway. The pathological findings in the colonoscopy were separated into four main groups: no confirmed neoplastic findings, non-advanced lesions, advanced lesions, and CRC. After the follow-up colonoscopy, a FIT sample kit was sent to the participants twice more for collecting fecal samples 2 and 12 months after the colonoscopy (64).

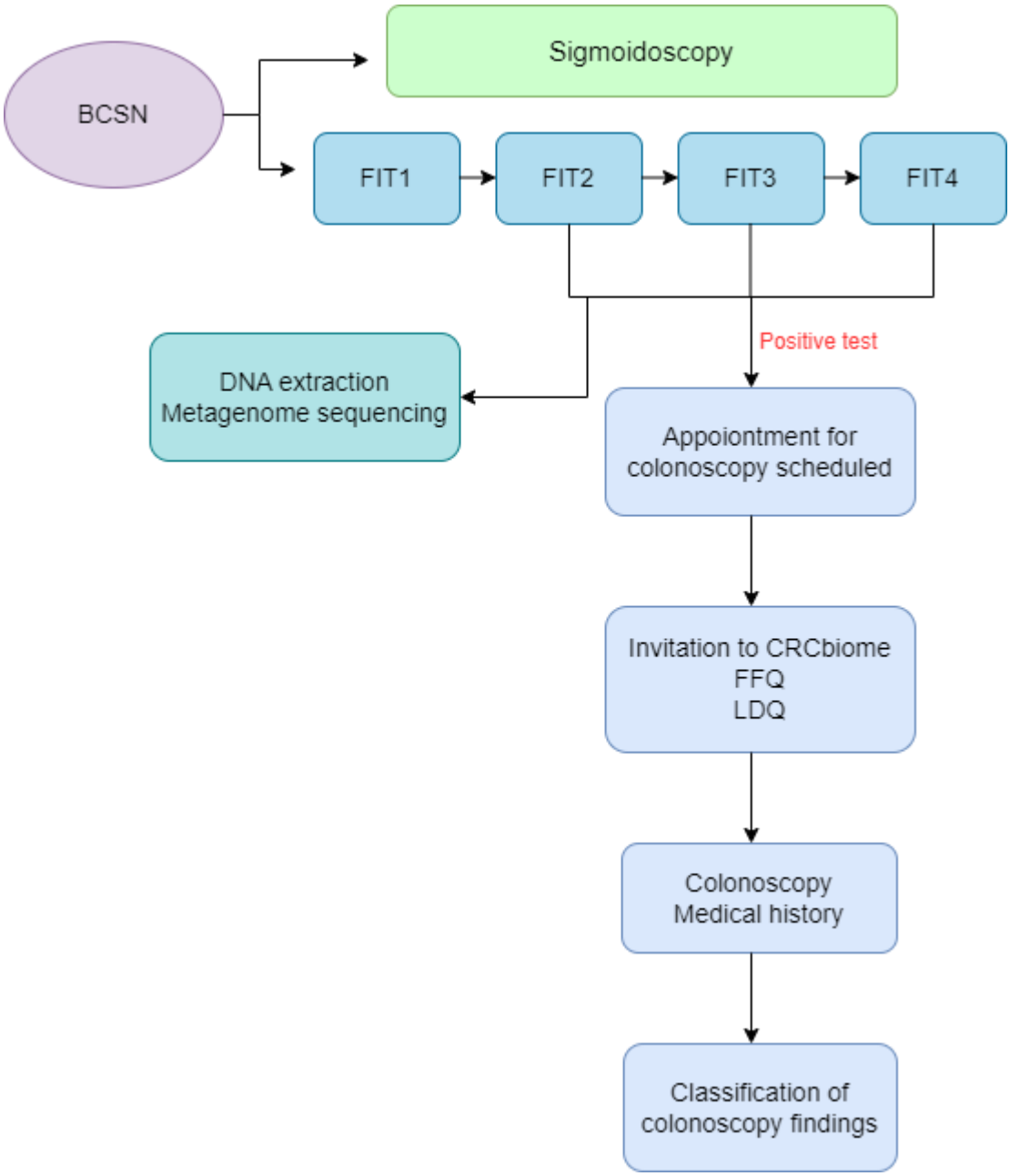

Figure 4 - *Timeline of the CRCbiome study*

Samples from three of the last FIT screenings from the BCSN were used as baseline samples for the CRCbiome. Positive test was counted as 15 µg hemoglobin per gram feces. Abbreviations: BCSN; Bowel Cancer Screening in Norway, FIT; Fecal Immunochemical Test, FFQ; Food Frequency Questionnaire, LDQ; Lifestyle and Demographics Questionnaire.

3.2.1 DNA extraction

All fecal samples were stored at -80°C and thawed before analysis. DNA was extracted from an aliquot of each sample using QIAsymphony automated extraction system with the belonging QIAsymphony DSP Virus/Pathogen Midikit. DNA purity and concentration were assessed using Nandrop2000 and Qubit (Thermo Fisher Scientific, USA), respectively (64).

3.2.2 Metagenome sequencing and sampling

The DNA extract was sent to the sequencing laboratory of the Institute for Molecular Medicine Finland FIMM Technology Centre, University of Helsinki, Finland for metagenome sequencing. The metagenome sequencing was performed by following Illumina library preparation. This includes purification, normalization, and amplification. Finished libraries were pooled and sequenced on the Illumina NovaSec system. Samples with sufficient sequencing depth from the FIT samples were included in the metagenome sample (64).

3.3 Dietary data

Self-reported dietary data was collected by using a food frequency questionnaire (FFQ) (**Appendix 2**) validated by the Department of Nutrition at the University of Oslo (UiO) (64). The collected dietary data was validated for energy intake (65-67), selected food items and food groups (67-70), and micronutrients and macronutrients (65, 67, 68). The dietary calculation system "kostberegningssystem" (KBS), developed at the Department of Nutrition at UiO, was used to calculate daily average dietary and nutrient intake based on the answers in the FFQ.

The FFQ is a 14-page semiquantitative questionnaire with 23 questions for assessing the diet over the past year. These questions cover the intake of 256 food items, including 8 items for milk, 5 items of yogurt, and 8 items of cheese spreads, as well as a selection of other meals and products containing dairy products. For each food item, answers are categorized in options for frequency of intake and amount per serving, where the participant chooses the option that suits them best. A free-text field is provided after most questions to complete the answer if their diet is not captured by the questionnaire. Participants with incomplete

questionnaires were called to correct ambiguities. Missing frequency was interpreted as zero intake. In the case of a value for frequency with missing amount, the amount per serving was interpreted as the smallest alternative (64).

To minimize errors due to inaccurate reporting, a standardized framework for reviewing the FFQ quality was developed in advance. The FFQ was considered of poor quality if one of the following criteria was present: 1) severe inconsistent or ambiguous reporting, 2) two or more pages missing, or 3) ≥75% missing food items and/or portion sizes. This procedure of the quality control of the FFQs is described in **Appendix 3** (64). Limit values for excessive low and high energy intake were set according to Willet (2012) and resulted in <600 kcal for women and <800 kcal for men, and >3500 kcal for women and >4200 kcal for men, respectively (64, 71).

3.3.1 Organizing of dairy variables

The dairy variables were calculated from grams into servings according to the serving sizes listed in **Table 1**. The servings were accordingly merged into variables of total dairy products, fluid milk, low-fat dairy products, high-fat dairy products, fermented dairy products, and cheese products. The content of calcium in dairy products varies per 100 g and serving. Because of the different content of calcium, as well as different amount of consumption, all statistical analyses were conducted by using dairy products in daily servings as exposure, but intake in grams is presented as supplementary information descriptively. The size of servings and calcium content are based on numbers from the two Norwegian web pages www.matvaretabellen.no (72) and www.kostholdsplanleggeren.no (73). "Matvaretabellen" (the Norwegian food composition table) is a database conducted by the Norwegian Food Safety Authority, that contains the energy and nutrient content of the most commonly consumed foods in Norway (72). "Kostholdsplanleggeren" is conducted by the Norwegian Directorate of Health and the Norwegian Food Safety Authority, and is a tool designed for planning and measuring the nutritional content of diets (73). Both the Norwegian food composition table and Kostholdsplanleggeren use data from the report "Mål, vekt og porsjonsstørrelser for matvarer" (Weight, measure and portion sizes for foods) as a reference for measures and serving sizes (74).

Table 1 *- Serving sizes and content of calcium in dairy products.*

Dairy product	Content of calcium pr 100 g	Size of serving	Content of calcium per serving
Milk	130 mg	200 g	260 mg
Cultured milk	110 mg	200 g	220 mg
Yogurt	126 mg	125 g	158 mg
Quark	129 mg	100 g	129 mg
White cheese	468 mg	20 g	93 mg
· Hard cheese	757 mg	20 g	151 mg
· Semi-hard cheese	447 mg	20 g	89 mg
· Cream cheese	201 mg	20 g	40 mg
Cream	100 mg	50 g	50 mg
Sour cream	111 mg	50 g	56 mg
Ice cream	128 mg	95 g	122 mg
Milk and cream products[1]		50 g	

Content of calcium per 100 g and per serving in different types of dairy products. Calcium content and serving sizes are obtained from the Norwegian Food Composition Table and "Kostholdsplanleggeren" *(72, 73)*. [1]: Milk and cream products include compound products made of milk and/or cream, e.g., vanilla sauce.

The Norwegian Directorate of Health recommends including low-fat dairy products in the daily diet to meet the recommended daily intake of calcium. They suggest a daily intake of dairy products that equals ¼ - ½ liter of milk (31).

Because of the combined regular and cultured milk in FFQ, only cultured milk from LDQ is used in the analysis of fermented dairy, combined with yogurt and cheese from FFQ. White cheese is referred to as cheese further in the thesis. The final dairy variables used in the analyses were total dairy, low-fat dairy, high-fat dairy, fermented dairy, fermented dairy including cheese, and cheese. The included dairy products within each variable are presented in **Figure 5**.

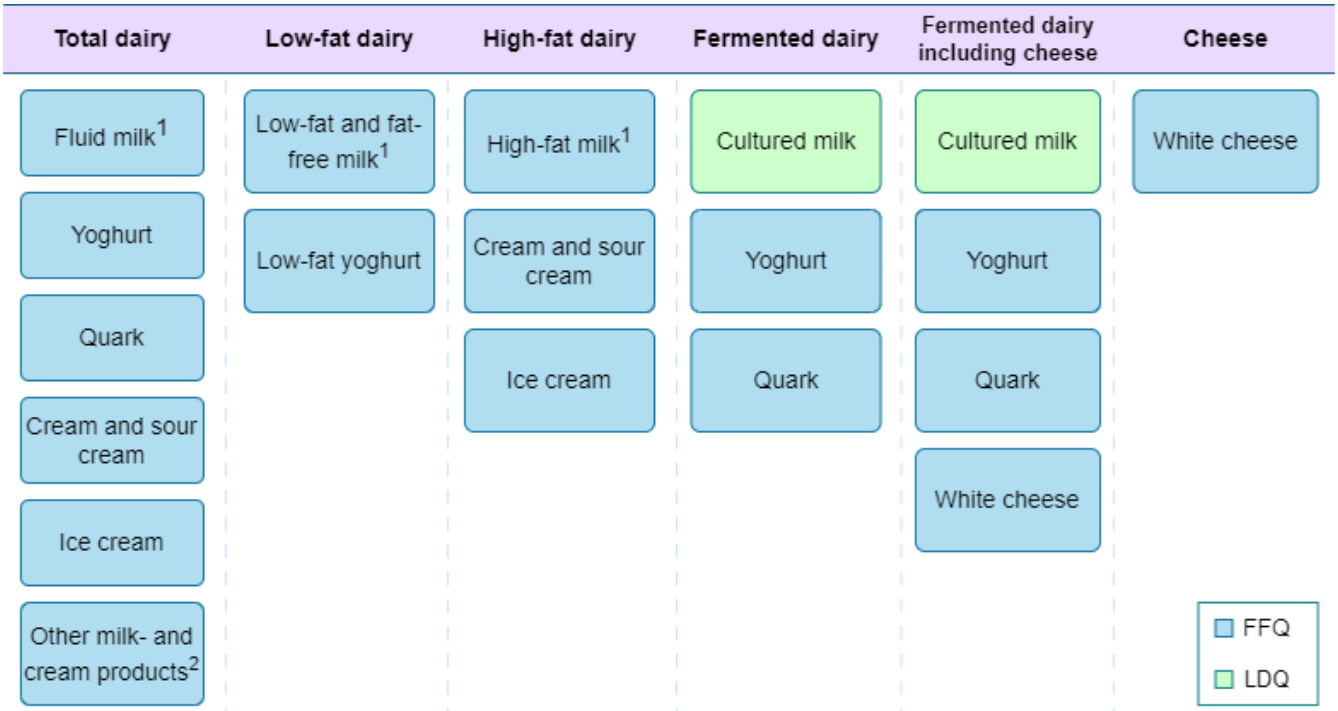

Figure 5 *- Organizing of dairy variables in this master's thesis.*

Different types of dairy products were assessed from a food frequency questionnaire and lifestyle and demographic questionnaire in the dairy variables used in this master's thesis. White cheese includes hard, semi-hard and cream cheese. Abbreviations: FFQ; Food Frequency Questionnaire, LDQ; Lifestyle and Demographic Questionnaire. [1]: Contains both regular and cultured milk. [2]: Other milk- and cream products are e.g., vanilla sauce.

3.4 Lifestyle and demographic data

Lifestyle and demographic information were collected with a self-reported lifestyle and demographics questionnaire (LDQ) (**Appendix 4**) of four pages at the same time as the FFQ. Before the study started, the LDQ was tested in a pilot population and adjusted based on the feedback. The final questionnaire consists of ten questions covering nationality, education, work status, marital status, first-degree relatives diagnosed with CRC, IBD, food intolerances, smoking and "snus" habits, physical activity, use of specific medications, appendix removal, method of delivery at birth, and a separate question on intake of regular and fermented milk. The questionnaire has multiple free text boxes making it possible for the participants to write other answers beside the alternatives listed. Data about regular milk and fermented milk was obtained from the LDQ to supplement the FFQ, as the FFQ do not distinguish between regular and fermented milk products. Two questions on intake of milk were included: "How many glasses of regular milk do you consume per day or week?" and "How many glasses of cultured milk do you consume per day or week?". Examples of cultured milk products were

included in the question. When the LDQ was returned, it was scanned with the Cardiff TeleForm program (InfoShare, Oslo) at the Cancer Registry of Norway (64). Notably, participants who had ceased smoking within the past ten years, according to the completed questionnaire, were despite their current smoking status classified as “smokers”. The FFQ collected data on weight and height and was used to calculate body mass index (BMI). Demographic information such as sex and age were obtained during the colonoscopy.

3.5 Outcome

The main outcome was based on the findings from the follow-up coloscopy. There is no consensus on what undergoes the term advanced colorectal neoplasia (ACN), as some studies include advanced adenomas, advanced serrated lesions, and CRC (75-77) while others only include advanced adenomas and CRC (14, 78, 79). Due to the growing evidence of serrated lesions’ malignant potential, we decided to define the outcome in the grouping as follows:

- No findings: negative colonoscopy, polyp without histology, and non-neoplastic findings
- Non-advanced lesions: non-advanced adenoma (<3 mm), non-advanced adenoma (≥3 mm), and non-advanced serrated lesion
- Advanced colorectal neoplasia: advanced adenoma, advanced serrated lesions, and CRC

Non-advanced serrated lesions included hyperplastic polyps sized <10 mm and sessile serrated lesions with no dysplasia or sized <10 mm. Advanced adenoma includes adenoma with villous histology, high-grade dysplasia, or sized ≥10 mm. Advanced serrated lesions included serrated lesions with dysplasia or sized ≥10 mm.

The secondary outcome is the alpha diversity in the gut microbiome. Metagenome sequencing in the baseline FIT samples is used as outcome of this master’s thesis.

3.5.1 Alpha diversity analysis

To measure richness and evenness, we used the biodiversity indices Shannon index and inverse Simpson index. Both the Shannon index and inverse Simpson index measure richness and evenness, but while the Shannon index puts greater weight on richness, the Simpson index puts greater weight on evenness. There is no consensus on which is better. The inverse Simpson index is the reciprocal of the Simpson index, meaning when the Simpson index measures an increasing diversity by decreasing numbers, the inverse Simpson index measures an increasing diversity with increasing numbers (57, 80). To measure both richness and evenness, both the Shannon and the inverse Simpson indices were utilized, along with relative richness as a third measure of alpha diversity.

3.6 Data management

A de-identified version of the dataset where each participant has a unique ID code was generated to protect the participant's anonymity, and only authorized data manager personnel had access to the complete dataset. The linkage of research data to registries was performed by a data controller. All research data was stored and analyzed in a secure platform "Tjenester for Sensitive data" (Services for Sensitive Data: TSD), at UiO (64, 81). All the analyses were performed using STATA^{TM} software, version 16.0 (Stata Corp, College Station, Texas, USA. A workflow manager was used to handle the metagenome sequencing data and standard filters were applied for quality control of the sequencing reads. Approval needs to be requested from the Norwegian Regional Committee for Medical and Health Research Ethics and data access committee for accessing and using the data (64).

3.7 Statistical analysis

Baseline characteristics are presented as total number (n) and percentage (%) within each colorectal lesion group for categorical variables, and median [p5, p95] for the continuous variables. Missing values from lifestyle and demographic variables are presented in a separate category labeled "missing". The intake of total dairy products, low-fat dairy products, high-fat dairy products, and fermented dairy products was analyzed for the association with each of non-advanced lesions and ACN. For this, both univariate and multivariate multinomial

logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (CI). Dairy servings were used as continuous variables and colorectal lesion groups as a categorical variable.

Variables for the intake of dairy products consumed per day used in the statistical analysis were fluid milk (g/day), regular milk (g/day), cultured milk (g/day) low-fat dairy (servings/day), high-fat dairy (servings/day), fermented dairy (servings/day), fermented dairy including cheese (servings/day), cheese (servings/day), and total dairy (servings/day). Sensitivity analysis only adjusting for age and sex was also performed. Before merging the variables of cultured milk from the LDQ with the fermented foods from the FFQ, Spearman's correlation was conducted to assess correlation between participants answers in intake of fluid milk from the two questionnaires. To investigate the individual association between low-fat dairy products and high-fat dairy products, and their association with each of the colorectal lesion groups, two separate multinomial logistic regression analyses were performed.

The multivariate analyses were adjusted for the known CRC risk factors: sex (male, female), age, smoking (smoking, not smoking), alcohol, red meat, processed meat, dietary fiber, family history of CRC in first-degree relatives (yes, no, unknown), IBD (yes, no), BMI and physical activity, in addition to the sociodemographic factors' nationality (Norwegian, not Norwegian), education (primary school, high school, university/college), work status (working, retired, other), and marital status (married/living together, not married/living together). Dietary risk factors, age, BMI, and physical activity were included as continuous variables, and remaining lifestyle- and sociodemographic factors were included as categorical variables. For all analyses considering the colorectal lesion groups, the category of "no findings" was used as reference category. Additionally, a supplementary multinomial logistic regression was done for intake of dietary calcium and colorectal lesions (**Appendix 5**). Intake of calcium was categorized in quartiles. All results were considered significant at p-values <0.05.

A selection of participants' stool samples was extracted for DNA and metagenome sequenced. A Shapiro-Wilks test and histogram were conducted to assess normality in Shannon index, inverse Simpson index, and richness. To investigate the association between intake of dairy products and each of the diversity measures, a one-way ANOVA with planned contrast analysis was used to assess the alpha diversity between those with the lowest,

median, and highest intake of total dairy. For this, the continuous variable of total intake of dairy products was separated into tertiles.

3.8 Ethics

The data was handled according to the STROBE guidelines and linked to the Norwegian Prescription Database and the Cancer Registry of Norway. All participation in the study was voluntary. The BCSN trial and the CRCbiome study were approved by the Regional Committee for Medical Research Ethics in southeast Norway (approval numbers 2011/1272 and 63148, respectively) (**Appendix 6**). The BCSN is registered at clinicaltrials.gov (Clinical trial number: 01538550).

3.9 Contributions

The student contributed to the CRCbiome study by validating a sample of the collected LDQs. The data was scanned and processed with the Cardiff TeleForm program. The student checked the scanned data for scanning errors and misinterpretations in the text. If an error was detected, it was corrected in line with the verification rules, which were set before the validating process started. This was to ensure that the data was validated equally by all parties involved and to secure the highest quality possible. Additionally, the student classified dairy products in both FFQ and LDQ, spilt certain original variables to obtain more accurate information about participants' dietary intake, and performed statistical analysis according to the aim of this thesis.

4 Results

In total, 1,659 participants at baseline were included in this master thesis (**Figure 6A**). Of these, 44 were excluded due to not completing colonoscopy, 15 were excluded due to reservation from participating after inclusion, 21 for having low quality in FFQ, 55 for excessive low or high energy intake, 38 for not responding to FFQ and finally, 20 for not responding to LDQ. This left 1,466 participants eligible for this master's thesis. Of these, 933 participants had metagenome samples (**Figure 6B**). In total, the study had 2,134 metagenome sequenced samples, but only 1,043 of these were from the baseline of the CRCbiome study, and 1,034 had sufficient sequencing depth. Of these, 20 were excluded for low quality in FFQ, 42 for excessive high or low energy intake, 27 for not responding to FFQ, and 12 for not responding to LDQ.

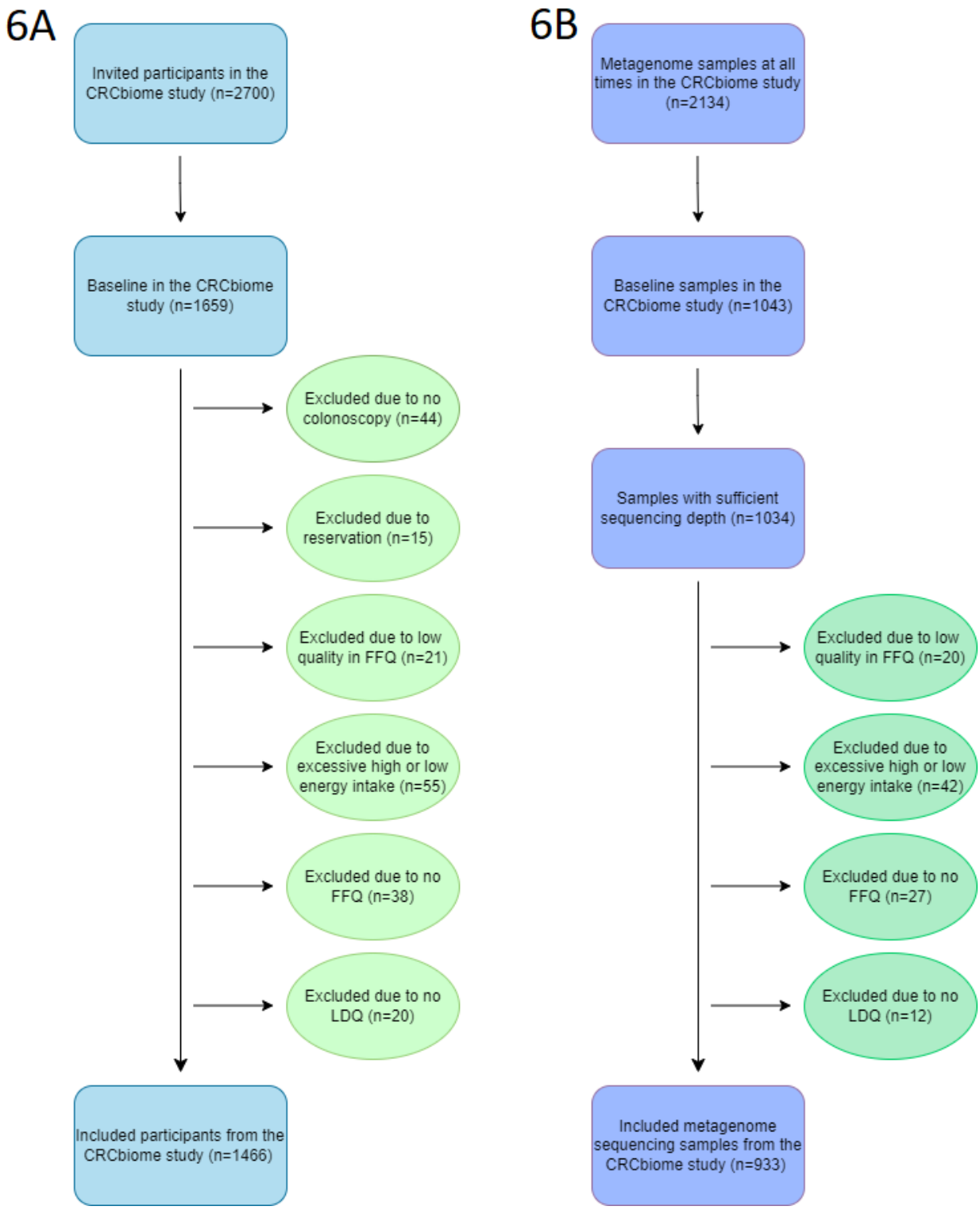

Figure 6 *- Flowchart of the participants in this master's thesis.*

6A describes the participants in the analysis of the colorectal lesion groups. 6B describes the samples eligible for the alpha diversity analysis. Abbreviations: FFQ; Food frequency questionnaire, LDQ; Lifestyle and demographics questionnaire.

4.1 Demographical and clinical characteristics

Demographical and clinical characteristics of the study population are presented in **Table 2** by colorectal lesion group. The number of participants in each group was 447 (30 %) in the group with no findings, 614 (42 %) in the group of non-advanced lesions, and 405 (28 %) in the group of ACN. The median age at baseline was 66.9 years (range 56 to 76 years). Of all participants, 45% were female and 92% were of Norwegian nationality. There were 40% who had high school as their highest education and 43% had university/college as their highest education. More than half of the participants were retired (54%). The median BMI was 26.9 kg/m^2 and the median amount of physical activity was 120 minutes per week. The majority were married or living together with a partner (80%) and were non-smokers (74%). At last, 98% did not have IBD and 75% did not have a family history of CRC.

Table 2 *– Self reported clinical and demographic characteristics of the study population.*

Variable	Total population n=1466	No findings n=447	Non-advanced lesions n=614	Advanced neoplasia n=405
Age[1] (years)	66.9 [57.8, 76.0]	66.1 [57.6, 76.2]	67.2 [57.8, 76.0]	67.8 [57.8, 75.9]
Sex				
Female	655 (44.7%)	227 (50.8%)	269 (43.8%)	159 (39.3%)
Male	811 (55.3%)	220 (49.2%)	345 (56.2%)	246 (60.7%)
Nationality				
Norwegian	1345 (91.8%)	410 (91.7%)	562 (91.5%)	373 (92.1%)
Not norwegian	82 (5.6%)	31 (6.9%)	30 (4.9%)	21 (5.2%)
Missing	39 (2.7%)	6 (1.3%)	22 (3.6%)	11 (2.7%)
Education				
Primary school	251 (17.1%)	85 (19.0%)	99 (16.1%)	67 (16.5%)
High school	580 (39.6%)	177 (39.6%)	241 (39.3%)	162 (40.0%)
University/college	631 (43.0%)	183 (40.9%)	273 (44.5%)	175 (43.2%)
Missing	4 (0.3%)	2 (0.5%)	1 (0.2%)	1 (0.3%)
Work status				
Working	498 (34.0%)	155 (34.7%)	215 (35.0%)	128 (31.6%)
Retired	795 (54.2%)	219 (49.0%)	338 (55.1%)	238 (58.8%)
Outside workforce[2]	173 (11.8%)	73 (16.3%)	61 (9.9%)	39 (9.6%)
Marrital status				
Married/living together	1171 (79.9%)	375 (83.9%)	478 (77.9%)	318 (78.5%)
Single/widower	294 (20.1%)	72 (15.1%)	136 (22.2%)	86 (21.2%)
Missing	1 (0.1%)	-	-	1 (0.3%)
Smoking status				
Smoking	380 (25.9%)	104 (23.3%)	163 (26.6%)	113 (27.9%)
Not smoking	1082 (73.8%)	341 (76.3%)	449 (73.1%)	292 (72.1%)
Missing	4 (0.3%)	2 (0.5%)	2 (0.3%)	-
BMI[1] (kg/m²)	26.9 [20.9, 34.5]	26.1 [20.4, 34.6]	26.7 [21.1, 34.7]	26.4 [21.1, 34]
<18.5	12 (0.8%)	3 (0.7%)	6 (1.0%)	3 (0.7%)
≥18.5 - <25	484 (33%)	180 (40.3%)	178 (29.0%)	126 (31.3%)
≥25 - <30	677 (46.2%)	176 (39.4%)	309 (50.3%)	192 (47.4%)
≥30 - <35	225 (15.4%)	67 (15.0%)	90 (14.7%)	68 (16.8%)
≥35	63 (4.3%)	21 (4.7%)	28 (4.6%)	14 (3.5%)
Missing	5 (0.3%)	0	3 (0.5%)	2 (0.5%)
Physical activity[1] (min/week)	120.0 [0.0, 480.0]	120.0 [0.0, 480.0]	120.0 [0.0, 480.0]	105.0 [0.0, 480.0]
<150	770 (52.5%)	233 (52.1%)	313 (51.0%)	224 (55.3%)
≥150 - <300	346 (23.6%)	94 (21.0%)	158 (25.7%)	94 (23.2%)
≥300	350 (23.9%)	120 (26.9%)	143 (23.3%)	87 (21.5%)
IBD				
Yes	32 (2.2%)	20 (4.5%)	7 (1.1%)	5 (1.2%)
No	1434 (97.8%)	427 (95.5%)	607 (98.9%)	400 (98.8%)
Family history of CRC[3]				
Yes	255 (17.4%)	68 (15.2%)	105 (17.1%)	82 (20.3%)
No	1092 (74.5%)	334 (74.2%)	463 (75.4%)	295 (72.8%)
Unknown	119 (8.1%)	45 (10.1%)	46 (7.5%)	28 (6.9%)

Physical activity is measured in minutes per week. BMI is measured in kg/m2. [1]: Continous variables are measured in median [p05,p95]. BMI and physical activity are given as both continous and categorical vairable. [2]: Outside workforce include: unemployed, homemaker, disability pension, long-term sick leave (>3 months), work clearance, allowance and rehabilitation. [3]: Family history is considered as parents, siblings and/or children with colorectal cancer. Abbreviations: min/week; Minutes per week, BMI; Body Mass Index, IBD; Inflmmatory Bowel Disease, CRC; Colorectal Cancer.

Characteristics of dietary risk factors for CRC are presented in T**able 3**. A higher median intake was observed in the group of ACN compared to the group with no findings in energy, red meat, processed meat and alcohol (9391 kilojoules (KJ) relative to 8950 KJ), red meat (27 g/d relative to 24 g/d), processed meat (47 g/d relative to 43 g/d) and alcohol (11 g/d relative to 7 g/d). A lower median intake was observed in the group of ACN compared to the group with no findings in the variables total dairy (265 g/d relative to 298 g/d) and dietary calcium (921 mg/d relative to 943 mg/d). This difference was not as visible in the variable showing daily servings of total dairy (3.3 servings/d relative to 3.5 servings/d). Intake of dietary fiber, fluid milk, yogurt and cheese were similar in all three colorectal lesion groups.

Table 3 *- Intake of food components considered as risk factors of colorectal cancer within each of the colorectal lesion groups.*

Variables	Median [p25, p75]			
	Total population n=1466	**No findings n=447**	**Non-advanced lesions n=614**	**Advanced neoplasia n=405**
Energy (KJ)	9044 [7206, 11177]	8950 [7127, 10984]	8899 [7155, 10924]	9391 [7478, 11610]
Total dairy (servings/d)	3.4 [2.1, 5.0]	3.5 [2.2, 5.1]	3.4 [2.2, 5.2]	3.3 [2.1, 4.6]
Fluid milk* (servings/d)	1.0 [0.1, 2.1]	1.0 [0.5, 2.0]	1.0 [0.1, 2.1]	1.0 [0.1, 2.1]
Yogurt (servings/d)	0.6 [0.0, 0.4]	0.1 [0.0, 0.4]	0.1 [0.0, 0.4]	0.0 [0.0, 0.3]
Cheese** (servings/d)	1.1 [0.6, 1.8]	1.0 [0.6, 1.7]	1.1 [0.5, 1.8]	1.1 [0.7, 1.7]
Total dairy (g/d)	283.9 [146.9, 519.0]	297.9 [164.8, 519.6]	291.5 [146.5, 535.6]	265.1 [127.2, 489.4]
Dietary calcium (mg/d)	935.5 [686.0, 1265.0]	943.0 [692.0, 1263.0]	942.0 [688.0, 1299.0]	921.0 [680.0, 1244.0]
Dietary fiber (g/d)	27.5 [21.7, 35.1]	27.7 [21.7, 34.8]	27.0 [21.3, 34.5]	28.3 [22.6, 36.6]
Red meat (g/d)	23.8 [13.5, 37.7]	23.6 [12.2, 35.8]	22.9 [13.5, 36.9]	27.1 [15.4, 43.2]
Processed meat (g/d)	44.2 [27.4, 65.1]	42.6 [26.6, 65.4]	44.0 [26.9, 63.4]	47.2 [29.8, 69.7]
Alcohol (g/d)	9.1 [2.2, 19.3]	6.8 [1.5, 15.7]	10.1 [3.5, 21.6]	10.8 [3.5, 21.6]

Fluid milk includes both regular and cultured milk. Cheese includes white hard, semi-hard and cream cheese.
Abbreviations: KJ; Kilojoule, g; Gram, d; Day.

Diet and lifestyle variables of continuous origin associated with CRC are presented by the correlation with the dairy variables used in the analysis in **Table 4**. The correlation between calcium and total dairy was the strongest of all variables. Age was not significantly correlated with any of the dairy variables, and BMI, red meat, and alcohol were only significantly correlated with three of the dairy variables, whereas this was a weak correlation. However, energy, calcium, and fiber were significantly correlated with all the dairy variables.

Table 4 *- Correlation between daily intake of dairy and lifestyle factors associated with colorectal cancer and dairy variables.*

Variables	Age	BMI	Physical activity	Energy	Calcium	Red meat	Processed meat	Alcohol	Fiber
Total dairy	0.037	-0.086**	0.064*	0.420**	0.799**	0.028	0.119**	-0.076*	0.228**
Low-fat dairy	-0.011	-0.031	0.100**	0.268**	0.577**	0.049	0.110**	-0.023	0.150**
High-fat dairy	-0.019	-0.007	0.009	0.305**	0.314**	0.093**	0.084*	-0.045	0.197**
Fermented dairy	0.037	-0.103**	0.101**	0.148**	0.286**	-0.079*	-0.104**	-0.075*	0.223**
Fermented dairy including cheese	0.039	-0.101**	0.121**	0.241**	0.401**	-0.047	-0.049	-0.053*	0.276**
Cheese	0.002	-0.012	0.073*	0.310**	0.397**	0.086**	0.111**	0.042	0.239**

*p<0.05, **p<0.001. Cheese includes white hard, semi-hard and cream cheese. Abbreviations: CRC; Colorectal Cancer, BMI; Body Mass Index.

4.2 Dairy and colorectal lesions

4.2.1 Intake of dairy products

Figure 7 presents an overview of intake of the different dairy products in the population. The bar chart shows the distribution of each dairy variable in daily servings in the categorization zero intake (0), >0-<1 (1), ≥1–2 (2), ≥2–<3 (3) and ≥3 (3+). For total dairy, the categories go to ≥8 (8+) daily servings in the same categorization, as 58% of the population has a daily intake of ≥3 servings of total dairy. None of the participants had zero intake of total dairy, and the mean intake was 3.4 daily servings and 384 g of total dairy. The mean intake of calcium was 936 mg. The dairy product with the highest content of calcium per serving was regular fluid milk by 260 mg per serving, while cream cheese had the lowest content of calcium by 40 mg per serving. The subtype of dairy with the highest daily intake was fermented dairy including cheese, which means this group contributed most to the total dairy intake. Of the study population, 15% consumed three or more daily servings of fermented dairy including cheese, whereas for fermented dairy and cheese separated, only 1% and 8% consumed three or more daily servings, respectively.

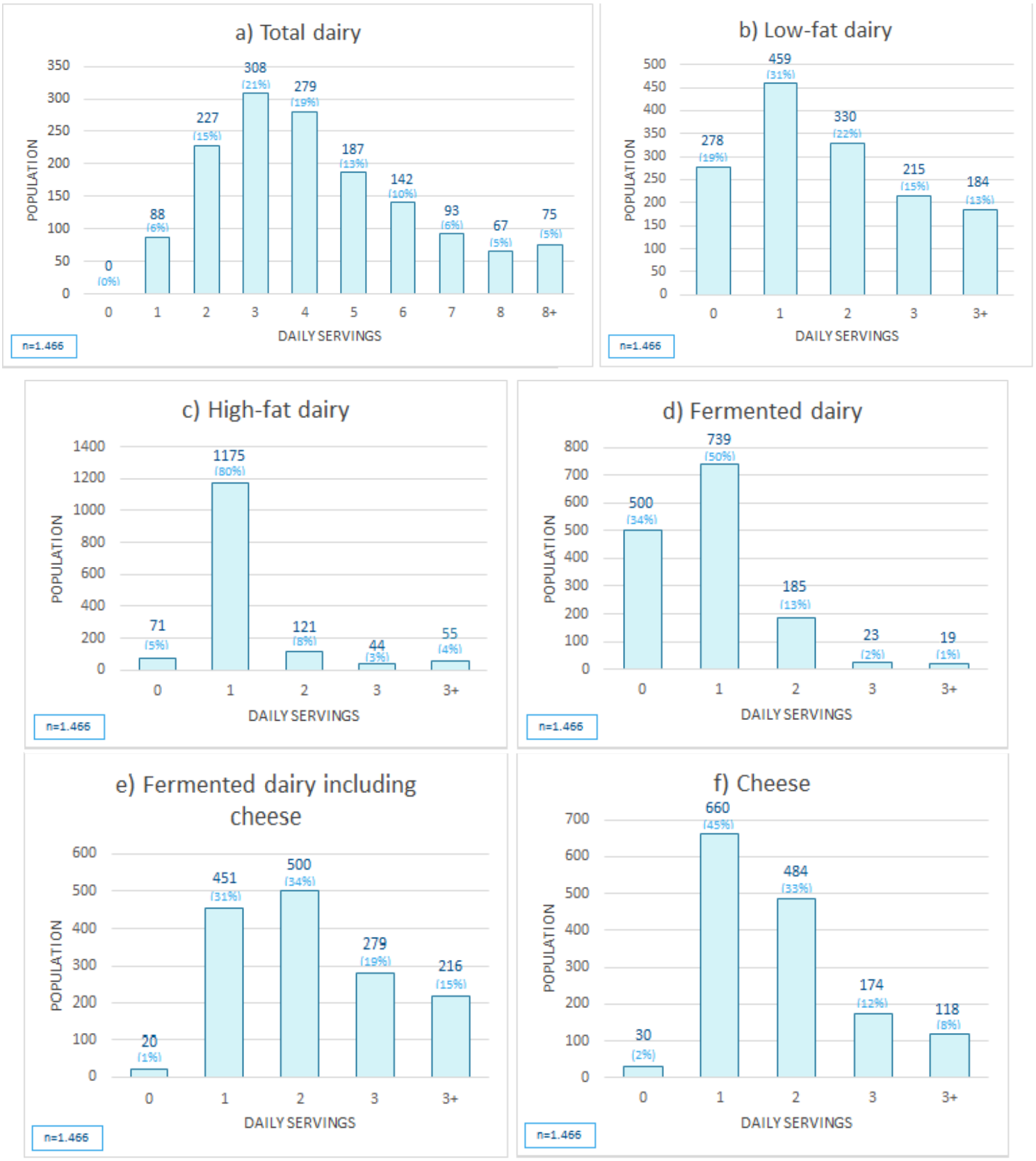

Figure 7 *– Daily intake of different subgroups of dairy products in the study population.*

Cheese includes white hard, semi-hard and cream cheese. Servings are categorized 0: zero intake, 1: >0-<1 serving/day, 2: ≥1-<2 servings/day, 3: ≥2-<3 servings/day and 3+: ≥3 servings/day. For total dairy, this trend continues until 8+: ≥8 servings/day. n=1,466.

4.2.2 Intake of dairy products and colorectal lesion groups

Table 5 presents the amount of total dairy products consumed in servings and an overview of the colorectal lesion groups. The groups consist of 447, 614, and 405 participants, respectively. The largest group of the population representing servings of any type of dairy product was those who consumed between two to three daily servings, which corresponded to 21% of the population.

Table 5 *- Intake of total dairy by colorectal lesion group.*

Daily intake of total dairy	No findings n=447	Non-advanced lesions n=614	Advanced neoplasia n=405	Total n=1466
<1 serving	26 (5.8%)	38 (6.2%)	24 (5.9%)	88 (6.0%)
≥1 - <2 servings	65 (14.5%)	91 (14.8%)	71 (17.5%)	227 (15.5%)
≥2 - <3 servings	92 (20.6%)	130 (21.2%)	86 (21.2%)	308 (21.0%)
≥3 - <4 servings	85 (19.0%)	108 (17.6%)	86 (21.2%)	279 (19.0%)
≥4 - <5 servings	59 (13.2%)	80 (13.0%)	48 (11.9%)	187 (12.8%)
≥5 - <6 servings	50 (11.2%)	60 (9.8%)	32 (7.9%)	142 (9.9%)
≥6 - <7 servings	29 (6.5%)	37 (6.0%)	27 (6.7%)	93 (6.3%)
≥7 - <8 servings	14 (3.1%)	39 (6.4%)	14 (3.5%)	67 (4.6%)
≥8 servings	27 (6.0%)	31 (5.1%)	17 (4.2%)	75 (5.1%)

Total dairy contains fluid milk (regular and cultured), yogurt, white hard, semi-hard and cream cheese, quark, sour cream, ice cream, cream, and non-specified milk- and cream products.

4.2.3 Associations between intake of dairy and colorectal lesions

4.2.3.1 Associations between intake of total dairy and colorectal lesions

The univariate multinomial logistic regression did not show a statistically significant association between intake of total dairy products and ACN (OR=0.95 95% CI 0.90, 1.01) per increment of one daily dairy serving (**Table 6**). When adjusted for confounders, the result turned statistically significant (OR=0.93, 95% CI 0.88, 0.99). There was no statistically significant association between intake of total dairy products and non-advanced lesions. The sensitivity analysis with age and sex as confounders was not statistically significant for either ACN or non-advanced lesions.

***Table 6** – Daily intake of dairy products per one serving increment and odds ratio and 95% confidence interval for non-advanced lesions and advanced neoplasia in the colorectum.*

Exposure	OR (95% CI)		
	No findings n=447	Non-advanced lesions n=614	Advanced neoplasia n=405
Total dairy			
Univariate model	Ref	1.00 (0.95, 1.05)	0.95 (0.90, 1.01)
Age and sex adjusted	Ref	0.99 (0.95, 1.04)	0.95 (0.90, 1.00)
Multivariate model	Ref	0.99 (0.94, 1.05)	0.93 (0.88, 0.99)
Low-fat dairy			
Univariate model	Ref	1.01 (0.93, 1.09)	0.93 (0.84, 1.02)
Age and sex adjusted	Ref	0.99 (0.91, 1.08)	0.91 (0.82, 1.00
Multivariate	Ref	0.99 (0.91, 1.08)	0.91 (0.82, 1.00)
High-fat dairy			
Univariate model	Ref	0.97 (0.88, 1.06)	0.94 (0.84, 1.06)
Age and sex adjusted	Ref	0.97 (0.88, 1.07)	0.94 (0.84, 1.06)
Multivariate model	Ref	0.97 (0.88, 1.07)	0.93 (0.82, 1.05)
Fermented dairy			
Univariate	Ref	0.94 (0.79, 1.12)	0.75 (0.60, 0.94)
Age and sex adjusted	Ref	0.95 (0.79, 1.14)	0.77 (0.61, 0.97)
Multivariate	Ref	0.94 (0.78, 1.15)	0.73 (0.58, 0.93)
Fermented dairy including cheese			
Univariate	Ref	1.02 (0.93, 1.12)	0.94 (0.84, 1.04)
Age and sex adjusted	Ref	1.02 (0.93, 1.12)	0.94 (0.85, 1.05)
Multivariate	Ref	1.02 (0.92, 1.12)	0.89 (0.80, 1.00)
Cheese			
Univariate	Ref	1.06 (0.94, 1.18)	1.00 (0.89, 1.14)
Age and sex adjusted	Ref	1.05 (0.94, 1.18)	1.00 (0.88, 1.14)
Multivariate	Ref	1.05 (0.93, 1.18)	0.95 (0.83, 1.09)

Cheese includes white hard, semi-hard and cream cheese. Multivariate model is adjusted for age (continuous), sex (male, female), nationality (Norwegian, not Norwegian), education (primary school, high school, university/college), work status (working, retired, outside workforce), marital status (married/living together, not married/widower), smoking status (smoking, not smoking), body mass index (continuous), physical activity (continuous), inflammatory bowel disease (yes, no) and family history of colorectal cancer (yes, no), as well as intake of red meat (continuous), processed meat (continuous), dietary fiber (continuous) and alcohol (continuous).

4.2.3.2 Associations between intake of dairy by fat content and colorectal lesions

There was no statistically significant association between either the intake of low-fat dairy or high-fat dairy per one daily serving increase and non-advanced lesions or ACN (**Table 6**). The sensitivity analysis with only age and sex as confounders did not show any association.

4.2.3.3 Associations between intake of fermented dairy and colorectal lesions

A scatter plot (**Figure 8**) and Spearman's correlation was run to assess the correspondence between the reported intake of fluid milk from FFQ and LDQ. There was a strong positive correlation between the fluid milk intakes (r_s=.789, *p=<0.000*).

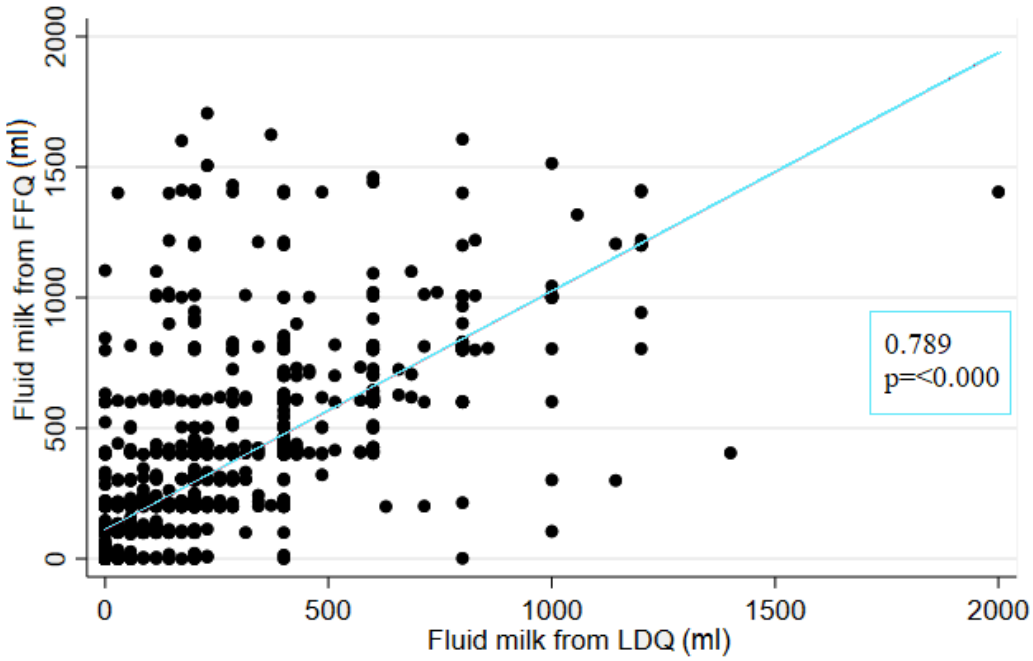

Figure 8 *- Scatter plot for fluid milk from FFQ and LDQ*

Presented in ml of daily intake of fluid milk. Fluid milk includes both regular and cultured milk. Abbreviations: FFQ; Food Frequency Questionnaire, LDQ; Lifestyle and Demography Questionnaire.

There was a statistically significant inverse association between intake of fermented dairy per one daily serving increase and ACN (OR=0.75 95% CI 0.60, 0.94) (**Table 6**). When adjusting for dietary and lifestyle-related risk factors, the significance remained (OR=0.73 95% CI 0.58, 0.93).

There was no statistically significant association between either intake of fermented dairy including cheese or cheese alone and ACN in the univariate and the multivariate analyses. There was no statistically significant association between fermented dairy, fermented dairy including cheese or cheese, and non-advanced lesions in the univariate and the multivariate analyses. The sensitivity analyses with only sex and age as confounders did not show any association.

4.3 Dairy intake and alpha diversity in the gut microbiome

The distribution of the population in the groups of low and high total intake of dairy products is presented in **Figure 9**. The normal distribution of the diversity measures in the dairy groups was validated by histogram and Shapiro-Wilk test (**Appendix 7**). Low intake of dairy products corresponds to a daily intake of 0.01 to 2.52 daily servings and high intake corresponds to a daily intake of 4.38 to 22.38 daily servings.

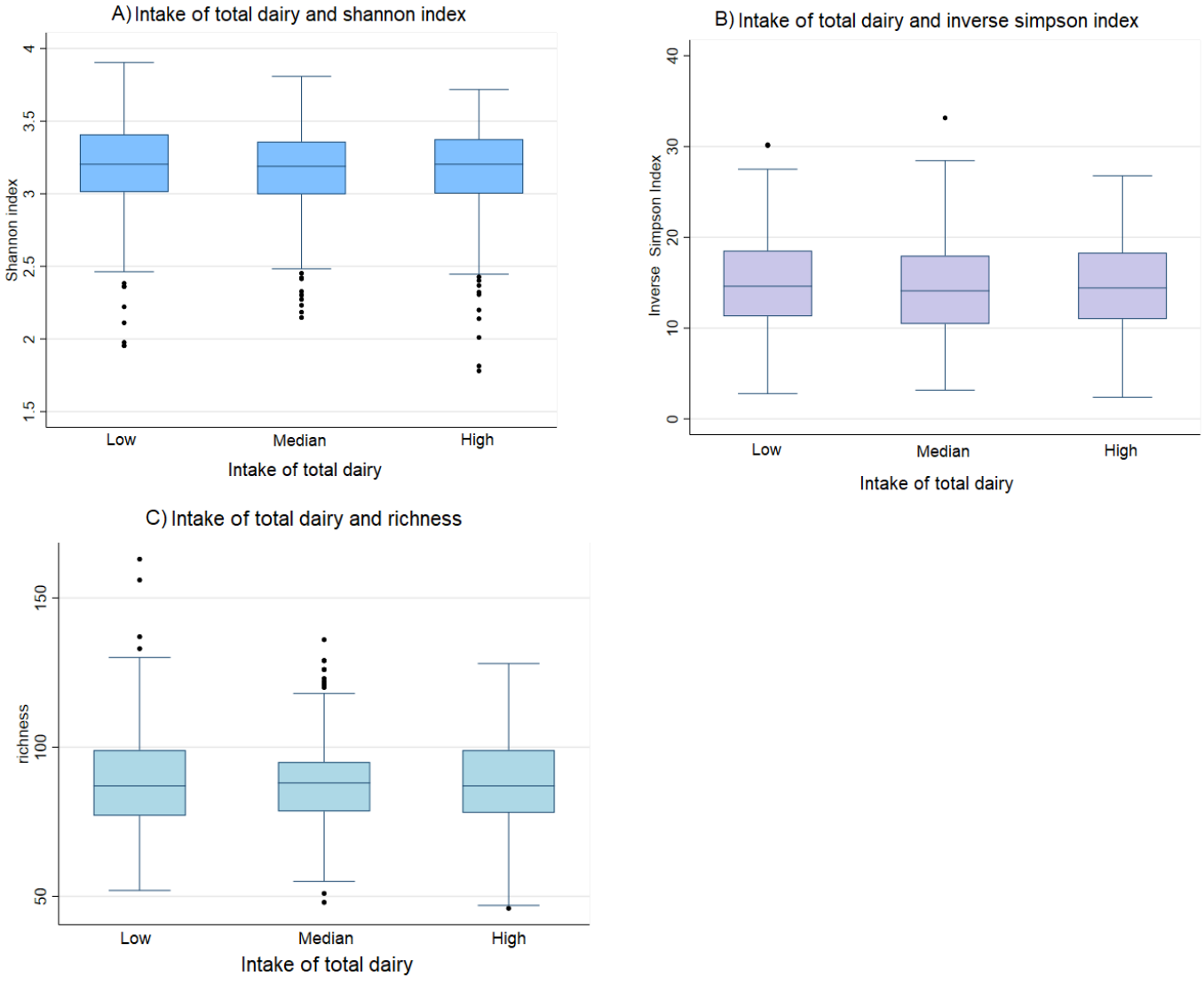

Figure 9 *- Distribution of the measured alpha diversity by Shannon index, Inverse Simpson index and Richness in participants with low, median and high intake of total dairy.*
Low intake indicates a daily intake of 0.01 to 2.51 servings of total dairy. High intake indicates a daily intake of 4.38 to 22.38 servings of total dairy.

There was no significant correlation between total dairy servings and Shannon index, inverse Simpson index, or richness (**Table 7**). The ANOVA with planned contras showed no significant differences in variance of alpha diversity by Shannon index, inverse Simpson index or richness between the groups of high and low intake of total dairy products (**Table 8**).

Table 7 *- Correlation between daily intake of total dairy servings and Shannon, Inverse Simpson and Richness*

Correlation with intake of total dairy	Observations	Spearman's rho	p
Shannon index	933	-0.022	0.498
Inverse simpson index	933	-0.007	0.834
Richness	933	-0.012	0.725

Significance: p<0.05. Total dairy is analyzed in servings per day.

Table 8 *- ANOVA with planned contrast by variance of Shannon index, Inverse Simpson index and Richness by groups of low and high intake of total dairy products.*

	P>F	Contrast	95% CI
Shannon index			
Median intak vs low intake	0.58	0.22	-0.57, 1.02
High intake vs low intake	0.82	-0.10	-0.91, 0.71
Inverse Simpson index			
Median intake vs low intake	0.95	-0.00	-0.05, 0.05
High intake vs low intake	0.50	-0.12	-0.07, 0.03
Richness			
Median intake vs low intake	0.25	-1.42	-3.84, 0.99
High intake vs low intake	0.20	-1.61	-4.08, 0.86

Low intake corresponds to a daily intake of 0.01 to 2.52 servings of total dairy, while high intake corresponds to a daily intake of 4.38 to 22.38 servings of total dairy.

5 Discussion

The main aim of this thesis was to investigate the association between intake of dairy products and the presence of colorectal lesions in FIT-positive participants identified in a CRC screening trial. Furthermore, we investigated how total dairy and subgroups of dairy products – including low-fat, high-fat, and fermented dairy – were associated with colorectal lesions, as well as how intake of dairy products were associated with the alpha diversity in the gut microbiome in a subset of the study population.

In general, the result of this thesis demonstrated a significant inverse association between intake of total dairy products and incidence of ACN among participants with a positive FIT. In the additional analyses, we observed a more nuanced pattern of results, with the only significant association observed being between intake of fermented dairy and ACN. However, no associations were found for non-advanced lesions. Furthermore, no association was observed between intake of dairy products and alpha diversity in the gut microbiome.

This thesis differs from previous research by examining not only CRC but also advanced adenomas and advanced serrated lesions as a part of the same outcome group, as well as non-advanced adenomas as a separate outcome group. While a strong inverse association between dairy consumption and CRC is widely acknowledged, the impact of specific subgroups of dairy and precursor lesions for the development of CRC is still scarce and more research is needed.

5.1 Methodological considerations

5.1.1 Study population

The participants for this thesis were participants in the CRCbiome study, which was conducted as a part of the population-based screening setting in the BSCN pilot study (64). The participants were limited to a specific area of Norway, namely former Østfold County and chosen municipalities in Vestre Viken. Only individuals who accepted the invitation to FIT participation in the BCSN and tested positive were considered for the CRCbiome study. The participation rate in the FIT arm of the BCSN was 68% after three FIT rounds. Further, 7-9% of the participants returned a positive FIT sample at each of the screening rounds. A total of 2700 individuals who returned a positive FIT during the recruitment period from 2017 to 2021 were invited to the CRCbiome study. The participation rate was 61%.

To be included in this master's thesis, participants had to participate in the FIT screening, attend colonoscopy, and be willing to fill out the 14 pages long FFQ and the LDQ. This might have caused a selection bias (82). Due to this selected population, the generalizability of the results should be done with caution. It is, however, expected that our study population is representative of a population of positive FIT screened.

A study in the BCSN investigated the non-participants of the study. They found that being young of age, having low socioeconomic status, being retired, and living alone had a negative impact on participation in the BSCN. After screening in the FIT arm, participants with immigrant status, those residing far from the screening center, and those using antidiabetic or psychotropic drugs were less likely to attend colonoscopy, despite a positive FIT. Females had a higher participation rate than males in the FIT arm of the study (83). In our study population, some differences are expected in the population due to our selected population. The risk of CRC is higher for men than for women, and as we only included FIT-positive individuals in the study population, it is likely with a higher proportion of men than women. Our population included 55% men. Compared to the median age for diagnosis of colon cancer (75 for women, 73 for men) and of rectal cancer (71 for women, 70 for men) (84), our population is younger, with a median age of 67. However, the aim of the CRCbiome and this master's thesis is to investigate precursor lesions for CRC, which develop over several years before eventually progressing to cancer (8, 64).

5.1.2 Assessment of dietary intake

Data considering dietary intake was assessed using a semi-quantitative FFQ, as well as the LDQ. The FFQ was validated by energy intake, selected food items and food groups, and micro- and macronutrients (65-70). Energy, micro, and macronutrients were measured based on the response in the FFQ. Participants were asked to recall their dietary intake for the past 12 months when completing both questionnaires. However, due to the quantitative answer options, they were required to indicate what they ate and in what quantity they consumed it over a day or week in the FFQ. This can cause measurement error, as a normal challenge with self-administered FFQ is that participants forget or avoid answering questions (85). Intake of regular and cultured milk is the only dietary items assessed by the LDQ, which represents only a small proportion of the total dietary intake. However, it was highly relevant to this master's thesis.

Alternative methods for collecting dietary data are food diaries or repeated 24-hour recall interviews. A food diary is considered the gold standard of dietary assessment, as it does not require recall and provides accurate information. Food diary also requires motivation and effort from participants, leading to selection bias, and increasing the risk of changed eating behavior during registration. Food dairy also requires significant training and follow-up work, which can be expensive and time-consuming. 24-hour recall interview is easy to remember, requires minimal effort from participants, and does not make people change behaviors during registration. Disadvantages of this method are that people tend to underestimate their dietary intake, as it only captures a one-day snapshot of the diet and it requires significant follow-up work (85).

In this study, an FFQ was chosen as the best alternative method despite its limitations. FFQ tends to underestimate energy intake (67), and it provides limited information and participants may have difficulty remembering. On the other side, it is easy and inexpensive to distribute to a large population, provides a reference over a longer period, and it only requires a one-time effort. However, it is important to validate the results of this method to ensure accuracy and reliability (85).

5.1.2.1 Dairy variables

The analyses were conducted using dairy variables in serving sizes rather than in grams or mean intake. This was due to both calcium intake in each serving and the relative size of each subgroup of dairy. For milk, 200 g was defined as one serving, and for cheese 20 g was defined as one serving. The serving size for milk is thereby ten times larger than the serving size for cheese. One serving of regular milk contains 260 mg of calcium and the same amount of white, hard cheese contains 1514 mg of calcium, indicating the issues of analyzing dairy products in gram. One serving of white, hard cheese, on the other hand, contains 93 mg of calcium, which is less than one serving of regular milk but was evaluated to be more comparable than the value for 200 g of cheese.

The variable of low-fat dairy did not include low-fat cheese, even though our data included cheese with different content of fat. Low-fat cheese has a reduced content of fat compared to regular cheese. To label products as “reduced in fat”, the criteria from the Norwegian Food Safety Authority is that it requires to be 30% lower in fat (or sugar) than the original product. In general, low-fat products have certain limit values. As for fluid low-fat products, it is required to contain no more than 1.5 g fat per 100 ml, and solid products no more than 3 g per 100 g to be referred to as having “low fat content” (86). Based on this, low-fat cheese is not necessarily a low fat-product. Therefore, it was not included in the low-fat and high-fat analysis.

Most studies that investigate fermented dairy do not include cheese, even though it is a fermented product (42). This does not apply to brown cheese, which is widely used in Norway (87, 88). The variables were separated into two main categories of white and brown cheese in our data, and then further separated into smaller groups of fat content. However, this introduces a measurement error, as the data on cheese did not differentiate between hard, semi-hard, and cream cheeses. Most of the semi-hard and cream cheeses are either added bacterial culture or made from white cheese, which means they are considered fermented cheeses. Some cheeses are, however, made directly from cow or goat milk without adding bacterial culture, which makes them non-fermented (88). This is a restriction from the dataset which contributes to a measurement error, as some non-fermented cheeses may be included in our analysis. Due to this, and to the usual practice of not combining fermented dairy and cheese in analyses, we conducted two sub-analyses of fermented cheese to compare the effect

of cheese on the results of fermented dairy. We considered cheese necessary to include, as cheese consumption in Norway on average was nearly 20 kg per person in 2020 (89).

Furthermore, the serving sizes of cheese are discussable. All cheese servings were set to 20 g, as our data did not differentiate between hard, semi-hard, and cream cheese. Semi-hard and cream cheese have slightly various serving sizes, from 10 to 40 grams per serving (74). Also, the serving size of sour cream and cream was set to 50 g. This was due to our dataset, as the variables for these foods were combined into one. Neither "Kostholdsplanleggeren" nor the report "Weights, measures and portion sizes" has any definite serving size for sour cream and cream, only weight for one tablespoon and one deciliter. We, therefore, put the serving size to 50 g, which corresponds to half a deciliter and approximately 3 tablespoons of sour cream and 5 tablespoons of cream, according to "Weights, measures and portion sizes" (73, 74). Because of the combined variable of sour cream and cream, sour cream was not included in the analysis of fermented dairy. We also did not include butter in any of our analyses. However, we included quark, even though it was only reported by one participant in "free text".

5.1.3 Collection and processing of data

A preponderance of the demographic, lifestyle, and dietary data collected in this study are self-reported, which can introduce measurement errors. Participants may inaccurately recall information, leading to under or overreporting, and some may provide answers that they believe the researcher wants to hear, rather than their true opinion or experience (82). However, there is no expectation of a systematic difference in the under or over-reporting, or misinterpreted answers by the participants. Additionally, misunderstandings of questions or tasks can result in inconsistent and incorrect responses leading to measurement errors.

To reduce the amount of incorrect and inconsistent answers, participants were contacted by telephone to quality control answers if there were any uncertainties. Additionally, questionnaires with over 75% missing answers were excluded (64). Although participants were instructed to complete the questionnaire before the colonoscopy to minimize information bias, 10% of the participants filled it out after the procedure. Analysis conducted in a previous study in the CRCbiome examined the impact of filling out the questionnaire after the colonoscopy, and only slight variations were discovered (90).

The LDQ used in this study was not validated, unlike the FFQ. As the dietary data was collected from two different questionnaires, this leaves a potential source of recall bias or measurement error, as the participants had the possibility to answer differently at questions measuring the same thing. To minimize this potential error, we examined the correspondence between LDQ and FFQ with Spearman's correlation, which indicated that the LDQ was able to measure dietary intake. Additionally, the LDQ underwent thorough quality control, including manually proofreading 86% of the questionnaires and correcting technical misinterpretations.

5.1.3.1 Methodological considerations of alpha diversity analysis

Only a selection of the study population was selected for DNA extraction and metagenome sequencing due to the capacity of the study. This selection was based on adequate sequencing depth of the available baseline FIT and resulted in 933 samples. The normal distribution of the data was confirmed by a histogram and a Shapiro-Wilk test, which demonstrated a satisfactory distribution for both richness and Inversed Simpson. However, a left-skewed normal distribution and a high value of V in the Shapiro-Wilks test were observed for the Shannon index, which is an indicator of nonnormality. Nevertheless, the population was considered sufficiently large to conduct a one-way ANOVA with planned contrast.

Measuring diversity involves several different measurement errors within each measure. Richness, which is considered the simplest measure by counting the number of individual species, is known for underestimating the true number of species in a sample. On the other hand, the Shannon index is highly sensitive in counting species, particularly in the singleton count, which represents species observed only once (55). The use of three indices compensates for the weakness in each of the indices and provides a more reliable result.

5.1.3.2 Considerations of statistical methods

To assess the association between our exposure and outcome, we conducted a multinomial logistic regression analysis. The multivariate model allowed us to adjust for risk factors and confounders. A one-way ANOVA with planned contrast was used to determine whether there was a significant variation between high and low daily intake of dairy products and alpha

diversity. Even though our study population was sufficiently large to assume a normal distribution, the Shapiro-Wilks test and a histogram of each of the alpha diversity variables were conducted to investigate the distribution of the population.

In the present master's thesis, the association between dairy products and outcome (colorectal lesion groups and alpha diversity) was investigated cross-sectionally, and we cannot determine the causal relationship between exposure and outcome.

5.2 Discussion of results

5.2.1 Associations between intake of total dairy and colorectal lesions

We found a statistically significant association between each increment of daily servings of total dairy products and 7% lower odds of having ACN in the multivariate model. The univariate model did not show any significant association, but after adjusting for confounders, the results changed. The reason for this is uncertain, but it suggests that the confounders included in the multivariate model may have contributed to this effect. This is also consistent with the fact that some of our confounders are known risk factors for CRC (2, 8).

Most previous research on this topic is done on CRC and not colorectal lesions, and there still is little evidence for the association between intake of total dairy and both non-advanced lesions and ACN. However, our findings are in line with those of Emami et al. (2022), who reported that dietary and dairy calcium intake was significantly associated with a reduced risk of colorectal adenoma incidence. They did not find this association for supplementary calcium. For advanced colorectal adenomas, they only investigated calcium intake in general and found a significant risk reduction of advanced colorectal adenomas by calcium (24). This is supported by an older study from 2010, which found calcium intake to be associated with a reduced recurrence of adenomatous lesions (27). To the best of our knowledge, no other studies have investigated the association between calcium or dairy intake and colorectal lesions.

Lopez-Caleya et al. (2022) and Keum et al. (2014) found that a daily intake of 300 mg of calcium was associated with a significant 6% and 8% risk reduction of CRC, respectively (25, 28). This is consistent with our 7% reduced odds of ACN per one increment of dairy serving intake. By combining the three major types of dairy products in our data (fluid milk, yogurt

and cheese), a mean serving consists of 183 mg of calcium per serving. The WCRF found a significant association between both dietary calcium and calcium supplements, and decreased risk of CRC from a daily intake of 200 mg of calcium, and suggest an inverse association up to 1,000 mg daily intake of calcium (2), while Emami et al. (2022) reported an even stronger protective effect up to 1,600 mg daily intake of calcium (24). We conducted a supplementary analysis of daily intake of dietary calcium and ACN (**Appendix 5**) to investigate whether our results were regarding dairy products themselves. No significant association was found in the univariate analysis, however, the multivariate analysis showed significance. This is in line with our analysis on total dairy, that showed no association in the univariate analysis, but significant associations in the multivariate analysis. This provides support for the theory that calcium is the main chemo-preventative mechanism of dairy products (24). However, Emami et al. (2020) observed that the association between calcium intake and colorectal lesions was only present for dietary and dairy calcium, but not supplementary calcium. This was suggested to be caused by levels of vitamin D, as the protective effect of supplementary calcium depends on vitamin D status (24). In addition to calcium, other bioactive compounds in dairy products are also thought to be of importance for CRC risk, but further research is needed to examine their potential effects (2, 26, 38).

As for intake of dairy products and CRC, our results are in line with several other studies and the WCRF, also finding a significant inverse association between intake of total dairy products and CRC (2, 35-37, 39), even though Ralston et al. (2014) only found this association in men (39). As the mechanisms and risk factors of CRC are thoroughly investigated, there is more uncertainty about colorectal lesions. Research from the last decade has identified that risk factors for different types of colorectal lesions, particularly adenomas and serrated lesions, differ slightly from each other. For instance, while increasing age and male sex may not be as strong risk factors for serrated lesions as they are for adenomas, smoking and alcohol are equally predictors for both (17). Additionally, due to the lesions' differences in frequency, severity, time of development, genetic events, and how easy they are to discover (16), more research is needed on colorectal lesions to establish risk factors and protective factors for both serrated lesions and adenomas.

Another interesting aspect is the trend of dairy intake and CRC incidence and mortality over the last decades in Norway. Within the last seven decades, the intake of high-fat milk has dropped by 92%, while low-fat milk has dropped by 44% in the last three decades. The intake of yogurt has increased by 63% over the last two decades, and there has been an increase in

cheese and sour cream/cream intake by 145% and 56% over the last seven decades, respectively (89). Despite the steady increase in CRC incidence and mortality in both women and men over the past seven decades, the incidence of colon cancer has decreased by 5.5% in men and 2.9% in women from 2018 to 2022. Similarly, the incidence of rectal cancer has decreased by 8.8% in men and 8.0% in women in the same period. At the same time, survival has increased in both men and women in the five-year period 2018 to 2022, indicating a decreasing mortality rate (5). Although it takes several years to develop CRC, the combination of a substantial decrease in milk intake and a trend towards lower CRC incidence is intriguing. Referring to our results in fermented dairy and the facts of increasing intake of yoghurt and cheese, it would be interesting to investigate this association in more detail.

5.2.2 Associations between intake of dairy by fat content and colorectal lesions

We did not find any significant association between either low-fat or high-fat dairy and non-advanced lesions or ACN. This could be because of the intake of low-fat and high-fat dairy products in our population. The majority of the population had less than one daily serving of high-fat dairy (85%) and half of the pop had less than one daily serving of low-fat dairy (50%). This may supply too little of both calcium and other bioactive compounds in dairy to detect a potential effect. Additionally, the observed 95% CI for low-fat dairy and ACN was 0.82, 1.00 in both multivariate analyses. A potential explanation for this is our small study sample, which could have contributed to weak statistical power.

Few studies have investigated the association between intake of dairy products by fat content and risk of colorectal lesions or CRC, and most of the existing studies have observed varied associations. Barrubés et al. (2019) found a significant inverse association between high intake of low-fat milk and reduced risk of colon cancer, but no such association was found for intake of low-fat dairy, high-fat dairy, or high-fat milk and CRC. An explanation presented was differences in reported frequency of consumption, as well as total amounts consumed (37). These results are similar to the results from a systematic review from 2022. Alegria-Lertxundi et al. (2022) did also investigate the association between high-fat milk, low-fat yogurt, and high-fat yogurt with CRC, but did not find any significant results. As for other high-fat dairy products, one of the analyzed case-control studies found an association between

intake of cream and colon cancer and an inverse association between intake of ice cream and distal colon cancer, which results in mixed evidence (35). Liu et al. (2021) observed an association between intake of low-fat dairy and reduced overall mortality, while high-fat dairy was associated with increased CRC mortality in a US population (40). Our results, in combination with the existing research, provides limited evidence for concluding with an association between intake of low-fat dairy or high-fat dairy and colorectal lesions.

5.2.3 Associations between intake of fermented dairy and colorectal lesions

We found that intake of fermented dairy was inversely associated with ACN with 27% lower odds for having ACN per increment of one daily serving. No association was found in the analyses including cheese, and no association was found for non-advanced lesions.

There is only one systematic review investigating intake of a fermented dairy and colorectal neoplasia, of our knowledge, where two of the included studies investigated association between intake of yogurt and colorectal lesions specifically (44). The two included studies investigating colorectal lesions observed a probable inverse association between yogurt intake and both colorectal adenomas with high malignant potential and serrated lesions (46), as well as an inverse association between intake of yogurt and large adenomas (≥10 mm) (91). Kim et al. (2022) concluded with a possible inverse association between intake of yogurt and colorectal neoplasia (44). Additionally, a cohort study observed that an intake of dairy products during adolescence was associated with a lower risk of advanced adenomas, but this association was not observed for non-advanced adenomas (48). Further, remaining studies investigated CRC, and some also reported results by location of the tumor additionally.

Barrubés et al. (2019) found no association between the overall intake of fermented dairy and CRC, but they found a significant inverse association between yogurt consumption and risk of CRC. However, because of notable heterogenicity in the studies conducted, these results should be interpreted with caution (37). Veettil et al. (2021) found an inverse association between yogurt consumption and CRC incidence, although they did not find this association for milk or cheese. However, dietary calcium was significantly inverse associated with CRC risk and was presented as a possible explanation of this effect (26). Similar findings were observed by Liang et al. (2020) by an inverse association between intake of yogurt and rectal

cancer (45). The systematic review by Alegria-Lertxundi et al. (2022) found no evidence supporting an association between intake of fermented dairy and CRC (35). However, one of the included cohort studies and one of the included case-control studies both reported an inverse association between intake of yogurt and proximal colon cancer, which is in line with the findings by Kim (2022), Veettil et al. (2021) and Liang et al. (2022) (26, 35, 44, 45). Although these findings regard the intake of yogurt, they are in line with our results of an inverse association between intake of fermented dairy and ACN. The median intake of yogurt in our population was 0.6 daily servings, whereas 50% of the population consumed zero to one daily servings of fermented dairy, and 34% consumed no fermented dairy at all. This means that a large proportion of the daily intake comes from yogurt consumption, which hypothesizes a possible effect of yoghurt.

As for cheese, the WCRF investigated the association between intake of cheese and CRC in their report from 2017 but concluded with inconsistent results and no significant associations (2). Two meta-analyses from 2012 and 2014 reported the same findings, with no association between intake of cheese and CRC (38, 39). Alegria-Lertxundi et al. (2022) did not observe any overall association between intake of cheese and CRC. However, two studies were highlighted for observing an association between high intake of cheese and decreased risk of CRC, as well as an intake of a French type of quark and increased risk of CRC (35). This supports the results from WCRF, by finding inconclusive results for intake of cheese and CRC (2). However, two meta-analyses observed an inverse association between intake of cheese and CRC among included case-control studies, and an inverse association between intake of cheese and proximal colon cancer, respectively (37, 45). Most studies concluded with no significant association between cheese and CRC. Although, our outcome is slightly different, as we investigated colorectal lesions, and our comparison studies are not entirely applicable, they are in line with our findings of no association between intake of cheese and colorectal lesions. Our analysis of fermented dairy including cheese was, however, close to significant (95% CI 0.80, 1.00), and reports a point estimate between fermented dairy and cheese.

5.2.4 Dairy intake and alpha diversity in the gut microbiome

The results showed no correlation between the alpha diversity indices and intake of total dairy products or differences in variance of alpha diversity in the groups of high and low intake of

total dairy products. To our knowledge, only one study has investigated the association between intake of dairy products and diversity in gut microbiome in humans. Swarte et al. (2020) found a significant association between dairy intake and the abundance of specific bacteria in the gut microbiome in middle-aged overweight subjects (62). This is the opposite of our findings. Swarte et al (2020) included 5 daily servings of dairy products for women and 6 daily servings of dairy products for men in the high-dairy group and additionally had larger servings of milk (250 ml) and yogurt (200 g) than in the current master's thesis, which had 200 ml and 125 g, respectively. The low-intake group had a maximum intake of one daily serving of dairy (62). In our study population, the median intake in the high-intake group was 5.6 daily dairy servings, and in the low-intake group 1.9 daily dairy intake servings. The differences in the volume of dairy products between our study and Swarte's are not large, but due to their larger serving sizes, this could potentially be a cause for the difference in association.

5.3 Strengths and limitations

A strength of this thesis is that even though the recruitment took place in a restricted area of Norway, the population was recruited from a general population including individuals aged 55 to 76 years old, all sociodemographic factors, and both sexes. This gives a good representation of the screening population. We used a validated FFQ and supplemented data about fermented milk from LDQ. This provided dietary data of high quality. Our analyzes investigated several groups of dairy products, which provided a thorough evaluation of dairy consumption in our data.

On the other side, observational studies in general have limitations. The results only found an association between exposure and outcome but cannot conclude causal connections. Even though the multivariate analysis could reveal the true association between total dairy and fermented dairy intake and ACN, it is necessary to replicate these findings for confirmation, as there is uncertainty whether CRC and ACN are related to all the same confounders. Another matter is that the participants were asked to recall their diet representing the past year. If the participants have changed their diet during recent years, this is of importance for our results, as most colorectal lesions and CRC develop over 10 years or more. This leads to uncertainty about whether the reported diet is relevant for the lesions detected during

colonoscopy. Another limitation of the assessment of dietary intake is that our variables are collected from two separate questionnaires, and only the FFQ was validated for dietary intake. Even though the LDQ was thoroughly quality controlled, it was not validated in the same way as the FFQ. Lastly, while the univariate analysis did not find any significant association between intake of total dairy and ACN, a significant association was observed in the multivariate analysis. Although this is not necessarily a limitation, it is unusual and may be related to the influence of confounders or other unknown factors.

5.3.1 Further perspectives

This master's thesis has contributed valuable information about different types of dairy products and their association with colorectal lesions. For further research, it is necessary to investigate the similar association in larger and more generalizable populations, as well as in prospective studies. Additionally, there are several unknown aspects of the mechanisms of all bioactive compounds found in dairy products, which highlights the need for trials to investigate these compounds.

As a secondary outcome, we investigated the differences in variance of alpha diversity between participants with high and low daily intake of total dairy products. Further, as we did not find any association between dairy and alpha diversity, it is interesting to investigate whether there is an association between fermented dairy and alpha diversity, more specifically, as this result found an even stronger association with ACN than the total dairy analysis. Another perspective is to investigate whether the intake of dairy products or fermented dairy products is associated with specific bacteria in the gut microbiome.

6 Conclusion

Intake of dairy products is known to be associated with the risk of CRC. The increasing global incidence of CRC underscores the importance of identifying modifiable risk factors for its precursor lesions. The main aim of this master's thesis was to investigate the association between dairy intake and CRC screening findings in a FIT-positive population.

- The first specific aim was to investigate whether there was an association between intake of total dairy products and colorectal lesions. We observed a significant association between each increment of daily servings of total dairy products and 7% lower odds of having ACN.
- The second specific aim was to investigate whether there was a different association between low-fat and high-fat dairy products and colorectal lesions. No differences in the associations were observed.
- The third specific aim was to investigate whether the intake of fermented dairy products was associated with colorectal lesions. We observed a significant association between each increment of daily servings of fermented dairy products and 27% lower odds of having ACN.
- The fourth specific aim was to investigate whether alpha diversity in the gut microbiome differs between persons who have a high and a low intake of total dairy. No significant associations were observed.

No associations were observed for non-advanced lesions. The findings of this master's thesis demonstrate a significant inverse association between intake of total dairy and ACN, and separately for intake of fermented dairy in a FIT-positive CRC screening population. The results support the evidence for an association between dairy intake and CRC risk and add support to the hypothesis that dairy intake is beneficial in reducing the risk of precancerous colorectal lesions. Given the potential public health implication of these findings, larger prospective studies are needed to investigate the effects of different dairy products on risk of colorectal lesions.

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Appendix

Appendix 1: Invitation to the CRCbiome study

*lopenummer* / _*ref_nr*_
navn
adresse

Oslo, _kort_dato_

DELTAKELSE I FORSKNINGSPROSJEKTET

STUDIE AV TARMBAKTERIER OG LIVSSTIL VED TARMSCREENING

Du mottar dette brevet fordi du har levert en avføringsprøve med blod og er invitert til en koloskopiundersøkelse i forbindelse med screening. I forbindelse med dette ønsker vi å invitere deg til å delta i et forskningsprosjekt for å studere om det er en forbindelse mellom tarmbakterier (tarmfloraen), livsstil og forekomst av polypper.

Dette er et tilleggsprosjekt til selve screeningen og din eventuelle deltakelse har ingen betydning for det tilbudet du får i screeningundersøkelsen. Målsettingen med dette tilleggsprosjektet er å finne ut hvilken betydning tarmbakteriene kan ha på tarmkreftrisikoen. Vi vil også undersøke om det er sammenheng mellom kosthold og livsstil, tarmflora og tarmkreftutvikling. Da kan vi forbedre råd om forebygging av kreft samt øke nøyaktigheten på testene.

Mer informasjon om prosjektet finner du på vår hjemmeside *kreftregisteret.no/crc-biome*

Ved spørsmål ta kontakt via e-post tarmkreftscreening@kreftregisteret.no eller telefon **22 45 13 00** (telefontid fra kl. 8.30 til 11.30).

HVA INNEBÆRER PROSJEKTET?

Deltagelse innebærer at du fyller ut to spørreskjemaer før din koloskopiundersøkelse, og tar to avføringsprøver i løpet av året som kommer.

Vi ber om at du fyller ut de to vedlagte spørreskjemaene, og returnerer dem i den frankerte svarkonvolutten eller tar dem med deg når du kommer til koloskopiundersøkelsen. Vi vil kontakte enkelte deltagere per telefon ved behov for utfyllende informasjon. Skjemaene tar totalt ca. en time å fylle ut.

Avføringsprøvene skal tas og sendes på samme måte som du gjorde i screeningundersøkelsen. Den første prøven skal tas ca. to måneder, og den andre ca. et år etter din koloskopiundersøkelse. Prøvetakingsutstyret vil bli sendt til deg i posten.

I prosjektet vil vi innhente og registrere opplysninger om deg. Vi vil registrere funn fra koloskopiundersøkelsen, avføringsprøvene og svar fra spørreskjemaene, og sammenstille disse med data fra hovedundersøkelsen Screening mot tarmkreft - forprosjekt. Opplysningene vil kobles mot sentrale helseregister slik som Kreftregisteret og Reseptregisteret.

MULIGE FORDELER OG ULEMPER

Du vil ikke ha noen direkte fordeler av å delta i studien. Resultater fra studien kan lede frem til ny og viktig kunnskap som kan gi bedre screeningverktøy i fremtiden.

Studien innebærer ingen ulemper for deg som deltager utover medgått tid til å fylle ut spørreskjemaene og avgi avføringsprøvene.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for din koloskopiundersøkelse. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte sekretariatet for tarmkreftscreening på Kreftregisteret med e-post: **tarmscreening@kreftregisteret.no** eller telefon nr. **22 45 13 00** (sentralbordet, telefontid ved tarmscreeningseksjonen er fra kl. 8.30 til 11.30).

HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Informasjon om deg vil bli anonymisert eller slettet senest fem år etter prosjektslutt.

HVA SKJER MED PRØVER SOM BLIR TATT AV DEG?

Avføringsprøvene du sender inn skal oppbevares i tarmscreeningens forskningsbiobank sammen med resten av prøvene fra *Screening mot tarmkreft - forprosjekt*.

Avføringsprøvene fryses og lagres slik at de kan brukes til å teste om det er andre substanser i avføringen som kan brukes til å påvise kreft eller kreftrisiko.

Disse analysene vil bli utført av våre samarbeidspartner. Informasjon om prosjektet vil publiseres på vår hjemmeside *kreftregisteret.no/crc-biome*

HVA SLAGS INFORMASJON KAN UNDERSØKELSENE I PROSJEKTET GI?

Avføringsprøvene og funn i koloskopiundersøkelsen skal, sammen med informasjonen fra spørreskjemaene, brukes til å undersøke bakterier og andre biomarkører (mikroRNA). Studien inneholder ikke analyser av arvemateriale (DNA).

FORSIKRING

Som deltaker i studien er du forsikret som enhver vanlig pasient i det offentlige helsevesen (pasientskadeerstatningsordningen).

OPPFØLGINGSPROSJEKT

Som deltakere i denne studien vil du kunne bli kontaktet igjen for å delta i oppfølgningsprosjekter.

GODKJENNING

Prosjektet er godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk (saksnr. 2011/1272).

Tusen takk for hjelpen!

Med vennlig hilsen

Øyvind Holme, leder, overlege
Pilotprosjektet for tarmscreening

Trine B. Rounge, forsker
Kreftregisteret

Paula Berstad, forsker
Kreftregisteret

Ved spørsmål ta kontakt via e-post **tarmscreening@kreftregisteret.no** eller telefon 22 45 13 00
(telefontid ved tarmscreeningseksjonen er fra kl. 8.30 til 11.30).

Besøk vår hjemmeside *kreftregisteret.no/crc-biome*

Appendix 2: Food Frequency Questionnaire (FFQ)

Prøv så godt du kan å gi et "gjennomsnitt" av dine spisevaner.
Ha det siste året i tankene når du fyller ut.

1. Hvor mye brød pleier du å spise?

Legg sammen det du bruker til alle måltider i løpet av en dag.
(1/2 rundstykke = 1 skive, 1 baguett = 4 skiver, 1 ciabatta = 2 skiver)

	Aldri/ sjelden	Antall skiver pr. dag ½	1	2	3	4	5	6	7	8	9	10	11	12+
Fint brød (loff, baguetter, fine rundstykker, ciabatta)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Mellomgrovt brød (helkornbrød, kneipp, grove rundstykker)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grovt brød (mer enn 50 % sammalt, mørkt rugbrød)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fint knekkebrød (kavring)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grovt knekkebrød (grov skonrok)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Sum skiver pr. dag = _____

Antall skiver pr. uke: _____ x 7 = _____. Tallet brukes i spørsmål 4.
(sum skriver pr. dag)

2. Hva pleier du å smøre på brødet?

Legg sammen det du bruker på skivene i løpet av en uke.
(1/2 rundstykke = 1 skive, 1 baguett = 4 skiver, 1 ciabatta = 2 skiver)

	Aldri/ sjelden	Antall skiver pr. uke 1-5	6-14	15-21	22-28	29-35	36-42	43-49	50-56	57+
Smør (meierismør)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Bremykt	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Brelett	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Myk margarin (Soft Flora, Soft Ekstra)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Soft Oliven	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Vita	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Soft Light, Vita Lett	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Melange	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Annen margarin	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Olivenolje, annen olje på brød	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Majones, remulade på brød	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

3. Hvis du bruker smør/margarin på brødet, hvor mye bruker du?

	Antall skiver ½	1	2	3	4	5 eller flere
En porsjonspakke smør/margarin på 12 g rekker til antall skiver:	☐	☐	☐	☐	☐	☐

4. Hvilke typer pålegg spiser du?

	Aldri/ sjelden	Antall skiver pr. uke 1	2-3	4-5	6-7	8-12	13-18	19-24	25-30	31+
Brunost/prim	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lett/mager brunost/prim	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Hvitost (eks. Norvegia, Gulost)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lett/mager hvitost	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Dessertost (eks. Brie, Gräddost, blåmuggoster)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Smøreost (eks. kremost, Philadelfia)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lett/mager smøreost	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Leverpostei	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Mager leverpostei	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Servelat	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kokt skinke, lettservelat, kalkunpålegg	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Salami, fårepølse, spekepølse	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kaviar	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Svolværpostei, Lofotpostei	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Makrell i tomat	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Røkt, gravet laks/ørret	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sardiner, sursild, ansjos	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Tunfisk	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Reker, krabbe	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Egg (kokt, stekt, eggerøre)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Syltetøy, marmelade	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lett syltetøy, frysetøy	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Peanøttsmør	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sjokolade-, nøttepålegg	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Annet søtt pålegg (eks. honning, Sunda, sirup)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cottage cheese	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Majonessalat (eks. italiensk salat)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Majonessalat lett (eks. lett italiensk salat)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Frukt som pålegg (eks. banan, eple)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grønnsaker som pålegg (eks. agurk, tomat)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

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Prøv så godt du kan å gi et "gjennomsnitt" av dine spisevaner.
Ha det siste året i tankene når du fyller ut.

5. Frokostgryn

Svar enten per måned eller per uke.

	Aldri/ sjelden	Gang pr. måned 1	2	3	eller 1	Gang pr. uke 2-3	4-5	6-7	8+		Mengde pr. gang 1	1½	2	3+
Havregrøt	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
Havregryn, 4-korn	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
Mysli, søtet (eks. Solfrokost)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
Mysli, usøtet (eks. Go'Dag)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
Cornflakes	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
Honnikorn/Frosties/Chocofrokost	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
All Bran, Weetabix, Havrefras o.l.	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
Puffet ris, havrenøtter	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐
	Aldri/ sjelden	**Gang pr. måned 1**	**2**	**3**	**eller 1**	**Gang pr. uke 2-3**	**4-5**	**6-7**	**8+**		**Mengde pr. gang 1**	**1½**	**2**	**3+**
Syltetøy til frokostgryn, grøt	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐
Sukker til frokostgryn, grøt	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ts)	☐	☐	☐	☐

6. Melk (Husk også å ta med melk du bruker på frokostgryn, grøt og dessert)

(1 glass = 2 dl)

	Aldri/ sjelden	Antall glass pr. dag ½	1	2	3	4	5	6	7+
Helmelk, kefir, kultur	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lettmelk	☐	☐	☐	☐	☐	☐	☐	☐	☐
Ekstra lettmelk	☐	☐	☐	☐	☐	☐	☐	☐	☐
Skummet melk, skummet kultur	☐	☐	☐	☐	☐	☐	☐	☐	☐
Biola/Cultura naturell	☐	☐	☐	☐	☐	☐	☐	☐	☐
Biola/Cultura med bær/frukt	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sjokolademelk, jordbærmelk	☐	☐	☐	☐	☐	☐	☐	☐	☐
Drikkeyoghurt	☐	☐	☐	☐	☐	☐	☐	☐	☐

7. Yoghurt (Husk å ta med yoghurt du bruker til frokostgryn)

Svar enten per måned eller per uke.

	Aldri/ sjelden	Gang pr. måned 1	2	3	eller 1	Gang pr. uke 2-3	4-5	6-7	8+	Beger pr. gang ½	1	2	3+
Yoghurt naturell (125 g)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Yoghurt med frukt (125 g)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Go'morgen yoghurt m/mysli	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lettyoghurt med frukt (125 g)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lettyoghurt m/mysli	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

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8. Kalde drikker

Svar enten per uke eller per dag, <1 betyr sjeldnere enn 1 gang. Merk at porsjonsenhetene er forskjellige, 1/5 liter tilsvarer ett glass (2 dl), mens 1/3 liter tilsvarer 0,33 liter glassflaske/boks.

	Aldri/ sjelden	Gang pr. uke <1	1-2	3-4	5-6	eller	Gang pr. dag 1	2	3	4+	Mengde pr. gang				
Vann (springvann)	☐	☐	☐	☐	☐		☐	☐	☐	☐	(glass)	1 ☐	2 ☐	3 ☐	4+ ☐
Flaskevann med/uten kullsyre (eks. Farris, Imsdal)	☐	☐	☐	☐	☐		☐	☐	☐	☐	(liter)	1/5 ☐	1/3 ☐	½ ☐	1+ ☐
Appelsinjuice	☐	☐	☐	☐	☐		☐	☐	☐	☐	(glass)	1 ☐	2 ☐	3 ☐	4+ ☐
Eplejuice, annen juice	☐	☐	☐	☐	☐		☐	☐	☐	☐	(glass)	1 ☐	2 ☐	3 ☐	4+ ☐
Eplenektar, annen nektar	☐	☐	☐	☐	☐		☐	☐	☐	☐	(glass)	1 ☐	2 ☐	3 ☐	4+ ☐
Saft med sukker	☐	☐	☐	☐	☐		☐	☐	☐	☐	(glass)	1 ☐	2 ☐	3 ☐	4+ ☐
Saft, kunstig søtet	☐	☐	☐	☐	☐		☐	☐	☐	☐	(glass)	1 ☐	2 ☐	3 ☐	4+ ☐
Brus med sukker	☐	☐	☐	☐	☐		☐	☐	☐	☐	(liter)	1/5 ☐	1/3 ☐	½ ☐	1+ ☐
Brus, kunstig søtet	☐	☐	☐	☐	☐		☐	☐	☐	☐	(liter)	1/5 ☐	1/3 ☐	½ ☐	1+ ☐
Iste med sukker	☐	☐	☐	☐	☐		☐	☐	☐	☐	(liter)	1/5 ☐	1/3 ☐	½ ☐	1+ ☐
Iste, kunstig søtet	☐	☐	☐	☐	☐		☐	☐	☐	☐	(liter)	1/5 ☐	1/3 ☐	½ ☐	1+ ☐
Alkoholfritt øl (eks. Vørterøl, Munkholm)	☐	☐	☐	☐	☐		☐	☐	☐	☐	(liter)	1/5 ☐	1/3 ☐	½ ☐	1+ ☐

9. Alkoholholdige drikker

Svar enten pr. måned eller pr. uke. Merk at porsjonsenhetene er forskjellige, 1/5 liter tilsvarer ett glass (2 dl), mens 1/3 liter tilsvarer 0,33 liter glassflaske/boks.

	Aldri/ sjelden	Gang pr. måned 1	2	3	eller	Gang pr. uke 1	2-3	4-5	6-7	Mengde pr. gang						
Øl, sterk øl, pils	☐	☐	☐	☐		☐	☐	☐	☐	(liter)	1/3 ☐	½ ☐	1 ☐	2 ☐	3 ☐	4+ ☐
Lettøl	☐	☐	☐	☐		☐	☐	☐	☐	(liter)	1/3 ☐	½ ☐	1 ☐	2 ☐	3 ☐	4+ ☐
Rusbrus, Cider m/alkohol	☐	☐	☐	☐		☐	☐	☐	☐	(liter)	1/5 ☐	1/3 ☐	½ ☐	1 ☐	1½ ☐	2+ ☐
Rødvin	☐	☐	☐	☐		☐	☐	☐	☐	(vinglass)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐
Hvitvin	☐	☐	☐	☐		☐	☐	☐	☐	(vinglass)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐
Hetvin (portvin, sherry o.l.)	☐	☐	☐	☐		☐	☐	☐	☐	(1 glass = 4cl)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐
Brennevin, likør	☐	☐	☐	☐		☐	☐	☐	☐	(1 dram = 4cl)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐
Blandede drinker, cocktail	☐	☐	☐	☐		☐	☐	☐	☐	(drink)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6+ ☐

Prøv så godt du kan å gi et "gjennomsnitt" av dine spisevaner.
Ha det siste året i tankene når du fyller ut.

10. Varme drikker

Svar enten per uke eller per dag, < 1 betyr sjeldnere enn 1 gang.

	Aldri/ sjelden	Gang pr. uke <1	1-2	3-4	5-6	eller 1	Gang pr. dag 2	3	4+	Mengde pr. gang (kopp) 1	2	3-4	5-6	7-8	9+
Kaffe - kokt og presskanne *1 kopp = 2 dl*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kaffe - traktet, filter *1 kopp = 2 dl*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kaffe - pulver (instant) *1 kopp = 2 dl*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Espresso *1 kopp = 0,3 dl*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Caffe latte *1 kopp = 3 dl*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cappucino *1 kopp = 3 dl*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kakao/varm sjokolade *1 kopp = 2 dl*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sort te (eks. Earl Grey, solbær) *1 kopp = 2 dl*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grønn te *1 kopp = 2 dl*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Urtete (eks. nype, kamille, Rooibois) *1 kopp = 2 dl*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

	Bruker ikke	Antall pr. kopp ½	1	2	3	4+
Sukker til te (ts/sukkerbit)	☐	☐	☐	☐	☐	☐
Sukker til kaffe (ts/sukkerbit)	☐	☐	☐	☐	☐	☐
Sukketter til te (stk)	☐	☐	☐	☐	☐	☐
Sukketter til kaffe (stk)	☐	☐	☐	☐	☐	☐
Melk/fløte til te (ss)	☐	☐	☐	☐	☐	☐
Melk/fløte til kaffe (ss)	☐	☐	☐	☐	☐	☐

11. Middagsretter

Vi spør både om middagsmåltidene og det du spiser til andre måltider. Legg til slutt sammen hvor mange retter per måned du har merket av for å se om summen virker sannsynlig.

	Aldri/ sjelden	Gang pr. måned 1	2	3	4	5-6	7-8	9+	Mengde pr. gang					
Kjøtt/kjøttretter														
Kjøttpølse av storfe/svin	☐	☐	☐	☐	☐	☐	☐	☐	(pølse)	½ ☐	1 ☐	1½ ☐	2 ☐	3+ ☐
Kjøttpølse av storfe/svin, lett/mager	☐	☐	☐	☐	☐	☐	☐	☐	(pølse)	½ ☐	1 ☐	2 ☐	3 ☐	4+ ☐
Kjøttpølse av kylling/kalkun	☐	☐	☐	☐	☐	☐	☐	☐	(pølse)	½ ☐	1 ☐	2 ☐	3 ☐	4+ ☐
Grillpølse/wienerpølse av storfe/svin	☐	☐	☐	☐	☐	☐	☐	☐	(pølse)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Grillpølse/wienerpølse av kylling/kalkun	☐	☐	☐	☐	☐	☐	☐	☐	(pølse)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Hamburger (m/brød)	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Karbonade	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Kjøttkaker, medisterkaker, kjøttpudding	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Kjøttsaus, gryterett med kjøttdeig	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Taco (tacoskjell med kjøtt og salat)	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Tortilla lefse (med kjøtt og salat)/ wrap	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Kebab	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	½ ☐	1 ☐	1½ ☐	2 ☐	3+ ☐
Lasagne, moussaka	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Pizza (en Grandiosa = ca 550 g)	☐	☐	☐	☐	☐	☐	☐	☐	(pizza)	1/8 ☐	1/4 ☐	½ ☐	3/4 ☐	1+ ☐
Calzone (1 stk = 250-300 g)	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	½ ☐	1 ☐	1½ ☐	2 ☐	2½+ ☐
Pai/quiche	☐	☐	☐	☐	☐	☐	☐	☐	(bit)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Vårruller	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Biff (svin, okse, lam)	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	½ ☐	1 ☐	1½ ☐	2 ☐	2½+ ☐
Koteletter (svin, okse, lam)	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	½ ☐	1 ☐	1½ ☐	2 ☐	2½+ ☐
Stek (svin, okse, lam)	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Stek (elg, hjort, reinsdyr, rådyr)	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Gryterett med helt kjøtt, frikassé, fårikål	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Lapskaus, suppelapskaus, betasuppe	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐

Middagsretter fortsetter neste side.....

Prøv så godt du kan å gi et "gjennomsnitt" av dine spisevaner.
Ha det siste året i tankene når du fyller ut.

Middagsretter forts...

	Aldri/ sjelden	Gang pr. måned 1	2	3	4	5-6	7-8	9+	Mengde pr. gang	1-2	3-4	5-6	7-8	9+
Kjøtt/kjøttretter forts...														
Bacon, stekt flesk	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	☐	☐	☐	☐	☐
Grillet kylling	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	¼ ☐	⅓ ☐	½ ☐	¾ ☐	1+ ☐
Kyllingfilet	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	½ ☐	1 ☐	1½ ☐	2 ☐	3+ ☐
Wok med kjøtt/kylling og grønnsaker	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Kyllinggryte	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Fisk/fiskeretter														
Fiskekaker, fiskepudding	☐	☐	☐	☐	☐	☐	☐	☐	(kake)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Fiskeboller	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1-2 ☐	3-4 ☐	5-6 ☐	7-9 ☐	10+ ☐
Torsk, sei, hyse, steinbit, uer (kokt)	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Torsk, sei, hyse, steinbit, uer (stekt, panert)	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Fiskepinner	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1-2 ☐	3-4 ☐	5-6 ☐	7-9 ☐	10+ ☐
Sild (fersk, speket, røkt)	☐	☐	☐	☐	☐	☐	☐	☐	(filet)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Makrell (fersk, røkt)	☐	☐	☐	☐	☐	☐	☐	☐	(filet)	½ ☐	1 ☐	1½ ☐	2 ☐	3+ ☐
Laks, ørret (kokt, stekt)	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Fiskegryte, fiskesuppe	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Fiskegrateng	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Reker, krabbe	☐	☐	☐	☐	☐	☐	☐	☐	(dl, renset)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Wok med sjømat og grønnsaker	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Annet														
Rømmegrøt	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Risengrynsgrøt, annen melkegrøt	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Pannekaker	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Suppe (tomat, blomkål, ertesuppe)	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Vegetarrett, vegetarpizza, grønnsaksgrateng	☐	☐	☐	☐	☐	☐	☐	☐	(bit/dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Hurtignudler (eks. Mr Lee)	☐	☐	☐	☐	☐	☐	☐	☐	(pakke)	½ ☐	1 ☐	1½ ☐	2 ☐	3+ ☐
Omelett	☐	☐	☐	☐	☐	☐	☐	☐	(av antall egg)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐

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12. Poteter, ris, spagetti, grønnsaker

Svar enten per måned eller per uke.
Disse spørsmålene dreier seg først og fremst om tilbehør til middagsretter, men spiser du for eksempel en rå gulrot eller salat til lunsj, skal det tas med her.

	Aldri/ sjelden	Gang pr. måned 1	2	3	eller 1	Gang pr. uke 2-3	4-5	6-7	8+		Mengde pr. gang				
Poteter, kokte og bakte	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Potetmos	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Potetsalat m/majones	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	1 ☐	2-3 ☐	4-5 ☐	6-7 ☐	8+ ☐
Fløtegratinerte poteter	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Stekte poteter	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Pommes frites (gatekjøkken, frityrstekt)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Pommes frites, varmet i ovn	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Bønner/linser	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Ris	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Spagetti, makaroni, pasta	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Pølsebrød, lomper	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Gulrot	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Hodekål	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skalk)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Kålrot	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	1/2 ☐	1 ☐	2 ☐	3 ☐	4+ ☐
Blomkål	☐	☐	☐	☐	☐	☐	☐	☐	☐	(hode)	1/8 ☐	1/6 ☐	1/4 ☐	1/3 ☐	1/2+ ☐
Brokkoli	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/8 ☐	1/4 ☐	1/2 ☐	3/4 ☐	1+ ☐
Rosenkål	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Løk, rå og stekt	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Salat (eks. issalat, ruccola)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1/2 ☐	1 ☐	1 1/2 ☐	2 ☐	2 1/2+ ☐
Paprika	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ring)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Avokado	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/4 ☐	1/2 ☐	3/4 ☐	1 ☐	1 1/2+ ☐
Tomat	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	1 1/2 ☐	2 ☐	2 1/2+ ☐
Mais	☐	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Frosne grønnsakblandinger	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐
Blandet salat (eks. salat, tomat, agurk, mais)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4 ☐	5+ ☐

Prøv så godt du kan å gi et "gjennomsnitt" av dine spisevaner.
Ha det siste året i tankene når du fyller ut.

13. Saus og dressing

	Aldri/ sjelden	Gang pr. måned 1	2	3	4	5-6	7-8	9+		Mengde pr. gang ½	1	1½	2	3+
Brun/hvit saus	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐	☐
Bearnéssaus, hollandés	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	☐	☐	☐	☐	☐
Smeltet margarin/smør	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐
Kryddersmør	☐	☐	☐	☐	☐	☐	☐	☐	(ts)	☐	☐	☐	☐	☐
Majones/remulade vanlig	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐
Majones/remulade lett	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐
Seterrømme (35 % fett)	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐
Lettrømme (20 % fett)	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐
Ekstra lett rømme (10 % fett)	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐
Dressing (eks. Thousand Island)	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐
Lett dressing (eks. lett Thousand Island)	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐
Oljedressing, vinagrette	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐
Soyasaus	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐
Pesto	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐
Tomatsaus, salsa	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	1-2 ☐	3-4 ☐	5-6 ☐	7-8 ☐	9+ ☐
Ketchup	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐
Sennep	☐	☐	☐	☐	☐	☐	☐	☐	(ss)	☐	☐	☐	☐	☐

14. Hvilken type smør/margarin/olje bruker du mest til matlaging?

(Velg en eller to typer)

Smør/margarin	Oljer
☐ Smør (meierismør)	☐ Olivenolje
☐ Bremykt	☐ Soyaolje
☐ Melange	☐ Maisolje
☐ Soft Flora, Soft Ekstra	☐ Solsikkeolje
☐ Vita	☐ Valnøttolje
☐ Soft Oliven	☐ Rapsolje
☐ Flytende margarin på flaske (Vita, Melange, Bremykt o.l.)	☐ Vita hjertego
☐ Annen margarin	☐ Andre oljer

15. Frukt

Svar enten per måned eller per uke.

	Aldri/ sjelden	Gang pr. måned 1	2	3	eller 1	Gang pr. uke 2-3	4-5	6-7	8+		Mengde pr. gang			
Eple	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Pære	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Banan	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Appelsin	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Klementiner	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4+ ☐
Grapefrukt	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Fersken, nektarin	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4+ ☐
Kiwi	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4+ ☐
Druer	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1-10 ☐	11-20 ☐	21-40 ☐	41+ ☐
Melon	☐	☐	☐	☐	☐	☐	☐	☐	☐	(skive)	1 ☐	2 ☐	3 ☐	4+ ☐
Jordbær (friske, frosne)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Bringebær (friske, frosne)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Blåbær	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Multer	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Rosiner	☐	☐	☐	☐	☐	☐	☐	☐	☐	(dl)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Tørket frukt (eks. aprikos, fiken)	☐	☐	☐	☐	☐	☐	☐	☐	☐	(stk)	1-5 ☐	6-10 ☐	11-15 ☐	16+ ☐
Frukt- og nøtteblanding	☐	☐	☐	☐	☐	☐	☐	☐	☐	(neve)	1 ☐	2 ☐	3 ☐	4+ ☐

16. Grønnsaker og frukt

Hvor mange porsjoner grønnsaker (utenom potet) spiser du vanligvis pr. dag? (En porsjon er f. eks. 1 gulrot, 1 bolle salat)

Mindre enn 1 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5+ ☐

Hvor mange frukt spiser du vanligvis pr. dag?

Mindre enn 1 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5+ ☐

Prøv så godt du kan å gi et "gjennomsnitt" av dine spisevaner.
Ha det siste året i tankene når du fyller ut.

17. Desserter, kaker, godteri

Svar enten per måned eller per uke.

	Aldri/ sjelden	Gang pr. måned 1	2	3	eller	Gang pr. uke 1	2-3	4-5	6-7	8+		Mengde pr. gang			
Iskrem (1 dl=1 pinne=1 kremmerhus)	☐	☐	☐	☐		☐	☐	☐	☐	☐	(dl)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Saftis/sorbet (1 dl=1 pinne)	☐	☐	☐	☐		☐	☐	☐	☐	☐	(dl)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Hermetisk frukt, fruktgrøt	☐	☐	☐	☐		☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4+ ☐
Frisk fruktsalat	☐	☐	☐	☐		☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4+ ☐
Pudding (eks. sjokolade, karamell)	☐	☐	☐	☐		☐	☐	☐	☐	☐	(dl)	1 ☐	2 ☐	3 ☐	4+ ☐
Vaniljesaus	☐	☐	☐	☐		☐	☐	☐	☐	☐	(dl)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Pisket krem	☐	☐	☐	☐		☐	☐	☐	☐	☐	(ss)	1 ☐	2 ☐	3 ☐	4+ ☐
Boller, julekake, kringle	☐	☐	☐	☐		☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Skolebrød, skillingsbolle	☐	☐	☐	☐		☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Wienerbrød, -kringle	☐	☐	☐	☐		☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Muffins, formkake	☐	☐	☐	☐		☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Vafler	☐	☐	☐	☐		☐	☐	☐	☐	☐	(plate)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Lefse, påsmurt	☐	☐	☐	☐		☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Sjokoladekake, brownie	☐	☐	☐	☐		☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Marsipankake, bløtkake	☐	☐	☐	☐		☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Søt kjeks, kakekjeks (eks. Cookies, Bixit, Hob Nobs)	☐	☐	☐	☐		☐	☐	☐	☐	☐	(stk)	1-2 ☐	3-4 ☐	5-6 ☐	7+ ☐
Kokosbolle	☐	☐	☐	☐		☐	☐	☐	☐	☐	(stk)	1 ☐	2 ☐	3 ☐	4+ ☐
Sjokolade (60 g) (eks. melkesjokolade, snickers)	☐	☐	☐	☐		☐	☐	☐	☐	☐	(stk)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Mørk sjokolade (70% kakao)	☐	☐	☐	☐		☐	☐	☐	☐	☐	(biter)	1-3 ☐	4-6 ☐	7-9 ☐	10+ ☐
Sjokoladebiter/konfekt	☐	☐	☐	☐		☐	☐	☐	☐	☐	(stk)	1-3 ☐	4-6 ☐	7-9 ☐	10+ ☐
Pastiller uten sukker	☐	☐	☐	☐		☐	☐	☐	☐	☐	(stk)	1-3 ☐	4-6 ☐	7-9 ☐	10+ ☐
Drops, pastiller, lakris, seigmenn	☐	☐	☐	☐		☐	☐	☐	☐	☐	(stk)	1-3 ☐	4-6 ☐	7-9 ☐	10+ ☐
Smågodt (1 hg = 100g)	☐	☐	☐	☐		☐	☐	☐	☐	☐	(hg)	1/2 ☐	1 ☐	2 ☐	3+ ☐
Potetgull	☐	☐	☐	☐		☐	☐	☐	☐	☐	(neve)	1-2 ☐	3-5 ☐	6-10 ☐	11+ ☐
Annen snacks (skruer, crisp, saltstenger, lettsnacks o.l.)	☐	☐	☐	☐		☐	☐	☐	☐	☐	(neve)	1-2 ☐	3-5 ☐	6-10 ☐	11+ ☐
Peanøtter, cashewnøtter (1 neve = 25 gram)	☐	☐	☐	☐		☐	☐	☐	☐	☐	(neve)	1-2 ☐	3-4 ☐	5-6 ☐	7+ ☐
Mandler, hasselnøtter, valnøtter (1 neve = 25 gram)	☐	☐	☐	☐		☐	☐	☐	☐	☐	(neve)	1-2 ☐	3-4 ☐	5-6 ☐	7+ ☐

18. Kosttilskudd (ts = teskje, bs = barneskje)

	Aldri/ sjelden	Gang pr. uke 1	2-3	4-5	6-7	Mengde pr. gang			
Tran	☐	☐	☐	☐	☐		1 ts ☐	1 bs ☐	1 ss ☐
Trankapsler	☐	☐	☐	☐	☐	(kapsler)	1 ☐	2 ☐	3 ☐	4+ ☐
Fiskeoljekapsler, omega-3 tilskudd	☐	☐	☐	☐	☐	(kapsler)	1 ☐	2 ☐	3 ☐	4+ ☐
Seloljekapsler	☐	☐	☐	☐	☐	(kapsler)	1 ☐	2 ☐	3 ☐	4+ ☐
Multipreparater	**Aldri/ sjelden**	**Gang pr. uke 1**	**2-3**	**4-5**	**6-7**	**Mengde pr. gang**	**1**	**2**	**3**	**4+**
Sana-sol	☐	☐	☐	☐	☐	(bs)	☐	☐	☐	☐
Biovit	☐	☐	☐	☐	☐	(bs)	☐	☐	☐	☐
Mulitvitamin og mineral (eks. Vitamineral)	☐	☐	☐	☐	☐	(tablett)	☐	☐	☐	☐
Multivitaminer (uten mineraler)	☐	☐	☐	☐	☐	(tablett)	☐	☐	☐	☐
Jernpreparater	**Aldri/ sjelden**	**Gang pr. uke 1**	**2-3**	**4-5**	**6-7**	**Mengde pr. gang**	**1**	**2**	**3**	**4+**
Duroferon Duretter, Ferromax	☐	☐	☐	☐	☐	(tablett)	☐	☐	☐	☐
Hemofer, hemjern	☐	☐	☐	☐	☐	(tablett)	☐	☐	☐	☐
Amino Jern	☐	☐	☐	☐	☐	(tablett)	☐	☐	☐	☐
Jernmikstur (eks. Floradix)	☐	☐	☐	☐	☐	(bs)	☐	☐	☐	☐
Annet	**Aldri/ sjelden**	**Gang pr. uke 1**	**2-3**	**4-5**	**6-7**	**Mengde pr. gang**	**1**	**2**	**3**	**4+**
B-vitaminer (flere b-vitaminer i samme tablett)	☐	☐	☐	☐	☐	(tablett)	☐	☐	☐	☐
C-vitamin (60 mg/tablett)	☐	☐	☐	☐	☐	(tablett)	☐	☐	☐	☐
D-vitamin (10 µg/tablett)	☐	☐	☐	☐	☐	(tablett)	☐	☐	☐	☐
E-vitamin (30 mg/tablett)	☐	☐	☐	☐	☐	(tablett)	☐	☐	☐	☐
Folat (folsyre) (200 µg/tablett)	☐	☐	☐	☐	☐	(tablett)	☐	☐	☐	☐

Annet (inkludert helsekostpreparater). Noter navn på preparatet, hvor ofte og hvor mye du tar pr. gang.

19. Måltider

Hvor ofte pleier du å spise følgende måltider i løpet av en uke? (Sett ett kryss for hvert måltid)

	Aldri/ sjelden	1 gang i uken	2 ganger i uken	3 ganger i uken	4 ganger i uken	5 ganger i uken	6 ganger i uken	Hver dag
Frokost	☐	☐	☐	☐	☐	☐	☐	☐
Formiddagsmat/lunsj	☐	☐	☐	☐	☐	☐	☐	☐
Middag	☐	☐	☐	☐	☐	☐	☐	☐
Kveldsmat	☐	☐	☐	☐	☐	☐	☐	☐

Hvor mange ganger i løpet av dagen pleier du å spise et eller annet utenom hovedmåltidene? (eks. godteri, frukt, brødskive)

Sjelden	1 gang om dagen	2 ganger om dagen	3 ganger om dagen	4 ganger om dagen	Mer enn 4 ganger om dagen
☐	☐	☐	☐	☐	☐

20. Kjønn

Mann ☐

Kvinne ☐

21. Alder

Alder: ☐☐ år

22. Vekt og høyde

Høyde: ☐☐☐ cm

Vekt: ☐☐☐ kg

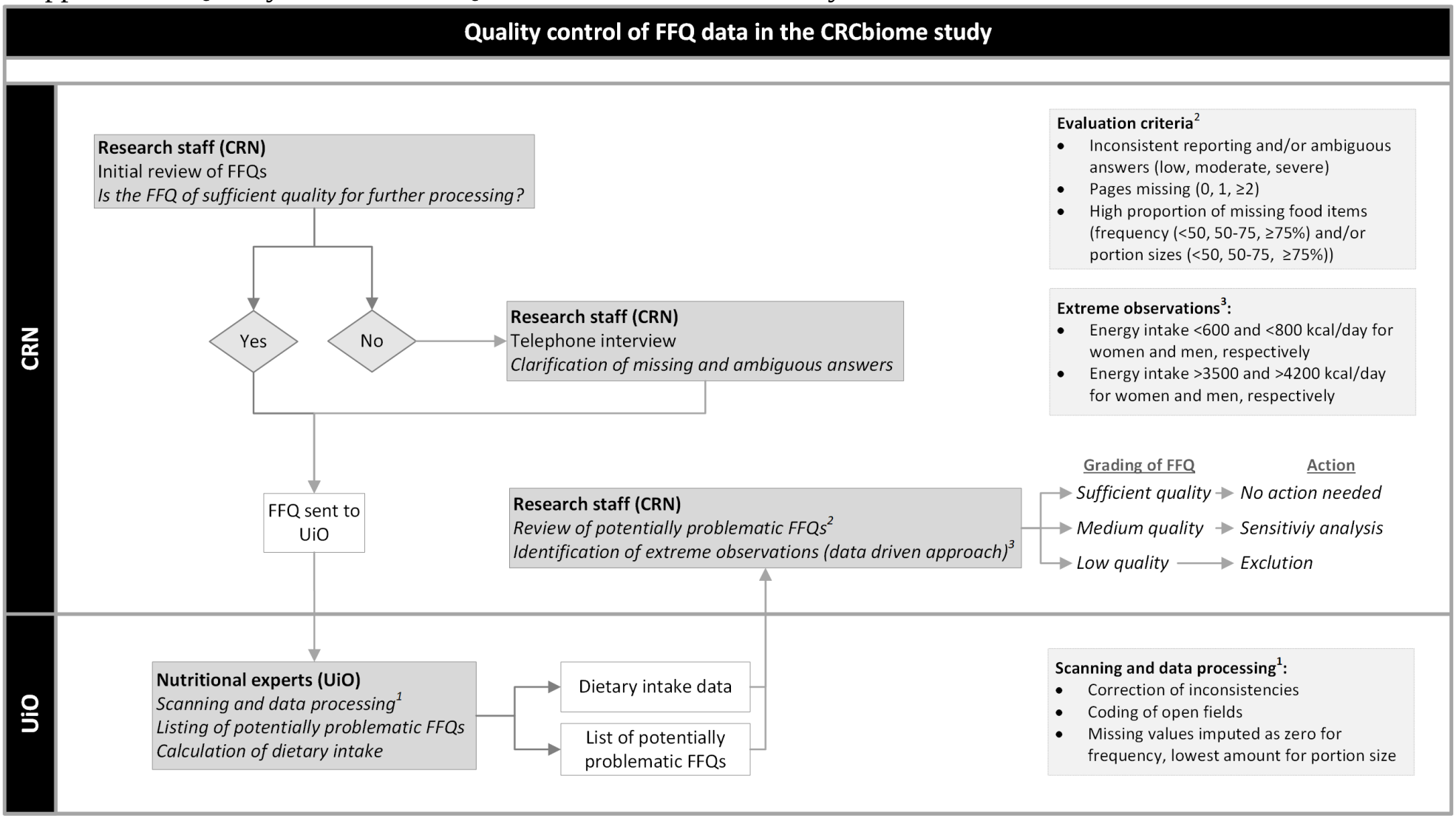
23. Eventuelle andre matvarer

Bruker du regelmessig matvarer, drikker eller andre produkter som ikke er nevnt i spørreskjemaet? Skriv ned dette så detaljert som mulig. Skriv også hvor ofte du spiser/drikker dette (ganger per måned eller uke) og hvor mye du spiser av dette per gang.

BRUK BLOKKBOKSTAVER

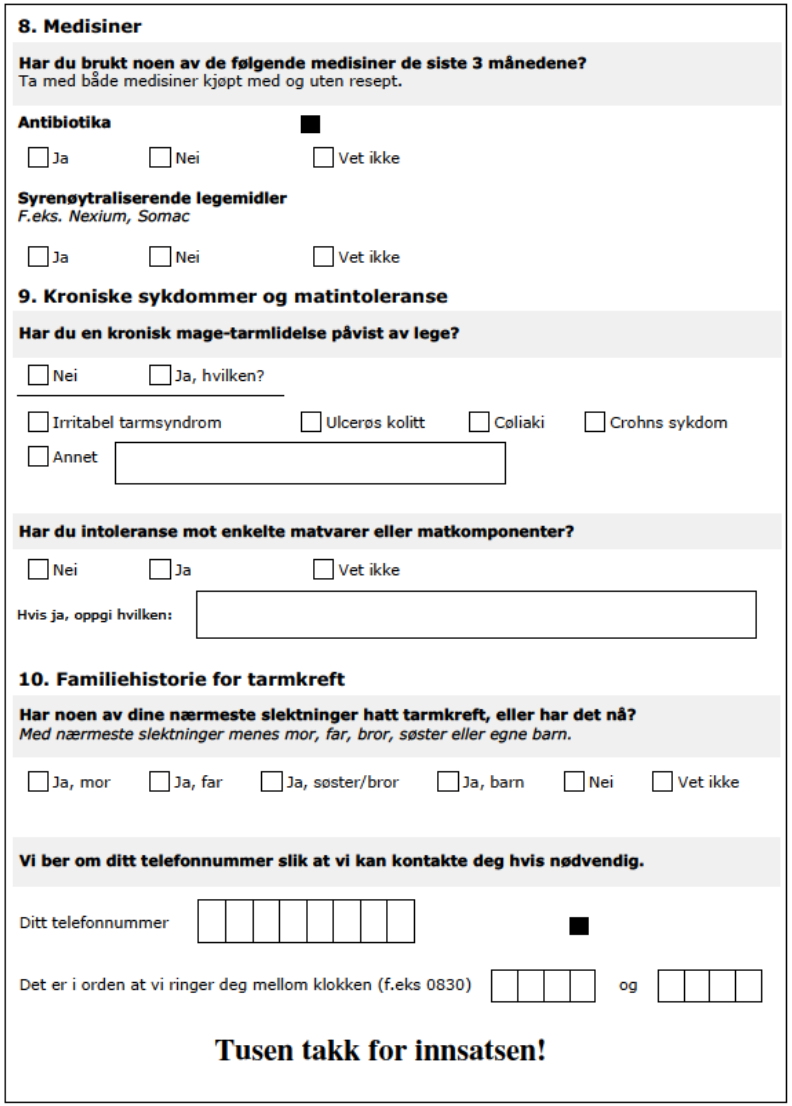
Tusen takk for innsatsen!

Appendix 3: Quality control of FFQ data in the CRCbiome study



Appendix 3 *- Upon receiving food frequency questionnaires (FFQs) from CRCbiome participants, completion is reviewed by researchers with expertise in nutritional epidemiology. Participants with FFQs of insufficient quality are contacted for clarification of inconsistencies and missing data. Reviewed questionnaires are then scanned using the Cardiff TeleForm program at the University of Oslo (UiO). Food and nutrient calculations are conducted using the software system KBS ("**K**ost**b**eregnings**s**ystem"/Dietary Calculation System) with the latest version of the food database, largely based on the Norwegian Food Composition Table (72). Missing answers are imputed as zero in line with common practice (67, 69, 92, 93). Any FFQs regarded as potentially problematic during the data handling process are listed. Dietary intake data and the list of potentially problematic FFQs are then returned to the Cancer Registry of Norway (CRN). Potentially problematic FFQs are reviewed according to a set of predefined criteria, including inconsistency in reporting, number of missing pages and amount of missing food items. Based on these criteria, FFQs are graded as being of low, medium or sufficient quality. Whereas low-quality FFQs will be excluded from all analysis where diet is the primary exposure, medium quality FFQs will be included unless sensitivity analysis indicates substantial attenuation of effect estimates. Lastly, in line with common practice in nutrition studies (71) observations with extreme energy intake levels in both the upper and lower range will be excluded.*

Appendix 4: Lifestyle and Demography Questionnaire



8. Medisiner

Har du brukt noen av de følgende medisiner de siste 3 månedene?
Ta med både medisiner kjøpt med og uten resept.

Antibiotika ■

☐ Ja ☐ Nei ☐ Vet ikke

Syrenøytraliserende legemidler
F.eks. Nexium, Somac

☐ Ja ☐ Nei ☐ Vet ikke

9. Kroniske sykdommer og matintoleranse

Har du en kronisk mage-tarmlidelse påvist av lege?

☐ Nei ☐ Ja, hvilken?

☐ Irritabel tarmsyndrom ☐ Ulcerøs kolitt ☐ Cøliaki ☐ Crohns sykdom

☐ Annet

Har du intoleranse mot enkelte matvarer eller matkomponenter?

☐ Nei ☐ Ja ☐ Vet ikke

Hvis ja, oppgi hvilken:

10. Familiehistorie for tarmkreft

Har noen av dine nærmeste slektninger hatt tarmkreft, eller har det nå?
Med nærmeste slektninger menes mor, far, bror, søster eller egne barn.

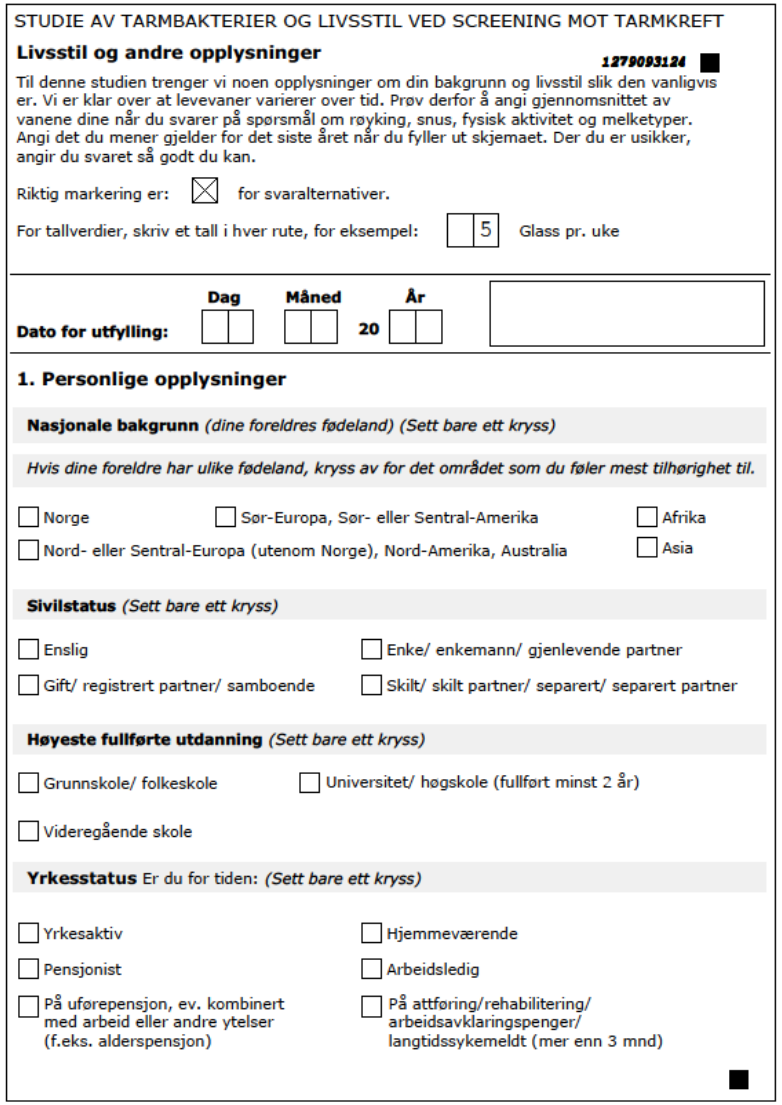
☐ Ja, mor ☐ Ja, far ☐ Ja, søster/bror ☐ Ja, barn ☐ Nei ☐ Vet ikke

Vi ber om ditt telefonnummer slik at vi kan kontakte deg hvis nødvendig.

Ditt telefonnummer ■

Det er i orden at vi ringer deg mellom klokken (f.eks 0830) og

Tusen takk for innsatsen!



STUDIE AV TARMBAKTERIER OG LIVSSTIL VED SCREENING MOT TARMKREFT

Livsstil og andre opplysninger 1279093124 ■

Til denne studien trenger vi noen opplysninger om din bakgrunn og livsstil slik den vanligvis er. Vi er klar over at levevaner varierer over tid. Prøv derfor å angi gjennomsnittet av vanene dine når du svarer på spørsmål om røyking, snus, fysisk aktivitet og melketyper. Angi det du mener gjelder for det siste året når du fyller ut skjemaet. Der du er usikker, angir du svaret så godt du kan.

Riktig markering er: ☒ for svaralternativer.

For tallverdier, skriv et tall i hver rute, for eksempel: | 5 | Glass pr. uke

Dato for utfylling: Dag | | Måned | | 20 År | |

1. Personlige opplysninger

Nasjonale bakgrunn *(dine foreldres fødeland) (Sett bare ett kryss)*

Hvis dine foreldre har ulike fødeland, kryss av for det området som du føler mest tilhørighet til.

☐ Norge ☐ Sør-Europa, Sør- eller Sentral-Amerika ☐ Afrika
☐ Nord- eller Sentral-Europa (utenom Norge), Nord-Amerika, Australia ☐ Asia

Sivilstatus *(Sett bare ett kryss)*

☐ Enslig ☐ Enke/ enkemann/ gjenlevende partner
☐ Gift/ registrert partner/ samboende ☐ Skilt/ skilt partner/ separert/ separert partner

Høyeste fullførte utdanning *(Sett bare ett kryss)*

☐ Grunnskole/ folkeskole ☐ Universitet/ høgskole (fullført minst 2 år)
☐ Videregående skole

Yrkesstatus Er du for tiden: *(Sett bare ett kryss)*

☐ Yrkesaktiv ☐ Hjemmeværende
☐ Pensjonist ☐ Arbeidsledig
☐ På uførepensjon, ev. kombinert med arbeid eller andre ytelser (f.eks. alderspensjon) ☐ På attføring/rehabilitering/ arbeidsavklaringspenger/ langtidssykemeldt (mer enn 3 mnd)

■

2. Røyking

Røyker du nå? *(Sett bare ett kryss)*

Ta med både fabrikklagde og hjemmerullede sigaretter. Hvis du har sluttet eller trappet ned antallet sigaretter flere ganger, prøv så godt du kan å gi et gjennomsnitt.

☐ Ja, daglig ☐ Ja, av og til

☐ Nei, ikke nå ☐ Nei, har aldri røykt

Hvis ja, hvor mye? ☐☐ Sigaretter pr. uke **eller** ☐☐ Sigaretter pr. dag

---

Hvis du har røykt tidligere og sluttet

Hvor mye pleide du å røyke? ☐☐ Sigaretter pr. uke **eller** ☐☐ Sigaretter pr. dag

Hvor mange år eller måneder er det siden du sluttet å røyke siste gang? ☐☐ år **eller** ☐☐ mnd

Hvor mange år eller måneder har du røykt totalt? ☐☐ år **eller** ☐☐ mnd

3. Snus

Bruker du snus? *(Sett bare ett kryss)*

Ta med både posesnus og snus i løsvekt. Hvis du har sluttet eller trappet ned antallet snusporsjoner flere ganger, prøv så godt du kan å gi et gjennomsnitt.

☐ Ja, daglig ☐ Ja, av og til

☐ Nei, ikke nå ☐ Nei, har aldri snust

Hvis ja, hvor mye? ☐☐ Porsjoner pr. uke **eller** ☐☐ Porsjoner pr. dag

---

Hvis du har brukt snus tidligere og sluttet

Hvor mye pleide du å snuse? ☐☐ Porsjoner pr. uke **eller** ☐☐ Porsjoner pr. dag

Hvor mange år eller måneder er det siden du sluttet å bruke snus siste gang? ☐☐ år **eller** ☐☐ mnd

Hvor mange år eller måneder har du brukt snus totalt? ☐☐ år **eller** ☐☐ mnd

4. Fysisk aktivitet

Har du noen kroniske sykdommer eller tilstander som gjør at du ikke kan utføre fysisk aktivitet?

☐ Nei ☐ Ja, angi grunn | ☐ leddgikt ☐ ryggplager ☐ hofte/kneplager ☐ annet

Tenk gjennom hvor lang tid i løpet av en vanlig uke du tilbringer i fysisk aktivitet?
Ta bare med episoder som varer i minst 10 minutter.
Hvor lang tid tilbringer du hver uke på:

Lett anstrengende aktiviteter som krever lite innsats (rolig gange, rolig sykling, hus- og hagearbeid):	Middels anstrengende aktiviteter som krever moderat innsats og får deg til å puste litt mer enn vanlig (sykle/svømme/gå på ski i moderat tempo, jogge, danse, styrketrening):	Meget anstrengende aktiviteter som krever hard innsats, får deg til å puste mye mer enn vanlig (aerobics, løpe/sykle/svømme/gå på ski i rask tempo):
timer per uke	timer per uke	timer per uke
☐ ingenting	☐ ingenting	☐ ingenting
☐ mindre enn 0,5 time	☐ mindre enn 0,5 time	☐ mindre enn 0,5 time
☐ 0,5 til 1 time	☐ 0,5 til 1 time	☐ 0,5 til 1 time
☐ 1,5 - 2 timer	☐ 1,5 - 2 timer	☐ 1,5 - 2 timer
☐ 2,5 - 3,5 timer	☐ 2,5 - 3 ,5 timer	☐ 2,5 - 3,5 timer
☐ 4-6 timer	☐ 4-6 timer	☐ 4-6 timer
☐ 7 eller flere timer	☐ 7 eller flere timer	☐ 7 eller flere timer

5. Bruk av melk vs. surmelk

Hvis du bruker melk hvor mye bruker du av hver type?

Som surmelk regnes alle typer kulturmelk, Cultura, Kefir, drikkbar Biola og tykkmelk. Mengden melk til en porsjon kornblanding regnes som et glass.

Hvor mye melk bruker du? ☐☐ Glass pr. uke **eller** ☐☐ Glass pr. dag

Hvor mye surmelk bruker du? ☐☐ Glass pr. uke **eller** ☐☐ Glass pr. dag

6. Keisersnitt

Ble du født med keisersnitt? *(Sett bare ett kryss)*

☐ Nei ☐ Ja ☐ Vet ikke

7. Fjerning av blindtarm

Er din blindtarm fjernet? *(Sett bare ett kryss)*

☐ Nei ☐ Ja ☐ Vet ikke

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Appendix 5: Association between intake of dietary calcium and colorectal lesion groups

Appendix 5 *- Daily intake of dietary calcium and colorectal cancer screening findings*

Exposure	No findings n=447	OR (95% CI) Non-advanced lesions n=614	OR (95% CI) Advanced neoplasia n=405
Calcium			
Univariate	Ref	1.01 (0.92, 1.13)	0.96 (0.85, 1.08)
Age and sex adjusted	Ref	1.00 (0.90, 1.12)	0.94 (0.83, 1.06)
Multivariate	Ref	1.00 (0.89, 1.14)	0.86 (0.75, 0.99)

Daily intake of dietary calcium per quartile increment and odds ratio and 95% confidence interval for non-advanced lesions and advanced neoplasia. Multivariate model is adjusted for age (continous), sex (male, female), nationality (Norwegian, not Norwegian), education (primary school, high school, university/college), work status (working, retired, outside workforce), marital status (married/living together, single/widowed), smoking status (smoking, not smoking), body mass index (continous), physical activity (continous), inflammatory bowel disease (yes, no) and family history of colorectal cancer (yes, no), as well as intake of red meat (continous), processed meat (continous), dietary fiber (continous) and alcohol (continous).

Appendix 6: Approval from the Regional Committees for Medical and Health Research Ethics

REK

REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst D	Finn Skre Fjordholm	+47 22 84 58 21	18.12.2019	63148
			Deres referanse:	

Trine Ballestad B Rounge

63148 Tarmbakterier og livsstil ved screening mot tarmkreft

Forskningsansvarlig: Kreftregisteret - Institutt for populasjonsbasert kreftforskning

Søker: Trine Ballestad B Rounge

Søkers beskrivelse av formål:

Tarmkreftsymptomer er ofte uspesifikke og sykdommen oppdages ofte for sent til at behandlingen kan forlenge livet. Dagens screeningtester er enten omfattende og ubehagelige eller unøyaktige. Det er et behov for bedre tester.
Det er sammenheng mellom den enkeltes tarmflora og tarmkreftutvikling. Livsstil kan påvirke tarmens bakterieflora og kreftrisiko, men dette samspillet er lite kjent. Ved å kartlegge alle bakterier som finnes i tarmen kan man utvikle tester som kan brukes til å oppdage forstadier og kreft tidlig.
Vårt hovedmål er å utvikle nye tester for tarmbakterier som kan brukes i fremtidige screeningprogram slik at prøvetagning forenkles og resultatet blir sikrere. Vi vil også undersøke om det er sammenheng mellom kosthold og livsstil, tarmflora og tarmkreftutvikling. Da kan vi forbedre råd om forebygging av kreft samt øke nøyaktigheten på testene.

REKs vurdering

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst D) i møtet 04.12.2019. Vurderingen er gjort med hjemmel i helseforskningsloven § 10.

Prosjektet er en samling av to nåværende delprosjekter under REK 2011/1272 D «Pilot på et kolorektalcancer screeningprogram» og REK 2010/3087 A «S-98052a NORCCAP».

Alle skriftlige henvendelser om saken må sendes via REK-portalen
Du finner informasjon om REK på våre hjemmesider rekportalen.no

Det fremgår at omfanget av prosjektet tidligere er godkjent av REK, og i søknaden vises det til to vedtak på endringssøknader i REK 2011/1272 datert den 17.3.2017 og 06.03.2018, og ett vedtak i REK 2010/3087 datert den 07.04.2016.

Det er en sammenheng mellom tarmens bakterieflora og risiko for kreft, og formålet med prosjektet er å undersøke denne sammenhengen nærmere. Deltagerne skal fylle ut to spørreskjema før gjennomføring av koloskopiundersøkelse. Denne undersøkelsen inngår i de to tidligere godkjente prosjektene, og data fra denne undersøkelsen blir tatt i bruk i dette prosjektet.

Det blir gjort analyser av en avføringsprøve fra REK 2011/1272. Videre skal det avleveres to avføringsprøver i løpet av et år.

Det hentes inn summariske opplysninger fra Kreftregisteret og Dødsårsaksregisteret. Fra Reseptregisteret hentes det inn opplysninger om bruk av antibiotika og medisiner som påvirker tarmen.

Komiteen har vurdert søknaden og har ingen innvendinger til studien som sådan. Komiteen har imidlertid flere merknader til informasjonsskrivet og godkjenner prosjektet på vilkår om at dette endres i henhold til disse.

Vilkår

- Det står i informasjonsskrivet at prøvene lagres «i en forskningsbiobank, sammen med resten av prøvene fra *Screening mot tarmkreft – forprosjekt*». Komiteen legger til grunn at det her er snakk om biobanken som er tilknyttet REK 2011/1272. Det bes om at det avklares hvilken biobank prøven skal lagres i, og at informasjonsskrivet oppdateres slik at navn på biobanken og ansvarshavende fremgår av informasjonsskrivet.

- Informasjonsskrivet må inneholde mer informasjon om prosjektet.

- I innledningen av skrivet bør også sammenhengen mellom prosjektet og REK 2011/1272 og REK 2010/3087 forklares nærmere.

Vedtak

Godkjent med vilkår

REK har gjort en helhetlig forskningsetisk vurdering av alle prosjektets sider. Prosjektet godkjennes med hjemmel i helseforskningsloven § 10, under forutsetning av at ovennevnte vilkår er oppfylt.

Vi gjør samtidig oppmerksom på at etter ny personopplysningslov må det også foreligge et behandlingsgrunnlag etter personvernforordningen. Det må forankres i egen institusjon.

I tillegg til vilkår som fremgår av dette vedtaket, er godkjenningen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknad og protokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 01.01.2034. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 01.01.2039. Forskningsfilen skal oppbevares atskilt i en nøkkel- og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse og omsorgssektoren».

Dersom det skal gjøres vesentlige endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK.

Prosjektet skal sende sluttmelding på eget skjema, senest et halvt år etter prosjektslutt.

Komiteens avgjørelse var enstemmig

Med vennlig hilsen

Finn Wisløff
Professor em. dr. med.
Leder

Finn Skre Fjordholm
Rådgiver

Kopi: Kreftregisteret ved øverste administrative ledelse: kreftregisteret@kreftregisteret.no; giske.ursin@kreftregisteret.no

Sluttmelding
Søker skal sende sluttmelding til REK sør-øst D på eget skjema senest seks måneder etter godkjenningsperioden er utløpt, jf. hfl. § 12.

Søknad om å foreta vesentlige endringer
Dersom man ønsker å foreta vesentlige endringer i forhold til formål, metode, tidsløp eller organisering, skal søknad sendes til den regionale komiteen for medisinsk og helsefaglig forskningsetikk som har gitt forhåndsgodkjenning. Søknaden skal beskrive hvilke endringer som ønskes foretatt og begrunnelsen for disse, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK sør-øst D. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst D, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering.

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst D	Nora Elkoland		04.05.2022	63148

Trine Ballestad B Rounge

Prosjektsøknad: Tarmbakterier og livsstil ved screening mot tarmkreft
Søknadsnummer: 63148
Forskningsansvarlig institusjon: Kreftregisteret - Institutt for populasjonsbasert kreftforskning

Prosjektsøknad: Endring godkjennes

Søkers beskrivelse

Tarmkreftsymptomer er ofte uspesifikke og sykdommen oppdages ofte for sent til at behandlingen kan forlenge livet. Dagens screeningtester er enten omfattende og ubehagelige eller unøyaktige. Det er et behov for bedre tester.
Det er sammenheng mellom den enkeltes tarmflora og tarmkreftutvikling. Livsstil kan påvirke tarmens bakterieflora og kreftrisiko, men dette samspillet er lite kjent. Ved å kartlegge alle bakterier som finnes i tarmen kan man utvikle tester som kan brukes til å oppdage forstadier og kreft tidlig.
Vårt hovedmål er å utvikle nye tester for tarmbakterier som kan brukes i fremtidige screeningprogram slik at prøvetagning forenkles og resultatet blir sikrere. Vi vil også undersøke om det er sammenheng mellom kosthold og livsstil, tarmflora og tarmkreftutvikling. Da kan vi forbedre råd om forebygging av kreft samt øke nøyaktigheten på testene.

Vi viser til søknad om prosjektendring mottatt 02.05.2022 for ovennevnte forskningsprosjekt. Søknaden er behandlet av sekretariatet i Regional komité for medisinsk og helsefaglig forskningsetikk (REK) på delegert fullmakt fra komiteen, med hjemmel i forskningsetikkforskriften § 7, første ledd, tredje punktum. Søknaden er vurdert med hjemmel i helseforskningsloven § 11.

REKs vurdering

REK har vurdert følgende endring:

Nye prosjektmedarbeidere:

- Ekaterina Avershina, forsker ved Kreftregisteret - Institutt for populasjonsbasert kreftforskning

- Frøya Grønvik, masterstudent ved UiT Norges arktiske universitet

REK sør-øst D
Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon:22 84 55 11 | **E-post**:rek-sorost@medisin.uio.no
Web:https://rekportalen.no

REK har vurdert den omsøkte endringen, og har ingen forskningsetiske innvendinger til endringen slik den er beskrevet i skjema for prosjektendring.

Vedtak

REK har gjort en forskningsetisk vurdering av endringen i prosjektet og godkjenner prosjektet slik det nå foreligger, jfr. helseforskningsloven § 11 annet ledd.

Vi gjør oppmerksom på at etter ny personopplysningslov må det også foreligge et behandlingsgrunnlag etter personvernforordningen. Det må forankres i egen institusjon.

Tillatelsen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, endringssøknad, oppdatert protokoll og de bestemmelser som følger av helseforskningsloven med forskrifter.

Sluttmelding
Prosjektleder skal sende sluttmelding til REK på eget skjema via REK-portalen senest 6 måneder etter sluttdato 01.01.2034, jf. helseforskningsloven § 12. Dersom prosjektet ikke starter opp eller gjennomføres meldes dette også via skjemaet for sluttmelding.

Søknad om endring
Dersom man ønsker å foreta vesentlige endringer i formål, metode, tidsløp eller organisering må prosjektleder sende søknad om endring via portalen på eget skjema til REK, jf. helseforskningsloven § 11.

Klageadgang
Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes på eget skjema via REK portalen. Klagefristen er tre uker fra du mottar dette brevet. Dersom REK opprettholder vedtaket, sender REK klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

Med vennlig hilsen

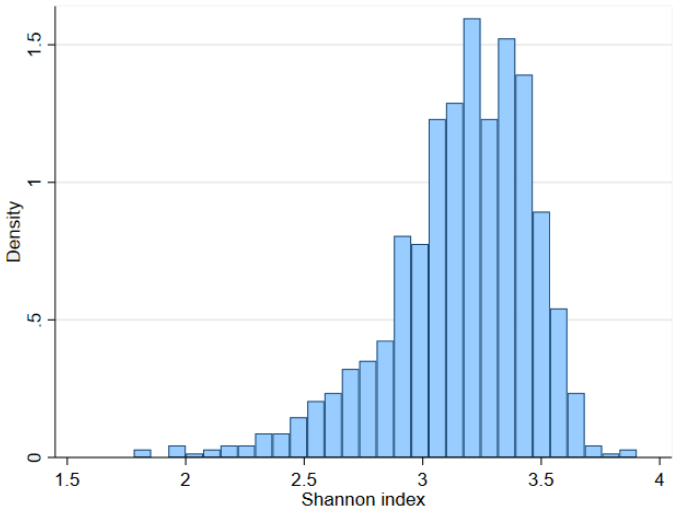
Jacob C. Hølen
sekretariatsleder REK sør-øst

Nora Eikeland
førstekonsulent

Kopi til:

Kreftregisteret - Institutt for populasjonsbasert kreftforskning

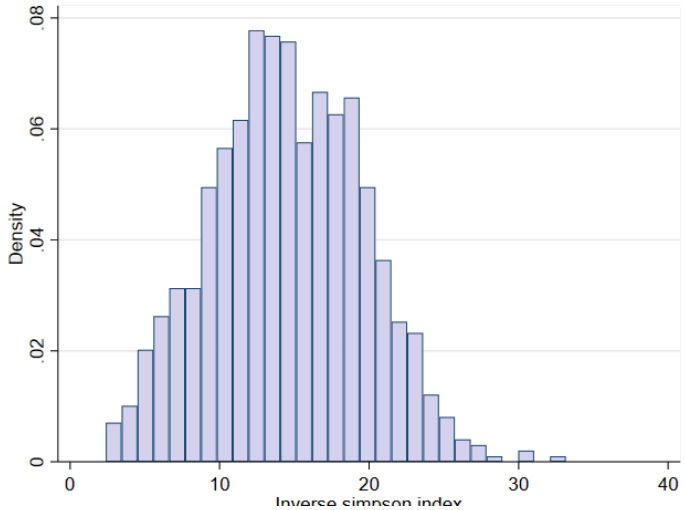
Appendix 7: Histogram and Shapiro-Wilk test for alpha diversity measures



Appendix 7A *- Histogram for Shannon index*

Appendix 7B *- Shapiro-Wilk test for Shannon Index*

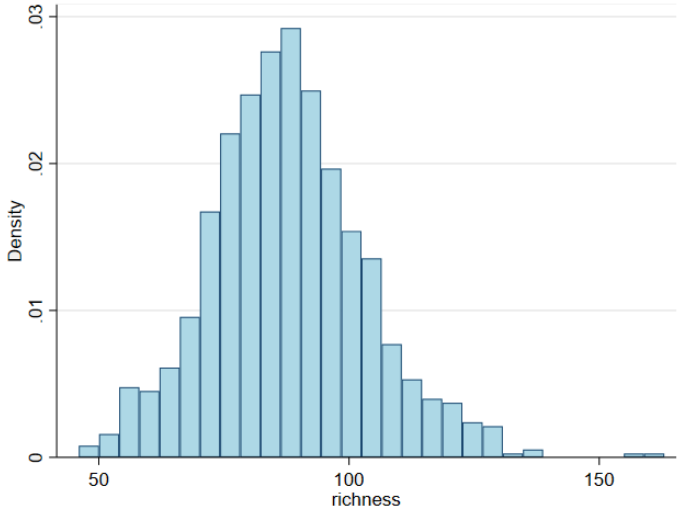
Variable	Observations	V	p
Shannon index	933	33.43	0.00



Appendix 7C *- Histogram for inverse Simpson index*

Appendix 7D *- Shapiro-Wilk test for inverse Simpson index*

Variable	Observations	V	p
Inverse Simpson index	933	2.37	0.02



Appendix 7E *- Histogram for richness*

Appendix 7F *- Shapiro-Wilk test for richness*

Variable	Observations	V	p
Richness	933	7.32	0.00