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The Association between the Energy-adjusted Dietary Inflammatory Index and the Risk of Colorectal Cancer in The Norwegian Women and Cancer Study (NOWAC)

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Master's Thesis in Clinical Nutrition (ERN-3900) May 2023

Acknowledgments

This thesis marks the end of a five-year-long journey at UiT The Arctic University of Tromsø. Writing this thesis has been both exciting and challenging, but I most appreciate everything that I have learned. I am lucky that got the opportunity to write about a subject that I am curious about and find very interesting.

I want to thank my main supervisor, Torill Enget Jensen, for the dedication and invaluable support in the process of writing this thesis. I greatly appreciate the guidance and thorough feedback that you have given me along the way. I would also like to thank Guri Skeie for the additional insights and helpful contributions as my co-supervisor.

I am also grateful for the support I have received from family and friends during my years as a student in Tromsø. Thank you, Andreas, for keeping up with me at the most stressful times. Not to mention, the great memories I share with my classmates.

Abbreviations

24HDR	24-hour dietary recall
APC	Adenomatous polyposis coli
BMI	Body mass index
CIMP	CpG island methylator phenotype
CIN	Chromosomal instability
CRC	Colorectal cancer
CRP	C-reactive protein
DII	The Dietary Inflammatory Index
E%	Percentage of total energy intake
E-DII	The Energy-adjusted Dietary Inflammatory Index
EPIC	The European Prospective Investigation into Cancer and Nutrition
FAP	Familial adenomatous polyposis
FFQ	Food frequency questionnaire
HDI	Human development index
IBD	Inflammatory bowel disease
ICD-10	10th revision of the International Classification of Diseases
IQR	Interquartile range
MHT	Menopausal hormone therapy
MMR	Mismatch repair
MSI	Microsatellite instability
MUFA	Monounsaturated fat
NOWAC	The Norwegian Women and Cancer Study
NSAIDs	Non-steroidal anti-inflammatory drugs
PUFA	Polyunsaturated fat
SFA	Saturated fat
SEASONS	The Seasonal Variation of Cholesterol Levels Study
SD	Standard deviation
SSPs	Sessile serrated polyps
T2D	Type 2 diabetes
TME	Tumor microenvironment
TSAs	Traditional serrated adenomas
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research

Abstract

Background: Colorectal cancer (CRC) is one of the most common cancer types and a leading cause of cancer death worldwide. Norwegian women had the highest incidence rate in 2020 compared to women in other countries. The development of CRC is largely impacted by inflammation, and diet has a potential role in the regulation of chronic inflammation. The Dietary Inflammatory Index (DII) is a tool developed to assess the inflammatory potential of an individual's diet. Existing evidence suggests that the dietary inflammatory potential is associated with the risk of CRC and that the risk may vary by anatomical subsite of the colon and rectum. However, the findings are inconsistent and should be further investigated. Due to the high incidence rate in Norway, the preventive potential is high and of special importance.

Aim: This thesis aimed to assess the association between the inflammatory potential of the diet, measured by energy-adjusted DII (E-DII), and the risk of CRC and cancer by anatomical subsite of the colon and rectum.

Methods: Data from a subsample of 37,226 women in the Norwegian Women and Cancer study (NOWAC) was utilized. E-DII scores were computed based on a food frequency questionnaire completed by the participants at baseline. Cox proportional hazards regression was used to assess associations between quartiles of the E-DII and the risk of CRC and cancer by anatomical subsites.

Results: 694 CRC cases were identified during an average of 20.3 years of follow-up. No significant associations were observed. The most positive association was seen between women in the highest (most pro-inflammatory) E-DII quartile and the risk of proximal colon cancer (age-adjusted $HR_{Q4\text{-}Q1}$: 1.27; 95% CI: 0.91–1.77; multivariable-adjusted $HR_{Q4\text{-}Q1}$: 1.21; 95% CI: 0.86–1.69).

Conclusion: The E-DII was not associated with the risk of CRC or cancer by anatomical subsite of the colon and rectum. There was a tendency towards a positive relationship between a more pro-inflammatory diet and an increased risk of proximal colon cancer, however, the results are inconclusive.

Sammendrag

Bakgrunn: Tykk- og endetarmskreft (CRC) er en av de hyppigste kreftformene og en ledende årsak til dødsfall som følge av kreftsykdommer på verdensbasis. Norske kvinner hadde i 2020 den høyeste insidensraten globalt sammenlignet med kvinner i andre kand. Inflammasjon er anerkjent som en medvirkende årsak til utviklingen av CRC. Samtidig har kosthold en potensiell rolle i reguleringen av kronisk inflammasjon. The Dietary Inflammatory Index (DII) er et verktøy som måler det inflammatoriske potensialet i et individs kosthold. Nåværende forskning tyder på at det inflammatoriske potensialet i kostholdet er assosiert med risiko for CRC og at sammenhengen kan variere mellom ulike tarmavsnitt. Funnene er imidlertid usikre og bør utforskes videre. På grunn av den høye forekomsten i Norge er det forebyggende potensialet høyt og av spesiell betydning.

Formål: Denne oppgaven hadde som mål å undersøke sammenhengen mellom det inflammatoriske potensialet i kostholdet, målt ved bruk av en energijustert versjon av DII (E-DII), og risiko for CRC og kreft i ulike tarmavsnitt.

Metode: Oppgaven brukte data fra et utvalg på 37 226 kvinner fra Kvinner og kreft-studien. E-DII-skårer ble kalkulert ut ifra et matfrekvensskjema som deltakerne fylte ut ved studiestart. Cox regresjon ble brukt til å undersøke sammenhengen mellom E-DII inndelt i kvartiler og risiko for CRC og kreft i ulike tarmavsnitt.

Resultat: 694 tilfeller av CRC ble identifisert i løpet av en gjennomsnittlig oppfølging på 20,3 år. Det ble ikke funnet noen statistisk signifikante sammenhenger. Den mest positive sammenhengen ble observert mellom kvinner i den høyeste (mest pro-inflammatoriske) E-DII-kvartilen og kreft i proksimale kolon (aldersjustert $HR_{Q4\text{-}Q1}$: 1.27; 95% CI: 0.91–1.77; multivariabel $HR_{Q4\text{-}Q1}$: 1.21; 95% CI: 0.86–1.69).

Konklusjon: E-DII var ikke assosiert med risiko for CRC eller kreft i ulike tarmavsnitt. Det var en tendens til en positiv sammenheng mellom et mer pro-inflammatorisk kosthold og økt risiko for kreft i proksimale kolon, men funnene er usikre.

Table of Contents

List of Tables

List of Figures

1 Introduction

1.1 Background

Colorectal cancer (CRC), also known as bowel cancer, is cancer that develops in the colon or the rectum, which together make up the large intestine (1). The incidence of CRC (number of new cases within a given time period) has markedly increased over the past several decades and is expected to continue increasing in the future (2). Diet and lifestyle are widely recognized as some of the most important factors in the prevention of CRC (3). Chronic inflammation contributes to the development of CRC (4), and increasing evidence suggests that diet plays a central role in the regulation of chronic inflammation within the body (5). However, it is unclear whether diet can influence the development of CRC by regulating chronic inflammation.

1.2 CRC epidemiology

Epidemiology is the study of the occurrence and distribution of diseases in a population, the factors determining these diseases, and how this can be applied to control health problems (6). Globally, the number of new CRC cases has more than doubled since 1990 (7). It is estimated that more than 1.9 million new cases occurred in 2020, accounting for about one in ten cancer cases worldwide (8). The increasing trends mainly reflect aging of the population, as well as changes in lifestyle and dietary patterns (2, 8). The highest incidence rates are seen in more developed countries, including European regions, Australia, New Zealand, North America and Eastern Asia, whereas the lowest incidence rates are seen in lower-income countries of African regions and South Asia (7, 8). The number of new CRC cases is substantially higher in men compared to women, and the difference is more apparent in developed regions (7, 8).

In Norway, CRC is the second most common cancer in both men and women (9). Around 4,500 new cases occurred in 2021, of which 70% were colon and 30% rectal cancers (9). While the risk of colon cancer is close to equal between men and women, men are 70% more likely to develop rectal cancer (2). It is estimated that 6% of women and 7% of men in Norway will develop CRC by the age of 80 (2). In 2020, Norwegian women had the highest incidence of CRC globally when compared to women in other countries (8). Additionally, they have had the highest incidence among women in the Nordic countries since 1990 (2).

CRC can be considered a marker of socioeconomic development (8). Incidence rates are increasing in transitioning countries, which likely reflects the adoption of Western eating

patterns and a more sedentary lifestyle (8, 10). Although CRC is rare in younger age groups, increasing rates of early-onset CRC, defined as diagnosis before the age of 50 years, have been observed in several high-income countries, including Norway (2, 8). The underlying causes of the increased risk are not yet fully understood and further research is needed, however, dietary habits, excess body weight, lack of physical activity and other lifestyle factors are believed to play a crucial role (8, 10). Meanwhile, among the elderly, the incidence rates appear to be stable or decreasing in countries with higher human development index, which also includes Norway (9, 10). This decrease has primarily been attributed to increased screening leading to earlier detection and removal of precancerous colorectal polyps (8, 10).

1.3 Risk and protective factors for CRC

1.3.1 Non-modifiable factors

Approximately 70% of CRCs are sporadic, meaning they occur without a family history or genetic predisposition to the disease (11). The largest risk factor for sporadic disease is increasing age (12). About 20% of CRC cases are familial, which refers to an accumulation of CRC in a family without a known gene defect (2). Individuals in these families have an increased risk of developing CRC, and the risk is thought to vary with the number of relatives with the disease, their age at diagnosis and how close the relation is (13). Less common but carrying an even higher risk of developing CRC are inherited syndromes, estimated to account for 2–5% of CRCs (14). The most common inherited syndromes are Lynch syndrome and familial adenomatous polyposis (FAP) (14). Individuals with these syndromes often develop CRC at a younger age compared to the general population (14).

Inflammatory bowel disease (IBD), which includes ulcerative colitis and Crohn's disease, is also an established risk factor for CRC (15). IBD involves chronic inflammation of the gastrointestinal tract, and the risk for CRC is determined by the extent, duration and activity of the disease (15). Similarly to individuals with inherited syndromes, IBD patients that develop CRC are affected at a younger age compared to patients with sporadic CRC (16). The risk of developing CRC is also affected by adult-attained height, with taller individuals having an increased risk (3).

1.3.2 Modifiable factors

Several modifiable factors are thought to play a significant role in the development of CRC. Cigarette smoking is an established risk factor, while long-term use of aspirin and other non-

steroidal anti-inflammatory drugs (NSAIDs), as well as menopausal hormone therapy (MHT) in postmenopausal women, have been found to reduce the risk of CRC (3, 15). Several dietary factors and additional lifestyle factors have been associated with CRC risk as well. The World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) has reviewed the research on the association between diet, nutrition, physical activity and CRC in a report that was last updated in 2018 (3). The lifestyle and dietary factors that showed strong evidence for a link with CRC risk will further be described. In the report, these factors were additionally classified as “convincing” or “probable” strong evidence.

Physical activity is thought to have a strong protective effect on CRC, and the evidence is considered convincing (3). It is suggested that physical activity has an indirect impact on CRC risk by reducing body fatness and consequently reducing insulin resistance and inflammation and a direct impact by stimulating digestion and reducing transit time, which may reduce exposure to potential carcinogens through the large intestine (3, 17). Furthermore, having overweight or obesity convincingly increases the risk of developing CRC (3). The increased risk is thought to be mediated through various mechanisms, including higher levels of insulin resulting from increased body fatness (3). Associated with this, although not mentioned in the report, type 2 diabetes (T2D) and other diseases related to insulin resistance have been found to elevate the risk of CRC (15, 17). Obesity is also associated with chronic low-grade inflammation, which is strongly associated with increased CRC risk (17).

Red and processed meat is found to be strongly associated with an increased risk of CRC, and WCRF/AICR concluded that the evidence for these associations were convincing for processed meat and probable for red meat (3). Potential mechanisms underlying the increased risk include the formation of the mutagenic and carcinogenic compounds heterocyclic amines and polycyclic aromatic hydrocarbons when meat is cooked at high temperatures (3, 17). In addition, red meat is rich in haem iron, which stimulates the endogenous formation of carcinogenic N-nitroso compounds in the intestine (3, 17). N-nitroso compounds are also present in processed meat, such as bacon and ham, as a result of the curing process (17). In addition to processed meat, the consumption of alcoholic drinks is convincingly associated with increased CRC risk (3). This association applies to the consumption of alcohol in amounts over 30 grams per day, which is equivalent to about two drinks per day (3). The underlying mechanisms are diverse and not completely clear, however, the effects on CRC risk are thought to primarily result from the toxic metabolites of alcohol (3, 17). For instance, ethanol is converted to acetaldehyde in the liver, which can be carcinogenic for the intestinal

cells (3). A high alcohol intake can also increase the production of reactive oxygen species, which are carcinogenic and can cause DNA damage (3).

Whole grains, which are sources of dietary fiber, along with dietary fiber from other food sources are associated with decreased risk of CRC, and the evidence is considered probable (3). Dietary fiber may lower CRC risk through increased fecal bulk and reduced intestinal transit time, which reduces the large intestine's exposure to carcinogens (3, 17). Moreover, fiber is fermented in the large intestine, in which potential anti-carcinogenic short-chain fatty acids, such as butyrate, are produced (3, 17). It is also suggested that diets rich in fiber may reduce CRC risk by reducing insulin resistance (3). Other dietary factors found probable to reduce CRC risk are dairy products and calcium supplements (3). The potential protective effect of dairy products is mainly due to their calcium content (3). Calcium may reduce the risk of developing CRC by binding unconjugated bile acids and free fatty acids, thus reducing their toxic effects within the large intestine (3). Other constituents of dairy products, such as vitamin D, butyrate and lactic acid-producing bacteria have also been suggested to contribute to the potential protective role of dairy products in CRC development (3, 17). Several other potential risk or protective factors for CRC have been studied but the available evidence is too limited to draw conclusions. According to WCRF/AICR, evidence is suggestive of a decreased risk of CRC with consumption of foods containing vitamin C, fish, vitamin D and multivitamin supplements and of increased risk with low intakes of fruits and non-starchy vegetables as well as with intake of foods containing haem iron (3).

1.4 CRC carcinogenesis

1.4.1 Anatomy of the large intestine

CRC refers to cancer that develops in the colon or rectum. The colon is the longest part of the large intestine, reaching from the end of the small intestine to the rectum, whereas the rectum is the last part of the large intestine and connects to the anus (1). Figure 1 illustrates the anatomical subsites of the large intestine. The cecum is a pouch that marks the beginning of the large intestine and is located on the right side of the abdomen (18). The appendix is a thin pouch attached to the cecum (18). The cecum is followed by the ascending colon that rises along the right side of the abdomen, connecting to the transverse colon that crosses the upper abdomen, before extending downward on the left side of the abdomen as the descending colon (18). Then follows the S-shaped sigmoid colon and the rectum, connected by the rectosigmoid junction. The bend where the ascending colon meets the transverse colon is

referred to as the hepatic flexure, while the bend where the transverse and descending colon meet is referred to as the splenic flexure (18).

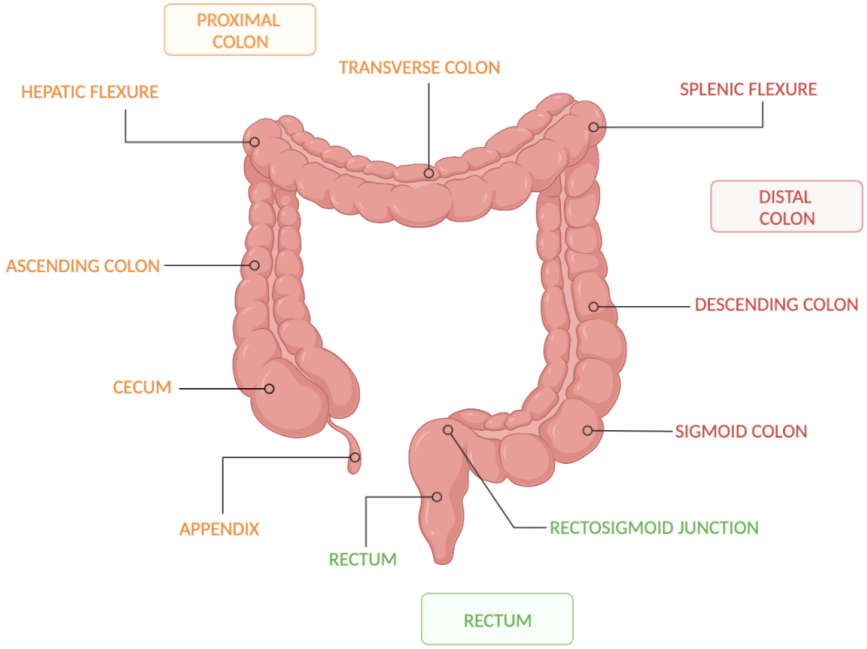

Figure 1. *Anatomical sites of the large intestine. (Created with BioRender.com)*

CRC can be defined according to the primary tumor location within the large intestine. Embryologically, two-thirds of the transverse colon and the anatomical sites proximal to the splenic flexure arise from the midgut, while the remaining one-third of the transverse colon and the anatomical sites distal to the splenic flexure arise from the hindgut (19). The splenic flexure is therefore commonly used as a cutpoint between proximal and distal colon cancer, also referred to as right- and left-sided CRC, respectively (19). The definitions of these terms sometimes differ, however, this thesis will distinguish between cancer in the proximal colon (appendix, cecum, ascending colon, hepatic flexure and transverse colon), distal colon (splenic flexure, descending colon and sigmoid colon) and rectum (rectosigmoid junction and rectum). Furthermore, the term “right-sided CRC” will refer to proximal colon cancer, while “left-sided CRC” will include both distal colon and rectal cancers.

1.4.2 Precancerous polyps

Colorectal polyps are small growths that arise from the surface of the intestinal lining (20). Polyps may be neoplastic, meaning they have the potential to develop into cancer, or non-neoplastic, meaning they are benign (20). The two main types of polyps that can cause CRC are adenomatous polyps, also known as adenomas, and serrated lesions (20).

The majority of CRCs arise from adenomas that transform into malignant tumors called adenocarcinomas (20). The progression from adenoma to adenocarcinoma is referred to as the adenoma-carcinoma sequence and is thought to occur over a period of 10 years or more (20). Adenomas are quite common and expected to be prevalent in half of all 70-year-olds, and while some may develop into CRC, most adenomas are harmless (21, 22). Adenomas can be characterized as tubular, villous or tubulovillous based on their histologic features (22). Tubular adenomas account for more than 80% of colorectal adenomas, while villous and tubulovillous adenomas each account for 5–15% of colorectal adenomas (22). Adenomas can further be classified as having low- or high-grade dysplasia, which refers to the degree of abnormal cell development (22). Advanced adenomas, defined as being either ≥10 mm in size, having high-grade dysplasia or containing villous elements are considered to have a higher risk of developing into CRC compared to non-advanced adenomas (20).

Although most CRCs arise from adenomas, more recent research supports an alternative pathway through serrated lesions (11). Serrated lesions can be divided into hyperplastic polyps, sessile serrated polyps (SSPs) and traditional serrated adenomas (TSAs) (22). Hyperplastic polyps are the most common non-neoplastic polyps and are usually not considered precursors of CRC (20, 22). SSPs, on the other hand, are thought to account for about 25% of CRC cases (2). They often appear flat or sessile and are commonly associated with dysplasia (2). TSAs have the potential of developing into CRC as well, however, they are not very common (2). TSAs may be sessile or have a stalk that attaches it to the intestinal surface and often exhibit diffuse but mild dysplasia (22).

1.4.3 Pathogenesis

The development of cancer from normal epithelial cells involves multiple steps and is driven by changes in the parts of the DNA that regulate cell growth (21). Inherited CRC syndromes, such as FAP and Lynch syndrome, are caused by specific germline mutations that occur in the reproductive cells and that are passed down from parent to offspring (11). Conversely, most sporadic cases of CRC are caused by a stepwise accumulation of somatic mutations, which refers to acquired mutations in non-reproductive cells (11). Some of the most important altered genes in CRC are the oncogene RAS and the tumor-suppressor genes adenomatous polyposis coli (APC) and TP53 (11). Mutations in oncogenes lead to activation of the genes, which promotes uncontrolled cell proliferation (11). Conversely, mutations in tumor-suppressor genes lead to inactivation of the genes, which leads to loss of their normal function

to control cell growth and division (11). Both events contribute to tumor development. Mutations in the APC gene are highly common and seen in approximately 80% of sporadic CRC cases (11). In addition, the inherited condition FAP is caused by germline mutations in the same gene (11).

Various molecular features are involved in colorectal carcinogenesis in which three main molecular pathways that lead to CRC have been identified: the chromosomal instability (CIN) pathway, the microsatellite instability (MSI) pathway and the CpG island methylator phenotype (CIMP) pathway (4, 12). About 70% of CRCs develop via the CIN pathway, which is initiated by mutations in the APC gene and characterized by chromosomal abnormalities, including loss or gain of an entire chromosome or chromosomal region (4, 11). The second pathway, MSI, is associated with approximately 15% of sporadic CRCs as well as the majority of CRCs related to Lynch syndrome (11). MSI is caused by the dysfunction of DNA mismatch repair genes that are involved in correcting mistakes that occur when DNA is copied during cell division (4). The result is an accumulation of DNA errors across the genome (11). Tumors with mismatch repair dysfunction are usually characterized by high levels of microsatellite instability due to a high mutation rate within the short, repeated DNA sequences called microsatellites (11, 23). The third pathway, CIMP, is an epigenetic alteration characterized by hypermethylation of CpG islands (genomic regions in the promoter region of genes), leading to inactivation of tumor-suppressor genes (12). Tumors that develop through serrated lesions are frequently characterized by CIMP mutations, and the CIMP pathway is also referred to as the serrated pathway (4). As the definitions of the three pathways may overlap, tumors can exhibit features from more than one pathway (4).

1.4.4 The tumor microenvironment

In addition to genetic alterations, the development of colorectal tumors seems to depend on the close interaction of mutated cells with their surrounding environment, called the tumor microenvironment (TME) (4). The TME is a complex network composed of cellular and non-cellular components that may vary between tumor types, but essential components include immune cells, stromal cells, blood vessels and extracellular matrix (24, 25). The cancer cells and components within the TME interact with each other in a mutual relationship that supports tumor growth and invasion (25).

1.4.5 The gut microbiota

The large intestine contains rich and diverse populations of bacteria, known as the gut microbiota, which have an important role in regulating the host immune system as well as protecting against pathogens (26). Dysbiosis, which refers to the disruption of healthy microbiota, has been linked to the development of CRC (4). Accordingly, there are observed notable differences in the bacterial composition in tissues of healthy individuals compared to those with CRC (4). The gut microbiota varies to a large extent between individuals, and among other factors, diet is recognized as an external factor with the ability to modulate its composition (26).

1.5 Right- versus left-sided CRC

There are differences in CRCs originating from distinct anatomical subsites. In terms of epidemiological differences, proximal colon tumors appear to be more common in women and older individuals, whereas distal colon tumors are more common in men and younger individuals (12). Over time, there has been a gradual shift in the distribution of CRC towards a higher proportion of right-sided colon tumors (15, 27). Although it appears to be a true increase in right-sided tumors, this change may in part be due to improvements in diagnosis, treatment and screening (15). In addition, colonoscopy appears to have higher efficacy in preventing left-sided than right-sided CRCs (15). Moreover, variations are seen in the premalignant colorectal polyps that lead to CRC. Tubular and tubulovillous adenomas are evenly distributed throughout the large intestine, however, they are more likely to have high-grade dysplasia at smaller sizes when located in the proximal colon (19). SSPs are more common in the proximal colon, while TSAs are often located in the rectosigmoid colon (22). Furthermore, mutations in the BRAF oncogene are more common in right-sided CRCs, while mutations in the APC and TP53 tumor-suppressor genes are more prevalent in left-sided CRCs (19). The two sites also exhibit distinct molecular features, in which right-sided CRCs are more likely to be characterized by MSI and CIMP, while tumors that develop through the CIN pathway are more likely to be left-sided (19). Furthermore, significant differences in the intestinal microbiota have been observed between patients who develop right- compared to left-sided CRCs (19).

Evidence has also indicated that lifestyle factors, including diet, is differently associated with the anatomical subsites of the colon and rectum. For instance, significant inverse associations have been observed for physical activity and colon cancer, but not rectal cancer (3, 28).

Furthermore, waist circumference has shown a stronger positive association with colon cancer than rectal cancer (3, 28). Moreover, current smoking has been found to be more strongly related to the risk of proximal colon and rectal cancer than distal colon cancer (28). As for dietary factors, the WCRF/AICR report found that the protective effects of dairy and wholegrains on CRC risk were statistically significant for colon cancer but not rectal cancer (3). The increased risk of CRC with intake of red and processed meat was also only significant for colon and not rectal cancer (3). In contrast, Hjartåker et al. found that meat consumption was more strongly related to the risk of distal colon and rectal cancer than proximal colon cancer (29). This study also observed that alcohol consumption was more strongly related to the risk of rectal cancer than colon cancer.

1.6 Inflammation, CRC and diet

1.6.1 Inflammation

Inflammation is a process that triggers the activation, recruitment and action of cells of the immune system in response to injury, infection or other harmful stimuli (30). It is common to distinguish between acute and chronic inflammation. Acute inflammation is a normal and necessary response to tissue injury or infection and is typically characterized by redness, heat, pain and swelling (31). Chronic inflammation is a state where the inflammatory response persists, often because the body fails to remove the cause of the inflammation (31). Chronic low-grade inflammation has been linked with an increased risk of several chronic diseases, including cardiovascular disease and cancer (32). In addition, obesity and increasing BMI have been associated with elevated levels of inflammatory markers, including C-reactive protein (CRP) and the cytokines IL-6 and TNF-α (32).

1.6.2 The role of inflammation in CRC

Chronic inflammation of the intestine is thought to contribute to CRC through various mechanisms and can result from several factors, including infections, dysregulated immune responses such as in IBD and environmental factors such as a poor diet (4). Inflammation contributes to both tumor initiation, which is the process where normal intestinal epithelial cells undergo genetic changes that transform them into potential tumor cells, and tumor promotion, where previously initiated cells grow into a tumor (4, 33). It has been suggested that inflammation is likely to affect tumor promotion but not initiation in sporadic CRC (33). Inflammation can, however, initiate tumor development in colitis-associated cancer, which is a subtype of CRC that is associated with inflammatory bowel disease (IBD) (33). Cytokines,

such as IL-1β, IL-6 and TNF-α, growth factors and other factors provided by the inflammatory environment can promote tumor growth, for example, by promoting angiogenesis (formation of new blood vessels) and suppressing the immune system's ability to fight the tumor (4, 33). Inflammation also has a great impact on the composition of the TME as well as the plasticity of cancer cells and surrounding cells within the TME (30).

1.6.3 The role of diet in inflammation

Evidence indicates that both dietary patterns and individual dietary components have the potential to affect the levels of chronic inflammation in the body. The Mediterranean diet, which is rich in fruit and vegetables, whole grains, legumes, seafood and healthy fats and low in red meat, has been associated with reduced levels of inflammation (34). One reason for this may be the high content of antioxidants, folate and flavonoids in plant-based foods, which are considered anti-inflammatory (34). Conversely, the Western diet, high in processed foods, red meat and fat and low in fruits, vegetables and whole grains, has been associated with higher levels of inflammation (34). Other individual food groups and nutrients, including fruit and vegetables, unsaturated omega-3 fatty acids, whole grains, fibre and vitamin A, C and E, have been linked with lower levels of inflammation, whereas saturated fatty acids, sodium and ultra-processed foods have been associated with higher levels of inflammation (34). Vitamin D may appear to have anti-inflammatory properties as well (3).

1.7 The Dietary Inflammatory Index (DII)

1.7.1 Development of the DII

Based on the potential role of diet in the regulation of chronic inflammation, the Dietary Inflammatory Index (DII) was developed to assess the overall inflammatory potential of an individual's diet (5). The DII is based on a comprehensive review of literature that has studied the effect of different dietary components on inflammation in the body (35). The review focused on dietary components affecting minimum one of six inflammatory biomarkers: IL-1β, IL-4, IL-6, IL-10, TNF-α and CRP (35). Levels of these biomarkers are commonly used as indicators of inflammation, and they were chosen due to their established role in inflammation as well as the available literature concerning them (5).

The first version of the DII was introduced in 2009 and was based on articles published from 1950 through 2007 (35). The index was validated in the Seasonal Variation of Cholesterol Levels Study (SEASONS) where it proved to be a valid tool for assessing the inflammatory

potential of the diet (35). However, the developers did not publish any research articles later using the first version of the DII (36).

A second, revised version of the DII was published in 2014, which included additional literature through 2010 and an improved method for calculating DII-scores (5). A total of 1,943 peer-reviewed articles identified 45 "food parameters", consisting mainly of micro- and macronutrients but also food items, that positively or negatively affected levels of the chosen inflammatory biomarkers (5). Based on the results in the articles, the authors created a scoring system that could classify individuals' diets according to values ranging from most anti-inflammatory to most pro-inflammatory (5). DII scores lie within a theoretical maximum range from −8.87 (maximally anti-inflammatory) to +7.98 (maximally pro-inflammatory) (5). The DII is standardized based on dietary intake data from 11 countries, from which global means and standard deviations (SD) for each food parameter have been calculated and included in a global referent database. In computing DII-scores, individual intakes of food parameters are compared to these referent values. The new DII version was also validated in SEASONS, where it appeared to have better construct validity than the first version (i.e., better measure the dietary inflammatory potential that it was designed to measure) (37).

1.7.2 The energy-adjusted DII (E-DII)

Over the next 4 years following the publication of the revised DII, the index formed the basis of over 160 peer-reviewed articles and 12 published meta-analyses (36). During the years of using the DII, the developers noted that there was great variation in energy and nutrient intakes and densities across populations (36). As a result, the energy-adjusted DII (E-DII) was presented in 2019 (36). This involved creating a referent database with energy-adjusted nutrient values based on data from the same 11 countries used to compute DII scores (36). The E-DII is calculated based on the same methods as for the DII, but with energy-adjusted nutrient scores in the global referent database (36). In addition, energy (kcal), which is one of the 45 food parameters in the DII, is not included in the E-DII (38). In comparison to the unadjusted DII, the E-DII has according to the developers led to improved prediction in studies (36). A detailed description of how DII/E-DII scores are calculated is presented in the method chapter.

1.7.3 The DII in relation to CRC

There have been conducted several meta-analyses exploring the link between the DII and CRC. Three meta-analyses have found an approximately 40% higher risk of CRC when

comparing the highest DII category (most pro-inflammatory) to the lowest (39-41). A fourth meta-analysis conducted a nonlinear dose-response meta-analysis where the results suggested that the risk of CRC was relatively stable at initial scores of the DII, before increasing somewhat linearly as the DII moved from the negative, more anti-inflammatory scores towards the positive, more pro-inflammatory scores (42). The observed positive association between a more pro-inflammatory diet and increased CRC risk appeared to be weaker in women than in men, suggesting that the relationship between the DII and CRC risk varies by sex (39, 40, 42). Studies have also reported that the association between the DII and CRC risk varies between different anatomical subsites of the large intestine (43, 44). However, the results are inconsistent and need further investigation.

Several mechanisms by which the DII is associated with the risk of CRC are proposed. A pro-inflammatory diet may increase insulin resistance through increasing inflammation (44). Insulin resistance is followed by increased circulating levels of insulin, triglycerides and non-esterified fatty acids, which can promote proliferation of epithelial cells in the colon and potentially expose them to reactive oxygen intermediates, which in turn can promote CRC (45). Moreover, it is hypothesized that diet can cause local inflammation and oxidative stress in the colon, resulting in focal proliferation and mutation of cells (44, 45).

2 Aim

The aim of this thesis was to assess the association between the E-DII and the risk of colorectal cancer and cancer by anatomical subsite of the colon and rectum among women in the Norwegian Women and Cancer study (NOWAC).

3 Materials and methods

3.1 The Norwegian Women and Cancer Study

The Norwegian Women and Cancer Study (NOWAC) is a population-based, prospective cohort study conducted by the Department of Community Medicine at UiT The Arctic University of Norway (46). The study was designed to explore the relationship between lifestyle factors and health, with a particular interest in female cancers. Between 1991 and 2007, the cohort recruited nearly 170,000 Norwegian women to participate. Invitations were sent by mail along with a questionnaire to women randomly sampled from the Norwegian Central Person Register. The register holds information on all Norwegian citizens, including a unique 11-digit identification number used in linkages to other national registers, ensuring an almost complete follow-up of participants (46). Of the women who were invited to participate in the study between 1991-97, 57% returned a questionnaire (46). Most questionnaires in NOWAC include four pages of core variables: menstrual and reproductive history, use of contraceptives and MHT, self-perceived health status, history of a variety of conditions and diseases, screening and family history of breast cancer, education, demographics (marital status, employment and household conditions and income), smoking status, physical activity, height and weight, and tanning habits and pigmentation (46).

3.2 Study sample

With the purpose of enrolling participants from NOWAC into the multicenter study EPIC (European Prospective Investigation into Cancer and Nutrition), women who were enrolled in 1991/92 and who agreed on being contacted again received a second questionnaire in 1998 with more detailed questions on diet (47). The crude response rate on this questionnaire was 82% (47). Those who filled out and returned this second questionnaire make up a subgroup of the NOWAC study that became part of EPIC. The Norwegian part of the EPIC cohort is the study sample of this thesis and includes 37,226 women born between 1943–57 (47).

Figure 2 presents the flow chart of participant exclusion, leading to the final number of women who were included in the analyses. Women were eligible for this thesis if they had data on the exposure variable (E-DII) (n = 37,187). Furthermore, women were excluded if they had a history of invasive cancer (except non-melanoma skin cancer), implausible energy intake (<2500 or >15,000 kJ) and missing information on the covariates education, smoking status, physical activity and BMI. Lastly, women were excluded if they had a follow-up time

of less than a year, meaning they received a cancer diagnosis, emigrated or died within the first year of follow-up.

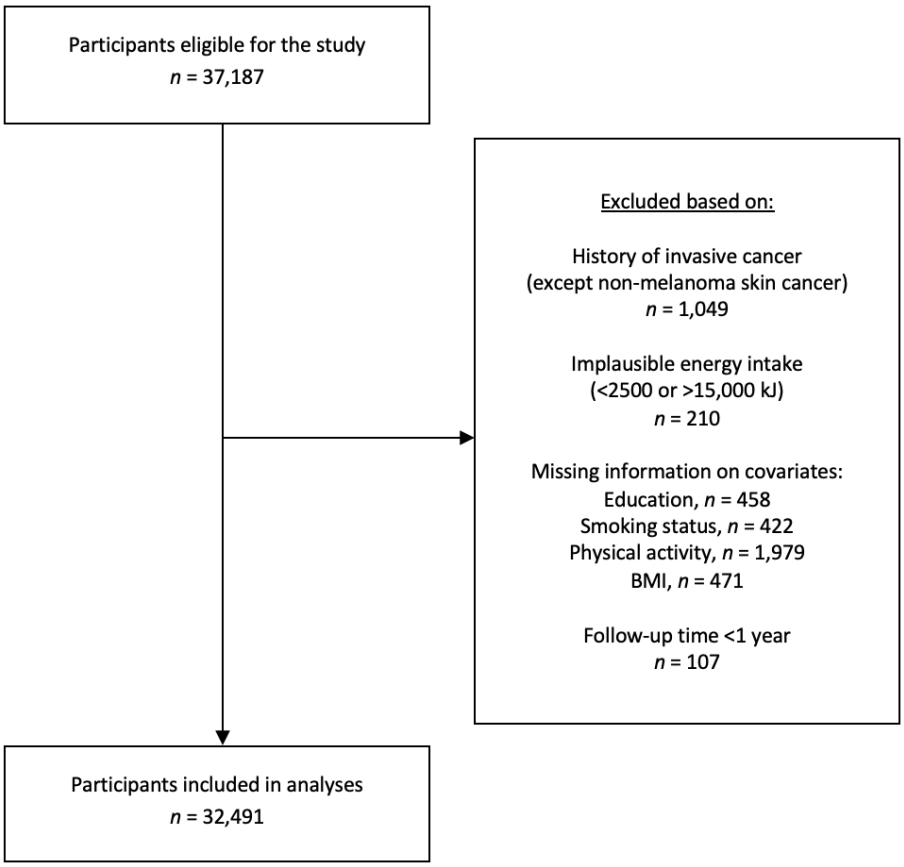

Figure 2. *Flow chart. Overview of participants included in the analyses after exclusions.*

Most variables utilized in this thesis were obtained from self-reported questionnaires, including education (years of schooling), smoking status (never, former, current), T2D (yes, no) and MHT use (never, former, current). Physical activity level (including recreational physical activity) was reported on a validated 10-point scale from 1-10, in which 1 represented "very low" and 10 represented "very high" level of physical activity (48). BMI was calculated based on self-reported height and weight (kg/m^2), which have previously proven to be a valid ranking of BMI in the NOWAC study (49). Information on age was obtained from the National Population Register in Norway.

Cancer diagnoses, deaths and emigrations were identified through linkage with the Cancer Registry of Norway and the National Population Register using the unique 11-digit personal identification number. NOWAC obtains the registry information through Statistics Norway (50).

3.3 Ethical considerations

The NOWAC study has previously received approval from The Regional Committee for Medical Research Ethics. Handling and storage of all data follow the permission given by the Norwegian Data Inspectorate (46). All women have given informed consent regarding participation in the study and linkages to national registers. Participants are at any time allowed to withdraw from the study (50).

3.4 Exposure

3.4.1 Dietary assessment

The inflammatory potential of the diet measured by the E-DII was the exposure variable in this thesis. Data on diet was obtained from the questionnaire completed by the participants in 1998, which included a four-page semiquantitative food frequency questionnaire (FFQ) (46). The FFQ asked participants to report how much and how often they consumed a variety of food items on average during the previous year (47). The FFQ included questions on 85 food items, in addition to alcohol consumption and dietary supplement use. The reported amounts consumed of each food item were converted to grams using a Norwegian weight and measurement table for foods, and the daily intake of energy and nutrients was calculated using the Norwegian Food Composition table (47, 51).

A validation study has compared the measures of the FFQ with the measures of four repeated 24-hour dietary recalls (24HDRs) in a group of 238 participants from the Norwegian EPIC cohort (52). The FFQ showed a good ability to rank the intake of foods eaten frequently as well as macronutrients in terms of energy percentages, and a weaker ability to rank the intake of foods eaten less frequently and certain micronutrients. A test-retest study found that the reproducibility of the FFQ was within the range reported for similar instruments but may attenuate estimates of disease risk (53).

The NOWAC subsample had available data on 29 of 44 food parameters used to calculate the E-DII. These included alcohol, vitamin B_{12}, vitamin B_6, β-Carotene, caffeine, carbohydrate, cholesterol, total fat, fiber, folic acid, iron, magnesium, monounsaturated fat (MUFA), onion, protein, polyunsaturated fat (PUFA), riboflavin, saturated fat (SFA), thiamin, vitamin A, vitamin C, vitamin D, vitamin E, flavan-3-ol, flavones, flavonols, flavonones, anthocyanidins and isoflavones. Food components included in the E-DII, but which were not available in the FFQ of NOWAC and therefore not included in this study are eugenol, garlic, ginger, niacin,

omega-3 and -6 fatty acids, saffron, selenium, *trans* fat, turmeric, zinc, green/black tea, pepper, thyme/oregano and rosemary.

3.4.2 Calculation of E-DII scores

Based on the literature review described in the introduction, each of the 45 food parameters received a score according to its association with the chosen inflammatory biomarkers. These values were then used in calculating individual E-DII scores based on reported food intake retrieved from FFQs. As part of previous work in the EPIC study, the E-DII scores of the women in this thesis had already been calculated in advance. A general description of how E-DII scores are calculated is written below. Figure 2 provides an example of how the DII-score (unadjusted for energy) is calculated for a simulated daily intake of saturated fat. Multiple steps are involved in calculating these scores, therefore, referring to the figure while reading the text may help for a better understanding. The numbered steps in the text correspond to the numbers in the figure. Unless otherwise specified, the description of how DII/E-DII scores are calculated is retrieved from the original DII-article (5).

Step 1

Each food parameter was assigned an inflammatory effect score based on the results and characteristics of the research articles. Each article received a value based on whether the effect of a food parameter was pro-inflammatory (+1), anti-inflammatory (-1), or had no effect (0). A pro-inflammatory effect was defined as significantly increased IL-1β, IL-6, TNF-α or CRP, or decreased IL-4 or IL-10, while an anti-inflammatory effect was defined as the opposite. If an article showed contradictory results, it received a value for each inflammatory effect reported. Articles were further weighted according to their study design. Human studies received the highest values (experimental = 10, prospective cohort = 8, case-control = 7, cross-sectional = 6), followed by experimental animal and cell-culture studies which received values 5 and 3, respectively. The developers first calculated a "raw inflammatory effect score" for each food parameter. This was done by assigning weights to each article by multiplying them with their respective study design. The weights for articles reporting anti-inflammatory, pro-inflammatory and no inflammatory effects were then summed separately. Further, the anti-inflammatory and pro-inflammatory weights were divided by the total weighted number of articles. Based on the values initially assigned to articles for their inflammatory effect, the anti-inflammatory (−1) fraction was subtracted from the pro-inflammatory (+1) fraction, resulting in the raw inflammatory effect score. The weight for

articles reporting no effect was included only in the total weighted number of articles. Next, the "overall inflammatory effect score" for each food parameter was calculated. Due to variations in the number and quality of articles on each food parameter, the authors determined a cut-off point to represent a robust pool of literature. They selected the median of the total weighted number of articles across all food parameters, which was 236. If a food parameter had a weighted number of articles ≥ 236, the "raw inflammatory effect score" was considered robust and used as the "overall inflammatory effect score". For food parameters with a weighted number of articles < 236, the score was adjusted by dividing the number of weighted articles by 236, and then multiplying by the "raw inflammatory effect score". The "overall inflammatory effect score" for each food parameter is presented in appendix 1.

Step 2

To meet the challenges of comparing the DII/E-DII across different populations with varying food cultures, the developers created a global database that provides mean and standard deviation values for the daily intake of each of the 45 food parameters in 11 different countries. Individual intakes of food parameters were expressed relative to these referent values by computing Z-scores. This was done by subtracting the global mean intake of a food parameter from the individual reported intake and dividing this value by its standard deviation. When computing energy-adjusted DII scores, the participants' food intake was adjusted for energy using the residual method, and then compared to the energy-adjusted version of the global referent database (36). The residual method computes nutrient intakes as residuals from a regression model, where the independent variable is total energy intake, and the dependent variable is absolute nutrient intake (54). To reduce the impact of "right skewing", which is commonly seen in the distribution of data on dietary intake, the Z-scores were converted to cumulative proportions based on the standard normal distribution (36). The values were then transformed into a symmetrical distribution centered around zero and bounded between −1 and +1 by multiplying the cumulative proportions by 2 and then subtracting 1 (36).

Step 3

Lastly, to obtain the "specific DII score" for a food parameter, the overall inflammatory effect score (derived from literature) calculated in step 1 was multiplied by the centered cumulative proportion value (based on reported intake) calculated in step 2. The specific DII scores for

each food parameter were summed to create an overall DII score, representing the inflammatory potential of an individual's diet.

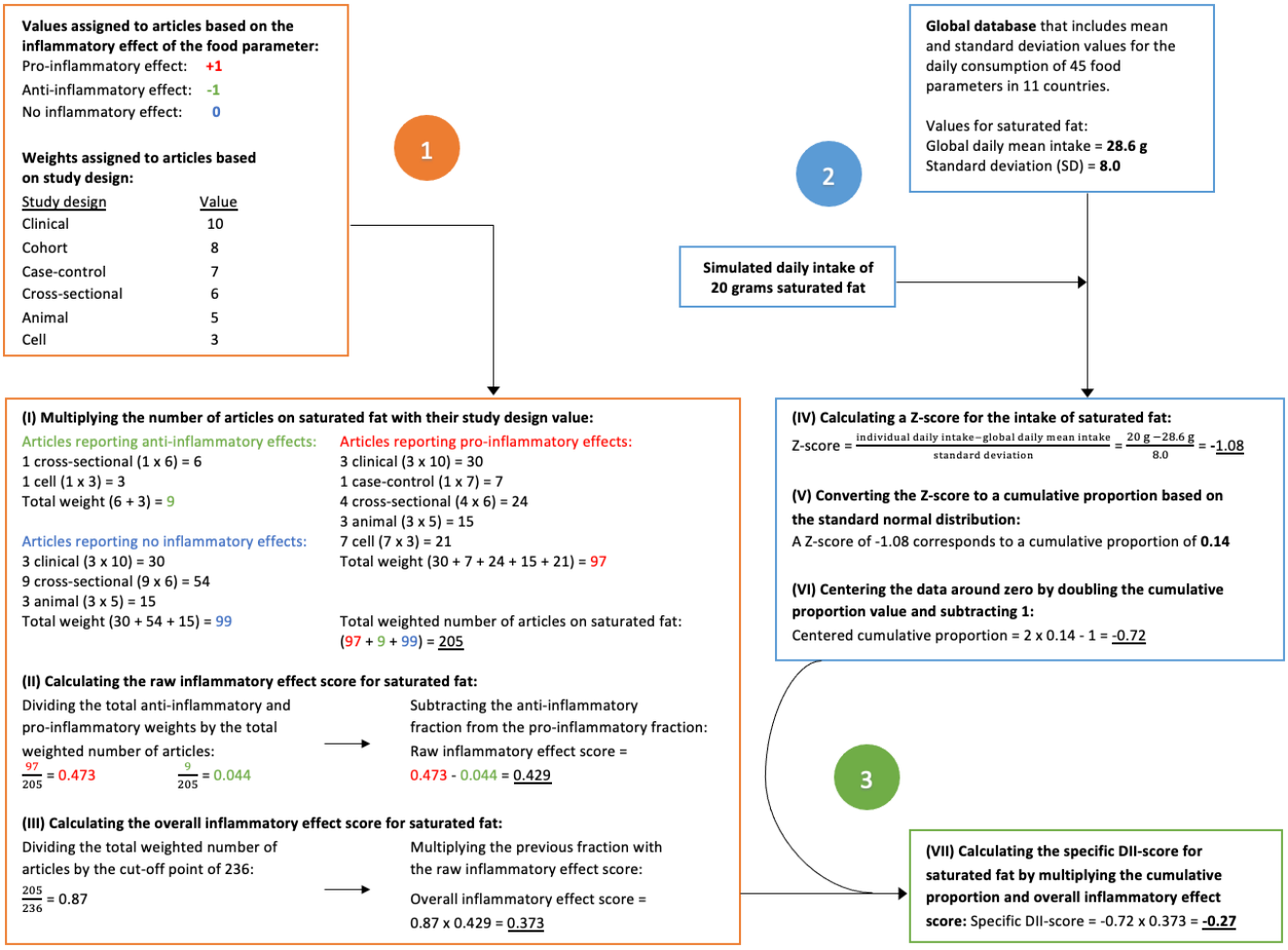

Figure 3. *Example of how the DII-score for a simulated daily intake of saturated fat is calculated. All values in step 1 and the global referent values for saturated fat in step 2 are retrieved from the original article on DII (5). The cumulative proportion in step 2 was obtained from a standard normal table.*

3.5 Outcome ascertainment

The outcome variables were CRC and cancer in the colon, proximal colon, distal colon and rectum. Data on incident CRC cases up to December 31, 2020 was available. CRC cases were classified according to the 10th Revision of the International Classification of Diseases (ICD-10) as shown in table 1. Proximal colon cancer included cancer within the cecum, appendix, ascending colon, hepatic flexure, transverse colon and splenic flexure (C18.0–18.5). Distal colon cancer included cancer within the descending and sigmoid colon (C18.6–18.7). Rectal cancer included cancer within the rectosigmoid junction (C19) and rectum (C20). Colon cancer included proximal and distal colon cancer (C18.0–18.7), in addition to cancer in

overlapping (C18.8) and unspecified (18.9) colon sites. CRC included cancer within all sites (C18–20).

Table 1. *The anatomical subsites of the colon and rectum and their associated ICD-10-codes*

Colorectal cancer site	ICD-10 code
Colon	
Proximal colon	
Cecum	C18.0
Appendix	C18.1
Ascending colon	C18.2
Hepatic flexure	C18.3
Transverse colon	C18.4
Distal colon	
Splenic flexure	C18.5
Descending colon	C18.6
Sigmoid colon	C18.7
Overlapping and unspecified colon sites	
Malignant neoplasm of overlapping sites of colon	C18.8
Colon unspecified	C18.9
Rectum	
Rectosigmoid junction	C19
Rectum	C20

3.6 Covariates

3.6.1 Selection of covariates

Covariates are variables that might be predictive of the outcome of interest (6). A covariate may be a confounding variable, which is a common cause of the exposure and outcome of interest that must be accounted for to avoid potential bias in the estimated effect (6). In this thesis, covariates were chosen *a priori* through literature, and a directed acyclic graph (DAG) was used to identify the variables that needed to be adjusted for when estimating the relationship between the E-DII and CRC. The following covariates were identified and included in the DAG based on literature: Age, height, educational level, smoking status, physical activity level, BMI, T2D, use of MHT and NSAIDs, IBD and genetic factors. The dietary variables alcohol, red and processed meat, dairy and fiber were also identified as covariates although not included in the DAG because of their role as food parameters or sources of food parameters in the E-DII. Since the E-DII is adjusted for energy, total energy intake was also not included.

3.6.2 Building a DAG to identify confounders

Directed acyclic graphs (DAGs) are tools that visualize causal relationships between variables and are used to help identify confounders as well as variables that should not be adjusted for, such as mediators (variables on the causal pathway between an exposure and an outcome) and colliders (common effects of an exposure and an outcome) (6, 55). DAGs illustrate causal relationships as nodes connected by arrows, where the nodes represent the variables, and the arrows represent the hypothesized relationships between them (55). The arrows indicate the direction of the relationship and can only point in one direction, hence "directed" (55). "Acyclic" refers to the fact that a node cannot be caused by itself and therefore, the graphs do not contain any cycles (55).

Figure 4 presents the DAG built to identify potential confounding variables in the relationship between the E-DII and CRC. The green node (E-DII) and the blue node (CRC) represent the exposure and outcome of interest, respectively. The white nodes (age, height, education, smoking, physical activity and T2D) are confounding factors. The blue node (MHT) is an ancestor of the outcome. The red node (BMI) is an ancestor of both the exposure and the outcome. The gray nodes (IBD, NSAIDs and genetic factors) are unobserved variables.

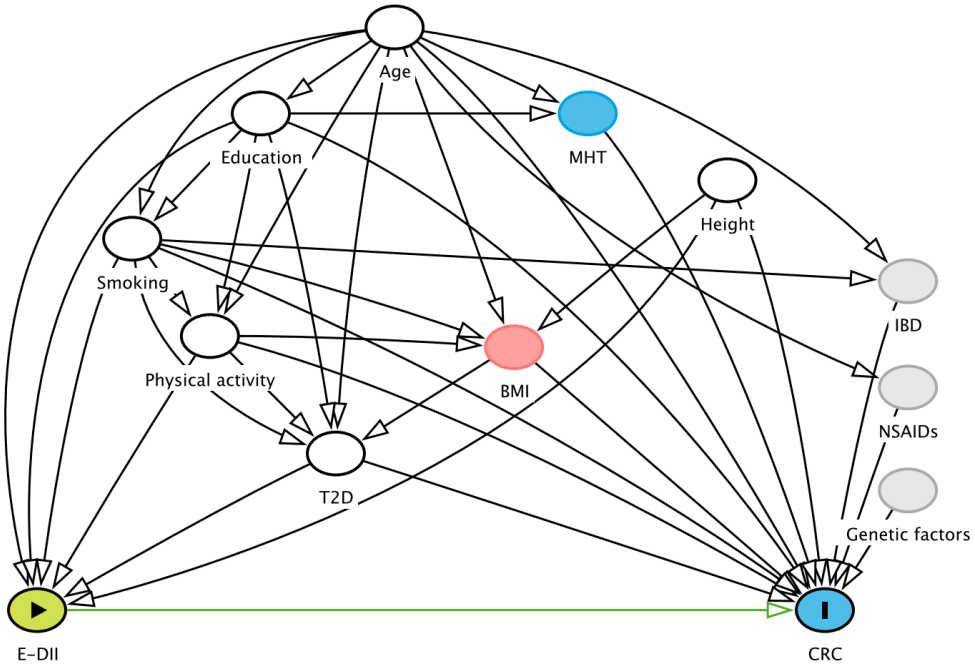

Figure 4. Directed acyclic graph illustrating the hypothesized causal relationships between covariates in the association between the E-DII and CRC. E-DII = energy-adjusted dietary inflammatory index, CRC = colorectal cancer, T2D = type 2 diabetes, BMI = body mass index, MHT = menopausal hormone therapy, IBD = inflammatory bowel disease, NSAIDs = non-steroidal anti-inflammatory drugs. *(Created with DAGitty (56)).*

Directed edges were drawn originating from every covariate, terminating at CRC, based on their role in CRC risk. As previously described in the introduction, increasing age, smoking, overweight and obesity (BMI), height, T2D, IBD and genetic factors are associated with increased risk of CRC, while physical activity and use of MHT and NSAIDs are associated with reduced risk of CRC. In addition, women with higher levels of education are found to have a lower risk of CRC (57).

Age is closely related to several lifestyle factors, and directed edges were drawn from age to every covariate, except for genetic factors. This is based on the assumptions that increasing age may lead to changes in food intake and dietary habits (E-DII), decreased level of physical activity, changes in smoking habits and changes in metabolism and body composition (BMI). Moreover, the access to education and the use of MHT and NSAIDs may have varied in the study population depending on their age. Increasing age is also a risk factor for many diseases including T2D, and may also affect the risk of IBD (58).

Based on the assumption that taller individuals have a higher energy expenditure compared to shorter people, leading to increased energy intake that can affect food choices, a directed edge was drawn from height to E-DII. In addition, height is a determinant in the calculation of BMI, hence, an arrow was drawn pointing from height to BMI.

Compared to people with shorter education, people with longer education are more likely to have a healthy diet as well as higher alcohol consumption. Moreover, they smoke less, are more physically active, less likely to have overweight or obesity, and more likely to have T2D (59). In addition, it is assumed that level of education can influence choices regarding the use of MHT. Therefore, directed edges were drawn from education to E-DII, smoking, physical activity, BMI, T2D and MHT.

Directed edges were further drawn from smoking to E-DII, physical activity, BMI, T2D and IBD. This is based on the assumptions that smoking affects both diet and BMI through decreased appetite and increased energy expenditure. Moreover, smoking is thought to be associated with alcohol consumption, and the effects of smoking may influence a person's level of physical activity. Lastly, smoking is a risk factor for T2D (60) and IBD (Crohn's disease, but not ulcerative colitis) (58).

BMI is a risk factor for T2D, and a directed edge was therefore drawn from BMI to T2D. Moreover, it is an ongoing discussion whether inflammation is a consequence of obesity, a

cause of obesity, or if the association is bidirectional (61, 62). It is possible that BMI is a mediator in the relationship between E-DII and CRC (E-DII → BMI → CRC). However, because of the uncertainty, no arrow was drawn between E-DII and BMI. Instead, BMI was considered a potential effect modifier in the E-DII-CRC association based on the assumption that BMI acts on CRC risk through pathways related to inflammation. Having overweight or obesity is associated with chronic low-grade inflammation, and it is possible that a pro-inflammatory diet might act differently in terms of CRC risk between individuals with under- or normal-weight and individuals with overweight or obesity.

Lastly, an arrow was drawn from T2D to E-DII based on the assumption that T2D may influence food choices, especially since dietary modification is a common strategy of managing the disease.

3.7 Statistical analyses

3.7.1 Descriptive statistics

Analyses were performed using Stata version 17.0 (63). The E-DII was converted to equally distributed quartiles for analyses. Descriptive statistics were conducted for baseline characteristics by quartiles of the E-DII (table 2). Some of the variables were categorized beforehand: BMI was categorized into <20 kg/m^2 (underweight), 20–24.9 kg/m^2 (normal weight), 25–29.9 kg/m^2 (overweight) and ≥30 kg/m^2 (obesity), education was categorized into <10, 10–12 and >12 years of schooling, and physical activity was divided into categories representing low (1–3), moderate (4–7) and high (8–10) levels of physical activity. Missing values for T2D (yes, no) were given the value of "no". Continuous variables are presented as means and standard deviations while categorical variables are presented as the number and percentage of participants in each category (n (%)).

Additional descriptive statistics were conducted for the intake of energy and selected food groups and nutrients by quartile of the E-DII (table 3). These variables are a combination of dietary covariates and food parameters (or sources of food parameters) included in the E-DII that were available in the dataset. The purpose of table 3 was to provide an insight into what drives high and low E-DII scores in the study sample. Before the descriptives were conducted, alcohol (g/d) was categorized into non-consumer and consumption below and above median, in which the median was based on the values of consumers. Moreover, a variable for dairy was computed by summarizing the intake of milk, hard white cheese and yogurt. Similarly,

red and processed meat was computed by summarizing the intake of roast (beef, pork and mutton), steak, chops, meatballs, hamburgers, sausages, sandwich meats and liver paté. The intake of energy and macronutrients (fat, carbohydrate and protein) is expressed as percentages of total energy intake (E%). Dietary variables are presented as medians and interquartile ranges, except for alcohol, which is presented as the number and percentage of participants in each category. The dietary data was not normally distributed, and the variables were therefore not adjusted for energy due to difficulties using the residual method on non-normally distributed data. Pearson's correlation was used to test for correlation between the E-DII and total energy intake.

3.7.2 Cox proportional hazards models

Cox proportional hazards regression was used to estimate Hazard ratios (HRs), 95% confidence intervals (CIs) and linear trends for the association between the E-DII and the risk of CRC and cancer by anatomical subsite of the colon and rectum (colon, proximal colon, distal colon and rectum). Age was used as time-scale, in which time of entry was considered age at baseline (i.e., age at completion of the second questionnaire in 1998) and time of exit was the age at end of follow-up (December 31, 2020), death, emigration or cancer diagnosis of any type, depending on which event occurred first. Statistical significance was defined as a p-value of less than 0.05. The assumption of proportional hazards was tested by visual inspection of Schoenfeld residuals.

Two Cox models were developed to assess the relationship between the E-DII and the CRC outcomes. The first model adjusted for age and is referred to as the age-adjusted model. The second, multivariable-adjusted model adjusted for age in addition to the confounding variables identified in the DAG. Height was included in the multivariate model as a continuous measure, whereas education, smoking, physical activity, and T2D were included as categorical measures in the same format as in the descriptive statistics. The lowest E-DII quartile, representing the most anti-inflammatory diet, was used as the reference category in all models. To test whether there was a linear trend in the outcome across the E-DII quartiles, each participant was assigned the median E-DII value for their quartile and then this variable was entered in the Cox models as a continuous measure.

To investigate whether BMI acted as an effect modifier in the association between the E-DII and CRC outcomes, additional analyses stratified by BMI were conducted. Cox analyses were carried out separately for participants with BMI <25 kg/m^2 (under- and normal weight) and

≥25 kg/m^2 (overweight and obesity). It was decided to divide BMI into two groups to ensure a sufficient number of cases in each group. Sensitivity analyses for both the main and BMI-stratified analyses were conducted by starting follow-up in 2001, three years after baseline. Women with less than three years of follow-up were therefore excluded from the analyses. The presence of subclinical disease at baseline may affect a participant's diet and modify the dietary intake being reported. Hence, sensitivity analyses may reduce the possibility of reverse causality in the observed associations between the E-DII and CRC.

4 Results

4.1 Descriptive statistics

Baseline characteristics of the study sample (n = 32,491) are presented in table 2. The E-DII ranged from −5.04 to 4.12 and was divided into quartiles: Q1 (−5.04, −0.76), Q2 (−0.76, 0.33), Q3 (0.33, 1.33) and Q4 (1.33, 4.12). The distribution of E-DII scores in the study sample was normally distributed as shown in the histogram in figure 5. Mean (SD) E-DII score of the whole sample was 0.21 (1.44). Q1 included participants with the lowest E-DII scores, representing the most anti-inflammatory diets, while Q4 included participants with the highest E-DII scores, representing the most pro-inflammatory diets. Individuals with a more pro-inflammatory diet (Q3 and Q4) were likely to have a higher BMI, be less educated (≤12 years), be current smokers and be less physically active compared to individuals with a more anti-inflammatory diet (Q1 and Q2). Q1 had a higher number of individuals with diabetes at baseline, as well as former and current users of MHT.

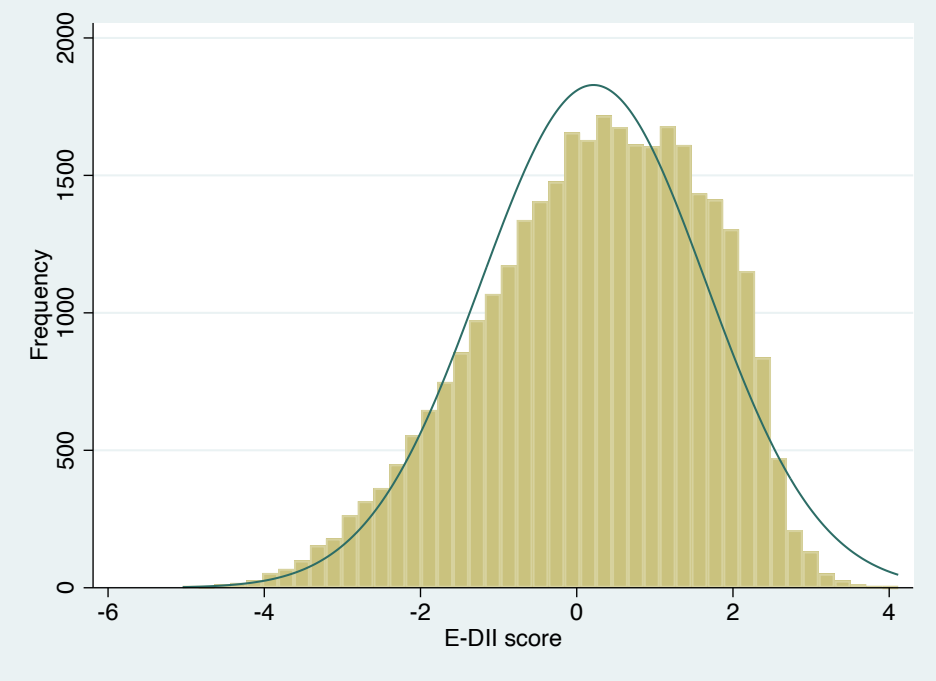

Figure 5. *Histogram of the distribution of E-DII scores in the study sample.*

Table 2. *Baseline characteristics of the study sample (n = 32,491) by quartiles of the E-DII, the NOWAC study*

E-DII quartile	**Q1**	**Q2**	**Q3**	**Q4**
n	8,123	8,123	8,123	8,122
E-DII score, median (IQR)	−1.56 (−5.04, −0.76)	−0.17 (−0.76, 0.33)	0.83 (0.33, 1.33)	1.90 (1.33, 4.12)
Characteristic				
Age at recruitment, years	48.2 (4.3)	47.7 (4.3)	47.5 (4.3)	47.0 (4.2)
Height, cm	167 (6)	167 (6)	167 (6)	166 (6)
BMI, kg/m^2				
<20	650 (8%)	623 (8%)	612 (8%)	650 (8%)
20–24.9	4,833 (60%)	4,650 (57%)	4,382 (54%)	4,518 (56%)
25–29.9	2,101 (26%)	2,190 (27%)	2,345 (29%)	2,219 (27%)
≥30	539 (7%)	660 (8%)	784 (10%)	735 (9%)
Educational level, years				
<10	1,485 (18%)	1,710 (21%)	1,854 (23%)	1,811 (22%)
10–12	2,682 (33%)	2,940 (36%)	3,011 (37%)	3,206 (40%)
>12	3,956 (49%)	3,473 (43%)	3,258 (40%)	3,105 (38%)
Smoking status				
Never	2,899 (36%)	2,913 (36%)	2,805 (35%)	2,484 (31%)
Former	3,034 (37%)	2,725 (34%)	2,643 (33%)	2,598 (32%)
Current	2,190 (27%)	2,485 (31%)	2,675 (33%)	3,040 (37%)
Physical activity level				
Low	679 (8%)	832 (10%)	1,096 (14%)	1,314 (16%)
Moderate	6,060 (75%)	6,229 (77%)	6,151 (76%)	5,973 (74%)
High	1,384 (17%)	1,062 (13%)	876 (11%)	835 (10%)
Diabetes at baseline, yes	125 (2%)	113 (1%)	90 (1%)	60 (1%)
MHT use				
Never	5,579 (69%)	5,774 (71%)	5,893 (73%)	6,011 (74%)
Former	547 (7%)	530 (7%)	519 (6%)	440 (5%)
Current	1,997 (25%)	1,819 (22%)	1,711 (21%)	1,671 (21%)

Characteristics are presented as mean (SD) for continuous measures and n (%) for categorical measures.
BMI = body mass index, MHT = menopausal hormone therapy, IQR = interquartile range

The intake of energy and selected food groups and nutrients in the study sample are presented in table 3. Women in Q1 with the most anti-inflammatory diets had the highest intake of total energy, fiber, calcium, vitamin A, vitamin D and fruit and vegetables, with values that decreased with increasing quartile. Women in Q1 and Q2 had the same intake of dairy, which was higher compared to women in Q3 and Q4. The intake of red and processed meat was lowest in Q1 and highest in Q4. Women in Q4 were more likely to consume alcohol, however, women in Q1 had the highest proportion of women consuming alcohol above median. There were minimal differences in the intake of fats, carbohydrate and protein in terms of energy percentages across the quartiles. Because the food groups and nutrients are not energy-adjusted, differences between quartiles may be partly due to differences in total energy intake. A moderate negative Pearson's correlation coefficient of −0.3 between the E-DII and total energy intake was observed, indicating that the total energy intake decreases as the pro-inflammatory potential of the diet increases.

Table 3. *Intake of energy and selected food groups and nutrients by quartiles of the E-DII, the NOWAC study*

E-DII quartile (range)	Q1 (−5.04, −0.76)[a]	Q2 (−0.76, 0.33)	Q3 (0.33, 1.33)	Q4 (1.33, 4.12)[a]
n	8,123	8,123	8,123	8,122
Energy, MJ/day	7.8 (6.8–9.1)	7.4 (6.3–8.7)	6.8 (5.7–8.0)	6.2 (5.2–7.3)
Total fat, E%	33 (29–36)	33 (30–37)	33 (30–37)	34 (31–38)
MUFA, E%	10 (9–12)	10 (9–12)	10 (9–12)	11 (10–12)
PUFA, E%	6 (5–7)	6 (5–7)	6 (5–7)	5 (5–6)
Carbohydrate, E%	48 (44–51)	47 (44–51)	47 (43–51)	46 (42–49)
Protein, E%	17 (16–19)	17 (16–19)	18 (16–19)	18 (16–19)
Fiber, g/day	26 (22–30)	23 (19–26)	20 (17–23)	17 (14–20)
Calcium, mg/day	773 (589–1019)	748 (559–989)	689 (512–929)	657 (479–890)
Vitamin D, µg/day	13 (7–19)	7 (4–13)	5 (3–6)	3 (2–5)
Vitamin A, µg/day	2241 (1688–2995)	1660 (1248–2182)	1200 (905–1562)	900 (683-1169)
Red and processed meat, g/day[b]	44 (28–63)	48 (32–68)	48 (33–67)	49 (33–67)
Dairy, g/day[c]	216 (95–360)	216 (95–374)	195 (89–322)	189 (82–316)
Fruit and vegetables, g/day	453 (336–597)	313 (229–414)	255 (185–337)	177 (116–245)
Alcohol				
Non-consumer	872 (11%)	743 (9%)	728 (9%)	238 (3%)
Below median	3,064 (38%)	3,874 (48%)	4,262 (53%)	4,518 (56%)
Above median	4,187 (52%)	3,506 (43%)	3,133 (39%)	3,366 (41%)

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.
N = 32,491. E% = percentage of total energy intake, MJ = megajoule, g = gram, mg = milligram, µg = microgram.
[a]Q1 = most anti-inflammatory; Q4 = most pro-inflammatory
[b]Red and processed meat includes roast (beef, pork and mutton), steak, chops, meatballs, hamburgers, sausages, sandwich meats and liver paté.
[c]Dairy includes total milk, hard white cheese and yogurt

4.2 The association between the E-DII and the risk of CRC and cancer by anatomical subsite of the colon and rectum

During an average of 20.3 years of follow-up, a total of 694 CRC cases were identified. Of these, there were 480 colon and 214 rectal cancer cases. 285 of the colon cancers were in the proximal colon and 184 in the distal colon. The results from the main analysis are presented in table 4 and will be further described.

CRC

Slightly positive associations between a more pro-inflammatory diet and increased CRC risk were observed, as indicated by elevated HRs in both the age-adjusted (HR: 1.07; 95% CI: 0.87–1.31) and multivariable-adjusted (HR: 1.04; 95% CI: 0.84–1.28) analyses when comparing Q4 (most pro-inflammatory) to Q1 (most anti-inflammatory). However, the results were not statistically significant. Furthermore, there was no evidence for a linear trend across quartiles, as indicated by the nonsignificant values for *p*-trend.

Colon cancer

No significant associations were seen between the E-DII and the risk of colon cancer. The highest HRs were seen in Q4 in the age-adjusted (HR: 1.11; 95% CI: 0.86–1.42) and multivariable-adjusted (HR: 1.06; 95% CI: 0.82–1.37) analyses. No linear trend was observed across the quartiles.

Proximal colon cancer

Positive associations between a more pro-inflammatory diet and increased risk of proximal colon cancer were seen in the age-adjusted ($HR_{Q4\ vs\ Q1}$: 1.27; 95% CI: 0.91–1.77) and multivariable-adjusted ($HR_{Q4\ vs\ Q1}$: 1.21; 95% CI: 0.86–1.69) models. The estimates for Q3 were of similar magnitude. However, the estimates were not statistically significant, and there was no evidence of a linear trend across the E-DII quartiles.

Distal colon and rectal cancer

No positive associations were seen between higher E-DII-quartiles and the risk of distal colon or rectal cancer. The association across quartiles was not statistically significant in either of the analyses.

Table 4. *Association between the E-DII and the risk of colorectal cancer and cancer by anatomical subsite of the colon and rectum, the NOWAC study*

E-DII quartile (range)	*n* (cases)	Age[1] HR (95% CI)	Multivariate[2] HR (95% CI)
Colorectal cancer			
Q1 (−5.04, −0.76)	8123 (184)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	8123 (168)	0.95 (0.77–1.18)	0.94 (0.77–1.17)
Q3 (0.33, 1.33)	8123 (168)	0.98 (0.79–1.21)	0.97 (0.78–1.19)
Q4 (1.33, 4.12)	8122 (174)	1.07 (0.87–1.31)	1.04 (0.84–1.28)
p-trend		0.56	0.76
Colon cancer			
Q1 (−5.04, −0.76)	8123 (123)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	8123 (117)	1.00 (0.77–1.29)	0.98 (0.76–1.26)
Q3 (0.33, 1.33)	8123 (121)	1.06 (0.83–1.37)	1.04 (0.81–1.34)
Q4 (1.33, 4.12)	8122 (119)	1.11 (0.86–1.42)	1.06 (0.82–1.37)
p-trend		0.39	0.59
Proximal colon cancer			
Q1 (−5.04, −0.76)	8123 (68)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	8123 (67)	1.05 (0.75–1.47)	1.02 (0.73–1.44)
Q3 (0.33, 1.33)	8123 (77)	1.25 (0.90–1.73)	1.21 (0.87–1.68)
Q4 (1.33, 4.12)	8122 (73)	1.27 (0.91–1.77)	1.21 (0.86–1.69)
p-trend		0.10	0.18
Distal colon cancer			
Q1 (−5.04, −0.76)	8123 (50)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	8123 (47)	0.97 (0.65–1.44)	0.96 (0.64–1.43)
Q3 (0.33, 1.33)	8123 (41)	0.86 (0.57–1.30)	0.85 (0.56–1.28)
Q4 (1.33, 4.12)	8122 (46)	1.00 (0.67–1.49)	0.97 (0.65–1.46)
p-trend		0.84	0.73
Rectal cancer			
Q1 (−5.04, −0.76)	8123 (61)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	8123 (51)	0.86 (0.60–1.25)	0.87 (0.60–1.26)
Q3 (0.33, 1.33)	8123 (47)	0.81 (0.56–1.19)	0.82 (0.56–1.21)
Q4 (1.33, 4.12)	8122 (55)	0.99 (0.69–1.43)	0.99 (0.68–1.43)
p-trend		0.80	0.81

N = 32,491

[1]The model is adjusted for age

[2]The model is adjusted for age, height, education, smoking, physical activity and type 2 diabetes

HR = Hazard ratio, CI = confidence interval, ref = reference

4.3 BMI-stratified analyses of the association between the E-DII and the risk of CRC and cancer by anatomical subsite of the colon and rectum

The results from the analyses stratified by BMI are presented in table 5 for the lower BMI group (<25 kg/m^2) and in table 6 for the higher BMI group (≥25 kg/m^2). Of all women, 20,918 were included in the lower BMI group, in which 436 CRC cases were identified. Of these, 301 cases were in the colon, 174 in the proximal colon, 118 in the distal colon and 135 in the rectum. In the higher BMI group, 11,573 women were included, in which 258 CRC cases were identified. Of these, there were 179 colon, 111 proximal colon, 66 distal colon and 79 rectal cancer cases.

CRC

The estimated effect of the E-DII on CRC risk continued to show non-significant associations in the BMI-stratified analyses. In the lower BMI group, HRs were slightly elevated, mainly in Q2 and Q3. The highest estimates were seen for Q3 with an age-adjusted HR of 1.07 (95% CI: 0.82–1.39) and a multivariable-adjusted HR of 1.05 (95% CI: 0.81–1.37). In the higher BMI group (≥25 kg/m^2), HRs in Q4 were elevated in both the age-adjusted (HR: 1.10; 95% CI: 0.79–1.53) and the multivariable-adjusted (HR: 1.07; 95% CI: 0.76–1.50) analyses. There was no evidence of a linear trend across the E-DII quartiles.

Colon cancer

No significant associations were seen between the E-DII and colon cancer in the BMI subgroup analyses. Similarly to the results for CRC, the estimates were elevated for Q2 and Q3 in the lower BMI group. The highest HRs were seen in Q3 in both the age-adjusted (HR: 1.22; 95% CI: 0.89–1.67) and the multivariable-adjusted (HR: 1.19; 95% CI: 0.87–1.63) analyses. In the higher BMI group, elevated HRs were seen in Q4 in the age-adjusted (HR: 1.22; 95% CI: 0.82–1.82) and multivariable-adjusted (HR: 1.16; 95% CI: 0.78–1.73) analyses. The association across quartiles was not significant.

Proximal colon cancer

In the analyses for proximal colon cancer, HRs were elevated for Q2, Q3 and Q4 in the lower BMI group. The highest HRs were observed in Q3 with an age-adjusted HR of 1.45 (95% CI: 0.95–2.22) and a multivariable-adjusted HR of 1.38 (95% CI: 0.90–2.10). In the higher BMI group, HRs were elevated in Q4 in the age-adjusted (HR: 1.23; 95% CI: 0.74–2.03) and

multivariable-adjusted (HR: 1.18; 95% CI: 0.71–1.97) analyses. However, the estimates did not achieve statistical significance, and no linear trend was observed across the quartiles.

Distal colon cancer

No significant associations were found between the E-DII and the risk of distal colon cancer in either of the BMI subgroups. HRs were elevated in Q4 in the higher BMI group, with an age-adjusted HR of 1.29 (95% CI: 0.68–2.48) and a multivariable-adjusted HR of 1.18 (95% CI: 0.61–2.29). There was no evidence for a linear trend across the quartiles.

Rectal cancer

No positive associations were seen between higher E-DII scores and the risk of rectal cancer in the higher BMI group. In the lower BMI group, HRs in Q4 were slightly elevated with an age-adjusted HR of 1.08 (95% CI: 0.68–1.69) and a multivariable-adjusted HR of 1.04 (0.66–1.65). No linear trend was observed across the quartiles.

Table 5. *Association between the E-DII and the risk of colorectal cancer and cancer by anatomical subsite of the colon and rectum in women with BMI <25 kg/m^2, the NOWAC study*

BMI <25 kg/m^2			
E-DII quartile (range)	***n* (cases)**	**Age[1] HR (95% CI)**	**Multivariate[2] HR (95% CI)**
Colorectal cancer			
Q1 (−5.04, −0.76)	5,483 (117)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	5,273 (113)	1.06 (0.82–1.37)	1.05 (0.81–1.36)
Q3 (0.33, 1.33)	4,994 (105)	1.07 (0.82–1.39)	1.05 (0.81–1.37)
Q4 (1.33, 3.85)	5,168 (101)	1.04 (0.79–1.35)	1.01 (0.77–1.32)
p-trend		0.75	0.92
Colon cancer			
Q1 (−5.04, −0.76)	5,483 (78)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	5,273 (79)	1.12 (0.82–1.53)	1.10 (0.80–1.50)
Q3 (0.33, 1.33)	4,994 (79)	1.22 (0.89–1.67)	1.19 (0.87–1.63)
Q4 (1.33, 3.85)	5,168 (65)	1.01 (0.73–1.41)	0.98 (0.71–1.37)
p-trend		0.70	0.85
Proximal colon cancer			
Q1 (−5.04, −0.76)	5,483 (40)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	5,273 (47)	1.32 (0.87–2.01)	1.26 (0.83–1.93)
Q3 (0.33, 1.33)	4,994 (47)	1.45 (0.95–2.22)	1.38 (0.90–2.10)
Q4 (1.33, 3.85)	5,168 (40)	1.27 (0.82–1.98)	1.20 (0.77–1.88)
p-trend		0.20	0.32
Distal colon cancer			
Q1 (−5.04, −0.76)	5,483 (34)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	5,273 (29)	0.92 (0.56–1.50)	0.93 (0.57–1.53)
Q3 (0.33, 1.33)	4,994 (30)	1.02 (0.62–1.67)	1.04 (0.64–1.71)
Q4 (1.33, 3.85)	5,168 (25)	0.84 (0.50–1.41)	0.85 (0.51–1.44)
p-trend		0.63	0.68
Rectal cancer			
Q1 (−5.04, −0.76)	5,483 (39)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	5,273 (34)	0.94 (0.60–1.49)	0.94 (0.59–1.49)
Q3 (0.33, 1.33)	4,994 (26)	0.78 (0.47–1.28)	0.77 (0.47–1.27)
Q4 (1.33, 3.85)	5,168 (36)	1.08 (0.68–1.69)	1.04 (0.66–1.65)
p-trend		0.99	0.91

N = 20,918

[1]The model is adjusted for age

[2]The model is adjusted for age, height, education, smoking, physical activity and type 2 diabetes

HR = Hazard ratio, CI = confidence interval, ref = reference

Table 6. *Association between the E-DII and the risk of colorectal cancer and cancer by anatomical subsite of the colon and rectum in women with BMI ≥25 kg/m², the NOWAC study*

BMI ≥25 kg/m²			
E-DII quartile (range)	***n* (cases)**	**Age[1] HR (95% CI)**	**Multivariate[2] HR (95% CI)**
Colorectal cancer			
Q1 (−5.01, −0.76)	2,640 (67)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	2,850 (55)	0.78 (0.55–1.12)	0.78 (0.54–1.11)
Q3 (0.33, 1.33)	3,129 (63)	0.84 (0.60–1.19)	0.83 (0.59–1.18)
Q4 (1.33, 4.12)	2,954 (73)	1.10 (0.79–1.53)	1.07 (0.76–1.50)
p-trend		0.60	0.72
Colon cancer			
Q1 (−5.01, −0.76)	2,640 (45)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	2,850 (38)	0.81 (0.52–1.24)	0.80 (0.52–1.23)
Q3 (0.33, 1.33)	3,129 (42)	0.84 (0.55–1.28)	0.81 (0.53–1.24)
Q4 (1.33, 4.12)	2,954 (54)	1.22 (0.82–1.82)	1.16 (0.78–1.73)
p-trend		0.35	0.52
Proximal colon cancer			
Q1 (−5.01, −0.76)	2,640 (28)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	2,850 (20)	0.69 (0.39–1.22)	0.69 (0.39–1.22)
Q3 (0.33, 1.33)	3,129 (30)	0.98 (0.58–1.64)	0.97 (0.58–1.63)
Q4 (1.33, 4.12)	2,954 (33)	1.23 (0.74–2.03)	1.18 (0.71–1.97)
p-trend		0.31	0.38
Distal colon cancer			
Q1 (−5.01, −0.76)	2,640 (16)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	2,850 (18)	1.06 (0.54–2.09)	1.02 (0.52–2.01)
Q3 (0.33, 1.33)	3,129 (11)	0.61 (0.28–1.31)	0.55 (0.26–1.20)
Q4 (1.33, 4.12)	2,954 (21)	1.29 (0.68–2.48)	1.18 (0.61–2.29)
p-trend		0.75	0.97
Rectal cancer			
Q1 (−5.01, −0.76)	2,640 (22)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	2,850 (17)	0.73 (0.39–1.38)	0.74 (0.39–1.40)
Q3 (0.33, 1.33)	3,129 (21)	0.84 (0.46–1.53)	0.87 (0.48–1.60)
Q4 (1.33, 4.12)	2,954 (19)	0.85 (0.46–1.57)	0.88 (0.47–1.64)
p-trend		0.65	0.75

N = 11,573

[1]The model is adjusted for age

[2]The model is adjusted for age, height, education, smoking, physical activity and type 2 diabetes

HR = Hazard ratio, CI = confidence interval, ref = reference

4.4 Sensitivity analyses

By starting follow-up three years after baseline, 479 women were excluded, leaving 32,012 women for sensitivity analyses. During an average of 17.5 years of follow-up, a total of 656 CRC cases were identified. The results did not reveal any significant changes from the original analyses.

Table 7. *Sensitivity analysis for the association between the E-DII and the risk of colorectal cancer and cancer by anatomical subsite of the colon and rectum, the NOWAC study*

E-DII quartile (range)	*n* (cases)	Age[1] HR (95% CI)	Multivariate[2] HR (95% CI)
		Colorectal cancer	
Q1 (−5.04, −0.76)	8005 (175)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	8012 (157)	0.94 (0.75–1.16)	0.93 (0.75–1.15)
Q3 (0.33, 1.33)	7998 (157)	0.96 (0.78–1.19)	0.94 (0.76–1.17)
Q4 (1.33, 4.12)	7997 (167)	1.08 (0.87–1.33)	1.04 (0.84–1.29)
p-trend		0.54	0.77
		Colon cancer	
Q1 (−5.04, −0.76)	8005 (117)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	8012 (110)	0.99 (0.76–1.28)	0.97 (0.74–1.26)
Q3 (0.33, 1.33)	7998 (113)	1.04 (0.81–1.35)	1.01 (0.78–1.32)
Q4 (1.33, 4.12)	7997 (114)	1.11 (0.86–1.44)	1.06 (0.82–1.38)
p-trend		0.39	0.61
		Proximal colon cancer	
Q1 (−5.04, −0.76)	8005 (65)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	8012 (64)	1.05 (0.74–1.48)	1.02 (0.72–1.44)
Q3 (0.33, 1.33)	7998 (72)	1.22 (0.87–1.71)	1.18 (0.84–1.65)
Q4 (1.33, 4.12)	7997 (72)	1.31 (0.94–1.84)	1.25 (0.89–1.75)
p-trend		0.08	0.15
		Distal colon cancer	
Q1 (−5.04, −0.76)	8005 (48)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	8012 (43)	0.92 (0.61–1.39)	0.91 (0.60–1.37)
Q3 (0.33, 1.33)	7998 (38)	0.83 (0.54–1.27)	0.81 (0.53–1.25)
Q4 (1.33, 4.12)	7997 (42)	0.95 (0.62–1.43)	0.91 (0.60–1.39)
p-trend		0.65	0.55
		Rectal cancer	
Q1 (−5.04, −0.76)	8005 (58)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	8012 (47)	0.84 (0.57–1.23)	0.84 (0.57–1.23)
Q3 (0.33, 1.33)	7998 (44)	0.80 (0.54–1.18)	0.80 (0.54–1.19)
Q4 (1.33, 4.12)	7997 (53)	1.00 (0.69–1.45)	0.99 (0.68–1.44)
p-trend		0.85	0.82

N = 32,012

[1]The model is adjusted for age

[2]The model is adjusted for age, height, education, smoking, physical activity and type 2 diabetes

HR = Hazard ratio, CI = confidence interval, ref = reference

Table 8. *Sensitivity analysis for the association between the E-DII and the risk of colorectal cancer and cancer by anatomical subsite of the colon and rectum in women with BMI <25 kg/m², the NOWAC study*

BMI <25 kg/m²			
E-DII quartile (range)	***n* (cases)**	**Age[1] HR (95% CI)**	**Multivariate[2] HR (95% CI)**
Colorectal cancer			
Q1 (−5.04, −0.76)	5,408 (111)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	5,196 (104)	1.03 (0.79–1.34)	1.01 (0.77–1.32)
Q3 (0.33, 1.33)	4,919 (101)	1.08 (0.83–1.42)	1.06 (0.80–1.39)
Q4 (1.33, 3.85)	5,094 (99)	1.07 (0.81–1.40)	1.03 (0.78–1.35)
p-trend		0.57	0.78
Colon cancer			
Q1 (−5.04, −0.76)	5,408 (74)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	5,196 (73)	1.09 (0.79–1.50)	1.07 (0.77–1.47)
Q3 (0.33, 1.33)	4,919 (76)	1.23 (0.89–1.70)	1.20 (0.87–1.65)
Q4 (1.33, 3.85)	5,094 (63)	1.03 (0.74–1.45)	1.00 (0.71–1.40)
p-trend		0.60	0.77
Proximal colon cancer			
Q1 (−5.04, −0.76)	5,408 (39)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	5,196 (44)	1.27 (0.82–1.95)	1.21 (0.79–1.87)
Q3 (0.33, 1.33)	4,919 (46)	1.46 (0.95–2.23)	1.38 (0.90–2.12)
Q4 (1.33, 3.85)	5,094 (39)	1.27 (0.82–1.99)	1.20 (0.77–1.88)
p-trend		0.19	0.31
Distal colon cancer			
Q1 (−5.04, −0.76)	5,408 (32)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	5,196 (26)	0.87 (0.52–1.46)	0.88 (0.52–1.48)
Q3 (0.33, 1.33)	4,919 (28)	1.00 (0.60–1.67)	1.02 (0.61–1.70)
Q4 (1.33, 3.85)	5,094 (24)	0.85 (0.50–1.44)	0.85 (0.50–1.46)
p-trend		0.67	0.69
Rectal cancer			
Q1 (−5.04, −0.76)	5,408 (37)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	5,196 (31)	0.91 (0.56–1.46)	0.90 (0.56–1.45)
Q3 (0.33, 1.33)	4,919 (25)	0.79 (0.47–1.31)	0.78 (0.47–1.29)
Q4 (1.33, 3.85)	5,094 (36)	1.13 (0.71–1.79)	1.08 (0.68–1.72)
p-trend		0.80	0.94

N = 20,617

[1]The model is adjusted for age

[2]The model is adjusted for age, height, education, smoking, physical activity and type 2 diabetes

HR = Hazard ratio, CI = confidence interval, ref = reference

Table 9. *Sensitivity analysis for the association between the E-DII and the risk of colorectal cancer and cancer by anatomical subsite of the colon and rectum in women with BMI ≥25 kg/m², the NOWAC study*

	BMI ≥25 kg/m²		
E-DII quartile (range)	***n* (cases)**	**Age[1] HR (95% CI)**	**Multivariate[2] HR (95% CI)**
		Colorectal cancer	
Q1 (−5.01, −0.76)	2,597 (64)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	2,816 (53)	0.79 (0.55–1.14)	0.79 (0.55–1.13)
Q3 (0.33, 1.33)	3,079 (56)	0.79 (0.55–1.13)	0.78 (0.54–1.12)
Q4 (1.33, 4.12)	2,903 (68)	1.09 (0.77–1.53)	1.06 (0.75–1.49)
p-trend		0.76	0.88
		Colon cancer	
Q1 (−5.01, −0.76)	2,597 (43)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	2,816 (37)	0.82 (0.53–1.27)	0.81 (0.52–1.26)
Q3 (0.33, 1.33)	3,079 (37)	0.78 (0.50–1.21)	0.75 (0.48–1.17)
Q4 (1.33, 4.12)	2,903 (51)	1.21 (0.81–1.82)	1.15 (0.76–1.73)
p-trend		0.46	0.65
		Proximal colon cancer	
Q1 (−5.01, −0.76)	2,597 (26)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	2,816 (20)	0.74 (0.41–1.32)	0.74 (0.41–1.32)
Q3 (0.33, 1.33)	3,079 (26)	0.91 (0.53–1.57)	0.90 (0.52–1.56)
Q4 (1.33, 4.12)	2,903 (33)	1.32 (0.79–2.22)	1.27 (0.75–2.14)
p-trend		0.25	0.32
		Distal colon cancer	
Q1 (−5.01, −0.76)	2,597 (16)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	2,816 (17)	1.01 (0.51–1.99)	0.97 (0.49–1.92)
Q3 (0.33, 1.33)	3,079 (10)	0.55 (0.25–1.22)	0.51 (0.23–1.12)
Q4 (1.33, 4.12)	2,903 (18)	1.11 (0.57–2.19)	1.02 (0.52–2.02)
p-trend		0.87	0.67
		Rectal cancer	
Q1 (−5.01, −0.76)	2,597 (21)	1.00 (Ref)	1.00 (Ref)
Q2 (−0.76, 0.33)	2,816 (16)	0.72 (0.38–1.38)	0.73 (0.38–1.40)
Q3 (0.33, 1.33)	3,079 (19)	0.80 (0.43–1.48)	0.82 (0.44–1.54)
Q4 (1.33, 4.12)	2,903 (17)	0.79 (0.42–1.51)	0.82 (0.43–1.57)
p-trend		0.51	0.59

N = 11,395

[1]The model is adjusted for age

[2]The model is adjusted for age, height, education, smoking, physical activity and type 2 diabetes

HR = Hazard ratio, CI = confidence interval, ref = reference

5 Discussion

5.1 Results

5.1.1 Summary of findings

This thesis aimed to examine the relationship between the E-DII and the risk of CRC and cancer by anatomical subsite of the colon and rectum in a group of Norwegian women. No statistically significant associations were observed in the conducted analyses. However, the findings indicated a stronger positive relationship between the E-DII and the risk of proximal colon cancer in comparison to other subsites, thereby suggesting a potential variation in cancer risk across the different colorectal subsites. The results for overall CRC will further be discussed before the results for cancer in anatomical subsites of the colon and rectum are discussed altogether. Lastly, the results from the BMI-stratified analyses are discussed.

5.1.2 The association between the E-DII and the risk of CRC

The main analysis showed slightly elevated HRs for quartile 4 in the age- and multivariable-adjusted analyses, however, no significant differences in CRC risk were seen between women across the different E-DII quartiles. As mentioned in the introduction, several meta-analyses have reported a higher risk of CRC with a more pro-inflammatory diet measured by the DII (39-42). However, significant heterogeneity was present among all meta-analyses, and weaker associations were reported for cohorts compared to case-control studies when stratifying by study design (39-42). Because cohort studies are considered to provide stronger scientific evidence than case-control studies, it is more relevant to compare the results of this thesis to other cohorts that have explored the association between the inflammatory potential of the diet and CRC risk.

As far as I know, the Multiethnic Cohort is the only cohort that, in line with this thesis, explored the association between the E-DII and CRC risk in women (64). The study observed a significantly increased risk of CRC for men and women in the highest E-DII quartile compared to the lowest, however, further analyses stratified by sex showed that the association was primarily driven by results in men and that the estimates for women were weaker and no longer significant for a linear trend across the E-DII quartiles. The results from the Multiethnic cohort are further supported by those of the National Institutes of Health-American Association of Retired Persons Diet and Health Study (NIH-AARP Diet and Health Study), which reported a significant association between the most pro-inflammatory quartile of the DII and an increased risk of CRC in men, but not in women (65). The EPIC cohort also

found an increased risk of CRC in men but not in women when comparing the most pro-inflammatory ISD quartile (a modified version of the DII) with the most anti-inflammatory quartile (66). The study sample included participants from several European countries, including the Norwegian study sample of this thesis. In contrast, the Women's Health Initiative and the Iowa Women's Health Study reported a significantly increased risk of CRC for women in quintile 5 (most pro-inflammatory) compared with women in quintile 1 (most anti-inflammatory) (43, 44).

The weaker and non-significant results observed for women in some studies support the findings in this thesis and suggest that the effect of a pro-inflammatory diet on CRC risk may vary between women and men. The reasons underlying this difference are unknown, however, sex differences are known to influence several aspects of CRC, including incidence rates, tumor site, molecular features and screening participation (67). The observed difference has also in part been attributed to biological and environmental factors, such as diet and hormones (67). The use of MHT in women has been linked with a reduced risk of developing CRC, in which part of the protective effect seems to act through the ability of estrogen to induce apoptosis and inhibit cell proliferation (67). Therefore, it is possible that hormonal factors, such as MHT use and changes in estrogen levels that occur during menopause, may have distorted the measured association between the E-DII and CRC risk in this thesis. The descriptive statistics of the study sample in this thesis showed that women in Q4 (most pro-inflammatory) were more likely to have never used MHT and less likely to be former and current users of MHT compared to the other quartiles. The NIH-AARP Diet and Health Study (65) and the EPIC study (66) conducted additional analyses that adjusted for hormone use in women, in which the estimates did not show any significant changes from the main analyses. Moreover, the Multiethnic Cohort performed stratified analyses by hormone use and found no significant differences in the association between the E-DII and CRC risk among women who were non-users, previous users or current users. Regardless, potential effects of MHT or other hormonal factors on the association between the E-DII and CRC risk cannot be ruled out.

Two studies did, however, find a significant association between the DII and CRC risk in women. It is possible that there is a true association that this thesis was not able to detect. The inconsistent results between cohorts may also be related to differences in study characteristics and methodology, such as study sample and size, adjustment for confounders, which food parameters were used to calculate the DII/E-DII, definition of anatomical subsites, how many quantiles the exposure variable was divided into and follow-up time. Although the E-DII and

DII scores fall within a comparable range, direct comparisons of studies using the different DII versions are not possible (64). The E-DII is also commonly adjusted for energy by the density method, which is a different approach than the residual method used in this thesis. This was seen, for example, in the Multiethnic Cohort (64) and should be noted when comparing the results of studies using the different approaches to adjust for the E-DII.

5.1.3 The association between the E-DII and the risk of cancer by anatomical subsite of the colon and rectum

Of all CRC cases, 69% were in the colon and 31% in the rectum. Furthermore, 63% of colon cancers were in the proximal colon and 35% in the distal colon. The stratified analyses by anatomical subsite did not reveal any statistically significant results in this thesis. HRs were elevated in the most pro-inflammatory categories in the analyses for proximal colon cancer, which might indicate that the E-DII differs in its association with cancer risk between the different anatomical subsites. The association across quartiles also showed a trend towards significance, which was most prominent in the age-adjusted analysis and persisted after excluding the first three years of follow-up in the sensitivity analysis. However, the results are highly uncertain and likely limited by the low number of cases for each subsite, especially the results for distal colon and rectal cancer which had the lowest number of cases.

Somewhat in line with the results of this thesis, the Women's Health Initiative reported a significantly increased risk of total colon and proximal colon cancer but not rectal and distal colon cancer in women when comparing the most pro-inflammatory DII quintile with the most anti-inflammatory (43). Similarly, the Iowa Women's Health Study found a significant association between women in the most pro-inflammatory DII quintile and an increased risk of colon but not rectal cancer. However, the association was only significant in the age-adjusted model and became non-significant after additional adjustment for covariates (44). On the other hand, the NIH-AARP Diet and Health Study found that in men, but not in women, the most pro-inflammatory DII quartile was significantly associated with increased risk of cancer in the colon and rectum, as well as in the proximal and distal colon (65). These results are also supported by the Multiethnic Cohort where a significant increased risk of both colon and rectal cancer was observed when comparing the highest quartile of the E-DII (most pro-inflammatory) with the lowest (64). However, the study did not conduct separate analyses by sex.

The observed differences between the anatomical subsites in this thesis and other studies may be related to the distinct features of the subsites, including differences in their epidemiology, premalignant lesions, molecular pathways and microbiota. Similarly to the varying effects observed for red and processed meat, dairy and wholegrains on cancer in different colorectal subsites (3), it is possible that this is true for the inflammatory potential of the diet as well. Supporting the findings in this thesis, recent research from the NOWAC study found that vitamin D intake was associated with a reduced risk of proximal colon cancer but not distal colon or rectal cancer (68). Moreover, the EPIC cohort observed an increased risk of proximal colon cancer but not distal colon and rectal cancer comparing the most pro-inflammatory ISD quartile to the most anti-inflammatory.

However, as observed for CRC, the results from other cohorts on the link between the DII/E-DII and cancer by anatomical subsite of the colon and rectum were inconsistent. The reasons for these disparities are unclear, although differences in study characteristics and methodology, as discussed for the results on CRC, may have influenced the results.

5.1.4 BMI-stratified analyses

BMI-stratified analyses were conducted to explore the possible effect modification of BMI, or in other words, to investigate if the effect of the E-DII on CRC risk varied depending on the women's level of BMI. Of all women, 64% were included in the lower BMI group (<25 kg/m^2) whereas 36% were included in the higher BMI group (≥25 kg/m^2). Moreover, 436 (63%) of the CRC cases were in the lower BMI group, and 258 (37%) were in the higher BMI group. For participants in the lower BMI group, the results suggested that a more pro-inflammatory diet was associated with an increased risk of proximal colon cancer, however, estimates were non-significant. The highest HR was seen in quartile 3, indicating a 38% increased risk of proximal colon cancer in the multivariable-adjusted analysis. Estimates for colon cancer were also elevated in the third quartile, which seemed to be driven by the results for proximal colon cancer. For participants in the higher BMI group, non-significant HRs were elevated in Q4 for proximal, distal and total colon cancer and slightly elevated for CRC. No association was seen with rectal cancer in either BMI group. Overall, BMI did not seem to modify the relationship between the E-DII and the CRC outcomes in this thesis. However, the small number of cases for each anatomical subsite comprises a large limitation to the results, especially in the higher BMI group which had the lowest number of cases. Hence, we were also unable to differentiate between those who had overweight and those who had obesity.

Although the evidence from this thesis is severely limited, the results are consistent with those of a few other studies. In the Women's Health Initiative, BMI was not found to modify the association between the DII and CRC (43). This finding was also observed in a case-control study from Spain studying the association between the E-DII and CRC (69), as well as in an American case-control study examining the association between the E-DII and newly diagnosed colorectal adenoma (70).

5.2 Methods

5.2.1 Study sample

NOWAC is a national, population-based cohort in which participants are followed over a longer period of time. The prospective cohort design is useful when studying causal relationships because it establishes temporality, meaning that the exposure precedes the outcome. In this case, E-DII scores were based on baseline diet measured before the occurrence of CRC diagnoses. Furthermore, because the sampling and follow-up of participants are based on linkages to national population registers, the women in NOWAC are considered representative of the Norwegian female population in the corresponding age groups (46, 50). In the external validation study of NOWAC, linkage to the registry of education found that in a sample of invited women, those who responded were slightly higher educated compared with the whole sample (50). This was also seen for women responding to a second questionnaire compared with all women responding to a first questionnaire (46). This can potentially be a source of selection bias, which refers to systematic differences between the characteristics of the study population and the characteristics of other populations, making the results less generalizable (6). Selection bias may also be present if the women who were excluded from the analyses in this thesis have different characteristics compared to those who remained in the analyses. However, this has not been investigated. The overall conclusion of the external validation study was that no major selection bias that could invalidate the estimation of population attributable risk was found (50). In addition, the observed cumulative incidence rates of cancer in NOWAC have not showed any marked differences when compared to national figures from the Norwegian Cancer Registry (46, 50). Lastly, the data at the Cancer Registry of Norway is found to be almost complete (98.8%), minimizing the risk of CRC cases being misclassified (71).

5.2.2 Dietary assessment

The use of self-reported FFQ to assess dietary intake is often associated with errors. FFQ is a retrospective assessment method that, in this study, required participants to estimate their dietary intake over the past year. To memorize and accurately estimate the dietary intake over a prolonged period is a difficult task that poses a risk of participants reporting incorrect information. For example, the answers may to a larger extent reflect their diet over the past week or month rather than the whole year. The use of FFQ is also susceptible to social desirability bias, which is a tendency of individuals to respond in a way that is consistent with societal norms (72). For example, foods that are perceived as healthy (e.g., fruit and vegetables) may be overreported while foods that are perceived as unhealthy (e.g., foods high in fat and sugar) may be underreported. The FFQ is also designed to assess Norwegian cuisine and may not be as suitable for capturing the diet of individuals from different food cultures.

The ability of the FFQ in NOWAC to assess the inflammatory potential of the diet has not been evaluated. Since the FFQ does not cover the entire diet, only 29 out of the 44 food parameters used to compute the E-DII were available. Nevertheless, validation studies have found that the DII still predicts levels of inflammatory markers when fewer food parameters are included (37, 73, 74). In addition, the range of E-DII scores in this thesis (-5.04 to 4.12) is close to the range observed for other DII scores derived from 25–30 food parameters (-5.5 to +5.5) (36). However, the distribution E-DII scores leaned slightly towards more positive, pro-inflammatory scores. Although this may be true for the study sample, it cannot be ruled out that the questionnaire may not have captured the anti-inflammatory potential of the diet as well as the pro-inflammatory potential. All the missing food parameters in this thesis (eugenol, garlic, ginger, niacin, omega-3 and omega-6 fatty acids, saffron, selenium, *trans* fat, turmeric, zinc, green/black tea, pepper, thyme/oregano and rosemary), except for *trans* fat, have negative weights and contribute to a more anti-inflammatory score. This may have led to underestimation of the anti-inflammatory potential of the diet. However, many of these food parameters are typically not consumed in high amounts in Norwegian cuisine, and their missing anti-inflammatory contribution is likely to be minimal. Furthermore, the validation study comparing the FFQ with repeated 24HDRs found that the FFQ under- and overestimated the intake of certain dietary factors used in the computation of the E-DII, including lower intakes of energy, carbohydrates, fat, alcohol, coffee and iron, and higher intakes of fiber, β -carotene and vitamin D (52). Under- or overestimating the women's intake

of food parameters may have led to inaccurate E-DII scores and further affected the observed relationship with CRC. Lastly, the E-DII was calculated based on the diet reported at baseline and did not account for any changes in diet and its inflammatory potential that may have affected CRC risk.

5.2.3 The E-DII

The E-DII has several strengths as a tool for measuring the inflammatory potential of the diet, including the comprehensive literature review on the relationship between diet and inflammation that the index is based on. In creating the E-DII, all available evidence from a diverse range of human populations using different study designs and dietary assessment methods was taken into account (36). Besides human studies, the DII also included evidence from cell culture and animal studies. By taking a large number of food parameters into consideration, the DII reflects the overall diet and may yield stronger relationships in studies on diet and disease compared with single nutrients that are studied in isolation (5). However, because the literature on which the DII is based on tested the specific inflammatory effects of the food parameters one at a time, the index is likely to not fully capture the combined effects and interactions of the included food items and nutrients (5).

The computation of DII/E-DII scores involves a series of steps which can be quite complicated to carry out. In addition, not all materials needed to compute the scores are available. For instance, the global database of energy-adjusted nutrient scores used in computing the E-DII has not been provided in any publications and is thus not readily accessible. For these reasons, the developers have been involved in most studies that have adopted the index (36). This also includes the EPIC cohort and thus the calculation of the E-DII scores of the women in this thesis. While this helps ensure correct and consistent use of the index, it also limits the involvement of other researchers who potentially could contribute with inputs on future improvements. That being said, some issues have already been addressed. For instance, a group of researchers have suggested alternative mathematical approaches to improve and optimize the calculation method of the DII (75). Furthermore, it has been made aware that the index likely overestimates the pro-inflammatory potential of the diet by including total fat in the computation because components of fat, including saturated, monounsaturated and polyunsaturated fats, are also included (76). Meanwhile, it is argued that the negative weight for alcohol overestimates the anti-inflammatory potential of the diet because the effect of alcohol is dose-dependent, and the negative association with

inflammatory markers has only been observed with moderate alcohol consumption (<30–40 g/d) (76). However, this is likely not an issue in this thesis since close to none of the women had a measured alcohol intake above 30–40 g/d.

In epidemiological analyses of diet and disease, it is generally recommended to use measures of nutrient intake that is independent of total energy intake (54). Intakes of most nutrients are usually positively correlated with total energy intake, meaning that individuals who eat more food also have higher intakes of nutrients, including both macro- and micronutrients (54). This was one of the reasons why the developers created an energy-adjusted version of the DII. They also observed negative correlations between energy density and nutrient density due to a tendency of more health-conscious people to choose nutrient-dense, energy-sparse foods, and of less health-conscious people to prefer energy-dense, nutrient-sparse foods (36). The most appropriate method for energy-adjustment is debated and may depend on the specific context of a study (77). For participants in this thesis, the intake of food parameters used to calculate E-DII scores was adjusted for total energy intake by the residual method and compared to a global database with energy-adjusted nutrient scores. The residuals represent the intake of nutrients that are independent of total energy intake and reflect the variation in nutrient intakes that is due to the nutritional composition of the diet. In that way, the residual method helps control for the confounding effect of energy on the association between the E-DII and CRC (54).

5.2.4 Covariates

Covariates were selected through literature and a DAG was used to identify the confounders included in the multivariate model. A strength in using a DAG is that it accounts for the role of each variable in relation to the exposure and outcome, which is often a limitation in alternative approaches used to identify confounding factors, such as data-driven methods (55). Data-driven methods may also pose a higher risk of bias by mistakenly adjusting for variables that should not be adjusted for in the model, such as mediators (78). However, the use of a DAG also has limitations. The DAG constructed in this thesis is largely based on assumptions, therefore, true causal relationships may have been omitted (78). This may have led to insufficient adjustment for confounding factors and further led to inaccurate estimates.

All variables identified as confounders in the DAG were available in the dataset. Including these variables in the multivariate model accounts for the fact that they may explain part of the observed association between the E-DII and CRC. However, the confounding factors

height, education, smoking, physical activity and T2D were collected from self-reported questionnaires, and it is therefore likely that some degree of measurement error that could lead to residual confounding is present. The observational study design of this thesis also opens for residual confounding of other unmeasured variables. For instance, the NOWAC questionnaires did not ask questions on some of the important risk factors for CRC, including family history of CRC, IBD or use of NSAIDs. Thus, it was not possible to explore these factors in relation to the E-DII-CRC association. As an example, NSAIDs are assumed to exert a stronger anti-inflammatory effect than what may be expected through an anti-inflammatory diet (44). Therefore, anti-inflammatory diets may have greater potential in protecting against CRC in non-users of NSAIDs. This was observed in the Women's Health Initiative (43) and the Iowa Women's Health Study (44), which reported that women who did not use NSAIDs had a higher risk of CRC with a more pro-inflammatory diet compared to women who were regular users.

BMI was explored as a potential effect modifier in the association between the E-DII and CRC risk. As mentioned under methods, it is possible that BMI is a mediator, or in other words, on the causal pathway in the relationship between E-DII and CRC. Thus, adjusting for BMI could underestimate the total effect of the E-DII on CRC risk because part of the effect that operates through BMI would be blocked (54). The validation of self-reported BMI did not observe significant differences in the distribution of BMI categories between self-reported and measured values (49). However, there was a small but significant underreporting of self-reported weight and thus BMI, in which the tendency to underreport was most common among women with overweight, and the largest degree of underreporting was found among women with obesity (49). Hence, underreporting resulting in misclassification of BMI category (<25 or ≥ 25 kg/m^2) of the women in this thesis can have led to biased estimates in the BMI-stratified analyses.

The covariates alcohol, red and processed meat, dairy and fiber were not included in the DAG because of their role as food parameters or sources of food parameters in the E-DII. Potentially including these variables in the multivariate models could lead to overadjustment resulting in inaccurate estimates of the E-DII-CRC association. However, since the dietary variables also act on CRC risk through other mechanisms than inflammation, not taking them into consideration may have led to residual confounding in this thesis.

The women's intake of food parameters was adjusted for energy before the E-DII scores were computed, and total energy intake was therefore not considered a covariate. A moderate negative Pearson's correlation coefficient of −0.3 between the E-DII and total energy intake was observed in this thesis, indicating that the total energy intake decreases as the pro-inflammatory potential of the diet increases. By testing the correlation between the unadjusted DII and total energy intake it was observed a more negative Pearson coefficient of −0.59, suggesting that the energy-adjustment removed part of the correlation between the E-DII and total energy intake, but that some correlation was still left. As a result, there might have been residual confounding of total energy intake that was not accounted for in the analyses.

5.3 Implications and future perspectives

This thesis adds to current evidence on the association between the DII/E-DII and CRC risk. The results of this thesis are unclear, although in line with studies reporting weaker associations in women as well as differences in CRC risk between anatomical subsites. Overall, the inflammatory potential of the diet appears to be related to the development of CRC, but the inconsistencies in sex- and subsite-specific associations need further investigation. This research is important as the incidence of CRC is increasing on a world basis and of special importance in Norway where the incidence among women rank highest compared to women in other countries.

The relationship between the E-DII and CRC should be assessed in larger study samples that include both women and men, a sufficient number of cases to provide robust estimates and a long follow-up due to the long latency period of CRC. Dietary assessment methods should aim to capture all food parameters through suitable methods such as 24HDRs or FFQ's designed to assess the inflammatory potential of the diet. Along with dietary assessment, it would be useful to measure levels of inflammatory biomarkers. Ideally, both methods measured repeatedly. This could, for example, allow studies to test if changes in diet over time reduce chronic inflammation and CRC risk. Furthermore, studies should investigate associations across different anatomical subsites, including proximal and distal colon. Investigating the underlying mechanisms by which diet-induced inflammation affects CRC risk, perhaps in the context of the various characteristics of the different subsites, could provide a better understanding of the observed differences in cancer risk between subsites. Data on factors that have important roles in CRC risk, including family history of CRC, IBD and use of NSAIDs and MHT, should be collected and explored in relation to the E-DII-CRC

association, for example through stratified analyses. Several countries also have screening programs for CRC, including Norway since 2022, which could potentially be used to great advantage in future research (2).

Due to the complex construct of the E-DII, it is difficult to transfer scores into specific dietary recommendations or to suggest how the index can be applied in clinical settings. Studies should look closer into what people with different index scores actually eat. The Mediterranean diet has already been linked with more anti-inflammatory DII/E-DII scores (79), which corresponds to the findings in this thesis where women with the most anti-inflammatory diets had higher intakes of fruit, vegetables and fiber and lower intakes of red and processed meat. Nevertheless, individuals that fall within the same index categories can have different combinations of food parameters in their diets, which may cause different outcomes. It is also not clear which scores that give the highest or lowest risks, and considering no linear trends were observed across the quartiles in this thesis, it would be interesting to explore if non-linear trends exist between the E-DII and CRC.

6 Conclusion

Our findings suggest that there is not a statistically significant association between the inflammatory potential of the diet, measured by the E-DII, and the risk of CRC or cancer by anatomical subsite of the colon and rectum in this population. However, consistent with previous studies, the results indicated a stronger positive relationship between a more pro-inflammatory diet and risk of proximal colon cancer compared to other subsites, thereby suggesting that the relationship between the E-DII and cancer risk may vary by anatomical subsite. Given the importance of providing preventive measures regarding CRC, further studies with improved study methods are warranted to better understand the relationship between the dietary inflammatory potential and CRC risk, taking the tumor location into account.

7 References

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Appendix 1

The overall inflammatory effect score for each of the 45 food parameters used in the computation of the DII.

Food parameter	Overall inflammatory effect score[1]	Included in NOWAC
Alcohol (g)	−0.278	✓
Vitamin B_{12} (µg)	0.106	✓
Vitamin B_6 (mg)	−0.365	✓
β-carotene (µg)	−0.584	✓
Caffeine (g)	−0.110	✓
Carbohydrate (g)	0.097	✓
Cholesterol (mg)	0.110	✓
Energy (kcal)[2]	0.180	✓
Total fat (g)	0.298	✓
Fiber (g)	−0.663	✓
Folic acid (µg)	−0.190	✓
Iron (mg)	0.032	✓
Magnesium (mg)	−0.484	✓
Monounsaturated fat (g)	−0.009	✓
Onion (g)	−0.301	✓
Protein (g)	0.021	✓
Polyunsaturated fat (g)	−0.337	✓
Riboflavin (mg)	−0.068	✓
Saturated fat (g)	0.373	✓
Thiamin (mg)	−0.098	✓
Vitamin A (RE)	−0.401	✓
Vitamin C (mg)	−0.424	✓
Vitamin D (µg)	−0.446	✓
Vitamin E (mg)	−0.419	✓
Flavan-3-ol (mg)	−0.415	✓
Flavones (mg)	−0.616	✓
Flavonols (mg)	−0.467	✓
Flavonones (mg)	−0.250	✓
Anthocyanidins (mg)	−0.131	✓
Isoflavones (mg)	−0.593	✓
Eugenol (mg)	−0.140	X
Garlic (g)	−0.412	X
Ginger (g)	−0.453	X
Niacin (mg)	−0.246	X

Food parameter	Overall inflammatory effect score[1]	Included in NOWAC
Omega-3 fatty acids (g)	−0.436	X
Omega-6 fatty acids (g)	−0.159	X
Saffron (g)	−0.140	X
Selenium (µg)	−0.191	X
Trans fat (g)	0.229	X
Turmeric (mg)	−0.785	X
Zinc (mg)	−0.313	X
Green/black tea (g)	−0.536	X
Pepper (g)	−0.131	X
Thyme/oregano (mg)	−0.102	X
Rosemary (mg)	−0.013	X

[1]Overall inflammatory effect scores are retrieved from the original DII-article (5)
[2]Not included in the E-DII
✓= yes, X = no