UiT The Arctic University of Norway

Faculty of Health Sciences / Department of Community Medicine

Inflammatory potential of the diet and risk of fibromyalgia in The Norwegian Women and Cancer (NOWAC) study

Elise Ellingsen

Master's thesis in clinical nutrition, ERN-3900, May 2022

Acknowledgements

First and foremost, I would like to express my gratitude to my main supervisor Guri Skeie for guiding me through the process of writing this thesis. I would like to thank you for your time devoted to my thesis, with regular meetings and thorough feedbacks. I would also like to thank my co-supervisor Torill Enget Jensen for taking your time to contribute with helpful inputs and second opinions during this process and Tonje Braaten, for your clarifying inputs on statistical questions.

The process of writing this thesis have been challenging but also educational, providing a feeling of mastery along the way and even enjoyment at times. I would like to express my gratitude to family and friends for support and encouragement during this time. I am very grateful to have shared this experience with my fellow master student and friend Marte, motivating and helping each other throughout this process have been invaluable. And my good friend Mari, thank you for letting me vent out my frustrations along the way and for keeping my motivation up with all the dinners, glasses of wine, laughs and good times during this last year.

I would like to express my gratitude to my parents, for encouraging me to follow my gut feeling in wanting to change my field of education a few years back, leading me to now have authored this masters' thesis in clinical nutrition, and for the invaluable support during my years as a student. And a special thanks to you, Mor.

Last but not least, I would like to thank all the women in the NOWAC study. Your participation is an important contribution to research, and you made this thesis possible.

Tromsø, May 2022
Elise Ellingsen

Abstract

Background: Fibromyalgia is a common condition in the general population and is recognized as one of the most common conditions related to chronic pain and rheumatology. Fibromyalgia is a condition with severe burden on those affected, and furthermore an economical burden on society. Nevertheless, the etiology is yet to be fully clarified. It has been suggested that inflammation could be a part of the development and maintenance of fibromyalgia, and it has been proven that diet affect inflammation. Therefore, it would be interesting to investigate the relationship between the inflammatory potential of the diet and risk of fibromyalgia.

Aim: To investigate the association between the inflammatory potential of the diet, measured by The Dietary Inflammatory Index (DII), and risk of fibromyalgia.

Methods and material: Self-reported data on diet, characteristics and fibromyalgia were included from 21 814 women in the Norwegian Women and Cancer (NOWAC) study. The DII and energy-adjusted DII (E-DII) derived from a food frequency questionnaire (FFQ) were calculated and divided into quartiles. Cox proportional hazards were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the association between the DII and risk of fibromyalgia.

Results: During an average 14.2 years of follow up a total of 692 cases of fibromyalgia were identified. Women in the third (DII HR_{Q3-Q1}:1.27, CI: 1.03,1.57) and fourth (E-DII HR_{Q4-Q1}:1.23, CI: 0.99,1.52) quartile were associated with an increased risk of fibromyalgia compared to women in the first quartile. When further adjusted for smoking status, education, gross household income, self-perceived health status, alcohol consumption and menopause status no significant associations were observed.

Conclusion: Overall, no evident association was found between DII and risk of fibromyalgia and further studies are required to establish the relationship between DII and fibromyalgia.

Sammendrag

Bakgrunn: Fibromyalgi er en relativt vanlig tilstand i befolkningen, og er ansett som en av de mest vanlige tilstandene relatert til kronisk smerte og reumatologi. Pasienter med fibromyalgi opplever stor sykdomsbyrde, og tilstanden fører til en økonomisk byrde for samfunnet. Likevel mangler det enda forskning for å oppklare årsaksmekanismen bak fibromyalgi. Det er foreslått at inflammasjon kan spille en rolle i utvikling og opprettholdelse av tilstanden, og samtidig har forskning vist at kosthold påvirker inflammasjon. Derfor vil det være interessant å undersøke sammenhengen mellom inflammatorisk potensiale i kostholdet og risiko for fibromyalgi.

Formål: Undersøke sammenhengen mellom det inflammatoriske potensialet i kostholdet, målt av The Dietary Inflammatory Index (DII), og risiko for fibromyalgi.

Metode og materiale: Selvrapportert data på kosthold, karakteristikk og fibromyalgi ble innhentet for 21814 kvinner fra den norske Kvinner og kreftstudien (NOWAC study). Skår for DII og energijustert DII (E-DII) ble kalkulert basert på informasjon om kosthold fra matfrekvensskjema (FFQ), og delt inn i kvartiler. Cox proporsjonal hasard regresjonsanalyse ble brukt for å beregne hasard ratio (HR) og 95% konfidensintervall (CI) for sammenhengen mellom DII og risiko for fibromyalgi

Resultat: I løpet av et gjennomsnitt på 14.2 år oppfølging ble det rapportert 692 tilfeller av fibromyalgi. Kvinner i tredje (DII $HR_{Q3\text{-}Q1}$:1.27, CI: 1.03,1.57) og fjerde (E-DII $HR_{Q4\text{-}Q1}$:1.23, CI: 0.99,1.52) kvartil hadde høyere risiko for fibromyalgi sammenlignet med kvinner i første kvartil i aldersjustert modell. Etter videre justering for røykestatus, utdanning, brutto inntekt i husstanden, selvopplevd helsestatus, alkoholinntak og menopausestatus ble ingen signifikant sammenheng observert.

Konklusjon: Det ble ikke funnet noen signifikant sammenheng mellom DII og risiko for fibromyalgi. Flere studier er nødvendig for å oppklare sammenheng mellom DII og fibromyalgi.

Table of Contents

List of Tables

List of Figures

Abbreviations

24HR	24-hour recall
7DDR	7-day dietary recall
ACR	American College of Rheumatology
APS	American Pain Society
BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
DAGs	Direct Acyclic Graph
DII	The Dietary Inflammatory Index
E%	Percentage of total energy intake
E-DII	Energy-adjusted Dietary Inflammatory Index
EPIC	The European Prospective Investigation into Cancer and Nutrition
EULAR	The European League Against Rheumatism
FFQ	Food frequency questionnaire
g/day	Grams per day
HR	Hazard ratio
HUNT study	Trøndelag Health study
IARC	International Agency for Research on Cancer
IL	Interleukin
mg/day	Milligrams per day
MJ	Megajoule
MUFA	Monounsaturated fatty acids
NNR	Nordic Nutrition Recommendations
NOWAC	The Norwegian Woman and Cancer study
PUFA	Polyunsaturated fatty acids
SD	Standard deviation
SEASONS study	The Seasonal Variation and Cholesterol Levels Study
SFA	Saturated fatty acids
TFA	Trans fatty acids
TNF-α	Tumour necrosis factor alpha
ug/day	Micrograms per day

1 Introduction

1.1 Inflammation

Inflammation is the body's defense mechanism against injury, infection, trauma, or toxins (1, 2). The etiologies for inflammation are varied ranging from microbial infections (caused by bacteria, virus, fungi etc.), physical agents (like burns, stress, trauma from cuts or radiation), and chemicals (drugs, toxins, alcohol) to immunological reactions (autoimmune diseases such as rheumatoid arthritis) (1). The inflammatory process ensures that phagocytic cells and different plasma substances are transported to the infected or damaged area to destroy or inactivate foreign organisms, remove damaged tissues and cells, and facilitate conditions for healing, repairing and reconstruction of damaged tissue (1, 2). Inflammation is associated with the clinical symptoms or cardinal signs of redness, heat, swelling, pain, and loss of function (1, 2). These symptoms and signs are a result of the vascular and cellular inflammatory responses. The damaged tissue sends out chemical factors that stimulate and mediate the inflammatory process. This leads to an increase in blood, fluids, and immune cells in the damaged tissue that cause swelling, redness, and heat. Pain is caused by signals from nerves and chemical mediators, and loss of function is a result of pain (1).

1.1.1 Acute and chronic inflammation

Inflammation can be divided into acute and chronic (1). Acute inflammation is initiated mostly by cells that are present in the tissue, such as dendritic cells, macrophages, Kupffer cells, histocytes and mastocytes (1). For instance, if bacteria manage to penetrate the skin, they will immediately be attacked by macrophages present in the tissue (2). These cells have a receptor on their outer surface that recognizes when bacteria are present in tissue or if the tissue has been damaged (1) and release inflammatory mediators that induce further inflammatory process(1, 2): Cytokines makes macrophages more mobile to attack the invading bacteria. Leukocytes release substances such as histamine that cause vasodilatation. Further the vasodilatation ensures that more fluid, immune cells (such as neutrophils and monocytes), and plasma proteins are transported to the affected area. This results in swelling, heat, and redness in the affected area. And further, this causes an increased hydrostatic pressure in the area that affect pain fibers and cause pain. Loss of function is a result of neurological reflex in response to pain (1, 2). The inflammatory mediators and biochemical cascade systems are required to maintain the inflammatory process: The complement system

(mostly activated by bacteria) and the coagulation and fibrinolysis systems (mostly activated by necrosis) (1). The acute inflammatory response requires constant stimulation (1, 2). Once the stimulus of acute inflammation is removed, the inflammatory mediators (having short half-lives) are degraded in the inflamed tissue, and the inflammatory response stops (1).

If there is a malfunction in the inflammatory process and the inflammatory stimulus persists over time, it turns into chronic inflammation (3). A persistent stimulation from leukocytes, that regulate inflammation through production of pro-inflammatory cytokines, could be caused by reactive oxygen species that damage and conditionally remodel tissue, or because of a situation that maintains these leukocytes at the site of inflammation (3). The inflammatory process is an essential part of the body's defense mechanism; however, an abnormality in these mechanisms may favor the development of various illnesses (4). It has been demonstrated that inflammation is a part of multifactorial diseases including chronic inflammatory rheumatic disorders such as rheumatoid arthritis, and a wide variety of conditions including type 2 diabetes, metabolic syndrome, obesity, atherosclerosis, inflammatory bowel disease, asthma, neurodegenerative diseases, cancer, and ageing (4).

1.1.2 Inflammatory mediators

The inflammatory process is mediated by inflammatory cells (leukocytes) such as macrophages, neutrophils, and lymphocytes (5) In response to the inflammatory process, these cells release substances that mediate the inflammatory process by preventing further tissue damage and resulting in healing and restoration of tissue function (5). These substances include vasoactive amines and peptides, eicosanoids, cytokines, and acute-phase proteins (5). Inflammation can be detected by measuring levels of these inflammatory mediators in serum, and they are therefore also defined as inflammatory biomarkers (6).

Cytokines

Cytokines are involved in both acute and chronic inflammatory process (6). Cytokines are involved in the inflammatory process as endogenous pyrogens (causing fever), by upregulating the production of pro-inflammatory cytokines and secondary mediators, activating the production of some acute-phase proteins, or attracting inflammatory cells (1). Interleukin-1α (IL-1α), interleukin-1β (IL-1β), Interleukin-6 (IL-6) and tumor necrosis factor

alpha (TNF- α) are the main pro-inflammatory cytokines (1). Anti-inflammatory cytokines can regulate the inflammatory response by affecting the synthesis and stimulation of pro-inflammatory cytokines (1). IL-4, IL-10 and IL-13 are the main anti-inflammatory cytokines (1).

Acute-phase protein

Acute-phase proteins are synthesized by the liver in response to pro-inflammatory cytokines. Acute-phase proteins are transported through the bloodstream to the site of inflammation where they remove the pathogens through opsonization ("tagging" foreign pathogens to be recognized and eliminated by phagocytes) and activating the complement system (1). C-reactive protein (CRP) is one of most renowned acute-phase proteins, and serum concentration of CRP is one of the most used measures of acute-phase proteins in clinical practice (1). CRP levels rise significantly during acute inflammation and can therefore be used for indicating the presence of significant infectious diseases or inflammatory conditions, and further as a diagnostic marker for inflammation (7).

1.1.3 The inflammatory potential of the diet

It has been proven that diet can affect level of inflammation in the body. Dietary patterns have been associated with inflammatory mediators (8-11). Components of a healthy diet, such as higher intake of whole grains, vegetables and fruit, nuts and fish are all associated with lower inflammation (10). The Mediterranean diet, which is based on fruit and vegetables, legumes, grain, lean meat, fish and unsaturated fat has been associated with lower concentrations of inflammatory mediators and thus have an anti-inflammatory effect (8-11). On the other hand, a Western diet, based on mostly red meat, saturated fats, processed and fried food, and food high on sugar have been associated with higher concentrations of inflammatory mediators and thus have a pro-inflammatory effect (8, 12)

Further, dietary factors have been associated with inflammation. Dairy products (10, 13) olive oil (12, 14, 15), unsaturated fats (12), fiber (12, 16, 17) and omega-3 fatty acids (10, 18-20) have been associated with having an anti-inflammatory effect. Foods with low glycemic index (GI) have shown an anti-inflammatory effect (10, 12) compared to foods with high GI that increase insulin and favor systemic inflammation (10). Vitamin D has proposed anti-inflammatory properties, being associated with a downregulating effect on pro-inflammatory

mediators and upregulating anti-inflammatory mediators (21). Trans fatty acids and products with added sugar (especially sugar sweetened beverages) have been associated with having a pro-inflammatory effect (12).

1.2 The Dietary Inflammatory Index (DII)

The Dietary Inflammatory Index (DII) is a validated dietary index, developed to investigate the association between the dietary inflammatory potential in relation to health outcome (22). The first article on DII was published in 2009, presenting an index constructed based on an extensive literature search, including articles from 1950 to 2007. This index was validated in Seasonal Variation and Cholesterol Levels Study (SEASONS), and the results confirmed the underlying hypothesis that diet plays a role in regulation of inflammation and that DII can measure the inflammatory potential of the diet (22).

A new and updated DII was published in 2014, describing an improved version of the DII (23). The index is based on how 45 different food parameters are associated with six different inflammatory biomarkers (IL-1β, IL-4, IL-6, IL-10, TNF-α and CRP) in literature. An overall inflammatory score was calculated for the 45 food parameters, including various micro- and macronutrients, whole foods, and non-nutrient substances (presented in Appendix 1). Of the 45 food parameters, eight are considered to have a pro-inflammatory effect and the rest are considered anti-inflammatory. The DII score can theoretically range from maximum anti-inflammatory -8.78 to maximum pro-inflammatory +7.98 when computed for all 45 food parameters (23).

The first improvement made to the updated version was that the literature database was extended to include articles published up to the end of 2010, resulting in a larger literature review and improved scoring system for the food parameters (23). The overall inflammatory effect score for each food parameter was calculated based on what inflammatory effect the food parameter showed in the articles reviewed. The study design of the articles was taken into consideration, with human studies weighing more and experimental cell culture studies weighing less in the calculation of the overall inflammatory effect. Further, robustness in number of articles and weight of study design was taken into consideration, and the overall inflammatory effect was adjusted if the literature basis for the food parameter was not considered robust. The second improvement was constructing a global composite database as

a reference of global average intake of the 45 food parameters (23). The database was based on food consumption data from 11 countries and provides a robust estimate of a mean and standard deviation for each food parameter. When calculating DII score for participants, their raw consumption of the food parameter is standardized to the world average database to provide consumption data comparable across populations. Mean and standard deviation from the world average database is used to calculate z-scores for the participants intake. The last improvement was a percentile scoring system (23). The calculated z-score is converted to a percentile score to minimize the effect of right skewing commonly seen in dietary data. The percentile score is centered on zero to achieve a value between -1 (maximal anti-inflammatory) and +1 (maximal pro-inflammatory). This last step also eliminates the non-comparability of units as the percentiles are independent of units of measurement (23). The steps for calculating the overall inflammatory effect score for the food parameters are described in more detail in the method chapter and an illustrated overview of the steps is presented in Appendix 3.

In 2019, the developers of DII published an article presenting the energy adjusted DII (E-DII) (24). During the 4 years prior to that, the DII had been used in over 200 studies and formed the basis of 12 meta-analyses. Over the years of using the DII among several different populations it was observed that the relationship between intake if energy, nutrients and nutrient densities were different across populations, and that this could affect the ability of the DII to assess the inflammatory potential of the diet, and further affect comparability of DII scores between different populations. For this reason, they created an energy adjusted version of the DII. In the E-DII, energy is not included as a food parameter. Instead, the participants intake is adjusted for energy before being related to an energy adjusted version of the world average database based on the same 11 countries in the original world average database (24).

1.2.1 Validation of the DII

The DII has been construct validated against inflammatory biomarkers in several different populations and for using different methods for dietary assessments (25-48). Construct validity is the extent to which the measurements used actually test the hypothesis or theory they are measuring, and it should demonstrate that the score in fact predicts the theoretical hypothesis it claims to measure (49). A construct validity of DII is confirming that DII actually is associated with inflammatory biomarkers and that higher DII scores, reflecting a

more pro-inflammatory diet, are associated with increased inflammatory mediators, reflecting a more pro-inflammatory state in the body,

The new and updated DII was first validated in SEASONS, showing an improved construct validity (25). They found that DII was associated with interval changes in high sensitivity CRP (hs-CRP) using both 24-hour dietary recall(24HR) and 7-day dietary recall (7DDR) for dietary assessments. Blood tests and dietary information were collected at baseline and at each subsequent quarter the following year resulting in a total of five assessments. Of the 45 DII parameters, 44 were obtained from the 24HR and 28 were obtained from the 7DDR (25). DII was further validated using food frequency questionnaires (FFQ) for dietary assessments in postmenopausal women (26). The FFQ assessed average dietary intake over the previous three months and provided 35 of the 45 food parameters for calculation of the DII. The DII was associated with hs-CRP, IL-6 and TNF-α.

The DII and E-DII have been validated in several populations across the world. An increase in DII score was associated with an increase in different inflammatory mediators in a study population consisting of adolescents from ten different European cities (27), an American population (28), an African American population (29), in a Belgian population (30), Iranian women (31), a Swedish population (32), an Italian population (33), a Korean population (34) a Japanese population (35), and for Japanese men (36). An increase in E-DII score was associated with an increase in different inflammatory mediators among elderly Australian men (40), an American population (39), an Irish population (38) and an elderly Scottish population (37). Different tools for dietary assessments were used and how many of the 45 food parameters available for calculating the DII varied across study populations and dietary assessments tools. For instance, these validation studies used different FFQs (29-33, 35-38), 24HRs (27, 28, 34, 39) and a diet history questionnaire administered by a research dietitian (40) to assess dietary information. Further, the DII/E-DII has been construct validated for specific patient groups or occupations. Higher DII scores were associated with higher levels of inflammatory mediators in mother-child pairs (41), police officers (42), hemodialysis patients(43) and patients with heart disease (44). E-DII has been validated in an anti-inflammatory diet intervention, where participants who worsened their E-DII sores had higher CRP compared to those who improved E-DII the most (45). Nevertheless, some of the validation studies found no significant association. (46-48).

1.3 Fibromyalgia

Fibromyalgia is a condition with chronic widespread pain (50). The core symptoms of fibromyalgia are generalized pain, fatigue, sleep disturbance and cognitive dysfunction. Other common symptoms include headaches, irritable bowel syndrome, paraesthesia (described as a feeling of numbness, pins-and-needles, or tingling sensation in the skin), morning stiffness, depression, and anxiety (51-53). Fibromyalgia is now considered to be one of the most common chronic pain syndromes and recognized as the second most common conditions in rheumatology, after osteoarthritis (54). Nevertheless, the etiology is yet to be established (50) Fibromyalgia is seen either alone or as a comorbidity in other rheumatic diseases such as rheumatoid arthritis, osteoarthritis and systemic lupus erythematosus (55). Fibromyalgia is diagnosed based on patients report of widespread pain, other somatic symptoms and exclusion of other conditions that may cause the symptoms (53).

The prevalence of fibromyalgia is observed to be in the range of 0.5% to 12%, depending on the population sampled and the method of ascertainment, and display a 3 to 1 ratio between women and men (56). Fibromyalgia can occur at all ages, however, occurs more frequently between the age of 30 and 50 years (56). Compared to other countries, the prevalence of fibromyalgia in Norway is relatively high (57). In a population of 93 000 men and women in the Trøndelag Health study (HUNT) the prevalence was 3.2% in total, 5% among women and 0.9% among men (57). A study of women in Arendal reported a prevalence of 10% (57). A previous master thesis, including 76 367 women from the Norwegian Woman and Cancer (NOWAC) study, reported a total prevalence of 8 % (58). At baseline 5% of the women reported fibromyalgia, and 3% reported new cases of fibromyalgia during follow-up (58).

Fibromyalgia treatment is focused on reducing pain and symptoms, treating comorbidities, and increasing quality of life (59). Available treatments for fibromyalgia include exercise, electrotherapy, pharmacologic therapies, psychological therapies, and complementary and alternative treatments. Current evidence on the suggested treatments for fibromyalgia are inconclusive or weak (59). A recent systematic review and meta-analysis found a reduction in pain in people with fibromyalgia treated with behavioural therapy, antidepressants, or central nervous system depressant (59). Use of antidepressants and nervous system depressant were also associated with increased quality of life. However, associations were weak (59).

Treatment of fibromyalgia can be challenging (55), and no gold standard for treatment has been developed (54). Chronic generalized pain is the primary target of fibromyalgia, however,

the numerous comorbidities contribute to fibromyalgia patients often requiring a more comprehensive treatment approach (55). Guidelines on treatment for fibromyalgia by the American Pain Society (APS) 2005 (60) and The European League Against Rheumatism (EULAR) 2017 (61) suggest a multidisciplinary approach with a combination of non-pharmacological and pharmacological treatment. At diagnosis, the patient should be educated on the condition, treatment options, pain management and self-management programs. Treatment should be tailored according to pain intensity, function, comorbidities, fatigue, sleep disturbance and patient preferences (60, 61). However, only 25%, at best, reported long-term effects of treatment, and therefore patients with fibromyalgia often seek alternative methods to control their symptoms (54). There are no national guidelines for diagnosis and treatment of fibromyalgia in Norway. However, a fibromyalgia survey questionnaire has been translated to Norwegian and the 2016 fibromyalgia survey diagnostic criteria was validated in a Norwegian population (62).

1.3.1 Suggested underlying mechanisms

The underlying mechanisms of fibromyalgia are unknown, but many theories are under investigation. It is thought to be a result of interaction between pathophysiological changes in the central nervous system, neuroendocrine system, autonomic nervous system, immune system, and stress regulation, as well as genetical vulnerability and psychological mechanisms (56, 63).

Fibromyalgia, part of the central sensitivity syndrome.

It is suggested that fibromyalgia is a part of the central sensitivity syndrome (64). This syndrome represents a heterogeneous group of disorders, among others, irritable bowel disease, chronic headache, temporomandibular disorders (chronic facial pain), and pelvic pain syndrome, that have common symptoms with pain being the most prominent feature (64). In central sensitization, “central” refers to the central nervous system as the source of symptoms or as the cause of symptom amplification (65). Central sensitization is defined as nociception-driven amplification of neural signalling within the central nervous system leading to pain hypersensitivity (66). Ultimately, the condition is manifested by abnormal intense perception of pain with minimal stimuli (51). Abnormalities along the entire pain pathway, from the peripheral activation of nociceptors to neurotransmitter changes to the somatosensory cortical interpretation of the central nervous system have been identified in patients with fibromyalgia

(51). The triggers for the central sensitization are unclear, but inflammatory states, autoimmune condition and physical trauma are some of the factors suggested as initial triggers (51).

The role of inflammation in fibromyalgia

A systematic review investigating the role of inflammation in the pathogenesis of fibromyalgia concludes that research so far confirms the immune system as an important part of the complex pathogenesis of fibromyalgia (55). Central neuroinflammation and central sensitization are connected closely in fibromyalgia (55). It is suggested that an imbalance between pro-inflammatory and anti-inflammatory cytokines provoke the induction and maintenance of pain and in that way participate in the widespread pain and hypersensitivity seen in fibromyalgia (67). One of the suggested hypotheses is that inflammatory cytokines could drive disturbance in neural networks during the interaction of the nervous system with immune cells, which eventually could lead to increased central and peripheral sensitization as well as neuroinflammation (67). When level of cytokines and neurotrophic factors increase in the cerebrospinal fluid it triggers central neuroinflammation leading to an increase in the central processing input and contributes to chronic pain, pain caused from stimuli that normally doesn't cause pain (allodynia), and extreme sensitivity to pain (hyperalgesia) in fibromyalgia (55).

Evidence of both neuroinflammation (assessed in cerebrospinal fluid) and chronic systematic inflammation (assessed in plasma) have been found in patients with fibromyalgia (68). It is suggested that fibromyalgia patients probably have low-grade inflammation (69). An increase in several inflammatory mediators in fibromyalgia have been seen in studies, however results are conflicting (55, 67). Skin biopsies in fibromyalgia patients showed an increase in number of mast cells, as well as the production of corticotropin releasing hormone and substance P (a neuro peptide) by the neurones, which in turn activate mast cells to release neuro-sensitizing substances which can aggravate low-grade inflammation (70).

1.3.2 Role of diet in fibromyalgia

Patients with fibromyalgia often seek alternative treatment options such as diets or dietary supplements, as a result of lacking treatment options and/or unsatisfactory effect of offered treatment (54). Evidence on the association between diet and fibromyalgia is still lacking,

however recent literature has shown an increasing interest in the effect of nutritional interventions on symptoms and QoL in patients with fibromyalgia (71-78). A study investigating the association between the Dietary Inflammatory Index and pressure pain hypersensitivity in women with fibromyalgia found an association between a pro-inflammatory diet and pain hypersensitivity (77). The findings suggest that an anti-inflammatory diet could be a strategy to improve pain hypersensitivity in women with fibromyalgia (77). Other diets associated with reduction of symptoms and/or increased quality of life in patients with fibromyalgia are a hypocaloric diet (78), FODMAP diet (76, 78) and different versions of plant based/vegan/vegetarian diets (72, 76, 78).

Dietary supplements were more commonly used among fibromyalgia patients than the general population in Norway, and the most widely used were vitamin D, magnesium, and omega-3 fatty acids (54). Supplements suggested to reduce symptoms in fibromyalgia patients in different studies are chlorella green algae, acetyl-L-carnitine, coenzyme Q10 and a mixture of vitamin E and C (76), phosphorus, iron, vitamin B1, vitamin B6, folic acid and vitamin C (73), Iron, probiotics and vitamin D (74). It has been suggested that there is a higher prevalence of vitamin D deficiency in fibromyalgia patients, however, no consensus has been reached about the relationship between fibromyalgia and vitamin D (75). Interventions with vitamin D supplements have shown to be effective on certain symptoms of fibromyalgia, however evidence is inconclusive (71, 75). In general, the overall strength of these studies was weak as a result of poor study design, wide study heterogeneity, small sample sizes and high degree of bias, and concludes that further research is required to provide more robust evidence for suggesting a specific intervention of diet or supplements in treatment of fibromyalgia (71-78).

1.3.3 Burden of fibromyalgia

Fibromyalgia is a condition with a severe burden on those affected. Fibromyalgia has high impact on quality of life, mental health, ability to perform daily activities and work. Patients with fibromyalgia report a low quality of life, compared to the general population (79). Patients experience lack of recognition and management of the condition from medical services, families, and society (80). Lack of recognition and invalidation may affect mental well-being, physical health, and social functioning (80). It also decreases social support and increases social rejection, and as a result, fibromyalgia patients may hide their symptoms and

isolate from society (80). Women with fibromyalgia, having a “invisible condition”, experienced that other did not believe in their condition, being accused of having poor work ethic, poor moral and exaggerate their symptoms (81). As a result, they isolated from a social life, or hid their symptoms in social settings causing them to collapse of fatigue afterwards (81).

Fibromyalgia is not only a burden on affected individuals, but also a burden on the society. Fibromyalgia is a significant cost burden, with the overall expense increasing alongside disease severity (82). Most of the total expenditures is indirect cost because of loss in productivity, reduced work hours, absenteeism, disability, unemployment, early retirement, informal care, and other out-of-pocket cost (82). Fibromyalgia comorbidity, such as depression, anxiety, and sleep disturbance result in extreme escalation of overall health care expenditures (82). Fibromyalgia patients have double the amount of consultations than healthy individuals over a year, and the total health-care cost are estimated to be three times higher for patients with fibromyalgia than for other individuals in a random population sample (83). Fibromyalgia, among other chronic pain conditions, is one of the most common causes of work-related disability leave (82). Work hours are frequently reduced by 50-75%, and it is not uncommon to become disabled and/or unemployed (82). Fibromyalgia was the medical cause of 2% of the cases receiving sickness benefits and caused 5% of all new cases of disability benefits in Norway in 2006. Fibromyalgia was, alongside osteoarthritis, one of the most prominent causes of receiving long-term benefits (84). It is suggested that increased disease awareness in society could lead to a better understanding of fibromyalgia patients and further reduction of costs (80).

1.3.4 Factors associated with fibromyalgia

Factors such as being female, higher age, lower levels of education, low socioeconomic status and living in rural districts have been suggested risk factors for fibromyalgia in a cross-sectional analysis (85). Risk factors of self-reported fibromyalgia have also been investigated in a recent prospective cohort (86). For self-reported fibromyalgia, having more somatic symptoms was associate with having more risk factors than for the individuals who had fewer somatic symptoms. This might suggest that those with more somatic symptoms had risk factors associated with both fibromyalgia and somatic symptoms, and for the individuals with

fewer somatic symptoms the observed risk factors were more likely to be associated specifically to fibromyalgia (86). Female sex, rheumatoid arthritis, osteoarthritis, irritable bowel disease, impaired sleep, migraine, and few years of education were the strongest predictors for fibromyalgia. Low income, analgesic consumption (consumption to achieve a rewarding dopamine effect), asthma/inhaler use, life events and difficulties score were significantly different only for those with low symptom score. Female sex, osteoarthritis, body mass index (BMI), and number of reported allergies were predictors of self-reported fibromyalgia, irrespective of the number of somatic symptoms (86).

Socioeconomic status

In addition to the two previously mentioned studies, low socioeconomic status such as few years of education and low income have been suggested a risk factor for fibromyalgia and similar pain-conditions in several prospective studies (87-93). Socioeconomic status has further been associated with severity of fibromyalgia symptoms (94). Patients with fibromyalgia and lower socioeconomic status, measured by lower level of education, had greater symptom severity, worse quality of life and reduced function than those with higher education (94).

Menopause

Fibromyalgia symptoms worsen in a significant portion of patients with the onset of menopause, and some patients reported that their symptoms began after menopause suggesting a relationship between these entities (95). Oestrogen deficit has been considered as a potentially promoting factor of symptoms in fibromyalgia, suggesting that shortening time of exposure to oestrogens may influence pain hypersensitivity (96). Women with fibromyalgia and early age-of-onset of menopause (≤49 years), displayed greater pain and non-pain sensitivity than women with fibromyalgia and late age-of-onset menopause (96). No difference in pain were seen between age-of-onset menopause in healthy controls (96). In a study of women with fibromyalgia, the women who had prior hysterectomy reported worse symptoms (score of pain, fatigue, stiffness and depression) than the women who had not (97). It is suggested that the abrupt decline in ovarian hormones possibly contribute to development of hypersensitivity in chronic musculoskeletal pain (97).

Body Mass Index and Obesity

There are indications that obesity might be involved in the pathogenesis of chronic pain syndromes, such as fibromyalgia (94). Obesity may be both an aggravating factor and a potential trigger for fibromyalgia (98). Obesity shows a complex mutual relationship with pain, mainly linked to the mechanical overload, the obesity-driven pro-inflammatory state and complex neurohormonal mechanisms (98). Over the last decades it has been recognized that obesity is associated with chronic low-grade inflammation in a variety of tissues, including adipose tissue, skeletal muscle, liver, pancreas islet, intestine and brain (99). Accumulation of abnormal or excessive fat occurring in obesity can predispose to a pro-inflammatory state and oxidative stress (100). The excess of macronutrients occurring in adipose tissues in obesity stimulates release of inflammatory mediators such as TNF-α, IL-6 and CRP, and a reduction of adiponectin (100).

Accumulating evidence suggest that pain and obesity are significantly related to each other, and obesity is potentially a marker of greater functional and psychological complications in chronic pain (101). An increase in BMI have been positively correlated with the experience of musculoskeletal pain (98). Among patients with fibromyalgia the average BMI was higher compared to average BMI for controls (94). For every 1-unit increase in BMI score, the odds of having fibromyalgia increased by 2.7% (94). Participants who had obesity had a 56% higher chance of having fibromyalgia than participants with normal weight (94). However, fibromyalgia may also favour or worsen the development obesity (98). Physical inactivity or overeating for achieving a rewarding effect by the opioid system, as a consequence of fibromyalgia, may contribute to development of obesity (98). Poor sleep and side effects of medication are other common adverse effects of chronic pain that may also contribute to weight gain (101).

1.4 Rationale of the study

To this date the evidence on fibromyalgia is still limited, and the understanding of the condition is incomplete. The condition is a severe burden to not only those directly affected, but also on society. Fibromyalgia has a high impact on quality of life, mental health, and ability to function in daily activities, social life, and work. Increased health care expenditures because of fibromyalgia comorbidity and reduced ability to work are some of the factors of fibromyalgia causing a substantial economic burden on society. Furthermore, fibromyalgia was one of the most prominent causes of receiving long-term benefits in Norway in 2006. It is suggested that a better understanding of fibromyalgia and awareness in society could improve understanding of fibromyalgia patients, and further reduction of cost, and this underlines the need for more research on fibromyalgia. Treatment of fibromyalgia is complicated and have been proven insufficient leading many to seek alternative methods for treatment, such as diets and dietary supplements. However, the relationship between diet and fibromyalgia is yet to be established in order to give advice on beneficial diets or supplements. There is an increased interest in inflammatory diets as prevention and treatment for diseases and conditions related to inflammation, and there is evidence of diet affecting inflammatory biomarkers. It is suggested that inflammation may play a role in the development of fibromyalgia and/or fibromyalgia symptoms. To my knowledge, no studies have investigated the role of diet as a risk factor for fibromyalgia. This thesis could contribute to increased knowledge on fibromyalgia, and how diet may affect risk of fibromyalgia. And more specifically, how the inflammatory potential of the diet is associated with the risk of fibromyalgia.

1.4.1 Aim of the study

The primary aim of this thesis was to investigate the association between the inflammatory potential of the diet, measured by the DII score, and risk of fibromyalgia in a subgroup of women from the NOWAC study. The secondary aim was to examine the characteristics of participants and participants' diet in relation to the DII score.

2 Methods

2.1 Data material

2.1.1 Study population

The NOWAC study is a nationally representative population based longitudinal cohort study with more than 170 000 women (102). It was initially conducted to investigate the relationship between internal and external hormones and female cancers, with focus on breast cancer. It started in 1991 and recruited women aged 30-70 randomly selected from the National Population Registry of Norway, sending out invitations and self-administered questionnaires by mail. The overall response rate was 57%. In 1998 women who had responded to the first questionnaire and agreed to being contacted again received an invitation to fill in a second questionnaire with more detailed questions on diet. Crude response rate to this questionnaire was 82%. This subgroup (n= 37208) is included in the European Prospective Investigation into Cancer and Nutrition (EPIC) study and constitutes the Norwegian EPIC cohort. Repeated collections of exposure information were carried out in 2003/2004 and 2017/2018.

Almost all questionnaires in the NOWAC examine four pages of core variables: Use of oral combined contraceptives, hormonal replacement therapy, reproductive history, age at menarche and menopause, smoking, physical activity, alcohol consumption, anthropometry, social economic status, screening for breast cancer, breast cancer in family, sunbathing habits and pigmentation and self-reported disease. Most of the questionnaires have in addition four pages asking for detailed information on dietary habits. In the 1998 questionnaire, dietary habits were assessed by a FFQ with 85 frequency questions on common food items consumed in Norway (103). Women were asked to record how often, on average, they had consumed each food item during the last year, and (for most items) to indicate the usual amount per consumption. In a validation study (104), the FFQ was compared to repeated 24HDRs (once during each of the four seasons over a year) in a subgroup of 238 women from the Norwegian EPIC cohort. The FFQ showed good ability to rank women for foods eaten frequently, and fairly good for macronutrients in terms of energy percentages. However, it showed weaker ability to rank women for foods eaten infrequently and for some micronutrients (104).

2.1.2 Inclusion/exclusion criteria

This thesis includes a subgroup of the NOWAC cohort, the Norwegian EPIC cohort, which consist of 37 208 women aged 41-55 at baseline. The 1998-questionnaire was used for baseline information, and further questionnaires collected in 2003/2004 and 2017/2018 were used for follow-up information on onset of fibromyalgia. The 1991-questionnare was inadequate for assessing the dietary information needed to calculate the DII, and therefore not used. The following exclusions were made prior to the analyses (Figure 4): Women with fibromyalgia at baseline, missing information on exposure variable and implausible energy intake were excluded from all analyses. For the main analyses, only women who responded to at least one of the two follow-up questionnaires were included. Women with missing information on covariates included in the multivariable model were excluded.

The cut-off for implausible energy intake in relation to energy requirement was set to highest and lowest 1% of ratio between energy intake and energy requirement. An energy exclusion variable was previously calculated for the women in this thesis by the EPIC team at the International Agency for Research on Cancer (IARC). By personal communication with Corinne Casagrande from IARC, I was informed that the energy requirement was calculated by the following recommendations of the FAO/WHO/UNU 1985 report (105). Basal metabolic rate was calculated based on participant sex, age, height, and weight and then multiplied with physical activity level 1.55 to calculate the energy requirement.

2.1.3 Ethics and privacy

The NOWAC study has received approval from The Regional Committee for Medical Research Ethics for the basic collection and storing of questionnaire information. All the women have signed an informed consent for later linkages to the national registers and are informed about their right to withdraw from the study at any time. Data is stored and handled according to the permission given by the Norwegian Data Inspectorate (102). The dataset used in this thesis does not contain person-identifying data and is considered anonymous. Research project with anonymous data does not require approval from Regional Ethics Committee or evaluation from data protection officer (106, 107).

2.1.4 Exposure variable: The DII score

The exposure variable is the DII score. The DII classifies the women's diets from anti-inflammatory to pro-inflammatory potential, with a higher DII score reflecting a more pro-inflammatory diet and a lower DII score reflecting a more anti-inflammatory diet. In this thesis, both the DII not adjusted for energy and E-DII adjusted for energy were used to assess the association between DII and risk of fibromyalgia. The exposure variables were divided into quartiles.

Calculation of the DII score

The overall inflammatory effect score for the 45 food parameters in the DII were constructed and calculated based on a literature review strategy, scoring algorithms, and standardization to global intake (23). When reviewing the literature, each article was assigned a value, based on what inflammatory effect it displayed for the food parameter. A pro-inflammatory effect (+1) was defined by significantly increased IL-1b, IL-6, TNF-a or CRP, or decreased IL-4 or IL-10. An anti-inflammatory effect (-1) was defined by significantly decreased IL-1b, IL-6, TNF or CRP, or increased IL-4 or IL-10. No significant inflammatory effect was assigned the value 0. The articles were then weighted by study design: 10 (experimental human study), 8 (prospective cohort), 7 (Case control), 6 (cross-sectional), 5 (experimental animal study) or 3 (experimental cell culture). The number of articles for each study design was multiplied with its respective value giving a weighted number of articles. The weighted number was summed separately for the articles showing pro-inflammatory-, anti-inflammatory- and no effect. A pro-inflammatory and an anti-inflammatory fraction is calculated based on weighted number articles for each, divided by the total weighted number of articles (including articles with no effect). A raw inflammatory score was calculated for each food parameter by subtracting the anti-inflammatory fraction from the pro-inflammatory fraction. To account for literature robustness a cut-off value of 236 weighted number of articles was set. This value was the median weighted number of articles for all food parameters. If the total weighted number of articles was <236 for the food parameter, the raw inflammatory score was multiplied by the total weighted number of articles and divided by 236 to create the overall inflammatory effect score. If weighted number of articles for the food parameter ≥236, the raw inflammatory effect was directly transferred as the overall inflammatory effect (23). Figure 1 illustrates an

example of calculation of the inflammatory effect for a food parameter. Saturated fat is used as an example, and the numbers are collected from the original article on DII (23).

Effect	Study design	Number of articles	Weighted number of articles	Fraction
Anti-inflammatory (-)	Clinical - 10	0	0	$\frac{9}{205} = 0.044$
	Cohort - 8	0	0	
	Case-control - 7	0	0	
	Cross-sectional - 6	1	6	
	Animal - 5	0	0	
	Cell - 3	1	3	
	Total	2	9	
Pro-inflammatory (+)	Clinical - 10	3	30	$\frac{97}{205} = 0.473$
	Cohort - 8	0	0	
	Case-control - 7	1	7	
	Cross-sectional - 6	4	24	
	Animal - 5	3	15	
	Cell - 3	7	21	
	Total	18	97	
No effect (0)	Clinical - 10	3	30	
	Cohort - 8	0	0	
	Case-control - 7	0	0	
	Cross-sectional - 6	9	54	
	Animal - 5	3	15	
	Cell - 3	0	0	
	Total	15	99	
Overall total		35	**205**	

Raw inflammatory effect = pro-inflammatory fraction – anti-inflammatory fraction
0.473 - 0.044 = 0.429

Overall inflammatory effect = 205/236= 0.87 → 0.87*0.429 = <u>0.373</u>

Figure 1. Example on how to calculate inflammatory effect for intake of saturated fat.
Numbers used in this example are collected from the original article describing the construction and calculation of DII (23).

The DII scores used in this thesis were previously calculated for the participants in the EPIC study (including the women in this thesis) by the EPIC team at the International Agency for Research on Cancer (IARC), with the assistance of the original developers of the DII (108). They had calculated the DII and two versions of the E-DII; one by using the residual method for energy adjustment and one by using the density method for energy adjustment (108). For this thesis, only the E-DII calculated by the residual method was chosen as the energy-adjusted version of DII. The DII scores for women in this thesis were calculated with information from baseline FFQ on participants intake of 31 food parameters (30 for the E-DII) including various micro- and macronutrients, whole foods, and non-nutrient substances. These include energy (not for E-DII), carbohydrates, proteins, lipids, ethanol, fibers, cholesterol, saturated fat, mono-unsaturated fat, poly-unsaturated fat, thiamin, riboflavin,

vitamin B12, vitamin B6, vitamin A, vitamin C, vitamin E, vitamin D, iron, magnesium, folic acid, beta-carotene, caffeine, onion, flavones, flavanones, anthocyanidins, flavan-3-ols, flavanols, isoflavones and tea. The women's intake of the food parameters was standardized to the world average database. Z-scores were calculated for each food parameter by subtracting the mean (from world average database) from the women's reported intake and further dividing by the standard deviation (from world average database). To reduce the effect of right skewing commonly observed in dietary data, the z-score was then converted to a percentile score. The percentile score was centered by doubling and subtracting 1 to achieve a symmetrical distribution centered around 0 and bounded between -1 and +1. The centered percentile-value was then multiplied by the food parameter's respective overall inflammatory effect score for each food parameter and summed to obtain the overall DII score for each woman in the study. Further, the E-DII was calculated in similar steps as described above except for that the women's intake was adjusted for energy using the residual method (109) before calculating the DII, and their intake was standardized to the energy-adjusted version of the world database. Figure 2. Illustrates the steps for calculating the inflammatory score for a food parameter from the woman's actual intake of the food parameter. The example is for saturated fat and was calculated for a random selected intake of saturated fat, however, mean and standard deviation were collected from the world average database presented in the original article of the DII (23). Conversion of z-score to percentile score was conducted in Excel and is not described in detail in this figure. The built-in Excel function *=NORM.S.DIST(z, cumulative)* was used, where z was replaced with the z-score, and cumulative was replaced with TRUE to return the cumulative distribution function.

Steps for calculating the DII score for saturated fat for a participant		
z-score was calculated based on participants intake and mean and standard deviation (SD) from world average database	$Z-score = \frac{participants\ intake - mean\ intake}{Standard\ deviation} = \frac{30-28.6}{8} = 0.175$ Participants intake of saturated fat = Average intake of saturated fat from world average database	30 grams Mean = 28.6 grams SD = 8
Z-score was converted to percentile score	Z-score = 0.175 → Percentile score = 0.57 (57%)	
The percentile score was cantered by doubling the value and then subtracting 1	Centred percentile: 0.57*2=1.14 → 1.14-1=0.14	
Calculating the DII score for saturated fat for the participant	Centred percentile for participants intake of saturated fat * overall inflammatory effect for saturated fat	0.14*0.373 = <u>0.053</u>

Figure 2. Example on how DII score is calculated for saturated fat.
Mean and standard deviation from the original article on DII (23).

2.1.5 Outcome variable: Year of onset of fibromyalgia

Self-reported status on year of onset of fibromyalgia from self-administered questionnaires was used as outcome variable. For a selected variety of conditions, including fibromyalgia, the women were asked to indicate if they had the condition by checking the box for what year the condition occurred (Figure 3).


For følgende tilstander kryss av for hvilket år tilstanden oppsto eller angi årstall for perioden før 1991.

	før 91	91	92	93	94	95	96	97	98
Muskelsmerter (myalgi)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Fibromyalgi/Fibrositt	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kronisk tretthetssyndrom	☐	☐	☐	☐	☐	☐	☐	☐	☐
Ryggsmerter ukjent årsak	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nakkeslengskade	☐	☐	☐	☐	☐	☐	☐	☐	☐
Osteoporose/(b.skjørhet)	☐	☐	☐	☐	☐	☐	☐	☐	☐

Figure 3. Question on year of onset fibromyalgia from baseline questionnaire

The variable for the first follow-up (2003/2004) consisted of seven values for year of onset fibromyalgia: before 1998, 1998, 1999, 2000, 2001, 2002, 2003 and 2004. The variable for the second follow-up (2017/2018) consisted of six values for year of onset fibromyalgia: before 2006, 2006-2007, 2008-2009, 2010-2011, 2012-2013, 2014-2015 and 2016. A continuous variable for year of onset fibromyalgia was constructed based on these variables. The values before 1998 and 1998 were not included in the new variable considering cases of fibromyalgia at baseline were excluded from all analyses. The value “before 2006” was included in the new variable as 2005, and further the first year of the intervals was chosen. If the women had reported year of onset fibromyalgia in both follow-up questionnaires, the year reported in the first follow-up questionnaire was used in the new variable.

2.1.6 Time metric: Follow-up time

The start of follow-up was set to 1998, the year of the baseline questionnaire. End of follow-up was set to 2016, considering it is the last year we have information on onset of fibromyalgia from the second and last follow-up questionnaire. Follow-up time is calculated from baseline (1998) to year of onset fibromyalgia or end of follow-up. Women were

censored if year of death or emigration occurred before event or end of follow-up. The NOWAC study was linked to the national population registry for information on emigration and death. Women who did not answer the second follow up- questionnaire were censored at the end of first follow-up. End of the first follow-up was set to 2004, as that is the last year we have information on onset of fibromyalgia from the first follow-up questionnaire.

2.1.7 Covariates

The following covariates were chosen based on literature and available data from the NOWAC study, and further tested for confounding statistically: Age (years), physical activity (scale 1-10, representing very low to very high activity level), weight (kg), height (cm), smoking status (never smoked, former smoker, current smoking), education (years of schooling), Income, representing gross income of household in Norwegian kroners (NOK), (under 150 000, 151 000-300 000, 301 000-450 000, 451 000-600 000 and over 600 000), self-perceived health status (very good, good, poorly, very poorly), diabetes at baseline (yes, no), menopause status (pre-, peri-, postmenopausal, info missing, hysterectomy <53, hormone replacement therapy<53), alcohol consumption (gram/day), use of liquid cod liver oil (yes, no), use of cod liver oil capsules (yes, no) and use of fish oil capsules (yes, no). All variables were self-reported, except for age, which was based on registry information. Smoking status and age were included as described above. Diabetes was kept as a binary variable (yes/no), however missing values were imputed as "no" (110). The validated 10-point scale level of activity (111) was categorized into three groups representing low (1-4), moderate (5-6) and high (7-10) activity level. Education was categorized into three groups (<10 years, 10-12 years, >12 years). Income was recoded from five to three groups (<300 000, 301 000-450 000, >450 000 NOK). Self-perceived health status was recoded from four to three groups (very good, good, poorly). Weight and height were used to calculate BMI (kg/m^2), proven to provide a valid ranking of BMI in the NOWAC study (112). BMI was then divided into four groups representing underweight (<20 kg/m^2), normal weight (20-24 kg/m^2), overweight (25-29 kg/m^2) and obesity (≥30 kg/m^2). For menopause status the last two categories were recoded to unknown and "info missing" as system missing (pre-, peri-, postmenopausal, unknown). Alcohol consumption was categorized in three groups by consumption status and median intake in consumers (non-consumer, intake below median, intake above median). Use of cod liver oil, cod liver oil capsules or fish oil capsules were combined into one variable:

Use of cod liver-/fish oil supplements (yes, no).

Dietary covariates

The following variables, in unit intake per day, were used for descriptive characteristic of diet: Energy (MJ), protein (E%), total fat (E%), saturated fatty acids (g), monounsaturated fatty acids (g), polyunsaturated fatty acids (g), trans fatty acids (g), carbohydrates (E%), sugar (E%), fiber (g), iron (mg), vitamin D (ug), folate (ug), fruit (g), vegetables (g), unprocessed meat (g), processed meat (g), fat fish (g), lean fish (g), fish spread (g), bread and cereals (g), yoghurt (g), cheese (g), milk (g). Percentage of energy intake (E%) were calculated for saturated-, monounsaturated-, polyunsaturated- and trans fatty acids from g intake for each and total energy intake per day. Intakes of fruit and vegetables were combined in to one variable of total intake of fruit and vegetables. Intake of unprocessed- and processed meat were summed into a variable for total meat (g/day). A variable for total intake of fish (g/day) were calculated from intake of lean fish, fat fish and fish spread. A variable for total intake of dairy products (g/day) were calculated from intake of milk, cheese, and yoghurt.

2.2 Statistical analyses

Baseline characteristics (Table 1) and baseline diet (Table 2, Table 3) are presented for all women in total, and for women in each of the DII quartiles. DII score is presented as median and range of the score. Age is presented as means and standard deviation. Categorical variables are presented as percentage and number of women in each category and continuous variables are presented as median intake (unit per day) and percentiles (25^{th} ,75^{th}). The range of DII-score differs in DII and E-DII and their respective quartiles and baseline characteristics were therefore investigated for both. However, the differences were marginal and baseline characteristics and diet are therefore presented only for the DII.

Cox proportional hazard regression model was used to estimate hazard ratio and 95% confidence intervals for the association between the DII score and fibromyalgia. SPSS Statistics 28 for Windows was used for conducting the statistical analyses and a p-value <0.05 was considered significant. Assumptions for proportional hazards were evaluated by visual inspection of log minus log-plots and testing for interaction with time by including a time dependent variable in the cox regression. Interaction between time and exposure variable was not significant, and the assumption of proportional hazards was fulfilled.

In the cox proportional hazard regression model fibromyalgia was the event variable, the DII score divided into quartiles was the exposure and calculated time of follow-up was the time metric. Two models were constructed. The first model was adjusted for age only. The second model was constructed by testing for confounding of the following covariates: Age, physical activity, smoking status, education, diabetes, menopausal status, alcohol consumption, income, self-perceived health status and use of cod liver-/fish oil supplements. All covariates that were not significantly associated using Wald test ($p>0.05$) were stepwise removed from the model. The covariate with the highest p-value was removed until all remaining covariates were significant. Possible interactions between the DII and BMI and smoking status were investigated using Wald test. Interaction between BMI and DII was significant ($p<0.001$), and therefore BMI was not considered a confounding covariate in the model but instead analyses stratified by BMI were conducted. Possible multicollinearity between covariates was examined, however non detected. For each covariate the confounding effect was calculated comparing beta coefficients of the exposure in model with and without covariate. The covariates that confounded 10% or more for at least one of the groups of exposure were kept in the multivariable model. During these steps the covariates diabetes, physical activity and use of cod liver/fish oil supplement were removed, and age, smoking status, education, income, menopausal status, self-perceived health status and alcohol consumption remained as confounding covariates.

Additionally, all analyses were conducted with the E-DII score that is energy adjusted by the residual method as the exposure variable. The E-DII was strongly correlated to the DII (Pearsons's coefficient $R= 0.93$). Test for trend over the categorical exposure variable was calculated by using median value of DII/E-DII score for each quartile to compute a continuous variable, and further including the variable in the cox regression analyses. Sensitivity analyses were conducted, starting follow-up time three years after baseline, to assess the robustness of the primary analyses.

Considering how event of fibromyalgia was recorded in this thesis, there were several events occurring at the same time (year of onset fibromyalgia). Tied events need to be handled in the Cox proportional hazard regression, and there are several methods for handling tied events. The Breslow method is the default for handling tied events in SPSS. Analyses were additionally run in SAS using the Exact method for handling tied events to inspect if using a

different method would impact the results. However, the difference in results were marginal and results using Breslow method in SPSS are presented in this thesis.

2.2.1 BMI-stratified analyses

Analyses stratified by BMI were conducted to investigate a possible effect modification of BMI on the association between DII/E-DII and risk of fibromyalgia. Cox proportional HR and 95% CI were investigated separately for women with under- or normal weight (<25 kg/m^2) and women with overweight or obesity (≥25 kg/m^2). The BMI-variable was initially divided in to four groups (as described in 2.1.7 Covariates). The two groups with the lowest and highest BMI consisted of a smaller percentage of the study population and therefore few cases in each group. To provide a robust number of cases in the DII quartiles in each group BMI was divided in to two groups for the stratified analyses. The interaction between DII and BMI was still significant after dividing into two groups ($p<0.001$). The number of women varies between the main analyses and the stratified analyses. A total of 1.2% (261) of the women included in main analyses were missing information on BMI, and therefore not included in the stratified analyses.

3 Results

3.1 Study sample

The flow chart (figure 4) shows the number of women in the study sample after exclusion and inclusion from the total sample of study cohort. Women were excluded if they reported fibromyalgia at baseline, had missing exposure variable and/or if they had implausible energy intake in relation to energy requirement. A total of 2 530 women reported fibromyalgia in 1998 or earlier year in the questionnaire from baseline or first follow-up, and 21 women were missing the exposure variable (DII-score). The cut-off for implausible energy intake in relation to energy requirement was set to top and bottom 1% (n=742) of ratio between energy intake and energy requirement. A total of 33 990 women were left after the exclusion criteria was applied. For the main analysis, only women who had replied to at least one of the follow-up questionnaires were included, resulting in a total of 25 092 women. Out of the cohort (37 208) a total of 74% (n=27 448) responded to the first follow-up questionnaire and 51% (n=18 990) responded to the second follow-up questionnaire. For the analyses on DII and fibromyalgia, women with missing values on covariates included in the multivariable model were excluded, resulting in a total sample of 21 814 women eligible for the main analyses (see details in figure 4). A total of 21 553 women were eligible for analyses stratified by BMI-groups, after excluding 261 women with missing information on BMI. After excluding women who had incident fibromyalgia, death, or emigration during the first 3 years after baseline (n=128), a total of 21 686 women were eligible for the sensitivity analyses.

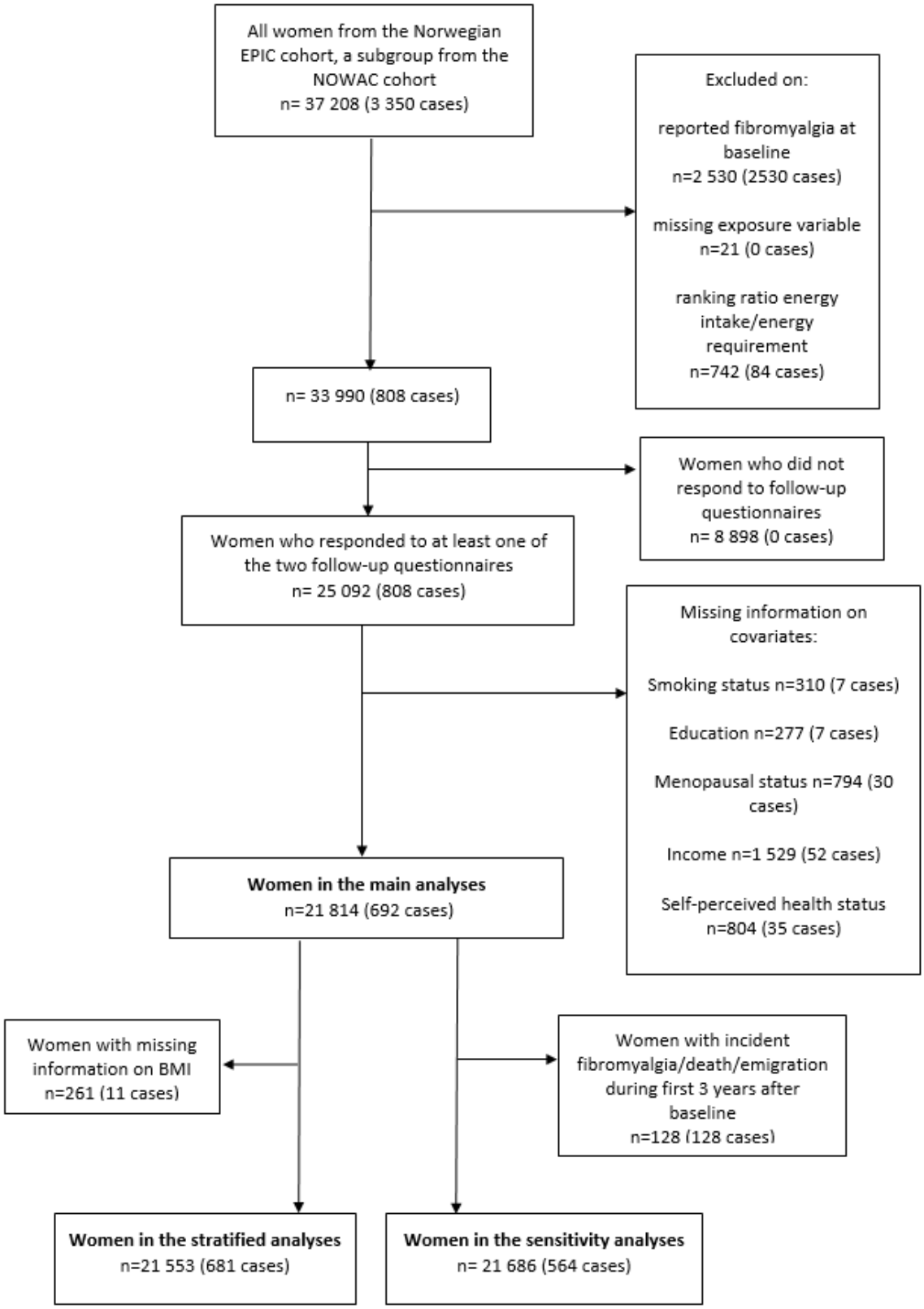

Figure 4. Flow chart of the study sample, The NOWAC study.
Describes women eligible for inclusion, fibromyalgia cases, exclusion and inclusion criteria and overview women in main, stratified and sensitivity analyses, reported as number of participant and cases of fibromyalgia.

3.2 Characteristics of the study population in total and in relation to DII score

Baseline characteristics were investigated for 21 814 women from the NOWAC study. Table 1 shows the baseline characteristics of the study population. Women in the first quartile had the lowest DII-score (-3.88-0.19) representing the most anti-inflammatory potential of the diet. Women in fourth quartile had the highest DII-score (2.65-5.09) representing the most pro-inflammatory potential of the diet.

The women ranged in age from 41-55 years, with a mean age of 47.6 years. Over half of the women had a BMI defined as normal weight (58.2%), a quarter of the group had overweight (26.6%) and two equally small groups had underweight or obesity (7.6%). A larger proportion of the group had moderate to high activity level, and a slightly larger proportion of the women had high activity level (29.3%) than low activity level (24.9). Most of the women had completed more than 10 years of education and approximately half (46.1%) of them had completed 12 years of education or more. A slightly larger portion (38%) of the women had a higher gross income for their household, than mid (30.2%) and lower (31.8%) income range. The women were more likely to never have smoked (36.8%) than to be currently smoking (28.5%). Most of the women consider their health to be good (58.4%) or very good (37.5%). Half of the women (49.3%) had not gone through menopause yet, less than a third were postmenopausal and the rest were either perimenopausal or had unknown menopausal status.

Compared to the women in the first quartile, women in the fourth quartile were more likely to be younger, have overweight or obesity, be less active, be currently smoking, have lower education and lower gross household income. Women in the fourth quartile were also less likely to consider their health status as very good and to be postmenopausal, compared to women in the first quartile.

Table 1: Baseline characteristics in quartiles of DII and in total for 21 814 women from the NOWAC study.

DII quartiles	**Q1**	**Q2**	**Q3**	**Q4**	**Total**
N	5 454	5 453	5 453	5 454	21 814
(case)	(155)	(158)	(196)	(183)	(692)
DII score	-0.71	0.84	2.03	3.35	1.46
Median (range)	(3.88,0.19)	(0.19,1.46)	(1.46,2.65)	(2.65,5.09)	(3.88,5.09)
Age (years)					
Mean (SD)	48.1 (4.28)	47.7 (4.29)	47.5 (2.27)	47.2 (4.24)	47.6 (4.29)
BMI (kg/m^2)					
<20	8.0 (433)	7.8 (420)	7.7 (418)	6.9 (396)	7.6 (1640)
20-24	61.7 (3324)	59.2 (3191)	55.3 (2983)	56.5 (3041)	58.2 (12539)
25-29	24.5 (1319)	26 (1408)	28.5 (1537)	27.5 (1481)	26.6 (5745)
≥30	5.8 (310)	7.0 (375)	8.5 (457)	9.1 (487)	7.6 (1629)
Physical activity level					
Low	18.0 (941)	22.6 (1183)	27.2 (1442)	32.0 (1664)	24.9 (5210)
Moderate	45.0 (2345)	47.6 (2495)	46.1 (2408)	44.2 (2302)	45.8 (9550)
High	37.0 (1933)	29.8 (1563)	26.7 (1393)	23.8 (1236)	29.3 (6125)
Smoking status					
Never smoked	38.6 (2103)	38.7 (2111)	37.1 (2022)	32.9 (1794)	36.8 (8030)
Former smoker	36.9 (2013)	35.0 (1909)	33.9 (1850)	33.0 (1800)	34.7 (7572)
Currently smoking	24.5 (1338)	26.3 (1433)	29.0 (1581)	34.1 (1860)	28.5 (6212)
Education (years)					
<10	15.2 (828)	18.4 (1003)	18.9 (1028)	20.6 (1126)	18.3 (3985)
10-12	33.1 (1806)	34.5 (1882)	35.9 (1958)	38.9 (2122)	35.6 (7768)
>12	51.7 (2820)	47.1 (2568)	45.2 (2467)	40.4 (2206)	46.1 (10061)
Gross income household (NOK)					
<300 000	29.8 (1624)	31.7 (1728)	31.3 (1705)	34.5 (1880)	31.8 (6937)
301 000- 450 000	28.9 (1578)	30.7 (1674)	30.7 (1677)	30.2 (1650)	30.2 (6579)
>450 000	41.3 (2252)	37.6 (2051)	38.0 (2071)	35.3 (1924)	38.0 (8298)

DII quartiles	**Q1**	**Q2**	**Q3**	**Q4**	**Total**
N	5 454	5 453	5 453	5 454	21 814
(case)	(155)	(158)	(196)	(183)	(692)
Self-perceived health status					
Very good	40.9 (2231)	36.6 (1998)	37.2 (2028)	35.2 (1919)	37.5 (8176)
Good	54.7 (2983)	59.4 (3293)	59.1 (3224)	60.5 (3299)	58.4 (12745)
Poorly	4.4 (240)	4.0 (216)	3.7 (201)	4.3 (236)	4.1 (893)
Menopause status					
Premenopausal	46.0 (2506)	49.0 (2670)	50.4 (2747)	51.7 (2821)	49.3 (10744)
Perimenopausal	11.0 (600)	10.6 (580)	10.7 (584)	11.7 (639)	11.0 (2404)
Postmenopausal	29.6 (1616)	26.7 (1455)	25.5 (1390)	23.5 (1283)	26.3 (5744)
Unknown	13.4 (732)	13.7 (748)	13.4 (731)	13.1 (711)	13.4 (2922)

Abbreviations: SD = standard deviation, BMI = body mass index, NOK = Norwegian kroners.

BMI missing 1.2 % (261)

Physical activity missing 4.3% (929)

3.3 Diet in relation to DII score

Table 2 shows intake of nutrients for women in each quartile of the DII and in total for all women. Energy is presented as megajoule (MJ), nutrients contributing to energy intake presented as percentage of energy intake (E%), and nutrients not contributing to energy as unit intake per day. Percentiles (25^{th} ,75^{th}) are presented for all the above. Median energy intake was 7.1 MJ among all participants, with highest intake among women in the first quartile (8.3MJ) and lowest intake among women in the fourth quartile (5.8MJ). The biggest difference in nutrient intake between quartiles of the DII score was seen for saturated fat (SFAs), fiber, iron, vitamin D and folate. Compared to the women in the first quartile, women in the fourth quartile had higher intake of SFAs (14.2 vs 12.8 E%) and lower intake of fiber (16 vs 27 g/day), iron (7 vs 12 mg/day), vitamin D (3 vs 13 ug/day) and folate (138 vs 229 ug/day).

Table 3 shows intake of selected food groups and alcohol, and use of supplements in quartiles of the DII and in total for all women. Intake of food groups are presented as median intake in grams per day and percentiles (25^{th}, 75^{th}). Intake of alcohol and use of supplement are presented as percentage and number of participants for each category. Half of the women used supplements of cod liver oil/fish oil (52.3%) and/or other supplements (57.9%). Median intake of alcohol for all women consuming alcohol was 2.4 gram/day. A slightly larger proportion of the women had intake of alcohol above median (45.3%), than women who had intake below median (37.8%) or were non-consumers (16.9%). Compared to women in the first quartile, women in the fourth quartile had lower intake of fruit and vegetables, fish, bread and cereals and dairy products, and were less likely to use supplements. Highest consumption of meat in total and processed meat was seen in women in the second quartile. However, differences in intake of meat were in general marginal between the quartiles of DII.

Table 2: Intake of energy and nutrients in quartiles of DII and in total for 21 814 women from the NOWAC study.

DII quartiles	**Q1**	**Q2**	**Q3**	**Q4**	**Total**
N	5 454	5 453	5 453	5 454	21 814
(Case)	(155)	(158)	(196)	(183)	(692)
DII score	-0.71	0.84	2.03	3.35	1.46
Median (range)	(-3.88,0.19)	(0.19,1.46)	(1.46,2.65)	(2.65,5.09)	(-3.88,5.09)
Median (p25,p75)					
Energy (MJ)	8.3 (7.3,9.4)	7.6 (6.6,8.5)	6.8 (5.9,7.7)	5.8 (4.9,6.6)	7.1 (6.0,8.3)
Protein (E%)	17.6 (16.2,19.1)	17.6 (16.2,19.2)	17.8 (16.4,19.4)	18.1 (16.5,19.9)	17.8 (16.3,19.4)
Total fat (E%)	32.3 (29.3,36.1)	32.9 (29.7,36.1)	32.7 (29.4,35.9)	33.2 (29.9,36.3)	32.7 (29.6,35.9)
SFAs (E%)	12.8 (11.4,14.2)	13.5 (12.0,14.9)	13.7 (12.1,15.3)	14.2 (12.5,15.8)	13.5 (12.0,15.0)
MUFAs (E%)	10.4 (9.3,11.5)	10.5 (9.3,11.7)	10.3 (9.2,11.5)	10.5 (9.4,11.7)	10.4 (9.3,11.6)
PUFAs (E%)	5.9 (5.1,6.9)	5.8 (4.9,6.9)	5.5 (4.7,6.6)	5.3 (4.6,6.3)	5.7 (4.8,6.7)
TFAs (E%)	0.6 (0.5,0.7)	0.7 (0.6,0.8)	0.7 (0.7,0.8)	0.7 (0.7,0.8)	0.7 (0.6-0.8)
Carbohydrates (E%)	48.8 (45.2,52.0)	48.1 (44.7,51.4)	48.1 (44.4,51.6)	47.2 (43.6,50.7)	48.0 (44.4,51.5)
Sugar (E%)	5.0 (3.5,6.8)	5.5 (3.9,7.5)	5.6 (3.8,7.8)	5.8 (3.9,8.2)	5.4 (3.7,7.6)
Fiber (g/day)	27 (23.5,30.7)	23 (19.9,29.1)	20 (17.4,22.9)	16 (13.4,18.6)	21 (17,25)
Iron (mg/day)	12 (9,13)	10 (8,11)	9 (7,10)	7 (6,9)	9 (7,11)
Vitamin D (ug/day)	13 (7,19)	7 (5,13)	4 (3,6)	3 (2,4)	5 (5,11)
Folate (ug/day)	229 (198,264)	192 (166,220)	169 (146,194)	138 (117,161)	179 (146,216)

MJ = mega joule, E% = percent of total energy, SFAs = saturated fatty acids, MUFAs= monounsaturated fatty acids, PUFAs=Polyunsaturated fatty acids, TFAs = trans fatty acids, g/day = grams per day, mg/day = milligrams per day, ug/day = micrograms per day, p25= 25th percentile, p75 = 75th percentile

Table 3. Intake of selected food groups and alcohol, and use of supplements in quartiles of DII and in total for 21 814 women from the NOWAC study

DII quartiles	**Q1**	**Q2**	**Q3**	**Q4**	**Total**
N	5 454	5 453	5 453	5 454	21 814
(Case)	(155)	(158)	(196)	(183)	(692)
DII score	-0.71	0.84	2.03	3.35	1.46
Median (range)	(-3.88,0.19)	(0.19,1.46)	(1.46,2.65)	(2.65,5.09)	(-3.88,5.09)
Median (p25,p75)					
Fruit and vegetables(g/day)	453 (338,585)	312 (233,415)	255 (186,341)	184 (121,250)	286 (193,411)
Total meat (g/day)	46 (30,66)	48 (33,68)	47 (32,62)	45 (31,62)	47 (31,65)
Processed meat (g/day)	31 (18,48)	34 (21,50)	32 (20,48)	30 (19,45)	32 (19,47)
Fish (g/day)	59 (38,87)	46 (29,68)	38 (23,57)	29 (16,44)	42 (24,64)
Bread and cereals(g/day)	182 (129,209)	180 (119,201)	134 (109,189)	111 (100,143)	140 (107,191)
Dairy (g/day)	245 (124,530)	228 (112,404)	209 (100,316)	185 (87,285)	218 (106,341)
% (n)					
Use cod liver-/fish oil supplements	76.6 (4179)	61.1 (3330)	42.7 (2330)	28.8 (1573)	52.3 (11412)
Use other supplements	64.0 (3490)	58.7 (3201)	56.1 (3058)	52.8 (2882)	57.9 (12631)
Alcohol					
Non consumer	20.8 (1137)	19.1 (1044)	17.9 (974)	10.0 (541)	16.9 (3696)
below median[1]	25.6 (1394)	36.2 (1973)	39.4 (2151)	49.8 (2718)	37.8 (8236)
above median[1]	53.6 (2923)	44.7 (2436)	42.7 (2328)	40.2 (2195)	45.3 (9882)

g/day = grams per day, p25 = 25th percentile, p75 = 75th percentile

[1]Median intake alcohol (based on women consuming alcohol) = 2.4 grams per day.

3.4 The association between the Dietary Inflammatory Index score and risk of fibromyalgia

Data from 21 814 women were analyzed. During an average 14.2 years of follow up (and a total of 309 393 person-years) a total of 692 cases of fibromyalgia were identified. Table 4 presents the association between the DII/E-DII and risk of fibromyalgia. For DII, the third quartile showed highest risk of fibromyalgia in both age-adjusted (HR_{Q3-Q1} 1.27 (1.03,1.57)) and multivariable-adjusted model (HR_{Q3-Q1}1.14 (0.92,1.41)). A significant association between the DII and risk of fibromyalgia was seen only for the age-adjusted model (P=0.048 for trend), and the association was no longer significant in the multivariable-adjusted model (P=0.610 for trend). For the E-DII, the risk of fibromyalgia increased along quartiles, with the highest risk in the fourth quartile for both age-adjusted (HR_{Q4-Q1} 1.23 (0.99,1.52)) and multivariable-adjusted model (HR_{Q4-Q1} 1.05 (0.84,1.31)). The association between the E-DII and risk of fibromyalgia was however not significant.

Table 4. Association between the Dietary Inflammatory Index (DII) score and risk of fibromyalgia in 21 814 women in the NOWAC study.

	DII					E-DII				
Quartile	Q1	Q2	Q3	Q4		Q1	Q2	Q3	Q4	
Range	-3.88,0.19	0.19,1.46	1.46,2.65	2.65,5.09		-5.04, -0.79	-0.79,0.30	0.30,1.30	1.30,4.12	
N	5 454	5 453	5 453	5 454		5 454	5 453	5 454	5 453	
case	155	158	196	183		151	173	177	191	
	Ref.	HR (95% CI)	HR (95% CI)	HR (95% CI)	P-trend	Ref	HR (95% CI)	HR (95% CI)	HR (95% CI)	P-trend
Age[1]	1.00	1.01 (0.81,1.30)	1.27 (1.03,1.57)	1.17 (0.94,1.45)	0.048	1.00	1.13 (0.90,1.40)	1.16 (0.94,1.45)	1.23 (0.99,1.52)	0.060
Multivariable[2]	1.00	0.93 (0.74,1.16)	1.14 (0.92,1.41)	1.00 (0.80,1.24)	0.610	1.00	1.03 (0.82,1.28)	1.03 (0.83,1.29)	1.05 (0.84,1.31)	0.662

HR = Hazard ratio, CI= confidence interval, Ref.= Reference group, DII = The dietary inflammatory index score, E-DII = The energy-adjusted dietary inflammatory index score

[1] Model is adjusted for age.

[2] Model is adjusted for age, smoking status, education, gross household income, self-perceived health status, alcohol consumption and menopause status.

3.4.1 The association between the Dietary Inflammatory Index and fibromyalgia stratified by BMI

Stratified analyses were conducted to explore the possible effect modification of BMI on the association between DII/E-DII and fibromyalgia. Analyses were stratified by two BMI-groups: under- or normal weight (BMI<25 kg/m^2) and overweight or obesity (BMI≥25 kg/m^2). A total of 261 women had missing information on BMI and were therefore excluded from this analysis. For the first BMI-group (BMI<25 kg/m^2) data from 14 149 women were analyzed and 367 cases of fibromyalgia identified. A higher risk of fibromyalgia was seen in the fourth quartile, for both DII and E-DII and in both age-adjusted and multivariable-adjusted model. However, no significant associations were observed. For the second BMI-group (BMI ≥25 kg/m^2) data from 7 374 women were analyzed, and a total of 314 cases of fibromyalgia were identified. For this group, a higher risk of fibromyalgia was seen in the third quartile for both DII and E-DII and in both models. A significant association was seen only for DII in the age-adjusted model for the third quartile compared to the first quartile ($HR_{Q3\text{-}Q1}$1 1.44 (1.05,1.96). Nevertheless, p-value for trend over quartiles was not significant (p=0.490)

Table 5. Association between The Dietary Inflammatory Index (DII) score and risk of fibromyalgia stratified by BMI in 21 553 women in the NOWAC study.

	DII					E-DII				
BMI <25 kg/m^2										
Quartile	Q1 -3.88,0.19	Q2 0.19,1.46	Q3 1.46,2.65	Q4 2.65,4.93		Q1 -5.04, -0.79	Q2 -0.79,0.30	Q3 0.30,1.30	Q4 1.30,3.84	
N	3 753	3 611	3 401	3 410		3 721	3 580	3 399	3 479	
case	91	91	83	102		85	94	84	104	
	Ref.	HR (95%CI)	HR (95%CI)	HR (95%CI)	P-trend	Ref.	HR (95%CI)	HR (95%CI)	HR (95%CI)	P-trend
Age[1]	1.00	1.03 (0.77,1.35)	1.01 (0.75,1.36)	1.23 (0.93,1.16)	0.194	1.00	1.13 (0.84,1.51)	1.07 (0.79,1.44)	1.28 (0.96,1.70)	0.136
Multivariable[2]	1.00	0.94 (0.67,1.26)	0.92 (0.68,1.24)	1.02 (0.76,1.36)	0.929	1.00	1.01 (0.75,1.36)	0.94 (0.67,1.28)	1.04 (0.77,1.40)	0.885
BMI ≥25 kg/m^2										
Quartile	Q1 -3.68,0.19	Q2 0.19,1.46	Q3 1.46,2.65	Q4 2.65,5.09		Q1 -5.01, -0.79	Q2 -0.79,0.30	Q3 0.30,1.30	Q4 1.30,4.12	
N	1 629	1 783	1 994	1 968		1 662	1 820	1 986	1 906	
case	62	65	110	77		64	76	91	83	
	Ref.	HR (95%CI)	HR (95%CI)	HR (95%CI)	P-trend	Ref.	HR (95%CI)	HR (95%CI)	HR (95%CI)	P-trend
Age[1]	1.00	0.95 (0.67,1.34)	1.44 (1.05,1.96)	0.99 (0.71,1.38)	0.490	1.00	1.07 (0.77,1.49)	1.18 (0.86,1.63)	1.06 (0.76,1.47)	0.618
Multivariable[2]	1.00	0.89 (0.63,1.26)	1.30 (0.95,1.78)	0.90 (0.64,1.26)	0.918	1.00	1.00 (0.72,1.40)	1.09 (0.79,1.50)	0.98 (0.70,1.38)	0.965

HR = Hazard ratio, CI= confidence interval, Ref.= Reference group, DII = The dietary inflammatory index score, E-DII = The energy-adjusted dietary inflammatory index score

[1] Model is adjusted for age.

[2] Model is adjusted for age, smoking status, education, gross household income, self-perceived health status, alcohol consumption and menopause status.

3.4.2 Sensitivity analyses

To assess the robustness of the primary analyses a sensitivity analysis was conducted starting follow up in 2001, 3 years after baseline. Data from 21 686 women was analyzed, and during an average follow-up of 11.2 years 564 cases of fibromyalgia were identified. The associations between DII/E-DII and fibromyalgia were not substantially changed in the sensitivity analyses.

Table 6. Sensitivity analyses: Association between The Dietary Inflammatory Index (DII) score and risk of fibromyalgia in 21 686 women in the NOWAC study.

	DII					E-DII				
Quartile	Q1	Q2	Q3	Q4		Q1	Q2	Q3	Q4	
Range	-3.88,0.19	0.19,1.46	1.46,2.65	2.65,5.09		-5.04, -0.79	-0.79,0.30	0.30,1.30	1.30,4.12	
N	5 422	5 421	5 422	5 421		5 422	5 421	5 421	5 422	
case	127	126	155	156		121	143	138	162	
	Ref.	HR (95% CI)	HR (95% CI)	HR (95% CI)	P-trend	Ref	HR (95% CI)	HR (95% CI)	HR (95% CI)	P-trend
Age[1]	1.00	0.98 (0.76,1.25)	1.21 (0.96,1.54)	1.20 (0.95,1.52)	0.048	1.00	1.15 (0.90,1.46)	1.12 (0.88,1.43)	1.27 (1.00,1.61)	0.067
Multivariable[2]	1.00	0.90 (0.71,1.16)	1.10 (0.86,1.39)	1.03 (0.81,1.31)	0.504	1.00	1.05 (0.83,1.35)	1.00 (0.78,1.28)	1.09 (0.85,1.39)	0.593

HR = Hazard ratio, CI= confidence interval, Ref.= Reference group, DII = The dietary inflammatory index score, E-DII = The energy-adjusted dietary inflammatory index score

[1] Model is adjusted for age.

[2] Model is adjusted for age, smoking status, education, gross household income, self-perceived health status, alcohol consumption and menopause status.

4 Discussion

In this thesis I investigated the association between the inflammatory potential of the diet, measured by DII, and risk of fibromyalgia and further the baseline characteristics and diet in relation to DII scores in Norwegian women. The following chapter interprets and discusses the previously presented results and furthermore strengths and limitations in method and material for this thesis.

4.1 Results

4.1.1 Characteristics in women in relation to DII score

Women with higher DII scores, eating a more pro-inflammatory diet, were more likely to be younger, less active, currently smoking, have completed less than 10 years of education, have overweight or obesity, have lower gross household income and were less likely to consider their health status as very good and to be postmenopausal than women with lower DII scores.

Similar characteristics were seen when comparing to seven studies with women in different life stage, age groups, population sizes and ranges of DII score (39, 41, 113-117). All but one study found that women with higher DII scores were more likely to be younger (41, 113-117). In one of the studies, this was seen only for the women under 55 years (117). The study that found no difference in age in relation to DII score consisted of elderly women 70 years or older (39). Four of the studies also found that women with higher DII scores were more likely to be smoking, lower educated and have higher BMI or overweight or obesity (41, 113, 114, 117). Two of the studies did not investigate smoking status (114, 115), and one found no significant difference in relation to DII score (39). One of the studies found no difference in education level (115), and two did not investigate differences in education level (39, 116). Two studies found no significant difference in BMI in relation to DII scores (39, 116). One study found that women with higher DII scores were more likely to have normal weight (115). This was among 249 young female college students, where most of the women were normal weighted and only 11% had higher BMI (overweight or obese) (115). Two of the studies found that women with higher DII scores were more likely to have lower income (41, 114). The remaining studies had not investigated difference in income in relation to DII

scores. For physical activity, two studies found that women with higher DII scores were more likely to be less active (39, 114), one found no significant difference (116) and the rest had not investigated physical activity in relation to DII scores. The four studies finding the most similar results were of pregnant women (41), postmenopausal women (113), women aged 20-65 (117) and women 20 year and older (114), with similar range of DII score as for the women in this thesis. For the three other studies, finding somewhat conflicting results, the studied populations were female college students (115), women 70 years or over (39) and women aged 18 to 45 where half of them had polycystic ovarian syndrome (116). The DII scores had a much wider range or lower median DII score than for the women in this thesis, and these studies also investigated fewer of the discussed characteristics.

4.1.2 Women's diet in relation to DII score

Women in the first quartile had the lowest DII scores and were eating the most anti-inflammatory diet. Women in the fourth quartile had the highest DII scores and were eating the most-proinflammatory diet. Distribution of macronutrients was quite similar across quartiles of the DII. The biggest differences in intake across quartiles were seen for energy, micronutrients, and fiber. Compared to women in the first quartile, women in the fourth quartile had lower intake of energy, fiber, iron, vitamin D and folate. They also had slightly higher intake of protein, total fat, SFAs, TFAs and sugar and slightly lower intake of PUFAs, however difference in intake between quartiles was marginal. Compared to women in the first quartile, women in the fourth quartile had lower intake of fruit and vegetables, fish, bread and cereals and dairy products, and were less likely to use supplements and be non-consumers of alcohol. There was only a marginal difference in intake of meat in relation to DII scores, with highest intake seen for women in the second quartile.

Similar results were found for micronutrients and fiber when comparing diet in relation to DII score in this thesis with findings from three other studies. They all found that women with higher DII scores had lower intake of fiber, vitamin D, iron, and folate (41, 115, 116). For energy and macronutrients results were somewhat conflicting between the studies. Intake of macronutrients were presented in grams per day in these studies, and for comparison intake of macronutrients in grams per day for the women in this thesis are presented in appendix 2 and show that women with higher DII scores had lower intake of all macronutrients. A study of 249 college students found lower intake of energy, protein, PUFAs and carbohydrates, and

higher intake of total fat, SFAs and MUFAs in women with higher DII scores (115). In A study of 1 808 pregnant women with higher DII scores had lower intake of protein and carbohydrates and higher intake of SFAs, MUFAs and TFAs (41). Information on energy intake was not provided. A study of 494 women (203 polycystic ovary syndrome patients and 291 controls) found higher intake of energy, protein, total fat, SFAs, MUFAs, PUFAs and carbohydrates in women with higher DII scores (116). Two of the studies had investigated intake of food groups in relation to DII score and they both found lower intake of fruit and vegetables in women with higher DII scores (41, 116). One of the studies found higher intake of red and processed meat in women with higher DII scores (116), and the other found highest intake in the second quartile of DII, similar to result in thesis (41). For intake of bread and cereals, results were conflicting. One fund lower intake of whole grains in women with higher DII scores (41), the other found higher intake of both whole grain and refined grains (116). Only one study investigated intake of fish and found that women with higher DII score had lower intake (41). The other study investigated intake of dairy and found lower intake among women with DII scores (116).

The differences in intake between the study populations could be a result of several factors. Dietary intake was assessed by FFQs in all three studies, however one was administered by a trained dietitian (115) and for the pregnant women diet was assessed twice (during first and second trimester) (41). Number of food parameters, and what food parameters, available for calculating the DII varied and could affect what scores the women obtained. Median DII score varied from -2.56 (41), -3.84 (116) to -0.35 (115) and were in the more anti-inflammatory spectrum of the DII score than for women in this thesis (+1.46). Furthermore, the populations studied are quite different and it is not unreasonable to think that young students, pregnant women, women with polycystic ovarian syndrome and the middle-aged women studied in this thesis could have different dietary habits.

Differences in diet in relation to DII score across populations could also be affected by differences in energy and nutrient density. Consuming more energy could mean eating more of everything and consuming less energy could mean eating less of everything. However, food choices could affect this relationship. On the one hand you could have healthy eaters choosing nutrient dense foods, resulting in a higher intake of nutrients along with an increase in energy. On the other hand, you have the unhealthy eaters, choosing foods high in energy and less nutrient dense. And for this reasons energy intake and intake of nutrients may differ

in relation to the DII score in different populations. The DII consists of 8 pro-inflammatory and 37 anti-inflammatory food parameters (presented in Appendix1). The pro-inflammatory parameters are energy, carbohydrate, total fat, saturated fat, trans fat, cholesterol, iron, and vitamin B12. In addition to some macronutrients, a large portion of the anti- inflammatory food parameters consist of micronutrients, flavonoids, and fiber. A participant consuming more whole grain, fruit, vegetables, and fish would consume more of the anti-inflammatory parameters that could drive the DII score in the anti-inflammatory direction. A participant consuming rather more refined grains, foods high in sugar and saturated fat, red and processed meat would consume more of the pro-inflammatory and less of the anti-inflammatory parameters that could drive the DII score in the pro-inflammatory direction. E-DII was constructed to calculate a DII score unrelated to differences in intake of energy and nutrients, and nutrient densities. DII scores range was slightly different in DII and E-DII with DII ranging from -3.88 to +5.09 for and the E.DII ranging from -5.04 to +4.12. However, intake of energy, nutrients, and food groups in quartiles of the E-DII was only marginally different when compared to intake in quartiles of the DII. For this reason, diet in relation to DII score was presented only for quartiles of DII.

Quality of the diet, according to Nordic (118) and Norwegian (119) recommendations for a healthy diet, differed across the quartiles. Reference energy requirements for women aged 31-60 ranges from 7.7 to 9.9 MJ per day from sedentary to active (118). Median energy intake for all women were lower than reference requirement. Only women in the first quartile were within the recommended range for energy. Nordic Nutrition Recommendations (118) for the nutrients are presented in table 7. Recommended intake is the amount needed to maintain a healthy diet and sufficient nutritional status in the general population of healthy individuals. Average requirement is defined as the amount required to maintain sufficient nutritional status in half of the population (118). Median intake of protein, total fat, carbohydrates, sugar and TFAs were within the recommended intake for all quartiles and in total. Median intake of SFAs was higher than recommended, and median intake of MUFAs and PUFAs were in the lower end of recommended range for all quartiles and in total. Only women in the first quartile met the recommendation for intake of fiber. Intake of iron was low compared to recommended intake, however all met the average requirements of intake. Only women in the first quartile meets the recommended intake of vitamin D, and women in the first and second quartile met average requirement. Median intake of folate was below recommendation for all, and only women the first quartile met average requirement.

Table 7. NNR 2012 recommendations

NUTRIENT	RECOMMENDED INTAKE[1]
PROTEIN	10-20 E%
CARBOHYDRATES	45-60 E%
SUGAR	<10 E%
FIBRE	25 g/day
TOTAL FAT	25-40 E%
SFAS	<10 E%
MUFAS	10-20 E%
PUFAS	5-10 E%
TFAS	<1 E% or as little as possible
VITAMIN D	10 ug/day (AR: 7.5 ug/day)
FOLATE	300 mg (AR: 200mg)
IRON	9-15 mg/day (AR: 6-10 mg/day)

[1] Nordic Nutrition Recommendations (118)

[2] AR = Average requirement.

The Norwegian dietary guidelines recommend eating 500 grams of fruit and vegetables per day, 300-450 grams of fish per week, choosing whole grain bread and cereals, limiting the amount of red meat and processed meat to less than 500 grams per week and including low-fat dairy products (119). Intake of fruit and vegetables was below recommendation in all quartiles, however, intake was fairly close to recommendation for first quartile. The first and second quartile met the recommendation for intake of fish, when daily median intake was multiplied for weekly intake. Intake of grains were measured for bread and cereals in total, and not measured specifically for whole grains. However, whole grain is one of the main sources for fiber in the diet (in addition to fruit and vegetables) and only women in the first quartile met recommendation for intake of fiber. Further, meat was presented as total meat and processed meats, and not for red meat separately. However, intake of meat in total was lower than 500g a week for all quartiles, when daily median intake was multiplied for weekly intake. Intake of alcohol was generally low among these women, with 2.4 g/day median intake of alcohol among consumers. It is recommended to limit intake to <10g/day (119). To summarize, this indicates that women in the first quartile, eating a more anti-inflammatory diet, met the recommendations of a healthy diet. And that women in the fourth quartile, eating a more pro-inflammatory diet, had less healthy diet compared to women in the first quartile.

4.1.3 Association between DII and risk of fibromyalgia

No significant associations were found between the DII/E-DII and risk of fibromyalgia in a sample of 21 814 women from the NOWAC study. For DII, a 27% higher risk of fibromyalgia was observed in women in the third quartile when compared to women in the first quartile, in the model only adjusted for age. When further adjusting for smoking status, education, gross household income, self-perceived health status, alcohol consumption and menopausal status the risk decreased to 14% and was no longer significant. For E-DII, women in the fourth quartile had 23 % higher risk of incident fibromyalgia than women in the first quartile in the age adjusted model. When further adjusting for all covariates in multivariable model, the risk decreased to only 5%. However, no significant associations were observed for E-DII. This suggests that the borderline significant association seen in the age-adjusted models are confounded by a factor adjusted for in the multivariable model.

To my knowledge, the association between DII and risk of fibromyalgia has not been investigated before. Further, no studies investigating the association between diet and risk of fibromyalgia in general were found either. This thesis contributes to new knowledge on this subject, and hence there were no similar studies to compare the results to. To this date, knowledge on the relationship between diet and fibromyalgia is mostly based on how diet and dietary interventions affect fibromyalgia severity and symptoms. A pro-inflammatory diet, assessed by higher DII scores, have been associated with pain hypersensitivity in women with fibromyalgia suggesting that an anti-inflammatory diet could be a strategy to improve pain hypersensitivity in women with fibromyalgia (77). A hypocaloric diet, vegetarian, and plant-based diets, low FODMAP diet and different dietary supplements have been associated with reductions in fibromyalgia symptoms and severity (71-78).

Since the DII was developed it has been used in over 200 studies and forms the basis for several meta-analyses (24) and an increase in DII score has for instance been associated with increased risk of several different types of cancer, all-cause mortality, cardiovascular disease related mortality and depression (120). Higher DII scores have been associated with higher risk of irritable bowel disease (121), rheumatoid arthritis (122) depression (123, 124) and adverse mental health (125), that all are a part of the fibromyalgia symptoms and comorbidity. Further, DII has been associated with several different conditions related to inflammation, suggesting that the inflammatory potential of the diet may affect the risk of conditions related

to inflammation. A mild to chronic inflammation is seen in patients with polycystic ovary syndrome, and higher DII scores have been associated with an increased odds of polycystic ovary syndrome diagnosis (116). Higher DII scores have also been associated with an increased risk of inflammatory bowel disease (126). One of the cancers associated with DII is colorectal cancer (127). Chronic systematic inflammation is suggested as a factor in developing colorectal cancer, and an increase in DII score has been associated with increased risk of colorectal cancer (127).

Effect modification of BMI on the association between DII and fibromyalgia

Result of analyses stratified by BMI showed that for women with BMI <25 kg/m^2 the highest risks were observed in the fourth quartile, when compared to first quartile. Women in the fourth quartile had 23% (DII) and 28% (E-DII) higher risk of fibromyalgia than women in the first quartile in the model adjusted for age. When further adjusting for all covariates in the multivariable model, there was no longer substantial difference in risk between quartiles. No significant associations were found for women in this BMI-group. For women with BMI ≥25 kg/m^2 the highest risks were observed in the third quartile, when compared to the first quartile. Women in the third quartile had 44% (DII) and 18% (E-DII) higher risk of fibromyalgia than women in the first quartile, when adjusted for age. A significant association was seen only for DII. When further adjusting for all covariates in the multivariable model, the risk decreased to 30% (DII) and 1% (E-DII) and were not significant.

Significant interaction between DII and BMI was seen for both BMI divided into four groups and two groups. To further investigate this interaction, analyses stratified by BMI were conducted to investigate if there was an effect modification of BMI. Investigating the effect modification means investigating if the causal effect of one exposure differs across levels of a second exposure (128). Specifically for this thesis, investigating if the association between the DII/E-DII and risk of fibromyalgia were different across levels of BMI. When adjusting for confounders, the goal is to eliminate the bias of a factor on the association between the exposure and outcome investigated. Effect modification, unlike confounders, is not considered as unwanted bias that needs to be eliminated, but a part of the causal reality that should be clarified/explained (128). For this reason, BMI was not adjusted for as a possible confounder in the models but instead investigated in stratified analyses.

Furthermore, there is a biological basis to investigate the effect modification on the association between DII and fibromyalgia. The effect modification of BMI might be related to the observation of different levels of inflammation in different BMI-groups. Having excess weight or obesity has been associated with chronic low-grade inflammation (99). Accumulation of abnormal or excessive fat occurring in obesity can predispose to a pro-inflammatory state and oxidative stress as the excess of macronutrients occurring in adipose tissues in obesity stimulates release of inflammatory mediators (100). On the basis of this there is reason to think that being exposed to a pro-inflammatory diet or an anti-inflammatory diet could have different effect for different BMI-groups. For instance, being exposed to a pro-inflammatory effect from the diet might be differently associated with risk of negative health outcome in individuals who already have an increased inflammatory state because of obesity, compared to in individuals not having an increased inflammatory state to begin with. Or that eating an anti-inflammatory diet might not have the same positive health effect in obese and normal weighted individuals. An effect modification of BMI was seen on the association between DII and risk of incident hypertension (129). The associations were strongest for normal weighted women (BMI 18.50-21.49). It was discussed that this was related to normal weighted individuals having lower levels of chronic inflammation and low-risk profile than overweight individuals, making them more susceptible to dietary induced inflammation than women with excess weight (129). In this thesis, there was not observed a definite effect modification of BMI on the association between DII and fibromyalgia. Even though there was a significant association observed for the third quartile compared to the first quartile in the age-adjusted model for BMI $\geq$25 kg/m^2 only, the overall conclusion is that there were no substantial differences. However, this might be a result of weakness in associations because of small groups and few events of fibromyalgia in each group.

4.2 Strengths and limitations

4.2.1 Study sample

The NOWAC study is a nationally population-based cohort study, representative for middle-aged women in Norway. An external validation of the NOWAC population found no major source of selection bias that could invalidate the estimation of population attributable risk and the NOWAC population did not differ significantly from the source population they were drawn from, except for being slightly higher educated (130). The sample size and number of cases in this thesis were fairly large, however it is possible that it was too small to investigate

the risk of fibromyalgia when taking into consideration that fibromyalgia is not a clearly defined condition or diagnosis, and a too small selection could weaken the association. It is possible that bias has occurred in the sample during exclusion/inclusion. Analyses were conducted for only the women responding to at least one of the two follow-up questionnaires, and this may have led to selection bias. However, a postal survey among non-responders found no difference in life-style factors between the responders and non-responders in the NOWAC study (130). Lack of time, too personal questions and concern about privacy were some of the listed reasons for not responding (130). Further, women with missing information on covariates adjusted for and stratified by in the analyses were excluded. Differences in the women included and the women lost to exclusion have not been investigated further in this thesis, and it is possible that there were systematic similarities in women excluded that could have systematically biased the result.

4.2.2 Dietary assessments

Information on dietary intake used to calculate the DII was self-reported and assessed by an FFQ. The FFQ aimed to assess the dietary habits over the last year. A limitation in this method is if the women have trouble remembering their dietary habits during the last year or have any difficulties in understanding or filling out the questionnaire leading to information bias. Furthermore, social desirability bias may have affected the dietary assessment by women reporting a diet they think is more socially accepted and therefore over/underreport intake of certain items. The NOWAC FFQ has been validated having good ability to rank participants for foods eaten frequently and fairly good for macronutrients in terms of energy percentages (104). However, weaker ranking abilities were seen for foods eaten less frequently and for micronutrients. Diet measures from the FFQ were compared with measures from four 24HRs over a year. Compared to the 24HRs, the FFQ measured lower intake of energy, fat, added sugar and alcohol and higher intake for fiber, vitamin D, and iron. For food groups included in descriptive statistics in thesis, the FFQ measured lower intake of milk and yoghurt, and higher intake of fruit, vegetables, fish, and fish products. There was no difference in intake of bread and cereals, cheese, meat, and meat products. The FFQ does not cover the entire diet, resulting in weaker ability to rank individuals according to nutrient intake (104). Further, measurements of serum phospholipids reflected habitual intake of fish and cod liver oil assessed by the questionnaire (131) and a study assessing the test-retest reproducibility of the FFQ observed level of reproducibility within the range reported for similar instruments (132).

To minimize the potential of measurement error of the diet, women with extreme energy intake were excluded. Diet was only assessed at baseline, and it is possible that changes in dietary habits have occurred during the years of follow up and could affect the association investigated.

Intake of micro- and macronutrients, whole foods, and non-nutrient substances assessed by the FFQ were further used to calculate the DII scores used as exposure variable in this thesis. Over- and underestimation of these food parameters may result in a misclassification of DII score. The fact that the FFQ does not cover the entire diet and showed a weaker ability to rank individuals on nutrient intake may have led to the calculated DII score not reflecting the actual inflammatory potential of the women's diet. Furthermore, the FFQ was not constructed to investigate inflammatory potential and has not been validated to be used to calculate the DII. Hence, the ability to assess the inflammatory potential of the diet has not been confirmed and might not be optimal. It is uncertain if the FFQ has the ability to assess the pro and anti-inflammatory parameters equally as good. Energy intake for women in this thesis was in general low, and women with higher DII scores had lower energy intake and in general lower intake of nutrients. This could be a result of selective underreporting of energy in general. However, it could also be that the questionnaire did not ask the right questions to assess the whole diet for all women, and as a result misclassify the women. For instance, the FFQ did not include taco or sushi as options of dishes, and these dishes could be a source of vegetables or fish, energy, and nutrients for some of the women if these dishes were commonly consumed. If the questionnaire did not include questions on the foods or dishes that were a substantial part of the diet for some of the women, it would not assess the complete diet for those women. And further this would lead to the calculated DII score not expressing their actual inflammatory potential of the diet.

Additionally, only 30/31 of the 45 food parameters were used for calculating the DII. Eugenol, garlic, ginger, niacin, omega-3 fatty acids, omega-6 fatty acids, saffron, selenium, trans fat, turmeric, zinc, pepper, thyme/oregano, and rosemary were not included in calculation of DII. This was either because they were not assessed in the FFQ or because they were not available for the other participants in EPIC and therefore not included for comparison reasons. Additionally, intake of onion, one of the included food parameters, was calculated from recipes containing onion as an ingredient, and not asked for specifically in the

FFQ. Considering spices and micronutrients are consumed in small amounts, it may not affect the DII score substantially. However, it is possible that the full potential effect of the DII score was not achieved when calculated for less than the 45 food parameters. Except for trans fatty acids, all the other food parameters missing were anti-inflammatory. This could have affected the ability to calculate the fully anti-inflammatory potential. For the women in this thesis the DII scores range from -3.88 to 5.09 for the DII, and this corresponds relatively well with DII usually ranging from -5.5 to +5.5 in studies calculating the DII based on 25-30 food parameters (24). However, the range stretches out more in the pro-inflammatory direction (+), than the anti-inflammatory direction (-). This could be a result of the diet for these women being in the more pro-inflammatory specter. However, it could be a result of missing several anti-inflammatory food parameters for calculating the DII. Furthermore, the possibility that it could be affected by the FFQ's ability to assess the food parameters cannot be excluded.

4.2.3 The Dietary Inflammatory Index

A strength in the using the DII is that it was constructed based on extensive and solid literature, and not just on a simple study or few studies in the same population such as other study- and population-derived indexes (24). The DII was designed to reflect all evidence from a wide variety of human populations using different study designs and dietary assessment methods (24). It also includes evidence from qualifying laboratory animal and cell culture experiments, although weighted lower than human studies (24). The DII has been thoroughly validated with inflammatory biomarkers in several different populations across the world, by using several different methods for dietary assessments, confirming its ability to assess the dietary inflammatory potential of the diet. Another strength is that the DII focus on dietary assessment that captures the composite effect of multiple dietary components rather than a single nutrient or a marginal selection of food items, making it possible to capture health effects that might not be detectable for single food components alone but for the combined effects of the components together. Considering we do not eat single nutrients or components of food, but a composite of nutrients and food components together, it is relevant investigating the effect of diet as a whole in form of dietary patterns or as in the DII, assessing the inflammatory potential of the diet.

A further strength relates to calculation of the DII. The method for calculation constructed by the developers of the DII is consistently used for assessing the DII, compared to other dietary

patterns such as the Mediterranean diet, where methods of assessing the dietary pattern differ in studies (133). Having said that, not all material needed for calculating the DII is accessible, and the study group behind developing the DII is usually involved when calculating the DII and has been involved in the majority of publications on DII. The fact that the material is not easily accessible may be a barrier for using the DII. The involvement of the study group in calculating the DII may both be a strength in the of calculation of the DII, however limiting other researchers' involvement in calculating the DII and further inputs om possible limitations or improvements to the DII.

It has been observed that the difference in the relationship between intake of energy, nutrients and nutrient densities across populations causes complications and limitations of the DII (24). Having a higher energy intake usually also means eating more of everything, resulting in a positive correlation between energy and nutrient intake. For "healthy eaters", choosing foods with high nutrient density and low in energy, an increase in energy will also cause an increase in nutrients. On the other hand, the "unhealthy eaters", choosing food high in energy and low nutrient density, will not have the same increase in nutrient intake related to increased energy intake (24). The developers of the DII aimed to strengthen the ability to assess the dietary inflammatory potential unrelated to overall consumption of energy by creating the E-DII (24). It is suggested that epidemiological studies on diet and disease should make an adjustment for energy intake, to be able to assess the effect of nutrient composition independent of total energy intake (109). When calculating the E-DII in this thesis, the women's intake was energy adjusted by the residual method before standardizing their intake to the energy-adjusted world average database. Using the residual method gives an estimation of energy adjusted intake as residuals from a regression model, where total intake of energy is the independent variable and intake of nutrient is the dependent variable (109). This is argued to provide a better estimation of the actual general variation of nutrients in the diet assessed unrelated to differences in energy intake (109), and could be an argument that E-DII gives a better estimation on the relationship between the inflammatory potential of the diet and risk of fibromyalgia.

However, in this thesis there was a strong correlation between categories of DII and E-DII, minimal difference in diet and similar results for fibromyalgia according to quartiles of DII and E-DII. This shows that for data used in this thesis, results for DII and E-DII were not substantially different, and the energy adjustment in E-DII did not necessarily obtain a better

estimate of the causal relationship between the inflammatory potential of the diet and risk of fibromyalgia. In the article presenting the E-DII, the authors claim that the E-DII seem to have improved prediction in comparison to the unadjusted DII scores, however, does not present or argue any further on what this claim is based on (24). And I have found no further discussion on this topic in other studies either. Despite the findings for DII and E-DII in this study, the possibility that E-DII is better to predict the relationship between inflammatory potential of the diet and health outcome in other populations cannot be ruled out. The role of total energy intake in the relationship between diet and disease is complex and it should be further investigated how energy intake should be handled in the DII. And further studies are required to assess whether E-DII provides a better estimation of the inflammatory potential of the diet than the DII.

It has been questioned that the DII might be overestimating the pro-inflammatory effect of fat and energy, by including energy as a food parameter in addition to food parameters contributing to energy intake and including total fat as food parameter in addition to separate fatty acids (134). And further overestimating the anti-inflammatory effect of alcohol, considering that the anti-inflammatory effect is only seen for low/moderate intake (135). Based on this, there is a possibility that the DII scores do not reflect the actual dietary inflammatory potential of the diet but reflect an overestimated inflammatory potential and lead to misclassification of participants.

4.2.4 Status of event and measured follow-up time

In this thesis, self-reported year of onset fibromyalgia was used as outcome variable. Using self-reported information on fibromyalgia instead of collecting information on diagnoses from registries or confirmed diagnosis by physician was a limitation. The self-reported question has not been validated and some of the women who reported fibromyalgia may not have met the diagnosis criteria for fibromyalgia. The self-reported fibromyalgia might be biased by self-diagnosis, be confused with other similar conditions, and some might have checked the box for the year they were diagnosed while others might have checked the box for when they started having symptoms. A cross-sectional validation of self-reported diabetes in the NOWAC study found that the self-reported diabetes from the FFQ was a valid measurement of diagnosed diabetes (110). However, the question on diabetes is formulated differently from

the fibromyalgia question. The question on diabetes in the questionnaire was “Do you have diabetes (yes/no)” and “at what age were you diagnosed” (110). Furthermore, the definition and diagnosis criteria for diabetes are more definite than for fibromyalgia, and probably less likely that the reported diabetes was self-diagnosed or wrongly diagnosed. For this reason, the validation may not be transferable for the fibromyalgia question.

Furthermore, there were limited years of onset fibromyalgia available in the questionnaires, resulting in inaccurate estimation on when the condition occurred or was diagnosed. A yearly count for condition is inaccurate compared to a date of diagnosis. However, it is reasonable to think that time of diagnosis might not be accurate for when condition occurred for many of the individuals with fibromyalgia. Fibromyalgia patients usually get the diagnoses years after onset of symptoms (136). The many different and vague symptoms in fibromyalgia, that also could be confused with several other conditions, and lack of knowledge and awareness of fibromyalgia may have led to patients waiting a long time from symptom debut to getting a diagnosis. Furthermore, different diagnostic criteria might have been used. The diagnostic criteria have been changed and updated over the years of follow-up in this thesis. The American College of Rheumatology (ACR) 1990 classification criteria were changed in 2010/2011 and further revised in 2016 (83). Considering that onset fibromyalgia is reported yearly and even for two-year intervals, there are clusters of events occurring at the same time. There are several methods for handling tied events in survival analysis, however the Breslow method is standard in SPSS. Other methods, such as the Exact method and Efron method have shown better ability to handle tied events (137, 138), and using Breslow method could be considered a limitation. Analyses were therefore conducted additionally in SAS statistic software using the Exact method for tied events, and changes in results were marginal. The method chosen for handling tied events was not considered to have a substantial impact on results so results from SPSS with Breslow method were used in this thesis.

4.2.5 Covariates

Self-reported weight and height have been proven a valid ranking of BMI for these women (112). A substantial agreement between self-reported and measured BMI values were found, however there was a small but statistically significant under-reporting of weight and therefore underreporting of BMI. The tendency to under-report was largest among overweight women, however largest degree of under-reporting was found among obese women (112). If women

were under-reporting their BMI they could have been misclassified in a lower BMI-groups, and this could further have led to bias to the results of the analyses stratified by BMI-groups. Furthermore, self-reported physical activity level measured on a 10-category scale have been validated as a good measure for physical activity in these women. Social desirability bias has been suggested to cause underreporting of smoking (139) and alcohol (140) creating possible bias towards the null. Reporting lower intake of alcohol was also seen in the validation of the NOWAC FFQ against 24HRs (104). A weakness in the question for alcohol in the FFQ was that the highest amount consumed alternative was "one glass or more per day" for wine, beer, or liquor. This possibly contributed to low reported intake of alcohol among these women, and alcohol consumption for women consuming higher amounts were probably not fully assessed.

4.2.6 Adjusting for possible confounders

Confounding covariates were identified statistically in this thesis. The mechanism of fibromyalgia is yet to be established, and so are the risk factors. Weak and inconclusive findings for possible risk factors made it difficult using causal diagrams like DAGs in a systematic way for establishing confounders. Further, no studies investigating association between diet and risk of fibromyalgia were found for comparison. Possible confounders were chosen based on literature (common confounders in association between diet and health outcome, and suggested risk factors for fibromyalgia) and the covariates available from the NOWAC dataset was further tested for statistically as described in method and material chapter. This may have resulted in an unsatisfactory and incorrect adjustment for confounding factors in the analyses. For that reason, the possibility that residual confounders may have influenced the association cannot be excluded.

5 Future perspectives

To this date, evidence on the relationship between diet and fibromyalgia have been focused on effect of dietary interventions on symptoms and severity of the condition. Fibromyalgia patients tend to seek alternative treatments, such as diet and dietary supplements, and therefore it is important to establish there is a causal effect. Nevertheless, it is also important to investigate if there is any way to prevent onset of fibromyalgia. The prevalence of fibromyalgia is high, with observed prevalence up to 10% for women in Norway (57, 58). Establishing a primary prevention strategy could reduce the prevalence of fibromyalgia and therefore it would be useful to further investigate the relationship between diet and risk of fibromyalgia to clarify if diet could be a part of a prevention strategy for onset of fibromyalgia.

Additionally, if inflammation contributes to development of fibromyalgia, factors affecting inflammation could also affect the risk of developing fibromyalgia, and it would be useful to further investigate how the inflammatory potential of the diet affects the risk of fibromyalgia. Further investigation on whether an anti-inflammatory diet could have an effect in reducing fibromyalgia severity and symptoms is also useful. Only one study has been published on this subject previously, and it suggested that an anti-inflammatory diet could be a strategy for reducing pain hypersensitivity in women with fibromyalgia (77). In this thesis, no overall evident associations were observed between inflammatory potential of the diet and risk of fibromyalgia, however, the limitations discussed in this thesis need to be taken into consideration for its ability to assess the association between DII and fibromyalgia. It would be interesting to investigate the association in a larger study population where DII have been construct validated against inflammatory biomarkers, and using dietary assessment validated for calculating the DII score. And further, including a robust number of cases of incident fibromyalgia, preferably diagnosed by the same criteria.

Furthermore, fibromyalgia is a complex condition and severity of the condition differs in individuals with varying degree of symptoms and comorbidities, and risk factors have been differently associated in fibromyalgia patients with low and high symptom score (86, 94). This could make it difficult to assess risk factors for fibromyalgia and should be taken into consideration in future studies assessing diet as a risk factor for fibromyalgia.

6 Conclusion

This thesis is, to my knowledge, the very first to investigate the association between the dietary inflammatory index and risk of fibromyalgia. The main findings in this thesis were that women with higher DII scores (eating a more pro-inflammatory diet) had a more unhealthy lifestyle, lower socioeconomic status and a less healthy diet than women with lower DII scores (eating a more anti-inflammatory diet). Overall, no evident associations were found between DII and risk of fibromyalgia. Initial analyses showed a significant interaction between BMI and the DII score. No substantial effect modification of BMI in relation to DII and risk of fibromyalgia was observed in the stratified analyses. However, based on these results, a possible effect modification by BMI cannot be ruled out and should be assessed in further studies.

Nevertheless, findings in this thesis are important contributions to the limited evidence and understanding of fibromyalgia, and the relationship between diet and risk of fibromyalgia. Further studies are needed, both to establish the inflammatory potential of the diet in relation to risk of developing fibromyalgia, but also to further investigate the effect of the inflammatory potential of the diet in relation to treatment of symptoms in people living with the condition.

References

1. Ansar W, Ghosh S. Inflammation and Inflammatory Diseases, Markers, and Mediators: Role of CRP in Some Inflammatory Diseases. New Delhi: New Delhi: Springer India; 2016. p. 67-107.
2. Sand O, Sjaastad ØV, Haug E, Toverud KC. Menneskets fysiologi. 2. utg. ed. Oslo: Gyldendal akademisk; 2014.
3. Roy S, Bagchi D, Raychaudhuri SP. Chronic inflammation : molecular pathophysiology, nutritional and therapeutic interventions. Boca Raton: CRC Press; 2013.
4. Scrivo R, Vasile M, Bartosiewicz I, Valesini G. Inflammation as "common soil" of the multifactorial diseases. Autoimmunity Rev. 2010;10(7):369-74.
5. Abdulkhaleq LA, Assi MA, Abdullah R, Zamri-Saad M, Taufiq-Yap YH, Hezmee MNM. The crucial roles of inflammatory mediators in inflammation: A review. Vet World. 2018;11(5):627-35.
6. Brenner DR, Scherer D, Muir K, Schildkraut J, Boffetta P, Spitz MR, et al. A review of the application of inflammatory biomarkers in epidemiologic cancer research. Cancer Epidemiol Biomarkers Prev. 2014;23(9):1729-51.
7. Ansar W, Ghosh S. Acute-Phase Proteins and Responses and Their Application in Clinical Chemistry. Biology of C Reactive Protein in Health and Disease. New Delhi: Springer India; 2016. p. 45-65.
8. Barbaresko J, Koch M, Schulze MB, Nothlings U. Dietary pattern analysis and biomarkers of low-grade inflammation: a systematic literature review. Nutr Rev. 2013;71(8):511-27.
9. Bonaccio M, Pounis G, Cerletti C, Donati MB, Iacoviello L, de Gaetano G. Mediterranean diet, dietary polyphenols and low grade inflammation: results from the MOLI-SANI study. Br J Clin Pharmacol. 2017;83(1):107-13.
10. Di Giosia P, Stamerra CA, Giorgini P, Jamialahamdi T, Butler AE, Sahebkar A. The role of nutrition in inflammaging. Ageing Res Rev. 2022;77:101596-.
11. Whalen KA, McCullough ML, Flanders WD, Hartman TJ, Judd S, Bostick RM. Paleolithic and Mediterranean Diet Pattern Scores Are Inversely Associated with Biomarkers of Inflammation and Oxidative Balance in Adults. J Nutr. 2016;146(6):1217-26.
12. Grosso G, Laudisio D, Frias-Toral E, Barrea L, Muscogiuri G, Savastano S, et al. Anti-Inflammatory Nutrients and Obesity-Associated Metabolic-Inflammation: State of the Art and Future Direction. Nutrients. 2022;14(6).
13. Bordoni A, Danesi F, Dardevet D, Dupont D, Fernandez AS, Gille D, et al. Dairy products and inflammation: A review of the clinical evidence. Crit Rev Food Sci Nutr. 2017;57(12):2497-525.
14. Vrdoljak J, Kumric M, Vilovic M, Martinovic D, Tomic IJ, Krnic M, et al. Effects of Olive Oil and Its Components on Intestinal Inflammation and Inflammatory Bowel Disease. Nutrients. 2022;14(4).
15. Pozzetti L, Ferrara F, Marotta L, Gemma S, Butini S, Benedusi M, et al. Extra Virgin Olive Oil Extracts of Indigenous Southern Tuscany Cultivar Act as Anti-Inflammatory and Vasorelaxant Nutraceuticals. Antioxidants (Basel). 2022;11(3).
16. Ma Y, Hébert JR, Li W, Bertone-Johnson ER, Olendzki B, Pagoto SL, et al. Association between dietary fiber and markers of systemic inflammation in the Women's Health Initiative Observational Study. Nutrition. 2008;24(10):941-9.

17. Ma Y, Griffith JA, Chasan-Taber L, Olendzki BC, Jackson E, Stanek EJ, 3rd, et al. Association between dietary fiber and serum C-reactive protein. Am J Clin Nutr. 2006;83(4):760-6.
18. Hart MJ, Torres SJ, McNaughton SA, Milte CM. Dietary patterns and associations with biomarkers of inflammation in adults: a systematic review of observational studies. Nutr J. 2021;20(1):24.
19. Miles EA, Calder PC. Influence of marine n-3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis. Br J Nutr. 2012;107 Suppl 2:S171-84.
20. Sears B, Ricordi C. Anti-inflammatory nutrition as a pharmacological approach to treat obesity. J Obes. 2011;2011.
21. Mousa A, Misso M, Teede H, Scragg R, de Courten B. Effect of vitamin D supplementation on inflammation: protocol for a systematic review. BMJ Open. 2016;6(4):e010804.
22. Cavicchia PP, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, et al. A new dietary inflammatory index predicts interval changes in serum high-sensitivity C-reactive protein. J Nutr. 2009;139(12):2365-72.
23. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hebert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr. 2014;17(8):1689-96.
24. Hébert JR, Shivappa N, Wirth MD, Hussey JR, Hurley TG. Perspective: The Dietary Inflammatory Index (DII)-Lessons Learned, Improvements Made, and Future Directions. Adv Nutr. 2019;10(2):185-95.
25. Shivappa N, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, et al. A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). Public Health Nutr. 2014;17(8):1825-33.
26. Tabung FK, Steck SE, Zhang J, Ma Y, Liese AD, Agalliu I, et al. Construct validation of the dietary inflammatory index among postmenopausal women. Ann Epidemiol. 2015;25(6):398-405.
27. Shivappa N, Hebert JR, Marcos A, Diaz LE, Gomez S, Nova E, et al. Association between dietary inflammatory index and inflammatory markers in the HELENA study. Mol Nutr Food Res. 2017;61(6).
28. Shivappa N, Wirth MD, Hurley TG, Hébert JR. Association between the dietary inflammatory index (DII) and telomere length and C-reactive protein from the National Health and Nutrition Examination Survey-1999-2002. Mol Nutr Food Res. 2017;61(4).
29. Wirth MD, Shivappa N, Davis L, Hurley TG, Ortaglia A, Drayton R, et al. Construct Validation of the Dietary Inflammatory Index among African Americans. J Nutr Health Aging. 2017;21(5):487-91.
30. Shivappa N, Hébert JR, Rietzschel ER, De Buyzere ML, Langlois M, Debruyne E, et al. Associations between dietary inflammatory index and inflammatory markers in the Asklepios Study. Br J Nutr. 2015;113(4):665-71.
31. Vahid F, Shivappa N, Hekmatdoost A, Hebert JR, Davoodi SH, Sadeghi M. Association between Maternal Dietary Inflammatory Index (DII) and abortion in Iranian women and validation of DII with serum concentration of inflammatory factors: case-control study. Appl Physiol Nutr Metab. 2017;42(5):511-6.
32. Bodén S, Wennberg M, Van Guelpen B, Johansson I, Lindahl B, Andersson J, et al. Dietary inflammatory index and risk of first myocardial infarction; a prospective population-based study. Nutr J. 2017;16(1):21.

33. Shivappa N, Bonaccio M, Hebert JR, Di Castelnuovo A, Costanzo S, Ruggiero E, et al. Association of proinflammatory diet with low-grade inflammation: results from the Moli-sani study. Nutrition. 2018;54:182-8.
34. Shin D, Lee KW, Brann L, Shivappa N, Hébert JR. Dietary inflammatory index is positively associated with serum high-sensitivity C-reactive protein in a Korean adult population. Nutrition. 2019;63-64:155-61.
35. Suzuki K, Shivappa N, Kawado M, Yamada H, Hashimoto S, Wakai K, et al. Association between dietary inflammatory index and serum C-reactive protein concentrations in the Japan Collaborative Cohort Study. Nagoya J Med Sci. 2020;82(2):237-49.
36. Kotemori A, Sawada N, Iwasaki M, Yamaji T, Shivappa N, Hebert JR, et al. Validating the dietary inflammatory index using inflammatory biomarkers in a Japanese population: A cross-sectional study of the JPHC-FFQ validation study. Nutrition. 2020;69:110569.
37. Corley J, Shivappa N, Hébert JR, Starr JM, Deary IJ. Associations between Dietary Inflammatory Index Scores and Inflammatory Biomarkers among Older Adults in the Lothian Birth Cohort 1936 Study. J Nutr Health Aging. 2019;23(7):628-36.
38. Phillips CM, Shivappa N, Hébert JR, Perry IJ. Dietary Inflammatory Index and Biomarkers of Lipoprotein Metabolism, Inflammation and Glucose Homeostasis in Adults. Nutrients. 2018;10(8).
39. Shivappa N, Wirth MD, Murphy EA, Hurley TG, Hébert JR. Association between the Dietary Inflammatory Index (DII) and urinary enterolignans and C-reactive protein from the National Health and Nutrition Examination Survey-2003-2008. Eur J Nutr. 2019;58(2):797-805.
40. Cervo MMC, Scott D, Seibel MJ, Cumming RG, Naganathan V, Blyth FM, et al. Proinflammatory Diet Increases Circulating Inflammatory Biomarkers and Falls Risk in Community-Dwelling Older Men. J Nutr. 2020;150(2):373-81.
41. Sen S, Rifas-Shiman SL, Shivappa N, Wirth MD, Hébert JR, Gold DR, et al. Dietary Inflammatory Potential during Pregnancy Is Associated with Lower Fetal Growth and Breastfeeding Failure: Results from Project Viva. J Nutr. 2016;146(4):728-36.
42. Wirth MD, Burch J, Shivappa N, Violanti JM, Burchfiel CM, Fekedulegn D, et al. Association of a dietary inflammatory index with inflammatory indices and metabolic syndrome among police officers. J Occup Environ Med. 2014;56(9):986-9.
43. Kizil M, Tengilimoglu-Metin MM, Gumus D, Sevim S, Turkoglu İ, Mandiroglu F. Dietary inflammatory index is associated with serum C-reactive protein and protein energy wasting in hemodialysis patients: A cross-sectional study. Nutr Res Pract. 2016;10(4):404-10.
44. Mayr HL, Itsiopoulos C, Tierney AC, Ruiz-Canela M, Hebert JR, Shivappa N, et al. Improvement in dietary inflammatory index score after 6-month dietary intervention is associated with reduction in interleukin-6 in patients with coronary heart disease: The AUSMED heart trial. Nutr Res. 2018;55:108-21.
45. Wirth MD, Shivappa N, Khan S, Vyas S, Beresford L, Sofge J, et al. Impact of a 3-Month Anti-inflammatory Dietary Intervention Focusing on Watermelon on Body Habitus, Inflammation, and Metabolic Markers: A Pilot Study. Nutr Metab Insights. 2020;13:1178638819899398.
46. Julia C, Assmann KE, Shivappa N, Hebert JR, Wirth MD, Hercberg S, et al. Long-term associations between inflammatory dietary scores in relation to long-term C-reactive protein status measured 12 years later: findings from the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) cohort. Br J Nutr. 2017;117(2):306-14.
47. Coheley LM, Shivappa N, Hebert JR, Lewis RD. Dietary inflammatory index® and cortical bone outcomes in healthy adolescent children. Osteoporos Int. 2019;30(8):1645-54.

48. Bondonno NP, Blekkenhorst LC, Bird AL, Lewis JR, Hodgson JM, Shivappa N, et al. Dietary inflammatory index and the aging kidney in older women: a 10-year prospective cohort study. Eur J Nutr. 2020;59(7):3201-11.
49. Ginty AT. Construct Validity. In: Gellman MD, Turner JR, editors. Encyclopedia of Behavioral Medicine. New York, NY: Springer New York; 2013. p. 487-.
50. Forseth KØ. Fibromyalgi. Nor J Epidemiol. 2009;18(1).
51. Neumeister MW, Neumeister EL. Fibromyalgia. Clin Plast Surg. 2020;47(2):203-13.
52. Clauw DJ. Fibromyalgia: A Clinical Review. JAMA. 2014;311(15):1547-55.
53. Hawkins RA. Fibromyalgia: A Clinical Update. J Am Osteopat Assoc. 2013;113(9):680-9.
54. Kvæl LAH, Løchting I, Molin M. Use of Dietary Supplements and Perceived Knowledge among Adults Living with Fibromyalgia in Norway: A Cross-Sectional Study. Nutrients. 2021;14(1).
55. Coskun Benlidayi I. Role of inflammation in the pathogenesis and treatment of fibromyalgia. Rheumatol Int. 2019;39(5):781-91.
56. Arnold LM, Bennett RM, Crofford LJ, Dean LE, Clauw DJ, Goldenberg DL, et al. AAPT Diagnostic Criteria for Fibromyalgia. J. Pain. 2019;20(6):611-28.
57. Ihlebæk C, Brage S, Natvig B, Bruusgaard D. Forekomst av muskel- og skjelettlidelser i Norge. Tidsskr Nor Laegeforen. 2010;130(23):2365-8.
58. Årnes AP, Krokstrand TT. The incidence and prevalence of Chronic Fatigue Syndrome, Back Pain of unknown origin, Fibromyalgia, and Myalgia in Norwegian women, and their association to physical activity. A prospective cohort study of material from the Norwegian Women and Cancer (NOWAC) study. UiT Norges arktiske universitet; 2014.
59. Mascarenhas RO, Souza MB, Oliveira MX, Lacerda AC, Mendonça VA, Henschke N, et al. Association of Therapies With Reduced Pain and Improved Quality of Life in Patients With Fibromyalgia: A Systematic Review and Meta-analysis. JAMA Intern Med. 2021;181(1):104-12.
60. Burckhardt CS, Goldenberg DL, American Pain Society. Guideline for the management of fibromyalgia syndrome pain in adults and children. Glenview, IL: American Pain Society; 2005.
61. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, et al. EULAR revised recommendations for the management of fibromyalgia. Annals of the Rheumatic Diseases. 2017;76(2):318-28.
62. Fors EA, Wensaas K-A, Eide H, Jaatun EA, Clauw DJ, Wolfe F, et al. Fibromyalgia 2016 criteria and assessments: comprehensive validation in a Norwegian population. Scand J Pain. 2020;20(4):663-72.
63. Littlejohn G, Guymer E. Key Milestones Contributing to the Understanding of the Mechanisms Underlying Fibromyalgia. Biomedicines. 2020;8(7).
64. Adams LM, Turk DC. Psychosocial factors and central sensitivity syndromes. Curr Rheumatol Rev. 2015;11(2):96-108.
65. St John AW, Aebischer JH, Friend R, Jones KD. Fibromyalgia: A clinical update. Nurse Pract. 2022;47(4):20-30.
66. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2-s15.
67. Peck MM, Maram R, Mohamed A, Ochoa Crespo D, Kaur G, Ashraf I, et al. The Influence of Pro-inflammatory Cytokines and Genetic Variants in the Development of Fibromyalgia: A Traditional Review. Cureus. 2020;12(9):e10276.
68. Bäckryd E, Tanum L, Lind AL, Larsson A, Gordh T. Evidence of both systemic inflammation and neuroinflammation in fibromyalgia patients, as assessed by a multiplex protein panel applied to the cerebrospinal fluid and to plasma. J Pain Res. 2017;10:515-25.

69. Ataoglu S, Ankarali H, Samanci R, Ozsahin M, Admis O. The relationship between serum leptin level and disease activity and inflammatory markers in fibromyalgia patients. North Clin Istanb. 2018;5(2):102-8.
70. Conti P, Gallenga CE, Caraffa A, Ronconi G, Kritas SK. Impact of mast cells in fibromyalgia and low-grade chronic inflammation: Can IL-37 play a role? Dermatol Ther. 2020;33(1):e13191.
71. Venkatesan N, Gyawali M, Botleroo RA, Ahmed R, Kareem R, Ogeyingbo OD, et al. Efficacy of Vitamin D Supplementation in the Improvement of Clinical Status in Pa-tients Diagnosed with Fibromyalgia Syndrome: A Systematic Review. Curr Rheumatol Rev. 2022.
72. Nadal-Nicolás Y, Miralles-Amorós L, Martínez-Olcina M, Sánchez-Ortega M, Mora J, Martínez-Rodríguez A. Vegetarian and Vegan Diet in Fibromyalgia: A Systematic Review. Int J Environ Res Public Health. 2021;18(9).
73. Correa-Rodríguez M, Rueda-Medina B, Casas-Barragán A, Tapia-Haro RM, Molina F, Aguilar-Ferrándiz ME. Dietary Intake Assessment, Severity of Symptoms, and Pain in Women with Fibromyalgia. Clin Nurs Res. 2021:10547738211012464.
74. Pagliai G, Giangrandi I, Dinu M, Sofi F, Colombini B. Nutritional Interventions in the Management of Fibromyalgia Syndrome. Nutrients. 2020;12(9):2525.
75. Martins YA, Cardinali C, Ravanelli MI, Brunaldi K. Is hypovitaminosis D associated with fibromyalgia? A systematic review. Nutr Rev. 2020;78(2):115-33.
76. Lowry E, Marley J, McVeigh JG, McSorley E, Allsopp P, Kerr D. Dietary Interventions in the Management of Fibromyalgia: A Systematic Review and Best-Evidence Synthesis. Nutrients. 2020;12(9).
77. Correa-Rodríguez M, Casas-Barragán A, González-Jiménez E, Schmidt-RioValle J, Molina F, Aguilar-Ferrándiz ME. Dietary Inflammatory Index Scores Are Associated with Pressure Pain Hypersensitivity in Women with Fibromyalgia. Pain Med. 2020;21(3):586-94.
78. Silva AR, Bernardo A, Costa J, Cardoso A, Santos P, de Mesquita MF, et al. Dietary interventions in fibromyalgia: a systematic review. Ann Med. 2019;51(sup1):2-14.
79. Verbunt JA, Pernot DH, Smeets RJ. Disability and quality of life in patients with fibromyalgia. Health Qual Life Outcomes. 2008;6:8.
80. Ghavidel-Parsa B, Bidari A, Amir Maafi A, Ghalebaghi B. The Iceberg Nature of Fibromyalgia Burden: The Clinical and Economic Aspects. Korean J Pain. 2015;28(3):169-76.
81. Asbring P, Närvänen AL. Women's experiences of stigma in relation to chronic fatigue syndrome and fibromyalgia. Qual Health Res. 2002;12(2):148-60.
82. Skaer TL. Fibromyalgia: Disease Synopsis, Medication Cost Effectiveness and Economic Burden. Pharmacoeconomics. 2014;32(5):457-66.
83. Sarzi-Puttini P, Giorgi V, Marotto D, Atzeni F. Fibromyalgia: an update on clinical characteristics, aetiopathogenesis and treatment. Nat Rev Rheumatol. 2020;16(11):645-60.
84. Brage S, Ihlebæk C, Natvig B, Bruusgaard D. Muskel- og skjelettlidelser som årsak til sykefravær og uføreytelser. Tidsskr Nor Laegeforen. 2010;130(23):2369-70.
85. Fitzcharles MA, Rampakakis E, Ste-Marie PA, Sampalis JS, Shir Y. The association of socioeconomic status and symptom severity in persons with fibromyalgia. J Rheumatol. 2014;41(7):1398-404.
86. Creed F. The risk factors for self-reported fibromyalgia with and without multiple somatic symptoms: The Lifelines cohort study. J Psychosom Res. 2022;155:110745.
87. Vandenkerkhof EG, Macdonald HM, Jones GT, Power C, Macfarlane GJ. Diet, lifestyle and chronic widespread pain: results from the 1958 British Birth Cohort Study. Pain Res Manag. 2011;16(2):87-92.

88. McBeth J, Lacey RJ, Wilkie R. Predictors of new-onset widespread pain in older adults: results from a population-based prospective cohort study in the UK. Arthritis Rheumatol. 2014;66(3):757-67.
89. Markkula RA, Kalso EA, Kaprio JA. Predictors of fibromyalgia: a population-based twin cohort study. BMC Musculoskelet Disord. 2016;17:29.
90. Muthuri SG, Kuh D, Bendayan R, Macfarlane GJ, Cooper R. Chronic physical illness in early life and risk of chronic widespread and regional pain at age 68: evidence from the 1946 British birth cohort. Pain. 2016;157(10):2382-9.
91. Andorsen OF, Ahmed LA, Emaus N, Klouman E. A prospective cohort study on risk factors of musculoskeletal complaints (pain and/or stiffness) in a general population. The Tromsø study. PLoS One. 2017;12(7):e0181417.
92. Collin SM, Bakken IJ, Nazareth I, Crawley E, White PD. Trends in the incidence of chronic fatigue syndrome and fibromyalgia in the UK, 2001-2013: a Clinical Practice Research Datalink study. J R Soc Med. 2017;110(6):231-44.
93. Uhlig BL, Sand T, Nilsen TI, Mork PJ, Hagen K. Insomnia and risk of chronic musculoskeletal complaints: longitudinal data from the HUNT study, Norway. BMC Musculoskelet Disord. 2018;19(1):128.
94. Blokh Kerpel A, Tiosano S, Amital D, Comaneshter D, Cohen AD, Amital H. [ASSOCIATION OF OBESITY, SMOKING AND SOCIOECONOMIC STRATA WITH THE FIBROMYALGIA SYNDROME]. Harefuah. 2019;158(9):583-6.
95. Dias RCA, Kulak Junior J, Ferreira da Costa EH, Nisihara RM. Fibromyalgia, sleep disturbance and menopause: Is there a relationship? A literature review. Int J Rheum Dis. 2019;22(11):1961-71.
96. Martínez-Jauand M, Sitges C, Femenia J, Cifre I, González S, Chialvo D, et al. Age-of-onset of menopause is associated with enhanced painful and non-painful sensitivity in fibromyalgia. Clin Rheumatol. 2013;32(7):975-81.
97. Vincent A, Whipple MO, Luedtke CA, Oh TH, Sood R, Smith RL, et al. Pain and other symptom severity in women with fibromyalgia and a previous hysterectomy. J Pain Res. 2011;4:325-9.
98. D'Onghia M, Ciaffi J, Lisi L, Mancarella L, Ricci S, Stefanelli N, et al. Fibromyalgia and obesity: A comprehensive systematic review and meta-analysis. Semin Arthritis Rheum. 2021;51(2):409-24.
99. Wu H, Ballantyne CM. Metabolic Inflammation and Insulin Resistance in Obesity. Circ Res. 2020;126(11):1549-64.
100. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci. 2017;13(4):851-63.
101. Okifuji A, Hare BD. The association between chronic pain and obesity. J Pain Res. 2015;8:399-408.
102. Lund E, Dumeaux V, Braaten T, Hjartåker A, Engeset D, Skeie G, et al. Cohort profile: The Norwegian Women and Cancer Study--NOWAC--Kvinner og kreft. Int J Epidemiol. 2008;37(1):36-41.
103. Brustad M, Braaten T, Lund E. Predictors for cod-liver oil supplement use--the Norwegian Women and Cancer Study. Eur J Clin Nutr. 2004;58(1):128-36.
104. Hjartåker A, Andersen LF, Lund E. Comparison of diet measures from a food-frequency questionnaire with measures from repeated 24-hour dietary recalls. The Norwegian Women and Cancer Study. Public Health Nutr. 2007;10(10):1094-103.
105. Energy and protein requirements. Report of a joint FAO/WHO/UNU Expert Consultation. World Health Organ Tech Rep Ser. 1985;724:1-206.
106. Lov om medisinsk og helsefaglig forskning (helseforskningsloven). LOV-2008-06-20-44. 2008 [cited 2022 April 7]. Available from: https://lovdata.no/pro/NL/lov/2008-06-20-44.

107. Regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK). Om å søke REK [cited 2022 april 7]. Available from: https://rekportalen.no/#hjem/s%C3%B8ke_REK.
108. Lécuyer L, Laouali N, Dossus L, Shivappa N, Hébert JR, Agudo A, et al. Inflammatory potential of the diet and association with risk of differentiated thyroid cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Eur J Nutr (accepted). 2022.
109. Willett W. Implications of Total Energy Intake for Epidemiologic Analyses. Nutritional Epidemiology: Oxford University Press; 2012.
110. Rylander C, Sandanger TM, Engeset D, Lund E. Consumption of lean fish reduces the risk of type 2 diabetes mellitus: a prospective population based cohort study of Norwegian women. PLoS One. 2014;9(2):e89845.
111. Borch KB, Ekelund U, Brage S, Lund E. Criterion validity of a 10-category scale for ranking physical activity in Norwegian women. Int J Behav Nutr Phys Act. 2012;9:2.
112. Skeie G, Mode N, Henningsen M, Borch KB. Validity of self-reported body mass index among middle-aged participants in the Norwegian Women and Cancer study. Clin Epidemiol. 2015;7:313-23.
113. Chen WY, Fu YP, Zhong W, Zhou M. The Association Between Dietary Inflammatory Index and Sex Hormones Among Postmenopausal Women in the US. Front Endocrinol (Lausanne). 2021;12:771565.
114. Zhang S, Bian H, Qiu S, Cai B, Jin K, Zheng X, et al. Associations between the dietary inflammatory index and urinary incontinence among women younger than 65 years. Sci Rep. 2021;11(1):9340-.
115. Bazyar H, Zare Javid A, Bavi Behbahani H, Shivappa N, Hebert JR, Khodaramhpour S, et al. The association between dietary inflammatory index with sleep quality and obesity amongst iranian female students: A cross‐sectional study. Int J Clin Pract. 2021;75(5):e14061-n/a.
116. Zirak Sharkesh E, Keshavarz SA, Nazari L, Abbasi B. The dietary inflammatory index is directly associated with polycystic ovary syndrome: A case-control study. Clin Endocrinol (Oxf). 2021.
117. Nuozhou L, Ying F, Xinyao L, Xue M, Fang M, Fang M. Association Between Dietary Inflammatory Index and Sex Hormone Binding Globulin and Sex Hormone in U.S. Adult Females. Frontiers in public health. 2022;10.
118. Nordisk Ministerråd. Nordic Nutrition Recommendations 2012: Integrating nutrition and physical activity. Copenhagen: Nordic Council of Ministers; 2014.
119. Kostråd for å fremme folkehelsen og forebygge kroniske sykdommer : metodologi og vitenskapelig kunnskapsgrunnlag. Oslo: Helsedirektoratet; 2011. 353 p.
120. Liu FH, Liu C, Gong TT, Gao S, Sun H, Jiang YT, et al. Dietary Inflammatory Index and Health Outcomes: An Umbrella Review of Systematic Review and Meta-Analyses of Observational Studies. Front Nutr. 2021;8:647122.
121. Eslampour E, Ghanadi K, Aghamohammadi V, Kazemi AM, Mohammadi R, Vahid F, et al. "Association between dietary inflammatory index (DII) and risk of irritable bowel syndrome: a case-control study". Nutr J. 2021;20(1):60.
122. Tandorost A, Kheirouri S, Moludi J, Seyedmardani S. Association of Dietary Inflammatory Index (DII) with disease activity and inflammatory cytokines in the patients with rheumatoid arthritis. Int J Clin Pract. 2021;75(11):e14792.
123. Jiang C, Yin H, Liu A, Liu Q, Ma H, Geng Q. Dietary inflammatory index and depression risk in patients with chronic diseases and comorbidity. J Affect Disord. 2022.
124. Li R, Zhan W, Huang X, Liu Z, Lv S, Wang J, et al. Association of Dietary Inflammatory Index (DII) and Depressive Disorders. J Inflamm Res. 2021;14:6959-73.

125. Phillips CM, Shivappa N, Hébert JR, Perry IJ. Dietary inflammatory index and mental health: A cross-sectional analysis of the relationship with depressive symptoms, anxiety and well-being in adults. Clin Nutr. 2018;37(5):1485-91.
126. Tian Z, Zhuang X, Zhao M, Zhuo S, Li X, Ma R, et al. Index-Based Dietary Patterns and Inflammatory Bowel Disease: A Systematic Review of Observational Studies. Adv Nutr. 2021;12(6):2288-300.
127. Syed Soffian SS, Mohammed Nawi A, Hod R, Ja'afar MH, Isa ZM, Chan HK, et al. Meta-Analysis of the Association between Dietary Inflammatory Index (DII) and Colorectal Cancer. Nutrients. 2022;14(8).
128. Bours MJL. Tutorial: A nontechnical explanation of the counterfactual definition of effect modification and interaction. J Clin Epidemiol. 2021;134:113-24.
129. MacDonald C-J, Laouali N, Madika A-L, Mancini FR, Boutron-Ruault M-C. Dietary inflammatory index, risk of incident hypertension, and effect modification from BMI. Nutr J. 2020;19(1):62.
130. Lund E, Kumle M, Braaten T, Hjartåker A, Bakken K, Eggen E, et al. External validity in a population-based national prospective study--the Norwegian Women and Cancer Study (NOWAC). Cancer Causes Control. 2003;14(10):1001-8.
131. Hjartåker A, Lund E, Bjerve KS. Serum phospholipid fatty acid composition and habitual intake of marine foods registered by a semi-quantitative food frequency questionnaire. Eur J Clin Nutr. 1997;51(11):736-42.
132. Parr CL, Veierød MB, Laake P, Lund E, Hjartåker A. Test-retest reproducibility of a food frequency questionnaire (FFQ) and estimated effects on disease risk in the Norwegian Women and Cancer Study (NOWAC). Nutr J. 2006;5:4.
133. Radd-Vagenas S, Kouris-Blazos A, Singh MF, Flood VM. Evolution of Mediterranean diets and cuisine: concepts and definitions. Asia Pac J Clin Nutr. 2017;26(5):749-63.
134. van Duijnhoven FJB, Brouwer JGM, van Woudenbergh GJ, Kampman E, Feskens EJM. Comment on “Perspective: The Dietary Inflammatory Index (DII)—Lessons Learned, Improvements Made, and Future Directions”. Advs Nut. 2020;11(1):177-8.
135. Solans M, Benavente Y, Saez M, Agudo A, Jakszyn P, Naudin S, et al. Inflammatory potential of diet and risk of lymphoma in the European Prospective Investigation into Cancer and Nutrition. Eur J Nutr. 2020;59(2):813-23.
136. Gendelman O, Amital H, Bar-On Y, Ben-Ami Shor D, Amital D, Tiosano S, et al. Time to diagnosis of fibromyalgia and factors associated with delayed diagnosis in primary care. Best Pract Res Clin Rheumatol. 2018;32(4):489-99.
137. Durdu K, Sena Keskin K. Tied Survival Times In Survival Analysis. Alphanumeric journal. 2017;5(1):85-102.
138. Hertz-Picciotto I, Rockhill B. Validity and Efficiency of Approximation Methods for Tied Survival Times in Cox Regression. Biometrics. 1997;53(3):1151-6.
139. Connor Gorber S, Schofield-Hurwitz S, Hardt J, Levasseur G, Tremblay M. The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. Nicotine Tob Res. 2009;11(1):12-24.
140. Davis CG, Thake J, Vilhena N. Social desirability biases in self-reported alcohol consumption and harms. Addict Behav. 2010;35(4):302-11.

Appendixes

Appendix 1. The 45 food parameters in the DII and their respective overall inflammatory effect score. Food parameters available for calculating DII in this thesis illustrated.

Food parameter in the DII	Overall inflammatory effect score	Food parameters used to calculate DII/E-DII in this thesis
Alcohol (g)	-0.278	X
Beta-Carotene (mg)	-0.584	X
Caffeine (g)	-0.110	X
Carbohydrate (g)	+0.097	X
Cholesterol (mg)	+0.110	X
Energy (kcal)	+0.180	X (not for E-DII)
Eugenol (mg)	-0.140	-
Total fat (g)	+0.298	X
Fiber (g)	-0.663	X
Folic acid (µg)	-0.190	X
Garlic (g)	-0.412	X
Ginger (g)	-0.453	-
Iron (mg)	+0.032	X
Magnesium (mg)	-0.484	X
Monounsaturated Fat (g)	-0.009	X
Niacin (mg)	-0.246	-
Omega-3 Fatty acids (g)	-0.436	-
Omega-6 Fatty acids (g)	-0.159	-
Onion (g)	-0.301	X
Protein (g)	-0.021	X
Polyunsaturated Fat (g)	-0.337	X
Riboflavin (mg)	-0.068	X

Food parameter in the DII	Overall inflammatory effect score	Food parameters used to calculate DII/E-DII in this thesis
Saffron (g)	-0.140	-
Saturated fat (g)	+0.373	X
Selenium (µg)	-0.191	-
Tea (g)	-0.536	X
Thiamin (mg)	-0.098	X
Trans fat (g)	+0.229	-
Turmeric (mg)	-0.785	-
Vitamin A (RE)	-0.401	X
Vitamin B12 (µg)	+0.106	X
Vitamin B6 (mg)	-0.365	X
Vitamin C (mg)	-0.424	X
Vitamin D (µg)	-0.446	X
Vitamin E (mg)	-0.419	X
Zinc (mg)	-0.313	-
Flavan-3-ol (mg)	-0.415	X
Flavones (mg)	-0.616	X
Flavanols (mg)	-0.467	X
Flavanones (mg)	-0.250	X
Anthocyanidins (mg)	-0.131	X
Isoflavones (mg)	-0.593	X
Pepper (g)	-0.131	-
Thyme/oregano (mg)	-0.102	-
Rosemary (mg)	-0.013	-

Appendix 2. Intake of macronutrients in grams per day

DII quartiles	**Q1**	**Q2**	**Q3**	**Q4**	**Total**
N	5 454	5 453	5 453	5 454	21814
(Case)	(155)	(158)	(196)	(183)	(692)
DII score	-0.71	0.84	2.03	3.35	1.46
Median (range)	(-3.88,0.19)	(0.19,1.46)	(1.46,2.65)	(2.65,5.09)	(-3.88,5.09)
Protein(g/day)	86 (75,99)	78 (68,90)	72 (62,82)	71 (61,82)	74 (62,87)
Total fat(g/day)	72 (60,86)	66 (55,80)	60 (49,72)	51 (41,62)	62 (50,76)
SFAs (g/day)	28 (23,34)	27 (22,33)	24 (20,30)	21 (17,27)	25 (20,31)
MUFAs (g/day)	23 (19,27)	21 (17,25)	18 (15,22)	16 (13,19)	19 (16,24)
PUFAs (g/day)	13 (11,16)	11 (9,14)	10 (8,12)	8 (7,10)	10 (8,13)
TFAs (g/day)	1 (1,2)	1 (1,2)	1 (1,2)	1 (1,2)	1 (1,2)
Carbohydrates (g/day)	238 (206,273)	213 (185,245)	193 (164,221)	160 (135,186)	200 (165,237)

Appendix 3. Flow chart with overview of the steps for calculating the overall inflammatory effect score for food parameters and how DII score for a participant can be calculated.