UiT The Arctic University of Norway

Faculty of health science

Nordic diet and mortality

The Norwegian Women and Cancer study

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Cover illustration by Hanna Resvoll-Holmsen

Urtemark med blant annet skogstorkenebb (Geranium sylvaticum) ved bredden av Ordojarvi i Øst-Finnmark, 1909

From the book entilted “Hanna Resvoll-Homsen, Natur bevart i bilder”

”Men vi maa videre. Foran os ligger fjeldet med den planteverden, vi hadde sat os som maal at faa et litet indblik i.”

- Hanna Resvoll-Holmsen

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Preface

The initial objective of this project was to further investigate the association between the Healthy Nordic Food Index (HNFI) and the risk of colorectal cancer (CRC) and mortality. In line with this aim, a manuscript examining the relationship between the HNFI and CRC risk was completed and submitted to a journal shortly after the onset of the COVID-19 pandemic. However, after several months, we were informed by the journal that they had been unable to find reviewers for the manuscript, resulting in its rejection.

During the waiting period, I had numerous concerns about using and interpreting composite indices in relation to health outcomes and tested alternative constructions for an index to use in the analyses between the healthy Nordic diet and CRC and mortality. However, these tests and discussions prompted a shift in the project's focus. I became interested in conducting a more detailed examination of the individual food groups that hold significance in the Nordic diet. This new direction aimed to provide a deeper understanding of the dietary components and their association with longevity within the context of the healthy Nordic diet.

This project offers a glimpse into the complex relationship between elements in a healthy Nordic diet and mortality, yet it is just the beginning. Reciting the words of Hanna Resvoll-Holmsen “But we must move on. In front of us lies the mountain with that plant life, we had set ourselves the goal of getting a little insight into.” The potential health benefits of the diversity of plants that have been integral to our nutritional and medicinal heritage, await further exploration. This includes whole grains and legumes once commonly cultivated, as well as wild berries and plants that have yet to be examined within the scope of research on the healthy Nordic diet. Given the growing disconnection between consumers and their food—geographically, practically, and in awareness—in a world also grappling the loss of natural habitats, the decline in biodiversity, climate changes, political instability, conflict, and the prevalence of NCDs, it is important to continue the exploration of local and traditional diets. This project is a small attempt!

Abstract

Background: Noncommunicable diseases (NCDs), including cancer and cardiovascular diseases (CVDs), are the leading causes of death among Norwegian women. Norway is aiming for a 33% reduction in premature mortality from NCDs by 2030. To achieve this goal, as well as other Sustainable Development Goals (SDGs) such as climate change mitigation, a shift towards healthy and sustainable diets is essential. Reviving traditional diets that utilise local foods, has been identified as crucial by the Food and Agriculture Organization of the United Nations (FAO). The healthy Nordic diet aligns with this necessary shift in dietary behaviours according to the World Health Organization (WHO).

Aim: This thesis aimed to explore adherence to the healthy Nordic diet and examine the associations between food groups within this diet and mortality. Additionally, it aimed to investigate dietary shifts towards a healthy Nordic diet and the association with mortality among women in Norway.

Methods: This thesis was conducted within the Norwegian Women and Cancer Study (NOWAC), a prospective national cohort study that includes more than 170,000 Norwegian women. Adherence to the healthy Nordic diet was assessed using the Healthy Nordic Food Index (HNFI). Cox proportional hazard models and restricted cubic splines were used to estimate the association between key food groups in the healthy Nordic diet and all-cause mortality. Additionally, specified substitution analyses were conducted to evaluate the associations between replacing red and processed meat with fish and cause-specific mortality.

Results: Most women were medium adherents to the HNFI, and higher adherence was linked to increased food and energy intake, as well as a healthier lifestyle. An increased intake of lean fish and whole grain products was associated with lower all-cause mortality. The relationship between the intake of Nordic fruits and vegetables, fatty fish, and low-fat dairy products and all-cause mortality was non-linear, with moderate intake proving to be optimal. Among those who consumed higher amounts of processed meat, replacing processed meat with lean fish was associated with lower all-cause, cancer, and CVD mortality, while replacing processed meat with fatty fish was associated to lower CVD mortality. Lower consumption of processed meat, as well as unprocessed red meat consumption was not associated with mortality.

Conclusion: Whole grain products, lean fish, and Nordic fruits and vegetables should be promoted as key components of the healthy Nordic diet to enhance longevity among Norwegian women. For women with higher processed meat intake, promoting the substitution of processed meat with lean fish could help reduce premature mortality, particularly from cardiovascular diseases (CVD). Further research is necessary to explore the potential health impacts of processed fatty fish and dairy products, as well as a broader range of healthy Nordic foods, to better understand the influence of the healthy Nordic diet on mortality.

Sammendrag

Bakgrunn: Ikke-smittsomme sykdommer, inkludert kreft og hjerte- og karsykdommer, er de vanligste dødsårsakene blant norske kvinner. Norge har satt som mål å redusere forekomsten av for tidlige dødsfall fra ikke-smittsomme sykdommer med 33 % innen 2030. For å oppnå dette målet, samt FNs bærekraftsmål relatert til bevaring av natur og miljø, er en overgang til et sunt og bærekraftig kosthold nødvendig ifølge FNs organisasjon for ernæring og landbruk (FAO). Verdens helseorganisasjon (WHO) fremhever det sunne nordiske kostholdet som et eksempel som er i tråd med disse målene.

Mål: Formålet med denne oppgaven var å utforske etterlevelse av et sunt nordisk kosthold og undersøke sammenhengene mellom matvaregrupper som er en del av dette kostholdet og dødelighet blant kvinner i Norge. I tillegg var det et mål å undersøke endringer mot et sunt nordisk kosthold og sammenhengen med dødelighet.

Metoder: Oppgaven bruker data fra Kvinner og Kreft studien (KK), som er en prospektiv nasjonal kohortstudie som omfatter mer enn 170 000 norske kvinner. Etterlevelse av et sunt nordisk kosthold ble målt ved hjelp av en konstruert indeks – the Healthy Nordic Food Index (HNFI). Cox proporsjonale hasardmodeller og «restricted cubic splines» ble brukt for å estimere sammenhengen mellom matvaregrupper i det sunne nordiske kostholdet og total dødelighet. I tillegg ble det utført spesifiserte substitusjonsanalyser for å estimere sammenhengen mellom å erstatte rødt og bearbeidet kjøtt med fisk og dødelighet knyttet til kreft og hjerte- og karsykdom.

Resultater: De fleste kvinnene var i kategorien for middels etterlevelse av et sunt nordisk kosthold målt med HNFI. Høy etterlevelse var assosiert med et høyere mat- og energiinntak, samt en sunnere livsstil. Økt inntak av mager fisk og fullkornsprodukter var forbundet med lavere totaldødelighet. Sammenhengen mellom totaldødelighet og inntak av nordiske frukt og grønnsaker, fet fisk og magre meieriprodukter var ikke lineær, og et moderat inntak var optimalt. Blant kvinnene med et noe høyere inntak av bearbeidet kjøtt, var det å erstatte bearbeidet kjøtt med mager fisk assosiert med lavere totaldødelighet, samt lavere dødelighet fra kreft og hjerte- og karsykdommer. Erstatning av bearbeidet kjøtt med fet fisk var også knyttet til lavere dødelighet fra hjerte- og karsykdommer. Lavere inntak av bearbeidet kjøtt, samt inntak av ikke-bearbeidet rødt kjøtt var ikke assosiert med dødelighet.

Konklusjon: Fullkornsprodukter, mager fisk og nordiske frukt og grønnsaker bør fremmes som viktige matvaregrupper i det sunne nordiske kostholdet for å øke levetiden blant norske kvinner. For kvinner med høyere inntak av bearbeidet kjøtt kan det å erstatte noe av dette kjøttet med mager fisk bidra til lavere dødelighet, spesielt av hjerte- og karsykdommer. Ytterligere forskning er nødvendig for å utforske mulige helseeffekter av bearbeidet fet fisk og meieriprodukter, samt et bredere utvalg av sunne nordiske matvarer, for å bedre forstå sammenhengen mellom det sunne nordiske kostholdet og dødelighet.

Thesis at a glance

PAPER I

Research question: To assess adherence to the Healthy Nordic Food Index, and to explore dietary composition and lifestyle factors associated with adherence to the index

Study sample: 81 516

Exposure: The Healthy Nordic Food Index

Outcome: Macro- and micronutrients, energy intake, food groups outside the Healthy Nordic Food Index, age, body mass index, physical activity, smoking, and region of living

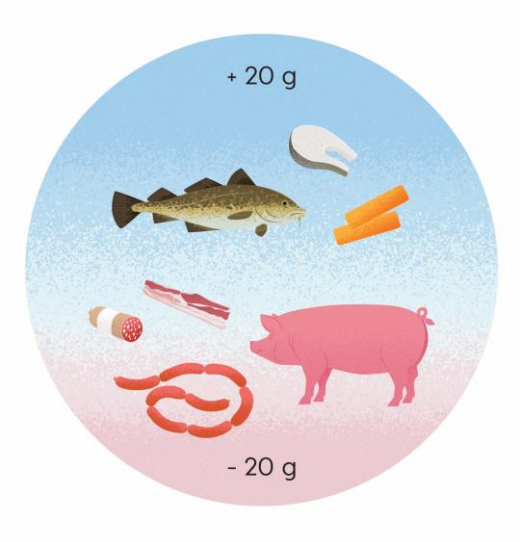
PAPER II

Research question: To evaluate the potential non-linear associations between food groups part of a healthy Nordic diet and all-cause mortality

Study sample: 83 669

Exposure: Nordic fruits and vegetables, lean fish, fatty fish, whole grain products, low-fat dairy products

Outcome: All-cause mortality



PAPER III

Research question: To examine the impact of replacing red and processed meat with lean or fatty fish on all-cause and cause specific mortality

Study sample: 83 304

Exposure: Processed meat (n=81 374), red meat (n=77 597), red and processed meat (n=82 245), replaced with lean or fatty fish

Outcome: All-cause mortality, cancer- (C00-C97), and CVD (IHD (I20-I25) and stroke (I60-I69)) mortality

Illustrations: Mette Kaada

List of papers

This thesis is based on the following papers:

Paper I

Jensen TE, Braaten T, Jacobsen BK, Barnung RB, Olsen A, Skeie G. Adherence to the Healthy Nordic Food Index in the Norwegian Women and Cancer (NOWAC) cohort. Food & Nutrition Research, 2018; 62: 1339. doi:10.29219/fnr.v62.1339

Paper II

Jensen TE, Braaten T, Jacobsen BK, Skeie G. Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study. BMC Public Health. 2022;22(1):169–16. doi: 10.1186/s12889-022-12572-8

Paper III

Jensen TE, Braaten T, Jacobsen BK, Ibsen DB, Skeie G. Replacing red and processed meat with lean or fatty fish and all-cause and cause-specific mortality in Norwegian women. The Norwegian Women and Cancer Study (NOWAC): a prospective cohort study. British Journal of Nutrition, 2024;131: 531-43. doi:10.1017/S0007114523002040

Abbreviations

AIC	Akaike information criteria
AR	Average requirement
BMI	Body mass index
BSDS	Baltic Sea Diet Score
CHD	Coronary heart disease
CI	Confidence interval
CRC	Colorectal cancer
CVD	Cardiovascular disease
EPIC	European Prospective Investigation into Cancer and Nutrition
FAO	Food and Agriculture Organization of the United Nations
FFQ	Food frequency questionnaire
GBD	Global burden of disease
HNFI	Healthy Nordic Food Index
HR	Hazard ratio
IARC	The International Agency for Research on Cancer
ICD-10	International Classification of Diseases, 10th Revision
IHD	Ischemic heart disease
LDL	Low-density lipoprotein
NCD	Non-communicable diseases
NND	New Nordic Diet
NNR	Nordic Nutrition Recommendations
NOWAC	Norwegian Women and Cancer Study
RCS	Restricted cubic splines
RRR	Relative risk ratio
SDG	Sustainable development goals
WCRF	World Cancer Research Fund
WHO	World Health Organization

1 Background

Aligned with the United Nations Sustainable Development Goals (SDG), the World Health Organisation (WHO), and its member states (including Norway) are aiming for a 33% reduction in premature mortality from noncommunicable diseases (NCDs) by 2030, using 2015 as the reference year (1). “Premature mortality” is defined as deaths that occur before the age of 70, specifically deaths between the ages of 30 and 69 in this context (2).

To achieve the goals on NCDs reduction, as well other SDGs such as clean water and sanitation, and climate change mitigation, a shift to healthy and sustainable diets is necessary (3, 4). The Food and Agricultural Organisation of the United Nations (FAO) emphasizes the importance of prioritizing the revival of traditional food systems to ensure that populations consume healthy diets to meet the public health challenges in a sustainable way (4).

In this context, the adaptation of traditional and culturally accepted diets that utilize local foods, cultivated in harmony with the natural environment and within dynamic ecosystems, emerges as a pivotal solution. According to WHO, regional diets such as the Mediterranean diet and the healthy Nordic diet align with this needed shift in dietary behaviours and food systems (5).

This thesis explores the relationship between a healthy Nordic diet, measured by the Healthy Nordic Food Index (HNFI), other dietary factors, and lifestyle factors among Norwegian women. It also focuses on how food groups within the healthy Nordic diet are associated to Norwegian women’s all-cause mortality, as well as dietary changes replacing red and processed meat with fish in relation to all-cause mortality, and deaths from cancer and cardiovascular diseases (CVDs) – two major NCDs. These NCDs share some common modifiable risk factors, and consequently, similar strategies for prevention.

1.1 Mortality in Norway, with focus on noncommunicable diseases and Norwegian women

1.1.1 Mortality in Norway

The latest data from the Norwegian Cause of Death Register for 2022 (updated data on mortality in Norway will not be published until May 30, 2024) shows that there were 45 947 registered deaths among people living in Norway, with women accounting for 50 % of these deaths. While the overall mortality rate in Norway has been declining for several decades, there was a noticeable increase in deaths during 2021 and 2022 (6).

The age-standardised mortality rate for 2022 was 917 per 100 000 individuals, the highest since 2015 (6). This increased mortality is partially attributed to the impact of COVID-19, but there was also a notable rise in deaths from cancer and cardiovascular diseases (CVDs). Moreover, the mortality rate among those under the age of 70 was higher than expected, with CVD-related deaths surpassing those associated with COVID-19 in this age group. The exact

reasons for relative increase in CVD-related deaths is unclear, but changes in reporting practices and the pandemic may have played a role (6).

1.1.2 Noncommunicable diseases and mortality

NCDs including the four primary types - CVD, cancer, diabetes, and chronic respiratory diseases- are the leading cause of death worldwide (2). The global trend is that mortality attributed to these four major NCDs has risen both in absolute numbers and in the proportions of all deaths between 1990 and 2019 (2). This increase is primarily due to a growing and ageing population, and the age-standardised mortality for the four major NCDs have generally decreased during this period, with the exception of diabetes (2). These primary NCDs are also the foremost cause of premature death among adults in both the affluent and many low-income countries.

Despite the increase in deaths during 2021 and 2022, there has in Norway been an overall 15 % decrease in NCDs related premature deaths, from 212 to 180 per 100 000 individuals, between 2015 and 2022 (1, 6). The decline has been seen in both men and women, although the premature mortality from NCDs is higher among Norwegian men than women (1, 6).

Cancer, which is a general term for diseases characterised by uncontrolled cell division, is the leading cause of death in Norway and the primary cause of premature mortality among Norwegian women as shown in Figure 1 (1, 7).

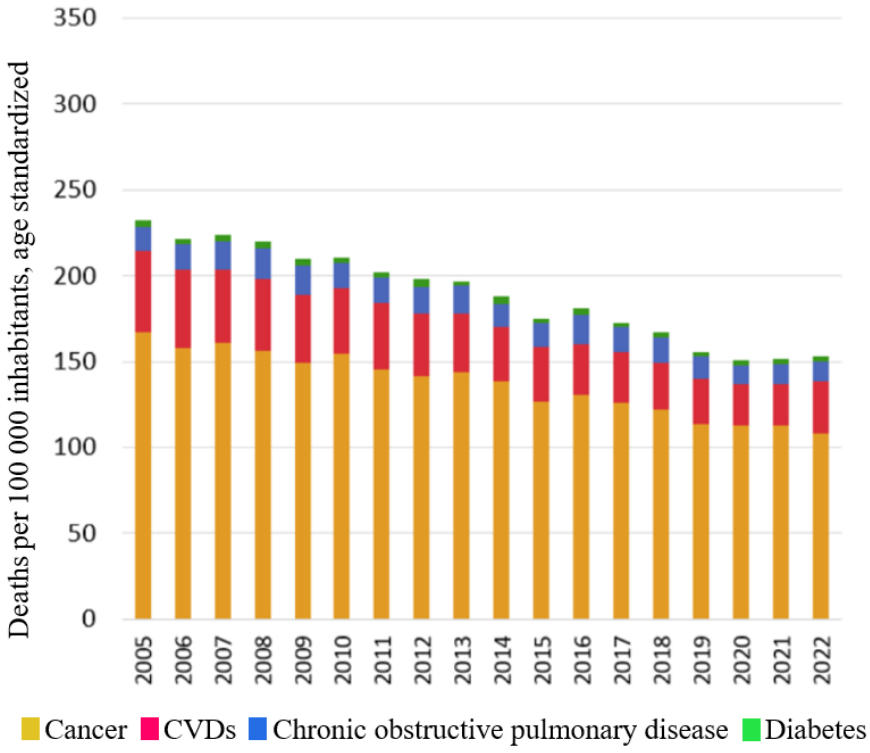


Figure 1 NCD mortality in Norwegian women aged 30-69, 2005-2022

Mortality from NCDs cancer, CVDs, COPD and diabetes in Norway, 2005-2022 for the age group 30-69 years. Deaths per 100,000 inhabitants, age standardised, women. Adapted from the Cause of Death Register, Institute of Public Health (1)

Mortality is an indicator of disease burden, and the incidence of cancer has increased fivefold in Norway since the 1950s, paralleling both a growing population, and the doubling of the proportion of the population aged over 70, which constituted 13 % in 2022 (7). The age-adjusted death rates from cancer have been relative stable since the 1960s, with a notable decline starting in 2000, however this decline is more pronounced in men (7).

Approximately, 38 000 Norwegians are diagnosed with cancer each year, and the number is expected to rise (7). Current estimates suggest that 38 % of Norwegian women will be diagnosed with cancer by the age of 80. The most prevalent cancers among Norwegian women include breast, colorectal, and lung cancer, which together account for about 60 % of new cancer cases. When compared with other Nordic countries, Norwegian women have the second-highest cancer incidence rate after women in Denmark, and the highest incidence of colorectal cancer (7).

Following cancer, CVDs are the leading cause of death in Norway in both women and men, accounting for 23 % of all deaths in 2022. As shown in Figure 1, CVDs are also the second leading cause of premature death among Norwegian women (6, 8).

CVD refers to conditions that affects the heart and blood vessels (8). Common CVDs include angina pectoris, myocardial infarction, stroke, arterial fibrillation, and heart failure. These conditions are often interrelated; for instance, ischemic heart disease (IHD), which encompasses both myocardial infarction and angina pectoris, is a significant contributor to the development of heart failure and atrial fibrillation. Additionally, arterial fibrillation and myocardial infarction are known risk factors of stroke (8).

IHD and stroke are the most common CVDs, and they account for around 80% of the CVD-related deaths (2). Even though IHD and stroke mortality are most common above the age of 70, they are also major contributors to premature mortality in the world causing nearly 30 % of all deaths in the age group 50-69 in 2019 (2).

Mortality rates from CVDs in Norway have been on downward trajectory since the 1970s, and particularly there has been a significant decline in deaths due to acute myocardial infarction (8). Since the 1990s, mortality rates from both myocardial infarction and stroke have decreased by more than 50%. When age-adjusted, the incidence of myocardial infarction in Norwegian women has decreased by 31%, while the occurrence of acute stroke has declined by 8% from 2017 to 2022. When compared to other Nordic countries, Norway and Iceland has the lowest mortality rates from CVDs (6, 8).

1.2 Common behavioural risk factors for noncommunicable diseases

The primary NCDs share some common behavioural risk factors including unhealthy diets, tobacco use, excessive alcohol consumption, and lack of physical activity (2). These factors

contribute to metabolic changes that increase the risk of NCDs, including hyperglycaemia, hyperlipidaemia, hypertension, and overweight/obesity as shown in Figure 2 (2).

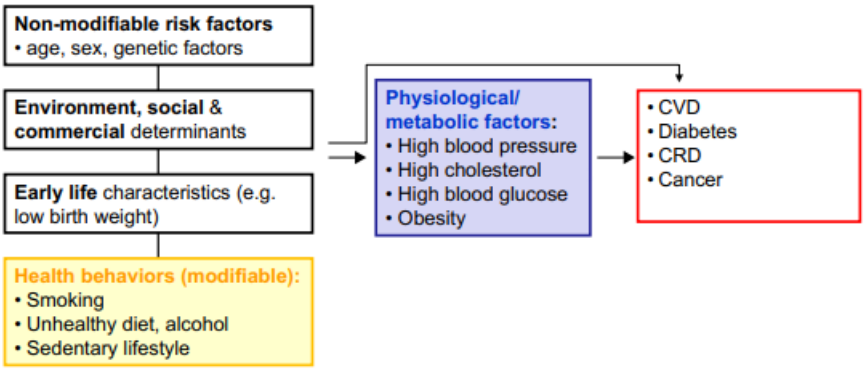


Figure 2 "The relationship between risk factors and NCDs"

By Nick Banatvala and Pascal Bovet, licensed under CC BY-ND 4.0 DEED

Dietary risk factors, particularly the overconsumption of red and processed meat, sugar-sweetened beverages, trans fatty acids, and sodium, alongside a low intake of fruits and vegetables, legumes, whole grains, nuts and seeds, milk, seafood omega-3 fatty acids, omega-6 fatty acids, calcium, and fibre, are leading contributors to NCDs (2, 4).

In Norway, the low intake of fruits and vegetables, combined with high consumption of sugar and salt, is estimated to contribute to 13 % of all deaths, surpassing the contribution from tobacco, which contributed to 12 % of all deaths (9).

1.2.1 Simplification of the diet – a fundamental contributor to dietary risk factors for noncommunicable diseases

FAO identifies simplification of the diet as a key issue leading to dietary risk factors associated with NCDs. In their report "Biodiversity and Nutrition, a common path" a complex relationship between nutrition and biodiversity is outlined, which includes genetic, species and ecosystem diversity (10). The trend towards industrial farming practises and a globalization of food systems, has led to a dramatic reduction in biodiversity since the beginning of agriculture. This loss of biodiversity, and the resulting decline in the variety of foods, has largely contributed to the loss of a variety of dietary components providing essential nutrients, and increased availability of energy-dense foods high in refined carbohydrates, fats, and salt, and low in essential nutrients (10).

The rise in ready-to-eat products, of which many are defined as ultra-processed foods, exemplifies this issue (11). A study analysing food sales suggest that this simplification of diets is evident in Norway, where a considerable portion of food expenditure is on ultra-processed foods, constituting 46.5% of the total, compared to 36.3% spent on minimally processed foods (12).

The decline in consumption of locally available foods is according to FAO closely linked to the rising rates of overweight, obesity and NCDs (10). These trends are not only bad for public health, but also to the environment (2, 11, 13).

The relationship between diets abundant in dietary species biodiversity and mortality was examined in a large European cohort study, which incorporated data from Norwegian women in the Norwegian Women and Cancer (NOWAC) study. The results indicated that a high level of diversity in the diet, encompassing a variety of foods from different species, was linked to lower all-cause mortality. This finding highlights the direct importance of dietary diversity for public health (14).

The opportunity to diversify our diets by incorporating a broader range of local foods, could not only conserve genetic diversity within individual regions but also our collective genetic heritage worldwide (14). Hence, regional diets, such as the healthy Nordic diet, could be a globally relevant strategy for preventing NCDs in a sustainable way (14).

1.3 The development of the healthy Nordic diet

Over the course of the 20th century, the dietary focus in the Nordic region has evolved from a culture of scarcity, where food preservation and consumption were based on availability, to a situation where food is abundant, with a diversity of choices, and a growing awareness of the connection between diet and health (15). In Norway, food and nutrition became important political issues during the 20th century, with health becoming a central aspect of food culture (15). The focus on health also permeates public discussions (15, 16). Despite the efforts, unhealthy diets persist as a primary risk factor for NCDs in Norway, a trend that is consistent across the Nordic region (17).

1.3.1 The Nordic collaboration

Nordic countries, including Norway, Sweden, Denmark, Iceland and Finland, have long history of collaboration to develop dietary guidelines known as the Nordic Nutrition Recommendations (NNR) (18), as well as on climate, the environment, and the conservation of genetic resources (17, 19).

The collaboration concerning NNR was initiated due to similarities in dietary habits and the prevalence of diet-related diseases like CVDs, type 2 diabetes, and obesity in the Nordic countries. From the beginning NNR primarily focused on setting dietary reference values for single nutrients to plan diets for groups in the population, while in the 5th edition from 2012 (NNR2012), the focus shifted to the entire diet placing greater emphasis on the role of dietary patterns in preventing chronic diseases related to diet (18). The updated version of the NNR2012 - NNR2023 - was published in June 2023 (20).

In addition to updating all the chapters from the previous edition (NNR2012), the latest edition (NNR2023) has placed increased emphasis on dietary patterns as well as sustainability and environmental considerations (20). Although NNR2023 did not play a role in shaping the

concept of the healthy Nordic diet, the NNR23 establishes the basis for forthcoming food-based dietary guidelines in Norway and points out the course for our future nutrition policies. Moreover, it revitalises some of the core principles of the healthy Nordic diet, by reaffirming the focus on dietary patterns and sustainability (20).

1.3.2 The "New" Nordic diet

The concept of a Nordic diet was not really defined until it became "new" (15). The new Nordic diet emerged in the early 2000 as a concept from the collaborative efforts by a group of chefs from various Nordic countries, who sought a new culinary identity shaped by the region's "terroir" (15).

Terroir is described as the alliance between humans and their territory, encompassing a unique combination of factors including culture, climate, landscape, and heritage (15, 21) (Figure 3). This synergy gives distinctive qualities and flavours to food, specific to a particular geographic area, and has been central in branding the new Nordic diet (15).

The collaboration among chefs, culminated in a manifesto for the new Nordic cuisine in 2003 based on principles related to health, gastronomic potential, Nordic identity, and sustainability, aiming to bridge the gastronomic potential of the regional foods with health and sustainability (21).

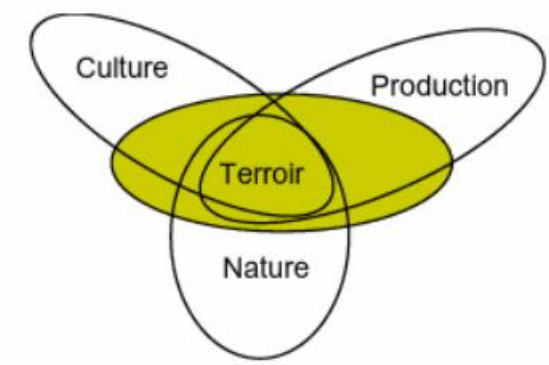


Figure 3 The concept of "terroir" by Marianne Østerlie,

Adapted from the report "Kortreist mat og smak med lokal identitet" by Marianne Østerlie, with permission from the author (22)

Following the establishment of the new Nordic cuisine as a prominent concept, driven by renowned restaurants like Noma in Copenhagen, researchers sought to translate the concept into a Nordic diet - based on principles of health and sustainability- to be applied in research context (23).

Several variations of terms such as the "new Nordic cuisine", the "new Nordic diet", the "Nordic diet", and the "healthy Nordic diet" have been used to describe both this culinary movement, and a healthy dietary pattern defined by a set of criteria and applied in nutritional epidemiological research over the last 10-15 years (23).

Consequently, there is no singular "Nordic diet", instead it is an umbrella term that is used to describe any interpretation of a dietary pattern that is based in scientific evidence on diet and health, with a focus on foods that originate from the Nordic region, as well as the more practical gastronomic new Nordic diet (23). In the following, the term "healthy Nordic diet" will be used when referring to the conceptualisation of dietary patterns that focuses on foods originating in the Nordic region with anticipated health benefits that are applied in research context (23).

1.3.3 Conceptualization of the healthy Nordic diet

The selection of foods for inclusion in the healthy Nordic diet have commonly been guided by these four criteria (24, 25):

1. The ability to be produced on a large scale within the Nordic countries without the use of external energy such as greenhouses.
2. A longstanding tradition of being used as a food source within the Nordic countries.
3. Demonstrating health benefits.
4. The ability to be consumed as food items, rather than limited to small amounts as spices or dietary supplements.

The healthy Nordic diet places particular emphasis on specific varieties of foods within the food groups commonly recognized as contributing to a balanced diet (18, 24). These five basic food groups include carbohydrate rich foods such as cereals and potatoes; fruits and vegetables; dairy products; protein foods such as fish, meat, and alternative options; and oils and fat (24, 26, 27). Within these food groups there are varieties that are emphasised in the healthy Nordic diet; i) Cereals: rye, oats and barley, ii) fruits, berries and vegetables: non starchy root vegetables, cabbages, apples and pears, wild berries such as blueberries, cloudberries, lingonberries and plums, iii) dairy: low-fat dairy, iv) Fish: lean and fatty fish and other seafood v) red and processed meat: either omitted or handled as a negative weighted factor, vi) oils and fat: rapeseed oil.

Regional foods that we define as part of the healthy Nordic diet today might however differ from what was consumed in the past. For instance, potatoes have a longstanding place in Nordic food traditions but are often excluded from the definition of a healthy Nordic diet, as the criteria for inclusion require clear evidence of health benefits in the scientific literature. Similarly, while full-fat dairy was traditionally consumed in the region, the contemporary interpretation of the healthy Nordic diet emphasises low-fat dairy options. Additionally, rapeseed oil is recommended as a healthier alternative to butter within this framework. This illustrates that the concept of food tradition is dynamic and constantly evolving, rather than being static, and that regional foods are selected and defined based on what is currently important for us (15).

The following will summarize the current recommendations and the traditional use of the basic food groups covered in this thesis – whole grains (whole grain bread and breakfast

cereals), fruits and vegetables (root vegetables, cabbages, apples/pears), dairy (low-fat milk and yoghurt), fish (lean and fatty fish) and red and processed meat.

1.3.3.1 Whole grains

Whole grain is defined to include all parts of the cereal seeds, including the bran, germ, and endosperm, in the same relative proportions found in the intact whole grain (28). Current food based dietary guidelines recommend an intake of 75-90 grams of whole grains daily, while the NNR2023 recommends a minimum of 90 grams, specifically excluding rice (20, 29). This recommendation is based on evidence linking diets rich in whole grains to lower risk of CVD, colorectal cancer, type 2 diabetes, and all-cause mortality (20).

Whole grains such as barley, rye and oats are rooted in Nordic food traditions, with a history of cultivation across the region, including areas above the Arctic Circle like northern parts of Norway (30). In the past, these whole grains were primarily consumed as porridge and crisp bread, while refined wheat-based products did not become common in the general population until the 19th century when leavened bread baking at home became more widespread (15).

Grains remain a staple in the Nordic diet, but currently, wheat is the most widely consumed grain in the Nordic region, accounting for 80 % of the total grain consumption, followed by rye, barley, and oats (24, 31). Estimates indicate that around 14-28% of the total grain consumption in the Nordic countries is in the form of whole grain, suggesting a predominance of refined grains (31). In Norwegian women, bread is the major source of whole grains and predominantly whole grain wheat, followed by rye mainly from crisp bread, and oat from porridge/breakfast cereals (32).

1.3.3.2 Vegetables, fruits, and berries

Fruits, berries, and vegetables, excluding potatoes and legumes, comprises a variety of plant foods that are commonly classified by their culinary uses in a nutritional context. Vegetables are generally defined as the edible parts of plants including leaves, roots, tubers, stems, and flowers. Fruits are the edible portions surrounding the seeds of plants and trees, while berries are small, seed-containing fruits (28). Norwegian dietary guidelines recommend a daily intake of at least 500 grams of fruits, vegetables and berries, while the NNR2023 suggests 500-800 grams to ensure a sufficient intake of dietary fibres, vitamin C, vitamin E, provitamin A, vitamin K, folate, potassium, and iron as well as a wide range of phytonutrients (20, 29). Increasing intake of these plant foods is associated with lower risk of cancer in the gastric tract and lungs, and is beneficial for cardiovascular health and longevity, with the most significant risk reduction observed at lower intake levels (33).

Historically, the consumption of fruits and vegetables in the Nordic region was relatively low, especially prior to the discovery of vitamins in 1912 (15). The awareness of the health benefits associated with vegetables grew following this discovery, leading to an increased intake. In Norway, the types of fruits and vegetables consumed were primarily root vegetables such as turnips and swede, which were commonly stored during winter and served as staples

before the introduction of potatoes. Carrots and cabbage were also common. Among fruits and berries, blueberries, lingonberries, and cloudberries were valued for their storability without sugar. Apples and pears were more common in the southern parts and in Denmark (15).

The current consumption of fruits and vegetables in the Nordic region falls short of the amounts recommended by food based dietary guidelines. In Norway, adults are estimated to consume less than 400 grams daily (34). According to recent reports, carrots, onions, tomatoes, and lettuce are the most consumed vegetables, while bananas, citrus fruits and apples are the most consumed fruits over the past decade (35). Data from 2022 commercial sales indicate that 3.1% of fruits and 53.4% of vegetables sold were produced in Norway. The proportion of domestically grown apples and pears were only 16.5% and 14.6 % respectively, while for carrots and swede, it was the 95.2 % and 99.8% (36).

1.3.3.3 Dairy

Milk is produced by the mammary glands of female mammals and is consumed by humans in various forms (28). The most consumed milk in the Nordic region is cow's milk. Cow's milk is a mix of approximately 3-4% proteins, 4% fat, and 5 % carbohydrates in the form of lactose suspended in water. Beyond direct consumption, milk serves as a raw material in the production of yogurt, cheese, creme and butter, which changes the nutritional composition of milk. For instance, cheese production involves coagulating casein proteins and separating it from the whey, resulting in a product richer in protein and fat and lower in water, water-soluble nutrients, and lactose (28).

Dairy products are commonly classified based on fat content into "high-fat" or "low-fat" categories, although there are distinctions within these groups. For instance, low-fat yogurt is typically defined as containing no more than 3% fat—a level comparable to that of whole milk—while low-fat milk is defined as having a fat content of no more than 1.8% (37). Additionally, dairy products are commonly categorized as either fermented or non-fermented, each encompassing a wide variety of products with diverse nutritional compositions such as cheese and yoghurt. In this thesis low-fat dairy products includes low-fat milk and yoghurt.

The food based dietary guidelines, including the updated NNR2023, advice a daily intake of 350-500 ml of low-fat milk and dairy products. This is due to their role as an important source of calcium, iodine, vitamin B12 and other micronutrients in the diet. The NNR2023 suggests that fermented and low-fat dairy products may contribute to a reduction in cardiometabolic risk factors, while high consumption of full fat milk could increase the risk of cardiovascular diseases (20, 29).

In the Nordic region, dairy farming has been crucial for centuries, utilizing grazing areas unsuitable for other types of agriculture. The cool climate and short growing seasons, particularly in the northernmost parts of the region, necessitated food preservation, and it wasn't until the 20th century that fresh milk became widely consumed. Historically, fermented

milk products were commonly consumed, often eaten together with cereals such as oats and barley (15).

Since the 1980s, there has been a transition from whole-fat to low-fat milk varieties, and in the past ten years low-fat and skimmed milk have accounted for approximately 80 % of milk consumption. Over the years, yoghurt consumption has increased slightly, while cheese consumption has more than doubled since the 1950s (35).

1.3.3.4 Fish

The term “seafood” encompasses a variety of marine species, including fish, shellfish, seaweed, kelp, and marine mammals (28). In Norway, fish is the most consumed seafood, and for nutritional purposes, it is typically classified by its fat content. The fat content varies between types of fish and between seasons, but in this thesis lean fish is defined as fish containing < 4 grams of fat per 100 grams including fish such as cod, pollock, haddock, plaice, redfish, catfish and tuna, while fatty fish are defined as fish containing ≥ 4 grams per 100 grams, including fish like trout, salmon and mackerel (38). Nutritionally, fish is like meat in relation to the low content of carbohydrate and high-quality complete protein. The fat in fish is primarily in liquid form, rich in omega-3 fatty acids (28).

The food based dietary guidelines, reinforced in the latest NNR2023 scientific update, recommend consuming 300-450 grams of fish per week, with at least 200 grams being fatty fish (20, 29). This guidance is based on the high-quality protein and essential nutrients fish provides, including omega-3 fatty acids, iodine, selenium, vitamin B12, and zinc. The NNR2023 bases this recommendation on evidence linking fish consumption with a lower risk of CVD and lower all-cause mortality. There is also probable evidence suggesting a protective effect against cognitive decline and a lower risk of pre-term birth and low birth weight (20). However, concerns about environmental contaminants in fish persists, which may pose health risks (39). The Norwegian Scientific committee for food and environment (VKM) has however conducted a risk-benefit assessment of fish consumption and concluded that the benefits of increasing fish intake to the recommended levels outweigh the potential risk (40).

Consumption of fish has longstanding traditions in the Nordics (15). In coastal regions, diets have historically included a higher consumption of fish, which was typically preserved through smoking, drying, and curing. Among these, cod, salmon, halibut and trout were considered higher-status fish compared to coalfish and haddock (15). Commercial sales data from 2022 indicate that cod and pollock account for 21 %, salmon and trout 21 %, mackerel and herring 8%, other types of fish 19%, and fish products, including sandwich spreads, 17 % of the total of fish and seafood sales (35).

1.3.3.5 Red and processed meat

Red meat is the edible part of mammals, including beef, mutton, goats, game and pork (28). Processed red meat is defined as meat that has undergone change by treatment such as curing, smoking, and salting, or by the addition of preservatives. While processed meat can include

poultry, the majority consists of red meats like pork and beef, including products such as cold cuts, sausages, ham, bacon and minced meat (if containing salt and additives) (28).

Norwegian dietary guidelines recommend limiting red and processed meat to no more than 500 grams per week (29). The NNR2023 advice keeping red meat consumption below 350 grams per week, and minimizing processed meat intake as much as possible (20). These guidelines are based on the strong evidence demonstrated by the World Cancer Research Fund (WCRF) on the relationship between red meat and risk of colon cancer (41). The evidence concerning processed meat is valued as a convincing cause for colorectal cancer. The International Agency for Research on Cancer (IARC) classifies processed meat as carcinogenic for humans and red meat as probably carcinogenic, based on observational, animal, and mechanistic studies (42).

Historically, beef, mutton, and goat were predominantly produced in Norway, whereas pork and poultry were more common in the southern part of the Nordic region. Social status greatly influenced the amount and type of meat consumed in the past- the elite enjoyed larger quantities of fresh meat, while peasants and the general population consumed smaller amounts often in the form of salted, dried, smoked or cured meats- what we now classify as processed meat (15).

Today, pork is the most consumed meat in Norway, followed by poultry, beef, and smaller amounts of mutton and goat meat. The daily consumption of red meat among women in Norway is estimated at 92 grams per day (raw weight), representing the highest intake when compared to women in other Nordic countries (34). Additionally, the majority of Norwegian women are categorised as having low adherence to the recommended intake levels for processed meat according to a study assessing adherence to the food based dietary guidelines in Norway (43).

1.4 Dietary pattern analyses

Studying the relationship between diet and risk of NCDs and mortality is inherently complex. In addition to major challenges related to accurately measure food intake, the diet comprises a diverse combination of various complex foods (44). Every food item in a diet is composed of a complicated matrix that includes a multitude of nutrients and compounds, many of which remain unidentified. The nutrients they provide are also inseparable from the energy they contribute to the diet. Furthermore, food preparation and preservation techniques can change the nutritional profile of foods, which may, in turn, impact health (44).

The challenge in isolating the effects of individual nutrients or foods on disease risk or mortality, has led to a shift towards a more holistic approach involving dietary pattern analyses within the field of nutritional epidemiology (45). This approach acknowledges the challenges that lies in the single food exposure and the inability to isolate the individual effect of one food from others often consumed together. This concept is often referred to as clustering, which occurs when the consumption of certain foods, such as fruits, is strongly

correlated with the intake of other foods, like vegetables. Another limitation with single food analyses in relation to health outcomes, is that it does not capture the synergetic effect of foods eaten together, as their combined effect might be greater than the sum of their individual effects. Dietary pattern analysis intends to address some of these complexities by including a broader segment of the total diet, more closely reflecting actual consumption patterns rather than focusing on individual foods (43, 46).

Methods for dietary pattern analysis are typically categorized into two overarching approaches (45). The first, a posteriori analysis, is data-driven and uses statistical methods such as principal component and factor analysis, which condenses observed dietary data into components that explains the most variance. This approach identifies the most influential factors that explain differences in the dietary data of the study population, and identified patterns can then be used to investigate the relationship between dietary patterns and health outcomes (45).

The second approach, a priori analysis, relies on existing literature or food-based dietary guidelines to establish predefined criteria that are used to define adherence to these dietary principles. This often involves the construction of an index which is a composite measurable indicator utilised to investigate the association between dietary patterns and disease risk or mortality (45). An index is designed by selecting and weighting components, which could be both foods, nutrients, or ratios between them, into a combined quantitative score (46). This approach is based on already existing knowledge on the association between single dietary components and health, with the aim to capture the combined impact of clustering and synergy (46). In the field of dietary pattern analyses in relation to all-cause mortality, a priori analyses is the most frequently used approach, in contrast to data-driven methods (47).

Several indices have been developed for use in dietary pattern analyses, however, concerns persist regarding the capacity to conclusively determine the health benefits associated with dietary patterns (46). This is due to a lack of consistency in the methodologies employed, which limits the ability to compare and synthesize results effectively. The Dietary Patterns Methods Project has examined and standardised four dietary indices frequently used within US populations, with the objective of evaluating their association with all-cause, cancer and CVD mortality (46). They found that high adherence to all four indices- the Healthy Eating Index 2010 (HEI-2010), the Alternative Healthy Eating Index 2010 (AHEI-2010), the alternate Mediterranean Diet (aMED) score, and the Dietary Approaches to Stop Hypertension (DASH)- each developed to measure adherence to a distinct set of dietary recommendations, were consistently associated with lower mortality from all outcomes in men and women (46). This led to the conclusion that they were valuable tools for informing dietary recommendations.

However, interpreting the association between a composite score, such as an index, and its relationship with disease or mortality comes with certain limitations. One key issue is that these indices may not fully capture the clustering of healthy dietary behaviours. This is

particularly true for participants who fall in the middle range of the scale. Those at the extreme ends—either with minimal adherence, meaning they do not meet any of the criteria defined for the intended dietary pattern, or with perfect adherence, meeting all criteria—provide clear data points. For example, with an index like the HEI-2010, which measures adherence to food-based dietary guidelines, a minimum score indicates non-compliance with the guidelines, while a maximum score signifies full compliance. However, for individuals with a medium score, indicating partial adherence, the actual clustering of healthy foods can vary significantly. Person 1 might adhere to one set of guidelines, while Person 2 adheres to a completely different set, leading to diverse dietary patterns that are not distinguished by the index. Regarding the potential synergistic effects of foods that are commonly consumed together, such interactions are possible but not guaranteed, and it is not feasible to determine the presence or extent of any synergistic relationships within a composite index (48).

Another challenge arises from the oversimplification inherent in these dietary indices. They often condense complex dietary information into broad categories or binary classifications, assigning the same values to all individuals within a category or to those with intakes above or below a certain threshold. This approach can mask nuances, as dietary intakes that are near the cut-off point may be more alike than those that fall within the same category.

Ultimately, there is a trade-off between the dietary pattern approach and single food approaches. Analyses of single food items may provide a deeper understanding of the relationship between individual dietary components and the risk of disease and mortality. On the other hand, dietary pattern analyses employing a composite score offer a more comprehensive perspective on how broader segments of the diet are associated with these health outcomes. Both methodologies are alternative tools in the pursuit to examine the relationship between healthy Nordic diets and mortality.

1.5 Operationalisation of the healthy Nordic diet

This section will begin by introducing the HNFI as a tool for measuring the healthy Nordic diet, followed by the approach of non-linearity in single food group analysis. Lastly, the approach to dietary changes analyses will be introduced.

1.5.1 The Healthy Nordic Food Index

Various indices have been designed to measure compliance with a healthy Nordic diet. Among the extensively studied are the HNFI, which was applied in Paper I in this thesis, the New Nordic diet (NND), and the Baltic Sea Diet score (BSDS). While each index was designed to assess the healthy Nordic diet, variations in selection of components, construction methods and framework relating to what dietary information was available in the various study populations have led to differences between the indices, and between the same index adapted to different study populations. This reflects the same challenges met with different indices that were tested and standardised in the Dietary Patterns Methods Project (46).

Commonly all three indices include: i) intake of whole grains (Nordic varieties like rye, oat and barley if available in dataset), ii) intake of root vegetables, iii) intake of cabbages, iv) intake of apples and pears v) intake of fish. The maximum score represents a combination of food groups that are most closely aligned with the healthy Nordic diet, and the minimum score the lowest alignment. Additionally, the NND score includes meal patterns, intake of potato relative to rice and pasta, intake of game, unsweetened milk relative to fruit juice, and water relative to sweetened beverages. The BSDS also include intake of other fruits and vegetables, potatoes and low-fat milk, red and processed meat, and total fat (E%) as negatively scored components, and alcohol consumption below a maximum upper limit (E%). An overview of the foods included in these indices are presented in relation to the suggested Norwegian food based dietary guidelines and NNR23 in the Appendix C (24-26).

Among these indices, the HNFI is the most straight forward, both in terms of the number and variety of components included, as well as the scoring methodology used. The HNFI exclusively incorporates foods considered to be healthy, omitting foods that are recommended for limited consumption. It does not account for nutrients or the ratios between included components such as the BSDS and the NND.

The HNFI comprises six food groups that are part of the recommended healthy diet (depicted in the Appendix C). Regarding the scoring, the cohort median intake of the included components serves as the cut-off in the HNFI which is similar to the methodology used in the original Mediterranean diet score (49). Participants whose intake is above the cohort median for a given food component receive the score of one for that factor. The HNFI comprises six food components, and each component can be assigned a score of zero or one. Consequently, the total possible score ranges from zero to six.

The HNFI was originally designed to explore the relationship between the healthy Nordic diet and mortality within the Diet, Cancer, and Health Cohort study in Denmark (25). The association observed in this study, which indicates that higher adherence to the HNFI is linked to lower all-cause mortality for both women and men, has subsequently been examined in other cohort studies. Roswall et al. found that adherence to the HNFI was associated with lower all-cause- and cancer mortality among Swedish women, although no association was observed with cardiovascular mortality (50). Additionally, a smaller study involving elderly men and women from northern Germany, demonstrated that adherence to the HNFI was associated with lower mortality (51). This finding of lower mortality with high adherence to the HNFI was also observed in a larger cohort within the European Prospective Investigation into Cancer and Nutrition (EPIC) (52).

However, a study that compared the HFNI with a healthy Mediterranean diet score in relation to mortality in Swedish women, suggested that the Mediterranean diet score had an advantage. This might be due to the fact that the Mediterranean score included a broader variety of fruits and vegetables, legumes, fermented dairy products, and use of olive or

rapeseed oil in addition to the HNFI components, and it also takes into accounting the consumption of red and processed meats and alcohol (53).

Building on these results, it appears that adherence to the healthy Nordic diet, as measured by the HNFI, may be beneficial to overall health, much like what has been found in relation with the BSDS and other dietary indices (46, 47, 54). How to interpret the significance of a higher index score for public health, considering the variability in high-scoring component intakes across different cohorts and populations, still remains a challenge.

1.5.2 Non-linearity of food groups in the healthy Nordic diet

The relationship between food and nutrient intakes and the risk of disease is often characterised by a U-shaped curve. This means that both low and high amounts or concentrations can increase the risk of disease compared to an optimal intake level (29).

The optimal intake level of foods in relation to health is typically defined as the consumption level associated with the lowest all-cause mortality, as per the Global Burden of Disease Study (GBD) and WHO guidelines (55). Studies of dietary patterns and mortality with the use of composite diet scores like the HNFI, have not been focusing on determining optimal intake levels, as the objective of these composite measures is quite the opposite—to step back from the details in order to capture a broader view.

However, the use of cohort-defined cut-offs which may be unrelated to optimal intake levels in the construction of the HNFI may partly explain why adherence to the index has not consistently demonstrated effective in relation to disease prevention. Studies have shown no significant relationship between high adherence to the HNFI and reduced risk of metabolic syndrome, cardiovascular disease (CVD), colorectal cancer, breast cancer, or type 2 diabetes in certain populations (56). Similarly, in Swedish women, adhering to the HNFI no association with lower risk of CVD (57), colorectal cancer (58), or breast cancer was observed (59). Additionally, a study within a nested Swedish cohort observed no association between metabolites, used as biomarkers for a healthy Nordic diet as measured by the HNFI, and risk of developing type 2 diabetes (60). Conversely, among Danish women, higher adherence to the HNFI has been linked to a lower risk of stroke (61), colorectal cancer (62), and lower risk of type 2 diabetes in women (63).

When looking at the individual food groups in the HNFI, the Danish cohort study found that only a higher intake of the whole grain rye bread (≥63 g/day) component of the HNFI was linked to lower mortality in Danish men, while in Danish women, only greater consumption of cabbages (≥16 g/day) and root vegetables (≥29 g/day) was associated with lower all-cause mortality (25). In the Swedish cohort, only the intake of the whole grain bread component above the cohort's median was associated with lower mortality in women (50). Yet, qualifying for higher adherence to the HNFI, does not necessarily require an increased intake of the foods that are individually associated with lower mortality, except at the maximum index score. Consequently, the risk estimates derived from such analyses comparing high versus

low adherence category for instance could reflect different combinations of HNFI components, and a score of 3 could represent two distinct dietary patterns.

This inconsistency in results related to the HNFI could possibly be related the hypothetical scenario illustrated in Figure 4. If the relationship between the food groups included and all-cause mortality follows a non-linear curve—indicating that both low and high levels of intake are associated with increased mortality—a positive score on the HNFI could encompass individuals at both lower and higher risk of mortality. Consequently, this would not accurately reflect the optimal impact of the healthy Nordic diet on mortality.

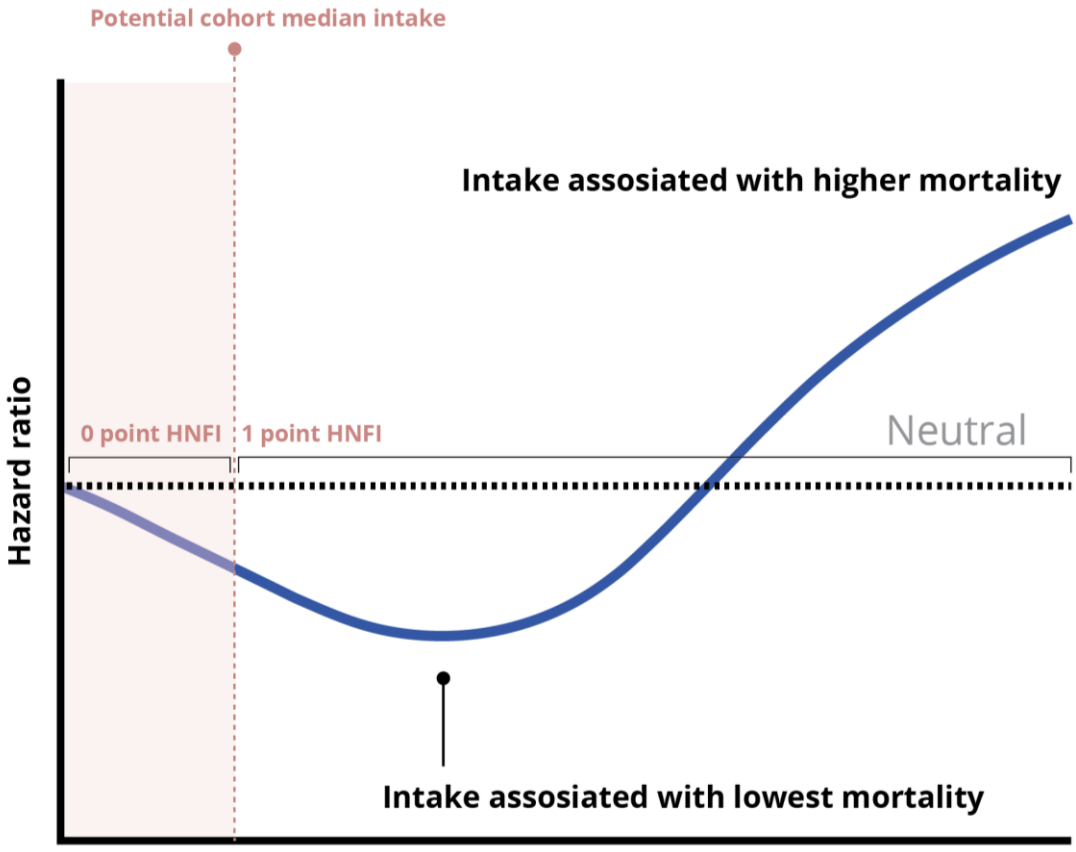


Figure 4 Hypothetical scenario of a non-linear association between food group intake and mortality in relation to the cohort median value

By Kari Wagelid Grønn

In a systematic review and meta-analysis of prospective studies, non-linear associations were observed between the consumption of fruits, vegetables, nuts, and dairy products and all-cause mortality (64). The study estimated that the impact of optimal consumption of whole grains, vegetables, fruits, nuts, legumes, and fish, and a reduced intake of red and processed meats, was associated with an 80% reduction in the relative risk of premature mortality (64). The study concluded that choosing optimal intake levels of food groups can have a significant impact on reducing the risk of premature mortality, with no additional mortality benefit observed beyond this point (64). Furthermore, it was underlined that the most effective

approach in a public health perspective, is to analyse food groups rather than nutrients, and to establishing optimal intake levels in relation to all-cause mortality (64).

The optimal intake levels of healthy Nordic food groups in the context of a healthy Nordic diet in Nordic populations is not well understood.

1.5.3 Towards a healthy Nordic diet

The updated NNR2023 guidelines suggest a further reduction in the consumption of meat, including poultry, to a maximum of 350 grams per week, down from the previously advised 500 grams for red and processed meat, for both health and environmental reasons (65). Thus, NNR2023 promotes a significant shift away from the current consumption levels of red and processed meat towards other dietary sources with a more favourable nutrient composition to maintain a stable energy intake (65). However, there is a lack in evidence to determine which protein sources should replace meat in order to inform public health guidelines (65).

Fish, of which it is recommended to increase the consumption, stand out as a suitable replacement offering not only high-quality proteins but also essential micronutrients like vitamin A, zinc, selenium, and vitamin B12. Fatty fish provides essential omega-3 fatty acids and vitamin D, while lean fish is a primary source of iodine in the Norwegian diet, potentially reducing the risk of suboptimal iodine intake among women in Norway.

A meta-analysis of prospective studies concluded that substituting red and processed meat with total fish was associated with lower all-cause mortality, although it did not significantly impact the incidence of CHD (66). The potential health impacts of replacing red and processed meat with lean or fatty fish are however, not documented well in the research. Additionally, there is a lack of clarity regarding the effects of unprocessed red meat consumption on mortality within the Nordic population (65). The health outcomes associated with the consumption of fatty versus lean fish also remain unclear (67).

Contrary to the guidelines proposed by NNR2023, the trends in meat and fish consumption over the past century have moved in the opposite direction in Norway. There has been a notable increase in meat consumption, which has increased from 28 to 60 kilograms per capita per year. While, fish consumption has declined, from 26 to 12 kilograms per capita per year (35). To gain deeper insights into how shifting from the current high-meat diet towards the healthy Nordic diet might influence mortality, specified substitution analyses serve as a viable alternative when dietary interventions are not feasible.

2 Rationale and aims of the thesis

The existing literature on healthy Nordic diets and longevity is constrained by the reliance on a priori constructed food indices that provide a broad understanding of the healthy Nordic diet and health. Data-driven analyses of dietary patterns in the Nordic countries suggest that while similar dietary patterns exist across Scandinavian countries, they may reflect subtle cultural differences, pointing to a need for country specific analyses (68).

There is a knowledge gap on the unique contributions of individual food groups that are integral to healthy Nordic diets and their associations with mortality, as well as the impact on mortality of replacing meat with alternative protein sources in such diets given that processed meat is a significant component of dietary patterns in the Nordic countries.

The overall aim of this thesis was to explore adherence to the healthy Nordic diet measured with the HNFI, and to explore the association between food groups part of the healthy Nordic diet and all-cause mortality using data from NOWAC. Additionally, the thesis aimed to investigate the potential benefits of changing towards a healthy Nordic diet by replacing red and processed meats - which are typically linked to the unhealthy part of the dietary pattern in Norway - with either lean or fatty fish, both of which are known for their health-promoting properties in the healthy Nordic diet.

The specific objectives of this thesis were:

- To assess adherence to the HNFI, and to explore dietary composition and lifestyle factors associated with adherence to the index
- To evaluate the potential non-linear associations between food groups part of a healthy Nordic diet and all-cause mortality
- To examine the impact of replacing red and processed meat with lean and fatty fish on all-cause and cause specific mortality

By addressing these objectives, this thesis aims to contribute to the current understanding of healthy Nordic diets and their potential as a sustainable approach to address public health challenges with NCDs.

3 Material and Methods

The results included in this thesis are based on a cross-sectional analysis (Paper I) and two prospective cohort studies (Paper II and Paper III), with data derived from NOWAC.

3.1 The Norwegian Women and Cancer study

The Norwegian Women and Cancer (NOWAC) study is a nationwide prospective cohort comprising over 170,000 participants and has previously been described in detail by Lund et al. (69). In brief, it was initially established with the aim of providing unique opportunities to conduct epidemiological cancer research in Norway. Including a national representative sample of women randomly selected from the Norwegian Central Population Registry, NOWAC provides external validity for estimating relative risks and attributable risks which is of interest to public health (70).

Recruitment for the study occurred in batches between 1991 and 2007. Participants completed a self-administered questionnaire on various factors such as hormonal and reproductive history, smoking and alcohol consumption, tanning habits, socio-economic status, height and weight, physical activity, participation in mammography screening, family history of breast cancer, other illnesses, and self-reported health. Follow-up questionnaires were sent to some participants, and most of the questionnaires included four pages of food frequency questions.

3.1.1 Study sample

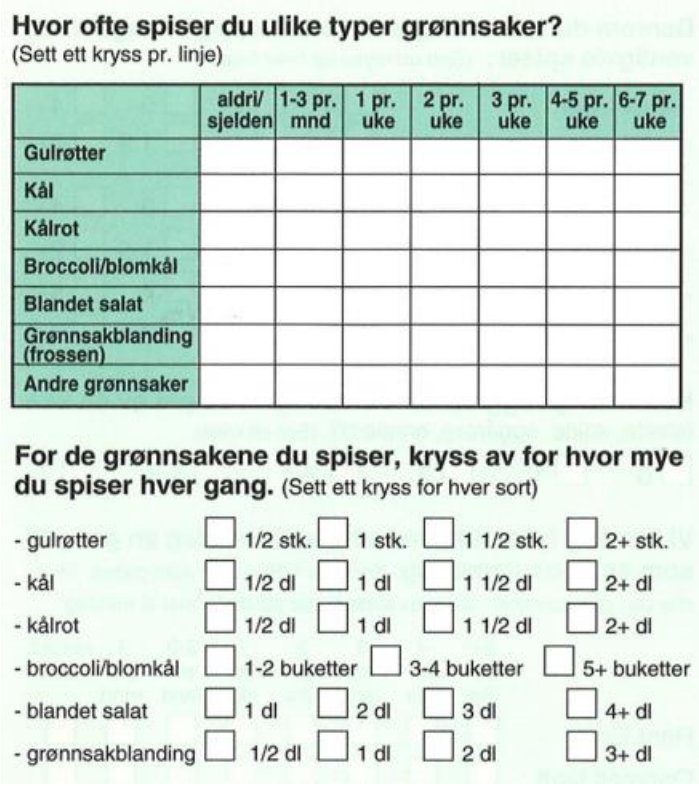
The baseline data for this thesis comprises the first mailings of the NOWAC study from 1996 to 1997 and 2003 to 2004, and the second mailing from 1998 to 1999 of participants enrolled in 1991 to 1992 who had not received a FFQ questionnaire at enrolment. The response rates for the first and second mailings were 57% and 81%, respectively, with a total of 101 321 women between the ages of 41 to 76 completing questionnaires that included the food frequency questions. After the publication of Paper I, five women withdrew from the NOWAC study, leaving 101,316 women eligible for inclusion in the last two papers.

In Paper I, after excluding participants with implausible energy intake, missing information on the HNFI components, and missing values on important covariates, our analyses included a total of 81 516 participants. In Papers II and III, we excluded those with zero follow-up time, implausible energy intake and missing values on important covariates resulting in a final sample of 83 669 participants in Paper II and 83 304 in Paper III. In Paper III, non-consumers of processed meat, of unprocessed red meat and of red and processed meat combined were excluded for the respective specified substitution analyses resulting in a study sample of 81 374 for processed meat, 77 597 for unprocessed red meat and 82 245 for red and processed meat combined.

3.2 Exposures

Dietary assessment

We evaluated dietary patterns and Nordic food groups through semi-quantitative Food Frequency Questionnaires (FFQs) designed to reflect the typical dietary habits of Norwegian women over the previous year, with special attention to traditional food items and fish intake. The FFQs provided participants with predetermined frequencies and portion sizes, using checkboxes for response alternatives with 4-7 frequency options. For certain food items, it was also inquired about usual serving sizes, with participants indicating their typical consumption in natural units (Figure 5).



Hvor ofte spiser du ulike typer grønnsaker?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd	1 pr. uke	2 pr. uke	3 pr. uke	4-5 pr. uke	6-7 pr. uke
Gulrøtter							
Kål							
Kålrot							
Broccoli/blomkål							
Blandet salat							
Grønnsakblanding (frossen)							
Andre grønnsaker							

For de grønnsakene du spiser, kryss av for hvor mye du spiser hver gang. (Sett ett kryss for hver sort)

- gulrøtter ☐ 1/2 stk. ☐ 1 stk. ☐ 1 1/2 stk. ☐ 2+ stk.
- kål ☐ 1/2 dl ☐ 1 dl ☐ 1 1/2 dl ☐ 2+ dl
- kålrot ☐ 1/2 dl ☐ 1 dl ☐ 1 1/2 dl ☐ 2+ dl
- broccoli/blomkål ☐ 1-2 buketter ☐ 3-4 buketter ☐ 5+ buketter
- blandet salat ☐ 1 dl ☐ 2 dl ☐ 3 dl ☐ 4+ dl
- grønnsakblanding ☐ 1/2 dl ☐ 1 dl ☐ 2 dl ☐ 3+ dl

Figure 5 Example from the NOWAC FFQs regarding questions on vegetable consumption and portion sizes

Standard portion sizes and weights from the Norwegian Weight and Measurement Table (71) was used to translate these food item intakes into grams. The energy and nutrient content of the foods were sourced from the Norwegian Food Composition Database (72).

The daily consumption of food items, along with their energy and nutrient contributions was calculated, using a specialized SAS statistical syntax developed by the Department of Community Medicine at the University of Tromsø, specifically for NOWAC.

In instances of missing data, conservative assumptions were employed: unreported frequencies were interpreted as non-consumption, and absent portion sizes were defaulted to

the smallest option provided. For composite question like apples/pears, we generated single food item amounts by applying frequency weights derived from a 24-hour dietary recall study conducted within the NOWAC cohort (73).

This thesis examines the HNFI and four key food groups that are representative of a healthy Nordic diet. It is important to note that these food groups do not cover the entire range of foods that comprise the healthy Nordic diet, rather our analyses were based on the information collected and available from the FFQs in the NOWAC study as visually illustrated in Figure 6.

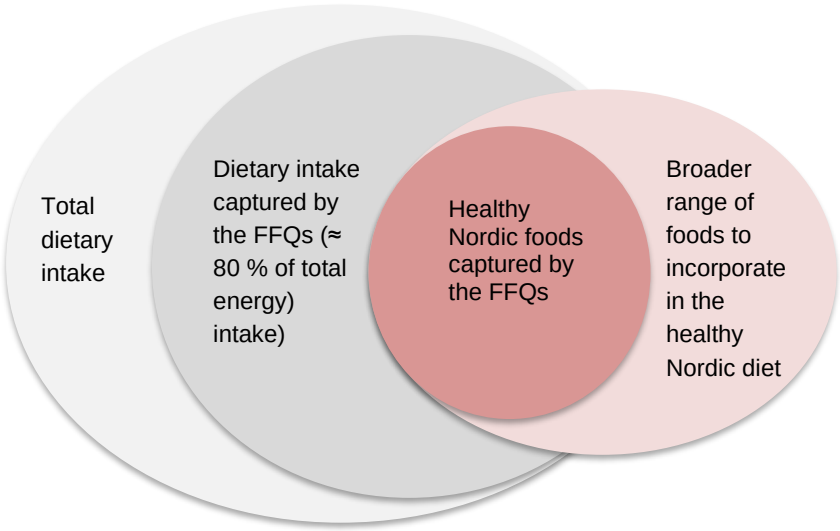


Figure 6 The FFQs coverage of foods included in the healthy Nordic diet in this thesis. The sizes of the circles are not in proportion to the actual coverage

The included food groups which are essential components of the healthy Nordic diet include fish, whole grain products, Nordic fruits and vegetables and low-fat dairy products. The last two papers provide further subdivision for fish, distinguishing between lean and fatty subtypes, while the first paper subdivides Nordic fruits and vegetables into three overarching subgroups: root vegetables, cabbages, and apples/pears.

Although dairy products are an important part of a Nordic diet, they have not consistently been included in analyses of a healthy Nordic diet due to a weaker or less certain association with positive health outcomes (74). However, low-fat milk is included in the BSDS and was deemed an important food group to include in this project on Nordic diets (54).

Lastly the fifth food group examined in this thesis was red and processed meat, which constitutes a significant component of the diet in Norway (20). Table 1 gives an overview of the foods included as exposures in the thesis.

Table 1 Food items included as exposures in the thesis, number of frequency questions in the FFQs used to calculate intake and variable handling

Food items (total number of frequency questions in FFQs	**Number of frequency questions in FFQs**	**Description of FFQ questions**	**Paper I**	**Paper II**	**Paper III**
			Variable handling (gram per day)		
Fish (14)	Lean fish (6) *	Poached Cod/pollock/ Saithe Fried Cod/pollock/ Saithe Catfish/flounder/redfish	Dichotomized by cohort median	Continuous Categories: < 15, 15-29, 30-44, ≥30	Continuous per 20-gram increment
		Processed: Fishcakes Fishfingers Tinned tuna			
	Fatty fish (6) *	Salmon/trout Mackerel Herring	Dichotomized by cohort median	Continuous Categories: < 5, 5-14, 15-29, ≥30	Continuous per 20-gram increment
		Processed: Mackerel in tomato/smoked Salmon, smoked/cured, Herring/anchovies			
	Fish spread (2)	Caviar* Other fish spread*			
Fruits and vegetables (6)	Root vegetables (2) *	Carrots Swede	Dichotomized by cohort median	Continuous Categories: < 100, 100-199, 200-299, ≥300	
	Cabbages (2) *	Cabbage Broccoli/cauliflower	Dichotomized by cohort median		
	Apples/pears (1)	Apples/pears	Dichotomized by cohort median		
	Mixed frozen vegetables (1) *	Frozen vegetables (typically a mix of carrots, broccoli, and cauliflower)			
Whole grain products (2)	Whole grain bread (1)	Whole grain bread	Dichotomized by cohort median	Categories: < 60, 60-119, 120-179, ≥180	
	Breakfast cereals (1)	Cereal/oatmeal/muesli	Zero intake/any intake		
Dairy (3)	Skimmed milk (1)	Skimmed milk (0,1% fat)		Continuous Categories: Non-consumers, < 200, 200-399, ≥400	
	Semi skimmed milk (1)	Skimmed milk (1-1,5 % fat)			
	Yoghurt (1)	Yoghurt (0-3 % fat)			
Red meat and processed meat (6)	Red unprocessed meat (3)*	Beef			Continuous per 20-gram increment
		Chops			
		Roast			
		Sausages/ wiener sausages			

Food items (total number of frequency questions in FFQs	Number of frequency questions in FFQs	Description of FFQ questions	Paper I	Paper II	Paper III
			Variable handling (gram per day)		
	Processed meat Sausages (3) *	Meatballs/hamburgers			Continuous per 20-gram increment
		Sandwich meat, liver pate			

* Separate portion size question in the FFQs

3.2.1 The healthy Nordic food Index (Paper I)

In Paper I, the HNFI, developed by Olsen et al., was applied to examine the dietary patterns of the NOWAC study participants (25). The purpose of the HNFI is to provide a composite measure that reflects the degree to which an individual's diet aligns with the criteria of the healthy Nordic diet. Figure 7 illustrates how the HNFI was applied in NOWAC.

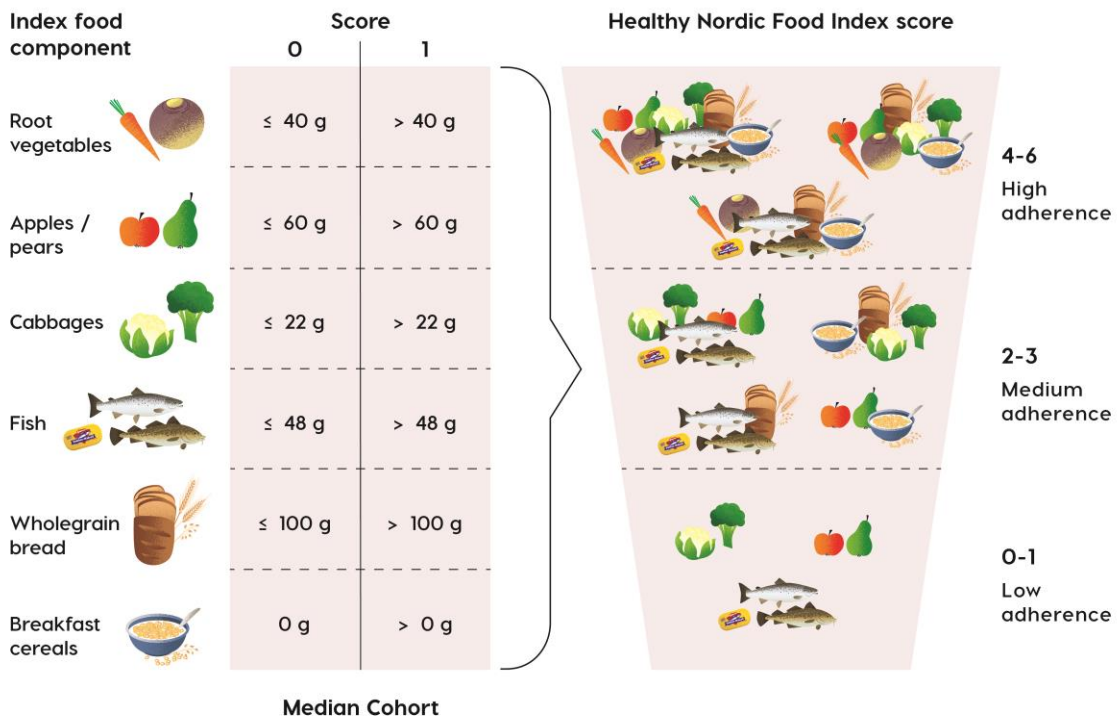


Figure 7 Construction of the HNFI in NOWAC

To compute the index score for each participant, the intake of each food item included in the index-fish, root vegetables (carrots and swede), cabbages (cabbage, broccoli/cauliflower), apples/pears, whole grain bread, and breakfast cereals- was divided by the cohort median. Participants who had intakes above the cohort median were assigned the score of 1, while those who consumed equal to or less than the cohort median were assigned the score of 0. For

breakfast cereals, where the median consumption was 0, the score of 1 was assigned to all participants who consumed any amount of breakfast cereal. Finally, the scores assigned for the six food groups were summed up to obtain a score ranging from 0 to 6. Participants with scores of 0-1 were classified as low adherers, those with scores of 2-3 were classified as medium adherers, and those with scores of 4-6 were classified as high adherers (Figure 6).

3.2.2 Healthy Nordic food groups (Paper II)

The objective in Paper II was to analyse the full intake range within each food group exposure, moving beyond the binary categorization used in the calculation of the HNFI, to assess the association between central components of the healthy Nordic diet and all-cause mortality. The aim was to evaluate the influence of these food groups on all-cause mortality within the context of a healthy Nordic diet and to investigate the relationship between different levels of intake and all-cause mortality allowing for non-linear associations.

We investigated the impact of the healthy Nordic food groups - lean fish, fatty fish, Nordic fruits, and vegetables (including root vegetables, cabbages, mixed frozen vegetables, and apples/pears), and low-fat dairy products- as continuous variables, measured in grams per day, and as categorical variables. Whole grain products (including whole grain bread and breakfast cereals) were only analysed categorically, as it could not be included as a continuous variable (Table 1).

Our analysis was particularly focused on investigating the potential differences in mortality associated with the consumption of lean versus fatty fish. To this end, we concentrated on pure fish foods that were free from other ingredients and could be clearly identified as either lean or fatty fish. Consequently, we separated the fish component of the HNFI into two distinct categories. We excluded fish spreads from our analysis due to their potential mixture with non-fish ingredients, such as tomatoes in mackerel in tomato sauce. Additionally, we omitted items like caviar and "other fish" that do not fit into the categories of lean or fatty fish.

To assess Nordic fruits and vegetables as a continuous exposure, we combined root vegetables, cabbages, and apples/pears, including mixed frozen vegetables that typically consist of carrots (a root vegetable element of the HNFI), broccoli, and cauliflower (the cabbage elements of the HNFI) into a singular exposure.

Moreover, we incorporated low-fat dairy products as an additional food group beyond what is included in the HNFI for our analysis.

3.2.3 Red and processed meat and lean and fatty fish with inclusion of processed fish, for specified substitution analyses (Paper III)

The primary objective of the final paper was to assess the impact of substituting a perceived unhealthy component of the typical Norwegian diet with food components that is part of the

healthy Nordic diet. In line with this aim, we included red and processed meat as a food group in the examination of the healthy Nordic diet.

Consistent with the approach in Paper II, we also analysed lean and fatty fish as distinct exposures in Paper III. However, to supplement the analyses from Paper II, we integrated processed fish into the lean and fatty fish categories in these analyses. This approach enabled us to investigate the association between lean and fatty fish consumption in accordance with the recommendations set forth in our dietary guidelines which includes processed fish (29). We did not include red and processed meats or lean and fatty fish that were part of mixed dishes such as soups and stews in our analyses. Table 1 provides a detailed summary of the food items included.

In Paper III, red and processed meat were analysed both individually and as a combined exposure. The meat and fish variables were treated as continuous exposures, with the analyses conducted in increments of 20 grams per day for individual exposure assessments, and 20 grams was used as the unit of substitution. The unit of 20 grams were chosen as this amount roughly equates to a serving size of meat or fish typically used on bread. Similarly, when evaluating the potential associated impact of replacing red and processed meat with equivalent servings of lean or fatty fish, the substitutions were quantified in 20-gram per day (Figure 8).

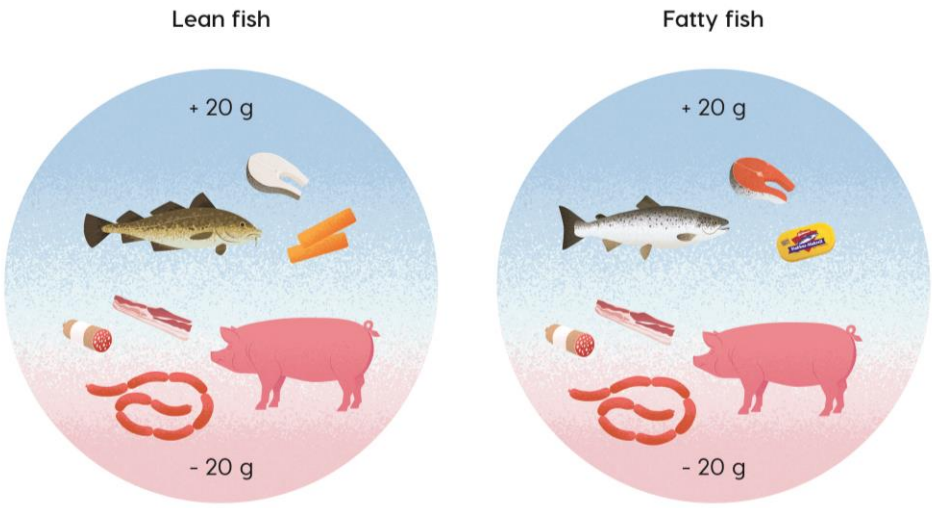


Figure 8 Exposures for specified substitution analyses of one unit increased lean or fatty fish and one equivalent unit reduced red or processed meat

3.3 Outcomes

The outcome of interest in Paper II and Paper III was mortality, including all-cause mortality and death attributed to cancer, and CVDs (ischemic heart disease (IHD) and stroke)), which are major subtypes of CVDs associated with atherosclerosis.

Mortality outcomes were classified according to the International Classification of Diseases, 10th Revision codes (ICD-10), including malignant neoplasms at all sites (C00-C97), IHD (I20-I25), and stroke (I60-I69). NOWAC study participants' death records were obtained by linking their unique personal identity number to the Norwegian Cause of Death Registry.

In Norway, the quality of the register data is high, with extensive coverage indicating that the register covers a large proportion of the population. Additionally, the completeness of the register, which refers to the registers ability to attain information about the individuals included, is good. Overall, the Norwegian Cause of Death Registry contains medical information on more than 98% of the deaths (75).

3.4 Covariates

Other variables considered in the analyses are described in the following.

Sociodemographic covariates

Information regarding participants' age (in years) was sourced from the National Population registry of Norway. Educational attainment was based on the self-reported number of years of schooling completed. In Paper I the region of residence within Norway was segmented into six regions: Oslo (the capital), East, South, West, Middle, and North. In the last two papers information on region of residence was omitted due to anonymisation of data.

Physical activity

The physical activity was estimated from self-reported data, where participants were asked to rate their current level of physical activity on a scale from 1, specified as "very low", to 10, meaning "very high". This scale accounted for physical activity at home, work, exercise, and walking. It has previously been validated as a reliable method for ranking physical activity levels among adult Norwegian women (76).

Smoking

The smoking variable was calculated using responses to questions about participants' smoking history, including whether they had ever smoked and if they were current daily smokers, and information about smoking intensity in five-year or ten-year periods. Those who reported they had smoked but were not current smokers were classified as former smokers. The intensity of smoking among former or current smokers was considered in Paper II and III and was assessed based on the age at which participants began smoking and their cumulative exposure measured in pack-years. Pack-years were determined by dividing the daily number of cigarettes smoked by 20 (the typical number of cigarettes in a pack) and then multiplying by the total number of years the individual had smoked.

Body mass index

Body Mass Index (BMI), expressed in kilograms per square meter (kg/meters^2), was calculated using self-reported weight (in kg) and height (in cm). Self-reported measures of

weight and height have been shown to be a reliable means of ranking BMI among middle-aged Norwegian women (77).

Type 2 diabetes (Paper III)

Information on the prevalence of type 2 diabetes was self-reported and collected from the lifestyle questionnaires. Participants were asked whether they have been diagnosed with diabetes (yes), and missing values were treated as no. The questionnaire did not distinguish between different types of diabetes, but a previous validation study found that 89.4 % of the diabetes cases that were identified were type 2 diabetes (78).

Dietary factors

Total energy intake, alcohol consumption (grams/day), and intake of other foods (grams/day) was captured through the FFQs which has been described more in detailed in section 3.2.

Subcohort

The FFQs have been slightly modified over the years in response to new hypotheses, the introduction of new food products, and the withdrawal of others from the market over the nearly 10-year period of data-collection. The number of items in the FFQ have broadly ranged between seventy to ninety frequency questions, resulting in minor variations between different versions of the FFQ (79). For stratification purposes, those FFQs completed within closer chronological proximity were grouped into five categories. These groups, or subcohorts, were included as a stratification variable in the statistical analyses.

3.5 Statistical analyses

For Paper I, the focus was on descriptive analyses based on cross sectional data, whereas Papers II and III involved time-to-event analyses to explore the relationship between Nordic food groups consumption, as well as substitution of food groups within the Nordic diet and mortality outcomes. We defined a statistically significance threshold of 5% ($p < 0.05$) in all papers. All statistical analyses were performed using Stata/MP software, version 14.0 (Paper 1) and version 16.0 (Papers II and III).

3.5.1 Cross-sectional analyses (Paper I)

To gain a better understanding of the overall diet in relation to adherence to the HNFI-score, Paper I analysed both the absolute intake, as well as energy-standardised intake, of certain non-index foods and nutrients. These dietary factors included the intake of macronutrients (protein, carbohydrates, total fat, polyunsaturated fatty acids, monounsaturated fatty acids, saturated fatty acids, trans-fatty acids, and alcohol) as percentages (E%) of the total energy intake.

Non-index foods included other fruits and vegetables (oranges, bananas, other fruits, tomatoes, salad greens, mixed vegetables, and other vegetables), dairy products, red and processed meat, white meat (chicken), and potatoes. Nutrients included sodium, added sugar,

fibre in addition to some essential micronutrients like vitamin D, folate, selenium, zinc, and iron. The micronutrient intakes were compared to the average requirement (AR) (18).

The AR represents the daily nutrient intake level estimated to meet the needs of half the individuals in the general population. It is commonly used as a measure to determine whether the nutrient intake within a group is adequate. The AR is used to calculate the recommended intake level, which is the average intake estimated to meet the needs of 97.5 % of the population (18).

Non-parametric trend tests

The non-parametric Jonckheere-Terpstra test (referred to as the nptrend test in Paper I) was used to analyse trends across ordered groups. Specifically, it was applied to investigate trends in the consumption of food groups included in the HNFI, as well as non-index foods and nutrients, across levels of adherence to the HNFI. The lowest level of adherence was used as reference group. This test was also applied to the energy-standardised intake of non-index foods and nutrients, and to evaluate participant characteristics such as age, education, BMI, physical activity, and smoking status across the adherence categories.

Multinominal logistic regression

While the Jonckheere-Terpstra test is used to test for trends across ordered adherence categories, multinominal logistic regression allows for the estimation of effect sizes. The regression method is appropriate when the dependent variable includes three or more categories. It was applied to calculate the Relative Risk Ratios (RRRs) and 95 % CI for various participant characteristics. The coefficients represent the "risk" of being in a specific adherence category relative to the reference category, per one-unit increase in the predictor variables.

The lowest adherence category was defined as reference group. We applied two distinct regression models estimating the associations between adherence categories of the HNFI and the participants age, education, BMI, physical activity levels, smoking status, and region of living. The partially adjusted model was adjusted for total energy intake (continuous), age (segmented into four categories: 41-50, 51-60, 61-70, 71-76 years), and subcohorts (n=5). The fully adjusted model additionally included education (<10, 10-12, >12 years of schooling); BMI (< 20, 20–24.9, 25–29.9, ≥ 30 (kg/m^2)); Physical activity levels (low, moderate, high); smoking status (never, former, current) and region of living (Oslo, East, south, West, Middle, North).

3.5.2 Cox proportional hazards regression models (Papers II and III)

To model time-to-event (death from any cause in Paper II, and death from any cause, death due to CVDs or cancer in Paper III) we used Cox proportional hazards regression models to estimate hazard ratios (HRs) with 95% confidence intervals (CI), using age as the time metric. Participants were tracked until they died, emigrated, or until the study ended (December 2018 for Paper II; December 2019 for Paper III). The proportional hazards assumption was mainly

evaluated by Schoenfeld residuals, and visually using log-log plots. The selection of covariates for inclusion in the analyses was based on existing literature. Variables that were thought to be common causes of both the exposures and the outcomes were included in our main models. This identification was guided using Directed Acyclic Graphs (DAGs) which graphically illustrates causal relationships between variables (80).

3.5.2.1 Adjustment models

In Paper II, we identified the fully adjusted model as the main model for estimating the association between healthy Nordic foods and all-cause mortality. However, in paper III we considered the model which controlled for confounders, but was not fully adjusted, as the main model. The rationale for this choice was that the fully adjusted model, which also controlled for other foods and variables that might act as potential mediators or confounders, did not significantly alter the estimates. Therefore, we opted for the parsimonious model for simplicity.

Age, which was the underlying time metric, and subcohorts (divided into 5 categories) were controlled for in all models. Subcohorts were incorporated in the models as a strata variable, which allows the hazard to vary over the subcohort categories, while maintaining a consistent estimation of the exposure across all subcohort categories. In Paper III energy intake (continuous) was included in all models, while in Paper II energy intake was included in the fully adjusted model.

The fully adjusted model in Paper II, and the main model in Paper III adjusted for physical activity (categorized as low (≤4), moderate (5–6), or high (≥7)), smoking categorized as never smokers; current heavy smokers who started smoking before the age of 20 and with 20 or more pack-years; current moderate smokers who started smoking before the age of twenty with 0-19 pack-years; current smokers late starter (women who started smoking after the age of 20), former smoker early starter (smoking initiation before the age of 20), and former smoker late starter (smoking initiation after the age of 20)), and alcohol intake (categorized as non-consumers; low consumers (0–5 gram/day) and higher consumers (> 5 gram/day)). Education was controlled for in both papers but were divided in three groups in Paper II (< 10, 10–12, > 12 years of schooling), and in four groups in Paper III (7–9, 10–12, 13–16 and ≥ 17 years of schooling).

Additionally in Paper II, the fully adjusted model also controlled for BMI groups (< 20, 20–24.9, 25–29.9, ≥ 30 (kg/m^2)), and processed meat which was divided into four categories (< 15, 15–29, 30–44, ≥ 45 g/day).

The fully adjusted model in Paper III additionally controlled for fruits and vegetables, dairy products, whole grain products, refined grain products, potatoes (continuous), BMI groups (< 20, 20–24.9, 25–29.9, ≥ 30 (kg/m^2)) and diabetes (yes/no).

3.5.2.2 Linear trend over categories (Paper II)

To test for a potential linear trend over consumption categories of the healthy Nordic foods in relation to all-cause mortality, a new variable was created by assigning the median intake value of each category to all participants within that category. Consequently, the estimated associations derived from these analyses remains constant for all consumption levels within each category, which gives a limited insight to the relationship across the entire range of consumption. To gain a more comprehensive understanding of these associations, we conducted subsequent analyses, maintaining the exposure variables as continuous measures, using Restricted Cubic Splines (RCS) described in section 3.5.2.4.

3.5.2.3 Interaction

Interaction terms were explored with a careful approach to avoid models that are overly complex. To test for interactions, we included interaction terms in the statistical models and evaluated the fit of models with and without these terms using likelihood-ratio tests. In Paper II, we examined potential interactions between smoking status and the Nordic food groups based on previous research on dietary patterns in NOWAC (81). Interaction terms were tested in the mutually adjusted categorical models. If the inclusion of the interaction term resulted in a model that fitted the variability in the data better- as evident by a significant likelihood-ratio test- we conducted separate analyses for ever smokers and never smokers.

3.5.2.4 Restricted cubic splines (Papers II and III)

The default assumption in regression models is linear associations, although this is often not the case in the relationships between nutrients/foods and health. To explore the potential for non-linear relationships across various consumption levels of healthy Nordic food groups (Paper II), as well as lean fish (including products with non-fish ingredients), fatty fish (including products with non-fish ingredients), and red and processed meat (Paper III) in relation to mortality outcomes, we used RCS to model the exposures in these studies.

When linearity between exposure and outcome is uncertain, splines offer a flexible method to model the association by transforming the exposure variable into piecewise non-linear functions. Within each interval, a separate curve is fitted by cubic polynomials, while the overall curve connects smoothly at the intersection points known as knots. Linear functions are applied before the first and after the last knot, enhancing the model's performance with extreme data values. The number of knots determines how many intervals the exposure variable is divided into. It is recommended to determine the position of the knots by percentiles (82). The number of knots can be chosen based on the Akaike information criteria (AIC), which is a measure based on goodness of fit (82). Models with the lowest AIC score are indicative of a better fit to the data, as they effectively balance model complexity with goodness of fit.

In our analyses, the placement and number of knots were determined based on percentiles, and by evaluating models with varying numbers of knots using the AIC. We compared

models with five, four, and three knots, selecting the model with the lowest AIC value to avoid overfitting. The models with three knots provided the best fit for our data, with knots placed at the 10th, 50th, and 90th percentiles.

We evaluated potential non-linear associations by visually examining plots that display the spline and tested it statistically by the Wald test. The Wald test assesses whether the inclusion of higher-level polynomial functions of the spline intervals provides a statistically significantly better fit compared to its linear components. If the Wald test is statistically significant, the null hypothesis of linearity is rejected, which supports that the relationship is non-linear.

3.5.2.5 Specified substitution analyses (Paper III)

Ibsen et al. describes two main statistical methods for examining changes in dietary composition with substitution models (83). When adjusted for total energy intake, the first, a non-specified substitution model (standard single food group analyses), assesses the impact of increasing consumption of a food of interest, without identifying which foods are reduced. This approach was utilised in Paper II. The second, a specified substitution model, which was applied in Paper III, investigates the associations of specific changes in dietary composition-increasing intake of lean or fatty fish while reducing red or/and processed meat consumption within a stable energy intake.

The specified substitution model can be executed using two equivalent methods. We adopted the "Leave one out" method, which involves including a composite variable that includes the target exposures (lean fish, fatty fish, and red and processed meat), along with other related food groups such as other types of fish and meats (e.g., white meat). All food groups included in the composite variable, except the one being substituted, are additionally included as single exposures in the Cox regression models. Alternatively, one could include all these food groups in the Cox regression models and determine the estimate for substitution by subtracting the beta coefficients of the foods being replaced.

Specified substitution analysis can be conducted as a between-person comparison using cross-sectional data (Paper III), or within individuals using repeated measurements. The estimated HR can be interpreted as the combined risk of dying within the study period, associated with a dietary shift towards more lean or fatty fish and away from red or processed meat, while maintaining the same energy intake.

In our analyses, substitutions were defined in terms of food weight, replacing 20 grams per day of red or/and processed meat with an equivalent weight of lean or fatty fish. This approach simplifies the interpretation from a public health standpoint but does not account for the residual energy difference in the model. For example, substituting 20 grams of processed meat with 20 grams of lean fish may result in a substantial energy discrepancy, as the caloric content of processed meat is higher than that of lean fish. This unaccounted energy must then be compensated for by other foods not controlled for. If the substitution unit was defined by

energy content, the model would estimate the impact of replacing an amount of red and processed meat with a certain energy content with an amount of lean or fatty fish of corresponding energy content, thus eliminating any residual energy differences.

3.5.2.6 Sensitivity analyses

We performed several sensitivity analyses to test the robustness of the results from our main analyses.

Firstly, to address concerns of reversed causation, which occurs when an outcome influences or precedes the exposure rather than the exposure preceding and influencing the outcome. This concern is relevant to Papers II and III, where there is a possibility that participants may have changed their eating habits due to an illness that led to them dying. Consequently, the food intake captured in the FFQs might reflect changes made in response to an illness that ultimately led to death, rather than the diet influencing the risk of illness and mortality. To reduce the risk of reversed causation, we started follow-up for all participants two years after baseline assessment and enrolment in the study. This approach ensured that participants who died or emigrated within the first two years of the study were excluded, thereby reducing the likelihood that reaction to early symptoms influenced the risk estimates.

Secondly, the underlying understanding is that the foods consumed affects ones BMI status, and BMI status subsequently influence mortality. In this scenario BMI is in the causal pathway between dietary intake and mortality outcomes, potentially serving as a mediator- where the food intake influences BMI, which in turn affects mortality (food intake → BMI → mortality). However, when BMI status and food intake are measured at the same timepoint, body size, measured by BMI in these studies, is a significant determinant of energy requirements, and since energy requirements influence the amount of food consumed, the relationship could also be in the other direction where food intake and mortality are both influenced by BMI, making BMI a confounder or a common cause of the exposure and the outcome (food intake ←BMI→ mortality).

The interpretation of these causal pathways between diet, BMI and mortality outcomes dictates whether BMI is included in the statistical models as a potential confounder or omitted because it is considered a mediating factor between diet and mortality. In Paper II, BMI was included as a potential confounder in the fully adjusted model, and a sensitivity analysis was conducted to assess the impact of excluding BMI. In Paper III, BMI was included as a covariate in the fully adjusted model for the main analyses but was not included in the model presented as the main model.

Due to concerns of missing data among covariates which can bias the results, we conducted multiple imputation in Paper III. Assuming that data was missing at random, we used multiple imputation by chained equations (84, 85). The missing values were imputed for several covariates including education, physical activity, smoking status, height, and weight. We used predictive mean matching for continuous variables and ordinal or nominal regression for

categorical variables. The imputed missing values were based on observed values from twenty duplicated datasets.

3.6 Ethical considerations

The NOWAC cohort has been granted approval for the collection and secure storage of questionnaire data. All data are stored and managed in accordance with the authorization granted by the Norwegian Data Protection Authority with reference number 07-00030. Participants gave informed consent, for the collection and storage of data, and for linkage to the Norwegian Cause of Death Registry, the Cancer Registry of Norway, and the Mammography Registry of Norway. The ethical approval for the NOWAC cohort was secured from the Regional Committee for Medical and Health Research Ethics in Norway (REK) with reference number P REK NORD 01/2003. This project is based on the ethical approval obtained in 2003, before the introduction of General Data Protection Regulation. Therefore, there are no separate approval from REK for this project. All women received information on the right to withdraw (70).

3.7 Language improvements

To enhance the language and readability of this text, I have used Google Translate and received proofreading and advice from colleagues at the department. Additionally, the AI tool ChatUiT, powered by the language model ChatGPT 3.5 Turbo, was used solely to correct grammatical errors, and enhance readability, not to generate text.

4 Results

4.1 Paper I

This paper was undertaken to describe the adherence to the healthy Nordic diet measured by the HNFI, and to describe the relationship between adherence to the HNFI and the dietary composition and lifestyle factors in Norwegian women.

A total of 81 516 women was included in the study. Most women (49%) were categorised as medium adherers, while 22.8 % were categorised as low adherers, and 28.2% were categorised as high adherers to the healthy Nordic diet as measured by the HNFI score.

High adherence to the HNFI was by design associated with higher intake of food groups within the healthy Nordic diet, but also to a higher absolute intake of foods outside the index score such as red and processed meat. High adherers also had a higher absolute intake of energy, fibre and micronutrients compared to those with low adherence. When intake of foods and micronutrients were analysed in relation to energy intake, high adherers consumed more fibre, fruits and vegetables, dairy products, chicken, and potatoes, and less red and processed meat per energy unit suggesting a better dietary composition among high adherers compared to low adherers.

The proportion of total fruits and vegetables intake that was covered by the Nordic fruits and vegetables - cabbages, root vegetables, and apples/pears- increased with higher adherence, from approximately 40 % coverage among low adherers to 52 % in the high adherence group.

High adherence was associated with being older, having higher education and being more physical active. Having overweight was associated with a higher likelihood of being in the high adherence category. Conversely, being a current smoker was more likely as a low adherer. Finally, women living in the western or northern region of Norway was more likely to be high adherers, compared to those living in Oslo.

4.2 Paper II

The objective of this paper was to examine the association between food groups central in the healthy Nordic diet – Nordic fruits and vegetables, whole grain products, fatty fish, lean fish, and low-fat dairy products – and all-cause mortality in a population of Norwegian women.

A total of 83 669 women were included in the study. During a median follow-up period of 20 years, 8 507 women died, most of them due to cancer or CVD. The older participants were more likely to be in the high consumption groups of both lean and fatty fish. Women with higher intake levels of healthy Nordic foods were likely to be more physical active and to have never smoked, except for those in the high consumption group of lean and fatty fish where the trend for smoking was reversed. There was a higher proportion of women having overweight (BMI 25.0–29.9 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) in the high consumption group of Nordic fruits and vegetables, while the opposite was observed for the whole grain

products group. Women with higher education were found in the highest consumption groups, except for lean fish, where a higher proportion of less educated women were in the highest intake category.

In the fully adjusted categorical analyses, we found that consuming 100–199 grams per day of Nordic fruits and vegetables, as compared to less than 100 grams per day, was associated with lower mortality (HR 0.91, 95% CI: 0.87–0.96). Similarly, a higher consumption of whole grain products was associated with lower mortality (p-value for trend across categories = 0.02). An intake of at least 45 grams per day of lean fish compared with less than 15 grams per day, was associated with lower mortality (HR 0.93, 95% CI: 0.88–0.99). However, no association was observed between fatty fish intake and mortality. Consumption of less than 200 grams per day of low-fat dairy products, compared to no consumption, was associated with lower mortality (HR 0.91, 95% CI: 0.85–0.96).

Restricted cubic spline regression analyses revealed a significant J-shaped association for the food groups of Nordic fruits and vegetables, low-fat dairy products, and fatty fish, but not for lean fish. The lowest mortality for Nordic fruits and vegetables consumption was observed at an intake of 200 grams per day (HR 0.83, 95% CI: 0.77–0.91) compared to no consumption. Similarly, the lowest mortality for low-fat dairy products, was observed at an intake of 200 grams per day (HR 0.96, 95% CI: 0.91–1.01), while intake of 800 grams per day or more was associated with higher mortality. The optimal intake level for fatty fish appeared to be between 10 and 20 grams per day, although this did not significantly differ from not consuming fatty fish at all. High intake of fatty fish, starting at 60 grams per day, was associated with higher mortality (HR 1.08, 95% CI: 1.01–1.16). Conversely, for lean fish, increased intake consistently lowered mortality, with an intake of 80 to 110 grams per day significantly linked to lower mortality (80 g/day: HR 0.93, 95% CI: 0.87–0.99).

A significant interaction between smoking status and consumption of Nordic fruits and vegetables was observed, leading to separate analyses for never and ever smokers. The median intake of Nordic fruits and vegetables was slightly higher in never smokers (173 grams per day) than ever smokers (159 grams per day). Categorical analyses indicated a significant trend among ever smokers, suggesting that increased consumption of fruits and vegetables was associated with lower mortality. The optimal intake level for ever smokers, as revealed by restricted cubic spline analyses, ranged from 200 to 250 grams per day (HR 0.79, 95% CI: 0.72–0.87). For never smokers, the optimal intake of fruits and vegetables was observed between 150 and 200 grams per day (HR 0.89, 95% CI: 0.78–1.02), although the estimates for this group was less certain.

4.3 Paper III

The main aim of this paper was to examine the association between replacing processed meat and red meat with lean and fatty fish in relation to all-cause mortality, and mortality caused by cancer and by CVD (ischemic heart disease (IHD) and stroke) among Norwegian women.

A total of 83 304 women were included in the study. During a median follow-up period of 21 years 9 420 women died, including 4 708 deaths from cancer and 1068 deaths from CVD (IHD and stroke).

The initial analyses using RCS indicated a significant non-linear relationship between processed meat intake and mortality outcomes, with the lowest risk of death occurring at an intake of about 30 grams per day. While not statistically significant, the data suggested that the lowest risk for all-cause and CVD mortality for red meat might be around 20 grams per day. For a combined intake of red and processed meat, the lowest mortality was observed at an intake of about 50 grams per day. Consequently, for the purpose of descriptive statistics and substitution analyses, the women were divided into groups of higher and lower consumption. The cutoff levels for higher consumption were established as follows: over 30 grams per day for processed meat, over 20 grams per day for red meat, and over 50 grams per day for a combination of both. The intake of fatty fish displayed a linear relationship with mortality outcomes, whereas lean fish consumption showed a non-linear trend with all-cause mortality. However, since all levels of lean fish intake were beneficial, both types of fish were treated as continuous variables across the entire range of intake levels in the substitution analyses.

Women with higher processed meat intake tended to have a less healthy lifestyle, a higher energy intake and higher intake of red meat and of lean fish. They were also younger than women with lower processed meat intake. Similarly, albeit weaker, patterns were observed among women with higher intakes of red meat.

In the unspecified substitution analyses, increasing consumption of processed meat was associated with higher all-cause, cancer and CVD mortality among higher consumers (>30 grams per day), while no association was observed among women consuming less than this. No statistically significant association with mortality was observed for consumption of red meat among lower or higher consumers. Increasing intake of red and processed meat combined was associated with higher mortality from all outcomes in higher consumers (>50 grams per day), but no association was observed among women with lower intake levels. Increasing consumption of lean fish was weakly associated with lower all-cause and cancer mortality, while higher all-cause, cancer and CVD mortality was observed for increasing consumption of fatty fish.

In the specified substitution analyses, we found that replacing 20 grams of processed meat per day with an equivalent amount of lean fish was associated with 8% lower all-cause (HR 0·92, 95% CI 0·89, 0·96), 8 % lower cancer (HR 0·92, 95% CI 0·88, 0·97) and 18 % lower CVD mortality (HR 0·82, 95% CI 0·74, 0·90) among women who consumed more than 30 grams of processed meat per day. For these women, replacing processed meat with fatty fish was associated with 13 % lower CVD mortality (HR 0·87, 95% CI 0·77, 0·97), however this substitution did not show a statistically significant association with all-cause or cancer mortality. No statistically significantly associations were found when replacing processed

meat with lean or fatty fish among women who consumed 30 grams or less of processed meat per day.

No significant associations were observed when red meat was replaced with either lean or fatty fish, regardless of whether the women were higher or lower consumers of red meat.

For women with a higher combined intake of red and processed meat (above 50 grams per day), replacing red and processed meat with lean fish was associated with lower all-cause and CVD mortality, although no association was found with cancer mortality. However, replacing red and processed meat with fatty fish did not show any associations with mortality outcomes in this group. Conversely, among those with lower consumption of red and processed meat, replacing meats with fatty fish was linked to higher all-cause and cancer mortality, while no significant associations were observed when replacing with lean fish.

5 Discussion

The aim of this thesis was to investigate adherence to the healthy Nordic diet as quantified by the HNFI, and to assess the health aspects of foods central in the Nordic diet among women in Norway. This included examination of key food groups integral to the healthy Nordic diet and their associations with mortality, and replacement of red and processed meat with fish in relation to cause specific mortality. In this chapter, a detailed discussion of the methodological approach and the results will be given.

5.1 Methods discussion

This section will address concerns related to study design and the validity of the results.

5.1.1 Study design

The large prospective cohort study design of NOWAC, with nearly complete follow-up data on mortality and emigration obtained through register data, enabled the use of both cross-sectional and prospective study designs in each paper to explore the aims of this thesis.

The descriptive approach in the first paper, was suited to explore adherence to the HNFI and identifying potential associations for further investigation. Papers II and III had a prospective design, enabling the establishment of a temporal relationship between dietary factors and mortality.

While randomized controlled trials (RCTs) are the strongest design for inferring causality between diet and health, they are not always feasible or ethical, particularly when assessing the impact on long-term health outcomes and mortality. The next best option is the prospective cohort study, which, even though being observational, have the advantage of establishing temporality as the exposure precedes the outcome. Specified substitution analyses, which was applied in Paper III, can provide insight into the health implication of dietary changes with the use of statistical methods when RCTs and interventions are not possible due to ethical considerations. The observational design also allows for large sample sizes and longer follow-up periods than what is feasible in RCT studies, modelling the impact of actual eating habits on health outcomes such as NCDs which develop over time.

However, the findings from these studies must be interpreted with some caution, acknowledging the potential influence of chance, bias, and confounding factors as alternative explanations for the observed associations. The next sections will discuss some issues related to internal and external validity.

5.1.2 Validity

The studies validities are related to how accurately the estimates are reflecting true situations and relationships. There are several factors that can compromise the validity of our estimates including selection bias, information bias, and choice of statistical methods including how confounding factors are accounted for which are discussed below.

5.1.2.1 Selection bias

Selection bias as explained in "A dictionary of epidemiology", refers to systematic distortion in the estimated association between the exposure and the outcome in the participants included in the study compared to the population they are selected from (86). If the distribution of exposures, the factors influencing both the exposures and the outcome, as well as the distribution of the outcome, vary between the study participants and the target population, this discrepancy can lead to results that do not accurately reflect the population they are meant to represent (87).

The sampling process in NOWAC, which used the central population registry in Norway, and the high quality of postal services ensured that nearly all women that were eligible, received the invitation to participate in the study (70). However, women born outside the Nordic countries had lower response rates, implying that the estimated level of adherence to the HNFI in Paper I, as well as the intake of traditional Nordic foods, might be overestimated compared to the target population (70). Furthermore, women from Northern Norway had higher response rates, and these women were also more likely high adherers of the HNFI than women living in the capital Oslo (Paper I).

In a previous study comparing the distribution of education, smoking habits, weight, parity, and oral contraceptive use across samples with different response rates in NOWAC, no statistically significantly differences were observed (88). When participants were compared to non-responders it was found that a larger proportion of the responders had longer education than non-responders, but the difference was minor (70). As education is believed to impact on dietary choices it might lead to the fact that low adherers of the HNFI are underrepresented impacting the descriptive in Paper I. In the last two papers we included education in the statistical models, which should minimise the impact of different education levels to influence the estimates, however the intake levels of the healthy Nordic food might be higher than the target population.

Moreover, the participants in NOWAC were younger than the target population, and one might anticipate an impact on cancer risk, and on mortality (70). However, the incidence rates of cancer within the NOWAC cohort were found to be similar to Norwegian women at the same age minimising the risk of selection bias in relation to outcome (70).

The reasons for not responding to the invitation to participate, included lack of time or interest, concerns of confidentiality, or simply forgetting to complete the questionnaire, which are factors that probably do not have a strong impact on selection bias (70).

In summary, while the potential for selection bias exists, the conclusion from the validation study suggests that the lack of significant differences in important exposures across varying response rates minimizes the risk of selection bias. However, it cannot be entirely dismissed for the studies in this thesis, which examines the relationship between Nordic diets and

mortality, as these factors have not been specifically examined in responders and non-responders.

5.1.2.2 Information bias

Information bias relates to imprecise or wrong measurements of an exposure, outcome or related factors (87). This is of special concern when the measurements are self-reported and when asking about past events. Such errors can lead to misclassification, which is when participants are placed in the wrong exposure or outcome groups. Misclassification can be either nondifferential, which arises when the misclassification is affecting all groups unrelated to the outcome, or differential when the misclassification differs between those who experience the event or not (87). In both situations the estimates are distorted, but when misclassification is nondifferential it usually leads to attenuation of the true associations.

Outcome

The Norwegian Cause of Death Registry provides almost complete coverage, capturing around 98 % of all deaths, with even higher coverage for women at 99 % (6, 89). However, the coverage is less complete for Norwegians who dies abroad (6). Nevertheless, misclassification of the outcome for all-cause mortality in Papers II and III is considered unlikely.

The registry follows the WHO guidelines for coding causes of death and uses a semi-automated international coding system of death (IRIS). For statistical purposes, only a single underlying cause of death is identified for each case. This underlying cause is defined as the initial event in the sequence leading to death, and it is considered the most significant, particularly from a preventive standpoint (6). However, while the underlying cause of death is prioritised, the registry does not provide details on the extent to which other contributing factors may have played a role in the death. It is therefore probably greater uncertainty associated with cause specific mortality outcomes such as cancer and CVD compared to all-causes mortality. To minimise the risk of reversed causation, where the exposure could be a consequence of the outcome rather than preceding it, we started follow-up two years after baseline in sensitivity analyses.

Exposure

The FFQ was initially developed to investigate the association between a traditional diet with high fish consumption and breast cancer risk, resulting in disproportionately high number of questions related to fish compared to other food groups included in the healthy Nordic diet, and to red and processed meat consumption. This focus may unintentionally induce an overreporting of fish consumption in NOWAC, potentially skewing the general intake in the cohort higher (73). However, this is likely affecting all participants equally, and thus resulting in nondifferential misclassification of fish exposures. However, it makes the precise determination of absolute fish consumption in relation to mortality outcomes uncertain. It is

particularly tied to uncertainties in the identified optimal intake levels, and the cut-off level above which higher intake levels were associated with higher mortality, for fatty fish.

While the FFQ captures many foods central in the healthy Nordic diet, it was not designed to capture the broader varieties of foods integral to a healthy Nordic diet. Consequently, the FFQ fails to sufficiently capture the intake of foods like rye crisp bread, oatmeal, kale, wild berries, and rapeseed oil to name a few. This could potentially result in misclassification, whereby individuals who consume greater amounts of oatmeal and rye crisp bread, for instance, may be incorrectly placed into lower categories of the HNFI than they truly belong to. However, since the HNFI was calculated solely for descriptive purposes in this thesis, any misclassification of index categories does not impact the conclusions drawn regarding mortality.

Several studies have been undertaken to evaluate the validity of the NOWAC FFQs. Specifically, the validity has been tested by comparing dietary data obtained from repeated 24-hour dietary recalls (73), as well as with biomarkers (90). Additionally, the reproducibility of the FFQs was examined in a test-retest study, where the FFQ was administered twice to the same individuals about three months apart (91).

The comparison with the dietary data obtained from the FFQ with measures from repeated 24-hour dietary recall, revealed a higher reported intake of milk and yoghurt as well as alcohol in the 24-hour dietary recall than in FFQ (73). Conversely, the intake of fruits and vegetables (not specified to the Nordic varieties), as well as fish and fish products were greater in the FFQ than the 24-hour dietary recall. No statistically significantly differences were observed in the reported intake of whole grain products, or meat and meat products (including white meat). Furthermore, habitual fish consumption, as measured by the FFQ, was reflected in the serum phospholipid fatty acids composition. The types of fish consumed were identified as being more critical than the portion size (90).

For fruits and vegetables there was a relatively high concordance between the FFQ and the 24-hour dietary recalls, with 39 % and 26 % of the women being classified in the same quintile for each food group, respectively. Furthermore, only 2% and 1 % of the women were placed in opposite quintiles for fruits and vegetables, indicating that the agreement is quite good. For fish and meat, the agreement was lower, yet only 4% of participants were classified in the extreme quintile for both groups, with 22 % and 26% agreement, respectively.

Regarding energy intake, the FFQ reported lower energy and macronutrient intakes, with exception of proteins, compared to the 24-hour dietary recalls. In nutrient density calculations, the FFQ showed lower estimates for energy from fat and alcohol, whereas fibre, beta carotene, and vitamin D were higher in the FFQ than in the recalls. In contrast, mineral intakes, such as iron, were lower in the FFQ. This is probably related to the handling of missing values in the NOWAC study, as missing frequencies was treated as no consumption

and imputed with null intake, and missing portion sizes was imputed with the smallest portion size which likely has resulted in underestimation of energy intake (92).

The reported intake of most food groups as measured by the initial FFQ was lower when filled in the second time in the test-retest study (91). For fruits, bread, breakfast cereals and fish a significant decrease was observed in the retest compared to the initial test. In contrast a significant increase was observed for red meat. There was a decrease in the intake of macronutrients and energy, as well as fibre and micronutrients. The Pearson's r, that measures correlations between the test and retest, had a median value of 0.66 indicating a quite strong correlation for most foods indicating that the FFQ can capture the usual diet over time (91). However, when the alcohol consumption from the FFQ was calibrated with that from the 24-hours dietary recalls, the risk estimates for the association between the calibrated alcohol consumption and risk of hypertension was attenuated, suggesting that calibration can affect the strength of associations.

In summary, we expect the types of misclassifications of dietary exposures in this thesis to be nondifferential, rather than systematically different between those who died and those who survived during the study periods.

5.1.2.3 Statistical validity

In Papers II and III the statistical analyses were conducted to investigate the potential causal relationship between Nordic dietary factors and mortality. However, evaluating causality in nutritional epidemiology is particularly challenging due to the complexity of dietary patterns and their connection with energy intake and various lifestyle factors that may also affect the outcome, which in this case is mortality.

Factors that have an impact on the exposure of interest and have a causal relationship with the outcome are described as being a potential confounder, and when not accurately accounted for in the statistical analyses, can skew the actual association between the exposure and the outcome. Consequently, the estimated associations between exposure and outcome may be weakened or attenuated, or on the contrary, overestimated (86).

Selection of confounding variables

We selected potential confounders for inclusion in our statistical models based on existing literature, and on our interpretation of these factors as potential confounders in the specific relationship between our exposures and outcome (Nordic food group/substitution between Nordic food groups ← third factor → mortality). We employed a consistent approach in the selection process and evaluated the various food groups equally, so the same adjustment factors were identified and adjusted for in all food groups, despite the possibility that certain factors might serve as confounders for one food group but not for others. However, the main models in Papers II and III mutually adjusted for each food group included as an exposure in the analyses.

Yet, in the specified substitution analyses (Paper III), if there is an imbalance in the distribution of a selected confounder between groups, such as one group having a higher proportion of smokers compared to the other, the estimates may be skewed by this confounder (83). For instance, in the substitution analyses replacing processed meat, which typically is correlated with smoking behaviours, with fish, often correlated with healthier lifestyle choices this could be a problem. To mitigate a potential bias being introduced by smoking in this scenario, separate analyses for non-smokers is suggested (83). However, in NOWAC, "traditional fish eaters" are more likely to be current smokers, as well as having a higher BMI, and lower income and education (81).

In line with the approach taken in Paper II, the preliminary analyses in Paper III initially differentiated between never smokers and ever smokers in sensitivity analyses. However, these results were excluded from the final revision to maintain clarity and focus within the paper due to its complexity. Despite this, conducting more comprehensive analyses on never smokers remains crucial, as our initial findings indicated a possible disparity in risk estimates for processed meat between never and ever smokers and mortality outcomes. Specifically, there appeared to be a more marked association between higher processed meat consumption and higher mortality risk among never smokers. Nevertheless, we did not perform separate analyses for red meat consumption, nor did we evaluate whether the observed differences were statistically significant.

Incomplete adjustments occur when not all confounders are fully accounted for, both measured and unmeasured factors, or when the variables that are adjusted for are not adequately corrected, leading to residual confounding. Residual confounding may result from measurement errors, the categorisation of continuous variables, or the assumption of linear associations between variables and outcome when the relationships are actually non-linear. In Paper II, the adjustment for processed meat consumption was tested for linearity before being included as a categorical variable. Conversely, in Paper III, other dietary factors that contribute to energy intake were included in the fully adjusted model as linear variables without testing for linearity. This approach was taken because these foods were considered based on the possibility that they might be consumed differently in relation to the replaced foods and thus influencing the estimates as underlying dietary patterns.

Incomplete adjustments for preexisting conditions, such as prior instances of cancer or CVDs, or established risk factors for NCDs like hypertension, could have impacted our findings. This is because dietary modifications made in response to these health issues before the study's baseline could introduce bias. However, in our analyses, we only accounted for diabetes in the fully adjusted model, uncertain of whether it is a confounder or a mediator, since it was the only self-reported preexisting disease in the questionnaire that had been validated (78). Moreover, considering that the objective of our studies was to investigate longevity in a general population- a population that naturally includes individuals at various stages of NCD development- we did not include other information about previous diseases. This approach

acknowledges the inherent diversity of health statuses within a typical population and focuses on the broader implications of diet on lifespan.

Incomplete adjustment for BMI is also possible considering that women in NOWAC with overweight not only report higher consumption of fruits and vegetables but also often report engaging in dieting behaviours, and lower total energy intake (93). In a prior study including Norwegian men and women, it was found that underreporting of energy was strongly associated with dieting and a desire to lose weight, and that female under-reporters consumed fewer high-fat and high-sugar foods, such as cakes, potato chips, chocolate, and sweets. Conversely, they reported a higher intake of potatoes, meat, and fish. Additionally, under-reporters consumed more fibre and vitamin C per unit of energy (94).

Energy intake

In our main models we included energy intake to control for confounding, as energy intake is associated with both disease risk and with food intake (food group intake ← energy intake → mortality). Energy intake is directly linked to the amount of food consumed as they contribute directly to energy intake, and because individuals with higher energy requirements typically consume more food. Greater food consumption is thus reflective of larger body size, which is as a major determinant of energy requirements, as well as of level of physical activity and of metabolic efficacy (95). The quantity of food required to obtain a health impact can also be tied to body size, which is why it is not recommended to assess absolute intake without considering its relation to energy intake (95).

Another reason to control for energy intake is to simulate the effects of dietary changes within a stable energy intake, where the increase in one food group necessitates a corresponding decrease in other energy-contributing foods (95). This concept aligns with what was previously described as non-specified substitution analyses, where the substitution between food groups is not controlled for, as applied in Paper II. While, in Paper III, we conducted specified substitution analyses, wherein the specific food substitutions were defined and controlled for within the analyses.

However, incorporating energy intake as a confounder when it may not be one can introduce errors in the statistical models, potentially leading to erroneous conclusions. The complexity arises because energy intake can also act as a mediator in the pathway from food intake to mortality outcomes (food group intake → energy intake → mortality). In this scenario, the type of food consumed contributes to various amounts of energy, which then affects mortality, rather than being a confounder. For instance, if the health benefit of Nordic fruits and vegetables on mortality are due to their lower energy contribution, then controlling for energy in the model could obscure the true effect of these foods on mortality.

The residual method offers a solution to this challenge. It is a statistical approach frequently used in nutritional epidemiology to adjust for total energy intake (96). This method involves a regression analysis where the food of interest is the dependent variable and energy intake are

the independent variable. The residuals, which is the difference between observed intakes and those predicted by the regression model based on energy intake, represent the portion of nutrient or food intake not accounted for by total energy intake. These residuals are then used as the exposure in the statistical models and estimates the impact of the nutrient or food independent of total energy consumption. This approach was initially tested in Paper I, but because the food groups are not normally distributed it could not be applied without more complex statistical analyses and was not pursued further in this thesis.

Missing

In this thesis, we conducted complete case analyses, excluding participants with missing values on any of the covariates included in the analyses (except dietary data as missing frequency had already been imputed with a value of zero if frequency information was missing). For Paper I, we conducted a detailed assessment to discern between genuinely missing data and zero intake within the variables used to calculate the HNFI. In this approach, we treated a missing response as an indication of zero intake if it occurred under a combined question where some, but not all, items were reported as consumed. For example, within the fruits and vegetables category, if a participant indicated consuming carrots but left the response for cabbages blank, we interpreted the absence of a response for cabbages as zero consumption rather than missing data. For the last two papers, we used the NOWAC standard, imputing missing frequencies with zero. Our aim was to maintain uniform treatment across all food variables, thereby avoiding the introduction of potential biases that might arise from differential treatment of missing versus zero intake responses.

Approximately 15 % of participants were excluded due to missing values on non-dietary covariates. Such exclusions could potentially introduce bias if the missingness is associated with the missing data- for instance, if individuals refrain from reporting their weight due to it perceived as too high or low. This concern was raised in the review process of Paper III, and thus to address the potential bias resulting from such exclusions we performed sensitivity analyses using Multiple Imputation (MI). This was done under the assumption that the data were missing at random, which suggests that the likelihood of missingness is not connected to unobserved data but may be associated with the observed data. The MI analyses yielded results that were consistent with our main analyses. This consistency coincides with findings from prior analyses and studies within the NOWAC cohort (48), suggesting that the missingness is likely not introducing any more biased results than the complete-case analyses.

HNFI

To examine whether the HNFI-score reflected a higher intake of beneficial or less beneficial non-index foods, we adjusted these foods in relation to energy intake and compared them across adherence scores. In retrospect, this was not the optimal approach. Instead, we should have constructed an energy-standardised HNFI and then compared this score with the energy-standardised intake of non-index foods to obtain a more accurate description of dietary balance in relation to the HNFI score (97).

The method of using cohort median intake as cut-off for scoring food components has some limitations. It introduces variability in what constitutes high adherence across different study populations and complicates direct comparisons across studies. Additionally, population-dependent cut-offs are not stable over time, making it difficult to compare adherence to the HNFI measured between two time points within individuals. For example, if there are general changes in the population's diet, such as an increased intake of fruits and vegetables, but some individuals do not adhere to this change, their HNFI might drop without their intake of that component being lower than at the first time point (97).

There are also some advantages with this method because of its flexibility to adapt different consumption levels between populations (97). For instance, the median intake of food components in the HNFI varies across studies (25, 98), and using the median allows for an even distribution of higher and lower consumers within the respective cohorts, which increase statistical power. In contrast, if a standardised cut-off were used, in populations where intake is generally lower, few might consume above the defined cut-off, generating uneven groups of comparison. However, in studies on disease associations it might be more relevant to use cut-offs that are based on epidemiological evidence (97).

Non-linear associations

We used both categorical models and RCS models in Paper II, and RCS in Paper III to test potential non-linear relationships between the Nordic food groups and mortality. The categorical models can be used for this purpose without the need for complex modelling techniques while being quite robust against the influence of outliers. The estimate from these categorical analyses is also quite easy to interpret and communicate as the comparison is between each category compared to the reference group. However, categorical analyses are limited due to loss of information as the same risk is assumed across the intake range within each category. Furthermore, the choice of cut-off for each category and choice of reference group can influence the estimates.

Continuous models allow for the use of all available datapoints of an exposure, avoiding the information loss with categorization. This can give a more detailed description of the relationship between food intake and mortality and enhancing statistical power. When continuous data are available, RCS is a valuable tool as they can capture non-linear relationships between food groups and mortality without imposing a predetermined shape of association, as linear regression models do with their inherent linearity assumption (82). The estimates derived from RCS can be assessed at any level of exposure and are as interpretable as linear regression coefficients.

Nevertheless, the selection and positioning of knots within the spline can influence the estimates. A data-driven strategy, such as using percentiles for knot placement, is often recommended over fixed levels, as it is more reflective of the underlying data distribution (82). Despite this, there remains a potential for overfitting (picking up noise), particularly if an excessive number of knots is used. To mitigate this risk, we evaluated models with five,

four, and three knots, ultimately selecting the model with the lowest AIC value. This approach ensures that while the model retains flexibility within the range of the knots, the estimates remain linear at the extremes—beyond the first and last knots (82).

In all papers we used cross-sectional dietary data, which provides a snapshot of the participant's diet at a single time point. This was the first analyses of the included food groups and mortality in the NOWAC, employing methods designed to investigate potential non-linearity and food substitution. For this purpose, we confined our analyses to baseline dietary data, despite the availability of repeated measurements that would allow us to explore dietary changes, or to potentially refine the accuracy of our estimates. Given the extended follow-up duration, dietary habits may have changed over time, suggesting that using repeated measurements might have yielded more precise estimations. Nonetheless, prior research within the NOWAC cohort that use repeated dietary assessments has demonstrated consistency with baseline data findings (99, 100).

In these analyses, we identified optimal intake levels of food groups in relation to mortality outcomes and calculate point estimates related for specific grams of intake. However, self-reported dietary measures are susceptible to errors, introducing uncertainties regarding precise intake levels. The NOWAC FFQ is validated to rank individuals by their intake, but FFQs in general perform poorly in estimating exact levels of intake (73). Therefore, the shape of the curves is likely more relevant, while the intake levels deemed optimal should be considered approximate estimates.

Specified substitution models

These analyses are constrained to statistical comparisons of average intakes among individuals, rather than actual dietary changes. Moreover, we relied on cross-sectional data from a single measurement of dietary exposures and covariates, which prevented us from estimating the impact of dietary changes over time within individuals.

We used grams as the unit of measurement for dietary substitutions, resulting in a model that incorporates both grams and energy. This approach has two challenges; 1. the model incorporates both weight and energy, 2. this results in an energy imbalance. It has been suggested that a more standardised approach, by using the energy contribution from foods in the substitutions, adjusted for total energy intake, or to include all food groups in the model instead of energy intake when grams are used as unit of substitution, yields more precise estimates (101).

Our dataset was limited to variables measured in grams. Converting these measurements to energy content would require additional calculations that were not feasible within the NOWAC dataset. However, we conducted preliminary tests by modelling the energy contributions from the foods included in the meat and fish exposures using food composition tables for estimation and including the substitution units as their energy contribution. These preliminary analyses yielded results similar to those obtained using grams as the unit of

measurement and adjusting for energy. Consequently, we decided not to present both models in the paper, considering its already complex nature with numerous analyses of different exposures and outcomes.

Weight as the unit of substitution introduces a residual energy imbalance that was not accounted for; this difference in energy is more pronounced between lean fish and processed meat compared to fatty fish and processed meat, owing to the lower energy content in lean fish (83). This allows for the possibility of different foods that may be associated with distinct health behaviours and dietary patterns to influence the estimates (83). For instance, different foods may be eaten together with either fish or meat, representing underlying dietary patterns, and these foods or underlying dietary patterns may be associated with mortality and thus affect the estimates. Additionally, the energy imbalance itself might impact mortality.

To address these complex relationships between dietary components and their association with potential underlying diseases that influence mortality, our fully adjusted model included consumption of fruits and vegetables, whole grain products, refined grain products, potatoes, and dairy products. Additionally, diabetes and BMI categories were adjusted for in an alternative model 3. However, these additional adjustments did not change the estimates from our less adjusted model, which suggests that these factors did not confound the association observed with the substitution of meat with fish.

5.1.3 External validity

The NOWAC study is considered to be a good representation of Norwegian women aged 30 to 70 years. Factors such as random sampling from the national registry increased the likelihood that the women that were invited to participate in the study would be representative of the broader population of Norwegian women, and selection biased is considered minimal (70). Furthermore, the cancer incidence rates were similar among participants in NOWAC and national figures from the Cancer registry, which supports the validity of the NOWAC cohort.

However, whether our results can be generalised to Norwegian women today is more uncertain. Since the data was collected about 20 years ago, it may not accurately reflect the dietary patterns of middle-aged women today. For instance, immigrants constitute an increasingly large segment of Norway's population. As of 2023, there were close to 900,000 immigrants and 200,000 Norwegian-born individuals with immigrant parents (102). Adherence to the HNFI is likely not representative of women from these groups within the population.

Furthermore, over the years since data collection, there have been some notable changes in the food consumption at a population level as outlined in the report "Developments in the Norwegian Diet 2023" (35). Generally, there has been an increase in the consumption of fruits and vegetables, while fish consumption has decreased, and meat consumption has increased.

These trends suggest that compliance with the HNFI may vary, among middle-aged women today.

5.2 Interpretation of results

5.2.1 The HNFI (Paper I)

Adherence to the healthy Nordic diet among Norwegian middle-aged women, as measured by the HNFI, was found to be relatively low, with only 28% of participants classified as high adherers (score 4-6).

Compared to a previous study on dietary patterns in NOWAC using data-driven analysis, several dietary patterns identified may overlap with different components in the HNFI. This study identified distinct groups such as "traditional fish eaters" and "traditional bread eaters," that were related to distinct foods. The largest group was labelled as "average," representing the largest segment of the sample. This dietary pattern was characterised by lower consumption of fish, vegetables, and whole grains, and higher consumption of meat, pizza, and rice. Another notable group, termed "healthy eaters," were characterized by consuming breakfast cereals, fruits, and skimmed milk and typically were younger than the traditional fish eaters who were the oldest women (81). This highlights the fact that for medium adherers to the HNFI, who represent most women (49%), various dietary patterns may be represented.

As discussed in Paper I, our findings were in line with previous studies in Denmark and Sweden. High adherence to the healthy Nordic diet among women according to the HNFI is around 35 % in Denmark (25) and 32 % in Sweden (98). Like our results, high level of adherence to the HNFI was associated with an increased intake of energy and red meat in Danish women. Concurrently, high adherence was also linked to healthier lifestyle choices, including smoking habits, higher education levels and more physical activity (25). Likewise, in the Swedish cohort study it was observed that women with high adherence to the HNFI had greater consumption of red meat, processed meat, sweets, sodium, potatoes, and total energy (98). Adherence was also linked with a higher fibre intake and a lower intake of saturated fats among the Swedish women (98).

These findings suggest that adherence to the HNFI is associated with a mix of dietary factors that includes both components that are beneficial and others that are less so for health across cohorts, and that an energy-standardised version of the HNFI might give a better description of the overall quality of the diet.

5.2.2 The Nordic food groups (Papers II and III)

In this section, for each food group, I will start with a summary of our findings. Following this, I will explore some of the biological mechanisms relevant to NCDs, as these are major contributors to mortality. Covering the complexities of the numerous biological mechanisms associated with all food groups and their relation to mortality is beyond the scope of this thesis. However, I will address some key mechanisms that may support a causal relationship between the consumption of Nordic food groups and mortality outcomes. I will also review results from other studies, with a particular emphasis on Nordic populations if relevant literature exists.

5.2.2.1 Nordic fruits and vegetables (Paper II)

We found that the association between Nordic fruits and vegetables and all-cause mortality was non-linear, with an optimal intake level observed around 200 grams per day, and a non-significant higher mortality when consumption exceeded roughly 450 grams per day. Additionally, we observed that Nordic fruits and vegetables may offer greater benefits for women who are current or former smokers compared to those who have never smoked.

Among the healthy Nordic food groups included in this thesis, Nordic fruits and vegetables consumption around optimal levels had the strongest association with all-cause mortality. However, it is also the category (along with whole grain products) where the diversity of Nordic varieties is least represented. As a result, our analysis is restricted to a relatively limited assortment, which constrains our capacity to comprehensively assess the impact of Nordic fruits and vegetables on all-cause mortality.

Biological mechanisms

Several mechanisms support a causal relationship between the consumption of Nordic fruits and vegetables and lower mortality. This could be attributed to the general characteristics of fruits and vegetables, which typically have low energy and high water content, aiding in weight management and potentially replacing less healthy food options (103). Additionally, the synergistic effects of various essential nutrients and phytochemicals are likely contributors to the observed benefits (104).

Of particular interest in disease prevention are the various phytochemicals (bioactive, non-nutritive compounds) found in plants (28). Polyphenol intake (a group of phytochemicals) has been associated with lower all-cause mortality (105), potential impacts on body weight status (106), and anti-carcinogenic actions (107). They are believed to work through the antioxidant and anti-inflammatory properties of polyphenols, as well as their favourable effects on blood pressure, lipid profiles, and insulin resistance.

There are also some key groups of phytochemicals found in the Nordic varieties of fruits and vegetables which include glucosinolates, carotenoids, and flavonoids that may be protective against cancer and CVD development (33). Broccoli, cauliflower, and cabbage belonging to the brassica vegetables, are particularly high in glucosinolates which are sulphur-rich compounds almost exclusively found in these plants (108). Upon ingestion, glucosinolates are metabolized into a range of bioactive compounds that can inhibit tumour growth (108). Another compound found in broccoli is indole which has phytoestrogenic activity, and may lower the risk of hormone-related breast cancer (109). Beyond their anticancer benefits, compounds in brassica vegetables also play a significant role in cholesterol metabolism and may be protective against CVD (109).

β-carotenes, a type of carotenoid found in high amounts in carrots, are associated with reduced all-cause mortality (110). This may be attributed to β-carotenes potent antioxidant properties, which play a crucial role in diminishing the oxidation of low-density lipoprotein

(LDL) cholesterol, thereby offering protection against the development of atherosclerosis and CVD. Additionally, as a provitamin A, β-carotene is involved in strengthening the immune system, further contributing to its potential health benefits (110).

Consumption of apples has been linked to a reduced risk of heart disease and related risk factors (111). This beneficial effect is believed to stem from the rich flavonoid content, including compounds such as quercetin and anthocyanins. These flavonoids enhance the health of the endothelium (the inner lining of blood vessels) which can aid in regulating blood pressure, and have also been found to inhibit cancer cells (107).

On the other hand, the non-linear association and the potential negative impact observed at higher intake levels may be attributed to the fact that excessive quantities of most nutrients and bioactive compounds can elevate the risk of disease compared to an optimal intake (29, 112).

Findings from other studies

Our findings are consistent with those from the systematic review and meta-analysis of prospective studies by Schwingshackl et al., which also reported on optimal intake levels of food groups. Similar, to our study, a non-linear association was observed between the intake of fruits and vegetables and mortality (64). The optimal combined intake level was identified at 500 grams per day, with approximately a 10% reduction in mortality for every 80-gram increment, up to a maximum benefit at 250 grams each for fruits and vegetables.

Current evidence on all fruits and vegetables supports our findings on the Nordic varieties regarding all-cause mortality, showing that risk reduction is more pronounced at lower intake levels compared to no consumption (33). However, the maximum benefit, or optimal intake levels, is achieved with an intake of approximately 400-480 grams per day (113), or even up to 800 grams per day for all fruits and vegetables (114), beyond which the risk reduction tends to plateau. However, our results do not support an increased benefit from consuming amounts of Nordic fruits and vegetables above these optimal levels, as mortality may be higher at the highest intake levels.

We observed 17% lower mortality at optimal intake levels for Nordic fruits and vegetables in relation to no consumption, compared to a 32% reduction in mortality for all fruits and vegetables at 800 grams per day in men and women, as reported by Aune et al. (114). In studies focusing on Nordic populations, Hjartåker et al. conducted a prospective cohort study involving Norwegian men and found that those who frequently consumed fruits, vegetables, and berries experienced a 10% lower all-cause mortality compared to those with lower consumption levels (115).

Among the Nordic varieties, there is evidence suggesting that brassica vegetables (broccoli, cauliflower, and cabbages), as well as apples and pears, may contribute to the observed beneficial effects in relation to all-cause mortality (114). Also, as previously mentioned,

Olsen et al. found that intake of cabbages and root vegetables above the cohort median was associated with lower all-cause mortality compared to those with lower consumption levels (25).

Our observations concerning current and former smokers are supported by a previous study that identified a protective effect from fruits and vegetable consumption against lung cancer among smokers (116).

5.2.2.2 Whole grain products (Paper II)

Our analyses indicate a linear association between increased consumption of whole grain products and lower all-cause mortality. Consuming 180 grams or more per day, compared to less than 60 grams, was associated with 11% lower all-cause mortality.

However, the limited dataset on varieties of whole grain species and whole grain products, as well as the whole grain content in the bread and breakfast cereals included in the exposure, restricts our understanding of the association between Nordic whole grains/whole grain products and mortality. This limitation is also combined by the predominance of wheat as the primary whole grain consumed in Norway.

Biological mechanisms

Several mechanisms support a causal association between whole grain products and lower mortality, likely due to the synergistic interactions among various types of fibres, micronutrients, lipids, and phytochemicals found in whole grains. These components collectively contribute to longevity for instance by enhancing blood lipid profiles, blood glucose levels, improving endothelial function, and diminishing inflammation (117).

Dietary fibres and carbohydrates, including arabinoxylan, pectin, β-glucan, and resistant starch, are integral to the health-promoting properties of whole grains. Viscous fibres such as β-glucan (abundant in oats and barley) and arabinoxylans (found in rye and wheat) reduce the glycaemic response and cholesterol absorption, thereby impacting blood glucose and lipid levels (117). Additionally, dietary fibres significantly influence the gut microbiota (comprising bacteria, viruses, archaea, and eukarya) primarily residing in the colon (118).

While the complex interplay between whole grain dietary fibres and the gut microbiota is beyond the scope of this thesis, it is important to comment that the gut microbiotas production of short-chain fatty acids (SCFAs) from fermentation of fibre may have a preventive role against CRC. The microbiota is also involved in the production of neurotransmitters and hormones through intricate pathways, which in turn regulate metabolic, cardiovascular, and immunological processes. Consequently, the gut microbiota is associated with the risk of CRC, cardiovascular disease (CVD), and related risk factors such as obesity and type 2 diabetes (118).

Findings from other studies

Consistent with the findings of Schwingshackl et al., we observed a linear association with whole grain products, similar to their observation on whole grains. In their study, the maximum benefit was noted at an intake of 90 grams of whole grains per day, which corresponded to a 21% reduction in mortality at this level. Assuming that the whole grain bread included in our whole grain products group contain about 50% whole grains, our results align with these findings (64).

Most of the literature supports the notion that increased consumption of whole grains or whole grain products is associated with lower all-cause mortality, with effect estimates indicating a 10-20% reduction in mortality among those with high consumption levels, and a somewhat stronger association within Scandinavian populations (119). This supports our findings, which show an approximately 11% lower mortality among women consuming the highest amounts of whole grain products compared to those consuming less than 60 grams per day (119).

While most research on whole grain has been in US populations mostly consuming wheat (119), studies in Scandinavian populations have linked total whole grain intake, including breakfast cereals and non-white bread, to lower all-cause and cancer mortality, with breakfast cereals also associated with lower CHD mortality (120). Doubling the intake of oat and rye, key components of the healthy Nordic diet, was associated with lower mortality among women (120).

Our findings suggest that whole grain products, which are predominantly wheat-based, appear to be beneficial. This observation aligns with results from the Swedish cohort study on the HNFI (50). In contrast, the consumption of rye bread did not show a significant association with the mortality of Danish women in the HNFI study (25). However, given the broad categorization of Danish participants into high or low consumers of whole grain rye, and the limited information regarding the impact of different whole grain varieties in both the Swedish cohort and our study, we can only assume that a higher intake of whole grain products including mainly wheat and smaller amounts of rye, barley, and oats, seems to offer protective benefits.

5.2.2.3 Low-fat dairy products (Paper II)

We found that the association between low-fat dairy products and all-cause mortality was non-linear, with an optimal intake level observed around 200 grams per day whereas higher intake levels above 800 grams per day was not beneficial. In the categorical analyses, consuming less than 200 grams of low-fat dairy products, compared to no consumption, was associated with 9% lower all-cause mortality. However, the estimate from the restricted cubic spline did not reach significance, indicating that the observation from the categorical analyses may not be very robust.

Biological mechanisms

This observed non-linear relationship may be attributed to the dual nature of dairy products, which are rich sources of numerous essential nutrients beneficial to health yet, may also contain saturated fat. Dairy products provide over 60 % of calcium and iodine, and approximately 40 % of dietary saturated fat in the Norwegian diet (121).

The recommendation of replacing high-fat dairy products with low-fat dairy stems from the theory that saturated fats contribute to the elevation of LDL-cholesterol levels (121), which are involved in the initiation and development of atherogenesis (122). Although our analyses focused on low-fat dairy products, they still contain some saturated fat, which may account for the observed higher mortality at increased consumption levels. However, current evidence reviewed in relation to NNR23, challenges the presumed link between dairy product consumption and dyslipidaemia. Notably, it highlights that higher consumption of fermented dairy products, such as yogurt and cheese, is associated with lower LDL-cholesterol levels (74).

The beneficial association we observed at lower intake levels of low-fat dairy products may be related to the protective link between dairy products and CRC (74), likely due to the calcium content in dairy products. Calcium can bind to bile acids and free fatty acids, thereby reducing the proliferation of cancer cells. A previous study in NOWAC observed a weak protective association between milk intake and CRC incidence (99). Additionally, the presence of live bacteria in some fermented products can enhance the bioavailability of certain nutrients, strengthen immune function, and combat pathogenic bacteria, potentially offering further protection against CRC (123).

Findings from other studies

Our result on low-fat dairy products is supported by Schwingshackl et al. This study observed a non-linear association between dairy consumption and mortality, identifying the optimal intake level at 200 grams per day, similar to our analysis on low-fat dairy. At this intake level, the estimates indicated a 3% reduction in mortality, whereas intakes above this level were associated with higher mortality (64).

Current evidence from the scoping review related to NNR23 concludes that dairy products, especially low-fat and fermented varieties such as yogurt and cheese, are beneficial for cardiometabolic risk factors and are associated with a lower risk of CRC (74). In relation to all-cause mortality some studies indicate that increased intake of fermented dairy products, such as yoghurt and cheese, are protective, while non-fermented milk consumption is associated with higher CHD mortality (124). In our analyses, the primary component of the low-fat dairy was low-fat milk, and we could not differentiate between fermented and non-fermented types, suggesting that our included dairy products (which did not include low-fat cheese) may not adequately capture the consumption of fermented dairy products.

Dose-response meta-analyses of prospective cohort studies have linked high-fat milk consumption to higher mortality from all causes, CVD, and cancer. Conversely, higher total dairy intake has been associated with lower CVD mortality (125). It is plausible that the higher mortality observed for high-fat milk in these meta-analyses is related to its saturated fat content. However, the fact that total dairy, likely consisting of products with even higher amounts of saturated fat, does not show convincing evidence for higher CVD risk (74), it is plausible that other factors in non-fermented milk may affect mortality. Since our analysis included low-fat milk, we cannot dismiss the possibility that the observed higher mortality at higher intake levels could be associated with other milk components, such as lactose content (123).

A meta-analysis of eight prospective cohort studies revealed that, although the highest consumption category of yogurt, compared to the lowest, did not show an association with mortality, a daily intake of 200 grams was linked to reduced mortality. This finding supports our results (126).

In a Swedish cohort with high non-fermented milk intake, individuals consuming non-fermented milk ≥ 2.5 times per day, compared to those consuming ≤ 1 time per week, experienced a 32 % higher all-cause mortality, regardless of fat content. On the other hand, a higher intake of fermented milk and yoghurt was linked to 10 % lower all-cause mortality, while cheese consumption correlated with 7% lower all-cause mortality for both women and men (127).

These findings are consistent with those from a previous cohort study in another Swedish population, which observed that each additional glass of milk was associated with 15 % higher all-cause mortality among women, and 3 % among men (128). However, in Denmark, a cohort study found no associations between total or fermented dairy and all-cause mortality, but a higher consumption of low-fat milk was associated with 23 % lower all-cause mortality (129). Yet another Danish study suggested that replacing milk, regardless of its fat content, with whole-fat yoghurt and cheese was associated to a lower risk of myocardial infarction, questioning the advice to replace high-fat dairy with low-fat alternatives for CVD prevention (130).

5.2.2.4 Lean fish and fatty fish (Papers II and III)

We found that the consumption of fatty fish that was associated with lowest all-cause mortality, was roughly between 10 and 20 grams per day compared to no consumption, although this observation was not statistically significant. However, higher consumption, exceeding 60 grams per day, was not beneficial among these women as we observed higher mortality above this consumption level (Paper II). When processed fatty fish products, like mackerel in tomato, were included in the fatty fish category in Paper III, fatty fish consumption was linearly associated with higher all-cause, cancer, and CVD mortality.

In contrast, increasing consumption of lean fish was weakly associated with lower mortality in Paper II. When processed lean fish products, such as fish fingers and fish cakes, were included in Paper III, the association with all-cause mortality became non-linear but also more markedly beneficial. The curve flattened between an intake of approximately 40 to 60 grams per day, suggesting that beyond this range, increased consumption was not associated with additional benefits for longevity. The consumption of lean fish was linearly associated with lower cancer and CVD mortality.

Biological mechanisms

Our results do not provide robust support for the current recommendations that at least 200 grams of the weekly intake for fish should be fatty fish. This finding is somewhat surprising as fatty fish is a main source of marine omega-3 long-chained fatty acids like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are thought to be protective against CVDs. Some key mechanism behind the importance of these fatty acids is that they are part of our cell membranes, influencing the fluidity of the cell membrane, signalling, and regulation of genes involved in lipid metabolism. They may also have anti-inflammatory effects (67).

However, the nutrient content, including beneficial fatty acids, varies among different fish species and there are notable differences in the nutritional composition of wild, and the most commonly consumed farmed, salmon (131). Wild Atlantic salmon, which feeds on marine foods, typically has high levels of EPA and DHA. In contrast, farmed salmon is primarily fed a diet with 70% plant-based ingredients, leading to a 50% reduction in omega-3 fatty acid content (131). This significant alteration of the diet for farmed salmon, could have implications for human health, considering the critical role of omega-3 fatty acids in the human body, particularly for cardiac-, immune- and brain cells (67, 131).

Fatty fish is also a source of persistent organic pollutants (POPs) that are linked to detrimental health effects including cancer, reproductive and developmental problems, and disruption of the immune and endocrine system (132). A Norwegian study published in 2021, examined the levels of essential nutrients— EPA, DHA, and vitamin D—and the presence of POPs in Norwegian Atlantic herring, Atlantic mackerel, and Atlantic farmed salmon (132). The nutrient content was assessed against recommended daily intake levels, while the contaminant levels were measured against the Tolerable Weekly Intake (TWI) thresholds established by EFSA. The findings suggest that adhering to the recommended intake levels for fatty fish, including farmed salmon, met the health benefits derived from their nutrients and the potential risks posed by the contaminants (132). This implies that consuming more than the recommended intake of fatty fish could result in exceeding the TWI for certain contaminants and could be reflecting the negative impacts of high fatty fish intake in our study.

Another factor that may support the observed negative impact of high consumption fatty fish in this thesis, is process-induced contaminants, such as polycyclic aromatic hydrocarbons (PAHs) and heterocyclic aromatic amines (HAAs). These compounds are classified as

carcinogens and can form during cooking or processing of both fish and meat, especially when subjected to high temperatures. Fatty fish and meats are more likely to have increased levels of PAHs, as the preparation of these foods involves melting of fat that generates smoke under high temperatures. Using fish with lower fat content can reduce the formation of PAH (133).

We observed a more pronounced association between the consumption of fatty fish and all-cause mortality in Paper III which included processed fish varieties such as canned or smoked fish. This observation may suggest a potential link between the processing methods of fatty fish and health outcomes. Among the processed fish products examined in Paper III, canned mackerel in tomato sauce was one component, and higher levels of N-Nitrosamines have been detected in canned fish products (see section 5.2.2.5 for a more detailed explanation of N-Nitrosamines and health implications). These findings point to the possibility that certain processing techniques or additives used in preserving fatty fish may contribute to the observed higher mortality.

The protein content varies among various fish species, and there is some evidence to suggest that proteins derived from lean fish may improve metabolism, such as enhancing insulin sensitivity, optimizing glucose metabolism, improving lipid profiles, and positively affecting body composition (134). The high content of proteins with high bioavailability along with the low energy density may also influence satiety which may be beneficial in appetite control (135). The health benefits of lean fish consumption may also be related to the displacement of other foods such as red and processed meat in the diet, which has been linked to higher all-cause mortality (136, 137).

Findings from other studies

Our results for lean and fatty fish are not directly comparable to the findings reported by Schwingshackl et al., who analysed total fish consumption. In their meta-analysis, they observed a 10% reduction in mortality at an intake level of 200 grams per day (64).

Based on the evidence from the comprehensive review on fish consumption for NNR23, it was concluded that there is strong evidence associating fish consumption with lower all-cause mortality, which supports our observations for lean fish. Additionally, weak associations were found between fish consumption and a reduced risk of cancer, while there was strong evidence supporting a protective association between fish consumption and risk of CVDs (67). High total fish intake was, specifically highlighted to be protective against CHD and stroke incidence, as well as myocardial infarction (MI).

A systematic review on prospective cohort studies, found a nearly U-shaped association between all-cause mortality and fish consumption in Western studies, with the most beneficial consumption level at around 20 grams of fish per day, while the association appeared to be linear in Asian studies (138). This might be related to types of fish consumed, preparation methods, and differences in local nutrients and contaminant levels.

In contrast to our results, a systematic review and meta-analysis of prospective cohort studies including studies from the US, Europe, and Asia, found that the highest versus the lowest intake of fatty fish was associated with 3 % lower all-cause mortality, while the association between lean fish and all-cause mortality was not significant (139). Yet, a large prospective cohort study across 10 European countries found no association between total fish consumption, whether lean or fatty, and all-cause mortality for either men or women (38). However, evidence suggests that lean fish, but not fatty fish, is associated with beneficial changes in risk factors for morbidity and mortality, such as improvements in abdominal obesity, lipid profile, and blood pressure in a study including Norwegian men and women (140).

5.2.2.5 Red and processed meat

Our findings indicate that consuming processed meat in quantities exceeding 30 grams per day is associated with higher all-cause, cancer and particularly with higher CVD mortality. This higher risk was not observed for those who consume less than this amount. Consumption of red meat was not associated with any mortality outcomes in our study.

Biological mechanisms

The potential negative health impact of processed meat consumption may be linked to various factors associated with carcinogenic substances and cardiometabolic disturbances.

IARC has classified processed meat as a Group 1 carcinogen, signifying that there is convincing evidence to support the conclusion that processed meat consumption cause cancer in humans (141). This conclusion is based on consistent findings across various epidemiological studies conducted in different populations, as well as mechanistic evidence derived from experiments on both human tissues and animals, suggesting that the association is not likely due to chance or confounding factors. Red meat has been categorized as a Group 2A carcinogen, meaning it is probably carcinogenic to humans. This classification reflects strong evidence that suggests a probable causal relationship between red meat consumption and an increased risk of cancer (141).

Several biochemical mechanisms have been proposed to explain the carcinogenic potential of red meats, with extra considerations for processed meats. One key mechanism is the presence of heme-iron in red and processed meat, which can facilitate the formation of endogenous N-Nitrosamines and lipid peroxidation products in the digestive tract which can induce DNA damage (142). It is estimated that up to 97% of our exposure to N-Nitrosamines arises from endogenous production within the body, with dietary sources accounting for the remaining contributions (143). The use of nitrites as preservatives in red meat processing can lead to the formation of N-Nitrosamines, particularly in meats that have been cooked or smoked. However, this is not exclusive to red meats; as previously mentioned, processed fish also exhibit elevated formation of N-Nitrosamines, and high level is found in canned and salted fish (143).

In relation to CVD mortality, it has been proposed that N-Nitrosamines may also act as a risk factor for CVDs by promoting the formation of free radicals, which contribute to the development of atherosclerosis, and by contributing to an increase in LDL-cholesterol levels (144). Similarly, excessive iron, may contribute to the development of CVDs through the induction of oxidative stress. Additionally, high iron levels can lead to diminished glucose sensitivity, owing to iron deposition in pancreatic cells (145). This can also adversely affect insulin secretion and heighten the risk of type 2 diabetes, which is a recognized risk factor for CVDs (145, 146) .

Cooking red meat at high temperatures results in the formation of HAAs and PAHs, as explained in relation to fish. Given that processed meats typically contain additional fat, they may produce greater quantities of these harmful compounds than unprocessed red meat (142).

Processed meats are significant sources of saturated fats which have been linked to an increased risk of cardiovascular disease (CVD) (145). Red and processed meat intake have also been connected to obesity which increases the risk of CVDs (147).

A distinguishing factor of processed meats is their high sodium content, unlike unprocessed red meats, which do not contain added sodium. High sodium intake can adversely affect the renin-angiotensin-aldosterone system, leading to increased blood pressure—a well-known risk factor for CVD (148).

Findings from other studies

In contrast to our findings, a linear association between both red and processed meat consumption and all-cause mortality was observed by Schwingshackl et al. (64). Consistent with our results, non-linear associations were observed between processed meat intake and all-cause and CVD mortality. Additionally, stronger associations with all-cause and CVD compared to cancer mortality were observed in dose-response meta-analyses of prospective cohort studies (136).

The overall body of evidence, based on a large number of studies and systematic reviews, indicates an association between higher all-cause mortality and increased consumption of red meat, particularly processed meat (65). However, the evidence regarding cancer mortality remains inconclusive (65, 149).

The EPIC study, which includes populations from several European and Nordic countries, including women participating in NOWAC, found that high versus low consumption of processed meat was associated with 44 % higher all-cause mortality for both men and women (150). High consumption was also associated with higher cancer and CVD mortality. Unlike studies in US populations, red meat consumption in Europe was not consistently associated to all-cause mortality, potentially due to lower consumption of meat in Europe compared to the US. In a Swedish cohort study, the highest versus lowest intake category of red meat was associated with 21 % higher all-cause mortality (151).

5.2.2.6 Non-linearity in relation to the HNFI

As the HNFI was initially developed to evaluate whether greater adherence to the healthy aspects of Nordic diets was associated with longevity (25), and given that this was the initial intent of our project, I will briefly discuss our findings in this thesis, in relation of utilizing the HNFI for this specific purpose.

A significant challenge in interpreting the risk estimates for the relationship between the HNFI and outcomes such as mortality, is that the score assign equal weight to each food group. This suggests that a higher index score, reflecting increased consumption across the included food groups, would uniformly contribute to mortality. Yet, as Paper II reveals, these food groups do not contribute equally to mortality. For example, when disaggregating the components of the HNFI, we find that Nordic fruits and vegetables exhibit a stronger association with mortality than the other food groups within a specific range of intake, and particularly compared to fatty fish. Should these foods have been analysed using the HNFI in relation to mortality, the interpretation of the findings, could mistakenly attribute health benefits to higher intake of fatty fish that are not supported by the data, while simultaneously misjudging the actual health benefits of Nordic fruits and vegetables.

Based on the analyses conducted in Paper II, our findings do not support the underlying assumption of a linear relationship between all foods incorporated as index components in the HNFI, where higher intake levels are presumed to be more beneficial and thus receive a higher score in the index. However, while constructing a composite score that accounts for non-linear associations by rewarding the optimal range of intake—and not the intake ranges outside this optimal range—is feasible, it would still require a complex weighting of components in relation to their individual contributions to the relevant outcome. Given the uncertainties in the food estimates generated from FFQs, defining cut-offs is not straightforward, and the issues with comparability across studies and populations would still prevail.

5.2.3 Specified substitution analyses (Paper III)

Our results suggest that the impact of replacing meat with fish on mortality vary according to the specific type of meat being replaced, the choice of fish used as substitute, the quantity of meat intake, and the mortality outcome being examined.

Our preliminary analyses indicated a non-linear relationship between processed meat consumption and mortality outcomes. Consequently, we conducted separate analyses for two groups: women whose level of processed meat consumption was associated with higher mortality (>30 grams per day), and those for whom processed meat intake did not show an association with mortality (≤ 30 grams per day).

We did not observe any associations when replacing processed meat with fish among women who consumed ≤ 30 grams per day; therefore, the subsequent results and discussions pertain to women with a higher intake of processed meat. Additionally, since no associations were

observed when replacing unprocessed red meat with fish and the combined intake of red and processed meat are driven by processed meat, the following discussion will focus on processed meat.

In women whose intake of processed meat is associated with higher mortality, substituting one unit of 20 grams of processed meat with an equivalent unit of lean fish may enhance longevity, with a particular impact on mortality from CVDs. Specifically, for every 20-gram substitution of processed meat with lean fish, we observed an 18% lower CVD mortality among these women. Additionally, our estimates indicate an 8% lower all-cause and cancer mortality per unit of processed meat substituted with lean fish. Substitution with fatty fish appears to be beneficial specifically for CVD mortality, with an estimated 13 % lower mortality per unit of substitution, but not in relation to all-cause or cancer mortality.

Biological mechanisms

Several mechanisms support a causal relationship between replacing processed meat with fish and lower mortality, particularly concerning CVD mortality among women with higher processed meat intake. These mechanisms are related to factors discussed in sections 5.2.2.4 and 5.2.2.5 and will only be briefly mentioned in the following.

Firstly, substituting processed meat with both types of fish decreases the intake of saturated fat and heme iron, both of which have been linked to a higher risk of cardiovascular diseases (CVDs) (sections 5.2.2.4 and 5.2.2.5). Replacing processed meat with fish not only reduces saturated fat consumption but also replaces it with EPA and DHA fatty acids. Unlike saturated fats, these fatty acids are known to benefit cardiovascular health (sections 5.2.2.4 and 5.2.2.5). Fatty fish contain higher amounts of these fatty acids compared to lean fish. Therefore, based on this component, replacing processed meat with fatty fish was expected to be more beneficial than replacing it with lean fish, however this is not supported in our data.

Furthermore, depending on the type of fish, as well as the processing and cooking methods used, replacing processed meat with fish can reduce exposure to harmful compounds such as PAHs, HAAs, and N-nitrosamines (sections 5.2.2.4 and 5.2.2.5). However, several of these compounds could similarly influence both processed meat and fatty fish consumption, which might explain the more pronounced benefits observed when substituting processed meat with lean fish. These include the formation of N- Nitrosamines and the presence of processing-induced contaminants, which are often the result of smoking, curing, or frying at high temperatures (sections 5.2.2.4 and 5.2.2.5). Cooking methods often differ by type of fish; for example, salmon is typically pan-fried, while cod is usually poached. These varying cooking techniques may play a role in the distinct health outcomes associated with replacing processed meat with different types of fish. However, this benefit from poached fish was not observed in relation to colon cancer incidence in NOWAC (152).

Findings from other studies

The extensive reviews conducted for the NNR23 highlighted that there is a knowledge gap regarding the health implications of substitutions for red and processed meat (65), and as highlighted in Paper III, to the best of my knowledge, there are no studies directly comparable to ours that conduct separate analyses concerning meat consumption while also differentiating between lean and fatty fish.

However, in a meta-analysis of prospective cohort studies that assessed the risk of CHD and all-cause mortality associated with substituting red and processed meat with fish/seafood and other protein sources, it was found that replacing one serving of total red meat with fish/seafood was linked to an 8% reduction in all-cause mortality which is similar to our results for lean fish (66). However, this substitution was not associated with the risk of CHD in the same meta-analysis (66). Specifically for the Danish cohort study, which was included in the above-mentioned meta-analyses, substituting processed meat—as well as the combined intake of red and processed meat, but not red meat alone—with total fish was associated with lower all-cause and cancer mortality (153). This supports our results regarding lean fish, and also the results on unprocessed red meat in a comparable Nordic population.

In relation to type 2 diabetes incidence, which is a risk factor for increased mortality, a study that assessed the impact of replacing red and processed meat with alternative protein sources, found no association when red and processed meat were replaced with fish in the EPIC-Inter Act study (154).

6 Conclusions

Drawing from three papers that investigate various aspects of the healthy Nordic diet and its impact on mortality among middle-aged Norwegian women, there are several conclusions that have been reached.

- Among middle-aged Norwegian women, adherence to the HNFI is relatively low with most women classified as medium adherers. High adherence is associated with a generally higher food and energy intake, aligning with findings from other Nordic countries. This suggests that energy standardization of the HNFI should be performed in future studies.
- Food groups central to the healthy Nordic diet may have non-linear associations with health outcomes. Establishing optimal intake levels is complex and warrants further examination in future studies.
- Our results underline the importance of a varied diet. Moderate consumption of the included food groups is either beneficial or not significantly associated with higher mortality at lower intake levels. Conversely, higher intake of perceived healthy foods like fatty fish and low-fat dairy, as well as processed meat, may not be beneficial.
- The promotion of Nordic fruits and vegetables, whole grain products, and lean fish consumption is supported as integral components of a healthy Nordic diet. In contrast, fatty fish, and specifically processed fatty fish products, may be less beneficial than previously assumed. This is particularly concerning and warrants further examination given the strong public health messages promoting increased consumption of fatty fish, including processed products.
- Replacing processed meat with lean fish in women consuming moderate or higher amounts of processed meat is recommended to enhance longevity.
- The promotion of both lean and fatty fish as replacements for moderate or high intake of processed meat is particularly supported for women with a higher risk of cardiovascular disease.

7 Future perspectives

In line with the goals on NCDs reduction with a necessary shift to healthy and sustainable diets as outlined in the background of this thesis, future research should continue to examine the health benefits of Nordic dietary patterns with emphasis on local and seasonal foods. I will suggest some future studies/perspectives on insights gained from this project:

1. Track adherence to the healthy Nordic diet over time, enabling monitoring of both overall dietary patterns and specific food group consumption within the diet.
2. Apply an energy-standardised version of a composite diet score to measure adherence to the healthy Nordic diet in relation to nutrient adequacy of the diet.
3. Investigate fatty fish, and particularly products of fatty fish, in relation to mortality and incidence of NCDs and related risk factors by:
    a. Conduct further research in cohort studies, including men, to explore the association between fatty fish and its products with mortality and other health outcomes such as CRC, type 2 diabetes, and CVDs.
    b. Analyze commonly consumed fatty fish products in Norway for N-Nitrosamines and other contaminants related to environmental factors and processing.
    c. Further explore the optimal consumption levels for fatty fish to balance benefits and potential risks, as previous attempts have been limited due to a lack of data.
4. Unprocessed meat and processed meat should be treated as separate exposures in analyses on health outcomes, as only processed meat consumption was associated with mortality.
5. Investigate transitioning towards a healthy Nordic dietary pattern for disease prevention with specified substitution analyses within individuals with repeated measurements to assess the impact on common NCDs such as CRC and other cancer outcomes, type 2 diabetes, CVD incidence and risk factors in both women and men. This approach will provide more robust data compared to cross-sectional analyses. Potential dietary changes to examine include:
    a. Replacing processed meat with lean and fatty fish to confirm our results.
    b. Replacing processed meat with legumes, fermented dairy products, and whole grains.
6. Examine food biodiversity in the context of the healthy Nordic diet:
    a. Study a broader variety of both wild and cultivated plants in relation to nutrient content and bioactive compounds specific to their terroir.
    b. Explore the relationship between food biodiversity and outcomes such as mortality, incidence of NCDs, and associated risk factors.
7. Examine motivators and barriers for changes towards a healthy Nordic dietary pattern with inclusion of specific varieties of Nordic fruits, berries and vegetables, legumes, whole grain rye, oats, and barley in younger adults.

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Paper I

food & nutrition research

ORIGINAL ARTICLE

Adherence to the Healthy Nordic Food Index in the Norwegian Women and Cancer (NOWAC) cohort

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Popular scientific summary

- This study assessed the dietary composition and lifestyle factors associated with adherence to the Healthy Nordic Food Index by energy-adjusted methods.
- Energy-adjustment pointed to a better dietary composition among high adherers.
- High adherers had a larger fraction of healthy Nordic foods at the expenses of other healthy foods in the diet.
- High adherers had an overall healthier lifestyle.
- Careful adjustment for confounders is warranted when assessing associations between the index and health outcomes.

Abstract

Background: High adherence to the Healthy Nordic Food Index has been associated with better health outcomes, but the results have not been consistent. The association between high adherence and higher intake of energy and healthy and less healthy foods has been persistent across countries, highlighting the need to examine potential confounding by energy intake.
Objective: This study aimed to examine energy-adjusted dietary factors and lifestyle factors related to the index in a Norwegian context.
Design: The study was cross-sectional within the Norwegian Women and Cancer cohort and included 81,516 women aged 41–76. Information about habitual food intake was based on a food frequency questionnaire (FFQ). The index incorporated six food groups (fish, root vegetables, cabbages, apples/pears, whole grain bread, and breakfast cereals). Ordered trend and regression analyses were performed to assess the association between the index and lifestyle and dietary factors with energy-adjusted models.
Results: Nearly one out of four women (22.8%) had low adherence, 49.0% had medium adherence, and 28.2% had high adherence to the index. Intake of energy and of both healthy and less healthy foods increased with increased adherence. Energy adjustment removed the associations between less healthy foods and high adherence and demonstrated a better dietary composition in high adherers. The healthy Nordic foods contributed more to the total food intake in high versus low adherers, and high adherence was associated with a healthier lifestyle.
Conclusion: High adherence was associated with a healthier lifestyle, both concerning diet and other factors. Energy adjustment of potential confounding foods removed associations between high adherence and less healthy foods. The Nordic foods accounted for a larger fraction of the diet among high adherers, at the expense of other healthy foods. Careful adjustment for confounders is warranted when assessing associations between the index and health outcomes.

Keywords: *healthy Nordic diet*; *dietary index*; *dietary pattern regional diet*; *the environmental impact of foods*; *energy adjustment*

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The Mediterranean diet has been related to improved health since the first major studies of the food patterns typical of Crete in the 1960s (1). This dietary pattern consists primarily of plant foods (i.e. fruit, vegetables, whole grain, potatoes, beans, nuts, and seeds), moderate amounts of fish and poultry, low amount of red meat,

and fat primarily from olives, and is strongly associated with reduced cardiovascular risk factors and disease (1–3). The use of indices that measure dietary patterns, such as in the studies on the Mediterranean diet, has become quite widespread in nutritional research (4). In recent years, there has been a growing interest in studying traditional Nordic foods by similar methods in order to investigate whether healthy regional based diets defined by an *a priori* index could display similar health benefits as the Mediterranean diet (5–8). In this context, several diet scores measuring adherence to healthy aspects of a Nordic diet have been developed, such as the Healthy Nordic Food Index, the New Nordic Diet, and the Baltic Sea Diet Score (7–9). High adherence to any of the three indices is associated with a more physically active lifestyle, and by design, high adherers have a higher intake of healthy foods such as whole grains, fish, fruits, and vegetables and thereby of essential nutrients. However, high adherence has been associated with a higher energy intake in all three indices, and with a higher intake of less healthy foods such as red meat and processed meat, and sweets in the Healthy Nordic Food Index and in the New Nordic Diet, and with a higher level of sodium in the Baltic Sea Diet Score. For individuals with higher energy requirements, and consequently a higher food intake, it could be easier to surpass the cutoff values and thereby get a high index score even with a less balanced diet. This is a general problem in studies on indices measuring dietary patterns, and this is why energy adjustment is recommended in these types of studies (10). The Healthy Nordic Food Index has not been investigated in a Norwegian context, but it is desirable to do so as high score on the index in some (11–14), but not all (15, 16), studies has been linked to lower risk of myocardial infarction, stroke, type-2 diabetes, and colorectal cancer in women in other countries. Furthermore, a new WHO report evaluated the health effects associated with a healthy Nordic diet and encourages the Nordic countries to investigate how it can be transformed into dietary advice that can be implemented in the population (17). In order to evaluate the effect of this, there is a need for baseline documentation and generally better understanding of factors related to the healthy Nordic diet in all Nordic countries.

The items included in the original Healthy Nordic Food Index (i.e. rye bread, fish, apples and pears, root vegetables, cabbages, and oatmeal) were chosen due to their positive association with health outcomes, the ability to be produced in the Nordic nature without the use of external energy, traditional use as foods in the region (e.g. not as spices), and availability in the FFQ used in the study (7). A diet based on local produce and food traditions is considered easier to comply with and takes the environmental impact of foods into account (14, 15, 18). This study aimed to describe how the Healthy Nordic Food Index was adapted to the information included in the Norwegian Women and Cancer (NOWAC) cohort and to describe the relationships between the adherence categories on the Healthy Nordic Food Index and the energy adjusted dietary composition and lifestyle factors in the NOWAC cohort.

Materials and methods

Participants

The NOWAC cohort is a prospective nationwide study with more than 170,000 participants (19). In short, the cohort recruitment took place from 1991 to 2007 in batches consisting of women randomly drawn from the central national population registry. Participants answered a self-administered questionnaire about hormonal and reproductive factors, smoking, alcohol, tanning habits, socio-economic conditions, height and weight, physical activity, participation in mammography screening, breast cancer in the family, other diseases, and self-reported health. Follow-up questionnaires were mailed to some of the participants. A majority of the questionnaires included four pages with food frequency questions. The baseline for this study is partly the first NOWAC mailing from 1996 to 1997 and 2003 to 2004 (response rate of 57 and 48%, respectively), and partly the second mailing (follow-up questionnaire) from 1998 to 99 to those enrolled in 1991 to 1992, who at enrolment had not answered an FFQ questionnaire (response rate of 81%). In total, this cohort comprises 101,321 women aged 41–76 at baseline, who answered questionnaires that included the food frequency questions. Participants with missing data on food items included in the Healthy Nordic Food Index (n = 3,913); with an extreme energy intake either <2,500 kJ (n = 924) or >15,000 kJ (n = 138) (20); or with missing data on height (n = 861), weight (n = 1,229), smoking status (n = 1,511), physical activity (n = 7,198), or years of education (n = 4,031) were excluded, leaving 81,516 participants for the analyses.

The NOWAC cohort has received approval for the collection and storing of questionnaire information. All data are stored and handled according to the permission given by the Norwegian Data Inspectorate. Participants have given informed consent, and ethical approval for the NOWAC cohort has been obtained from the Regional Committee for Medical and Health Research Ethics (REK).

Dietary assessment

Diet was assessed using a semi-quantitative FFQ. The FFQ was designed to capture the typical diet during the past year, covering traditional foods in Norway with special emphasis on fish consumption (21). The response

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options were given in fixed frequencies and quantities check-boxes, with 4–7 frequency categories (e.g. carrots: never/seldom, 1–3 per month, 1 per week, 2 per week, 3 per week, 4–5 per week, and 6–7 per week). For some food items, an additional question concerning the typical amount consumed per occasion (portion size) was reported as natural units such as slices of bread, florets of broccoli and number of potatoes, or household units such as tablespoons, with alternatives ranging from 3 to 5 (e.g. carrots: 1/2 a carrot, 1 carrot, 1½ carrots, and 2+ carrots). The Norwegian Weight and Measurement Table, which has standardized portion sizes and weights, was used to convert the consumption of food items to grams (22). Information about energy and nutrient content in foods was obtained from the Norwegian Food Composition Database (23). The calculations of daily intake of food items, energy, and nutrients were done using a statistical program for SAS (SAS Institute Inc., Cary, NC, USA) developed at the Department of Community Medicine, University of Tromsø, for the NOWAC cohort. Missing values were substituted by conservative estimations, missing frequencies were treated as no consumption, and missing portion sizes were assumed to reflect the smallest portion size asked for. Food groups such as apples/pears were divided into single food items on the background of frequency weights obtained from a 24-h dietary recalls study within the NOWAC cohort (24).

Absolute and relative nutrient intakes

Total energy intake were calculated in kilojoule (KJ). The contribution of macronutrients (protein; carbohydrates; total fat; polyunsaturated-, monounsaturated-, saturated-, and trans-fatty acids; and alcohol) was calculated as energy percentages (E%) of total energy intake and compared across adherence categories. The energy-adjusted intake of food items/nutrients was calculated by absolute intake of the food items/nutrients divided by energy intake (KJ) and scaled to intake per 7 MJ, which was the median energy intake in the cohort. This energy intake was chosen to compare absolute and energy-adjusted intake on the same relative scale.

The Healthy Nordic Food Index

The Healthy Nordic Food Index, first developed by Olsen et al., was applied as closely as possible for comparability with previous studies using the index (7). Six food groups were included in the index: fish, root vegetables (carrots and swede), cabbages (cabbage, broccoli/ cauliflower), apples/pears, whole grain bread, and breakfast cereals. Due to the available questions in the FFQ used in the NOWAC cohort, and to some extent differences in food culture between Denmark and Norway, the original rye bread category was replaced by whole grain bread, and breakfast cereals (breakfast cereals/oatmeal/muesli) replaced the original oatmeal category (Table 1). The index

Table 1. Food items from the food frequency questionnaire included in the calculation of the Healthy Nordic Food Index in the Norwegian Women and Cancer cohort

Index food category (number of questions)	Description of food items included in the index food category	Changes	Scoring criteria	Separate portion size question
Fish (12)			Median	
Fish as a main course (6)	• Poached cod, pollock, haddock, Pollack • Fried cod, pollock, haddock, Pollack • Catfish/flounder/redfish • Salmon/trout • Mackerel • Herring		Subcohorts 4 and 5 include a category for 'other fish'	Yes
Fish spread (6)	• Mackerel in tomato/smoked • Mackerel • Caviar • Herring/anchovies • Salmon, smoked/cured • Other fish spread	Subcohort 1 includes questions on tuna and sardine. Subcohort 1 and 2 include three categories, that is, mackerel in tomato/smoked mackerel, caviar, and other fish spread.		No*
Root vegetables (2)	• Carrots • Swede		Median	Yes
Cabbage (2)	• Cabbage • Broccoli/cauliflower		Median	Yes
Apples/pears (1)	• Apples/pears		Median	No
Whole grain bread (1)	• Whole grain bread	Subcohorts 4 and 5 include a question on kneipp bread (partly whole grain).	Median	No
Breakfast cereals (1)	• Cereal/oatmeal/muesli		Consumers/ non-consumers	No

*Correspond to the number of slices of bread with fish spread in the FFQ.

components fish, root vegetables, and cabbages were based on several questions in the FFQ, whereas information on intake of whole grain bread, breakfast cereals, and apples/pears originated from single question. Table 1 shows the food items in the FFQ that were included in the six food groups incorporated in the index. To compute the index score for each participant, the intake of each food item included in the index was divided by the cohort median to assign each participant either 1 point if they were equal to or above the study median, or 0 point if below the study median. For breakfast cereals, the median consumption was 0, so 1 point was given to the participants who consumed any breakfast cereals. Finally, the assigned points for the six food groups were summed up, giving each participant a score between 0 and 6.

Participants with 0–1 points were defined as low adherers, those scoring 2–3 points were defined as medium adherers, and those scoring 4–6 points were defined as high adherers (7).

Foods and nutrients not included in the index

Comparison of the absolute intake (gram/day) and the energy-adjusted intake (gram/7 MJ) of some food items outside the index that contribute to the total energy intake was included in the analysis to get a better understanding of the dietary composition associated with adherence to the index. Some of these food items are not associated with a clear positive or negative health effect (i.e. milk and milk products, chicken, and potatoes), whereas red meat and processed meat, sodium and added sugar are considered less healthy, and other fruits (orange, banana, and 'other fruits') and other vegetables (tomato, salad, and two general categories 'other vegetables' and 'vegetable mix') are considered healthy, but not incorporated in the index.

Fiber (gram) and sodium (milligram) were calculated as absolute intake (gram or milligram/day) and as energy-adjusted intake (gram or milligram/7 MJ). Intake of some essential micronutrients (vitamin D, folate, selenium, zinc, and iron) was included on the basis of surveys in the Nordic countries which have shown that the recommended intake of these nutrients could be difficult to fulfil through the diet alone (25). Micronutrients were calculated as absolute intake (unit/day), and compared to the average requirement (AR), and as energy-adjusted intake (unit/7 MJ). AR is defined as 'the lowest long-term intake level of a nutrient that will maintain a defined level of nutritional status in an individual' (25).

Basic characteristics

Information on age, years of education, body mass index (BMI), physical activity, smoking habits, and region of living was compared across adherence categories.

Age was divided into four age categories: aged 41–50, 51–60, 61–70, and 71–76 years. BMI was based on self-reported weight and height (kg/m^2) (26) and was categorized as below normal weight (BMI <20), normal weight (BMI ≥20–24.9), overweight (BMI ≥25–29.9), and obese (BMI ≥30). Smoking habits were categorized as never, former, and current smokers. Physical activity was divided into low, medium, and high level based on a 10-point scale (27). Years of education was divided into three categories: <10 years of schooling, 10–12 years of schooling, or >12 years of schooling. Region of living in Norway was divided into six regions (Oslo, east, south, west, middle, and north).

Statistical analysis

Median values with 25th and 75th percentiles or proportions (in percentages) were used to present the intake of food items and the basic characteristics of the participants. The food items (both those included and those not included in the Healthy Nordic Food Index) were analyzed using a nonparametric test for trend across ordered groups (nptrend in Stata), which is an extension to the Wilcoxon rank-sum test. Nptrend is testing for a linear trend over the three adherence categories, and it gives the two-sided p-value. It was applied to investigate if the daily intake of food items/nutrients, both as absolute measures and as energy-adjusted measures, was linearly associated with adherence categories (low, medium and high).

The same trend test, in addition to multinomial logistic regression models with the index category as the dependent variable and the low adherence category used as the reference category, was used to analyze associations between adherence categories, and basic demographic and lifestyle characteristics.

Multinomial logistic regression can be used when the outcome variable has more than two categories (28). We found it appropriate to treat the index score variable as categorical instead of ordered for the regression analysis to fit two models comparing medium adherence with low adherence and high adherence with low adherence. Since the outcome variable has three categories, the estimates from the multinomial logistic regression models are given as relative risk ratios (RRR) with 95% confidence intervals.

All regression models were adjusted for energy intake, age, and subcohort. The subcohorts (n = 5) were defined in batches with similar FFQs and time of recruitment. As the data were collected over a period of almost 10 years, some questions have been removed or added, due to the introduction of new foods, discontinuation of foods, or new study hypotheses generated for the subcohorts. A mutually adjusted model that also included education, BMI, physical activity, smoking status, and region of living was applied. All analyses were conducted using the software Stata/MP version 14.0. The significance criterion was set to 5% ($p < 0.05$).

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Results

The number of food items from the FFQ that was included in the calculation of the six index food groups varied from 12 items in the fish category to 2 items in the root vegetables and the cabbage categories, and a single item in the apples/pears, whole grain bread and breakfast cereals categories (Table 1). There were 81,516 women included in the final analyses, distributed as follows across adherence categories: low adherence (score 0–1) 22.8%, medium adherence (score 2–3) 49.0%, and high adherence (score 4–6) 28.2% (Table 2). The intake of all food groups incorporated in the Healthy Nordic Food Index is presented in Table 2. By design, all incorporated food groups increased across adherence categories ($p < 0.001$ for all food groups), with the biggest difference in the food group apples/pears ranging from a median intake of 20 gram/day to 140 gram/day in low and high adherers, respectively. The increment from medium to high adherers was larger than from low to medium adherers for all food groups incorporated in the index.

Intake of energy and macronutrients is presented in Table 3. Participants in the high-adherence category had a higher intake of energy (8.1 MJ in subjects with high adherence, 6.8 MJ medium adherence, 5.8 MJ low adherence) ($p < 0.001$). Although statistically highly significantly related, E% from proteins was only weakly associated with adherence categories, whereas E% from carbohydrates increased slightly, and E% from total-, saturated-, polyunsaturated-, monounsaturated- and trans-fatty acids, and from alcohol slightly decreased across adherence categories ($p < 0.001$ for all relationships).

Table 2. Consumption of foods (gram/day) in the Healthy Nordic Food Index in the low-, medium-, and high-adherence categories in the Norwegian Women and Cancer cohort

Healthy Nordic Food Index components (gram/day)	All women		Healthy Nordic Food Index score					
	n = 81,516		0–1 (22.8%)		2–3 (49.0%)		4–6 (28.2%)	
	Median	P25–P75**	Median	P25–P75	Median	P25–P75	Median	P25–P75
Fish*	48	29–74	29	17–41	47	29–71	69	52–96
Root* vegetables	40	21.1–74.6	17.9	9.3–30.7	38.4	23.1–67.1	69	51.9–97.8
Cabbage*	22	10–45	11	5–19	22	10–43	44	25–67
Apples/pears*	60	20–140	20	9–60	60	20–140	140	60-140
Whole grain bread*	100	100–180	100	34–100	100	100–180	180	100–180
Breakfast cereals*	0	0–21	0	0–0	0	0–21	21	0–31

* Corresponds to a significant ($p < 0.001$) nonparametric test for trend over ordered groups.

**25th and 75th percentile.

Table 3. Consumption of energy and macronutrients in the low-, medium- and high-adherence categories in the Norwegian Women and Cancer cohort

Energy and macronutrients	All women		Healthy Nordic Food Index score						*p*-value (direction of association)*
	n = 81 516		0–1		2–3		4–6		
	Median	P25–P75**	Median	P25–P75	Median	P25–P75	Median	P25–P75	
Energy (MJ)	7.0	5.8–8.2	5.8	4.9–6.9	6.8	5.8–8.0	8.1	7.0–9.3	<0.001 (+)
Protein (E%)	18.1	16.5–19.9	17.9	16.2–19.7	18.2	16.6–20.0	18.2	16.8–19.8	<0.001 (+)
Carbohydrates (E%)	46.2	42.4–50.0	45.1	41.1–49.0	46.1	42.3–49.9	47.2	43.6–50.0	<0.001 (+)
Total fat (E%)	33.3	30.0–36.7	34.5	31.0–38.0	33.4	30.1–36.7	32.4	29.2–35.2	<0.001 (-)
Saturated fat (E%)	13.2	11.6–14.8	13.9	12.2–15.6	13.2	11.7–14.8	12.6	11.2–14.2	<0.001(-)
Polyunsaturated fat (E%)	5.8	4.9–7.0	5.8	4.8–7.0	5.8	4.9–7.0	5.8	4.9–6.8	<0.005 (-)
Monounsaturated fat (E%)	10.4	9.2–11.7	10.8	9.6–12.2	10.4	9.2–11.6	10.1	9.2–11.7	<0.001 (-)
Trans fatty acids (E%)	0.6	0.5–0.7	0.7	0.5 –0.8	0.6	0.5–0.7	0.6	0.5–0.7	<0.001 (-)
Alcohol (E%)	0.8	0.2–2.2	1.0	0.3–2.7	0.8	0.2–2.2	0.7	0.2–1.8	<0.001 (-)

**p*-value generated form a nonparametric test for trend over ordered groups, (+) relates to a positive trend over adherence categories, and (-) relates to an inverse trend over adherence categories.

**25th and 75th percentile.

Comparison of absolute intake and energy-adjusted intake of food items/nutrients not included in the index is presented in Table 4. Absolute intake of fiber, micronutrients, sodium, red meat and processed meat, added sugar, fruits and vegetables, milk and milk products, chicken, and potatoes increased with index category ($p < 0.001$ for all food items and nutrients). The differences in intake became less pronounced after energy adjustment but were still profound for fruits and vegetables, whereas the association with red meat and processed meat and added sugar became inversely associated with a high index category. The difference between absolute intake and energy-adjusted intake of red meat and processed meat increased from a difference of absolute intake of 5 gram/day (from 89 to 94 gram/day) between low- and high-adherence categories to a difference of 27 gram/7 MJ (from 108 to 81 gram) between the low- and high-adherence categories after energy adjustment ($p < 0.001$). The percentage of total fruits and vegetables covered by the items included in the index (cabbages, root vegetables, and apples/pears) varied across the adherence categories from 39.9% coverage in the low-adherence category, 49.7% coverage in the medium-adherence category, to 51.8% in the high-adherence category (results not presented). Participant characteristics in the low-, medium-, and high-adherence categories are presented in Table 5. The high adherers tended to be older, be more educated, have higher BMI, be more physically active, and be non-smokers ($p < 0.01$ for trend over categories for all characteristics).

The relative risk ratios from the multinomial regression analysis are presented in Table 6. The mutually adjusted model showed a greater likelihood of being in the high-adherence category if reporting a higher age and having more than 12 years of schooling (RRR 1.50, 95% CI 1.41–1.59). Being overweight (BMI ≥25–29.9) relative to being in the normal BMI category (≥20–24.9) increased the likelihood of being a high adherer with 32% (RRR 1.32, 95% CI 1.26–1.39). High level of physical activity increased the likelihood of being a high adherer by about 2.63 times (95% CI 2.41–2.87), and being a current smoker gave a 33% reduced likelihood of being in the high-adherence category relative to never having smoked (RRR 0.67, 95 % CI 0.63–0.71). Relatively to women who live in the Norwegian capital Oslo, women living in the western part (RRR 1.91, 95 % CI 1.76–2.09) or in the northern parts (RRR 1.76, 95 % CI 1.60–1.92) were more likely to be high adherers.

Discussion

The Healthy Nordic Food Index was adapted to the data in the NOWAC cohort. Absolute consumption of the index food groups in the NOWAC cohort seems to be higher than for similar food groups in the Swedish Women's Lifestyle and Health cohort, and to the women

Table 4. Comparison of absolute and energy adjusted intake of foods/nutrients not included in the calculation of the Healthy Nordic Food Index in the low-, medium-, and high-adherence categories in the Norwegian Women and Cancer cohort

Energy, foods, and nutrients	Absolute intake (unit/day)									Energy adjusted (unit/7 MJ)									
	All women		Healthy Nordic Food Index category						*p*-value (direction of association)*	All women		Healthy Nordic Food Index category						*p*-value (direction of association)*
	n = 81 516		0–1		2–3		4–6			*n* = 81 516		0–1		2–3		4–6		
	Median	P25–P75*	Median	P25–P75*	Median	P25–P75*	Median	P25–P75*		Median	P25–P75*	Median	P25–P75*	Median	P25–P75*	Median	P25–P75*	
Fiber (g)	21	17–26	16	13–18	21	18–24	27	24–31	<0.001 (+)	21	18–24	18	16–21	21	19–24	23	21–26	<0.001 (+)
Zinc (mg)	9	7–10	7	6–9	9	7–10	10	9–12	<0.001 (+)	9	8–10	9	8–10	9	8–10	8	8–9	<0.001 (–)
Selenium (µg/d)	58	46–71	45	37–55	57	47–69	70	59–84	<0.001 (+)	58	49–69	54	46–64	58	49– 70	61	52–72	<0.001 (+)
Iron (mg)	9	7–11	7	6–9	9	7–10	11	9–12	<0.001 (+)	9	8–10	9	8–10	9	8–10	9	8–10	<0.001 (+)
Folate (µg/d)	178	145–218	140	115–169	175	147–208	218	186–258	<0.001 (+)	178	157–206	167	146–192	178	156– 205	189	167– 216	<0.001 (+)
Vitamin D (µg/d)	6	4–12	4	3–7	6	4–11	8	6–15	<0.001 (+)	6	4–11	5	4–8	6	4–11	7	5–13	<0.001 (+)
Sodium (mg)	2322	1912–2783	1950	1609–2310	2305	1927–2713	2692	2282–3147	<0.001 (+)	2346	2132–2571	2346	2123–2577	2354	2135–2585	2334	2134–2542	<0.001 (–)
Red meat and processed meat (g)	91	63–124	89	61–121	91	63–124	94	64–126	<0.001 (+)	92	66–122	108	78–141	93	67–122	81	58–106	<0.001 (–)
Added sugar (g)	20	13–31	18	11–28	20	13–30	23	16–33	<0.001 (+)	21	14–29	22	14–32	21	14–30	20	14–27	<0.001 (-)

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Table 5. Participant characteristics in the low, medium and high Healthy Nordic Food Index adherence category in the Norwegian Women and Cancer cohort (percentage distribution)

Basic characteristics	All women	Healthy Nordic Food Index score			
	n = 81,516	0–1 points *n* = 18,510	2–3 points *n* = 40,038	4–6 points *n* = 22,968	*p*-value*
	%	%	%	%	
Age					<0.001
41–50	46.7	52.9	46.6	41.8	
51–60	44.4	40.1	44.0	48.6	
61–70	8.5	6.6	9.0	9.2	
71–76	0.4	0.4	0.4	0.5	
Education					<0.001
<10	23.7	24.8	24.5	21.5	
10–12	34.6	36.6	34.5	33.4	
>12	41.7	38.6	41.0	45.2	
BMI (kg/m^2)					0.003
<20	6.5	7.2	6.4	6.1	
≥20–24.9	53.9	54.6	53.3	54.2	
≥25–29.9	30.3	28.7	30.8	30.7	
≥30	9.4	9.6	9.6	9.0	
Physical activity					<0.001
Low	12.8	17.7	12.9	8.9	
Moderate	72.7	70.9	73.3	73.0	
High	14.5	11.4	13.9	18.1	
Smoking status					<0.001
Never	37.1	33.6	36.7	40.4	
Former	33.6	30.7	33.6	35.9	
Current	29.3	35.7	29.6	23.7	
Region of living					
Oslo	9.2	11.7	8.9	7.8	
East	36.0	39.3	35.7	34.0	
South	4.8	4.7	4.8	4.9	
West	21.6	17.5	21.0	26.0	
Middle	7.9	8.7	7.8	7.3	
North	20.5	18.2	21.9	20.0	

Percentage distribution by columns.
*p-value from the nonparametric test for trend over ordered groups.
BMI, body mass index.

in The Diet, Cancer and Health study (6, 7). Whether this reflects an actual difference in intake between countries, or is due to different assessment or criterion in the quantification of food intake in the FFQs, has not been investigated. However, compared to consumer surveys on household level and national 24-h dietary recall surveys in Norway, the intake of the index food groups reported in the NOWAC cohort seems reasonable (29). The macronutrient distribution was quite similar across adherence categories and within the Nordic Nutrition Recommendations (6, 7, 25). This is similar to what has been found in other studies on the Healthy Nordic Food Index (6, 7). Compared to low and medium adherence, high adherence coincided with a higher energy intake, a higher absolute intake of both healthy and less healthy foods, and a higher intake of foods with no clear association with beneficial health outcomes. Median intake in all adherence categories was within the Nordic Nutrition Recommendations for alcohol, carbohydrates, proteins, total fat, monounsaturated fat and polyunsaturated fat, but the consumption of saturated fat was higher than recommended in all adherence categories (25). As the high-adherence category had a higher absolute intake of some micronutrients, they were more likely to meet the average requirements for vitamins and minerals (25). The average requirement for zinc and selenium was met by all

Table 6. Relative risk ratios for medium and high Healthy Nordic Food Index adherence category (with low adherence category as reference) according to non-dietary factors in the Norwegian Women and Cancer cohort

	Medium adherence				High adherence			
	Energy adjusted		Mutually adjusted		Energy adjusted		Mutually adjusted	
	RRR*	95% CI	RRR	95% CI	RRR	95% CI	RRR	95% CI
Age								
41–50	1				1			
51–60	1.42	1.37–1.48	1.42	1.36–1.47	2.00	1.91–2.10	2.03	1.94–2.13
61–70	1.91	1.78–2.10	1.87	1.74–2.02	2.84	2.61–3.10	2.89	2.65–3.16
71–76	1.83	1.36–2.46	1.93	1.43–2.60	3.12	2.22–4.40	3.48	2.46–4.92
Education								
<10	1				1			
10–12	0.91	0.87–0.96	1.03	0.98–1.08	0.98	0.92–1.04	1.18	1.11– 1.26
>12	0.99	0.94–1.04	1.16	1.10–1.22	1.17	1.11–1.24	1.50	1.41–1.59
BMI (kg/m^2)								
<20	0.80	0.75–0.87	0.85	0.78–0.91	0.63	0.57–0.69	0.70	0.64–0.77
≥20–24.9	1		1		1		1	
≥25–29.9	1.22	1.17–1.27	1.19	1.14–1.24	1.35	1.29–1.42	1.32	1.26–1.39
≥30	1.16	1.09–1.24	1.18	1.11–1.26	1.22	1.13–1.31	1.30	1.20–1.41
Physical activity								
Low	1				1			
Moderate	1.29	1.22–1.35	1.34	1.28–1.41	1.73	1.62–1.85	1.83	1.71–1.97
High	1.48	1.38–1.59	1.59	1.48–1.70	2.35	2.16–2.56	2.63	2.41–2.87
Smoking status								
Never	1				1			
Former	1.08	1.04–1.13	1.10	1.05–1.15	1.13	1.07–1.19	1.18	1.12–1.25
Current	0.79	0.75–0.82	0.87	0.83–0.91	0.55	0.52–0.58	0.67	0.63–0.71
Region of living								
Oslo	1				1			
East	1.13	1.06–1.20	1.14	1.07–1.22	1.18	1.09–1.27	1.20	1.11–1.30
South	1.19	1.08–1.32	1.20	1.08–1.32	1.27	1.13–1.44	1.29	1.14–1.46
West	1.42	1.32–1.52	1.45	1.35–1.55	1.82	1.67–1.98	1.91	1.76–2.09
Middle	1.12	1.03–1.21	1.13	1.04–1.23	1.14	1.03–1.26	1.18	1.06–1.31
North	1.61	1.50–1.73	1.58	1.47–1.70	1.77	1.62–1.93	1.76	1.60–1.92

*Relative risk ratios from multinomial logistic regression.
RRR, relative risk ratios; BMI, body mass index.

adherence categories, but only the high-adherence category met the average requirement for iron, folate, and vitamin D. Participants in the high-adherence category exceeded the upper limit for sodium. These results confirm and extend findings in previous studies, which link a high index score with higher food intake in general, and with a higher intake of both healthy foods and foods considered less healthy (6, 7). However, after energy adjustment, high adherers still had higher intake of fiber, micronutrients (except zinc), and fruits and vegetables, but zinc and the food items/nutrients considered less healthy (i.e. red meat and processed meat, added sugar, and sodium) and the foods with no clear health effect were inversely associated with a high index score.

Even though there were highly significant associations for all foods and nutrients analyzed, some are not considered to be of any clinical importance. The marginal differences in actual intake between adherence categories for these food items were statistically significantly associated only because of the high number of participants in the study. Nevertheless, it shows that the index does not merely measure a higher intake of all foods, but that high adherence is associated with better dietary quality. The association between high adherence to a healthy Nordic diet and higher intake of healthy foods, but not with a higher intake of meat and sweets, is supported by Bjørnaråa et al. in a Norwegian study on the New Nordic Diet (5). Furthermore, the higher fraction of the healthy Nordic fruits and

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vegetables in the diet among medium and high adherers compared to low adherers shows that the index measures a healthy Nordic diet and not only a healthy diet. However, it also shows that low adherers of the index get a higher fraction of their total fruits and vegetables from food items outside the index. As these food items, such as tomatoes, oranges, and salad, also have anticipated health benefits, it should be taken into consideration in future studies on the association between the index and health outcomes.

High adherers were more physically active, had higher education, were older and were less likely current smokers. This is in accordance with what was found in the previous studies on the Healthy Nordic Food Index, as well as in studies on the Baltic Sea Diet Score and in relation to the New Nordic Diet (6–9). The association with BMI and adherence category was positive even though the low-adherence category had the highest proportion of women in both the lowest and highest BMI categories. A positive association between BMI and adherence category was found in the Swedish Women Lifestyle and Health study, whereas a high adherence score was related to lower BMI in the New Nordic Diet, as it is in relation the Mediterranean diet (6, 9, 30). In the NOWAC cohort, BMI has been identified as a predominant factor in explaining weight loss attempts, and women trying to lose weight reported a diet with less fat and more fiber, fruits, and vegetables compared to women not trying to lose weight (31). This may explain why we find that high BMI is associated with high adherence.

Women living in the west and north had a higher likelihood of being in the high-adherence category than women living in Oslo. These were the regions with the highest intake of fish, in particular the northern region. The high fish consumption in the northern parts of Norway has been confirmed in national dietary surveys (32). West and north also had a higher intake of root vegetables, possibly reflecting a more traditional dietary pattern in these regions, as the total intake of fruits and vegetables were higher in Oslo compared to north (median 322 gram/day vs. 259 gram/day) and about the same as in the west (330 gram/day). The type of fruits and vegetables more commonly consumed in Oslo might be of a more exotic kind as it is the capital and assumedly more influenced by trends and immigration. The assortment of imported fruits and vegetables is therefore probably better in Oslo than in the rest of the country.

Strengths and limitations

The construction of the index is based on the median of the index variables, as in previous studies on the Healthy Nordic Food Index and the Mediterranean Diet Score (6, 7). Other indices use other scoring criteria such as quintiles or recommended values (4). One could argue that the use of the median criteria will simplify the information to a greater extent compared to other methods. However, The Dietary Patterns Methods Project (4) has made standardized methods for several indices using different scoring criteria with the aim of comparing their ability to capture a healthy diet and their association with mortality. They found that all indices captured the essence of a healthy diet, and the associations with reduced mortality were of similar strength. Hence, they did not recommend one dietary pattern over the other, and neither any particular scoring method in the construction of an index. In addition, when considering the positive health effects associated with the Healthy Nordic Food Index, it seems that the use of the median criteria is an acceptable method. The median cutoff is quite robust against misclassification of extreme values and might be appropriate when considering the accuracy of the FFQ data.

The use of FFQ is likely to introduce errors. These could be both random and systematic. As this FFQ has more questions concerning fish intake compared to the other index food groups, this might introduce overreporting of fish. We have to assume that overreporting due to a higher number of FFQ questions will affect all respondents to the same degree. This will result in a higher intake, but also a higher median cutoff value, and hence not influence the ranking to a major degree. Overreporting of fiber intake has been found in a NOWAC validation study, and overreporting of healthy foods is a well-known challenge with FFQs. If overreporting of healthy foods is systematically related to factors associated with the adherence categories (i.e. education and physical activity), it could bias the association between adherence category and other factors. It is a limitation that the FFQ was not initially designed to assess compliance with a healthy Nordic diet and thus does not capture all relevant food groups such as wild berries (i.e. cloudberries, blueberries, and raspberries), rye and oatmeal-specific whole grain, game, and rapeseed oil (18). However, the intake of foods such as wild berries and game in the general population was not high (29), neither was the intake of rapeseed oil at the time of data collection (33). Even though these are relevant foods in line with the rationale of the index and are relevant in promotion of a healthy Nordic diet, it is not likely that questions about these food items in the FFQ could have enhanced the precision or validity of the index as a measurement tool for a healthy Nordic diet, as most women would not have had a measurable intake. In relation to the Healthy Nordic Food Index, it seems that the six incorporated food items are sufficient to find associations with health outcomes and therefore is a valid tool. It cannot, however, be ruled out that the associations could have been even stronger and more consistent with the inclusion of more healthy Nordic foods. The index food groups 'whole grain bread' and 'breakfast cereals' are based on single question from the FFQ. It is

likely that a more detailed assessment of types of whole grain bread and whole grain products in the breakfast cereals category would give a more precise assessment of the type and amount of whole grain in the diet. However, in a study part of the NOWAC cohort, it was found that whole grain bread captured 84% of the total whole grain consumption in Norwegian women, and approximately 80% of the grains in the cereal category were whole grains (34). Differences in the food components included in the index could affect the associated health outcomes in unknown directions and thereby the comparability of the index between countries. This might be particularly relevant for the index food items that include whole grains as there are some cultural differences between the types of grains commonly consumed in the Scandinavian countries. Danish women consume mostly rye, whereas wheat is the most commonly consumed grain in Norway (34).

The FFQ has been validated through several studies (21, 24, 35, 37). Measurement of serum phospholipids showed that fatty fish intake was reflected in serum (36). A repeated 24-h dietary recalls study (24) found that the FFQ gave a good ranking (Spearman's correlation coefficient) of the participants' intake of foods/drinks consumed frequently (e.g. coffee and milk) and fairly good for macronutrients, but weaker for foods infrequently eaten (e.g. desserts) and for some micronutrients. The FFQ performed well on ranking high and low consumers when compared to recall data, and for the purpose of this study, an adequate ranking of participants is more important than estimating the absolute intake. The food groups in the validation study are not completely overlapping the food items incorporated in the index except for fish, which had a Spearman's correlation coefficient of 0.26 (24). The study also showed an underestimation of energy, fat, added sugar, and alcohol in the FFQ when compared to the 24-h dietary recalls, whereas fiber intake was overestimated compared to the 24-h dietary recalls. A test–retest study on the reproducibility of the FFQ concluded that the FFQ performed within the range described for comparable instruments (21). The large sample size also gives strength to the study as it is representative of the women in Norway at the time of data collection (35).

An advantage of using the *a priori* approach (which is hypothesis-driven based on assumptions of the foods that are included) is that the index is analytically simple to construct, and the results can more easily be compared to other studies than, for instance, data-driven explorative constructs (4). The benefit with measuring dietary patterns and dietary quality is that it adds the possibility of capturing health effects that might not be detectable for the single food component alone, due to the synergistic and combined effects of the components of the included food items (38). In addition, a dietary pattern is more comparable to what people eat, as we do not live eating single food item.

Conclusion

This study links high adherence to a healthy Nordic diet, measured by the Healthy Nordic Food Index to a higher food and energy intake, and to a higher intake of some essential micronutrients. Trend analysis showed a positive relationship between both healthy and less healthy foods and higher adherence categories, but energy adjustment of potential confounding foods removed associations between high adherence and less healthy foods. The results point to an overall better composition of the diet among high adherers compared to low and medium adherers of the Healthy Nordic Food Index. However, both the absolute intake and the relative intake of Nordic and other fruits and vegetables suggest that the index captures Nordic foods and not just healthy foods and lifestyle in general. Furthermore, the healthy Nordic foods accounted for a larger fraction of the diet among high adherers, at the expense of other healthy food items (i.e. salad, tomatoes, oranges, and other vegetables). High adherence was associated with a healthier lifestyle, a higher level of education, and older age. This clustering of healthy lifestyle factors and a better dietary composition among high adherers should be taken into account in further studies on the Healthy Nordic Food Index and health outcomes.

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Corrigendum

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In the published article, the final portion of Table 4 was not published, specifically the last four lines of Table 4.

Additionally, there was an inaccuracy in the description of the scoring methodology used to calculate the Healthy Nordic Food Index. It was incorrectly stated that an intake below the median is scored as zero points, and an intake at or above the median is scored as one point. The scoring was conducted such that an intake at or below the median received a score of zero, and an intake above the median was awarded a score of 1. This has now been updated (page 4 in the publication) as follows: 'To compute the index score for each participant, the intake of each food item included in the index was divided by the cohort median to assign each participant either a score of 1 if they were above the study median, or a score of 0 if equal to or below the study median'.

The authors sincerely regret any inconvenience this may have caused.

These discrepancies do not affect any of the numerical data or the results presented in the tables. The overall results and conclusions are upheld.

Table 4. Comparison of absolute and energy-adjusted intake of foods/nutrients not included in the calculation of the Healthy Nordic Food Index in the low, medium, and high adherence categories in the Norwegian Women and Cancer cohort

Energy, foods and nutrients	Absolute intake (unit/day)									Energy-adjusted (unit/7MJ)								
	All women *n* = 81,516		Healthy Nordic Food Index category						P (direction of association)*	All women *n* = 81,516		Healthy Nordic Food Index category						P (direction of association)*
			0–1		2–3		4–6					0–1		2–3		4–6		
	Median	P25–P75	Median	P25–P75	Median	P25–P75	Median	P25–P75		Median	P25–P75	Median	P25–P75	Median	P25–P75	Median	P25–P75	
Fibre (g)	21	17–26	16	13–18	21	18–24	27	24–31	<0.001 (+)	21	18–24	18	16–21	21	19–24	23	21–26	<0.001 (+)
Zinc (mg)	9	7–10	7	6–9	9	7–10	10	9–12	<0.001 (+)	9	8–10	9	8–10	9	8–10	8	8–9	<0.001 (–)
Selenium (µg/day)	58	46–71	45	37–55	57	47–69	70	59–84	<0.001 (+)	58	49–69	54	46–64	58	49–70	61	52–72	<0.001 (+)
Iron (mg)	9	7–11	7	6–9	9	7–10	11	9–12	<0.001 (+)	9	8–10	9	8–10	9	8–10	9	8–10	<0.001 (+)
Folate (µg/day)	178	145–218	140	115–169	175	147–208	218	186–258	<0.001 (+)	178	157–206	167	146–192	178	156–205	189	167–216	<0.001 (+)
Vitamin D (µg/day)	6	4–12	4	3–7	6	4–11	8	6–15	<0.001 (+)	6	4–11	5	4–8	6	4–11	7	5–13	<0.001 (+)
Sodium (mg)	2,322	1,912–2,783	1,950	1,609–2,310	2,305	1,927–2,713	2,692	2,282–3,147	<0.001 (+)	2,346	2,132–2,571	2,346	2,123–2,577	2,354	2,135–2,585	2,334	2,134–2,542	<0.001 (–)
Red-and processed meat (g)	91	63–124	89	61–121	91	63–124	94	64–126	<0.001 (+)	92	66–122	108	78–141	93	67–122	81	58–106	<0.001 (–)
Added sugar (g)	20	13–31	18	11–28	20	13–30	23	16–33	<0.001 (+)	21	14–29	22	14–32	21	14–30	20	14–27	<0.001 (–)
Fruit/vegetables (g)	305	203–444	183	115–258	296	213–403	456	344–593	<0.001 (+)	309	210–440	217	138–315	303	213–429	397	294–528	<0.001 (+)
Milk and milk products (g)	219	108–360	185	89–308	217	107–352	245	129–438	<0.001 (+)	218	115–374	224	110–389	220	115–373	213	118–360	<0.001 (–)
Chicken (g)	16	6–16	6	6–16	16	6–16	16	6–16	<0.001 (+)	13	6–20	13	6–22	13	6–20	12	5–19	<0.001 (–)
Potatoes (g)	126	50–126	63	50–126	126	50–126	126	50–126	<0.001 (+)	100	51–143	96	49–158	105	51–143	96	50–143	<0.001 (–)

*p-value generated from a nonparametric test for trend over ordered groups, (+) relates to a positive trend over adherence categories, and (–) relates to an inverse trend over adherence categories.

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Paper II

BMC Public Health

RESEARCH ARTICLE

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Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study

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Abstract

Background: The shape of the associations between intake of foods basic in a healthy Nordic diet and long-term health is not well known. Therefore, we have examined all-cause mortality in a large, prospective cohort of women in Norway in relation to intake of: Nordic fruits and vegetables, fatty fish, lean fish, wholegrain products, and low-fat dairy products.

Methods: A total of 83 669 women who completed a food frequency questionnaire between 1996 and 2004 were followed up for mortality until the end of 2018. Cox proportional hazards regression models were used to examine the associations between consumption of the Nordic food groups and all-cause mortality. The Nordic food groups were examined as categorical exposures, and all but wholegrain products also as continuous exposures in restricted cubic spline models.

Results: A total of 8 507 women died during the 20-year follow-up period. Nordic fruits and vegetables, fatty fish and low-fat dairy products were observed to be non-linearly associated with all-cause mortality, while higher intake of lean fish and wholegrain products reduced all-cause mortality. Intake levels and hazard ratios (HR) and 95% confidence intervals (CI) associated with lowest mortality were approximately 200 g/day of Nordic fruits and vegetables (HR 0.83 (95% CI: 0.77–0.91)), 10–20 g/day of fatty fish (10 g/day: HR 0.98 (95% CI: 0.94–1.02)) and 200 g/day of low-fat dairy products (HR 0.96 (95% CI: 0.81–1.01)) compared to no consumption. Consumption of fatty fish $\geq$ 60 g/day compared to no intake statistically significantly increased the mortality (60 g/day: HR 1.08 (95% CI: 1.01–1.16)), as did consumption of low-fat dairy products $\geq$ 800 g/day compared to no intake (800 g/day: HR 1.10 (95% CI: 1.02–1.20)). After stratification by smoking status, the observed association between Nordic fruits and vegetables and all-cause mortality was stronger in ever smokers.

Conclusion: The associations between intake of foods basic in healthy Nordic diets and all-cause mortality may be non-linear. Therefore, assumptions of linear associations between traditional Nordic food groups and health outcomes could lead to wrong conclusions in analyses of healthy Nordic diets.

Keywords: Healthy Nordic diet, Sustainable diet, Fatty fish, Lean fish, Low-fat dairy, Wholegrains, Fruits and vegetables, All-cause mortality, Non-linear, Cohort study

Background

Over the past decade there has been a movement towards health-promoting regional and environmentally friendly diets, and healthy Nordic diets have gained much attention in this context [1–8]. Healthy Nordic diets can be

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described as dietary patterns with emphasis on foods that have traditionally been used and cultivated in the Nordic region, such as fish, wholegrains like rye and oats, root vegetables, cabbages, fruits like apples and pears, rapeseed oil and, to a varying degree, including low-fat dairy products [1, 2].

In a previous study on healthy Nordic diet and mortality by Olsen et al., it was concluded that traditional Nordic foods should be considered in public health recommendations [1]. Optimal intake levels of traditional Nordic foods, and the ideal composition of healthy Nordic diets for long-term health are, however, uncertain. Subsequent studies have supported the results by Olsen et al. and linked high compliance with healthy Nordic diets to longevity in populations across Nordic countries, and to reduced risk of cardiovascular diseases, type 2 diabetes, and colorectal cancer [3–8]. The evidence is, however, not conclusive [9–12].

The heterogeneity of cut-off points used to classify intake level of foods included in healthy Nordic diet scores might be the reason for failure to identify credible evidence for health benefits of a healthy Nordic diet [12]. Differences in cut-off points between studies also create confusion for public health recommendations. Another dilemma with combined diet scores, such as those commonly used to measure adherence to healthy Nordic diets, is the assumption that they follow a linear scale, while dose–response relationships between foods and health-outcomes can be non-linear [13].

It is therefore relevant to examine potentially non-linear associations between food groups basic in healthy Nordic diets, and long-term health. Hence, the aim of this study is to evaluate the shape of the associations between the intake of Nordic fruits and vegetables, fatty fish, lean fish, wholegrain products, and low-fat dairy products and all-cause mortality, using a modelling tool that allows non-linear relationships.

Materials and methods

Study design and setting

The design of the Norwegian Women and Cancer Study (NOWAC) has been described in detail previously [14]. Briefly put, a random sample of 172 000 women drawn from the Norwegian National Population Registry was enrolled in two waves from 1991 to 2007. Participants completed a mailed, self-administered baseline questionnaire including questions about anthropometric, sociodemographic, dietary, reproductive, and lifestyle factors. Follow-up questionnaires were collected over approximately 6-year intervals after recruitment.

The sample for this prospective cohort study included 101 316 women aged 41–76 who completed a food frequency questionnaire (FFQ) during baseline mailing (waves 1996–1997 and 2003–2004; response rates of 57% and 48%, respectively), or during the first follow-up (wave 1991–1992 enrolment did not cover FFQ data; a response rate of 81%). Women with no follow-up ($n=16$) were excluded. We further excluded women with implausible daily energy intake (< 2 500 kJ ($n=1$ 033) or > 15 000 kJ ($n=141$)), and women with missing information on the following variables: body mass index (BMI) ($n=2$ 272), physical activity ($n=8$ 548), smoking habits ($n=1$ 407), and education ($n=4$ 230), leaving a total number of 83 669 women for the present analysis.

Assessment of Nordic foods intake

Diet was assessed using validated, semi-quantitative food frequency questionnaires (FFQ) with approximately 85 frequency items [15–17]. A representative sample of the questionnaires used has previously been published [18]. The FFQ was designed to measure the typical diet during the past year with special emphasis on fish consumption. The response options were given with four to seven frequency categories ranging from never/seldom to six or more per week. Portion sizes for some food items were provided as natural (e.g., number of carrots) or household units (e.g., tablespoons).

The Norwegian Weight and Measurement Table with standardised portion sizes and weights was used to convert the consumption of food items to grams [19], and information about the nutrient content in foods was obtained from the Norwegian Food Composition Database [20]. The calculations of daily intake of food items, energy and nutrients were made using a statistical syntax in SAS (SAS Institute Inc., Cary, NC, USA) developed at the Department of Community Medicine, University of Tromsø, for the NOWAC cohort. Missing frequency values were treated as no consumption, and missing portion sizes were set to the smallest portion size alternative.

We have considered consumption of five traditional Nordic food groups as exposure of interest, selected to reflect components of a healthy Nordic diet [1, 2]; Nordic fruits and vegetables (apples/pears, broccoli/cauliflower, cabbage, carrots, swede); fatty fish classified as fish with ≥ 4% fat in the meat (salmon, trout, herring, mackerel); lean fish containing < 4% fat in the meat (cod, haddock, plaice) excluding products like fish cakes, fish balls, fish spread and stew; wholegrain products (wholegrain bread and breakfast cereals); low-fat dairy products (skimmed- and semi-skimmed milk, and yoghurt). We analysed lean and fatty fish separately because they are specified in our dietary guidelines as sources of specific essential nutrients such as vitamin D and omega-3 fatty acids from fatty fish, and iodine from lean fish [21]. Each food group was divided into four consumption categories, which were roughly based on serving sizes, dietary

advice, or multiples thereof. Cut-off points for each food group are given in the tables where the categorical analyses are presented (Table 2).

Assessment of covariates

The following covariates were included in the analysis: physical activity, body mass index (BMI), smoking status, education, and intake of energy, alcohol and processed red meat.

Physical activity level was included based on validated self-report on a ten-point scale estimating physical activity at home, at work, exercising and walking, and was categorised as low (1–4 points), medium (5–6 points) or high (7–10 points) [22].

BMI (kg/m^2) was calculated based on self-reported height and weight and has been found to provide valid ranking of BMI in NOWAC [23]. BMI was categorised in four categories: < 20, 20–24.9, 25–29.9, ≥ 30 kg/m^2.

The smoking variable was computed by combining information on smoking status (never, former, and current), with age at smoking initiation for those who have ever smoked and additionally information of pack years for current smokers who started smoking < 20 years of age. Smoking exposure was then divided into six categories: never smoker, current heavy smoker (smoking 20 or more cigarettes per day since smoking initiation) early starter (age at start smoking < 20), current moderate smoker (smoking less than 20 cigarettes per day since smoking initiation) early starter, current smoker late starter (age at start smoking ≥ 20), former smoker early starter, former smoker late starter.

Education level was based on self-reported years of schooling and was divided into three categories (< 10, 10–12, > 12 years of schooling). Energy intake (kJ per day) was included in the analyses as a continuous variable excluding energy from alcohol. Intake of alcohol was included as a categorical variable as a group of non-consumers and two categories representing low and higher intake (g/day): non-consumers, 0–5, > 5. Intake of processed red meat included meatballs, hamburgers, sausages, and sandwich meats (e.g., liver pâté), and was divided into four categories (g/day): < 15, 15–29, 30–44, ≥ 45.

As a common procedure for dietary analyses in the NOWAC study, subcohorts ($n = 5$) were included in the analyses [18]. Subcohorts were constructed by grouping together the FFQs that were most similar as some dietary questions have been added to the FFQ due to new products available on the market, improvements of the questionnaire and specific hypotheses, and which were completed closest together in time, as the data were collected over a period of almost ten years.

Outcome

The women were followed from return of the FFQ and until death or censoring, which was the date of emigration or end of follow-up on 31 December 2018. The source for death record linkage was the Norwegian Cause of Death Registry, which is the official cause of death statistics for Norway issued by the Norwegian Institute of Public Health [24].

Statistical methods

We present the distribution of covariates for the lowest and the highest consumption categories of the Nordic food groups, as mean (and standard deviation) for age, as median intake (and 10th–90th percentile) for energy, and percentages (%) for the covariates expressed categorically. Spearman's rank-order correlation was used to test the associations between the intake of the Nordic food groups. Cox proportional hazards regression models, with age as the underlying time scale, were used to examine the associations between consumption of the five Nordic food groups and all-cause mortality. The proportional hazards assumption was tested with a Schoenfeld residuals test.

Covariates included in the analysis were chosen based on the literature and selected with the use of Directed Acyclic Graphs (DAGs) (Supplemental Fig. 1) [25]. Factors known to be associated with mortality such as smoking, physical activity, BMI, intake of alcohol, intake of processed red meat and education, were included risk factors in the DAG. In addition, total energy intake and central comorbidities were included in the DAG. We constructed two different models, one adjusted for age and one multivariable-adjusted model.

The multivariable model was adjusted for age, the healthy Nordic food groups (mutually adjusted), physical activity, BMI group, smoking status, education, intake of energy, alcohol, and processed red meat. Both models examined the Nordic food groups expressed as categorical exposures, and four of the Nordic food groups were further examined in the multivariable-adjusted model as continuous exposures with restricted cubic splines. The wholegrain products variable could not be examined with restricted cubic splines because it is only based on two FFQ frequency questions and the distribution of values could not be approximated to a continuous variable.

The number of knots in the restricted cubic splines was determined by testing and comparing models with three, four and five knots according to the Akaike and Bayesian information criteria to compare how well the different models fit the data. Models with the smallest AIC value were judged to fit the data better, resulting in three knots at fixed percentiles (10, 50, 90) of the distribution

[26]. The p-value for non-linearity in the restricted cubic spline analysis was calculated by performing a Wald test of the null hypothesis that the coefficient of the second spline was equal to zero. In all models, subcohorts ($n=5$) were included as a stratum variable.

Previous analyses in NOWAC have shown associations between dietary patterns and smoking habits [27]. We therefore explored potential interactions between the Nordic food groups and smoking habits, by adding product terms in the mutually adjusted categorical models and performing likelihood-ratio tests to compare model fit between the models with and without these terms. If a statistically significant interaction effect was observed, we performed separate analyses for never and ever smokers.

We performed various sensitivity analyses. To minimise the chance of reverse causation (by including women who were ill and therefore had changed their food habits) we started follow-up two years after enrolment. As findings for Nordic fruits and vegetables in part could reflect the influence of the consumption of other fruits and vegetables [28], we made further adjustments including other fruits and vegetables in the multivariable-adjusted model. We decided to include BMI as a confounding factor even though BMI may be considered a mediating factor between diet and health outcomes. The reason for this was that the relationship between BMI and reported food intake measured at one time point is difficult to determine, and over- and under-reporting of different food groups has been related to BMI status [29]. As a sensitivity analysis, we tested omitting BMI in the multivariable-adjusted model for the categorical analyses (Supplemental Table 3). A p-value <0.05 was considered statistically significant. The statistical analyses were performed using Stata / MP 16.0.

Results

Descriptive

During a median of 20.0 (range 0.0–22.6) years of follow-up, 8 507 women died, mainly from cancer (ICD-10 codes C00-C97) ($n=4$ 469) and cardiovascular diseases (ICD-10 codes I00-I99) ($n=1$ 538). Table 1 shows the number of participants, number of deaths, median intake of the Nordic foods, and the distribution of the covariates in the highest and lowest categories of the Nordic foods Table 1.

The oldest women were in the high-consumption group of lean and fatty fish. Within the other Nordic food groups, the age differences between categories were minimal. We found a general tendency of women in the high-consuming categories within the Nordic food groups being more physically active, and more likely to be never smokers except among high consumers of lean and fatty fish. Across all food groups, energy intake was higher in the high-consumption categories. The proportions of women reporting overweight (BMI 25.0–29.9 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) were higher among high consumers of Nordic fruits and vegetables, whereas the opposite was observed within the wholegrain products group. Women in the highest consumption groups generally had higher education, except from the food group lean fish, where we see a higher proportion of women with low education in the highest intake category.

The highest correlation coefficient between the intake of the different Nordic food groups was found between lean and fatty fish, but the correlation was still quite low $r_s=0.21$ (Supplemental Table 1).

Categorical analyses for all Nordic food groups

Table 2 describes all-cause mortality according to intake categories of the Nordic food groups. Consumption of Nordic fruits and vegetables in all intake categories higher than <100 g/day was associated with lower mortality in the age-adjusted model, but when further adjusted in the multivariable-adjusted model, it was only intake of 100–199 g/day compared to <100 g/day that remained significant (HR 0.91 (95% CI: 0.87–0.96)). For fatty fish, the intake of 15–29 g/day compared to <5 g/day was associated with reduced mortality in the age-adjusted model, but after further adjustments in the multivariable-adjusted model, consumption of fatty fish was no longer associated with mortality. Intake of lean fish ≥ 45 g/day compared to <15 g/day reduced all-cause mortality (HR 0.93 (95% CI: 0.88–0.99)), and a linear trend over categories was found ($P=0.04$). For low-fat dairy products, an intake of <200 g/day compared to non-consumption was associated with reduced mortality in the multivariable-adjusted model (HR 0.91 (95% CI: 0.85–0.96). Increased intake of wholegrain products was associated with lower mortality in the multivariable-adjusted model (P for trend over categories $=0.02$).

Restricted cubic spline regression analyses

The restricted cubic spline regression analyses showed a significant J-shaped association for the food groups Nordic fruits and vegetables (Fig. 1A), low-fat dairy products (Fig. 1B) and fatty fish (Fig. 1C), but not for lean fish (Fig. 1D) Fig. 1 (Additional file 1).

For Nordic fruits and vegetables, the nadir (the intake level associated with lowest mortality) was observed at 200 g/day (HR 0.83 (95% CI: 0.77–0.91) compared to no consumption) (Fig. 1A). For low-fat dairy products, the nadir was observed at 200 g/day (HR 0.96 (95% CI: 0.91–1.01) compared to no consumption. Consumption of low-fat dairy products ≥ 800 g/day compared to no consumption increased mortality (Fig. 1B). For fatty fish,

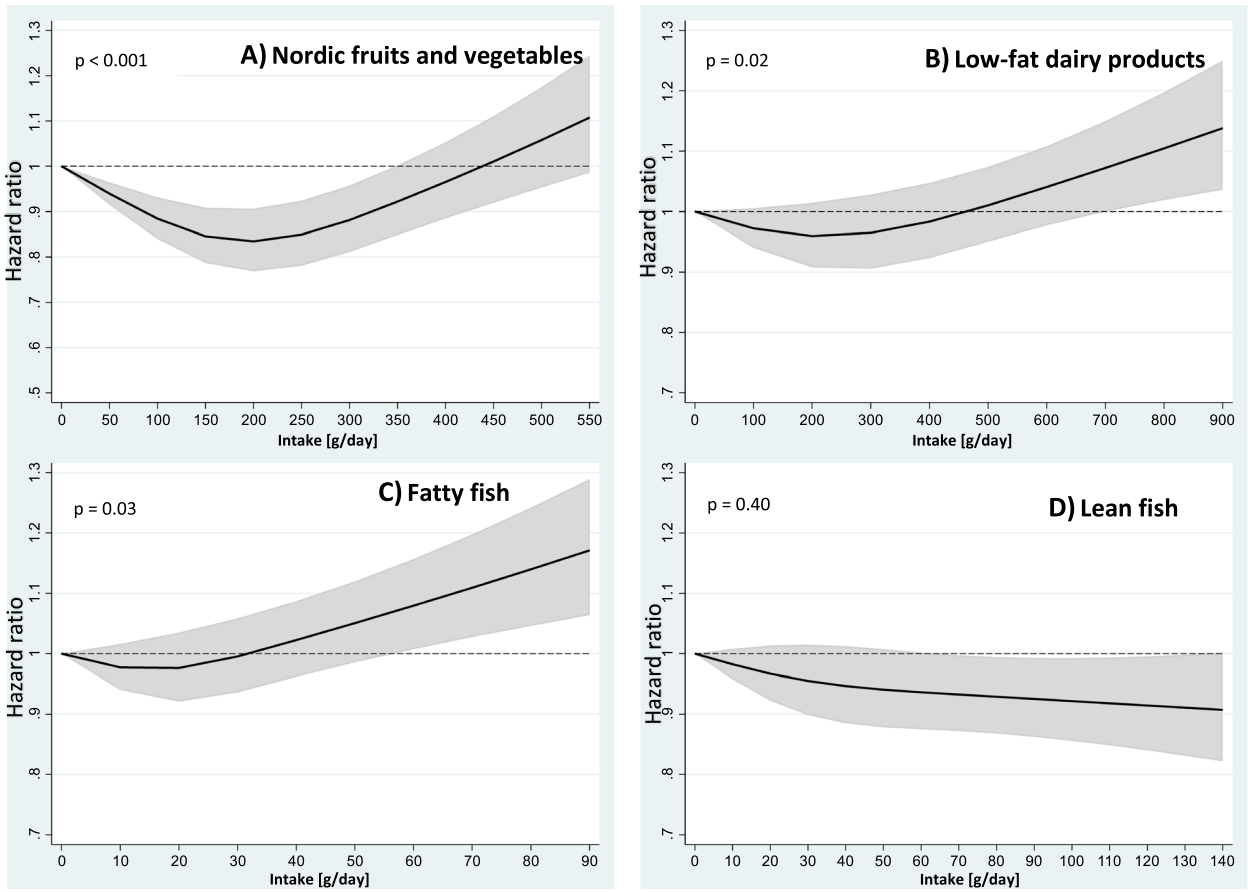

Fig. 1 Intake of Nordic food groups and all-cause mortality by restricted cubic spline regression. From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study. Nordic food groups modeled by restricted cubic splines with 3 knots at percentiles 10%, 50% and 90% (Nordic fruits and vegetables 57; 164; 336. Low-fat dairy products 0; 138; 550. Fatty fish 0; 13; 35. Lean fish 0; 24; 66 g/day). Black line hazard ratio, grey area 95% confidence interval. Mutually adjusted for the healthy Nordic food groups, age (underlying timescale), BMI < 20, 20–24.9, 25–29.9, ≥ 30 (kg/m2), physical activity (low, medium, high), smoking status (never, current heavy smoker early starter, current moderate smoker early starter, current smoker late starter, former smoker early starter, former smoker late starter), education (< 10, 10–12, > 12 years of schooling), intake of energy (kJ/day continuous), alcohol (non-consumer, 0–5, > 5 g/day), and processed red meat (< 15, 15–29, 30–44, ≥ 45 g/day), stratified by subcohorts (n = 5)

the nadir was observed at an intake level of 10–20 g/day (20 g/day: HR 0.98 (95% CI: 0.92–1.03)), but the mortality was not significantly lower than for not consuming fatty fish at all (Fig. 1C). Excessive consumption, on the other hand, was associated with increased mortality from 60 g/day (HR 1.08 (95% CI: 1.01–1.16)). For lean fish, we observed that increased intake reduced mortality, and that intake between 80–110 g/day was statistically significantly associated with all-cause mortality (80 g/day: HR 0.93 (95% CI: 0.87–0.99)) (Fig. 1D).

Intake of Nordic fruits and vegetables and mortality in never and ever smokers

We observed a significant interaction between smoking status and Nordic fruits and vegetables regarding all-cause mortality, and thus separate analyses for never and ever smokers are also presented. The median consumption of Nordic fruits and vegetables was 173 g/day (P10: 65 g/day, P90: 342 g/day) in never smokers, and 159 g/day (P10: 53 g/day, P90: 332 g/day) in ever smokers (Supplemental Table 2).

In the categorical analysis, intake between 100–199 g/day compared to < 100 g/day was associated with reduced mortality among never smokers with similar strength as in the unstratified analysis (HR 0.89 (95% CI 0.81–0.99). However, for ever smokers, increased intake was associated with lower mortality in the multivariable-adjusted model (*P* for trend over categories < 0.001) (Table 3). In the restricted cubic spline regressions, the observed association was only significant in ever smokers with the

Table 1 Population distribution, intake of Nordic food groups and baseline information according to intake categories of Nordic food groups. From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study

Nordic food groups	**Nordic fruits and vegetables**		**Wholegrain products**		**Fatty fish**		**Lean fish**		**Low-fat dairy products**	
Lowest and highest intake categories (g/day)	**< 100**	**≥ 300**	**< 60**	**≥ 180**	**< 5**	**≥ 30**	**< 15**	**≥ 45**	**Non-consumers**	**≥ 400**
Median intake (g/day)	65	368	34	180	0	42	6	61	0	550
Number of women	20 537	11 727	14 724	28 435	23 792	11 921	28 254	18 012	13 916	16 702
Number of deaths	2 530	1 022	1 419	2 869	2 497	1 403	2 529	2 486	1 554	1 992
Covariates										
Age, mean (SD)	51.2 (6.6)	52.2 (5.9)	52.1 (6.1)	51.1 (6.5)	51.0 (6.5)	53.1 (6.4)	51.0 (6.1)	53.4 (6.9)	51.7 (6.3)	51.5 (6.9)
Physical activity n (%)										
Low	6 811 (33)	2,500 (21)	4 494 (30)	6 918 (24)	6 984 (29)	2 872 (24)	8 076 (29)	4 672 (26)	4 202 (30)	4 374 (26)
Medium	8 582 (42)	4 752 (41)	6 027 (41)	12 594 (44)	10 138 (43)	4 919 (41)	11 744 (41)	7 690 (43)	5 703 (41)	7 256 (44)
High	5 144 (25)	4 475 (38)	4 203 (29)	8 923 (32)	6 670 (28)	4 130 (35)	8 434 (30)	5 650 (31)	4 011 (29)	5 072 (30)
BMI n (%)										
< 20	1 686 (8)	606 (6)	900 (6)	2 348 (8)	1 690 (7)	705 (6)	2 070 (7)	962 (5)	1 212 (9)	981 (6)
20–24.9	11 336 (55)	5 948 (51)	7 442 (51)	16 232 (57)	12 690 (53)	6 285 (53)	15 478 (55)	9 181 (51)	7 472 (54)	9 179 (55)
25–29.9	5 666 (28)	3 869 (33)	4 771 (32)	7 513 (27)	7 164 (30)	3 701 (31)	8 143 (29)	5 924 (33)	3 912 (28)	5 026 (30)
≥ 30	1 849 (9)	1 304 (11)	1 611 (11)	2 342 (8)	2 248 (10)	1 230 (10)	2 563 (9)	1 945 (11)	1 320 (9)	1 516 (9)
Smoking status n (%)										
Never	6 452 (31)	4 477 (38)	4 434 (30)	10 820 (38)	8 263 (35)	4 078 (34)	9 846 (35)	6 078 (34)	4 434 (30)	10 820 (38)
Current heavy smoker early starter	2 129 (10)	508 (5)	1 453 (10)	1 719 (6)	1 686 (7)	885 (7)	2 209 (8)	1 227 (7)	1 453 (10)	1 719 (6)
Current moderate smoker early starter	3 365 (16)	1 090 (9)	2 165 (15)	3 784 (13)	3 515 (15)	1 431 (12)	3 770 (13)	2 366 (13)	2 165 (15)	3 784 (13)
Current smoker late starter	2 408 (12)	875 (8)	1 338 (9)	2 753 (10)	2 371 (10)	1 296 (11)	2 373 (9)	2 280 (13)	1 338 (9)	2 753 (10)
Former smoker early starter	3 961 (19)	3 217 (27)	3 821 (26)	5 885 (21)	5 122 (21)	2 677 (23)	6 902 (24)	3 439 (19)	3 821 (26)	5 885 (21)
Former smoker late starter	2 222 (11)	1 560 (13)	1 513 (10)	3 474 (12)	2 835 (12)	1 554 (13)	3 154 (11)	2 622 (14)	1 513 (10)	3 474 (12)
Education n (%)										
< 10 years	5 882 (29)	2 284 (19)	3 530 (24)	7 062 (25)	6 930 (29)	2 848 (24)	5 562 (20)	6 655 (37)	3 801 (27)	4 440 (26)
10–12 years	7 258 (35)	3 953 (34)	5 345 (36)	9 432 (33)	8 664 (36)	3 797 (32)	9 911 (35)	6 057 (34)	5 017 (36)	5 813 (35)
> 12 years	7 397 (36)	5 490 (47)	5 849 (40)	11 941 (42)	8 198 (35)	5 276 (44)	12 781 (45)	5 300 (29)	5 098 (37)	6 449 (39)
Alcohol n (%)										
Non-consumers	4 447 (22)	2 415 (21)	2 646 (18)	6 914 (24)	6 403 (27)	2 030 (17)	5 241 (19)	4 556 (25)	3 218 (23)	3 949 (24)
0–5 (g/d)	11 029 (54)	6 590 (56)	7 981 (54)	15 621 (55)	12 991 (55)	6 203 (52)	15 235 (54)	9 971 (56)	7 156 (51)	9 159 (55)
> 5 (g/d)	5 061 (24)	2 722 (23)	4 097 (28)	5 900 (21)	4 398 (18)	3 688 (31)	7 778 (27)	3 485 (19)	3 542 (26)	3 594 (21)
Energy P50 (P10–P90) MJ/d	6.1 (4.1–8.5)	7.5 (5.4–10.3)	5.5 (3.6–8.1)	7.9 (6.1–10.3)	6.4 (4.3–8.9)	7.5 (5.3–10.2)	6.4 (4.3–8.8)	7.3 (5.1–10.0)	6.2 (4.1–8.8)	7.6 (5.6–10.1)
Processed red meat intake n (%)										
< 15 (g/d)	4 034 (20)	2 903 (25)	3 599 (24)	4 269 (15)	4 538 (19)	2 852 (24)	6 328 (23)	3 540 (20)	2 948 (21)	2 599 (16)
15–29 (g/d)	6 135 (30)	3 311 (28)	4 493 (31)	7 379 (26)	6 693 (28)	3 491 (29)	8 236 (29)	5 293 (29)	3 905 (28)	4 718 (28)

Table 1 (continued)

Nordic food groups	Nordic fruits and vegetables		Wholegrain products		Fatty fish		Lean fish		Low-fat dairy products	
30–44 (g/d)	5 029 (24)	2 676 (23)	3 502 (24)	7 274 (26)	5 986 (25)	2 743 (23)	6 827 (24)	4 369 (24)	3 287 (24)	4 472 (27)
≥ 45 (g/d)	5 339 (26)	2 837 (24)	3 130 (21)	9 513 (33)	6 575 (28)	2 835 (24)	6 863 (24)	4 810 (27)	3 776 (27)	4 913 (29)

Percentage distribution by columns

SD standard deviation

g/day gram per day

MJ/d mega Joule per day

P50 median intake, *P10* the 10 th percentile, *P90* the 90 th percentile

Table 2 Hazard ratios (HR) and all-cause mortality according to intake categories of healthy Nordic food groups. From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study

Healthy Nordic food groups	Intake categories (g/day)	Total N	No. of deaths	All-cause mortality		
				Age-adjusted*	Multivariable-adjusted model**	P for trend
				HR (95% CI)	HR (95% CI)	
Nordic fruits and vegetables	< 100	20 537	2 530	1.00	1.00	0.94
	100–199	32 501	3 168	0.79 (0.75–0.83)	0.91 (0.87–0.96)	
	200–299	18 904	1 787	0.77 (0.72–0.82)	0.96 (0.90–1.02)	
	≥ 300	11 727	1 022	0.78 (0.73–0.84)	1.00 (0.91–1.08)	
Wholegrain products	< 60	14 724	1 419	1.00	1.00	0.02
	60–119	24 439	2 669	0.91 (0.85–0.97)	0.96 (0.90–1.03)	
	120–179	16 071	1 550	0.78 (0.73–0.83)	0.91 (0.84–0.98)	
	≥ 180	28 435	2 869	0.84 (0.79–0.90)	0.89 (0.82–0.97)	
Fatty fish	< 5	23 792	2 497	1.00	1.00	0.17
	5–14	25 882	2 517	0.94 (0.89–1.00)	1.01 (0.95–1.07)	
	15–29	22 074	2 090	0.90 (0.85–0.96)	0.99 (0.93–1.05)	
	≥ 30	11 921	1 403	0.98 (0.92–1.05)	1.06 (0.99–1.14)	
Lean fish	< 15	28 254	2 529	1.00	1.00	0.04
	15–29	22 562	2 023	0.92 (0.87–0.97)	0.96 (0.91–1.02)	
	30–44	14 841	1 469	0.93 (0.87–0.99)	0.99 (0.92–1.05)	
	≥ 45	18 012	2 486	0.95 (0.90–1.01)	0.93 (0.88–0.99)	
Low-fat dairy products	Non-consumers	13 916	1 554	1.00	1.00	0.14
	< 200	34 848	3 078	0.79 (0.74–0.84)	0.91 (0.85–0.96)	
	200–399	18 203	1 883	0.78 (0.73–0.84)	0.96 (0.90–1.03)	
	≥ 400	16 702	1 992	0.84 (0.78–0.90)	0.99 (0.92–1.06)	

HR hazard ratio, *CI* confidence interval

* Age-adjusted with age as underlying timescale and subcohorts (n = 5) included as strata variable

** Age-adjusted and mutually adjusted for the healthy Nordic food groups, BMI < 20, 20–24.9, 25–29.9, ≥ 30 (kg/m^2), physical activity (low, medium, high), smoking status (never, current heavy smoker early starter, current moderate smoker early starter, current smoker late starter, former smoker early starter, former smoker late starter), education (< 10, 10–12, > 12 years of schooling) intake of energy (kJ/day continuous), alcohol (non-consumer, 0–5, > 5 g/day), and processed red meat (< 15, 15–29, 30–44, ≥ 45 g/day)

nadir at 200–250 g/day (HR 0.79 (95% CI: 0.72–0.87). In never smokers, the nadir was observed at 150–200 g/day (150 g/day: HR 0.89 (95% CI: 0.78–1.02); 200 g/day: HR 0.89 (95% CI: 0.76–1.05) (Fig. 2). Furthermore, consumption of Nordic fruits and vegetables > 500 g/day increased mortality among never smokers, but there were only 33 deaths registered at this consumption level Fig. 2 (Additional file 2).

Sensitivity analyses

Sensitivity analysis, starting follow-up two years after enrolment excluding 350 cases, did not change the results (Supplementary Fig. 2). Further adjustments including other fruits and vegetables in the multivariable-adjusted model did not influence the results (Supplementary Fig. 3). Omitting BMI in the multivariable-adjusted categorical model did not lead to changes in the results (Supplemental Table 3).

Discussion

We observed a J-shaped trend between intake of Nordic fruits and vegetables, fatty fish and low-fat dairy products and all-cause mortality, implying that with increasing intake of some traditional Nordic food groups, mortality might change in a non-linear fashion. As the null hypothesis of linearity was not rejected for lean fish, we conclude that the non-linear components did not add more information to those data than a linear model. For wholegrain products, our results were limited to categorical analysis, but a test for trend over categories pointed to a linear association with mortality.

The restricted cubic splines allow for predictions for any value of the variable, compared to only four probabilities in our categorical analyses, or compared to the alternative of modelling a linear relationship. Thus, the estimates from the splines add more information to the results and are therefore emphasized. The results from both modelling tools point in the same

Table 3 Hazard ratios (HR) and all-cause mortality according to intake categories of Nordic fruits and vegetables stratified by smoking status. From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study

All-cause mortality								
	Never smokers				Ever smokers*			
Intake categories of Nordic fruits and vegetables (g/day)	Total N	No. of deaths	HR (95% CI)	P for trend	Total N	No. of deaths	HR (95% CI)	P for trend
< 100	6 452	588	1.00	0.10	14 085	1 942	1.00	< 0.001
100–199	11 654	905	0.89 (0.81–0.99)		20 847	2 263	0.86 (0.80–0.91)	
200–299	7 232	605	1.03 (0.91–1.15)		11 672	1 182	0.82 (0.76–0.89)	
≥ 300	4 477	333	1.07 (0.93–1.24)		7 250	689	0.84 (0.76–0.92)	

HR hazard ratio, *CI* confidence interval

Age-adjusted and mutually adjusted for the healthy Nordic food groups, BMI < 20, 20–24.9, 25–29.9, ≥ 30 (kg/m^2), physical activity (low, medium, high), education (< 10, 10–12, > 12 years of schooling), intake of energy (kJ/day continuous), alcohol (non-consumer, 0–5, > 5 g/day), and processed red meat (< 15, 15–29, 30–44, ≥ 45 g/day)

* Additionally, adjusted for pack-years

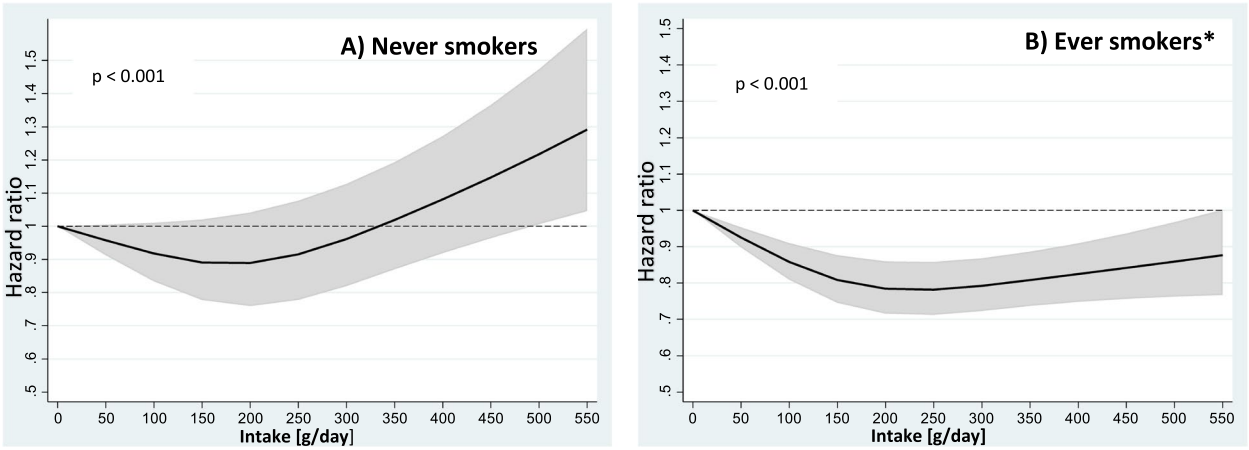

Fig. 2 Intake of Nordic fruits and vegetables and all-cause mortality by restricted cubic splines stratified by never and ever smokers. From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study. Nordic fruits and vegetables modeled by restricted cubic splines with 3 knots at percentiles 10%, 50% and 90% (Never smokers: 65; 173; 343. Ever smokers: 53; 160; 332). Black line hazard ratio, grey area 95% confidence interval. Age-adjusted and mutually adjusted for the healthy Nordic food groups, BMI < 20, 20–24.9, 25–29.9, ≥ 30 (kg/m2), physical activity (low, medium, high), education (< 10, 10–12, > 12 years of schooling), intake of energy (kJ/day continuous), alcohol (non-consumer, 0–5, > 5 g/day), and processed red meat (< 15, 15–29, 30–44, ≥ 45 g/day). *Additionally, adjusted for pack-years

direction, but the effect estimates associated with the nadir from the restricted cubic spline models show a stronger negative association for Nordic fruits and vegetables, and a weaker negative association for low-fat dairy products than what we observed in the categorical analyses. However, as most self-reported dietary assessment methods are better suited for ranking than estimating absolute intake, the absolute consumption levels found to be associated with the lowest mortality in this study, as shown in Table 2 and the figures, are probably not as important as the shape of the curves.

The maximum benefit of consuming Nordic fruits and vegetables was achieved at around 200 g/day, which is below the recommended intake of all fruits and vegetables of five servings per day [21]. Optimal health benefits of fruit and vegetable consumption achieved at a more modest intake level than currently recommended (around three to four servings per day) have also been found in the PURE study [30]. Non-linear inverse associations of fruit and vegetable intake with all-cause mortality have been shown in previous meta-analyses [31, 32], but with dose–response curves that differed from our J-shaped curve for Nordic fruits and vegetables. Aune et al. found that the benefit of increasing fruits and vegetables intake was larger at lower intake levels but observed reductions of risk up to 800 g/day [32], while

Wang et al. found that the benefit of fruits and vegetables plateaued at approximately 5–6 servings per day [31].

The benefit of consuming Nordic fruits and vegetable seemed stronger in ever- than in never-smokers. Similar tendencies were reported in the European Prospective Investigation into Cancer and Nutrition, which also included a subsample of women from NOWAC [33]. In addition, a meta-analysis of prospective cohort studies on the association between consumption of fruits and vegetable and risk of lung cancer found stronger associations with lung cancer among smokers. Antioxidant properties of fruits and vegetables are protective against increased oxidative stress caused by smoking [34].

The impact of dairy intake on mortality has been extensively studied, but results are not conclusive [35, 36]. The divergence of results could be due to variation between the different types of dairy products being investigated (i.e., total dairy, specific categories of dairy such as milk, yoghurt, cheese, low-fat/high-fat dairy), different cut-off points between studies, but also the quality of the underlying diet in different populations. Still, when comparing results on low-fat milk consumption as a specific dairy category and mortality in Nordic populations, one study finds an increased mortality [37] while another found no association [38]. It is noted that the fat content in yoghurt, which was part of the low-fat dairy products in the present study, could be up to 3.4%, and therefore not necessarily considered low-fat. Hence, our results are not directly comparable with these studies. Our analysis showed a non-linear association with low-fat dairy and mortality, much in line with what Ding et al. found for total dairy consumption in three prospective cohort studies in women and men [39].

We observed that consumption up to the recommended 200 g of fatty fish/week (29 g/day) was within a non-significant beneficial range, but when intake reached 60 g/day there was a significantly increased mortality. In contrast, higher consumption of lean fish reduced all-cause mortality. Several large cohort studies have not been able to show any reduced mortality linked to frequent fish consumption [40, 41], but some protective associations are found in metaanlyses [42–44]. Engeset et al. found a non-linear trend with fatty fish consumption and mortality in the European Prospective investigation into Cancer and Nutrition cohort, which included a part of our sample [41]. Also, a study on fish consumption and mortality in a cohort of Swedish men and women found a U-shaped association between consumption of fish and all-cause mortality, which was more pronounced in women [45]. Furthermore, when they considered lean and fatty fish separately, they found no associations between consumption of lean fish and mortality, but up to 68% increased mortality in women who consumed 50 g/day fatty fish compared to the median intake level (9 g/day).

Even though fish is a good source of essential nutrients, it is also a source of environmental contaminants such as dioxins, which are classified as carcinogens, and accumulates in the adipose tissue [21, 46, 47]. While lean fish store fat in the liver, fatty fish store it in the fillet itself, which then contains more of these substances compared to lean fish. One can speculate whether this is related to the observed increased mortality associated with high consumption of fatty fish, but not with lean fish.

The observed protective effect of wholegrain products on all-cause mortality in the present analysis is supported by meta-analyses of prospective cohort studies including populations from the US, Europe, and Asia [48, 49]. In the meta-analysis by Aune et al., reductions in mortality for whole grains were observed up to an intake of 225 g per day and they found a steeper reduction at lower intake levels. In a study on Norwegian wholegrain eaters by Jacobs et al. included in the meta-analyses, they found an inverse association between a calculated wholegrain consumption score and mortality, with the highest score being most beneficial [50]. This score was calculated based on slices of bread multiplied by percentages of wholegrain and was thus based on more detailed information on wholegrain consumption than was available in the present study.

These findings imply that if linear associations between traditional Nordic foods and health outcomes are assumed, it might lead to wrong conclusions as the relationships can be non-linear. Furthermore, they imply that lean and fatty fish might be differently associated to health outcomes, and that this aspect therefore should be investigated further in future studies. Also, the search for optimal intake levels of traditional foods should be emphasised in further studies on regional sustainable diets, both for health and to reduce the burden of food production on the environment.

Establishing optimal intake levels of foods for health is, however, not straightforward, given the limitations inherent in FFQs to provide precise estimates of actual food intake. Furthermore, analyses on isolated foods does not consider synergistic and antagonistic interactions between food groups existing within the same diet, and possibly also with other lifestyle factors, which might explain why isolated foods sometimes show a seemingly confusing pattern on health. These interactions might be better captured with dietary pattern analyses, but as indicated by our results, careful consideration on how to score individual foods in construction of a combined diet score is warranted.

Strengths and limitations

The strengths of this study include a large sample size, a high number of deaths and the long follow-up (median 20 years), providing enough statistical power in the analysis. Linkage to registry is a strength as all deaths are confirmed. Furthermore, the risk of sampling bias is considered low due to the selection of women through the National Registry. Another strength is that a validated questionnaire was used to assess food intake and covariates [15–17, 22, 23].

The study is, however, limited by having only one assessment of diet, as dietary habits probably have changed during follow-up. Recalling the habitual diet with the use of FFQ over the past year could be challenging and give rise to misclassification of dietary exposures, but this is expected to be non-differential. In addition, the FFQ was not designed to measure all foods that are part of a healthy Nordic diet and hence does not capture all relevant food components such as wild berries and vegetables like kale or distinguish between specific varieties of Nordic wholegrains such as rye and barley. Furthermore, precise assessment of dietary exposure is difficult and measurement errors are inevitable in nutritional epidemiology. Also, even though we adjusted for covariates that were unevenly distributed across intake categories of the Nordic food groups, residual confounding due to imprecise assessment of these factors as well as unmeasured factors is likely. The results must be interpreted with caution as the moderate consumers are probably more representative of what most people eat, while both low and high consumers can be different in many ways (e.g., extreme dieters, vegans, people with allergies).

Conclusion

Nordic fruits and vegetables, low-fat dairy products and fatty fish was non-linearly associated to all-cause mortality, while increased intake of lean fish and wholegrain products reduced all-cause mortality among middle-aged and older women.

While high consumption of fatty fish increased all-cause mortality, the opposite was found for lean fish, suggesting that they should not be treated as one food group in relation to health outcomes.

Consumption of Nordic fruits and vegetables was most beneficial in women that were either current or former smokers, implying that dietary interventions might be especially important for women with higher risk of premature death due to smoking. Our results indicate that more attention to nonlinear associations is warranted in analyses of diet and health-outcomes.

Abbreviations

NOWAC: The Norwegian Women and Cancer Study; BMI: Body mass index; FFQ: Food frequency questionnaire; DAGs: Directed Acyclic Graphs; HR: Hazard ratio; CI: Confidence interval; PURE study: The Prospective Urban Rural Epidemiology study; REK: The Regional Committee for Medical and Health Research Ethics.

Supplementary Information

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Additional file 1.

Additional file 2.

Additional file 3: Table 1. Spearman correlation coefficients between intake of Nordic food groups. From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study. **Table 2.** Population distribution and intake of Nordic fruits and vegetables stratified by never and ever smokers. From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study. **Table 3.** Hazard ratios (HR) and all-cause mortality according to intake categories of Nordic food groups leaving BMI out of the multivariable-adjusted model. From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study. **Figure 1.** DAG constructed for the analyses for estimating the total effect of Nordic foods on all-cause mortality. From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study. **Figure 2.** Intake of Nordic food groups and all-cause mortality by restricted cubic spline regression excluding death cases that occurred in first two years of follow-up. From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study. **Figure 3.** Intake of Nordic fruits and vegetables and all-cause mortality by restricted cubic spline regression, estimates further adjusted for other fruits and vegetables. From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study.

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Authors' contributions

TEJ: Conception and design, analysis, and interpretation of data, writing and revision of the manuscript and supervision of study. TB: Conception and design, acquisition of data, analysis and interpretation of data, revision of the manuscript. BKJ: Conception and design, interpretation of data, writing and revision of the manuscript. GS: Conception and design, acquisition of data, interpretation of data, major contributor in the writing and revision of the manuscript and supervision of study. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to restrictions that apply to the availability of these data, which were used under licence for the current study, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The NOWAC cohort has received approval for the collection and storage of questionnaire information. All data are stored and handled according to the permission given by the Norwegian Data Protection Authority (Ref.nr. 07–00030). Participants have given written informed consent, and ethical approval for the NOWAC cohort has been obtained from the Regional Committee for Medical and Health Research Ethics (REK) (Ref.nr. 200300119–5).

Consent for publication.

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

“Non-linear associations between foods basic in a healthy Nordic diet and all-cause mortality in the Norwegian Women and Cancer study: a prospective cohort study”

Supplemental Tables 1-3

Supplemental Table 1. Spearman correlation coefficients between intake of Nordic food groups

From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study

Healthy Nordic food groups	Nordic fruits and vegetables intake	Wholegrain intake	Fatty fish intake	Lean fish intake	Low-fat dairy intake
Nordic fruits and vegetables intake	1				
Wholegrain intake	0.05	1			
Fatty fish intake	0.19	0.01	1		
Lean fish intake	0.15	0.09	0.21	1	
Low-fat dairy intake	0.02	0.14	0.02	0.07	1

Supplemental Table 2. Population distribution and intake of Nordic fruits and vegetables stratified by never and ever smokers

From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study

Smoking status	Total N	No. of deaths	Nordic fruits and vegetables intake Median intake (P10-P90) (g/day)	Nordic fruits and vegetables intake categories (g/day)			
				<100	100-199	200-299	≥300
Never smokers	29 815	2 431	173 (65-342)	68	150	237	366
Ever smokers	53 854	6 076	160 (53-332)	63	148	237	369

Supplemental Table 3. Hazard ratios (HR) and all-cause mortality according to intake categories of Nordic food groups leaving BMI out of the multivariable-adjusted model

From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study

Healthy Nordic food groups	**Intake categories (g/day)**	**Total N**	**No. of deaths**	**All-cause mortality**		
				Age-adjusted*	Multivariable-adjusted model **	P for trend
				HR (95% CI)	HR (95% CI)	
Nordic fruits and vegetables	< 100	20 537	2 530	1.00	1.00	0.94
	100–199	32 501	3 168	0.79 (0.75–0.83)	0.91 (0.86–0.96)	
	200–299	18 904	1 787	0.77 (0.72–0.82)	0.95 (0.89–1.01)	
	≥ 300	11 727	1 022	0.78 (0.73–0.84)	0.98 (0.91–1.06)	
Wholegrain products	< 60	14 724	1 419	1.00	1.00	0.02
	60–119	24 439	2 669	0.91 (0.85–0.97)	0.97 (0.90–1.03)	
	120–179	16 071	1 550	0.78 (0.73–0.83)	0.91 (0.85–0.99)	
	≥ 180	28 435	2 869	0.84 (0.79–0.90)	0.91 (0.85–0.98)	
Fatty fish	< 5	23 792	2 497	1.00	1.00	0.17
	5–14	25 882	2 517	0.94 (0.89–1.00)	1.01 (0.95–1.07)	
	15–29	22 074	2 090	0.90 (0.85–0.96)	0.99 (0.93–1.05)	
	≥ 30	11 921	1403	0.98 (0.92–1.05)	1.06 (0.98–1.13)	
Lean fish	< 15	28 254	2 529	1.00	1.00	0.04
	15–29	22 562	2 023	0.92 (0.87–0.97)	0.96 (0.91–1.02)	
	30–44	14 841	1 469	0.93 (0.87–0.99)	0.98 (0.92–1.05)	
	≥ 45	18 012	2 486	0.95 (0.90–1.01)	0.93 (0.88–0.99)	
Low-fat dairy products	Non-consumers	13 916	1 554	1.00	1.00	0.14
	<200	34 848	3 078	0.79 (0.74–0.84)	0.90 (0.84–0.95)	
	200–399	18 203	1 883	0.78 (0.73–0.84)	0.94 (0.88–1.01)	
	≥400	16 702	1 992	0.84 (0.78–0.90)	0.97 (0.91–1.04)	

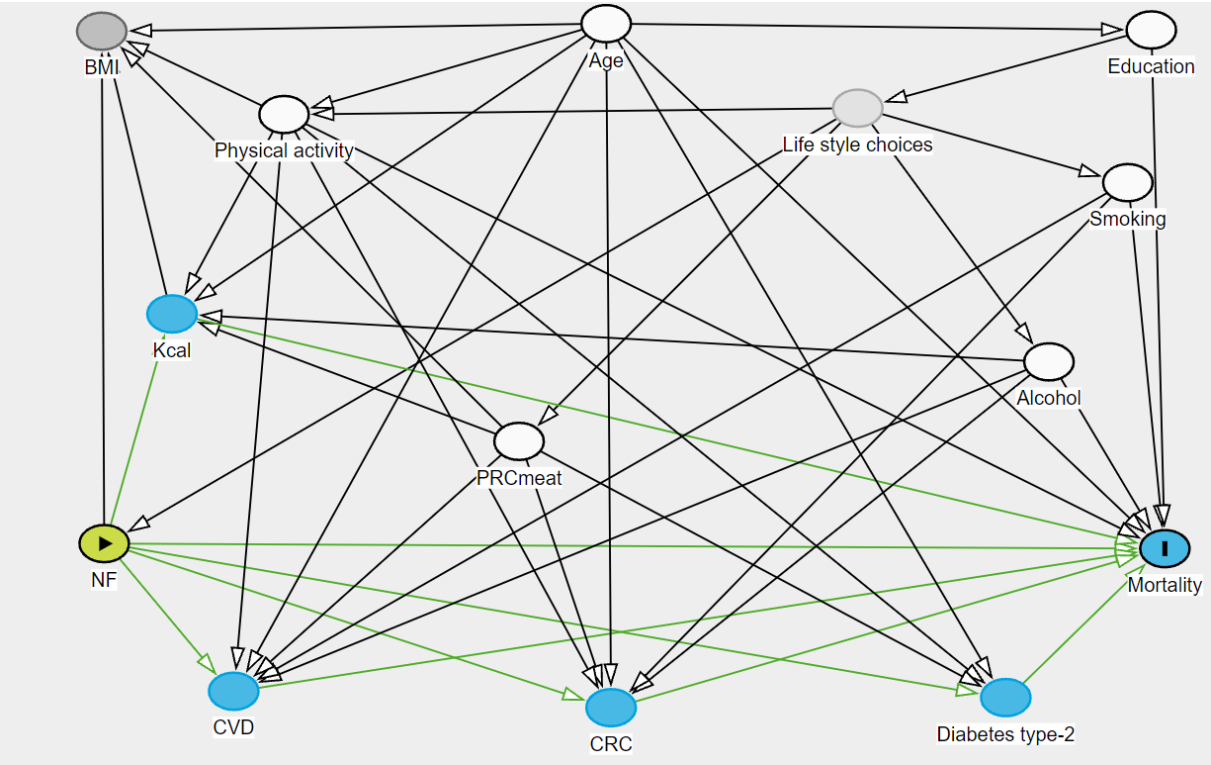
* Age-adjusted with age as underlying timescale and subcohorts (n=5) included as strata variable

** Age-adjusted and mutually adjusted for the healthy Nordic food groups, physical activity (low, medium, high), smoking status (never, current heavy smoker early starter, current moderate smoker early starter, current smoker late starter, former smoker early starter, former smoker late starter), education (<10, 10-12, >12 years of schooling), intake of energy (kJ/day continuous), alcohol (non-consumer, 0–5, > 5 grams/day), processed meat (< 15, 15–29, 30–44, ≥ 45 grams/day)

Supplemental Figures 1-3

Supplemental Figure 1. DAG constructed for the analyses for estimating the total effect of Nordic foods on all-cause mortality

From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study

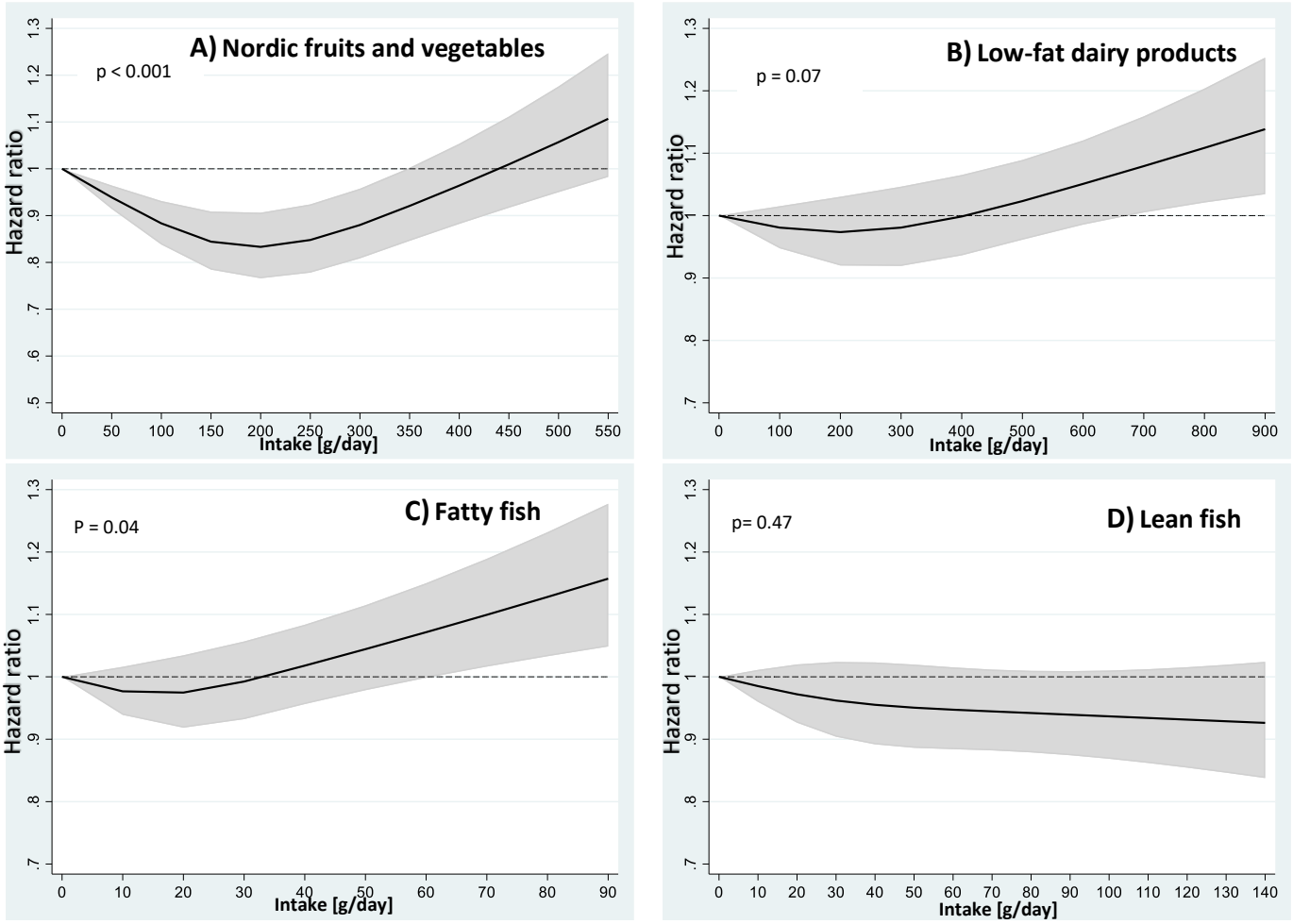


Red circle:
Light grey circle: unobserved variables
Blue circles: observed variables
Yellow circle: exposure
Blue circle with I: outcome
White circles: adjusted variables
NF= healthy Nordic foods
CRC= colorectal cancer
CVD= cardiovascular disease
BMI= Body Mass Index
PRCmeat= processed red meat
Kcal= energy intake

The figure is created from www.dagitty.net

Supplemental Figure 2. Intake of Nordic food groups and all-cause mortality by restricted cubic spline regression excluding death cases that occurred in first two years of follow-up

From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study



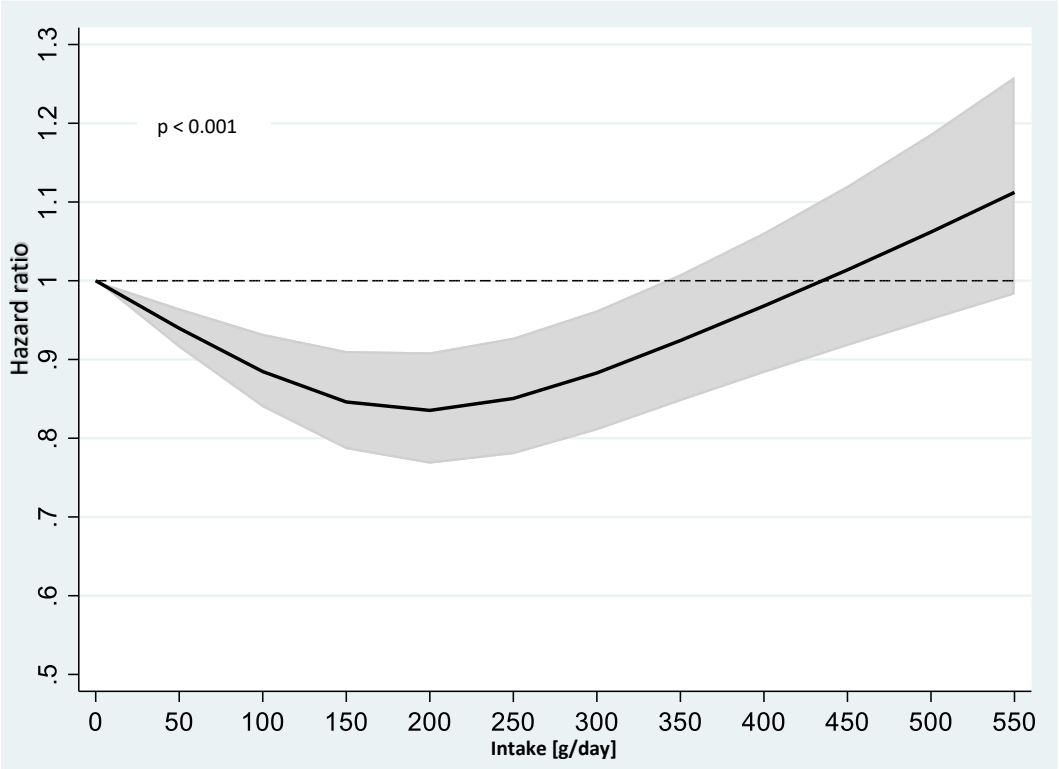
Nordic food groups modeled by restricted cubic splines with 3 knots at percentiles 10%, 50% and 90% (Nordic fruits and vegetables 57;164;336. Low-fat dairy products 0;138;550. Fatty fish 0;13;35. Lean fish 0;24;66 g/day).

Black line hazard ratio, grey area 95% confidence interval

Mutually adjusted for the healthy Nordic food groups, age (underlying timescale), BMI <20, 20-24.9, 25-29.9, ≥30 (kg/m^2), physical activity (low, medium, high), smoking status (never, current heavy smoker early starter, current moderate smoker early starter, current smoker late starter, former smoker early starter, former smoker late starter), education (<10, 10-12. >12 years of schooling), intake of energy (kJ/day continuous), alcohol (non-consumer, 0-5, >5 gram/day), and processed red meat (<15, 15-29, 30-44, ≥45 gram/day), subcohorts (n=5) included as strata variable

Supplemental Figure 3. Intake of Nordic fruits and vegetables and all-cause mortality by restricted cubic spline regression, estimates further adjusted for other fruits and vegetables

From: Non-linear associations between healthy Nordic foods and all-cause mortality in the NOWAC study: a prospective study



Nordic fruits and vegetables modeled by restricted cubic splines with 3 knots at percentiles 10%, 50% and 90% (57; 164; 336 g/day).

Black line hazard ratio, grey area 95% confidence interval

Mutually adjusted for the healthy Nordic food groups, age (underlying timescale), BMI < 20, 20–24.9, 25–29.9, ≥ 30 (kg/m^2), physical activity (low, medium, high), smoking status (never, current heavy smoker early starter, current moderate smoker early starter, current smoker late starter, former smoker early starter, former smoker late starter), education (<10, 10-12, >12 years of schooling), intake of energy (kJ/day continuous), alcohol (non-consumer, 0–5, > 5 grams/day), processed red meat (< 15, 15–29, 30–44, ≥ 45 grams/day) and other fruits and vegetables (<100, 100-199, 200-299, ≥300), subcohorts (n=5) included as strata variable

Paper III

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Replacing red and processed meat with lean or fatty fish and all-cause and cause-specific mortality in Norwegian women. The Norwegian Women and Cancer Study (NOWAC): a prospective cohort study

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Abstract

Nordic Nutrition Recommendations recommend reducing red and processed meat and increasing fish consumption, but the impact of this replacement on mortality is understudied. This study investigated the replacement of red and processed meat with fish in relation to mortality. Of 83 304 women in the Norwegian Women and Cancer Study (NOWAC) study, 9420 died during a median of 21·0 years of follow-up. The hazard ratios (HR) for mortality were estimated using Cox proportional hazards regression with analyses stratified on red and processed meat intake due to non-linearity. Higher processed meat (> 30 g/d), red and processed meat (> 50 g/d), and fatty fish consumption were associated with higher mortality, while red meat and lean fish consumption were neutral or beneficial. Among women with higher processed meat intake (> 30 g/d), replacing 20 g/d with lean fish was associated with lower all-cause (HR 0·92, 95 % CI 0·89, 0·96), cancer (HR 0·92, 95 % CI 0·88, 0·97) and CVD mortality (HR 0·82, 95 % CI 0·74, 0·90), while replacing with fatty fish was associated with lower CVD mortality (HR 0·87, 95 % CI 0·77, 0·97), but not with all-cause or cancer mortality. Replacing processed meat with fish among women with lower processed meat intake (≤ 30 g/d) or replacing red meat with fish was not associated with mortality. Replacing processed meat with lean or fatty fish may lower the risk of premature deaths in Norwegian women, but only in women with high intake of processed meat. These findings suggest that interventions to reduce processed meat intake should target high consumers.

Keywords: **Red and processed meat: Lean fish: Fatty fish: Substitution analyses: Cause-specific mortality**

Red meat mainly refers to meat derived from pork, cattle, sheep and goat[1,2]. Processed meat primarily consists of red meat that has undergone modifications like curing, salting, or smoking and often contains minced fatty tissues. It includes items such as bacon, sausages, ham, salami, liver pate and similar products[1]. Red meat is an important source of energy and nutrients such as proteins, essential amino acids, vitamin B_6, vitamin B_{12}, Zn and Fe[1]. However, red meat, especially processed meat, is also a significant source of SFA and of substances formed during processing that can have adverse effects on health[1,3].

There is strong evidence that processed meat consumption increases the risk of colorectal cancer, and probable evidence that red meat consumption also increases the risk[4,5]. Red meat, and particularly processed meat, is a probable risk factor for type 2 diabetes and CVD, which are leading causes of death in high-income countries[6–9]. The evidence indicates that the association with mortality is stronger and more consistent for processed meat compared with red meat[9]. The precise mechanisms underlying the adverse health effects linked to the consumption of red and processed meat are not yet fully established[1,3]. However, the presence of saturated fats and heme iron, in addition to Na and processed induced substances such as heterocyclic aromatic amines, and lipid peroxidation products, have been proposed to contribute to the increased mortality and disease from processed meat consumption compared with red meat consumption[1,3].

Abbreviations: HR, hazard ratio; IHD, ischemic heart disease; NOWAC, the Norwegian Women and Cancer Study.

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Reducing the intake of red and processed meat, as recommended by dietary guidelines, must however be compensated by an increased intake of other energy-contributing foods to maintain a balanced energy intake[1,10]. Fish serves as viable alternative to red and processed meat, providing high-quality protein and essential nutrients such as vitamins A and B_{12}, Fe, and Zn[2]. Additionally, fish has a low content of SFA and is a source of the long-chain *n*-3 fatty acids, EPA and DHA, I, Se, and vitamin D[2].

Increasing fish intake while reducing red and processed meat consumption could have potential benefits for public health, but there are only a few studies that have specifically examined the implications of this replacement on mortality in specified substitution analyses[11–14]. While these studies found lower mortality by replacing red and/or processed meat with alternative sources of protein, including fish, they did not differentiate between replacement of red and processed meat with lean or fatty fish. Findings from the Norwegian Women and Cancer Study (NOWAC) study indicates that a higher consumption of lean fish could have potential benefits in relation to all-cause mortality, whereas lower intake of fatty fish showed a neutral association with all-cause mortality, and higher intake was linked to higher all-cause mortality[15]. Another NOWAC study found that lean fish consumption, but not fatty fish, was associated with lower risk of type 2 diabetes mellitus, suggesting that distinguishing between types of fish is important when examining associations with cause-specific mortality[16].

When conducting analyses using specified food substitution models, there is an assumption that the relationship between exposure and outcome(s) is linear. While there is evidence supporting a linear relationship between red and processed meat consumption and mortality[9], there are also indications of potential non-linear associations[7,8,17,18].

Therefore, the main objective of this study was to investigate how replacing red and processed meat with lean or fatty fish is associated with all-cause mortality, and mortality related to cancer and CVD (ischemic heart disease (IHD) and stroke), within a cohort of Norwegian women. In support of the main objective, the study aims to consider potential non-linear associations between red and processed meat and fish consumption and cause-specific mortality outcomes, as well as the associations between red and processed meat and fish consumption and mortality outcomes without the substitution.

Methods

Study population

We used data from the NOWAC study, including women who have answered a questionnaire about different lifestyle factors, in particular food frequency questions. Data were collected in the period between 1996 and 1998 or 2003 and 2005, from women aged between 41 and 70 years at inclusion. Women were randomly selected from the National Registry of Statistics Norway[19]. The study sample has been found to be representative as no major source of selection bias was revealed in a study assessing the external validity of the NOWAC cohort[20]. The study found minor differences between responders and the total sample regarding education and parity, but no significant differences in relation to cancer incidence rates.

A total of 101 316 women were available for inclusion in this study. Women with zero person-years of follow-up (*n* 20), implausible energy intake (< 2500 kJ/d (*n* 1053) or > 15 000 kJ/d (*n* 140)), and missing values for the covariates of physical activity (*n* 8539), education (*n* 4684), smoking (*n* 1306) and BMI (kg/m^2) (BMI) (*n* 2270) were excluded from the analytical sample. A total of 83 304 women were included in the analyses for lean and fatty fish consumption and mortality, while non-consumers of processed meat (*n* 1930), of red meat (*n* 5707) and of red and processed meat (*n* 1059) were excluded in the analysis of red and processed meat and mortality outcomes and in the substitution analyses, respectively; see Fig. 1 for clarification.

The NOWAC cohort received approval for the collection and storage of the questionnaire information. All data were stored and handled according to permission provided by the Norwegian Data Protection Authority (Ref.nr. 07–00030). Participants provided written informed consent, and ethical approval for the NOWAC cohort was obtained from the Regional Committee for Medical and Health Research Ethics (REK) (Ref.nr. 200300119–5).

Exposure

Dietary data were collected using validated semi-quantitative FFQ which were developed to measure usual food intake over the past year[21–23]. The respondents were asked to report the average food consumption in four to seven frequency categories ranging from never/seldom to six or more per week. The FFQ have been slightly improved and adapted as new hypotheses have been generated, new products have been introduced, and other products have been removed from the market during the data collection period of almost 10 years. In total seven, grouped into five for stratification, slightly different versions of the FFQ part of the lifestyle questionnaires have been used to collect dietary data in this cohort. The items included in the FFQ varied from approximately seventy-three to ninety frequency questions, but most of the questions used to estimate the exposures in this study have remained consistent over time[24]. In addition to the frequency questions, there were separate portion size questions for most fish, meat and fish and meat products consumed as main dishes. For sandwich spreads, participants reported how many slices of bread they consumed with the various spreads, and this was multiplied with standard portions[25]. To account for small variations between different versions of the FFQ, those which were completed closest together in time were grouped together in subcohorts (*n* 5), and subcohorts were used as a stratification variable as per NOWAC analytical strategy[24].

In this study, red meat included beef, chops and roast, and processed meat included sausages, meatballs/burgers, and sandwich meat made from red meat (not including processed poultry) but excluded red and processed meat as part of combined dishes, such as pizza and stew. Lean fish included cod, saithe, haddock, plaice, catfish, flounder, redfish, fish cakes, fried fish and tuna in oil/water but excluded lean fish as part of

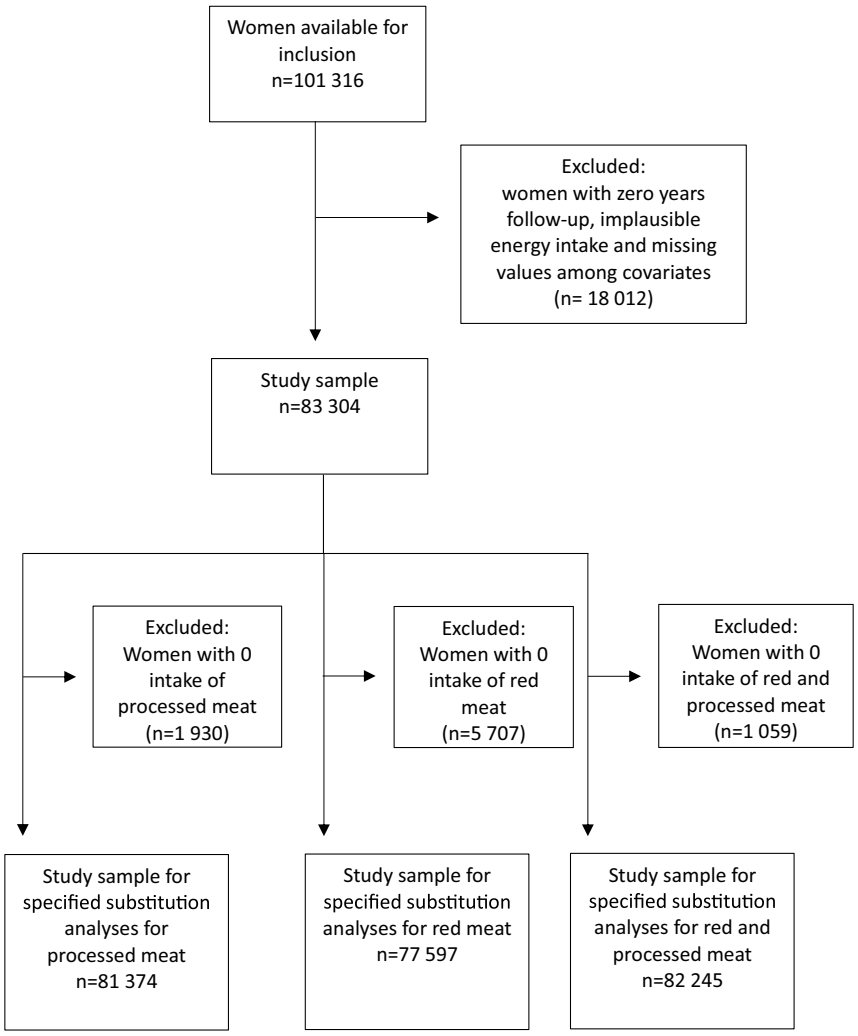

Fig. 1. Flow chart with overview of participants included in the analytic samples.

other combined dishes. Fatty fish included salmon, trout, herring, mackerel, mackerel spread, sardine in oil, pickled herring, smoked and cured salmon but excluded fatty fish as part of other combined dishes. Subtypes of fish or fish products, which could not be defined as lean or fatty fish such as 'other fish', shellfish, liver, caviar and roe were not included in the lean or fatty fish exposures but were rather controlled for in the analyses. Red and processed meat and lean and fatty fish were expressed as continuous exposures with 20 g/d increments in the analyses, and substitutions of red and processed meat with lean or fatty fish were expressed in servings of 20 g/d.

The daily intake of food and energy was calculated for each participant by converting consumption frequency and portion size to g/d, based on information about standardsed portion sizes and weights obtained from the Norwegian Weight and Measurement Table[25], and information about nutrient content in foods obtained from the Norwegian Food Composition Database[26]. The calculations were done using a statistical syntax in SAS (SAS Institute Inc., Cary, NC, USA), developed at the Department of Community Medicine, UiT The Arctic University of Norway, for the NOWAC cohort.

Outcomes

The outcomes of interest were all-cause mortality and death due to cancer and the major subtypes of CVD of which atherosclerosis is a common risk factor, that is, IHD and stroke. Mortality outcomes were defined according to the International Classification of Diseases, 10th Revision codes: cancer including malignant neoplasms at all sites (C00-C97), CVD including IHD (I20-I25) and stroke (I60-I69). To obtain information on death, the NOWAC study participants were linked to the Norwegian Cause of Death Registry using the unique personal identity number. Participants were followed up until the date of emigration or death or 31 December 2019, whichever came first.

Covariates

Included covariates were chosen *a priori* based on literature and directed acyclic graphs (online Supplementary Fig. 1).

Information on age (years) was based on information from the National Population Registry in Norway, whereas all the other covariate information was obtained from the lifestyle questionnaires (which included the FFQ). The variable for

physical activity was based on self-reported physical activity levels on a scale from low (1) to high (10), including physical activity at home, work, exercise and walking[27]. The smoking variable was computed by combining information about smoking status (never, former and current), age at smoking initiation and the number of pack-years (number of cigarettes smoked per d, divided by 20, multiplied by the number of years smoked). Information on education was based on self-reported number of years of schooling. Total energy intake, excluding energy from alcohol (kJ/d), alcohol intake (g/d) and other foods (g/d), were obtained from the FFQ.

BMI was calculated as weight divided by the square of height based on validated self-reported weight (kg) and height (m)[28]. Information about prevalent diabetes (yes/no) was self-reported and obtained from lifestyle questionnaires[16].

Statistical analyses

Descriptive statistics were used to calculate baseline characteristics for the total cohort and for low and high consumers of processed meat and low and high consumers of red meat, using proportions for categorical variables and medians and 10th and 90th percentiles for continuous variables. The cut points for high and low consumption were based on the restricted cubic spline analyses (see below and results).

Cox proportional hazard models with age as the underlying timescale were used to estimate hazard ratios (HR) between the intake of processed meat, red meat, the total intake of red and processed meat, lean and fatty fish, and mortality, and between the substitution of processed meat, of red meat, and of the total intake of red and processed meat with lean or fatty fish and mortality. The proportional hazards assumption was evaluated visually using log-log plots and Schoenfeld residuals.

The association between intake of processed meat, red meat, red and processed meat, lean and fatty fish, and mortality outcomes was investigated for non-linearity using restricted cubic splines with three knots placed at the 10th, 50th and 90th percentiles.

Specified substitution analysis was performed using the 'Leave-one-out' method to estimate the association between the replacement of 20 g/d of processed meat, 20 g/d of red meat and 20 g/d of red and processed meat with 20 g/d of lean or fatty fish[29]. The model for substitution of processed meat with lean or fatty fish can be parameterised as

$$\begin{aligned} log(h(t;x)) = {} & log(h_1(t)) + y_1 fattyfish_1 + y_2 leanfish_2 \\ & + y_3 otherfish_3 + y_4 shellfish_4 + y_5 chicken_5 \\ & + y_6 redmeat_6 + {}_{ytotal}(fattyfish + leanfish \\ & + otherfish + shellfish + chicken + redmeat \\ & + processedmeat)_{total}, \end{aligned}$$

where the total variable is the sum of the intakes of processed meat, red meat, lean fish, fatty fish, and other foods in similar food groups, that is, other fish (including 'other fish', roe, caviar and liver), shellfish and chicken. When processed meat was not included and red meat was, the coefficient for lean or fatty fish represented the replacement of processed meat with lean or fatty fish, respectively.

We adjusted for various covariates in four different models. Model 1a was mutually adjusted for lean fish, fatty fish, red meat, processed meat, other fish, shellfish, and chicken, and additionally adjusted for age (continuous timescale), energy intake (continuous kJ/d (excluding energy from alcohol)), and for subcohorts (n 5), which was included as a stratum variable.

In model 1b, which is specified as our main model, we additionally adjusted for physical activity divided into three categories (low (≤ 4), moderate (5–6) or high (≥ 7)), smoking divided into six categories (never smokers, current heavy smokers, current moderate smokers, current smokers late starter, former smoker early starter and former smoker late starter) and alcohol intake divided into three categories (non-consumers, low consumers (0–5 g/d) and higher consumers (> 5 g/d)). In model 2, we further adjusted for the consumption of other food groups that are related to meat consumption and mortality, including fruits and vegetables, dairy products, wholegrain products, refined grain products and potatoes (all continuous in g/d). In model 3, we further adjusted for BMI category (< 20, 20–24·9, 25–29·9, ≥ 30 kg/m^2) and diabetes (yes/no).

Stata/MP 16.0 was used to perform statistical analyses. Statistical significance was set at $P < 0{\cdot}05$.

Sensitivity analysis

The following two sensitivity analyses were conducted:

(1) Because of concerns for reverse causation, we performed analyses starting at follow-up for all participants 2 years after enrolment.
(2) Because of concerns due to missing data among covariates, we performed multiple imputation for the specified substitution analyses with processed meat and lean or fatty fish under the assumption that missing data could be missing at random. The imputation was performed by chained equations for missing data for the covariates: education (7–9, 10–12, 13–16 and ≥ 17 years of schooling), physical activity (continuous scale 1–10), smoking status (never smoker, current heavy smoker, current moderate smoker, current smoker late starter, former smoker early starter and former smoker late starter), height (cm) and weight (kg). The other covariates included in our models and mortality outcomes were included in the imputation models. The missing values were replaced with imputed values estimated based on observed values from twenty duplicated datasets. Imputed values were drawn with the use of predictive mean matching with the 100 nearest neighbours for physical activity, height and weight which were based on linear scales, and with the use of ordinal regression and multinominal regression to impute missing values for education and smoking, respectively.

Results

We included 83 304 women in this study, of whom 9420 died during follow-up, including 4708 deaths from cancer and 1068 deaths from CVD (IHD or stroke) during a median follow-up time of 21·0 years (Table 1).

Table 1. Baseline characteristics for all women and for women with low and high intake of processed meat and for women with low and high intake of red meat

Characteristics	Cohort		Processed meat ≤ 30 g/d		Processed meat > 30 g/d		Red meat ≤ 20 g/d		Red meat > 20 g/d	
No. of participants *n*	83 304		39 119		42 255		55 476		22 121	
No. of total deaths	9420		4637		4515		6240		2482	
No. of deaths from cancer	4708		2227		2363		3080		1295	
No. of deaths from CVD	1068		550		491		716		275	
Age at baseline in years	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
	51·6	6·4	52·5	6·5	50·8	6·1	51·8	6·6	51·2	5·9
Education*	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
7–9	19 873	23·9	9151	23·4	10 384	24·6	12 855	23·2	5934	26·8
10–12	28 984	34·8	13 023	33·3	15 452	36·6	18 978	34·2	8341	37·7
13–16	23 040	27·7	11 089	28·4	11 377	26·9	15 743	28·4	5562	25·1
≥ 17	11 407	13·7	5856	15·0	5042	11·9	7900	14·2	2284	10·3
Smoking*										
Never	29 684	35·6	14 359	36·7	14 592	34·5	20 890	37·7	6605	29·9
Current heavy smoker, early starter	5647	6·8	2300	5·9	3254	7·7	3248	5·9	2106	9·5
Current moderate smoker, early starter	10 816	13·0	4502	11·5	6173	14·6	6702	12·1	3561	16·1
Current smoker, late starter	7915	9·5	3710	9·5	4064	9·6	4977	9·0	2516	11·4
Former smoker, early starter	18 990	22·8	9027	23·1	9473	22·4	12 675	22·9	4887	22·1
Former smoker, late starter	10 252	12·3	5221	13·4	4699	11·1	6984	12·6	2446	11·1
Physical activity*										
Low	22 198	26·7	10 009	25·6	11 742	27·8	14 594	26·3	6206	28·1
Medium	36 028	43·3	16 788	42·9	18 500	43·8	24 160	43·6	9527	43·1
High	25 078	30·1	12 322	31·5	12 013	28·4	16 722	30·1	6388	28·9
Alcohol* (g/d)										
Non consumers	16 740	20·1	7776	19·9	8401	19·9	11 638	21·0	3384	15·3
0–5	45 895	55·1	21 600	55·2	23 379	55·3	31 066	56·0	11 953	54·0
> 5	20 669	24·8	9743	24·9	10 475	24·8	12 772	23·0	6784	30·7
BMI*										
< 20	5414	6·5	2525	6·5	2644	6·3	3495	6·3	1369	6·2
20–24·9	44 873	53·9	21 651	55·4	22 075	52·2	30 006	54·1	11 628	52·6
25–29·9	25 188	30·2	11 730	30·0	13 035	30·9	16 848	30·4	6882	31·1
≥ 30	7829	9·4	3213	8·2	4501	10·7	5127	9·2	2242	10·1
No. of participants with diabetes	1483	1·8	624	1·6	834	2·0	992	1·8	389	1·8
Dietary covariates	Median	Percentile 10–90	Median	Percentile 10–90	Median	Percentile 10–90	Median	Percentile 10–90	Median	Percentile 10–90
Energy intake (kJ/d)	6790	4686–9343	6289	4343–8623	7301	5238–9845	6678	4636–9142	7205	5050–9916
Processed meat (g/d)	30	9–62	18	8–27	45	32–73	28	10–59	38	15–71
Red meat (g/d)	13	3–28	11	2–25	16	5–32	11	4–17	26	21–41
Lean fish (g/d)	36	10–84	33	8–83	39	12–86	35	10–82	39	11–91
Fatty fish (g/d)	16	3–43	16	3–44	16	3–42	16	3–42	17	3–46
Fruits and vegetables (g/d)	304	125–598	310	125–614	295	124–572	300	124–586	307	129–603
Wholegrain products (g/d)	121	34–201	111	34–201	121	34–201	121	34–201	121	34–201
Refined grain products (g/d)	34	10–76	31	10–73	36	10–78	34	10–73	34	10–78
Potatoes (g/d)	126	22–189	126	22–189	126	22–189	126	22–189	126	22–189
Dairy products (g/d)	219	45–604	210	44–592	228	49–614	221	49–604	218	42–609

No, number of participants.
* Percent by columns.

Test for linearity

The restricted cubic spline analyses showed that the association between the intake of processed meat and mortality was significantly non-linear, with the nadir of the curve around an intake of 30 g processed meat/d (Fig. 2(a)). The intake of red meat did not show a significant deviation from linearity in relation to mortality outcomes, but the level of intake that exhibited a non-significant trend towards the lowest all-cause and CVD mortality was approximately 20 g per d (Fig. 2(b)). Red and processed meat combined was significantly non-linearly associated with mortality outcomes, with the nadir of the curve around an intake of 50 g/d (online Supplementary Fig. 2). Based on these results, we decided to split the subsequent analyses between higher (> 30 g/d) and lower (≤ 30 g/d) intakes of processed meat, between higher (> 20 g/d) and lower (≤ 20 g/d) intakes of red meat and between higher (> 50 g/d) and lower intakes of red and processed meat (≤ 50 g/d).

The restricted cubic spline analysis estimating the association between lean fish consumption and all-cause mortality was non-linear with the curve being at its steepest between 0 g/d and approximately 40 g/d, before flattening out about 60 g/d (Fig. 2(c)). Since all intake levels of lean fish were beneficial, we treated it as a linear exposure in the following analyses. Fatty fish intake did not deviate from linearity in relation to mortality outcomes and was thus treated as a linear exposure in the following analyses (Fig. 2(d)).

Baseline characteristics for high and low consumers of red and processed meat

Table 1 presents the baseline characteristics of all participants and the high and low processed meat consumers, and the high and low red meat consumers. We note that there were tendencies to a less health-conscious lifestyle among high consumers of processed meat, but also higher energy intake, and consequently higher intakes of most food groups including red meat and lean fish. They were also younger and had lower education than low consumers. There were similar tendencies, but weaker, among higher consumers of red meat.

Red and processed meat and fish consumption in relation to mortality

Processed meat consumption was associated with higher all-cause, cancer and CVD mortality among women consuming > 30 g/d, while no significant association was observed between processed meat consumption and mortality outcomes among women consuming ≤ 30 g/d (Table 2). No significant associations between red meat consumption and mortality outcomes were observed either among high or low consumers of red meat (Table 2). Total consumption of red and processed meat was associated with higher all-cause, cancer and CVD mortality among women with higher red and processed meat intake (> 50 g/d), while no significant association was observed among women consuming ≤ 50 g of red and processed meat/d (Table 2). Lean fish consumption was marginally associated with lower all-cause and cancer mortality, while fatty fish consumption was marginally associated with higher all-cause and cancer mortality and with higher CVD mortality (Table 2).

Specified substitution analyses

Replacing 20 g processed meat/d with 20 g lean fish was associated with 8% lower all-cause mortality (HR 0·92, 95% CI 0·89, 0·96), 8 % lower cancer mortality (HR 0·92, 95% CI 0·88, 0·97) and 18 % lower CVD mortality (HR 0·82, 95% CI 0·74, 0·90) among women consuming > 30 g processed meat/d (Table 3). Replacing 20 g processed meat/d with 20 g fatty fish was among high consumers of processed meat associated with 13 % lower CVD mortality (HR 0·87, 95% CI 0·77, 0·97), but not statistically significantly with all-cause mortality (HR 0·97, 95% CI 0·93, 1·01) or cancer mortality (HR 0·96, 95% CI 0·90, 1·01) (Table 3). Replacing processed meat with lean or fatty fish was not significantly associated with mortality outcomes among lower consumers of processed meat ≤ 30 g/d (Table 3).

Replacing 20 g of red meat/d with 20 g of lean fish was among women consuming > 20 g red meat/d not statistically significantly associated with all-cause mortality (HR 0·93, 95 % CI 0·86, 1·01), cancer mortality (model 1b: HR 1·03, 95 % CI 0·92, 1·17) or CVD mortality (HR 0·88, 95 % CI 0·69, 1·12) (Table 4). Among higher red meat consumers (> 20 g/d), replacing red meat with fatty fish was not significantly associated with all-cause mortality (HR 0·99, 95 % CI 0·91, 1·08), cancer mortality (HR 1·06, 95 % CI 0·93, 1·21) or CVD mortality (HR 1·00, 95 % CI 0·77, 1·29) (Table 4). No associations were observed between replacement of red meat with fish among women consuming ≤ 20 g of red meat/d (Table 4).

Overall, additional adjustments for other foods (model 2) and potential mediators BMI and diabetes (model 3) did not lead to significant changes in any of the presented associations (Table 2–4).

For the specified substitution analyses replacing red and processed meat with lean fish, we observed lower all-cause and CVD mortality, but not cancer mortality, among women consuming > 50 g of red and processed meat/d (online Supplementary Table 1(a)). No associations with mortality were observed with replacing red and processed meat with lean fish among low consumers of red and processed meat (online Supplementary Table 1(b)). Replacing red and processed meat with fatty fish was not associated with mortality outcomes among high consumers of red and processed meat (online Supplementary Table 1(a)), while higher all-cause and cancer mortality was observed with replacing red and processed meat with fatty fish among low consumers of red and processed meat (online Supplementary Table 1(b)).

Sensitivity analyses

Starting follow-up for all participants 2 years after enrolment did not change our main results (online Supplementary Table 2–3).

Conducting multiple imputation for handling missing data among covariates gave similar results as our complete-case analyses (online Supplementary Table 4).

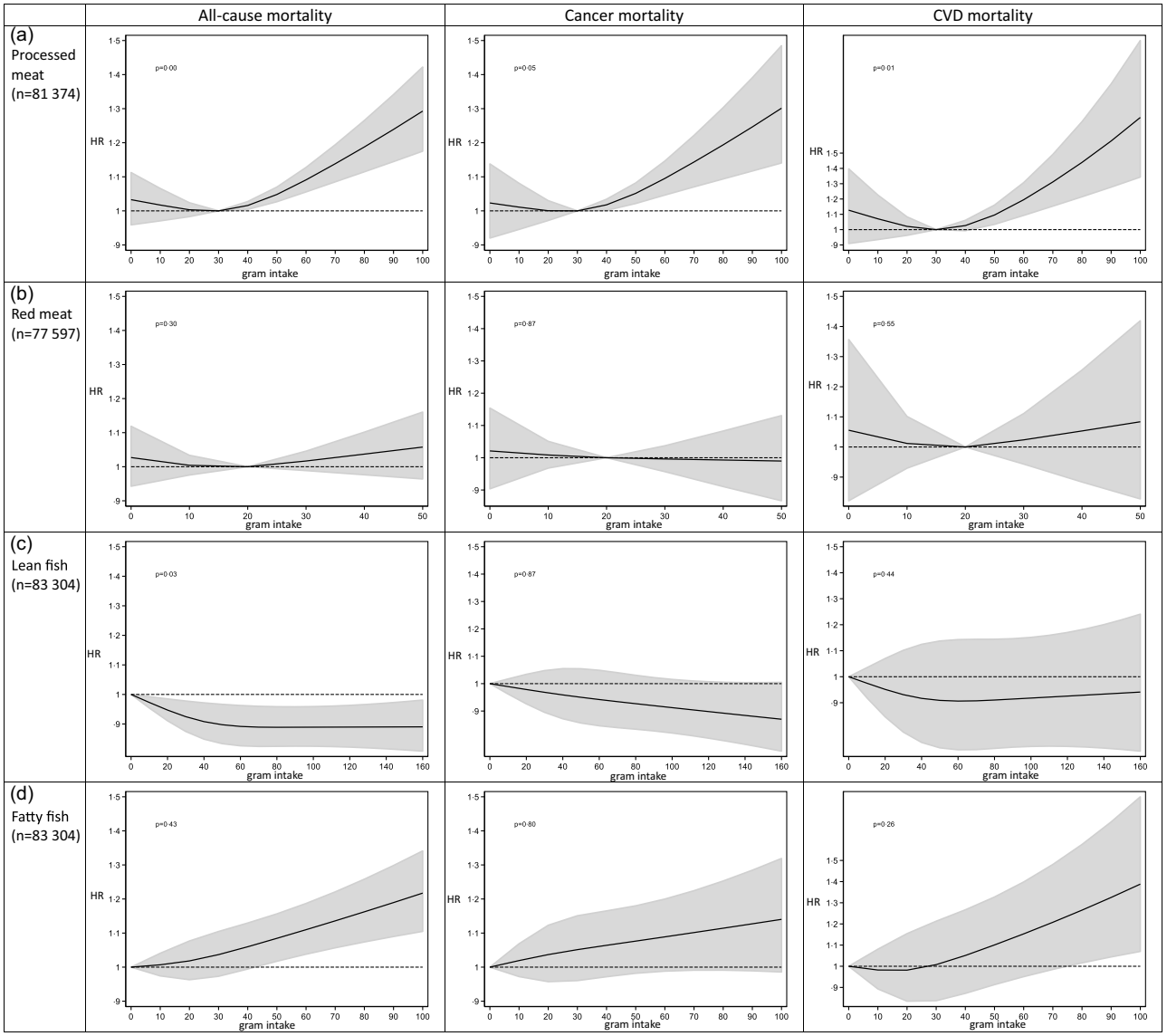

Fig. 2. Intake of processed meat, red meat, lean and fatty fish and cause-specific mortality by restricted cubic spline regression.

Discussion

In this prospective cohort study of Norwegian women, we observed non-linear associations between processed meat and red and processed meat consumption and mortality which led to separate analyses for high and low consumers of meat. We observed that higher consumption of processed meat can increase the risk of premature death including death from cancer and IHD and stroke, while this risk was not evident at lower consumption levels of processed meat. Red meat consumption was not significantly associated with mortality even at higher intake levels. Expanding our analyses to the combined intake of red and processed meat revealed similar associations as with processed meat. Higher intake of lean fish was beneficial, while higher fatty fish intake was associated with higher all-cause and CVD mortality. Among women with higher processed meat intake (> 30 g/d), replacing processed meat with lean fish was associated with 8% lower all-cause mortality and cancer mortality and with 18% lower CVD mortality (per 20 g/d replacement). Replacement of processed meat with fatty fish among higher processed meat consumers was associated with 13% lower CVD mortality per 20 g/d replacement. No associations were observed in women with lower processed meat intake. Replacing red meat with lean or fatty fish was not significantly associated with mortality outcomes. When the substitution analyses were expanded to the combined intake of red and processed meat, only substitution with lean fish was beneficial among high consumers, while among low consumers we observed higher all-cause and cancer mortality when replaced with fatty fish.

Explanation of findings

The stronger associations between processed meat intake compared with red meat intake and mortality in high consumers of meat are probably due to different nutritional composition and

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Table 2. Hazard ratios (HR) and cause-specific mortality according to intake of processed meat, red meat, red and processed meat combined, lean and fatty fish

	All-cause mortality							
	Model 1a††		Model 1b‡‡		Model 2§§		Model 3‖‖	
Per 20 g/d	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Processed meat > 30 g per d*	1·12	1·09, 1·16	1·07	1·04, 1·11	1·07	1·04, 1·11	1·06	1·03, 1·10
Processed meat ≤ 30 g per d†	1·00	0·92, 1·08	0·97	0·89, 1·05	0·98	0·90, 1·06	0·97	0·90, 1·06
Red meat > 20 g per d‡	1·16	1·07, 1·26	1·06	0·97, 1·14	1·06	0·98, 1·15	1·06	0·97, 1·15
Red meat ≤ 20 g per d§	1·07	0·97, 1·19	1·00	0·90, 1·11	1·00	0·90, 1·11	1·01	0·91, 1·12
Red and processed meat > 50 g per d‖	1·12	1·08, 1·15	1·06	1·03, 1·09	1·06	1·02, 1·09	1·05	1·02, 1·08
Red and processed meat ≤ 50 g per d¶	1·03	0·98, 1·08	0·98	0·94, 1·03	0·99	0·95, 1·04	0·99	0·95, 1·04
Lean fish**	0·99	0·98, 1·01	0·99	0·97, 1·00	0·99	0·98, 1·00	0·99	0·98, 1·00
Fatty fish**	1·04	1·02, 1·06	1·03	1·01, 1·06	1·04	1·02, 1·06	1·04	1·02, 1·06
	Cancer mortality							
	Model 1a		Model 1b		Model 2		Model 3	
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Processed meat > 30 g per d*	1·12	1·07, 1·17	1·08	1·03, 1·13	1·08	1·04, 1·13	1·08	1·04, 1·13
Processed meat ≤ 30 g per d†	0·96	0·86, 1·08	0·93	0·83, 1·04	0·93	0·83, 1·05	0·93	0·83, 1·05
Red meat > 20 g per d‡	1·05	0·94, 1·18	0·97	0·86, 1·09	0·97	0·86, 1·09	0·97	0·86, 1·09
Red meat ≤ 20 g per d§	1·04	0·89, 1·20	0·97	0·83, 1·13	0·97	0·84, 1·13	0·98	0·84, 1·14
Red and processed meat > 50 g per d‖	1·09	1·05, 1·13	1·04	1·00, 1·08	1·05	1·00, 1·09	1·04	1·00, 1·09
Red and processed meat ≤ 50 g per d¶	1·00	0·94, 1·07	0·96	0·90, 1·02	0·96	0·90, 1·03	0·96	0·90, 1·03
Lean fish**	0·99	0·97, 1·01	0·98	0·97, 1·00	0·98	0·96, 1·00	0·98	0·97, 1·00
Fatty fish**	1·04	1·01, 1·07	1·03	1·00, 1·06	1·03	1·00, 1·06	1·03	1·00, 1·06
	CVD mortality							
	Model 1a		Model 1b		Model 2		Model 3	
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Processed meat > 30 g per d*	1·26	1·16, 1·37	1·19	1·09, 1·30	1·20	1·10, 1·31	1·16	1·06, 1·27
Processed meat ≤ 30 g per d†	1·09	0·87, 1·38	1·06	0·84, 1·34	1·09	0·86, 1·38	1·06	0·83, 1·34
Red meat > 20 g per d‡	1·23	0·98, 1·55	1·09	0·86, 1·37	1·10	0·87, 1·39	1·10	0·87, 1·39
Red meat ≤ 20 g per d§	1·03	0·76, 1·40	0·94	0·69, 1·29	0·95	0·70, 1·30	0·95	0·69, 1·29
Red and processed meat > 50 g per d‖	1·22	1·13, 1·32	1·14	1·05, 1·23	1·14	1·05, 1·23	1·12	1·03, 1·21
Red and processed meat ≤ 50 g per d¶	1·07	0·93, 1·22	1·01	0·88, 1·15	1·04	0·91, 1·19	1·02	0·89, 1·17
Lean fish**	1·01	0·98, 1·05	0·99	0·96, 1·03	1·00	0·97, 1·04	1·00	0·96, 1·03
Fatty fish**	1·08	1·02, 1·14	1·07	1·02, 1·13	1·07	1·02, 1·13	1·06	1·01, 1·12

* *n* 42 255, no. of deaths = 4515, no. of cancer-related deaths = 2363, no. of CVD-related deaths = 491.
† *n* 39 119, no. of deaths = 4637, no. of cancer-related deaths = 2227, no. of CVD-related deaths = 550.
‡ *n* 22 121, no. of deaths = 2482, no. of cancer-related deaths = 1295, no. of CVD-related deaths = 275.
§ *n* 55 476, no. of deaths = 6240, no. of cancer-related deaths = 3080, no. of CVD-related deaths = 716.
‖ *n* 34 959, no. of deaths = 3784, no. of cancer-related deaths = 2002, no. of CVD-related deaths = 420.
¶ *n* 47 286, no. of deaths = 5501, no. of cancer-related deaths = 2645, no. of CVD-related deaths = 635.
** *n* 83 304, no. of deaths = 9420, no. of cancer-related deaths = 4708, no. of CVD-related deaths = 1068.
†† Mutually adjusted for red meat, processed meat, lean fish, fatty fish, chicken, other fish, shellfish (with the exposure omitted in the respective analyses), age (underlying timescale) and energy intake (continuous kJ/d excluding energy from alcohol), stratified by subcohorts (*n* 5).
‡‡ Model 1a + adjusted for education (7–9, 10–12, 13–16 and ≥ 17 years of schooling), alcohol (non-consumer, 0–5, > 5 g/d), smoking (never, current heavy smoker, current moderate smoker, current smoker late starter, former smoker early starter, former smoker late starter) and physical activity (low, medium, high).
§§ Model 1b + adjusted for other foods: fruits and vegetables, wholegrain products, refined grain products, potatoes, dairy products (g/d continuous).
‖‖ Model 2 + adjusted for BMI categories (< 20, 20–24·99, 25–29·99, > 30), diabetes (yes/no).

preparation methods of red and processed meat. Processed meat usually has higher energy density and lower levels of essential nutrients typically present in red meat as well as higher levels of Na and additives. The observed differences in mortality by replacing processed meat with fish in different strata of processed meat intake may be attributed to that the incorporation of processed meat in the diet enhances dietary diversity and provides essential nutrients like Fe. Alternatively, it is plausible that adverse health effects from processed meat primarily manifest when the intake of some nutrients and substances reaches a threshold, and thus that replacing lower intake levels of processed meat with fish has less impact. Moreover, a higher consumption of processed meat tends to displace other food items, resulting in reduced dietary variety. Lower intake of SFA or the replacement of SFA with unsaturated fatty acids may play a significant role in the strongest association observed between the substitution of processed meat with lean or fatty fish in relation to CVD mortality in high processed meat consumers[30,31]. The observed linear association between higher intake of fatty fish and higher all-cause mortality is somewhat different from our previous analyses on fatty fish and all-cause mortality in the NOWAC cohort where we observed a

Table 3. Hazard ratios (HR) and cause-specific mortality according to specified substitution analyses of processed meat with lean or fatty fish for women consuming > 30 g and ≤ 30 g processed meat per d

3a. Specified substitution analyses for processed meat intake > 30 g per d								
	All-cause mortality (no. of deaths = 4515)							
n 42 255	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/d	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Lean fish for processed meat	0·89	0·86, 0·92	0·92	0·89, 0·96	0·92	0·89, 0·96	0·93	0·90, 0·97
Fatty fish for processed meat	0·93	0·89, 0·97	0·97	0·93, 1·01	0·97	0·93, 1·01	0·97	0·93, 1·01
	Cancer mortality (no. of deaths = 2363)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/d	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Lean fish for processed meat	0·90	0·85, 0·94	0·92	0·88, 0·97	0·92	0·87, 0·96	0·92	0·87, 0·97
Fatty fish for processed meat	0·93	0·88, 0·98	0·96	0·90, 1·01	0·95	0·90, 1·01	0·95	0·90, 1·01
	CVD mortality (no. of deaths = 491)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/d	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Lean fish for processed meat	0·79	0·72, 0·87	0·82	0·74, 0·90	0·82	0·74, 0·91	0·84	0·76, 0·93
Fatty fish for processed meat	0·82	0·73, 0·92	0·87	0·77, 0·97	0·87	0·77, 0·97	0·89	0·79, 1·00
3b. Specified substitution analyses for processed meat intake ≤ 30 g per d								
	All-cause mortality (no. of deaths = 4637)							
n 39 119	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/d	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Lean fish for processed meat	0·99	0·91, 1·08	1·01	0·93, 1·10	1·01	0·93, 1·10	1·02	0·93, 1·10
Fatty fish for processed meat	1·05	0·96, 1·14	1·07	0·98, 1·16	1·07	0·98, 1·17	1·07	0·98, 1·17
	Cancer mortality (no. of deaths = 2227)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/d	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Lean fish for processed meat	1·02	0·90, 1·14	1·05	0·93, 1·18	1·04	0·93, 1·18	1·04	0·92, 1·18
Fatty fish for processed meat	1·07	0·94, 1·20	1·10	0·97, 1·24	1·10	0·98, 1·25	1·10	0·98, 1·25
	CVD mortality (no. of deaths = 550)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/d	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Lean fish for processed meat	0·93	0·73, 1·18	0·95	0·75, 1·20	0·93	0·74, 1·19	0·96	0·75, 1·22
Fatty fish for processed meat	1·01	0·79, 1·28	1·02	0·80, 1·30	0·99	0·78, 1·27	1·02	0·80, 1·31

* Mutually adjusted for red meat, lean fish, fatty fish, chicken, other fish, shellfish, age (underlying timescale) and energy intake (continuous kJ/d excluding energy from alcohol), stratified by subcohorts (*n* 5).
† Model 1a + adjusted for education (7–9, 10–12, 13–16, ≥ 17 years of schooling), alcohol (non-consumer, 0–5, > 5 g/d), smoking (never, current heavy smoker, current moderate smoker, current smoker late starter, former smoker early starter, former smoker late starter) and physical activity (low, medium, high).
‡ Model 1b + adjusted for other foods: fruits and vegetables, wholegrain products, refined grain products, potatoes, and dairy products (g/d continuous).
§ Model 2 + adjusted for BMI categories (< 20, 20–24·99, 25–29·99, > 30) and diabetes (yes/no).

J-shaped curve[15]. This might be explained by the inclusion of processed fish such as mackerel in tomato which contains added sugar, Na and preservatives, in current analyses.

Findings from other studies

To the best of our knowledge, no previous studies are directly comparable to the present one, as they have not examined the association between replacing red and/or processed meat with lean or fatty fish, while stratifying the analyses based on intake level of red and processed meat. Nevertheless, a few previous studies have assessed the association between replacing red and processed meat with fish and mortality. None of these studies were, however, restricted to women, nor did they present sex-specific results. Nielsen et al. found similar results as we did in The Danish Diet, Cancer and Health cohort study, which is quite comparable to our cohort study, both in terms of geographical proximity and food culture[11]. Their findings indicated that replacing processed meat with fish or poultry showed a stronger association with lower mortality compared with replacing red

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Table 4. Hazard ratios (HR) and cause-specific mortality according to specified substitution analyses of red meat with lean or fatty fish for women consuming > 20 g and ≤ 20 g red meat per d

4a. Specified substitution analyses for red meat intake > 20 g per d								
	All-cause mortality (no. of deaths = 2482)							
n 22 121	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/d	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Lean fish for red meat	0·86	0·79, 0·93	0·93	0·86, 1·01	0·93	0·86, 1·01	0·93	0·86, 1·02
Fatty fish for red meat	0·90	0·83, 0·98	0·99	0·91, 1·08	0·99	0·91, 1·08	0·99	0·91, 1·08
	Cancer mortality (no. of deaths = 1295)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/d	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Lean fish for red meat	0·96	0·85, 1·08	1·03	0·92, 1·17	1·03	0·92, 1·16	1·03	0·91, 1·16
Fatty fish for red meat	0·98	0·86, 1·11	1·06	0·93, 1·21	1·06	0·93, 1·21	1·06	0·93, 1·21
	CVD mortality (no. of deaths = 275)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/d	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Lean fish for red meat	0·80	0·63, 1·01	0·88	0·69, 1·12	0·88	0·69, 1·12	0·88	0·69, 1·12
Fatty fish for red meat	0·90	0·67, 1·12	1·00	0·77, 1·29	1·00	0·77, 1·29	0·98	0·76, 1·27
4b. Specified substitution analyses for red meat intake ≤ 20 g per d								
	All-cause mortality (no. of deaths = 6240)							
n 55 476	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/d	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Lean fish for red meat	0·93	0·83, 1·03	0·99	0·89, 1·10	0·99	0·89, 1·10	0·98	0·88, 1·09
Fatty fish for red meat	0·97	0·87, 1·08	1·04	0·93, 1·15	1·04	0·93, 1·15	1·02	0·92, 1·14
	Cancer mortality (no. of deaths = 3080)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/d	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Lean fish for red meat	0·95	0·82, 1·11	1·01	0·87, 1·17	1·01	0·86, 1·17	1·00	0·86, 1·16
Fatty fish for red meat	1·00	0·86, 1·17	1·07	0·91, 1·24	1·06	0·91, 1·24	1·06	0·91, 1·23
	CVD mortality (no. of deaths = 716)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/d	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Lean fish for red meat	0·98	0·72, 1·35	1·06	0·78, 1·45	1·06	0·77, 1·45	1·06	0·77, 1·45
Fatty fish for red meat	1·03	0·75, 1·41	1·11	0·81, 1·53	1·10	0·80, 1·51	1·10	0·80, 1·52

* Mutually adjusted for processed meat, lean fish, fatty fish, chicken, other fish, shellfish, age (underlying timescale) and energy intake (continuous kJ/d excluding energy from alcohol), stratified by subcohorts (*n* 5).
† Model 1a + adjusted for education (7–9, 10–12, 13–16, ≥ 17 years of schooling), alcohol (non-consumer, 0–5, > 5 g/d), smoking (never, current heavy smoker, current moderate smoker, current smoker late starter, former smoker early starter, former smoker late starter) and physical activity (low, medium, high).
‡ Model 1b + adjusted for other foods: fruits and vegetables, wholegrain products, refined grain products, potatoes, and dairy products (g/d continuous).
§ Model 2 + adjusted for BMI categories (< 20, 20–24·99, 25–29·99, > 30) and diabetes (yes/no).

meat. Specifically, they observed that 150 g of processed meat/week (which is comparable to 20 g/d used in present study), with total fish, was associated with lower all-cause and cancer mortality, but not with CVD mortality, in men and women. Deviating results on CVD mortality between our studies might be explained by the different definitions of CVD-related deaths, as Nielsen et al. included ICD-10 codes I00-I99, while we only included IHD and stroke, which are the leading causes of CVD-related deaths. In line with our results, Pan et al. found that replacing one serving of processed meat per d (85 g/d) with one serving of fish was associated with 10 % lower all-cause mortality in a cohort of men and women from the USA[13]. In contrast to our results, they found that red and processed meat intake was linearly associated with higher mortality, and that substituting red meat with fish was associated with lower mortality, although to a lesser extent than the association observed with processed meat[19]. In another study from the USA, Etemadi et al. found that intake of both red and processed meat was associated with higher mortality, and that 20 g per 1000 kcal increased daily intake of fish and similarly decreased intake of red and

processed meat was associated with 5% lower all-cause mortality in men and women[14]. One more study including US men and women by Zhong *et al.* found that substituting both red meat and processed meat with fish could reduce all-cause mortality[12]. In line with our results, van den Brandt *et al.* observed that processed meat intake was associated with overall higher mortality in men and women, while red meat intake was not[32]. However, they found no deviation from linearity between processed consumption and all-cause, cancer or CVD mortality. They observed higher all-cause and cause-specific mortality from higher fish consumption, and that replacing processed meat with fish was not significantly associated with all-cause, cancer or CVD mortality, but the HR was elevated for all outcomes. One might consider whether consuming fish like salmon and herring of possible Baltic Sea origin which exhibits higher levels of dioxins and polychlorinated biphenyls (PCBs) than fishes of non-Baltic origin could potentially have undermined the benefits of replacing processed meat with fish in the Dutch study[33]. However, these are mere speculations since the origin of the fish consumed is unknown.

Strengths and limitations

These findings should be interpreted with caution, as the lower mortality observed from replacing processed meat and red and processed meat combined with particularly lean fish is limited to interpretation using statistical methods and is not based on an observed effect from actual dietary changes. However, intervention studies are poorly suited for investigating dietary interventions and outcomes that require a long follow-up period, such as mortality. The strength of this study was that it included a nationally representative cohort of women with a low risk of sampling bias and high external validity. The linkage to the death registry of Norway, which confirms all deaths, lowers the risk of misclassification, although the cause of death may be misclassified. The large sample size and long follow-up time provided a high number of deaths, strengthening the statistical power in the analyses and making it possible to perform analyses in subsamples of the study sample. Furthermore, validated FFQ with detailed information on different types of fish facilitated a good measure of lean and fatty fish exposure and allowed for separate analyses of lean and fatty fish. However, the study was limited by self-reported dietary intake, which is prone to error and unlikely to be precise. The meat consumption, as estimated through four repeated 24-h dietary recalls in a validation study, was however not significantly different from the amount estimated using the FFQ. Conversely, the intake of fish, as estimated in the FFQ, was higher than the estimations derived from the 24-h dietary recalls[22]. The actual consumption of meats and fish is nevertheless underestimated due to the unknown amount from combined dishes. In the validation study, combined dishes were treated as grams of the dish and not as grams of its ingredients. Another limitation is that we were unable to capture changes in diet or covariates over time, as we only used one time point for exposure measurements.

Errors due to self-reporting of covariates and residual confounding from unmeasured factors can introduce bias. Hence, we cannot rule out that the beneficial effect on mortality from replacing processed meat with fish can be attributed to lifestyle factors associated with fish consumption or high consumption of processed meat, or with other foods often consumed together with these protein sources. For example, the composition of meals with fish compared with processed meat might be healthier in general. This has been shown in a study comparing nutritional composition between red meat dinners (including processed meat) and fish dinners in Norwegian adults where fish dinners generally had a healthier profile with less energy and a higher percentage of energy from proteins than red meat dinners[34]. Adjusting for other foods in our analyses did, however, not change the association between replacing processed meat and red meat with lean or fatty fish. In a previous study on dietary patterns in NOWAC, fish eaters were characterised by a high intake of fat and boiled coffee, current smoking, lower education, and higher BMI than women belonging to different dietary clusters, indicating a less healthy lifestyle among fish eaters[35]. These characteristics may however not accurately reflect the diverse range of dietary habits and lifestyles among all fish eaters, as fish consumption has been associated with overall healthier meal compositions and lifestyles[34,36]. It is also likely that there may be some residual confounding by smoking, a major predictor of mortality, in the analysis. The relatively high number of participants with missing data for included covariates could bias the observed associations. However, the fact that our main results for substitution of processed meat with lean or fatty fish were similar after imputing missing values suggests that the observed associations from the complete-case analyses is quite robust. Furthermore, we chose to do substitution by weight, rather than by energy, and the difference in energy content between red and processed meat and particularly with lean fish leaves an unspecified energy substitution that must be replaced by other foods that were not controlled in the analyses.

Public health implications

The findings of this study align with the Nordic Nutrition Recommendations 2023, which suggest limiting the consumption of red and processed meat to a maximum of 350 g per week for health purposes, as we observed that an intake above this was associated with higher mortality[1]. However, our results emphasise the significant role of processed meat in explaining the positive association between red and processed meat consumption and mortality.

The potential reduction of premature deaths in high processed meat consumers by replacing some of the processed meat intake with particularly lean fish could be substantial in a public health perspective as the estimated intake of processed meat among women in Norway is higher than recommended[1,37]. The replacement of processed meat with fish of equal serving size is applicable to traditional Norwegian meal settings and can provide an easy interpretation from a public health perspective. Implementing such a transition is however not straightforward, and a study conducted by Erkkola *et al.* in Finland highlighted that when

individuals make transitions away from red meat consumption, they tend to shift their dietary preferences towards poultry over fish[38].

Conclusion

Our study indicates that higher consumption of processed meat, but not red meat, is associated with higher cause-specific mortality, while lower processed meat consumption may not increase the risk of premature death among women in Norway. While lean fish consumption was associated with lower all-cause mortality, higher consumption of fatty fish was associated with higher all-cause and CVD mortality.

Replacing processed meat with lean fish in higher processed meat consumers could potentially lower the risk of premature deaths from all causes, including cancer and CVD in Norwegian women. Replacing processed meat intake with fatty fish may specifically reduce the risk of early death from IHD and stroke in women with higher processed meat consumption. It is important to highlight that our observations regarding benefits of replacing processed meat with fish were restricted to women with higher processed meat consumption. Further investigation is warranted to confirm these results and to understand the potential effects of replacements of processed meat with lean and fatty fish in women with lower processed meat intake and in men.

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There are no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114523002040

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Replacing red and processed meat with lean or fatty fish and all-cause and cause specific mortality in the Norwegian Women and Cancer Study (NOWAC): a prospective cohort study

Contents

Replacing red and processed meat with lean or fatty fish and all-cause and cause specific mortality in the Norwegian Women and Cancer Study (NOWAC): a prospective cohort study

Supplemental Tables

Supplemental table 1. Hazard ratio (HR) and cause specific mortality according to specified substitution analyses for red and processed meat with lean or fatty fish for women consuming >50 grams/day and ≤ 50 grams/day of red and processed meat

ST1a. Specified substitution analyses for red and processed meat intake > 50 grams/day								
n= 34 959	All-cause mortality (No. of deaths = 3 784)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/day	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Lean fish for red and processed meat	0.90	0.87-0.93	0.94	0.91-0.97	0.94	0.91-0.97	0.95	0.92-0.98
Fatty fish for red and processed meat	0.93	0.89-0.97	0.97	0.93-1.01	0.97	0.93-1.02	0.98	0.94-1.02
	Cancer mortality (No. of deaths = 2 002)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/day	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Lean fish for red and processed meat	0.93	0.88-0.97	0.96	0.92-1.01	0.96	0.91-1.01	0.96	0.91-1.01
Fatty fish for red and processed meat	0.94	0.88-1.00	0.97	0.92-1.03	0.97	0.91-1.03	0.97	0.91-1.03
	CVD mortality (No. of deaths = 420)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/day	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Lean fish for red and processed meat	0.81	0.73-0.89	0.85	0.77-0.93	0.85	0.77-0.94	0.86	0.78-0.95
Fatty fish for red and processed meat	0.86	0.77-0.97	0.92	0.82-1.04	0.93	0.82-1.04	0.93	0.83-1.05
ST1b. Specified substitution analyses for red and processed meat intake ≤ 50 grams/day								
n= 47 286	All-cause mortality (No. of deaths = 5 501)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/day	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Lean fish for red and processed meat	0.96	0.91-1.01	1.00	0.94-1.05	0.99	0.95-1.04	0.99	0.95-1.04
Fatty fish for red and processed meat	1.02	0.97-1.07	1.07	1.01-1.12	1.06	1.00-1.11	1.06	1.00-1.11
	Cancer mortality (No. of deaths = 2 645)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/day	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Lean fish for red and processed meat	0.97	0.91-1.04	1.01	0.94-1.09	1.00	0.93-1.08	1.00	0.93-1.08
Fatty fish for red and processed meat	1.03	0.96-1.11	1.08	1.00-1.16	1.08	1.00-1.16	1.07	1.00-1.16
	CVD mortality (No. of deaths = 635)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/day	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Lean fish for red and processed meat	0.96	0.83-1.11	1.00	0.87-1.16	0.98	0.85-1.14	1.00	0.86-1.15
Fatty fish for red and processed meat	1.01	0.87-1.17	1.06	0.91-1.23	1.03	0.89-1.20	1.04	0.90-1.21

HR, hazard ratio
CI, confidence interval
CVD, cardiovascular disease
* Mutually adjusted for lean and fatty fish, chicken, other fish, shellfish, age (underlying timescale), energy intake (continuous kJ/day excluding energy from alcohol), stratified by subcohorts (n=5)
† model 1a + adjusted for education (7-9, 10-12, 13-16, ≥ 17 years of schooling), alcohol (non-consumer, 0–5,>5 g/day), smoking (never, current heavy smoker early starter, current moderate smoker early starter, current smoker late starter, former smoker early starter, former smoker late starter), physical activity (low, medium, high)
‡ model 1b + adjusted for other foods (fruits and vegetables, whole grain products, refined grains, potatoes, dairy products (grams/day continuous))
§ model 2 + adjusted for BMI categories (<20, 20-24.99,25-29.99, >30), type 2 diabetes

Replacing red and processed meat with lean or fatty fish and all-cause and cause specific mortality in the Norwegian Women and Cancer Study (NOWAC): a prospective cohort study

Supplemental Table 2. Hazard ratios (HR) and cause specific mortality according to specified substitution analyses of processed meat with lean or fatty fish for women consuming >30 grams/day and ≤ 30 grams/day of processed meat starting follow-up two years after baseline

ST2a. Specified substitution analyses for processed meat intake > 30 grams/day						
n= 42 076	All-cause (No. of deaths = 4 350)		Cancer (No. of deaths = 2 265)		CVD (No. of deaths = 468)	
Per 20 g/day	HR	95% CI	HR	95% CI	HR	95% CI
Lean fish for processed meat	0.92	0.89-0.96	0.92	0.88-0.97	0.81	0.73-0.89
Fatty fish for processed meat	0.97	0.93-1.01	0.96	0.90-1.02	0.86	0.76-0.96
ST2b. Specified substitution analyses for processed meat intake ≤ 30 grams/day						
n= 38 921	All-cause (No. of deaths = 4 454)		Cancer (No. of deaths = 2 105)		CVD (No. of deaths = 531)	
Per 20 g/day	HR	95% CI	HR	95% CI	HR	95% CI
Lean fish for processed meat	1.01	0.93-1.10	1.05	0.93-1.19	0.92	0.72-1.17
Fatty fish for processed meat	1.06	0.97-1.15	1.09	0.96-1.23	0.98	0.76-1.26

HR, hazard ratio
CI, confidence interval
CVD, cardiovascular disease
Mutually adjusted for red meat, lean and fatty fish, chicken, other fish, shellfish, age (underlying timescale), energy intake (continuous kJ/day excluding energy from alcohol), education (7-9, 10-12, 13-16, ≥ 17 years of schooling), alcohol (non-consumer, 0–5,>5 g/day), smoking (never, current heavy smoker, current moderate smoker, current smoker late starter, former smoker early starter, former smoker late starter), physical activity (low, medium, high), stratified by subcohorts (n=5)

Replacing red and processed meat with lean or fatty fish and all-cause and cause specific mortality in the Norwegian Women and Cancer Study (NOWAC): a prospective cohort study

Supplemental Table 3. Hazard ratios (HR) and cause specific mortality according to specified substitution analyses of red meat with lean or fatty fish for women consuming >20 grams/day and ≤ 20 grams/day of red meat starting follow-up two years after baseline

ST3a. Specified substitution analyses for red meat intake > 20 grams/day						
n= 22 009	All-cause (No. of deaths = 2 378)		Cancer (No. of deaths = 1 231)		CVD (No. of deaths = 260)	
Per 20 g/day	HR	95% CI	HR	95% CI	HR	95% CI
Lean fish for processed meat	0.94	0.86-1.02	1.03	0.91-1.16	0.92	0.71-1.18
Fatty fish for processed meat	1.00	0.91-1.09	1.06	0.93-1.21	1.03	0.79-1.35
ST3b. Specified substitution analyses for red meat intake ≤ 20 grams/day						
n= 55 235	All-cause (No. of deaths = 6 017)		Cancer (No. of deaths = 2 936)		CVD (No. of deaths = 691)	
Per 20 g/day	HR	95% CI	HR	95% CI	HR	95% CI
Lean fish for processed meat	0.98	0.88-1.10	1.00	0.85-1.17	1.11	0.80-1.53
Fatty fish for processed meat	1.02	0.92-1.14	1.04	0.89-1.21	1.17	0.85-1.62

HR, hazard ratio
CI, confidence interval
CVD, cardiovascular disease
Mutually adjusted for processed meat, lean and fatty fish, chicken, other fish, shellfish, age (underlying timescale), energy intake (continuous kJ/day excluding energy from alcohol), education (7-9, 10-12, 13-16, ≥ 17 years of schooling), alcohol (non-consumer, 0–5,>5 g/day), smoking (never, current heavy smoker, current moderate smoker, current smoker late starter, former smoker early starter, former smoker late starter), physical activity (low, medium, high), stratified by subcohorts (n=5)

Replacing red and processed meat with lean or fatty fish and all-cause and cause specific mortality in the Norwegian Women and Cancer Study (NOWAC): a prospective cohort study

Supplemental Table 4 Hazard ratios (HR) and cause specific mortality according to specified substitution analyses of processed meat with lean or fatty fish for women consuming >30 grams/day and ≤ 30 grams/day of processed meat using multiple imputation for missing values on confounding covariates

ST4a. Specified substitution analyses for processed meat intake > 30 grams/day								
n= 49 545	All-cause mortality (No. of deaths = 5 853)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/day	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Lean fish for processed meat	0.90	0.87-0.93	0.93	0.90-0.96	0.93	0.90-0.96	0.94	0.91-0.97
Fatty fish for processed meat	0.93	0.87-0.96	0.97	0.93-1.00	0.97	0.93-1.00	0.97	0.94-1.01
	Cancer mortality (No. of deaths = 2 910)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/day	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Lean fish for processed meat	0.91	0.87-0.96	0.94	0.90-0.98	0.94	0.89-0.98	0.94	0.90-0.98
Fatty fish for processed meat	0.94	0.89-0.99	0.97	0.92-1.02	0.96	0.92-1.02	0.97	0.92-1.02
	CVD mortality (No. of deaths = 701)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/day	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Lean fish for processed meat	0.80	0.74-0.87	0.83	0.76-0.90	0.83	0.76-0.90	0.85	0.78-0.92
Fatty fish for processed meat	0.84	0.77-0.93	0.89	0.81-0.98	0.88	0.80-0.97	0.90	0.82-0.99
ST4b. Specified substitution analyses for processed meat intake ≤ 30 grams/day								
n= 47 912	All-cause mortality (No. of deaths = 6 455)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/day	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Lean fish for processed meat	0.99	0.90-1.04	0.98	0.92-1.06	0.98	0.91-1.05	0.98	0.92-1.05
Fatty fish for processed meat	1.02	0.95-1.09	1.03	0.96-1.11	1.03	0.96-1.11	1.03	0.96-1.11
	Cancer mortality (No. of deaths = 2 922)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/day	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Lean fish for processed meat	0.94	0.85-1.05	0.97	0.87-1.07	0.96	0.86-1.07	0.96	0.86-1.06
Fatty fish for processed meat	0.99	0.89-1.10	1.01	0.91-1.13	1.01	0.91-1.13	1.01	0.91-1.12
	CVD mortality (No. of deaths = 809)							
	Model 1a*		Model 1b†		Model 2‡		Model 3§	
Per 20 g/day	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Lean fish for processed meat	0.97	0.80-1.18	0.98	0.81-1.20	0.97	0.80-1.19	1.00	0.82-1.21
Fatty fish for processed meat	0.99	0.81-1.20	1.00	0.82-1.22	0.99	0.81-1.21	1.01	0.83-1.24

HR, hazard ratio
CI, confidence interval
CVD, cardiovascular disease
* Mutually adjusted for lean and fatty fish, chicken, other fish, shellfish, age (underlying timescale), energy intake (continuous kJ/day excluding energy from alcohol), stratified by subcohorts (n=5)
† model 1a + adjusted for education (7-9, 10-12, 13-16, ≥ 17 years of schooling), alcohol (non-consumer, 0–5,>5 g/day), smoking (never, current heavy smoker early starter, current moderate smoker early starter, current smoker late starter, former smoker early starter, former smoker late starter), physical activity (low, medium, high)
‡ model 1b + adjusted for other foods (fruits and vegetables, whole grain products, refined grains, potatoes, dairy products (grams/day continuous))
§ model 2 + adjusted for BMI categories (<20, 20-24.99,25-29.99, >30), type 2 diabetes

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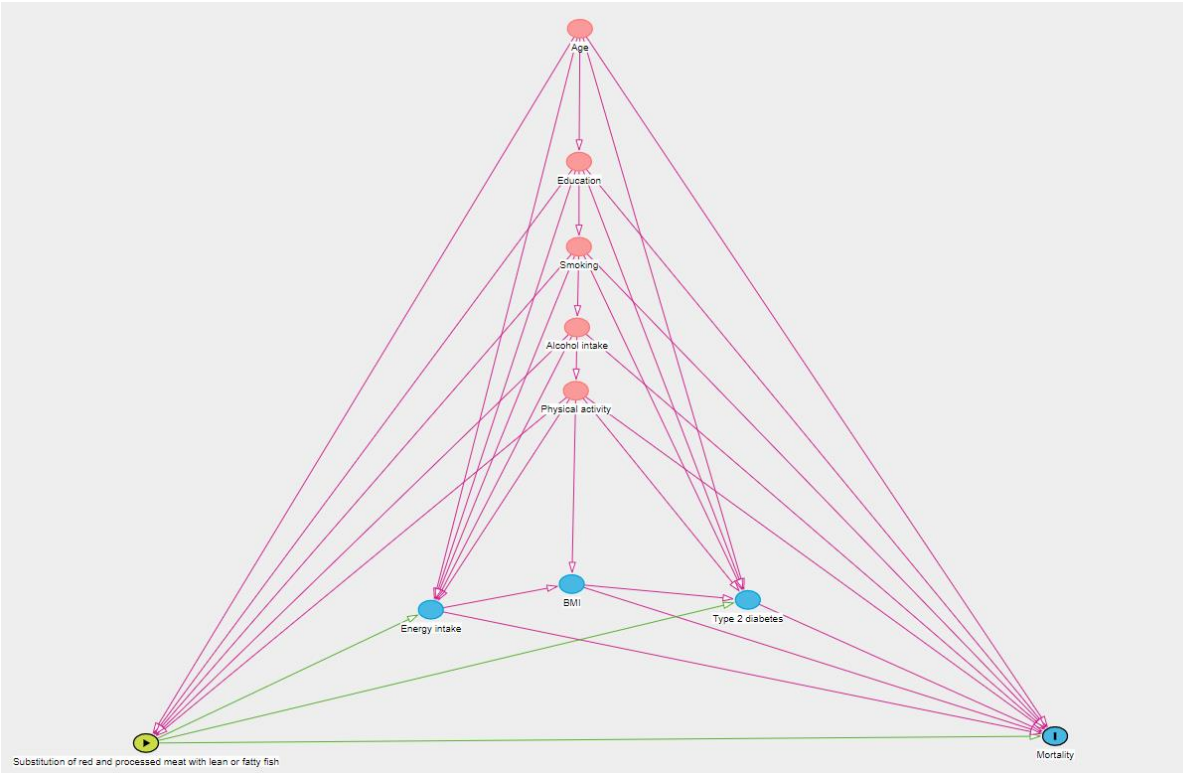
Supplemental Figures

Supplemental Figure 1. Directed acyclic graph (DAG) illustrating the hypothesized causal relationships between covariates in the association between the substitution of red and processed meat with lean or fatty fish and mortality



exposure outcome ancestor of outcome ancestor of exposure *and* outcome causal path biasing path

BMI= body mass index

The DAG illustrates the hypothesized causal relationships between covariates in the association between the substitution of red and processed meat with lean or fatty fish and mortality. The direction of the arrows illustrates the assumed direction of the causal relationship between the covariates and the exposure and outcome. The arrows direction is based on the following assumptions:

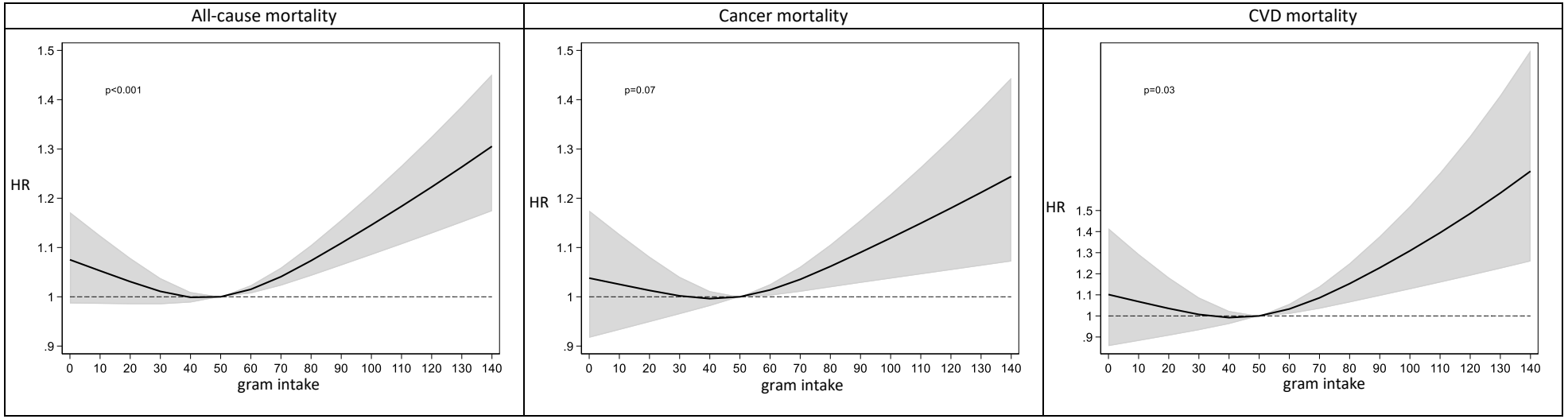
Increasing age, smoking, and high alcohol intake are associated with higher mortality, while higher levels of education and physical activity are linked to lower mortality.

Age-related changes, along with the influence of education, smoking, alcohol consumption and physical activity, impact food intake, food choices, and other lifestyle factors. Smoking is associated with higher red and processed meat intake, alcohol consumption, and a person's level of physical activity. As these factors affects both the exposure and outcome as illustrated in the DAG, they are identified as confounders in the relationship between substitution of red and processed meat with lean or fatty fish and mortality.

Food and energy intake play a role in BMI, BMI is also a risk factor of type 2 diabetes. Furthermore, processed meat consumption has been linked to a higher risk of type 2 diabetes, while the intake of lean fish has been found to reduce the risk of type 2 diabetes. Both BMI and type 2 diabetes are associated with mortality and are thus considered mediators in the hypothesized causal pathway between substituting red and processed meat with lean or fatty fish meat and mortality. However, it's important to note that BMI is also related to energy needs and energy expenditure, which can lead to increased food and energy intake in individuals with higher BMI. Additionally, being diagnosed with type 2 diabetes may induce dietary changes. Therefore, both BMI and type 2 diabetes can act as mediators as illustrated in the DAG (Substitution of red and processed meat with lean or fatty fish → BMI → type 2 diabetes → mortality) or confounders (Substitution of red and processed meat with lean or fatty fish ← BMI / type 2 diabetes → mortality) in the relationship between substitution of red and processed meat with lean or fatty fish and mortality.

Replacing red and processed meat with lean or fatty fish and all-cause and cause specific mortality in the Norwegian Women and Cancer Study (NOWAC): a prospective cohort study

Supplemental Figure 2. Intake of red and processed meat and cause specific mortality by restricted cubic spline regression



HR, hazard ratio

CVD, cardiovascular disease

Black line hazard ratio, gray area 95% confidence interval, p-value for non-linear trend.

Red and processed meat intake modelled using restricted cubic splines with three knots at percentiles 10%, 50% and 90% (18, 45, 84 grams/day), 50 grams ref. value.

Mutually adjusted for lean fish, fatty fish, chicken, other fish, shell fish, age (underlying timescale), energy intake (continuous kJ/day excluding energy from alcohol), education (7-9, 10-12, 13-16, ≥ 17 years of schooling), alcohol (non-consumer, 0–5,>5 g/day), smoking (never, current heavy smoker, current moderate smoker, current smoker late starter, former smoker early starter, former smoker late starter), physical activity (low, medium, high), stratified by subcohorts (n=5) (model 1b)

Appendices

A. NOWAC Invitation letter, Orientation about the survey [Norwegian]
B. NOWAC FFQ series 28 [Norwegian]
C. Foods included in the HNFI, the BSDS and the NND in relation to the Norwegian food based dietary guidelines and NNR23

Appendix A

INSTITUTT FOR SAMFUNNSMEDISIN
UNIVERSITETET I TROMSØ
9037 TROMSØ
Telefon 77 64 48 16

KVINNER OG KREFT

Orientering om undersøkelsen

Du samtykket i 1991/92 til å fylle ut et fire siders spørreskjema som du mottok i posten – «Kvinner, livsstil og helse»/«Kvinner og kreft». Spørreskjemaet tok opp en rekke forhold knyttet til ditt liv som barnefødsler, p-pille bruk, kosthold, røking og sosiale forhold. Formålet med undersøkelsen var å se om disse forhold har betydning for utvikling av kreft hos kvinner. Resultatene vil bli publisert i dagspressen og i internasjonale fagtidsskrifter. Ansvarlig for undersøkelsen er professor Eiliv Lund.

Vi retter nå en ny forespørsel til deg om du nok en gang vil besvaré det vedlagte spørreskjema. Begrunnelsen for å kontakte deg på ny er at mange av de spørsmålene du besvarte sist gjaldt levevaner som vi vet endrer seg med alderen. De fleste spørsmålene vil dreie seg om årene siden siste utfylling.

Undersøkelsen er tilrådd av Regional komite for medisinsk forskningsetikk i Nord-Norge. Adressen din henter vi fra det sentrale personregister ved hjelp av Statistisk Sentralbyrå. Som forrige gang inneholder spørreskjemaet kun løpenummer uten annen identifikasjon, for derved å gi dine opplysninger et bedre personvern.

Med noen års mellomrom frem til år 2018 vil vi sammenholde opplysningene som du har gitt i undersøkelsen med opplysninger fra Kreftregisteret og Dødsårsaksregisteret. Ved å studere materialet på nytt, håper vi å finne ut årsakene til at noen kvinner får kreft. Alle opplysningene fra spørreskjemaene og registrene vil bli behandlet konfidensielt og etter de regler Datatilsynet har gitt i sin tillatelse.

Det er frivillig om du vil være med i undersøkelsen. Du kan senere trekke deg uten begrunnelse og uten at det vil få noen konsekvenser for deg. Opplysninger du har gitt kan du be om å få slettet.

Vi vil be deg om å besvare det vedlagte spørreskjemaet så riktig som mulig. Dersom ingen av de oppgitte svaralternativ dekker din situasjon, sett kryss for det alternativet som ligger nærmest. Gi eventuelt merknader eller tilleggsopplysninger i skjemaet. Vi spør også alle som deltar om tillatelse til fornyet kontakt om noen år i form av et liknende spørreskjema.

I tillegg vil vi senere kontakte en del av deltakerne for å få tatt en blodprøve. Det vil skje hos nærmeste lege og være gratis. Enkelte kvinner vil også bli forespurt om å delta i et kostholdsintervju over telefon.

For spørsmål om p-pille bruk og bruk av hormoner i overgangsalderen finner du bilder i denne brosjyren som skal være et hjelpemiddel (brosjyren skal ikke returneres). Spørreskjemaet sendes tilbake i vedlagte konvolutt som vi betaler svarporto for.

Med hilsen

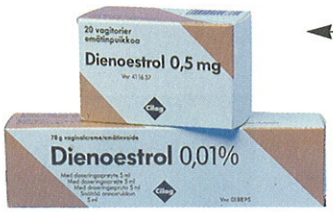
Eiliv Lund

Eiliv Lund
professor dr.med.

Bruk av østrogener i og etter overgangsalderen

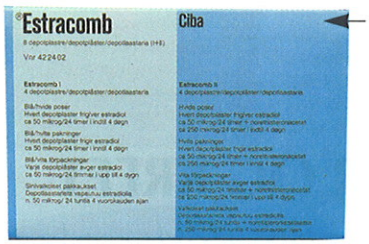
Denne brosjyren er et hjelpemiddel for å huske riktig navn på de hormontabletter/plaster/salver/stikkpiller du har brukt. Under bildene er det oppgitt hvilke år disse var i salg. For noen hormontabletter/plaster finnes det esker med samme utseende, men med ulik styrke av hormonene. Vi ber deg tenke nøye gjennom navnet på de hormon-tabletter/plaster/salver/stikkpiller du har brukt. Eldre avregistrerte preparater er ikke gjengitt med bilder, det gjelder:

Nr. 201 **Dietylstilbøstrol** 1mg stikkpiller til skjeden (1976-92)
Nr. 202 **Dietylstilbøstrol** 0,1 mg tabletter (1980-85)
Nr. 203 **Dietylstilbøstrol** 0,5 mg stikkpiller (1976-81)
Nr. 204 **Primodos** tabletter (1961-74)
Nr. 205 **Østriol** 1 mg tabletter (1975-95)
Nr. 206 **Østriol** 0,25 mg tabletter (1961-83)

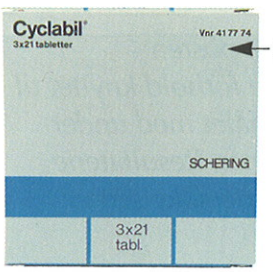


Nr. 108. Solgt fra 1976

Nr. 109. Solgt fra 1954

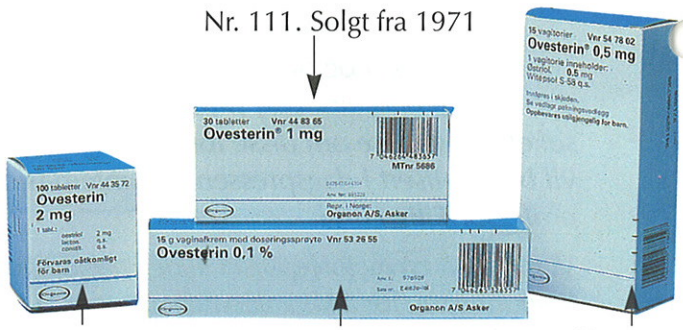


Nr. 110. Solgt fra 1994



Nr. 101. Solgt fra 1978

Nr. 111. Solgt fra 1971

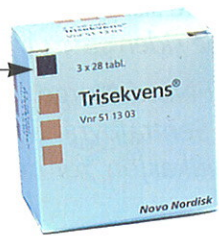


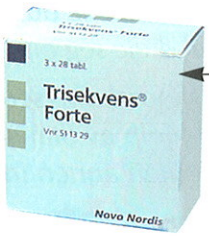
Nr. 112. Solgt fra 1989

Nr. 113. Solgt fra 1983

Nr. 114. Solgt fra 1984

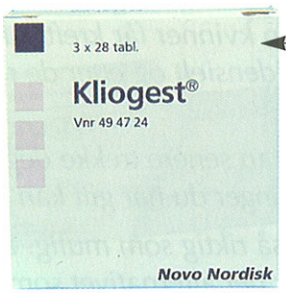
Nr. 102. Solgt fra 1978





Nr. 103. Solgt fra 1978

Nr. 104. Solgt fra 1953



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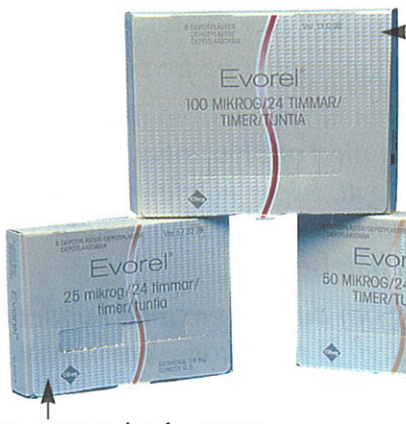
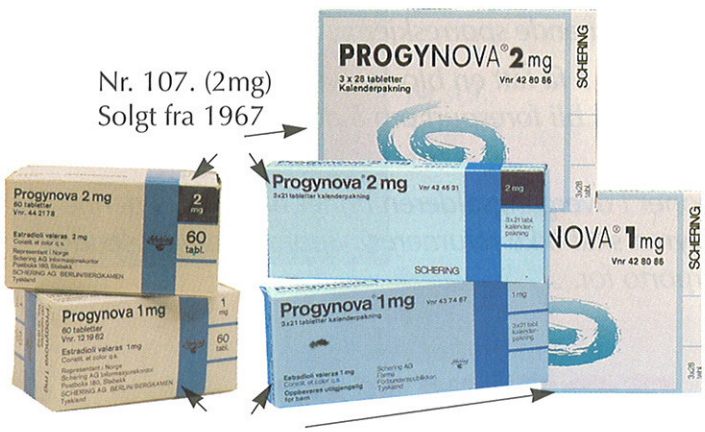


Nr. 115. Solgt fra 1995

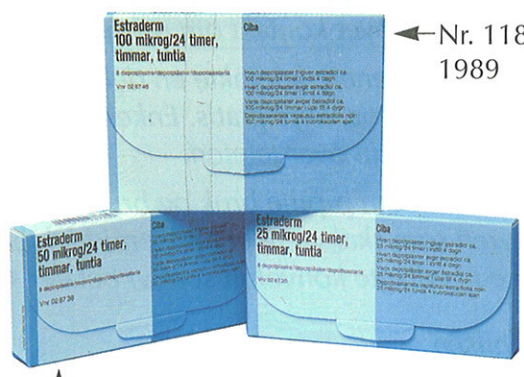
Nr. 117. Solgt fra 1994

Nr. 116.Solgt fra 1995



Nr. 107. (2mg) Solgt fra 1967

Nr. 106. (1mg) Solgt fra 1970



Nr. 118. Solgt fra 1989

Nr. 120. Solgt fra 1989

Nr. 119. Solgt fra 1989

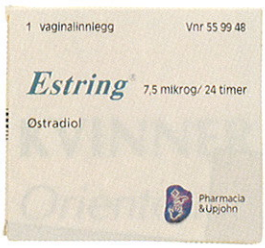
Nr. 121
Solgt fra
1996.

Nr. 123
Solgt fra
1996.

Nr. 122
Solgt fra
1996.

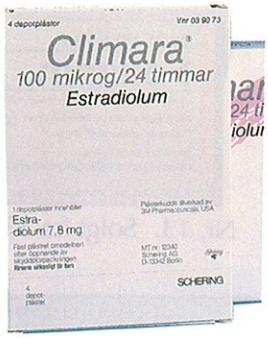
Nr. 124
Solgt fra
1996.

Nr. 126
Solgt fra
1997.



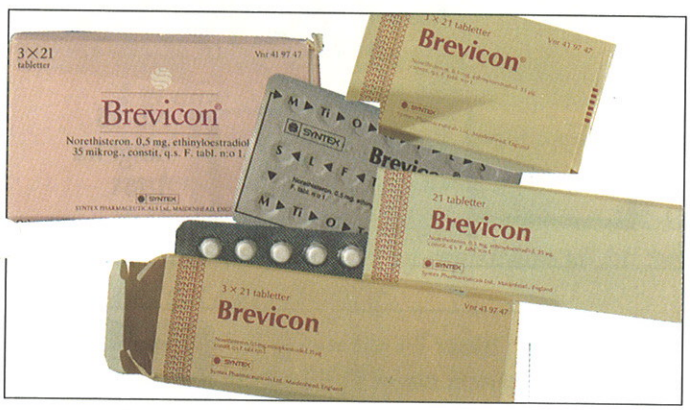
Nr. 125
Solgt fra 1996.

Nr. 127
Solgt fra
1997.



P-pille merker i salg 1991-98

Denne brosjyren er et hjelpemiddel for å huske riktig navn på de p-piller du har brukt de siste årene. Bildene er ordnet alfabetisk. Under bildene er det oppgitt hvilke år p-pillene var i salg.
For noen p-piller finnes det esker med samme utseende, men med ulik størrelse, avhengig av om de inneholder p-piller for en eller flere måneder.
Vi ber deg tenke nøye gjennom navnet på de p-pillene du har brukt.



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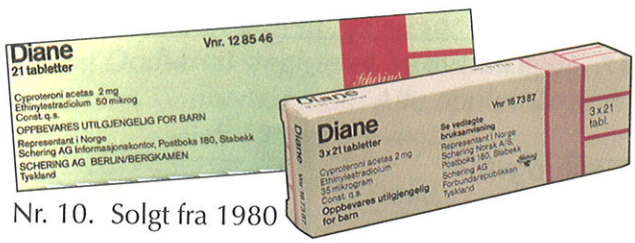
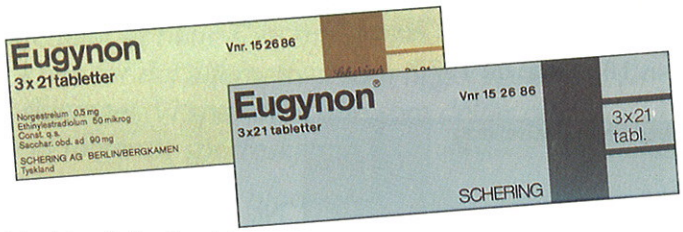
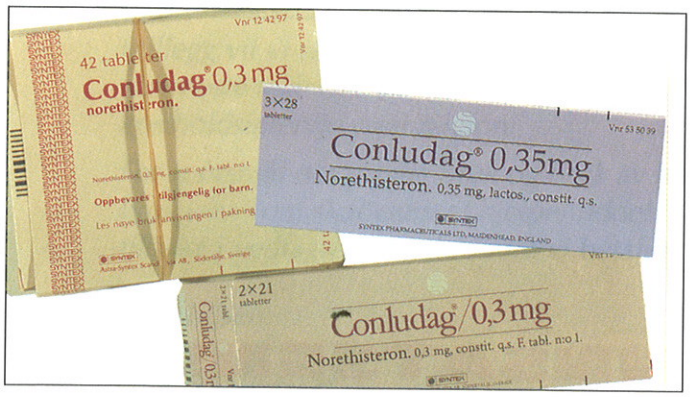


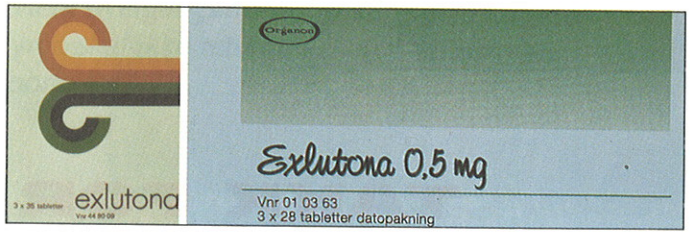
Nr. 10. Solgt fra 1980



Nr. 11. Solgt fra 1969



Nr. 7. Solgt fra 1971



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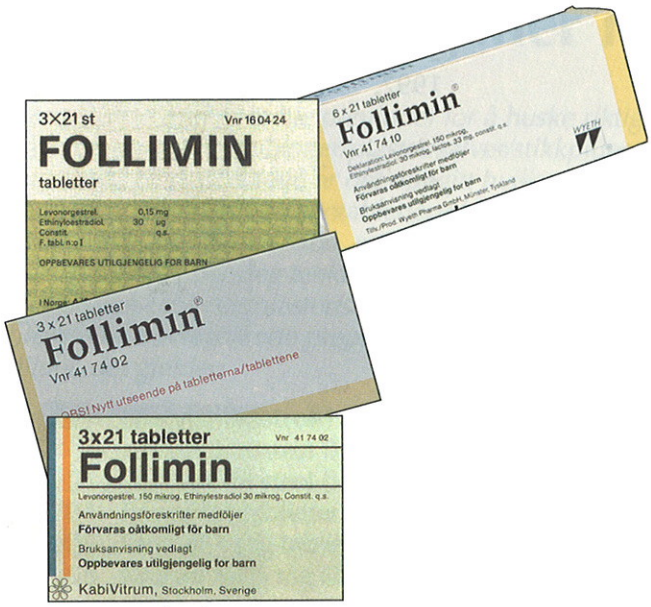
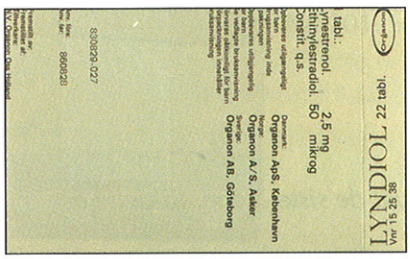
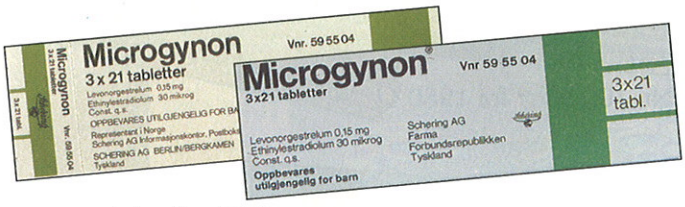


Nr. 13. Solgt fra 1978



Nr. 16.
Solgt fra 1965

Nr. 17. Solgt fra 1985



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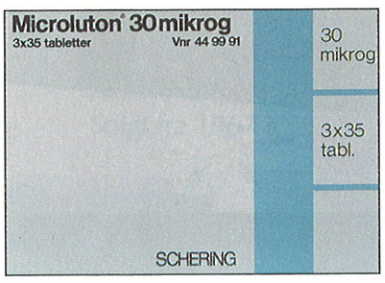
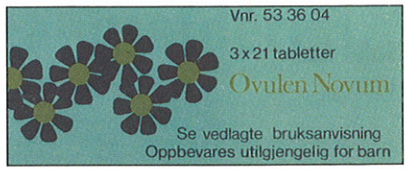
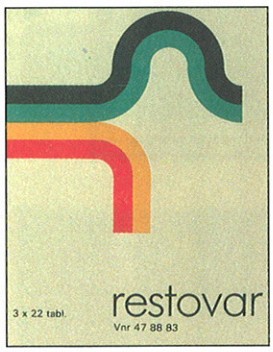


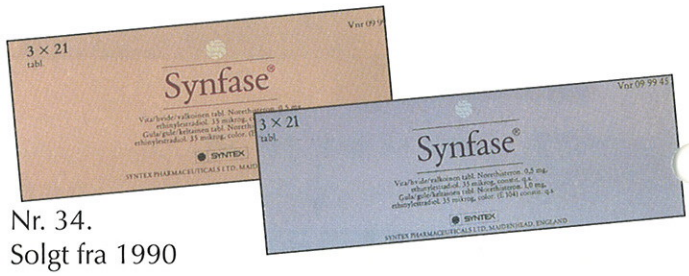
Nr. 19.
Solgt fra
1973

Nr. 28. Solgt fra 1970





Nr. 31. Solgt fra 1977



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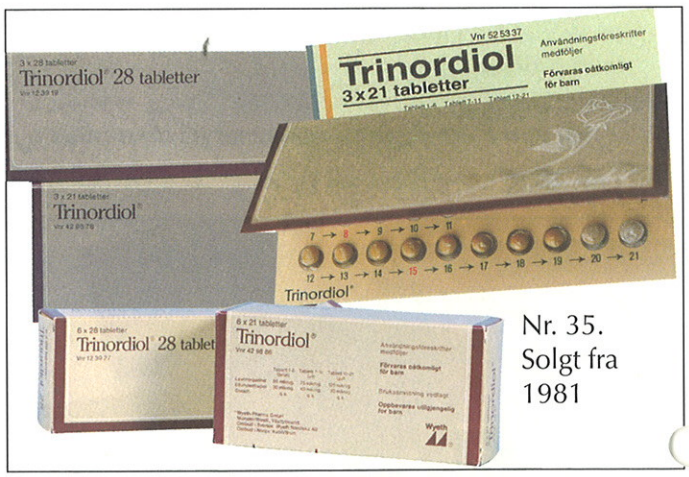
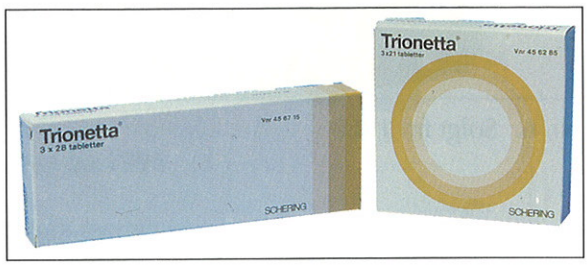
Solgt fra 1990



Nr. 35.
Solgt fra
1981



Nr. 36.
Solgt
fra
1981

TAKK FOR INNSATSEN!

LUNDBLAD GRAFISK AS, TROMSØ - TLF. 77 67 51 01

Appendix B

Høst 1998

KVINNER OG KREFT

KONFIDENSIELT

Hvis du samtykker i å være med, sett kryss for JA i ruten ved siden av. Dersom du ikke ønsker å delta kan du unngå purring ved å sette kryss for NEI og returnere skjemaet i vedlagte svarkonvolutt.

Hvis du vil være med, så ber vi deg fylle ut spørreskjemaet så nøye som mulig, se orienteringen på brosjyren for nærmere opplysninger.

Med vennlig hilsen

Eiliv Lund
Professor dr. med

uts. 28 + 29

Jeg samtykker i å delta i spørreskjema-undersøkelsen JA ☐ NEI ☐

I hvilken kommune har du bodd lengre enn ett år?

Kommune:	Alder			
1. Fødested:	Fra	0 år	til	år
2.	Fra	år	til	år
3.	Fra	år	til	år
4.	Fra	år	til	år
5.	Fra	år	til	år
6.	Fra	år	til	år
7.	Fra	år	til	år

Menstruasjonsforhold

Er menstruasjonen din;

☐ Regelmessig (naturlig)
☐ Uregelmessig
☐ Uteblitt pga. legemiddelbruk, sykdom, trening, annet
☐ Sluttet/stoppet

Hvis du ikke har menstruasjon;

har den stoppet av seg selv? ..... ☐
operert vekk begge eggstokkene? ..... ☐
operert vekk livmoren? ..... ☐
annet, angi ..... ☐

Alder da menstruasjonen opphørte? ..... år

Graviditeter etter 1991

Fyll ut for hvert barn du har født etter 1991 fødselsår og antall måneder du ammet (fylles også ut for dødfødte eller for barn som er døde senere i livet). Dersom du ikke har født barn, fortsetter du ved neste spørsmål.

Barn Nr.:	Fødselsår	Antall måneder med amming

P-Pillebruk etter 1991

Har du noen gang brukt p-piller, minipiller inkludert, etter 1991? ☐ Ja ☐ Nei

Bruker du p-piller nå? ☐ Ja ☐ Nei

Vi vil be deg om å besvare spørsmålene om p-pillebruk etter 1991 mer nøye. For hver periode med sammenhengende bruk av samme p-pille merke håper vi du kan si oss hvor gammel du var da du startet, hvor lenge du brukte det samme p-pillemerket og navnet på p-pillene.
Dersom du har tatt opphold eller skiftet merke, skal du besvare spørsmålene for en ny periode. Dersom du ikke husker navnet på p-pillen, sett usikker. For å hjelpe deg til å huske navnet på p-pille merkene ber vi deg bruke den vedlagte brosjyren som viser bilder av p-pille- merker som har vært solgt i Norge. Vennligst oppgi også nummeret på p-pillen som står i brosjyren.

Årstall	Alder ved start	Brukt samme p-pille sammenhengende år	måneder	Nr.	P-pillene (se brosjyren) Navn

Hormonspiral

Har du noengang brukt hormonspiral (Levonova)? ☐ Ja ☐ Nei

Hvis Ja; hvor lenge har du brukt hormonspiral i alt? ..... år

Hvor gammel var du første gang du du fikk innsatt hormonspiral? ..... år

Bruker du hormonspiral nå? ☐ Ja ☐ Nei

Holdning til bruk av østrogen

Hvilket av følgende alternativer dekker best ditt syn på østrogenbehandling i forbindelse med overgangsalderen (sett ett kryss)

Positivt - en hjelp som bør tilbys alle kvinner ☐
Et nødvendig onde- bør bare brukes av de med store plager ☐
Negativt- bør ikke «klusse med naturen» ☐

Bruk av hormonpreparater med østrogen i overgangsalderen

Har du noen gang brukt østrogentabletter/plaster?

☐ Ja ☐ Nei

Hvis Ja; hvor lenge har du brukt østrogentabletter/plaster i alt? ..... år

Hvis du har brukt østrogenpreparater i *kun 1 år eller mindre;* hvorfor har du brukt midlene så kort tid?

- Har nettopp startet behandlingen ☐
- Er kvitt plagene ☐
- Redd for skadevirkninger ☐
- Fikk plagsomme bivirkninger ☐
- Annet ☐

Hvor gammel var du første gang du brukte østrogentabletter/plaster? ..... år

Hvorfor begynte du å bruke østrogentabletter/plaster?

- Lindre plager i overgangsalderen (hetetokter, uopplagthet, underlivsplager mm) ☐
- Forebygge benskjørhet (osteoporose) ☐
- Forebygge hjerte/kar sykdom ☐
- Annet ☐

Bruker du tabletter/plaster nå? ☐ Ja ☐ Nei

UTFYLLENDE SPØRSMÅL TIL ALLE SOM HAR BRUKT ELLER BRUKER PREPARATER MED ØSTROGEN I FORM AV TABLETTER ELLER PLASTER.

For hver periode med sammenhengende bruk av samme østrogenpreparat håper vi du kan si oss hvor gammel du var da du startet, hvor lenge du brukte det samme østrogenpreparatet, og navnet på dette. Dersom du har tatt opphold eller skiftet merke, skal du besvare spørsmålene for en ny periode. Dersom du ikke husker navnet på østrogenpreparatet sett «usikker». For å hjelpe deg til å huske navnet på østrogenpreparatene ber vi deg bruke den vedlagte brosjyren som viser bilder av østrogenpreparater som har vært solgt i Norge. Vennligst oppgi også nummer på østrogentabletten/plasteret som står i brosjyren.

Periode	Alder ved start	Brukt samme østrogen-tablett/plaster Sammenhengende år	måned	Østrogentablett/ plaster (se brosjyre) Nr.	Navn
Første					
Andre					
Tredje					
Fjerde					
Femte					

Har østrogenpreparatene gitt deg bivirkninger? ☐ Ja ☐ Nei

Hvis Ja; kryss av for hvilke bivirkninger:

- Uregelmessige blødninger ☐
- Brystspenning ☐
- Kvalme/magesmerter ☐
- Hodepine ☐
- Hudreaksjoner ☐
- Vektøkning ☐ ☐ Ant kg
- Annet ..... ☐

Førte de overnevnte bivirkninger til at du forandret østrogenbehandlingen din? ☐ Ja ☐ Nei

Hvis ja;

- Skiftet østrogenpreparat ☐
- Sluttet ☐
- Annet, angi ☐

Østrogenpreparat til lokal bruk i skjeden

Har du noen gang brukt østrogenkrem/stikkpille? ☐ Ja ☐ Nei

Bruker du krem/stikkpille nå? ☐ Ja ☐ Nei

Selvopplevd helse

Oppfatter du din egen helse som; (Sett ett kryss)

☐ meget god ☐ god ☐ dårlig ☐ meget dårlig

Sykdom

Har du eller har du hatt noen av følgende sykdommer?

	Ja	Nei	Hvis Ja: Alder ved start
Høyt blodtrykk	☐	☐	
Hjertesvikt/hjertekrampe	☐	☐	
Årebetennelse	☐	☐	
Blodpropp i legg eller lår	☐	☐	
Hjerteinfarkt	☐	☐	
Slag	☐	☐	
Migrene	☐	☐	
Epilepsi	☐	☐	
Sukkersyke (diabetes)	☐	☐	
Endometriose	☐	☐	
Hypothyreose	☐	☐	
Depresjon (oppsøkt lege)	☐	☐	

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)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Brudd									
Underarmen (håndledd)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Ryggvirvel (kompresjon)	☐	☐	☐	☐	☐	☐	☐	☐	☐
Andre brudd angi :.....	☐	☐	☐	☐	☐	☐	☐	☐	☐

Sosiale forhold

Er du: (Sett ett kryss) ☐ gift ☐ samboer ☐ annet

Hvor mange personer er det i ditt hushold? .....

Yrke? .....

Hvor høy er bruttoinntekten i husholdet pr. år?

☐ under 150 000 kr ☐ 151 000–300 000 kr
☐ 301 000–450 000 kr ☐ 451 000–600 000 kr
☐ over 600 000 kr

Røykevaner

	Ja	Nei
Har du noen gang røkt?	☐	☐

Hvis Ja, ber vi deg om å fylle ut hvor mange sigaretter du i gjennomsnitt røkte pr. dag i perioden 1991-1998.

	Antall sigaretter hver dag						
Årstall	0	1-4	5-9	10-14	15-19	20-24	25+
1991-94							
1995-98							

	Ja	Nei
Røker du daglig nå?	☐	☐
Bor du sammen med noen som røker?	☐	☐

Hvis Ja, hvor mange sigaretter røker de til sammen pr. dag? .....

Brystkreft i nærmeste familie

Har noen nære slektninger hatt brystkreft;

	Ja	Nei'	Vet ikke	Alder ved start
datter	☐	☐	☐	
mor	☐	☐	☐	
mormor	☐	☐	☐	
farmor	☐	☐	☐	
søster	☐	☐	☐	

Hvor mange helsøsken har du? ☐ **Søstre** ☐ **Brødre**
(oppgi antall)

Hvilket nummer i søskenflokken er du? Nummer ☐

Undersøkelser for kreft

Hvor ofte undersøker du brystene dine selv?
(sett ett kryss)

Aldri ..... ☐
Uregelmessig ..... ☐
Regelmessig (omtrent hver måned) ..... ☐

Går du til regelmessig undersøkelse av brystene dine med mammografi? (sett ett kryss)

Nei ..... ☐
Ja, med to års mellomrom eller mindre ..... ☐
Ja, med to års mellomrom ..... ☐

Fysisk aktivitet

Vi ber deg angi din fysiske aktivitet etter en skala fra svært lite til svært mye. Skalaen nedenfor går fra 1-10. Med fysisk aktivitet mener vi både arbeid i hjemmet og i yrkeslivet, samt trening og annen fysisk aktivitet som turgåing o.l. Sett ring rundt det tallet som best angir ditt nivå av fysisk aktivitet.

Alder	Svært lite									Svært mye
30 år	1	2	3	4	5	6	7	8	9	10
I dag	1	2	3	4	5	6	7	8	9	10

Hvor mange timer pr. dag i gjennomsnitt går eller spaserer du utendørs?

	mindre enn ½ time	½-1 time	1-2 timer	mer enn 2 timer
Vinter				
Vår				
Sommer				
Høst				

	Ja	Nei
Arbeider du utendørs i yrkessammenheng?	☐	☐

Hvis ja:
hvor mange timer pr. uke? .....Sommer .....vinter

Høyde og vekt

Hvor høy er du? ..... cm

Hvor mye veier du i dag? ..... kg

Kosthold

Vi er interessert i å få kjennskap til hvordan kostholdet ditt er **vanligvis.** Kryss av for hvert spørsmål om hvor ofte du **i gjennomsnitt siste året** har brukt den aktuelle matvaren, og hvor mye du pleier å spise/drikke hver gang.

Hvor mange glass melk drikker du vanligvis av hver type? (Sett ett kryss pr. linje)

	aldri/ sjelden	1-4 pr. uke	5-6 pr. uke	1 pr. dag	2-3 pr. dag	4+ pr. dag
Helmelk (søt, sur)	☐	☐	☐	☐	☐	☐
Lettmelk (søt, sur)	☐	☐	☐	☐	☐	☐
Skummet (søt, sur)	☐	☐	☐	☐	☐	☐

Hvor mange kopper kaffe drikker du vanligvis av hver sort? (Sett ett kryss for hver linje)

	aldri/ sjelden	1-6 pr. uke	1 pr. dag	2-3 pr. dag	4-5 pr. dag	6-7 pr. dag	8+ pr. dag
Kokekaffe	☐	☐	☐	☐	☐	☐	☐
Traktekaffe	☐	☐	☐	☐	☐	☐	☐
Pulverkaffe	☐	☐	☐	☐	☐	☐	☐

Hvor mange glass juice, saft og brus drikker du vanligvis? (Sett ett kryss for hver linje)

	aldri/ sjelden	1-3 pr. uke	4-6 pr. uke	1 pr. dag	2-3 pr. dag	4+ pr. dag
Appelsinjuice	☐	☐	☐	☐	☐	☐
Saft/brus med sukker	☐	☐	☐	☐	☐	☐
Saft/brus sukkerfri	☐	☐	☐	☐	☐	☐

Hvor ofte spiser du yoghurt (1 beger)? (Sett ett kryss)

☐ aldri/sjelden ☐ 1 pr. uke ☐ 2-3 pr. uke ☐ 4+ pr. uke

Hvor ofte har du i gjennomsnitt siste året spist kornblanding, havregryn eller müsli? (Sett ett kryss)

☐ aldri/nesten aldri ☐ 1-3 pr. uke ☐ 4-6 pr. uke ☐ 1 pr. dag

Hvor mange skiver brød/rundstykker og knekkebrød/skonrokker spiser du vanligvis?
(1/2 rundstykke = 1 brødskive) (Sett ett kryss for hver linje)

	aldri/ sjelden	1-4 pr. uke	5-7 pr. uke	2-3 pr. dag	4-5 pr. dag	6+ pr. dag
Grovt brød						
Fint brød						
Knekkebrød o.l.						

Nedenfor er det spørsmål om bruk av ulike påleggstyper. Vi spør om hvor mange brødskiver med det aktuelle pålegget du pleier å spise. Dersom du også bruker matvarene i andre sammenhenger enn til brød (f. eks. til vafler, frokostblandinger, grøt), ber vi om at du tar med dette når du besvarer spørsmålene.

På hvor mange brødskiver bruker du? (Sett ett kryss pr. linje)

	0 pr. uke	1-3 pr. uke	4-6 pr. uke	1 pr. dag	2-3 pr. dag	4+ pr. dag
Syltetøy og annet søtt pålegg						
Brun ost, helfet						
Brun ost, halvfet/mager						
Hvit ost, helfet						
Hvit ost, halvfet/mager						
Kjøttpålegg, leverpostei						

Videre kommer spørsmål om fiskepålegg.
På hvor mange brødskiver pr. uke har du i gjennomsnitt siste året spist? (Sett ett kryss pr. linje)

	0 pr. uke	1 pr. uke	2-3 pr. uke	4-6 pr. uke	7-9 pr. uke	10+ pr. uke
Makrell i tomat, røkt makrell						
Kaviar						
Annet fiskepålegg						

Hva slags fett bruker du vanligvis på brødet?
(Sett gjerne flere kryss)

☐ bruker ikke fett på brødet
☐ smør
☐ hard margarin (f. eks. Per, Melange)
☐ myk margarin (f. eks. Soft)
☐ smørblandet margarin (f. eks. Bremykt)
☐ Brelett
☐ lettmargarin (f. eks. Soft light, Letta)

Dersom du bruker fett på brødet, hvor tykt lag pleier du smøre på? (En kuvertpakke med margarin veier 12 gram).
(Sett ett kryss)

☐ skrapet (3 g) ☐ tynt lag (5 g) ☐ godt dekket (8 g)
☐ tykt lag (12 g)

Hvor ofte spiser du frukt? (Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd	1 pr. uke	2-4 pr. uke	5-6 pr. uke	1 pr. dag	2+ pr. dag
Epler/pærer							
Appelsiner o.l.							
Bananer							
Annen frukt (f.eks. druer, fersken)							

Hvor ofte spiser du ulike typer grønnsaker?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd	1 pr. uke	2 pr. uke	3 pr. uke	4-5 pr. uke	6-7 pr. uke
Gulrøtter							
Kål							
Kålrot							
Broccoli/blomkål							
Blandet salat							
Grønnsakblanding (frossen)							
Andre grønnsaker							

For de grønnsakene du spiser, kryss av for hvor mye du spiser hver gang. (Sett ett kryss for hver sort)

- gulrøtter ☐ 1/2 stk. ☐ 1 stk. ☐ 1 1/2 stk. ☐ 2+ stk.
- kål ☐ 1/2 dl ☐ 1 dl ☐ 1 1/2 dl ☐ 2+ dl
- kålrot ☐ 1/2 dl ☐ 1 dl ☐ 1 1/2 dl ☐ 2+ dl
- broccoli/blomkål ☐ 1-2 buketter ☐ 3-4 buketter ☐ 5+ buketter
- blandet salat ☐ 1 dl ☐ 2 dl ☐ 3 dl ☐ 4+ dl
- grønnsakblanding ☐ 1/2 dl ☐ 1 dl ☐ 2 dl ☐ 3+ dl

Hvor mange poteter spiser du vanligvis (kokte, stekte, mos)? (Sett ett kryss)

☐ spiser ikke/spiser sjelden poteter

☐ 1-4 pr. uke ☐ 5-6 pr. uke

☐ 1 pr. dag ☐ 2 pr. dag

☐ 3 pr. dag ☐ 4+ pr dag

Hvor ofte bruker du ris og spaghetti/makaroni ?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1-3 pr. mnd	1 pr. uke	2 pr. uke	3+ pr. uke
Ris					
Spaghetti, makaroni					

Hvor ofte spiser du risengrynsgrøt? (Sett ett kryss)

☐ aldri/sjelden ☐ 1 pr. mnd ☐ 2-3 pr. mnd ☐ 1+ pr. uke

Hva slags fett blir vanligvis brukt til matlaging i din husholdning? (Sett gjerne flere kryss)

☐ smør

☐ hard margarin (f. eks. Per, Melange)

☐ myk margarin (f. eks. Soft)

☐ smørblandet margarin (f. eks. Bremykt)

☐ soyaolje ☐ olivenolje ☐ maisolje

Fisk

Vi vil gjerne vite hvor ofte du pleier å spise fisk, og ber deg fylle ut spørsmålene om fiskeforbruk så godt du kan. Tilgangen på fisk kan variere gjennom året. Vær vennlig å markere i hvilke årstider du spiser de ulike fiskeslagene.

	aldri/ sjelden	like mye hele året	vinter	vår	sommer	høst
Torsk, sei, hyse, lyr						
Steinbit, flyndre, uer						
Laks, ørret						
Makrell						
Sild						

Med tanke på de periodene av året der du spiser fisk, hvor ofte pleier du å spise følgende? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd	2-3 pr. mnd	1 pr. uke	2 pr. uke	3+ pr. uke
Kokt torsk, sei, hyse, lyr						
Stekt torsk, sei, hyse, lyr						
Steinbit, flyndre, uer						
Laks, ørret						
Makrell						
Sild						

Dersom du spiser fisk, hvor mye spiser du vanligvis pr. gang? (1 skive/stykke = 150 gram)
(Sett ett kryss for hver linje)

- kokt fisk (skive) ☐ 1 ☐ 1,5 ☐ 2 ☐ 3+
- stekt fisk (stykke) ☐ 1 ☐ 1,5 ☐ 2 ☐ 3+

Hvor mange ganger pr. år spiser du fiskeinnmat?
(Sett ett kryss pr. linje)

	0	1-3	4-6	7-9	10+
Rogn	☐	☐	☐	☐	☐
Fiskelever	☐	☐	☐	☐	☐

Dersom du spiser fiskelever, hvor mange spiseskjeer pleier du å spise hver gang? (Sett ett kryss)

☐ 1 ☐ 2 ☐ 3-4 ☐ 5-6 ☐ 7+

Hvor ofte bruker du følgende typer fiskemat?
(Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd	2-3 pr. mnd	1 pr. uke	2+ pr. uke
Fiskekaker/pudding/ boller					
Plukkfisk, fiskegrateng					
Frityrfisk, fiskepinner					
Andre fiskeretter					

Hvor stor mengde pleier du vanligvis å spise av de ulike rettene? (Sett ett kryss for hver linje)

- fiskekaker/pudding/boller (stk.) (2 fiskeboller=1 fiskekake) ☐ 1 ☐ 2 ☐ 3 ☐ 4+
- plukkfisk, fiskegrateng (dl) ☐ 1-2 ☐ 3-4 ☐ 5+
- frityrfisk, fiskepinner (stk.) ☐ 1-2 ☐ 3-4 ☐ 5-6 ☐ 7+

Hvor ofte spiser du skalldyr (f. eks. reker, krabbe)**?**
(Sett ett kryss)

aldri/ sjelden	1 pr. mnd	2-3 pr mnd	1+ pr. uke
☐	☐	☐	☐

I tillegg til informasjon om fiskeforbruk er det viktig å få kartlagt hvilket tilbehør som blir servert til fisk. Hvor ofte bruker du følgende til fisk? (Sett ett kryss pr. linje)

	aldri/ sjelden	1 pr. mnd	2-3 pr. mnd	1 pr. uke	2+ pr. uke
Smeltet eller fast margarin/fett					
Seterrømme (35%)					
Lettrømme (20%)					
Saus med fett (hvit/brun)					
Saus uten fett (hvit/brun)					

For de ulike typene tilbehør du bruker til fisk, vær vennlig å kryss av for hvor mye du vanligvis pleier spise.

- smeltet/fast fett (ss) ☐ 1/2 ☐ 1 ☐ 2 ☐ 3 ☐ 4+
- seterrømme (ss) ☐ 1/2 ☐ 1 ☐ 2 ☐ 3 ☐ 4+
- lettrømme (ss) ☐ 1/2 ☐ 1 ☐ 2 ☐ 3 ☐ 4+
- saus med fett (dl) ☐ 1/4 ☐ 1/2 ☐ 3/4 ☐ 1 ☐ 2+
- saus uten fett (dl) ☐ 1/4 ☐ 1/2 ☐ 3/4 ☐ 1 ☐ 2+

Andre matvarer

Hvor ofte spiser du følgende kjøtt- og fjærkreretter?
(Sett ett kryss for hver rett)

	aldri/ sjelden	1 pr. mnd	2-3 pr. mnd	1 pr. uke	2+ pr. uke
Steik (okse, svin, får)					
Koteletter					
Biff					
Kjøttkaker, karbonader					
Pølser					
Gryterett, lapskaus					
Pizza m/kjøtt					
Kylling					
Andre kjøttretter					

Dersom du spiser følgende retter, oppgi mengden du vanligvis spiser: (Sett ett kryss for hver linje)

- steik (skiver) ☐ 1 ☐ 2 ☐ 3 ☐ 4+
- koteletter (stk.) ☐ 1/2 ☐ 1 ☐ 1,5 ☐ 2+
- kjøttkaker, karbonader (stk.) ☐ 1 ☐ 2 ☐ 3 ☐ 4+
- pølser (stk. à 150g) ☐ 1/2 ☐ 1 ☐ 1,5 ☐ 2+
- gryterett, lapskaus (dl) ☐ 1-2 ☐ 3 ☐ 4 ☐ 5+
- pizza m/kjøtt (stykke à 100 g) ☐ 1 ☐ 2 ☐ 3 ☐ 4+

Hvor mange egg spiser du vanligvis i løpet av en uke (stekte, kokte, eggerøre, omelett)? (Sett ett kryss)

☐ 0 ☐ 1 ☐ 2 ☐ 3-4 ☐ 5-6 ☐ 7+

Vi ber deg fylle ut hovedrettene til middag en gang til som en oppsummering. Kryss av i den ruten som passer hvor ofte du i gjennomsnitt i løpet av siste år har spist slik mat til middag

	5+ pr. uke	4 pr. uke	3 pr. uke	2 pr. uke	1 pr. uke	2-3 pr. mnd	1 pr. mnd	nesten aldri
Rent kjøtt	☐	☐	☐	☐	☐	☐	☐	☐
Oppmalt kjøtt	☐	☐	☐	☐	☐	☐	☐	☐
Fet fisk (makrell, laks o.l.)	☐	☐	☐	☐	☐	☐	☐	☐
Mager fisk (torsk o.l.)	☐	☐	☐	☐	☐	☐	☐	☐
Fiskemat	☐	☐	☐	☐	☐	☐	☐	☐

Hvor ofte spiser du iskrem (til dessert, krone-is osv.)?
(Sett ett kryss for hvor ofte du spiser iskrem om sommeren, og ett kryss for resten av året)

	aldri/ sjelden	1-3 pr mnd	1 pr. uke	2-3 pr. uke	4+ pr. uke
– om sommeren	☐	☐	☐	☐	☐
– resten av året	☐	☐	☐	☐	☐

Hvor mye is spiser du vanligvis pr. gang? (Sett ett kryss)

☐ 1 dl ☐ 2 dl ☐ 3 dl ☐ 4+ dl

Hvor ofte spiser du bakervarer som boller, kaker, wienerbrød, vafler, småkaker? (Sett ett kryss)

	aldri/ sjelden	1-3 pr. mnd	1 pr. uke	2-3 pr. uke	4-6 pr. uke	7+ pr. uke
Gjærbakst(boller)						
Kaker						
Pannekaker						
Vafler						
Småkaker						

Hvor ofte spiser du dessert? (Sett ett kryss)

	aldri/ sjelden	1-3 pr. mnd	1 pr. uke	2-3 pr. uke	4-6 pr. uke	7+ pr. uke
Pudding Sjokolade/karamell						
Riskrem, fromasj						
Kompott, fruktgrøt hermetisk frukt						

Hvor ofte spiser du sjokolade? (Sett ett kryss)

☐ aldri/sjelden ☐ 1-3 pr. mnd ☐ 1 pr. uke
☐ 2-3 pr. uke ☐ 4-6 pr. uke ☐ 1+ pr. dag

Dersom du spiser sjokolade, hvor mye pleier du vanligvis å spise hver gang? Tenk deg størrelsen på en Kvikk-Lunsj sjokolade, og oppgi hvor mye du spiser i forhold til den.

☐ 1/4 ☐ 1/2 ☐ 3/4 ☐ 1 ☐ 1,5 ☐ 2+

Hvor ofte spiser du salt snacks? (Sett ett kryss)

	aldri/ sjelden	1-3 pr. mnd	1 pr. uke	2-3 pr. uke	4-6 pr. uke	7+ pr. uke
Potetchips						
Peanøtter						

Tilberedningsmåte

Har du mikrobølgeovn? ☐ Ja ☐ Nei

Hvis Ja; hvor mange ganger pr. uke bruker du mikrobølgeovnen til ganger pr. uke

middagslaging? .....
annet? .....

Hvilken farve foretrekker du på stekeskorpen?

☐ Lys brun ☐ Middels ☐ Mørk brun

Hvor ofte spiser du stekt eller grillet mat?

	aldri/ sjelden	1-3 pr. mnd	1 pr. uke	2-3 pr. uke	4-6 pr. uke	7+ pr. uke
Mørkt kjøtt (biff ol.)						
Lyst kjøtt (kylling ol.)						
Oppmalt kjøtt (kjøttkaker ol.)						
Bacon						
Fisk						

Bruker du stekefettet eller sjyen etter steking?

☐ nei, aldri ☐ av og til
☐ som oftest ☐ ja, alltid

Tran og fiskeoljekapsler

Bruker du tran (flytende)? ☐ Ja ☐ Nei

Hvis ja; hvor ofte tar du tran?
Sett ett kryss for hver linje.

	aldri/ sjelden	1-3 pr. mnd	1 pr. uke	2-6 pr. uke	daglig
- om vinteren	☐	☐	☐	☐	☐
- resten av året	☐	☐	☐	☐	☐

Hvor mye tran pleier du å ta hver gang?

☐ 1 ts ☐ 1/2ss ☐ 1+ss

Bruker du tranpiller/kapsler? ☐ Ja ☐ Nei

Hvis ja; hvor ofte tar du tranpiller/kapsler?
Sett ett kryss for hver linje.

	aldri/ sjelden	1-3 pr. mnd	1 pr. uke	2-6 pr. uke	daglig
- om vinteren	☐	☐	☐	☐	☐
- resten av året	☐	☐	☐	☐	☐

Hvilken type tranpiller/kapsler bruker du vanligvis, og hvor mange pleier du å ta hver gang?

	ja	antall pr. gang
Møllers trankapsler	☐	.....
Møllers omega-3 kapsler	☐	.....
Møllers dobbel	☐	.....
annet, navn	☐	.....

Bruker du fiskeoljekapsler? ☐ Ja ☐ Nei

Hvis ja; hvor ofte tar du fiskeoljekapsler?

aldri/ sjelden	1-3 pr. mnd	1 pr. uke	2-6 pr. uke	daglig
☐	☐	☐	☐	☐

Hvilken type fiskeoljekapsler bruker du vanligvis, og hvor mange pleier du å ta hver gang?

	ja	antall pr. gang
Triomar	☐	.....
Almarin	☐	.....
Nycomed Omega-3	☐	.....
annet, navn	☐	.....

Kosttilskudd

Bruker du annet kosttilskudd (eks. vitaminer, mineraler)? ☐ Ja ☐ Nei

Hvis ja; hvor ofte tar du slike kosttilskudd?

aldri/ sjelden	1-3 pr. mnd	1 pr. uke	2-6 pr. uke	daglig
☐	☐	☐	☐	☐

Navn .....

Alkohol

Er du total avholdskvinne? ☐ Ja ☐ Nei

Hvis Nei, hvor ofte og hvor mye drakk du i gjennomsnitt siste året? (Sett ett kryss for hver linje)

	aldri/ sjelden	1 pr. mnd	2-3 pr. mnd	1 pr. uke	2-4 pr. uke	5-6 pr. uke	1+ pr. dag
Øl (½ L)	☐	☐	☐	☐	☐	☐	☐
Vin (glass)	☐	☐	☐	☐	☐	☐	☐
Brennevin (drinker)	☐	☐	☐	☐	☐	☐	☐

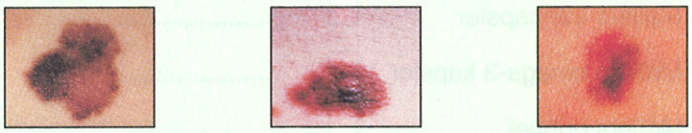
Solvaner

Får du fregner når du soler deg? ☐ Ja ☐ Nei

Hvor mange føflekker har du sammenlagt på begge armer (fra fingertuppene til skuldrene)?

☐ 0 ☐ 1-10 ☐ 11-50 ☐ 51+

Hvor mange uregelmessige føflekker større enn 5 mm har du sammenlagt på begge armene (fra fingrene til armhulene)? Tre eksempler på føflekker større enn 5 mm med uregelmessig form er vist i nedenfor.



5 mm

☐ 0 ☐ 1 ☐ 2-3 ☐ 4-6 ☐ 7-12 ☐ 13-24 ☐ 25+

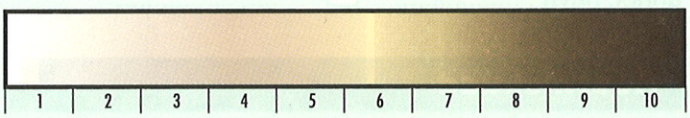
Hvor mange små, regelmessige føflekker har du sammenlagt på begge armene (fra fingrene til armhulene)?

☐ 0 ☐ 1-10 ☐ 11-50 ☐ 51+

Hva er din opprinnelige hårfarge? (sett ett kryss)

☐ mørkbrunt, svart ☐ brun ☐ blond, gul ☐ rød

For å kunne studere effekten av soling på risiko for hudkreft ber vi deg gi opplysninger om hudfarge
Sett ett kryss på den fargen som best passer din hudfarge (uten soling)



Hvor ofte dusjer eller bader du?

	Mer enn 1 g dagl	1 g dagl	4-6 g pr. uke	2-3 g pr. uke	1 g pr. uke	2-3 g pr. mnd.	Sjelden aldri
Med såpe/shampo							
Uten såpe/shampo							

Hvor mange ganger pr. år er du blitt forbrent av solen slik at du har fått svie og blemmer med avflassing etterpå? (ett kryss for hver aldersgruppe)

Årstall	Aldri	Høyst 1 gang pr. år	2-3 g. pr. år	4-5 g. pr. år	6 eller flere ganger
1991-94					
1995-98					

Hvor mange uker soler du deg pr. år i syden?

Årstall	Aldri	1 uke	2-3 uker	4-5 uker	7 uker eller mer
1991-94					
1995-98					

Hvor mange uker pr. år soler du deg i Norge eller utenfor syden?

Årstall	Aldri	1 uke	2-3 uker	4-5 uker	7 uker eller mer
1991-94					
1995-98					

Når bruker du krem med solfaktor (sett evt. flere kryss):

☐ påsken ☐ i Norge eller utenfor syden ☐ solferie i syden

Hvilke solfaktorer bruker du i disse periodene?

	påsken	i Norge eller utenfor syden	solferie i syden
- I dag	.....	.....	.....
- For 10 år siden	.....	.....	.....

Hvilke solkremmerker bruker du? Angi faktor hvis du husker.

	Ja	faktor		Ja	faktor
Piz Buin	☐	....	Cosmica	☐	....
Ambre Solairé	☐	....	Natusan	☐	....
HTH	☐	....	Delial	☐	....
Andre, angi navn.....		....			

Hvor ofte har du solt deg i solarium?

Alder	Aldri	Sjelden	1 gang pr. mnd.	2 ganger pr. mnd.	3-4 ganger pr. mnd	oftere enn1 gang pr. uke
1991-94						
1995-98						

Til slutt vil vi spørre deg om ditt samtykke til å kontakte deg på nytt pr. post.
Vi vil hente adressen fra det sentrale personregister.

☐ Ja ☐ Nei

Takk for at du ville delta i undersøkelsen

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Appendix C

Overview of the foods included in the HNFI, BSDS and NND
in relation to the Norwegian food based dietary guidelines and NNR23

Food groups	**Grains**		**Fruits and vegetables**			**Fish and seafood, meat**		**Dairy**	**Oils and fat**
FBDG, Norway (2011)	70-90 g whole grains/day		≥ 500 g/day			400-450 g/week, at least 200 g fatty fish 500 g/week (upper limit) red and processed meat		3 portions low fat dairy products	-
NNR 2023	90 g whole grains		500-800 g/day			400-450 g/week, at least 200 g fatty fish 350 g/week (upper limit) meat		350-500 ml/day low fat dairy products	25 g/day plant oils
Nordic, foods	**Rye, barley, oats**	**Whole grains**	**Berries, Apples/ Pears**	**Root vege-tables**	**Cabbages**	**Fish/sea food**	**Meat**	**Low fat dairy**	**Rape-seed oil**
HNFI (Olsen et al. 2011)	Whole grain rye bread + oatmeal		Apples and pears (would like to include cloudberries, blueberries and cowberries but the FFQ did not include information about these berries)	Raw or cooked root vegetables-mainly carrots	Cauliflower, Brussels sprouts, broccoli, kale, white cabbage, and red cabbage	Fish as hot meal and in open sandwiches	-	-	-
HNFI (Roswall et al. 2015)	Oatmeal	Whole-grain bread	Apples/pears	Carrot; yellow turnip and beetroot	White/red cabbage; cauliflower; broccoli/Brussels sprouts	Atlantic herring/herring/mackerel; salmon; cod/pollock/ pike; shellfish	-	-	-
BSDS (Kanerva et al. 2013)	Rye, oats, barley		Bilberries, lingonberries, apples, pears	Roots, different cabbages tomatoes, lettuce, cucumbers		Salmon, Baltic herring, mackerel	Included as a negative component: beef, pork, processed meat products and sausages	Low-fat milk < 2% fat	Ratio of PUFA:SFA (high use of rapeseed oil and low use of butter)

NND (Hillesund et al. 2014)	Oatmeal porridge	Whole grain breads relative to refined breads	Wild berries, apples, pears, plums and strawberries	Carrots, rutabaga and various types of onions Kale, cauliflower, broccoli and brussels sprouts + potatoes relative to rice and pasta	Fish, seafood	Game	Unsweetened milk relative to fruit juice