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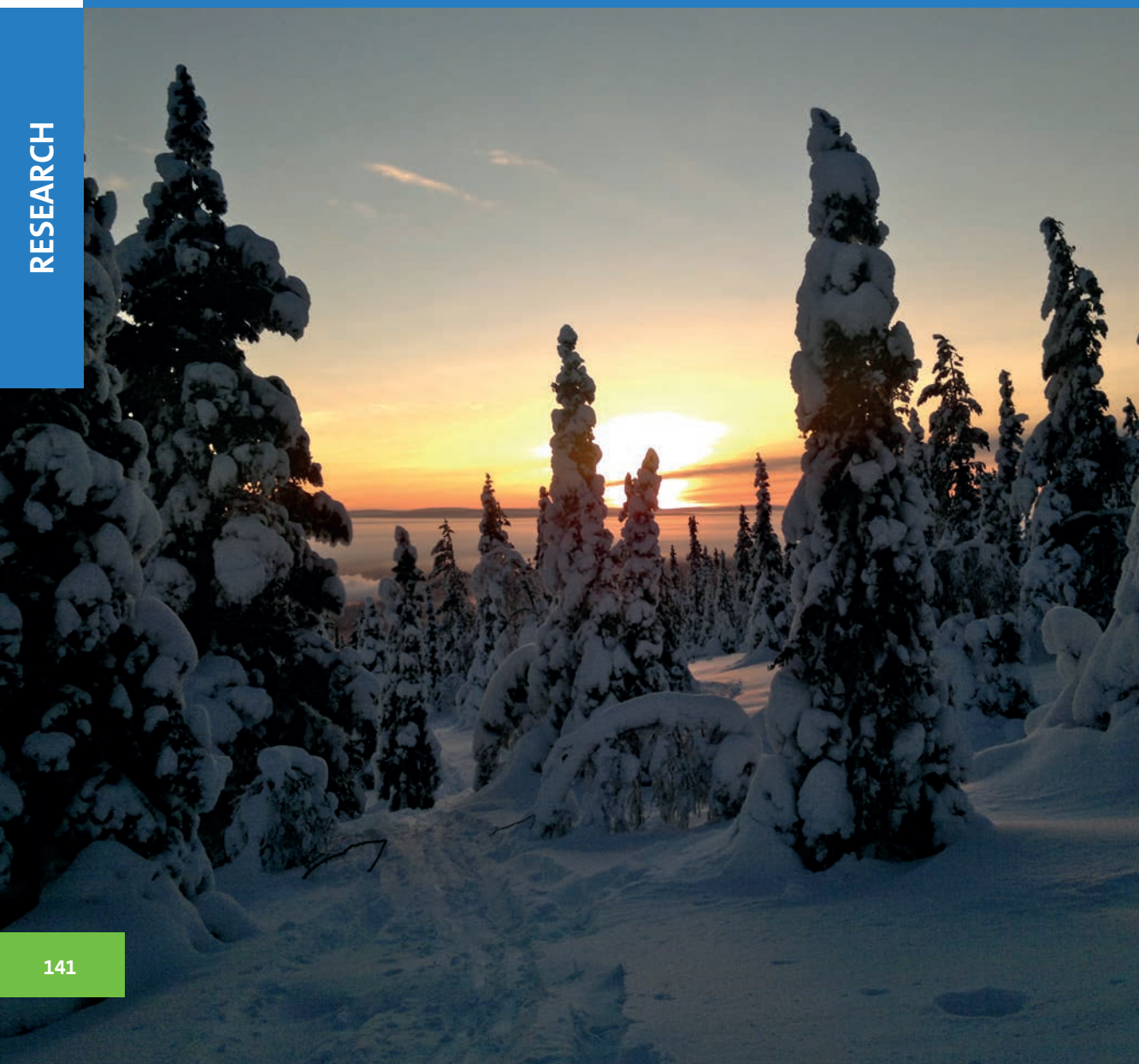
Noora Kanerva

The healthy Nordic diet, obesity and obesity-related metabolic risk factors

RESEARCH



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Noora Kanerva

The healthy Nordic diet, obesity and obesity-related metabolic risk factors

ACADEMIC DISSERTATION

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Abstract

Noora Kanerva, The healthy Nordic diet, obesity and obesity-related metabolic risk factors. National Institute for Health and Welfare. Research 141. 111 pages. Helsinki, Finland 2014.
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Obesity causes metabolic dysregulations that increase the risk of cardiovascular disease (CVD) and type 2 diabetes (T2D). Diet is known to play a key role in preventing obesity. In epidemiological studies, because single food and nutrient studies focusing on obesity have produced generally inconsistent results, nutrition researchers have shifted to exploring the health related effects of the whole diet, measured with dietary scores. Recently, a diet constructed of healthy Nordic foods has been suggested as having obesity and metabolic health enhancing features. However, there is a lack of population-based studies on this topic.

The aim of the research presented in this thesis was to develop a dietary score reflecting the healthy Nordic diet, and to assess its associations with obesity, metabolic risk factors (e.g., low-grade inflammation, lipid fractions) and T2D in an epidemiological setting.

This study was based on data from three health surveys conducted between 2001-2007: the DILGOM study (n = 5024), the National Health 2000 Survey (n = 6772), and the Helsinki Birth Cohort Study (n = 2003). In clinical examinations, the weight, height, waist circumference and blood pressure of participants were measured, and blood samples were drawn. Information on the past medical history was derived from nationwide health registers. Participants' habitual diet was assessed with a validated food frequency questionnaire, which was used to derive the Baltic Sea Diet Score (BSDS) reflecting the healthy Nordic diet. The BSDS included nine components typical of the Nordic diet, which were scored according to the predictable health effect of each component, using sex- and population specific quartile cut-offs. The final summary score ranged between 0-25 points.

Participants with high adherence to the healthy Nordic diet (BSDS $\geq$ 17) had significantly higher intake of carbohydrates, fibre, vitamins, minerals and sodium,

and lower intake of saturated fat and alcohol compared to those who did not adhere to the diet (BSDS ≤ 9). Moreover, those who adhered to the diet were 35-52% less likely to be abdominally obese and 27-42% less likely to have elevated C-reactive protein (CRP) concentrations compared to the others. In contrast, women adhering to the healthy Nordic diet were 40% more likely to have a low concentration of high-density lipoprotein (HDL) cholesterol than the others. The BSDS did not associate with T2D incidence during 10 years of follow-up.

In conclusion, the BSDS appears to be a valid tool for measuring adherence to a healthy diet. The findings related to abdominal obesity and low-grade inflammation, if proven causal, may lead to decrement in chronic disease risk, and therefore, be relevant from the public health perspective.

Keywords: Nordic, diet, score, obesity, diabetes, low-grade inflammation, HDL cholesterol.

Tiivistelmä

Noora Kanerva, Pohjoismaisen ruokavalion yhteys lihavuuteen ja sen metabolisiin riskitekijöihin. Väestötutkimus. Terveyden ja hyvinvoinnin laitos. Tutkimus 141. 111 sivua. Helsinki, Finland 2011.
ISBN 978-952-302-326-0 (painettu); ISBN 978-952-302-327-7 (verkkojulkaisu)

Lihavuus aiheuttaa aineenvaidunnallisia häiriöitä, jotka johtavat kohonneeseen sydän- ja verisuonitautien sekä tyypin 2 diabeteksen riskiin. Ruokavaliolla on tärkeä rooli lihavuuden ja sen riskitekijöiden ehkäisyssä. Yksittäisiin ravintoaineisiin ja ruokiin keskittynyt tutkimus on kuitenkin tuottanut osittain ristiriitaisia tuloksia, minkä vuoksi on alettu tutkimaan myös ruokavalion kokonaisvaikutuksia. Epidemiologisessa ravitsemustutkimuksessa kokonaisruokavaliota voidaan tutkia ruokavalioindeksin avulla. Pohjoismaisiin terveellisiin ruokiin perustuvan ruokavalion on väitetty ehkäisevän lihavuutta ja sen riskitekijöitä. Kokeellisten tutkimusten tulokset ovat lupaavia, mutta väestötason tutkimuksia ei vielä ole julkaistu.

Tutkimuksen tavoite oli kehittää terveellistä Pohjoismaista ruokavaliota kuvaava indeksi ja tutkia sen yhteyttä lihavuuteen, metabolisiin riskitekijöihin (esim. matala-asteinen tulehdus ja veren rasva-arvot) sekä tyypin 2 diabetekseen väestötasolla.

Tutkimuksessa käytettiin vuosina 2001-2007 kerättyjä väestötutkimusaineistoja: DILGOM tutkimus (n = 5024), Terveys 2000 tutkimus (n = 6772) ja Helsingin syntymäkohorttitutkimus (n = 2003). Tutkimuksessa mitattiin tutkittavien pituus, paino, vyötärönympärys ja verenpaine, sekä otettiin verinäyte. Tutkittavien lääkkeiden käytöstä, sairaalakäynneistä ja kuolinsyistä saatiin tietoa kansallisten rekistereiden kautta. Tutkittavien tavanomaista ruoankäyttöä mitattiin frekvenssityyppisellä ruoankäyttökyselyllä, jonka tietoja käytettiin terveellistä pohjoismaista ruokavaliota kuvaavan Itämeren ruokavalioindeksin laskemiseen. Indeksi sisälsi yhdeksän pohjoismaiselle ruokavaliolle tyypillistä osatekijää, jotka kukin pisteytettiin niiden todennäköiseen terveysvaikutukseen perustuen, käyttäen tutkimuspopulaation ja sukupuolen mukaisia pisterajoja. Indeksin vaihteluväliksi muodostui 0-25 pistettä.

Terveellistä Pohjoismaista ruokavaliota eniten noudattavat (Itämeren ruokavalioindeksi ≥ 17 pistettä) saivat enemmän hiilihydraatteja, kuituja, vitamiineja ja mineraaleja, ja vähemmän tyydyttynyttä rasvaa sekä alkoholia verrattuna niihin, jotka eivät noudattaneet Pohjoismaista ruokavaliota (Itämeren ruokavalioindeksi ≤ 9 pistettä). Lisäksi Pohjoismaista ruokavaliota noudattavilla keskivartalolihavuuden riski oli 35-50 % pienempi sekä kohonneen C-reaktiivisen proteiinin pitoisuuden riski 30-40 % pienempi verrattuna muihin tutkittaviin. Toisaalta, naisilla, jotka noudattivat pohjoismaista ruokavaliota, hyvälaatuisen kolesterolin (HDL) pitoisuus oli 40 % todennäköisemmin suositeltua pienempi verrattuna muihin tutkittaviin. Itämeren ruokavalioindeksi ei ollut yhteydessä tyypin 2 diabeteksen ilmaantuvuuteen kymmenen vuoden seuranta-aikana.

Itämeren ruokavalioindeksiä voidaan käyttää tutkittavien ruokavalion terveellisyyden mittarina väestötutkimuksissa. Mikäli Pohjoismaisen ruokavalion yhteys keskivartalolihavuuteen ja matala-asteiseen tulehdukseen osoittautuu kausaaliseksi, ruokavalion noudattaminen voi johtaa pienentyneeseen kroonisten tautien riskiin, mikä on kansanterveydellisesti merkittävä asia.

Avainsanat: Pohjoismainen ruokavalio, Itämeri, indeksi, lihavuus, matala-asteinen tulehdus, tyypin 2 diabetes, HDL kolesteroli.

Contents

List of original papers

This thesis is based on the following original articles (sub-studies) which are referred to in the text by their Roman numerals. In addition, some unpublished material is presented.

I Kanerva N, Kaartinen NE, Schwab U, Lahti-Koski M, Männistö S. The Baltic Sea Diet Score: a tool for assessing healthy eating in Nordic countries. Public Health Nutr 2014;17(8):1697-705.

II Kanerva N, Kaartinen NE, Schwab U, Lahti-Koski M, Männistö S. Adherence to the Baltic Sea Diet consumed in the Nordic countries is associated with lower abdominal obesity. British J Nutr 2012;109(3):520-528.

III Kanerva N, Kaartinen NE, Rissanen H, Knekt P, Eriksson JG, Sääksjärvi K, Sundvall J, Männistö S. Associations of the Baltic Sea diet with cardiometabolic risk factors – a meta-analysis of three Finnish studies. British J Nutr 2014;112:616-626.

IV Kanerva N, Loo B-M, Eriksson JG, Leiviskä J, Kaartinen NE, Jula A, Männistö S. Associations of the Baltic Sea diet with obesity-related markers of inflammation. Ann Med 2014;46(2):90-96.

V Kanerva N, Rissanen H, Knekt P, Havulinna AS, Eriksson JG, Männistö S. The healthy Nordic diet and incidence of Type 2 Diabetes - 10 year follow-up. Diabetes Res Clin Pract 2014; Sep 3:1-4. [Epub ahead of print].

Abbreviations

AHEI	Alternate Healthy Eating Index
BMI	Body mass index
BSDS	Baltic Sea Diet Score
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DILGOM	DIetary, Lifestyle and Genetic determinants of Obesity and Metabolic syndrome
E%	Percentage of the total energy intake
EPIC	European Prospective Investigation on Cancer
FFQ	Food frequency questionnaire
HBCS	Helsinki Birth Cohort Study
HDL	High-density lipoprotein
Health 2000	National Health 2000 Survey
HEI	Healthy Eating Index
HMW	High molecular weight
HPFS	Health Professionals Follow-up Study

HR	Hazard ratio
IL-6	Interleukin 6
LDL	Low-density lipoprotein
MDS	Mediterranean Diet Score
MetS	Metabolic syndrome
NHANES	National Health and Examination Survey
NHS	Nurses Health Study
OR	Odds ratio
OGTT	Oral glucose tolerance test
PA	Leisure-time physical activity
PUFA	n-3 polyunsaturated fatty acids
SE	Standard error
THL	National Institute for Health and Welfare
TNF-α	Tumour necrosis factor alpha
T2D	Type 2 diabetes
US	United States
VLDL	Very low-density lipoprotein
WC	Waist circumference
WHO	World Health Organization

1 Introduction

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health. Obesity has recently been ranked 6th among the most important risk factor contributing to premature deaths and years lived with disability (Murray and Lopez 2013) due to its close relationship with several chronic diseases, for example breast cancer, sleep apnoea and hypertension (WHO 2000).

Adipose tissue, especially in the abdominal area, is the site of synthesis of many metabolically active proteins that take part in the regulation of local metabolic processes and modulate the risk of developing chronic diseases (Elks and Francis 2010). For instance, many studies have reported a positive association between obesity, inflammation and insulin resistance (Chan and Woo 2010). The complex pathological processes related to obesity reflect interactions between genes and the environment: genes determine the risk, which is modulated by environmental and socioeconomic factors such as urbanization and income, as well as lifestyle factors such as physical activity, sleep and diet. There is some evidence that dietary factors may regulate metabolic fluxes and homeostasis through the transcriptional and translational control of enzyme activity, e.g. the type of fat regulates adiposity and insulin sensitivity (Chan and Woo 2010). Further studies are, however, needed to understand the heterogeneity in metabolic responses to various dietary factors.

Effective long-term weight loss and weight maintenance depends on permanent changes in the diet and physical activity. Thus, the promotion of a healthy diet is an important aspect of prevention policies (Ministry of Social Affairs and Health 2008). Recommendations have traditionally been based on a single nutrients or foods, but these have not been successful in preventing the obesity epidemic among the general population. Clearly, more effective tools are needed to produce comprehensible public health messages and facilitate policymaking (Rowe et al. 2011). To provide such tools, nutrition researchers have taken a new approach and focused on the quality of the whole diet. In epidemiological studies, this is put into practice by

creating summary values of the whole-diet to measure how well an individual adheres to a pre-defined (healthy) diet (Waijers et al. 2007). These summary scores or indices have the advantage of taking into account the complex interactions and cumulative effects of multiple nutrients or foods within the entire diet.

Several dietary scores have been designed to match certain populations in particular geographical areas. For example, one of the most known dietary scores was developed to reflect adherence to the traditional diet of the Mediterranean region (Trichopoulou et al. 1995). However, differences in food cultures, local resources and ecological aspects, might make it difficult for other populations, such as Scandinavians, to adopt this diet. Therefore, in January 2011, the University of Eastern Finland, the Finnish Heart Association and the Finnish Diabetes Association launched the Baltic Sea Diet Pyramid (Uusitupa and Schwab 2011). The Pyramid illustrates a healthy Nordic diet based on local foods: apples and berries; roots and cabbages; rye, oats and barley; low-fat milk products; rapeseed oil; and salmon and freshwater fishes. Furthermore, the healthy Nordic diet is recommended to be low in red and processed meat products, and moderate in alcohol. Two recent randomized and controlled trials have implied that individuals with metabolic syndrome could benefit from the healthy Nordic diet in treating obesity, hypercholesterolemia, endothelial dysfunction, insulin resistance and chronic low-grade inflammation (Adamsson et al. 2011, Uusitupa et al. 2013). However, large population-based studies on the association of the diet with health outcomes are lacking.

The aim of the research presented in thesis was to develop a dietary score reflecting the healthy Nordic diet, and to examine its associations with obesity, obesity-related metabolic risk factors (low-grade inflammation, hypercholesterolemia, hypertriclyceridemia, elevated glucose concentration, hypertension) and with the incidence of type 2 diabetes (T2D) during 10-year follow-up in an epidemiological setting.

2 Review of the literature

2.1 Obesity

2.1.1 Definition

The World Health Organization (2000) defines overweight and obesity as excess fat tissue that has accumulated to an extent that presents a risk to health. Obesity and overweight can be described with anthropometric measures, such as the body mass index (BMI). BMI is calculated by dividing weight (kg) by the square of height (m^2). Reference values for BMI vary by sex, age and ethnicity. As an example, the common cut-offs used for Caucasians (such as Finns) are presented in Table 1 (WHO 2000).

Table 1. Classification of body size according to BMI.

Class	BMI value (kg/m^2)
Underweight	< 18.5
Normal weight	18.5-24.9
Overweight	25.0-29.9
Obese	30.0-39.9
Morbidly obese	≥ 40.0

The harmful effects of obesity largely depend on body fat distribution. Compared to overall obesity, health risks relate more closely to visceral (abdominal) fat mass (Huxley et al. 2010). Abdominal obesity can be assessed with a measure of the waist circumference (WC). For Caucasians, WC > 94 cm in men and WC > 80 cm in women indicate an increased risk of chronic diseases (WHO 2008), whereas WC > 102 cm for men and > 88 cm for women indicate a high risk of chronic diseases (WHO 2008). In Finland, the Current Care Guidelines for adult obesity recommends cut-offs of > 100 cm for men and > 90 cm for women to be used in clinical practice (Working Group of the Finnish Medical Society Duodecim and Finnish Association for the Study of Obesity 2011).

Besides BMI and WC, many other methods exist to define obesity. For example, the waist-to-hip ratio, sagittal abdominal diameter and body fat composition (e.g. fat percentage) are suitable measures for describing body size and shape. However, BMI and WC are the most commonly used measures in health surveys.

2.1.2 Prevalence and trends

Since the 1980s, the prevalence of obesity has doubled globally from 4.8-7.9% to 9.8-13.8% (Finucane et al. 2011). Within the high-income countries, North American men had the highest prevalence of obesity (29.2%), whereas Asian-Pacific men and women had the lowest prevalence (< 10%) in 2008 (Finucane et al. 2011).

The Finnish population used to be one of the heaviest populations in Scandinavia, but nowadays, Icelanders has become even more obese, whereas populations in Sweden, Norway and Denmark are remaining among the leanest populations in Europe (Rasmussen et al. 2012). Compared to the rest of the world, the prevalence of obesity in Finland is at the average level (Stevens et al. 2012). As in many other countries, the number of obese Finnish men and women increased between 1980-2002 from 11.3% to 20.7% and from 17.9% to 24.1% respectively (Figure 1) (Lahti-Koski et al. 2010), the intra-individual change in body weight being 0.31-0.35 kg per year (Pajunen et al. 2012). Adverse changes in fat distribution were seen during the 1990s, as the pace of the cross-sectional increase in BMI slowed, but WC continued to steadily increase (Lahti-Koski et al. 2007). The youngest and leanest Finns have gained weight intra-individually more rapidly compared to the oldest and obese during the decades (Pajunen et al. 2012), but according to cross-sectional observations, this trend has been attenuated in the 2010s (Männistö et al. 2012a).

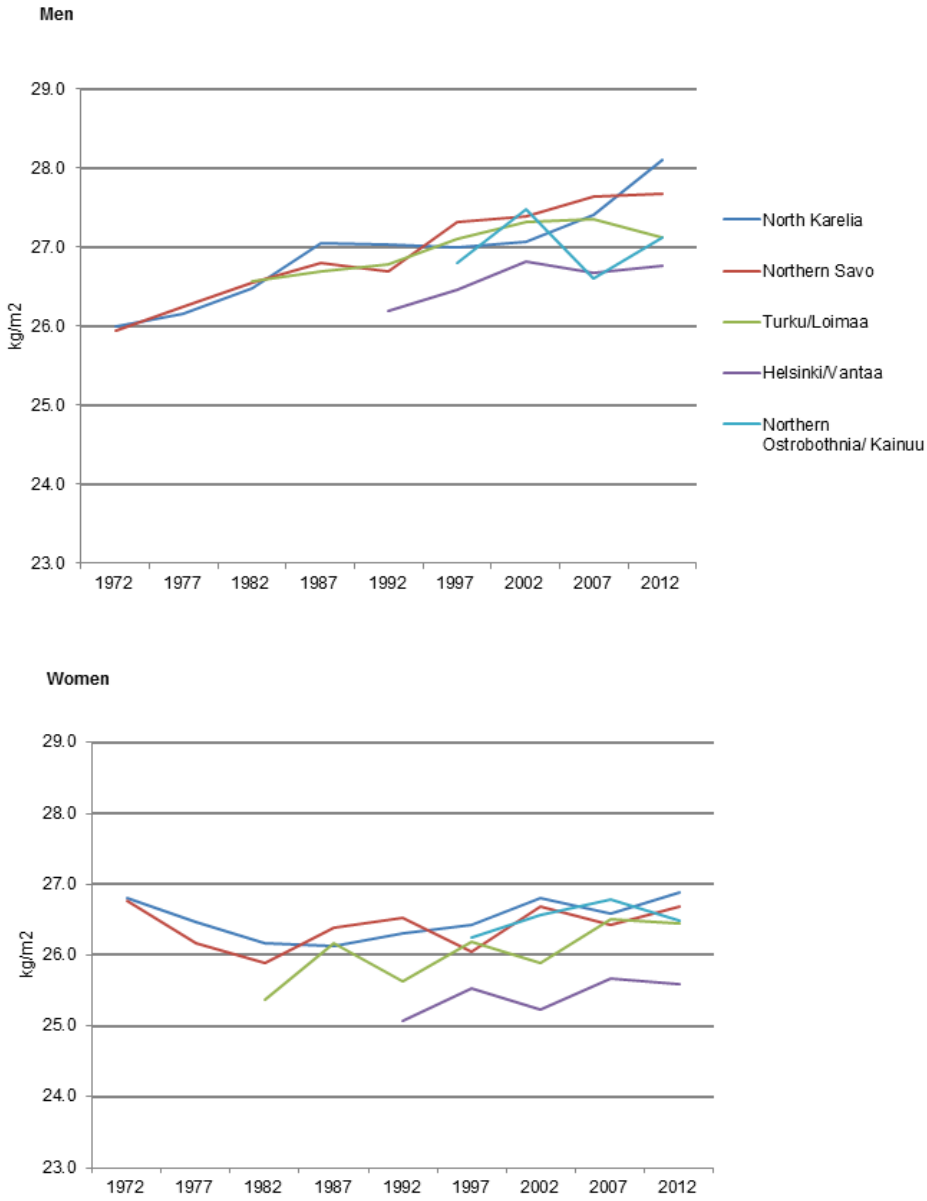

Figure 1. Trend in age-adjusted BMI for Finnish men and women in 5 geographical areas between 1972-2012 (Männistö et al. 2012a). Reprinted with the kind permission of the National Institute for Health and Welfare.

In 2010, a levelling-off of obesity was reported among North American women (Flegal et al. 2012) and among some European populations (Neovius et al. 2008, Großschädl and Stronegger 2012, Howel 2012), including Finnish men and women (Lundqvist et al. 2012, Männistö et al. 2012a). Despite this promising trend, the effect of the quality of the data and possible biases, especially increase in selective non-participation, set a question mark on the reliability of the results. Furthermore, overweight and obesity have stabilized to a level that is too high from a public health perspective. Two-thirds of Finnish men and nearly half of women are at least overweight, whereas one-fifth of the population is obese (Lundqvist et al. 2012, Männistö et al. 2012a). Furthermore, every third Finnish adult is abdominally obese. Clearly, effective actions targeted at the promotion of healthy dietary habits and physical activity are needed to maintain the positive development (Kansallisen lihavuusohjelman ohjelmaryhmä 2013).

2.1.3 Adipose tissue as an endocrine organ

Adipose tissue is known to be the main storage site for energy, but is also an important regulator of macronutrient homeostasis and many metabolic processes. In obese individuals, a long-term excess intake of energy over expenditure leads to lipid accumulation in the adipose tissue, causing an increase in the number and size (hypertrophy) of adipocytes (Galic et al. 2010, Elks and Francis 2010). Adipocyte hypertrophy triggers an increase in macrophage infiltration, leading to chronic low-grade inflammation via a complex interplay between macrophages and adipocyte-excreted cytokines, known as adipokines (Figure 2). At present, the adipokines with the most established role in inflammation include adiponectin, leptin, tumour necrosis factor alpha (TNF-α), interleukine 6 (IL-6), and C-reactive protein (CRP).

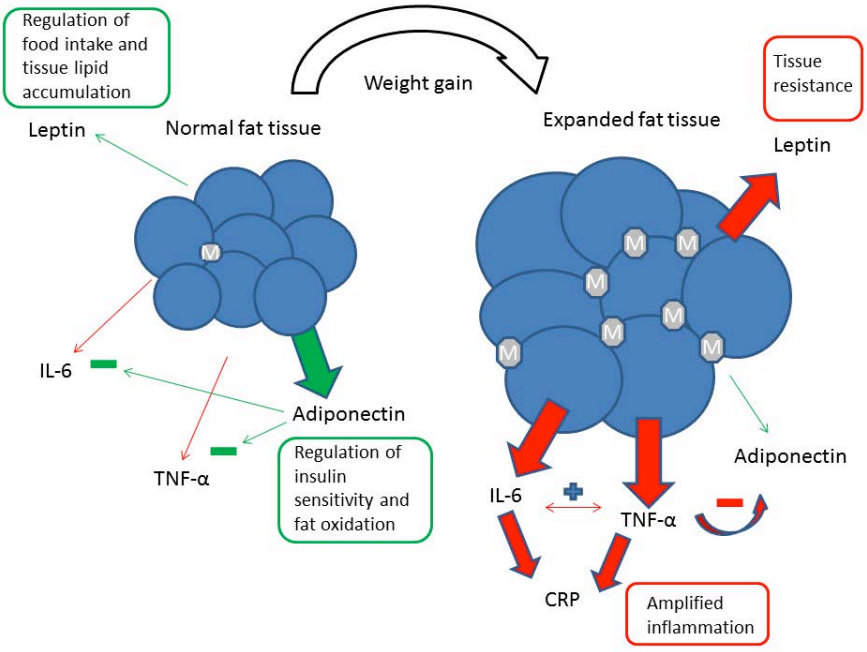

Figure 2. Adapted from Forsythe et al. (2008). In lean individuals (left), anti-inflammatory adiponectin suppresses inflammatory cytokines, as leptin regulates normal food intake and inhibits lipid accumulation in peripheral tissues. In obese individuals (right), the production of anti-inflammatory adiponectin is inhibited (Matsubara et al. 2002, Auguet et al. 2014), and peripheral tissues develop resistance against an increased leptin concentration (Zhou and Rui 2013). The dysregulated adipokines induce greater macrophage production in adipose tissue which stimulates the production of TNF-α and IL-6. These two cytokines are the main moderators of acute-phase inflammatory CRP production (Calabro et al. 2009). CRP activates pathways mainly culminating in nuclear transcription factor kappa B. This factor amplifies the vicious cycle of inflammation by further perpetuating the macrophage recruitment process and overproduction of inflammatory adipokines.

2.1.4 Links to altered metabolism and chronic diseases

The inflammatory milieu together with lipid accumulation, provides perfect conditions for the development of metabolic abnormalities, such as dyslipidaemia (Wietlisbach et al. 2013). The exact molecular mechanisms still remain unclear. However, excess fat accumulation in the liver triggers hypertriglyceridemia and a decreased high-density lipoprotein (HDL) cholesterol concentration (Klop et al. 2013).

Furthermore, fat accumulation in the pancreas and inflammatory modulation of cell signaling and gene transcription impairs insulin secretion and insulin sensitivity, causing increased glucose concentrations (Hotamisligil et al. 1993, Donath and Shoelson 2011, Taylor 2013). Insulin resistance together with inflammation and an increased leptin concentration promote altered vascular function, leading, for example, to increased blood pressure (Kotsis et al. 2010).

Table 2. International criteria for metabolic syndrome according to Alberti et al. (2009).

Components	**Cut-offs**
Waist circumference	Country-specific cut-offs
Elevated triglyceride concentration	≥ 1.7 mmol/l or use of triglyceride-lowering medication *
Low HDL cholesterol concentration	< 1.0 mmol/l for men and < 1.3 mmol/l for women or use of HDL-lowering medication *
Hypertension	Systolic BP ≥ 130 mmHg; diastolic BP ≥ 85 mmHg or use of BP-lowering medication
Elevated fasting glucose concentration	≥ 5.6 mmol/l or use of anti-diabetic medication

Abbreviations: BP, blood pressure.
* Fibrates and nicotinic acid.

These disorders toghether with obesity tend to accumulate and cluster over time. Cluster of three or more metabolic disorders is known as metabolic syndrome (MetS) (Table 2) (Alberti et al. 2009). Individuals with MetS have a two-fold higher

risk of developing cardiovascular disease (CVD) or T2D compared to individuals with only one of the MetS components (Gami et al. 2007, Ford et al. 2008a, Ford et al. 2008b, Mottillo et al. 2010). According to the latest estimates, the prevalence of MetS is over 50% among Finnish men in all age groups and among over 45-year-old women (Jula et al. 2012). Among under 45-year-old women, one-third have MetS. These prevalences have remained somewhat stabile over the last 10 years.

Not all obese individuals develop MetS. In fact, some of the obese people do not display any of the metabolical abnormalities which are normally found in obese individuals. The prevalence of these "metabolically healthy obese" people is approximately 10% among obese Finnish men and 15% for obese Finnish women (Pajunen et al. 2011). The mechanisms protecting these obese people from getting metabolic abnormalities are still unknown, but may be related to disposition of fat more into subcutaneous than visceral fat storages, especially liver (Naukkarinen et al. 2014). Furthermore, it is not clear to which extent the lack of metabolic abnormalities impacts the future risk of mortality (Kramer et al. 2013).

2.2 The role of diet in the development of obesity and obesity-related risk factors

The diet in the Nordic countries has traditionally been high in animal fat, whole grains, dairy products and fish, but low in fruits and vegetables. In the 1970s and 1980s, nationwide attempts were undertaken to change adverse dietary habits at the population level in order to decrease the prevalence of CVD (Groth and Fagt 2001, Männistö et al. 2010b, Johansson et al. 2012). According to food balance sheets and national diet surveys, the use of animal fats has decreased and the consumption of fruits and vegetables has increased over the last decades. The overall consumption of milk has decreased and shifted from whole milk to low-fat milk (Groth and Fagt 2001, Männistö et al. 2010b, Johansson et al. 2012). The consumption of red and processed meat has considerably increased whereas the consumption of fish has not markedly changed. Generally, a positive trend towards nutrition recommendations among Scandinavians has been observed, and simultaneously the prevalence of

CVD has decreased. However, the dietary changes have not been effective against obesity, since the number of overweight and obese people has steadily increased during the last decades (Lahti-Koski et al. 2010). Thus, there is still room for improvement. For instance, compared to other European countries Scandinavians have the lowest consumption of fruits and vegetables, and the highest consumption of animal, processed and refined foods (Agudo et al. 2002, Slimani et al. 2002). Unhealthier dietary habits are also seen in nutrient intake levels. In the European Prospective Investigation on Cancer (EPIC), a multi-centre follow-up study including over 400 000 participants aged 25-70 years from 10 countries, the Mediterranean region had the highest intake of vitamin E, whereas in the Nordic countries, the intake of vitamin E was the lowest, reflecting unhealthy dietary habits (Freisling et al. 2010).

In the following sections, dietary factors that have had essential role in health promotion in Nordic countries, and their relationship with obesity, low-grade inflammation, CVD and T2D are reviewed.

2.2.1 Protecting factors

High consumption of fruits, vegetables, and whole grains may prevent obesity because of their low energy and high fibre content, which increases the feeling of satiety and reduces the feeling of hunger (Slavin 2005). Dairy consumption may prevent obesity through the modulation of gut microbiota or through calcium-regulated fatty acid metabolism (Christensen et al. 2009, Gonzalez et al. 2012). In reviews, the preventive effect of fruits and vegetables (Alinia et al. 2009, Ledoux et al. 2011, Boeing et al. 2012, Fogelholm et al. 2012), whole grains (Giacco et al. 2011, Fogelholm et al. 2012, Karl and Saltzman 2012) and dairy products (Louie et al. 2011, Fogelholm et al. 2012, Kratz et al. 2013) on weight gain and obesity has been graded as “possible” or “suggestive”. In other words, even though several positive results exist, there have been a number of studies not showing associations or having poor quality is substantial.

A landmark meta-analysis was conducted with 120 877 individuals aged 30-60 years at baseline who participated one of the three large cohorts from the United States (US): the Nurses' Health Study (NHS) I and II and the Health Professionals Follow-up Study (HPFS). This analysis demonstrated that compared to those with the lowest fruit and vegetable consumption each additional daily serving was associated with 0.1-0.2 kg less weight gain within each 4-year period (Mozaffarian et al. 2011). These analyses did not adjust for the intake of energy intake because the authors considered it to be a moderator between food and weight gain. However, the EPIC study researchers found that a 100 g increase in daily fruit and vegetable consumption did not generally associate with annual weight change over 5 years when the energy intake of participants remained constant (Buijsse et al. 2009, Vergnaud et al. 2012). More recent study results in US and Australia are showing similar inconsistencies as the earlier studies have shown (Heo et al. 2011, Shay et al. 2012, Aljadani et al. 2013).

Compared to those with the lowest whole-grain consumption, a large meta-analysis by Mozaffarian et al. (2011) showed that each additional daily serving associated with a 0.2 kg lower weight gain for each 4-year period when energy intake was not adjusted. In contrast, a recent meta-analysis of clinical trials revealed no dose-response relationship (Pol et al. 2013). Applying energy restriction to the intervention did not change the association between whole-grain consumption and body weight. However, the majority of the trials have lasted under two months and were not directly designed to measure the effect of whole-grain consumption on weight reduction. Furthermore, most whole-grain studies have only included US populations, and the generalizability of the results to other populations is therefore questionable.

Cross-sectional evidence indicates an inverse association between dairy food consumption and obesity (Murphy et al. 2013). Dairy products can be classified in many different ways, such as to low- or high-fat dairy, which hampers the summarizing of results and drawing of conclusions. In US cohorts, each additional daily serving of low-fat yoghurt was associated with a 0.4 kg lower weight gain within each 4-year period (Mozaffarian et al. 2011, Wang et al. 2014). In European

and Scandinavian populations, which generally consume more dairy foods compared to US populations, an inverse association between dairy intake (milk, sour milk, yoghurt, cheese and butter) and WC (Romaguera et al. 2011) or weight (Rosell et al. 2006, Holmberg and Thelin 2013) has also been observed. The observational results have been similar regardless of energy-adjustment. A meta-analysis of randomized clinical trials comparing diets of high dairy consumption (total dairy) with control diets having an equal amount of protein found no difference in weight or WC between the groups unless energy restriction was applied to the intervention (Abargouei et al. 2012). Similarly, another recent meta-analysis with a more diverse range of dairy foods found only a marginally significant weight loss in long-term interventions (≥ 1 year) with no energy restriction (Chen et al. 2012).

2.2.2 Inconclusive factors

Fat quality and quantity, as well as fish and alcohol consumption have many health effects, for example on heart health, but their association with obesity is not well established. The difficulty in examining the role of total fat intake on obesity is that a decrease in fat intake is always substituted with another macronutrient in order to maintain the energy balance. Due to the high energy content of fat, researchers have recommended a low-fat diet for obesity prevention. However, the inconclusive evidence gained in the 1990s got many researchers to believe that reducing total fat intake without reducing total energy intake does not play a major role in obesity (Willett and Leibel 2002). Even today, the evidence is so evenly dispersed that strong conclusions cannot be drawn (Fogelholm et al. 2012, Hooper et al. 2012). In most recent publications from the EPIC study, no association between energy-adjusted total fat intake and weight change was found (Forouhi et al. 2009).

Due to the unexpected findings, the focus has moved to research related to fat quality. So far, saturated fat intake has not been consistently associated with obesity, but a high intake of trans-fat has been positively associated with weight gain compared to individuals with a low intake of trans-fatty acids (Mozaffarian et al. 2011, Fogelholm et al. 2012). Moreover, high omega-3 polyunsaturated fatty acids

(PUFA) contribute to reduce fat mass by modulating the process of fatty acid oxidation (Lorente-Cebrián et al. 2013), but although studies have yielded mixed results, as reviewed by Fogelholm et al. (2012) and Lorente-Cebrián et al. (2013). Clinical trials published later on have supported these reviews (Munro and Garg 2012).

In US cohorts, women with a high fish intake had an even higher prevalence of obesity (Iso et al. 2001), whereas men with a high fish intake had a lower prevalence of overweight compared to the others (He et al. 2002). However, because obesity was not the primary outcome of the studies, these associations were not examined in detail. In two studies from the EPIC cohort and one Danish study, higher consumption of fish did not associate with a change in weight or WC with (Jakobsen et al. 2012, Jakobsen et al. 2013) or without (Halkjær et al. 2004) energy adjustment. The European studies reported a lower range in fish intake compared to the US studies. One European clinical trial including overweight men showed that as part of an energy-restricted diet, inclusion of fish (fatty or lean fish) resulted in greater weight loss compared to a traditional weight-loss diet (Thorsdottir et al. 2007).

Likewise to fat, also alcohol is closely related to energy intake and is therefore difficult to examine. In the 1990s, many cross-sectional studies demonstrated an inverse association between alcohol intake and obesity (Hellerstedt et al. 1990, Männistö et al. 1997), but more recent large cross-sectional studies have reported a positive association (Bergmann et al. 2011), whereas prospective and experimental trials have failed to provide any convincing evidence (Sayon-Orea et al. 2011b). According to Lukasiewicz et al. (2005), the J-shaped association between alcohol and obesity may hamper research, leading to inconsistent results. Furthermore, it is unclear whether the source of alcohol (beer, wine or spirits) has an effect on weight gain. It appears that wine consumption is not associated with weight gain, whereas beer and spirit consumption may promote it (Halkjær et al. 2009, Sayon-Orea et al. 2011a, Sayon-Orea et al. 2011b, Bendsen et al. 2013).

2.2.3 Predisposing factors

Meat contains a large amount of high-quality proteins, which are generally thought to be the most satiating of all macronutrients (Brennan et al. 2012). In contrast, a high intake of meat is often associated with higher weight gain in prospective population studies (Fogelholm et al. 2012). Meat is often categorized into red and white meat for research purposes. White meat is used to refer to poultry, whereas red meat is usually defined as beef, pork, lamb, game, or offal of these animals. Furthermore, red meat can be divided into processed and unprocessed meat.

In a Finnish population-based cross-sectional study, participants with the highest red meat consumption (mean intake of processed and unprocessed meat 340 g/d in men and 221 g/d in women) had a higher risk of obesity and excess WC when compared to those with the lowest red meat consumption (mean intake 67 g/d in men and 36 g/d in women) (Fogelholm, Kanerva and Männistö. Unpublished results). In the EPIC study, each 250 g of additional daily red meat consumption (processed and unprocessed) related to 2 kg of weight gain over 5 years of follow-up when energy intake was adjusted (Vergnaud et al. 2010). In US cohort studies, each additional daily serving of both processed and unprocessed red meat related to a 0.43 kg weight gain for each 4-year period even participants' energy intake was not adjusted (Mozaffarian et al. 2011).

In two randomized controlled trials on overweight and obese women, a high protein diet with a high intake of lean red meat resulted in similar weight change compared to the controls, despite that the other study included energy restriction and a physical activity program (Melanson et al. 2003) and the other one an isocaloric diet with no increase in physical activity (Noakes et al. 2005). Furthermore, a randomized cross-over trial on healthy men and women that examined isocaloric diets including a high consumption of lean beef, pork or poultry (~150 g/d) showed no differences in weight change (Murphy et al. 2014). According to the inconsistent findings in epidemiological and intervention studies, it is unclear whether weight gain is solely related to processed red meat or also to unprocessed meat.

2.2.4 Dietary factors, inflammation, CVD and T2D

In a comprehensive review by Calder et al. (2011), vitamins and minerals found in fruits, vegetables and wholegrain, as well as PUFA found in fish are listed as anti-inflammatory agents that can decrease obesity-induced inflammation. In contrast, saturated and trans-fatty acids may promote inflammation with enhanced oxidative stress. Furthermore, heme iron which is high in red meat, appears to promote inflammation, but the evidence is too scarce to draw any conclusions (Calder et al. 2011).

Strong epidemiological evidence for fruits and vegetables (Mente et al. 2009, Hartley et al. 2013) and whole grain (Mente et al. 2009, Ye et al. 2012, Cho et al. 2013, Åkesson et al. 2013) support their preventive role against CVD, but only a few interventions have confirmed these findings. However, the intervention studies may be confounded by the short follow-up period (< 1 year), and heterogeneous designs and reported endpoints.

Moderate evidence from cohort studies and clinical trials indicates that PUFA, especially from fish oils, decrease the risk of CVD (Mente et al. 2009, de Oliveira Otto et al. 2013, Lorente-Cebrián et al. 2013). Furthermore, in older large trials (Hjermann et al. 1986, Multiple Risk Factor Intervention Trial Research Group 1996, Howard et al. 2006) and more recent meta-analyses (Jakobsen et al. 2009, Siri-Tarino et al. 2010) of prospective US and European cohort studies of which two were Finnish (the Finnish Mobile Clinic Health Examination Survey and the Alpha Tocopherol and Beta-Carotene study), the substitution of saturated fat with PUFA has associated with a decreased risk of CVD. However, the most recent meta-analysis on 32 prospective cohort studies from the US, Europe and Asian-Pacific countries did not reveal any association between PUFA and CVD, which was confirmed in a meta-analysis of 27 randomized controlled studies on PUFA supplementation (Chowdhury et al. 2014).

For alcohol, cohort studies indicate lower risk of CVD among those with moderate consumption, but there have been no clinical trials to confirm this finding (Mente et al. 2009). There is no evidence that total milk intake affects the risk of

CVD. The intake of processed or unprocessed red meat increased the risk of CVD mortality by 18-21% in the US cohorts (Pan et al. 2012) and in a Swedish mammography cohort (Larsson et al. 2011).

The association between dietary factors and T2D has generally been insufficiently studied. The most convincing evidence indicates a suggestive protective association between low-fat milk products, whole grains and the risk of T2D (Åkesson et al. 2013). The role of fruits and vegetables is less clear (Harding et al. 2008). An increased risk of T2D is found in individuals with a high consumption of red meat, particularly processed meat (Männistö et al. 2010a, Mozaffarian et al. 2011, Fretts et al. 2012, Micha et al. 2012, Pan et al. 2013), and alcohol (Koppes et al. 2005, Pietraszek et al. 2010). Surprisingly, some studies have found a higher risk of T2D in individuals with a high fish consumption (Kaushik et al. 2009, Patel et al. 2012), but these results are contradictory (Salas-Salvado et al. 2011a, Wu et al. 2012).

Concerning fat quantity, in the Finnish Diabetes Prevention Study, a low total fat intake reduced the risk of T2D (Lindström et al. 2006). However, later published interventions have not confirmed this finding (Salas-Salvado et al. 2011a). The Finnish Diabetes Prevention Study found also that a higher intake of saturated fat increased the risk of T2D, whereas PUFA and the T2D risk did not associate (Lindström et al. 2006).

2.2.5 Summary

The plausible associations between dietary factors and obesity, inflammation, CVD and T2D are summarized in Table 3. Evidence for the role of individual dietary items in obesity, inflammation and the risk of CVD and T2D cannot be interpreted as strong. The results are scattered, only a few high-quality studies exist, and the exposure (definition of a food) and endpoints (e.g., cholesterol concentration, T2D incidence) have varied between studies. Energy intake is not handled similarly between studies (e.g., adjustment or restriction) and there appears to be no clear pattern of how energy intake affects the results. For example, association between total fat intake and obesity appears to be highly dependent on total energy intake, but the association between red

meat intake and obesity is not. Moreover, a high proportion of the evidence is derived from US populations which may not be generalized to other populations, such as Scandinavians, due to differences in the food culture.

Table 3. Summary of the association between dietary factors and obesity, inflammation, CVD and T2D.

Food group / nutrient	Obesity / weight gain	Inflammation	CVD	T2D
Fruits, berries and vegetables	↓	↓	↓	-
Wholegrain	↓	↓	↓	↓
Dairy	↓	-	-	↓
Fish	-	↓	↓	-
Fat quantity	↑*	-	-	-
Fat quality	↑ (trans-fat)	↑ or ↓†	↑ or ↓†	↑ (saturated fat)
Alcohol	-	-	↓‡	↑§
Red and processed meat	↑	-	-	↑

* Positive association when total fat intake is not adjusted for energy intake. When energy intake is adjusted, no association between total fat intake and obesity exists.

† A higher intake of trans-fat has positive association with the outcome whereas a higher intake of PUFA has inverse association.

‡ Moderate consumption recorded as ≤ 20 g/d ethanol for men and ≤ 10 g/d ethanol for women.

§ High consumption recorded as > 20 g/d ethanol for men and > 10 g/d ethanol for women.

2.3 The whole-diet approach

2.3.1 Rationale

Historically, nutrition research has focused on exploring the mechanisms and effects of single nutrients in order to prevent nutritional deficiencies. When multifactorial chronic diseases overtook single-factor deficiencies, this approach remained unchanged. Consequently, several clinical trials have produced confusing results on

diet-disease relationships. Some studies investigating potentially healthy nutrients, such as beta-carotene, have not found health-improving effects when these nutrients were exracted from their natural food environment and consumed as supplements (The ATBC Study Group 1994).

The accumulating experiences led to intense criticism. Overlooking the balance, multiple interactions and cumulative effects of foods and nutrients, as well as their natural occurence within the diet, was claimed to cover true associations with chronic diseases or at least underestimate them (Jacobs and Tapsell 2007, Tucker 2010). Moreover, because the development of chronic diseases is pathophysiologically complex and includes many metabolic phases, it seems unlikely that only a few nutrients would modulate it. Thus, the totality of the diet should be taken into account when analyzing associations between dietary factors and chronic diseases. From an epidemiological point of view, including all nutrients in a statistical model, in order to control for confounding, would not be meaningful (Hu 2002). Thus, new methods were needed in order to assess the diet as a whole in large epidemiological studies.

The whole diet can be studied in at least in three ways, all of which have their own analytical challenges (Table 4) (Tucker 2010): the hypothesis-oriented *a priori* method, the data-driven *a posteriori* method or a combination of these two, called reduced rank regression. In an *a priori* method, researchers use a predefined dietary pattern as a template to calculate a score (= index), which reflects adherence to the pattern. The pattern is usually based on nutritional recommendations or traditional diets (Waijers et al. 2007). After the score is calculated, the association between the score and chronic disease can be estimated. In the *a posteriori* method, data collected from health surveys are used to identify dietary patterns that naturally exist in the population and then study these patterns in relation to chronic diseases. Statistical techniques involve factor or cluster analysis, which allows for grouping of participants according to their food group intake. Reduced-rank regression is a mixture of *a priori* and *a posteriori* approaches and aims at identifying food group combinations that explain the maximum amount of variation in outcome variables (Hoffmann et al. 2004).

Table 4. Comparison of the methods used to define whole-diet quality. Adapted from Tucker (2010).

Methods	Input	Output	Advantages	Limitations
Dietary scores (*a priori*)	Foods or nutrients based on a priori selected dietary recommendations / pattern.	Summary score reflecting adherence to the dietary pattern	Valid tool to measure adherence to dietary recommendations, and can be used in exploring diet-disease relationships.	If not culturally adapted, may overestimate the population's adherence to the diet.
Factor analysis (*a posteriori*; Principal component analysis)	Intake of food groups, expressed as % contribution to total energy intake or servings/day.	Factor scores for food group intake, weighted by their intercorrelations.	Good statistical power and overcomes the problem of collinearity of multiple foods in statistical analysis.	Scores are abstract and can be achieved with different combinations of foods. Identification of dietary patterns in sub-groups may be difficult.
Cluster analysis (*a posteriori*)	Food group intake as above.	Groups of individuals based on maximally separated eating patterns.	Describes dietary patterns of sub-groups specifically. Results can be easily transferred to reality.	Power to detect associations with outcomes may be poor without large sample size.
Reduced rank regression (combined method)	Food group intake (as in factor analysis).	Factor scores of food combinations, forced to maximize their predictive power on outcome variable.	Maximizes associations between food group intakes and risk markers. Produces powerful risk estimate.	Patterns created are highly outcome-specific and not necessary meaningful for overall health.

2.3.2 Dietary score methodology

From here onwards, this doctoral thesis focuses on describing the dietary score method and reviewing the current literature concerning dietary scores, obesity, inflammation, CVD and T2D.

Before the whole-diet can be assessed, data on habitual dietary intake have to be collected, for example with a diet record, 24-hour recall or food frequency questionnaire (FFQ). Of these methods, the FFQ and multiple 24-hour recall are the most commonly used ones in large epidemiological studies. The FFQ illustrates the usual dietary intake over long periods and aims to rank participants from high to low intake, whereas the 24-hour recall gives more detailed intake data over a short period. In addition, the FFQ allows for calculations of estimated nutrient and food intakes by using food composition databases and nutrient calculation software. The FFQ has been shown to have reasonable reproducibility and validity for dietary score purposes compared to multiple, non-consecutive 24-hour recalls (Newby et al. 2003, Benitez-Arciniega et al. 2011).

After the data-set has been collected, foods or nutrients to be included in the dietary score can be selected, based on the pre-defined dietary pattern, for example a diet based on nutrition recommendations. Then, the selected components are quantified according to cut-offs in order to assign points. In the literature, three different strategies for cut-off selection have been used: population- and sex-specific median cut-offs (Trichopoulou et al. 1995), quantile division in order to obtain low, intermediate and upper ranges (Patterson et al. 1994), and scoring proportional to the extent to which a single component meets its dietary recommendation (Kennedy et al. 1995). Single cut-off values are simpler and easier to use, but they cannot distinguish between associations of the outcome variables with intermediate intake levels from those with extreme intake levels. Quantile cut-offs might better suit the precise examination of different impact levels. Regardless of the cut-off method used, several scores have successfully illustrated high diet quality.

Next, depending on the consumption level of each component, individuals are given points according to the selected cut-offs. In most scores, a higher intake of healthy foods results in higher points, whereas high intake of presumably unhealthy foods results in low points. In some foods, such as high-fat dairy products or alcohol, case-specific scoring should be carried out since the associations of these foods with diseases varies (Waijers et al. 2007). However, when all components have been given points, they are summed to form one score or index for each individual, so that usually a high summary score reflects high adherence to the diet (Waijers et al. 2007).

Several dietary scores have been developed. The most commonly used dietary scores are presented in Table 5. The first dietary score ever developed was the Diet Quality Index by Patterson et al. (1994) which was revised by Haines et al. (1999) (Table 5). The score was constructed according to the nutrition recommendations for the US population, and it mainly includes nutrient components, focusing on fat and cholesterol intake. The most explored dietary score is the Mediterranean Diet Score (MDS) based on the traditional diet in the Mediterranean region (Willett et al. 1995, Trichopoulou et al. 1995). Since the first study on MDS, researchers have made several different modifications to this score, for instance to use it in measuring dietary quality among non-Mediterranean populations (Romaguera et al. 2009). Other well-known scores include the Healthy Eating Index (HEI) (Kennedy et al. 1995, Guenther et al. 2008 and 2013), based on the dietary guidelines for the US population, and its rival, the Alternate Healthy Eating Index (AHEI) (McCullough et al. 2002, Chiuve et al. 2012) which gives greater weight to the quality than the quantity of fat, carbohydrates and meat intake, and takes into account multivitamin use (Table 5). In the 1990s, the Dietary Approaches to Stop Hypertension (DASH) trial revealed that a diet high in fruits, vegetables and low-fat dairy products, and low in total and saturated fat, cholesterol and sodium significantly reduced blood pressure compared to the control group without any medication or weight loss (Appel et al. 1997a). Since then, the DASH diet has been examined in several trials, but a dietary score has also been developed in order to facilitate examination of the DASH diet in epidemiological studies (Table 5) (Fung et al. 2008a).

Table 5. The most commonly used dietary scores.

Dietary Score	Publication	Components	Scoring
Diet Quality Index (DQI)	Patterson et al. 1994 (revised by Haines et al. 1999).	Total fat, SFA, protein, cholesterol, sodium, calcium, fruits, and vegetables, and grains and legumes.	Tertile cut-offs according to adherence to dietary recommendations for each component: High adherence = 0 points, intermediate adherence = 1 point, and low adherence = 2 points.
Mediterranean Diet Score (MDS)	Trichopoulou et al. 1995. (Modified several times)	Ratio of MUFA to SFA, alcohol (red wine), fruits and nuts, vegetables, legumes, cereals (including potatoes), meat, and dairy.	Population- and sex-specific median cut-off: Points 1 (high adherence) or 0 (low adherence) according to adherence to healthy intake.
Healthy Eating Index (HEI)	Kennedy et al. 1995 (revised by Guenther et al. 2008, 2013).	Total fat, SFA, cholesterol, sodium, fruits, vegetables, grains, meat, milk, and dietary variety (16 different kinds of food items over a 3-day period).	Points given proportionately from 0 (low adherence) to 10 (high adherence), according to adherence to the US nutrition recommendations.
Alternative Healthy Eating Index (AHEI)	McCullough et al. 2002 (revised by Chiuve et al. 2012).	Ratio of MUFA and PUFA to SFA, trans-fatty acids, fibre, alcohol, fruits, vegetables, nuts, ratio of white meat to red meat, and multivitamin consumption.	Points given proportionately from 0 (low adherence) to 10 (high adherence), according to adherence to the US nutrition recommendations.
Dietary Approaches to Stop Hypertension (DASH) -score	Fung et al. 2008.	Sodium, fruits, vegetables, nuts and legumes, whole grains, red and processed meat, low-fat dairy, and sweetened beverages.	Population- and sex-specific quintile cut-offs for components. Points from 1 (low adherence) 5 (high adherence) according to adherence to healthy intake.

Abbreviations: SFA, saturated fat; MUFA, monounsaturated fat.

2.3.3 Dietary scores and the risk of obesity

Mozaffarian et al. (2011) calculated an aggregate score of changes in single food consumption habits, in order to assess the cumulative effect of healthy *versus* unhealthy food intake. They found that individuals in the lowest score quintile (consuming more potato chips, fried potatoes, desserts, red and processed meat, sugar-sweetened beverages, butter and cheese) was associated with a 1.7 kg higher weight gain for each 4-year period compared to those in the highest quintile (consuming more fruits and vegetables, nuts, whole grain and yoghurt). Using a similar aggregate score, researchers of the EPIC-study found only a modest 0.11 cm lower gain in WC per year over 5.5 years of follow-up when comparing participants in the highest score quintile (increased healthy food consumption) with those in the lowest quintile (increased unhealthy food consumption) (Romaguera et al. 2011).

Few studies have evaluated the association betiween HEI or other dietary scores and obesity (Gao et al. 2008, Kimokoti et al. 2010), but the MDS has been extensively explored. Before 2008, about half of the studies published indicated that the Mediterranean diet associated with an approximately 30% lower risk of overweight or obesity (Buckland et al. 2008). Subsequently, the EPIC study reported a cross-sectional (Romaguera et al. 2009) and longitudinal (Romaguera et al. 2010) inverse association between high MDS, obesity and WC. In the former study, the MDS was associated with lower WC in both men and women, and the latter study found a 10% lower risk of obesity or overweight over 5 years of follow-up among participants who adhered to the MDS. However, the risk estimates for Scandinavian countries (Sweden, Denmark, and Norway) were not statistically significant. In a Spanish cohort of over 10 000 university students, the MDS associated with incident weight gain, but not with incident obesity, among participants in the highest MDS tertile compared to those in the lowest tertile (Beunza et al. 2010). Furthermore, a large Mediterranean multi-centre trial, called PREDIMED, found an inverse association between the baseline MDS, WC and BMI (Martinez-Gonzalez et al. 2012). Overall, a high MDS appears to associate with lower weight at least among Mediterranean populations. Other dietary scores based on a healthy diet have also been associated with lower levels of obesity.

2.3.4 Dietary scores and metabolic risk factors

A limited number of epidemiological studies have examined the association between dietary scores and obesity-related metabolic risk factors. Despite the low number of studies, the results have been consistent. Most recently, the consortium of epidemiological genetic studies reported a cross-sectional association between an aggregate score of a healthy dietary intake and lower fasting glucose and insulin concentrations among over 30 000 participants (Nettleton et al. 2013). Other cross-sectional studies have reported lower concentrations of inflammatory markers among participants with high AHEI, MDS and DASH- scores (Fung et al. 2005, Mantzoros et al. 2006, Fargnoli et al. 2008). The study of Fung et al. (2005) found that adherence to AHEI and the MDS decreased CRP concentrations by a similar magnitude among NHS participants, but no study has compared these scores with the DASH -score.

The effect of Mediterranean diet on MetS has recently been reviewed by Salas-Salvado et al. (2011a), Esposito et al. (2013) and Khazrai et al. (2014). The Mediterranean diet was beneficial in preventing MetS in three observational studies with 6 to 8 years of follow-up (Tortosa et al. 2007, Rumawas et al. 2009, Kesse-Guyot et al. 2013). Adherence to the MDS associated with a lower risk of MetS, decreased WC and an increased HDL cholesterol concentration in all three studies but only two of them found reductions in triglyceride and fasting glucose concentrations and blood pressure (Rumawas et al. 2009, Kesse-Guyot et al. 2013). Variety in assessing dietary habits may have induced these differences. Tortosa et al. (2007) assessed dietary intake with the FFQ only once at baseline, whereas Kesse-Guyot et al. (2013) assessed each partisipant's dietary intake at least three times with 24-hour recalls during the first two years of the study and Rumawas et al. (2009) assessed dietary intake three times with FFQs during 10 years of the study.

2.3.5 Dietary scores and the risk of CVD and T2D

Most of the dietary scores have associated inversely with major chronic diseases, such as CVD and T2D. Adherence to the DASH diet promoted CVD prevention over 20 years of follow-up in the NHS (Fung et al. 2008b), and was associated with a lower T2D incidence in the HPFS (de Koning et al. 2011). Furthermore, a pooled estimate of these cohorts showed that HEI and AHEI were associated with a 21-24% lower risk of CVD and an 18-33% lower risk of T2D (Chiuve et al. 2012). In the Womens' Health Initiative cohort study, the risk reduction in CVD for AHEI among ~ 80 000 women aged 50-79 years was of a similar magnitude (Belin et al. 2011). However a nested case-control study of the EPIC InterAct study did not confirm the association between DASH, AHEI and T2D among European populations (InterAct Consortium 2014), whereas the association of these diet scores with CVD has not been examined in European studies. Heterogeneity between EPIC countries (e.g, variability in dietary assessment tools and general cohort characteristics) and considerably shorter follow-up periods compared to the US studies most likely caused the differences in the results.

The MDS has been related to a lower risk of CVD in prospective studies (Hoevenaar-Blom et al. 2012, 2013, Grosso et al. 2013). Moreover, the MDS has associated with an 8% reduction in overall mortality and a 10% reduction in CVD-related mortality among US and European participants according to meta-analysis by Sofi et al. (2008, 2010, 2013). Two reviews that recently evaluated the evidence concluded that prospective studies indicate a protective role of the Mediterranean diet against T2D (Salas-Salvado et al. 2011a, Esposito and Giugliano 2014).

2.3.6 Whole-diet approach in randomized controlled trials

Several randomized controlled trials have examined the DASH and the Mediterranean diet. The DASH diet has been found to be associated with metabolic risk factors. When combined with weight reduction the DASH diet may improve HDL cholesterol, triglyceride and glucose concentrations compared to a control diet among individuals with T2D or MetS (Appel et al. 1997b, Azadbakht et al. 2005,

Blumenthal et al. 2010, Azadbakht and Esmaillzadeh 2011), whereas improvements in blood pressure can also be seen without weight change (Appel et al. 1997). The effect of the DASH diet in reducing the CVD risk over 10 years has been estimated using the Framingham risk score (Chen et al. 2010). Compared to the control diet, the DASH diet reduced the 10-year CVD risk by 18%. Randomized trials have consistently shown a preventive role of the DASH diet against T2D, but whether this association is independent of weight loss is still unclear (Hinderliter et al. 2011, Shirani et al. 2013).

Of the trials studying the Mediterranean diet, only a few have been conducted in non-Mediterranean populations, and many have included energy restriction and physical exercise, which limits the generalizability of the results. The meta-analyses have revealed decreased body weight, BMI (Esposito et al. 2011) and MetS (Kastorini et al. 2011, Esposito et al. 2013) in the Mediterranean diet group *versus* the control group. However, in trials without energy restriction or increased physical activity, positive improvements have only been found in the glucose concentration and blood pressure. Two studies published after an up-date of the meta-analysis of MetS (Esposito et al. 2013) are in line with the evidence (Toledo et al. 2013, Damasceno et al. 2013). Some trials have also indicated a protective role for the Mediterranean diet against low-grade inflammation (Urpi-Sarda et al. 2012a, 2012b). The risk of CVD decreased markedly over a follow-up of 4.8 years according to a higher MDS in the PREDIMED trial (Estruch et al. 2013), but these results have been critizised as being biased because of the low incidence of CVD (3.4% and 3.8% in the intervention groups and 4.4% in the control group).

2.3.7 Summary

Admittedly, the health effects related to the Mediterranean diet, DASH-diet and the diets based on the AHEI are well established. However, the main concern is that majority of these studies have only been conducted among Mediterranean and US populations. Studies in other European countries have found only modest or no association between these scores and health outcomes. The null findings may in part reflect heterogeneity in study populations and variety in variable assessment tools.

Furthermore, the level of adherence to the predefined diets varies between countries because of the differences in food cultures. Therefore, locally-tailored diets are needed to effectively measure the associations between a healthy diet and health outcomes in other populations, such as Scandinavians.

2.4 Towards a health enhancing Nordic diet

Over the last 5-10 years, the powerful marketing of the Mediterranean diet and other "fashion diets" has led to the public opinion that a healthy diet is something exotic that cannot be constructed from locally-grown foods. To break this illusion, nutritionists in Scandinavia have started to take measures to prove that a health-promoting Nordic diet is acheavable. In the literature, Bere and Brug (2009) were the first ones to propose a dietary pattern characterized by healthy Nordic foods, such as berries, roots, rye, oats and barley, fatty fish, low-fat milk products and rapeseed oil. Between 2007 and 2009, several randomized trials were set up in Finland and other Nordic countries to examine the health-related effects of the Nordic diet (Table 6). Based on these trials, the University of Eastern Finland together with the Finnish Diabetes Association and the Finnish Heart Association released the Baltic Sea Diet Pyramid in 2011 which illustrates healthy Nordic food choices (Figure 3) (Uusitupa and Schwab 2011).

Figure 3. The Baltic Sea Diet Pyramid published with the kind permission of the Finnish Diabetes Association.

2.4.1 Studies on the healthy Nordic diet

The trials examining the healthy Nordic diet are presented in Table 6. The Scandinavian multicentre trial (Sysdiet) was conducted in six intervention centers distributed in Finland (Kuopio and Oulu), Denmark (Aarhus), Iceland (Reykjavik) and Sweden (Lund and Uppsala) (Uusitupa et al. 2013). The study recruited participants aged 30-65 years with BMI 27-38 kg/m^2 who met at least two of the criteria for MetS (Table 2). From the 309 individuals screened 213 were randomized to follow a healthy diet constructed of Nordic foods or to a low-fibre-high-saturated-fat diet over 18-24 weeks. Another quite similar, but smaller trial was conducted in Sweden (Nordiet) on 88 mildly hypercholesterolemic individuals over 6 weeks

(Adamsson et al. 2011). The Danish intervention with the Nordic diet was developed as a part of the multidisciplinary research project entitled "Optimal well-being, development, and health for Danish children through a healthy New Nordic Diet" (Poulsen et al. 2014). A total of 181 abdominally obese individuals were randomly assigned for 26 weeks to the Nordic diet group or to a control group that consumed the average Danish diet. Furthermore, a Finnish intervention study (Sysdimet) compared the effects of a healthy diet including Nordic food items (local wholegrains, fish, vegetable oils, bilberries) and a wholegrain-enriched diet with a control group on participants with features of MetS and impaired glucose metabolism over 12 weeks (de Mello et al. 2011).

The Scandinavian trials on hypercholesterolemic subjects (Adamsson et al. 2011) and individuals with the MetS (de Mello et al. 2011, Uusitupa et al. 2013) reported improved lipid profiles (Adamsson et al. 2011, Lankinen et al. 2011, Uusitupa et al. 2013) and lowered inflammation (de Mello et al. 2011, Uusitupa et al. 2013) in their Nordic diet groups (without energy restriction or an increment in physical activity) compared to the control groups (Table 6). Furthermore, the healthy Nordic diet reduced weight without any energy restriction in the Swedish (Adamsson et al. 2011) and Danish trials (Poulsen et al. 2014). Some evidence also supports improved insulin sensitivity (Lankinen et al. 2011, Magnusdottir et al. 2014), but in most studies, this was only seen in participants who lost weight during the intervention (Adamsson et al. 2011, Uusitupa et al. 2013, Poulsen et al. 2014). In addition, a positive effect on blood pressure without weight loss was found in a small subset of participants using ambulatory blood pressure measurement (Brader et al. 2014). In summary, the evidence from randomized clinical trials indicates that a healthy Nordic diet may lead to weight loss without any energy restriction as well as an improvement in cardiovascular risk factors, such as inflammation. However, the trials have been short (maximum duration 24 weeks), and long-term studies are therefore needed to evaluate the effect on disease incidence.

Table 6. Summary of randomized controlled trials exploring the effect of healthy Nordic diet on obesity and obesity-related risk factors.

Study	Study population	Design	Diet	Outcomes	Results
Adamsson et al. 2011 (Sweden) (Nordiet)	88 mildly hypercholesterolaemic men and women aged 25-65 years.	RCT for 6 weeks, no energy restriction or increase in physical activity.	*Healthy Nordic diet:* apples, berries, vegetables, low-fat dairy products, fatty fish, oats and barley, soy, almonds and psyllium seeds. *Control diet:* participants' habitual diet.	Cardiovascular risk factors.	Change from baseline in Nordic diet group: BMI ↓ 4%, total-chol ↓ 16%, LDL-chol ↓ 21%, HDL-chol ↓ 5%, LDL/HDL ratio ↓ 14%, insulin resistance ↓ 9%, systolic PB ↓ 5%. All changes were significantly greater compared to the control group.
Lankinen et al. 2011 (Finland) (Sysdimet)	106 men and women with impaired glucose metabolism aged 40-70 years.	RCT for 12 weeks, no energy restriction or increase in physical activity.	*Healthy diet:* rye bread and wholegrain products, fatty fish 3 times/week, and bilberries 3 portions/day. *Wholegrain enriched diet*: same cereal products than in the healthy diet group. *Control group*: only refined grains, no fish or berries allowed.	Cardiovascular risk factors.	Healthy diet group: two-hour glucose concentration and area-under-curve for glucose decreased, plasma portion of n-3 PUFA, DHA and EPA increased. No changes in two other groups were observed.
de Mello et al. 2011 (Finland) (Sysdimet)	As above.	As above.	As above.	Markers of inflammation.	Intervention groups vs control group: CRP concentration ↓.

Abbreviations: chol, cholesterol; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; RCT, randomized controlled trial.

To be continued on page 45.

Table 6. Continued from page 44.

Study	Study population	Design	Diet	Outcomes	Results
Uusitupa et al. 2013 (Finland, Sweden, Denmark, Iceland) (Sysdiet)	200 men and women with metabolic syndrome (mean age 55 years).	RCT for 18-24 weeks with 4-week run-in period. No energy restriction or increase in physical activity.	*Healthy Nordic diet*: Nordic wholegrain products, berries, fruits and vegetables, rapeseed oil, fish 3 times/week, and low-fat dairy. *Control diet*: Habitual diet.	Insulin sensitivity, lipid profile, and anti-inflammatory markers.	Healthy Nordic diet *vs.* control diet: non-HDL-chol↓ 0.18 mmol/l; LDL/HDL ratio ↓ 0.15; IL-1 Rα concentration ↑.
Magnusdottir et al. 2014 (Finland, Sweden, Denmark, Iceland) (Sysdiet)	As above.	As above.	As above.	Insulin sensitivity.	Healthy Nordic diet did not affect glucose metabolism compared to control diet.
Poulsen et al. 2014 (Denmark) (New Nordic Diet)	181 abdominally obese men and women aged 20-66 years.	RCT for 26 weeks. No energy restriction or increase in physical activity	*Healthy Nordic diet:* berries, roots, cabbages, legumes, potatoes, fresh herbs, mushrooms, nuts, wholegrain, livestock and game meat, fish, and seaweed. *Control diet:* common Danish diet.	Change in weight, lipids and glucose concentrations and BP.	Nordic diet compared to baseline: weight ↓ 4.7 kg; systolic BP ↓ -5.1 mmHg; diastolic BP ↓ 3.2 mmHg. All changes significantly greater compared to the control group. Changes in glucose and insulin concentration were not significant after adjustment for weight change.

Abbreviations: chol, cholesterol; IL-1rα, interleukine-1 receptor alpha: RCT, randomized controlled trial.

2.4.2 Dietary scores based on the healthy Nordic diet

Only a few epidemiological studies exploring the association between a healthy Nordic diet and health outcomes has been published. The study of Olsen et al. (2011) examined ~ 50 000 Danish adults aged 50-64 years who took part in The Diet, Cancer and Health Study and a observed reduced mortality rate-ratio over 12 years of follow-up in participants with higher adherence to the healthy Nordic diet, illustrated with a healthy Nordic Food Index (including fish, cabbages, rye bread, oatmeal, apples and pears, and root vegetables). In the same cohort, a one point increment in the Nordic Food Index lowered the colorectal cancer incidence by 9% (Kyrø et al. 2013). However, the index failed to take into account important aspects of the Nordic diet, such as dairy products and rapeseed oil, and no further studies have been published using this index. Thus, no epidemiological studies had evaluated the association of the healthy Nordic diet with obesity or obesity-related metabolic risk factors. Clearly, more large-scale studies are needed to address the association between a healthy Nordic diet and health at the population level.

3 Aims of the study

The general aims of the research presented in this thesis were to examine the associations between the healthy Nordic diet and both obesity and obesity-related metabolic risk factors at the population level, using a dietary score as an indicator of adherence to the diet. The specific aims of sub-studies I-V were as follows:

1. To develop a Baltic Sea Diet Score (BSDS) based on the healthy Nordic diet, and to assess whether the new score associates with nutrient intakes that are considered important in promoting health in Finland (I).

2. To examine the associations between the BSDS and anthropometric measures including BMI and WC (II).

3. To examine the associations of the BSDS with cardiometabolic risk factors and obesity-related low-grade inflammation (III, IV).

4. To assess whether the BSDS is related to the incidence of T2D during a 10-year follow-up period, and whether the metabolic health status of participants at baseline modifies this association (V).

4 Methods

4.1 Study of Dietary, Lifestyle and Genetic determinants of Obesity and Metabolic syndrome (DILGOM) (I-IV)

The DILGOM study included men and women aged 25 to 74 years who originally participated in the National FINRISK Study conducted in 2007 (Vartiainen et al. 2010). The National FINRISK Study is carried out by the National Institute of Health and Welfare (THL) every five years to monitor risk factors for chronic diseases in the Finnish population.

In 2007, a random sample of 10 000 people aged 25 to 74 years was drawn from the Finnish Population Information System. The sample was stratified according to gender, 10-year age group and five large geographical regions. Participants received via mail an invitation letter to participate in a health examination and a self-administered health questionnaire. Of the invited individuals, 6258 participated in the health examinations conducted between January and March.

To gather more detailed information on obesity, MetS and T2D, all participants of the FINRISK 2007 Study were invited to be a part of the DILGOM study, conducted between April and June 2007 (Table 7). Of the invited participants, 5024 participated (2325 men and 2699 women). This phase also included a health examination and health questionnaires.

4.2 The Helsinki Birth Cohort Study (HBCS) (III-V)

The participants of the HBCS were born at Helsinki University Central Hospital as singletons between 1934 and 1944, attended child welfare clinics in Helsinki, and lived in Finland in 1971, when a unique personal identification number was assigned to each Finnish citizen (Ylihärsilä et al. 2008). The original cohort comprised of 4630 men and 4130 women.

Those cohort members, who were still alive and lived in Finland, were sent a health questionnaire in 2000 (n = 7078). In total, 4515 individuals returned the questionnaire. From these participants, a sample of 2902 individuals residing in the Helsinki metropolitan area was derived, using random number tables, and invited to a health examination conducted between 2001 and 2004. Eventually, 2003 individuals participated (928 men and 1075 women) (Table 7).

4.3 The National Health 2000 Survey (Health 2000) (III-V)

The Health 2000 aimed at determining the health and functional capability of Finns aged ≥ 30 years, and collected information on the most important health disorders and associated needs for care, rehabilitation and aid (Heistaro 2005). The baseline survey was conducted during 2000 and 2001.

A nationally representative sample of 8028 people was drawn from the Finnish Population Information System. The sample frame was regionally stratified according to the five university hospital regions. In the first stage of sampling, 80 healthcare districts were sampled as a cluster. In the second stage, a random sample of individuals from each of the 80 healthcare districts was drawn. All participants were sent via mail an invitation letter to participate in a health interview conducted in their home. Those who participated in the interview (n = 6986) were reserved a time for a health examination. Eventually, 6772 individuals came to the health examination between September 2000 and March 2001 (3011 men and 3761 women) (Table 7).

Table 7. Descriptive statistics of the DILGOM, HBCS and the Health 2000 studies.

	DILGOM	HBCS	Health 2000
Data collected	2007	2001-2004	2000-2001
Invited, n *	6258	2902	6986
Participated, n †	5024	2003	6772
Returned FFQ, n ‡	4996	2003	6373
Age range, y	25-79	56-70	≥ 30
Women, %	53.7	53.7	55.5

* Number of participants invited to the health examination.

† Number of participants who arrived to the health examination.

‡ Number of participants who returned FFQ.

4.4 Ethical approval

The FINRISK 2007 Study, the DILGOM study, the HBCS and Health 2000 were all conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa for study phases. All participants provided informed consent.

4.5 Diet assessment

4.5.1 The FFQ

In all three studies, dietary habits were assessed once using a semiquantitative FFQ (Männistö et al. 1996) that was developed at THL. The FFQ aims to measure habitual dietary intake over the preceding 12 months. The FFQ has been validated against dietary records (Männistö et al. 1996, Paalanen et al. 2006, Kaartinen et al. 2012) and its reproducibility has been examined (Männistö et al. 1996). The HBCS and the Health 2000 used a version described in Paalanen et al. (2006) whereas the DILGOM study used a more recent, updated version of the FFQ (Kaartinen et al. 2012). The updated FFQ versions did not differ substantially from each other.

In the DILGOM study and the HBCS, participants completed the FFQ at the study site, where a trained study nurse reviewed the questionnaire. In the Health 2000, the participants were asked to complete the FFQ at home after the health examination and send it back to THL (Table 7).

In the FFQ, participants recorded their average consumption of 128 to 131 food items and mixed dishes in nine frequency categories ranging from “never or seldom” to “at least six times a day”. The participants could also report other frequently consumed foods not included on the list. The portion size was fixed for each food item and mixed dish (e.g. glass, or slice). In the DILGOM study and the HBCS, the portion sizes were calculated separately for both sexes based on information from the National FINDIET 2007 Survey, whereas in the Health 2000, the same portion sizes were used for men and women. Nutritionists entered the data into the study database, and the average daily food, nutrient and energy intakes were calculated

using the national food composition (Fineli®) database and in-house software (Reinivuo et al. 2010).

4.5.2 The Baltic Sea Diet Score (BSDS)

The healthy Nordic diet illustrated in the Baltic Sea Diet Pyramid (Figure 3) served as a template for the score. The pyramid contains 10 food groups. Of these, Nordic fruits and berries, vegetables, cereals, fish and red meat (including processed meat) were directly included in the BSDS (Table 8). Of dairy products, only low-fat and fat-free milk were included. Furthermore, the ratio of PUFA to saturated fat and trans-fatty acids (the fat ratio) was used to illustrate fat quality. In addition, two components not directly illustrated in the pyramid, were included: total fat intake as a percentage of the total energy intake (E%) and alcohol consumption.

The BSDS components, except alcohol, were scored according to population- and sex-specific consumption quartiles within each study. For fruits and berries, vegetables, cereals, low-fat milk, fish and the fat ratio, the lowest intake quartile was coded as 0, the second lowest as 1, the third as 2, and the highest quartile as 3. For meat products and total fat, the scoring was reversed. For alcohol, the cut-off was assigned according to the moderate consumption level recommended in Nordic countries. Men consuming ≤ 20 g and women consuming ≤ 10 g of ethanol per day received 1 point: otherwise 0 points were awarded. The resulting BSDS ranged from 0 to 25, with higher score values representing greater adherence to the healthy Nordic diet.

Table 8. Components and scoring of the Baltic Sea Diet Score.

Components	Contents	Scoring	Range of points
Fruits, and berries	Apples, pears and berries	Positive *	0-3
Vegetables	Tomatoes, cucumber, leafy vegetables, roots, cabbages and peas	Positive	0-3
Cereals	Rye, oats, and barley	Positive	0-3
Low-fat milk	Low-fat and fat-free milk	Positive	0-3
Fish	Salmon and freshwater fishes	Positive	0-3
Red meat	Beef, pork, processed meat products and sausage	Negative †	0-3
Total fat intake	Total fat intake (E%)	Negative	0-3
Fat ratio	The ratio of PUFA to saturated fat and trans-fatty acids	Positive	0-3
Alcohol	Ethanol intake	Negative ‡	0-1
TOTAL			0-25

* Highest consumption quartile received the highest points.

† Lowest consumption quartile received the highest points.

‡ Moderate ethanol intake ≤ 20 g for men and ≤ 10 g for women received 1 point, otherwise, 0 points were given.

4.6 Clinical examinations

At the study sites, trained nurses measured weight, height, WC and blood pressure using standardized international protocols. All anthropometric measures were assessed with light clothing and with bare feet. Height was measured to the nearest 0.1 cm (except in Health 2000 to 0.5 cm) and weight to the nearest 0.1 kg. WC was measured at the midpoint between the lowest rib and iliac crest to the nearest 0.5 cm with the use of a soft measuring tape. BMI was calculated as weight in kilograms (kg) divided by the square of height in metres (m^2). Overweight or obesity was defined as BMI ≥ 25.0 kg/m^2 (WHO 2000) and abdominal obesity as ≥ 100 cm for men and ≥ 90 cm for women (Working Group of the Finnish Medical Society Duodecim and Finnish Association for the Study of Obesity 2011).

The study nurses drew blood samples. In the HBCS, after the fasting samples were taken, participants who did not report diabetes went through a standard 75 g oral glucose tolerance test (OGTT) (V). The participants received a 75 g dose of glucose solution to drink within a five-minute time frame, and after two hours another blood sample was drawn. All studies stored blood samples at -70 °C prior to analysis.

4.7 Laboratory analysis

Research laboratories used automated clinical chemistry analysers and routine clinical chemistry methods to measure serum lipid fractions (total cholesterol, HDL cholesterol, and triglycerides) (Lie et al. 1976, Lopes-Virella et al. 1977, Fossati and Prencipe 1982) (III, V). LDL cholesterol concentrations were calculated, using Friedewald's formula (Friedewald et al. 1972). Furthermore, high-sensitivity CRP (hs-CRP) was analysed with immunoturbidimetric methods, using an Abbot Architect ci8200 analyzer (Abbott Laboratories, Abbott Park, IL, USA) in the DILGOM study, Optima analyzer (Orion Diagnostica, Espoo, Finland) in the Health 2000, and a Konelab T-serie High Sensitivity CRP analyzer (Thermo Fisher Scientific Oy, Vantaa, Finland) in the HBCS (III-IV). In the DILGOM study and HBCS, high-molecular-weight (HMW) adiponectin was analysed with an enzyme linked immunosorbent assay (HMW adiponectin ELISA kit, Millipore, St Charles, MO, USA) (IV). Furthermore, IL-6, TNF-α and leptin were analysed with multiplex sandwich immunoassays (HBCS: IL-6, TNF-α, leptin; DILGOM: leptin with a Milliplex Human Metabolic Hormone Panel, Millipore, and IL-6 and TNF-α with a Milliplex High Sensitivity Human Cytokine kit, Millipore) (IV).

4.8 Obesity-related metabolic risk factors (III, V)

We used international guidelines to define elevated or low values of obesity-related metabolic risk factors (Table 9). Assessment of low-grade inflammation has no univocal recommendation, but some evidence of a higher risk of CVD exists at hs-

CRP concentrations of ≥ 3.0 mg/l (Pearson et al. 2003), which we used as a cut-off in sub-study III.

Table 9. Criteria for obesity-related metabolic risk factors.

Components	Cut-offs
Elevated triglyceride concentration	≥ 1.7 mmol/l or use of triglyceride-lowering medication [*†]
Elevated total cholesterol	≥ 5.0 mmol/l or use of lipid-lowering medication [‡§]
Low HDL cholesterol concentration	< 1.0 mmol/l for men and < 1.3 mmol/l for women or use of HDL-lowering medication [*†]
Elevated LDL cholesterol concentration	≥ 3 mmol/l or use of lipid-lowering medication [‡§]
Hypertension	Systolic BP ≥ 130 mmHg; diastolic BP ≥ 85 mmHg or use of BP-lowering medication [†I]
Elevated fasting glucose concentration	≥ 5.6 mmol/l or use of anti-diabetic medication [†II]
Elevated hs-CRP concentration	≥ 3.0 mg/l [¶]

Abbreviations: BP, blood pressure.

[*] Fibrates and nicotinic acid.

[†] Harmonizing criteria for MetS by Alberti et al. (2009).

[‡] Recommendations of the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (2012).

[§] Anatomical Therapeutic Chemical codes beginning with C10A.

[I] Anatomical Therapeutic Chemical codes beginning with C02.

[II] Anatomical Therapeutic Chemical codes beginning with A10.

[¶] American Heart Association's recommendations for inflammatory markers in CVD (Pearson et al. 2003).

4.9 Register data (III-V)

The Social Insurance Institute's register for reimbursements of pharmaceutical expenses was used to derive information on the use of lipid- and blood pressure-lowering medication (III-IV). Furthermore, the nationwide administrative registers which reliably cover all medication use, hospitalizations and death were used to identify incident cases of T2D (V). Participants were linked to these registers with a

unique personal identification number assigned to each Finnish citizen. The identification of diabetes cases was based on the presence of any of the ICD-10 codes E10-E14 in at least one of the three registers: the Drug Reimbursement Register, the Finnish Hospital Discharge Register and the National Causes-of-Deaths Register. In addition, information from the National Prescription Register on the purchases of antidiabetic drugs (Anatomical Therapeutic Chemical codes beginning with A10) was exploited in order to detect individuals who had been diagnosed with diabetes, but had not yet received a reimbursement. This information has been available since 1995.

4.10 Assessment of background variables

In all studies, health questionnaires were used to collect information on the participants' socioeconomic characteristics, lifestyle variables and medical history. In the DILGOM study and HBCS, these questionnaires were self-administered whereas in the Health 2000, experienced interviewers completed the questionnaires. Education, smoking status, and leisure-time physical activity (PA) were assessed in each study with slightly different categorizations standardized for sub-studies III-IV.

In each study, education was assessed by inquiring about the total number of school years (III-V) or classifying participants into three educational levels according to their birth year (low, middle, and high) (I-II). Smoking status was reported in the health questionnaires by using 4-6 categories (I, III-V). For example, the DILGOM study categorized smoking status as follows: never smoker, quit > 6 months ago, quit < 6 months ago, and current smoker (I). The existing categories were merged into three categories: non-smoker, ex-smoker and current smoker (III-V). Furthermore, each study queried about participant PA as the frequency of activity per week and as the intensity of the PA (I-V). The scale for PA ranked from "inactive" to "highly active".

4.11 Study design and exclusion criteria

The four first sub-studies of this thesis had a cross-sectional design, whereas sub-study V had a longitudinal design. The first two included only the DILGOM study participants. Sub-study III pooled all three datasets. Furthermore, sub-study IV included the DILGOM study and the HBCS, whereas sub-study V pooled data from the HBCS and the Health 2000.

All sub-studies of this thesis included participants who completed and returned the FFQ to the study centre (DILGOM n = 4996, HBCS n = 2003, Health 2000 n = 6373). Exclusions were made due to incomplete FFQs (DILGOM n = 74, HBCS n = 2, Health 2000 n = 375). Moreover, men and women were excluded if their daily energy intake (cut-offs) corresponded to 0.5% at either end of the daily energy-intake distribution range (DILGOM n = 42 and HBCS n = 20) or if their daily energy intake values were < 600 or > 7000 kcal/d (Health 2000 n = 18).

In sub-studies II-V, further exclusions of pregnant women (DILGOM n = 27, Health 2000 n = 34), and participants with missing information for outcome variables. Furthermore, those with hs-CRP concentrations > 10 mg/l were excluded in sub-studies III (total n = 415) and IV (total n = 259), since they were likely to indicate other than obesity-related inflammation. In sub-study V, participants with prevalent diabetes (Health 2000 n = 246 and HBCS n = 147) were also excluded.

4.12 Statistical methods

The BSDS was divided into quintiles in each study for analysis. In sub-studies II-IV, the contribution of each BSDS component to the association between the BSDS and outcome variables was also examined separately. The normality of the variables was examined, using QQ-plots and histograms, and logarithmic transformation was applied if necessary for variables with a skewed distribution. Potential confounding variables for each study were first listed, based on the literature. Second, a likelihood ratio test (II) or linear regression (III-V) was used to explore which of these variables were actual confounders in the current data, i.e. independently associated with both the outcomes and exposures (Rothman 1986).

The results are presented as means and their standard errors (SE) (I, IV). The *P*-value for trend was usually obtained with linear regression and the *P*-value for the difference between quintiles with analysis of variance and Tukey's test (I, IV). *P*-value for the fit of the model was obtained from likelihood ratio test (II). Furthermore, odds ratios (OR) (II, III) or hazard ratios (HR) (V) and their 95% confidence intervals (CI) are reported. In all studies, the results were confirmed by re-running analyses with and without those participants whose reported energy intake did not correspond to their estimated physical needs (ratio of energy intake to basic metabolic rate ≤ 1.14) (Goldberg et al. 1991, Black 2000).

Analyses were performed with R statistical software (R Development Core Team 2012), versions 2.13.0 and 2.15.1 (I-V) and SAS version 9.2 (SAS Institute, Cary, NC, USA) (III, V). *P*-values < 0.05 were considered statistically significant.

4.12.1 Studies of single datasets (I, II, IV)

In sub-study I, the BSDS was developed and its association with nutrient intakes separately assessed for men and women, using data from the DILGOM study. The association of the BSDS with social and lifestyle variables was explored. Nutrient intakes were log-transformed to satisfy the normality assumption, and then adjusted for each individual's energy intake by using the residual method (Willett and Stampfer 1986) prior to the analysis. The analyses were controlled for age, education level, smoking, PA, energy intake and BMI. In order to investigate whether the score cut-off method affected the results, the BSDS was also calculated using sex-specific population consumption medians, and all analyses were run using both scores.

In sub-study II, the association between the BSDS and the prevalence of overweight or obesity and abdominal adiposity was tested using logistic regression analysis (GLM procedure of the Epicalc package in R). The likelihood ratio test (LRtest procedure of the Epicalc package in R) was used to test the significance of each variable in the model. Analyses were adjusted for age, PA and energy intake. Educational level and smoking did not significantly improve the model, and they were not therefore included in the final analyses. To adjust for body fat distribution,

analyses of abdominal obesity were conducted with and without adjustment for BMI.

In sub-study IV, concentrations of HMW adiponectin, leptin, TNF-α, IL-6 and hs-CRP were log-transformed to satisfy the normality assumption, and their linear associations with the BSDS were explored in the DILGOM study, and results replicated in the HBCS. The analyses were adjusted for age, sex, education years, smoking, PA, energy intake and WC. HMW adiponectin was also adjusted for the use of antidiabetic medication and hs-CRP for the use of statin medication. Finally, if relevant, the final model was adjusted for other inflammatory markers to explore whether they mediated the association.

4.12.2 Studies of meta-analysis (III, V)

ORs or HRs and 95% CIs were first calculated for outcome variables according to the BSDS quintiles in each dataset. Second, the estimates were pooled, using the random-effects model. This two-stage process allows for between-studies diversity in study methods (e.g. different laboratories used) and heterogeneity in the associations of the outcomes and with the exposure or covariates. In the meta-analysis, the pooled OR and its 95% CI for the mass of data were obtained by combining the study-specific log[OR]s and weighting them by the inverse of their variance in a random-effects model (DerSimonian and Laird 1986). The *P*-value for the test of the trend was obtained from a Wald's test of the pooled estimates, using the median values of BSDS quintiles as a continuous variable in the model (Stram 1996). Homogeneity among the ORs from the original studies was tested using Q statistics.

In sub-study III, analyses between the BSDS, dyslipidaemias, hypertension and inflammation were adjusted for age, education, smoking status, PA and BMI. When hypertension was used as an outcome variable, the analysis was also adjusted for sodium intake. Sensitivity analyses were run with and without participants who had probably received dietary counselling due to prevailing illness. In this case, these participants were considered to be those taking lipid-lowering or blood pressure-

lowering medication. Furthermore, in interaction analyses, the possible effect modification by BMI and WC was examined.

In sub-study V, the association between baseline BSDS and incident T2D during 10 years of follow-up was assessed in the HBCS and the Health 2000. The follow-up time was defined as the number of days from the baseline examination to the dates of T2D occurrence, death or the end of follow-up, whichever came first. Participants with diabetes at baseline were excluded. The analysis was adjusted for age, education, smoking status, PA, energy intake, vitamin D intake and WC. Effect modification by the metabolic-health status was explored by modelling the interaction term between the metabolic-health variable and BSDS and conducting stratified analysis. Sensitivity analyses were performed excluding the first two years of follow-up, excluding participants with impaired fasting plasma glucose at baseline and, in the HBCS, only including participants whose T2D status was confirmed at baseline with OGTT.

5 Results

In the following sections, the main findings from sub-studies I-V and some unpublished results are presented.

5.1 The BSDS and socioeconomic and lifestyle factors (I)

The range in socioeconomic and lifestyle factors between the BSDS quintiles is presented in Table 10. Table 10 only shows associations for the DILGOM study participants, but generally similar associations were also seen in the HBCS and the Health 2000. Participants in the highest BSDS quintile tended to be older than those in the lowest quintile. Furthermore, the proportion of highly educated participants was higher, and the percentage of current smokers was lower in the highest BSDS quintile compared to the lowest. As the number of inactive participants was lower in the highest compared to the lowest BSDS quintile, the intake of energy increased across the quintiles in both men and women. Accordingly, BMI tended to decrease across the BSDS quintiles. In summary, individuals adhering to the healthy Nordic diet also adhered to a generally healthy lifestyle.

The average intakes of the score components according to BSDS quintiles are presented in Table 11 for the DILGOM study participants. As expected, consumption of Nordic fruits and berries, vegetables, cereals, fish and low-fat milk, as well as the fat ratio increased markedly in relation to the BSDS quintiles, and the intake of total fat and alcohol decreased in relation to the quintiles.

Table 10. Associations of the BSDS with socioeconomic and lifestyle characteristics among men and women in the DILGOM study (I).

	BSDS quintiles *						
Characteristics	**1**	**SE**	**3**	**SE**	**5**	**SE**	***P*** †
Men, *n* = 2217							
Range	2-9		13-14		17-25		
n	494		411		419		
Age, y	48	< 1	54	< 1	59	< 1	< 0.01
High education (%)	29.1		38.5		42.8		< 0.01
Current smoker (%)	30.6		17.7		10.0		< 0.01
Low PA (%)	28.7		15.1		9.2		< 0.01
BMI, kg/m^2	27.2	0.2	26.9	0.2	27.0	0.2	0.07
Energy intake, kJ/d	10 350	180	11 950	194	12 820	196	< 0.01
Women, *n* = 2493							
Range	1-9		13-14		18-25		
n	567		456		397		
Age, y	46	< 1	52	< 1	58	< 1	< 0.01
High education (%)	30.7		33.6		37.2		< 0.05
Current smoker (%)	21.9		12.3		7.5		< 0.01
Low PA (%)	31.0		17.0		10.3		< 0.01
BMI, kg/m^2	27.0	0.2	26.9	0.2	26.5	0.2	0.06
Energy intake, kJ/d	8230	130	9370	142	10 500	156	< 0.01

* Values are adjusted for age.

† For continuous variables, the *P*-value for trend was obtained from linear regression. For categorical variables, the *P*-value for difference between quintiles was obtained from the χ^2 test.

Table 11. Intake of score components according to the BSDS quintiles in the DILGOM study (II).

Score components	BSDS quintiles *					
	1	**SE**	**3**	**SE**	**5**	**SE**
Men, *n* = 2190						
Score range	2-9		13-14		17-25	
Fruits and berries	47	4	118	2	190	4
Vegetables	167	6	266	3	365	7
Cereals	59	1	88	1	117	2
Low-fat milk	246	12	353	7	460	14
Fish	36	2	50	1	63	2
Red meat	218	3	170	2	122	3
Total fat, E% †‡	34.9	0.2	31.4	0.1	27.8	0.2
Fat ratio †§	0.40	0.01	0.47	0.01	0.55	0.01
Alcohol ¶	14.2	0.6	11.3	0.3	8.3	0.7
Women, *n* = 2530						
Score range	1-9		13-14		18-25	
Fruits and berries	78	4	159	2	239	5
Vegetables	223	6	331	4	440	7
Cereals	55	1	81	1	108	1
Low-fat milk	162	8	251	5	340	9
Fish	24	1	35	1	45	1
Red meat	144	2	107	1	70	2
Total fat, E% †‡	34.1	0.1	30.3	0.1	26.5	0.2
Fat ratio †§	0.41	0.01	0.49	0.01	0.57	0.01
Alcohol ¶	5.3	0.2	4.2	0.1	3.2	0.2

* Values are the age- and energy-adjusted mean and SE (g/d).

† Values are only adjusted for age.

‡ Total fat intake as a percentage of the total energy intake.

§ Ratio of PUFA to trans-fatty acids and saturated fatty acids.

¶ As ethanol.

5.2 Nutrient intakes (I)

Among men, participants in the highest BSDS quintile had a nearly two-fold higher intake of fibre and one-third lower intake of saturated fat compared to those in the lowest BSDS quintile (Table 12). Furthermore, a lower intake of PUFA (E%) and alcohol (E%), and a higher intake of carbohydrates (E%) was observed among men who adhered to the healthy Nordic diet. Women showed similar linear trends for energy-yielding nutrients and fibre, and similar differences between the highest and lowest quintiles compared to men. However, women showed no linear association between BSDS and PUFA. Moreover the intake of sucrose (E%) among was lower in the highest score quintile compared to the lowest quintile.

The intake of vitamins A, D and C, folate, calcium and iron increased markedly according to the BSDS quintiles in men, and apart from calcium also in women. Furthermore, the intake of these nutrients was significantly higher in the highest quintile compared to the lowest. Lastly, the two cut-off methods (quartile cut-offs vs. median cut-offs) did not yield substantially different results for nutrient intake levels according to the BSDS quintiles (substudy I; Table 3, page 1701).

Table 12. Nutrient intakes according to adherence to the BSDS in DILGOM men.

	BSDS quintiles *					
Nutrients	**1**	**SE**	**5**	**SE**	***P*** **†,§**	***P*** **‡,§**
n = 2217	494		419			
Carbohydrates, E%	43.7	0.2	52.2	0.3	< 0.01	< 0.01
Protein, E%	17.5	0.1	18.0	0.1	< 0.01	0.15
SFA, E%	15.1	0.1	10.2	0.1	< 0.01	< 0.01
PUFA, E%	6.1	0.1	5.8	0.1	< 0.01	< 0.01
Sucrose, E%	8.8	0.2	9.4	0.2	0.05	0.46
Alcohol, E%	3.8	0.2	2.2	0.2	< 0.01	< 0.01
Fibre, g/d	20.7	0.3	36.3	0.3	< 0.01	< 0.01
Vitamin A, RE ‖	1080	30	1250	30	< 0.01	< 0.01
Vitamin D, µg/d	8.0	0.2	11.6	0.2	< 0.01	< 0.01
Vitamin C, mg/d	128	3	228	4	< 0.01	< 0.01
Folate, µg/d	335	3	455	4	< 0.01	< 0.01
Calcium, mg/d	1230	19	1530	22	< 0.01	< 0.01
Iron, mg/d	14.3	0.1	17.5	0.1	< 0.01	< 0.01
Sodium, mg/d	3610	25	3690	28	< 0.01	< 0.01

Abbreviations: SFA, saturated fat.

* Values are age- and energy-adjusted (except ofr energy-yielding nutrients) means and SE.

† The *P*-value for trend was analysed with linear regression using the BSDS as a continuous exposure variable in the model.

‡ The differences between the 1st and 5th quintiles were analysed, using Tukey's test.

§ Adjusted for age, education, smoking, PA, energy intake (except for energy-yielding nutrients) and BMI.

BMI and ‖ RE = retinol equivalent.

5.3 Obesity (II)

In the DILGOM study, 60.8% of men and 54.0% of women had BMI ≥ 25 kg/m^2. Furthermore, 34.7% of men had WC ≥ 100 cm and 35.8% of women had WC ≥ 90 cm. The BSDS did not associate with overweight or obesity in either sex (substudy II; Table 3, page 525). However, in the age- and energy-adjusted model (Model 1; Table 13), men in the highest BSDS quintile were 43% less likely to be abdominally obese compared with the lowest score quintile. For women, the OR was 30% lower. In the fully adjusted model (Model 2; Table 13), the inverse association with abdominal obesity remained significant for men. For women, there was no difference in prevalence of abdominal obesity between the highest and the lowest BSDS quintile, but there was a significant trend towards lower WC with higher BSDS values (Model 3; Table 13). When the analysis was stratified for age, the decrement in the ORs tended to be more pronounced among younger participants compared with the older ones in both sexes. After excluding potential under-reporters, all results remained unchanged.

In component-specific analysis, the factor contributing the most to the association between BSDS and abdominal obesity was high cereal consumption in both men (5th quintile OR 0.46; 95% CI 0.29, 0.72) and women (5th quintile OR 0.50; 95% CI 0.31, 0.80). Among men, moderate or low consumption of alcohol also significantly associated with lower abdominal obesity (OR 0.57; 95% CI 0.39, 0.85). No associations between other BSDS components and prevalence of abdominal obesity were found.

Table 13. Odds ratios for abdominal obesity according to the BSDS quintiles in the DILGOM study (II).

Model	BSDS quintiles *				
	1 (ref)	3	5	*P* †	*P* ‡
Men, *n* = 2190					
WC ≥ 100 cm, *n*	167/491	136/406	135/410		
Model 1 §	1.00	0.69 (0.52-0.93)	0.57 (0.42-0.78)	< 0.01	< 0.01
Model 2 ǀ	1.00	0.91 (0.67-1.23)	0.79 (0.58-1.08)	0.13	< 0.05
Model 3 ǁ	1.00	0.73 (0.45-1.18)	0.48 (0.29-0.80)	< 0.01	< 0.01
< 54 years (*n* = 1059) ǁ ¶	1.00	0.96 (0.46-2.01)	0.23 (0.08-0.62)	< 0.01	< 0.05
≥ 54 years (*n* = 1131) ǁ ¶	1.00	0.55 (0.28-1.06)	0.50 (0.26-0.96)	0.19	< 0.01
Women, *n* = 2530					
WC ≥ 90 cm, *n*	196/557	165/449	147/387		
Model 1 §	1.00	0.83 (0.63-1.09)	0.70 (0.52-0.94)	< 0.01	< 0.01
Model 2 ǀ	1.00	1.01 (0.77-1.34)	0.98 (0.72-1.34)	0.31	0.61
Model 3 ǁ	1.00	0.71 (0.44-1.14)	0.65 (0.39-1.09)	0.08	0.03
< 53 years (*n* = 1242) ǁ ¶	1.00	0.45 (0.18-1.12)	0.17 (0.05-0.58)	< 0.01	0.17
≥ 53 years (*n* = 1288) ǁ ¶	1.00	0.56 (0.24-1.32)	0.59 (0.25-1.37)	0.71	< 0.05

* Values are ORs (95% CI) obtained from logistic regression.

† *P*-value obtained from likelihood ratio test.

‡ *P*-value obtained from linear regression, using BSDS as a continuous variable.

§ Adjusted for age and intake of energy.

ǀ Adjusted for age, PA and intake of energy.

ǁ Adjusted for age, PA, intake of energy and BMI.

¶ Cut-off for age is the gender-specific median.

5.4 Cardiometabolic risk factors (III)

Of the men and women included in the meta-analysis (n = 11 928), 83% had an elevated total serum cholesterol concentration or used lipid-lowering medication, 78% had elevated LDL cholesterol concentration or used lipid-lowering medication, 18% of men and 29% of women had a low HDL cholesterol concentration, 37% had an elevated triglyceride concentration and 20% had an elevated hs-CRP concentration.

When comparing participants in the highest BSDS quintile with the lowest quintile, the pooled risk of an elevated hs-CRP concentration was 42% lower in men (Model 1, Table 14) and 27% lower in women, whereas the risk of a low HDL cholesterol concentration was 40% higher among women, but not among men. Among men, a slight positive trend between higher BSDS and the risk of elevated LDL cholesterol was found (Model 2). These associations were not modulated by different BMI or WC levels. Furthermore, no evidence emerged of heterogeneity between studies.

In sensitivity analysis, participants using medications were excluded in order to examine the association of diet with untreated hypercholesterolemia or hypertension (Table 14). In men, the risks generally attenuated in relation to the total and LDL cholesterol concentration (Model 1 vs. Model 2, Table 14), whereas among women, the ORs did not change. In both sexes, the risk of elevated hs-CRP attenuated, but remained significantly lower in the highest BSDS quintile compared to the lowest, whereas the risk of low HDL cholesterol strengthened in the highest BSDS quintile compared to the lowest.

To determine whether some of the BSDS components were driving the associations observed, the associations between individual BSDS components and elevated hs-CRP and low HDL-cholesterol concentrations were examined. In both sexes, higher intakes of fruits and berries and of cereals decreased the risk of elevated hs-CRP. In contrast, the risk of a low HDL cholesterol concentration tended to increase in relation to the low-fat milk intake, but decreased with a lower total fat intake.

Table 14. Odds ratios for pooled (DILGOM, HBCS and Health 2000) cardiometabolic risk factors according to the BSDS quintiles (III).

	BSDS quintiles [*]					
Model	**1 ref**	**3**	**95% CI**	**5**	**95% CI**	***P*** [†]
Men, *n* = 5494						
Total-chol [‡]						
Case *n*	905/1146	828/1022		902/1080		
Model 1 [§]	1.00	0.98	0.77, 1.24	1.04	0.72, 1.50	0.80
case *n* [‖]	666/892	544/726		511/670		
Model 2 [§‖]	1.00	0.92	0.72, 1.18	0.87	0.65, 1.17	0.25
LDL-chol [‖]						
Case *n*	878/1146	840/1022		909/1080		
Model 1	1.00	1.24	0.97, 1.58	1.23	0.97, 1.56	< 0.05
Case *n* [‖]	645/892	559/726		516/670		
Model 2	1.00	1.16	0.91, 1.48	1.07	0.81, 1.40	0.40
HDL-chol [¶]						
Case *n*	210/1146	173/1022		204/1080		
Model 1	1.00	0.93	0.73, 1.18	1.14	0.77, 1.69	0.41
Case *n* [‖]	171/892	129/726		131/670		
Model 2	1.00	0.92	0.70, 1.22	1.21	0.90, 1.61	0.43
Trigly [††]						
Case *n*	465/1146	444/1022		532/1080		
Model 1	1.00	1.02	0.85, 1.23	1.29	0.98, 1.71	0.11
Case *n* [‖]	285/892	218/726		203/670		
Model 2	1.00	0.89	0.70, 1.31	0.96	0.75, 1.24	0.34
Hypertens [‡‡]						
Case *n*	804/1146	720/1022		807/1080		
Model 1	1.00	0.85	0.69, 1.05	0.92	0.73, 1.16	0.67
Case *n* [‖]	701/1043	613/915		694/967		
Model 2	1.00	0.84	0.68, 1.04	0.91	0.68, 1.22	0.65
hs-CRP [§§]						
Case *n*	243/1099	190/991		154/1059		
Model 1	1.00	0.81	0.64, 1.02	0.58	0.43, 0.78	< 0.01
Case *n* [‖]	159/835	106/678		81/643		
Model 2	1.00	0.76	0.57, 1.01	0.59	0.36, 0.97	0.05

Continues on page 70.

Table 14. Continues from page 69.

Model	BSDS quintiles * 1 ref	3	95% CI	5	95% CI	*P* †
Women, *n* = 6334						
Total-chol ‡						
Case *n*	920/1260	852/1110		1149/1379		
Model 1 §	1.00	0.93	0.75, 1.16	1.01	0.80, 1.26	0.77
Case *n* |	752/1086	653/911		797/1026		
Model 2 §|	1.00	0.92	0.74, 1.15	0.93	0.70, 1.23	0.36
LDL-chol ||						
Case *n*	903/1260	835/1110		1122/1379		
Model 1	1.00	0.98	0.80, 1.22	1.04	0.75, 1.44	0.51
Case *n* |	736/1086	641/911		775/1026		
Model 2	1.00	0.99	0.80, 1.24	0.97	0.68, 1.40	0.94
HDL-chol ¶						
Case *n*	342/1260	301/1110		410/1379		
Model 1	1.00	1.11	0.91, 1.36	1.40	1.07, 1.83	< 0.01
Case *n* |	300/1086	255/911		328/1026		
Model 2	1.00	1.16	0.93, 1.44	1.67	1.12, 2.48	< 0.01
Trigly ††						
Case *n*	323/1260	335/1110		428/1379		
Model 1	1.00	1.06	0.81, 1.38	1.08	0.89, 1.32	0.20
Case *n* |	200/1086	165/911		170/1026		
Model 2	1.00	0.99	0.77, 1.28	0.68	0.43, 1.06	0.08
Hypertens ‡‡						
Case *n*	649/1260	641/1110		919/1379		
Model 1	1.00	0.96	0.79, 1.17	1.07	0.88, 1.31	0.37
Case *n* |	558/1169	577/1946		822/1282		
Model 2	1.00	0.99	0.81, 1.20	1.08	0.89, 1.31	0.39
hs-CRP §§						
Case *n*	300/1207	240/1075		251/1336		
Model 1	1.00	0.91	0.73, 1.13	0.73	0.58, 0.91	< 0.01
Case *n* |	208/962	158/806		140/916		
Model 2	1.00	0.93	0.72, 1.20	0.69	0.53, 0.91	0.17

Abbreviations: chol, cholesterol; trigly, triglyceride; hypertens, hypertension.

* Values are OR and 95% CI.

† The two-sided *P*-value (Wald's test) for the linear trend across BSDS quintiles was tested, using median values of BSDS quintiles as continuous variables.

‡ Cholesterol concentration ≥ 5.0 mmol/l or use of lipid-lowering medication.

§ Adjusted for age, education, smoking, PA and BMI.

| Users of lipid-lowering medication (total, LDL and HDL cholesterol concentrations, and triglyceride concentration), blood pressure-lowering medication (hypertension) or statins (hs-CRP concentration) are excluded from the analysis.

|| LDL cholesterol concentration ≥ 3.0 mmol/l or use of lipid-lowering medication.

¶ HDL cholesterol concentration < 1.0 mmol/l for men and < 1.3 mmol/l for women.

†† Triglyceride concentration ≥ 1.7 mmol/l.

‡‡ Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or use of blood pressure-lowering medication.

§§ Hs-CRP concentration ≥ 3.0 mmol/l.

5.5 Obesity-related inflammatory markers (IV)

Associations between the BSDS and adiponectin, leptin, IL-6, TNF-α, and hs-CRP and examined separately first in the DILGOM study and then in the HBCS. In the DILGOM study, inverse association between the BSDS and HMW adiponectin concentrations was found when adjusted for the age and sex of participants. Additional adjustments for the length of education, smoking status, PA and WC strengthened this association, which did not change after further adjustments for the use of anti-diabetic medication and other inflammatory markers (Table 15). In the DILGOM study, an inverse association between the BSDS and hs-CRP concentrations was also found. The association remained unchanged after all adjustments. In the HBCS, the association between BSDS and hs-CRP concentrations was replicated, but the association between BSDS and adiponectin was not found (Table 15). BSDS did not associate with leptin, IL-6 or TNF-α in either study.

Next, the individual associations of each BSDS component with hs-CRP concentrations were examined in DILGOM study and in the HBCS. In both study populations, participants with a high intake of fruits and berries and of cereals, a low intake of red and processed meat, and a moderate intake of alcohol had a lower hs-CRP concentration than the others (substudy IV; Table III, page 5). Other BSDS components did not associate with hs-CRP concentrations. In the DILGOM study, the associations between single BSDS components and adiponectin concentrations were also examined. Of the BSDS components, only a high alcohol intake significantly contributed to higher adiponectin concentrations (data not shown).

Table 15. Concentrations of inflammatory markers according to BSDS quintiles in the DILGOM study and the HBCS (IV).

	BSDS quintiles *						
Inflammatory markers	**1**	**SE**	**3**	**SE**	**5**	**SE**	***P*** †
DILGOM, *n* = 4579							
Leptin, pg/ml ‡	8880	1.02	8960	1.02	9260	1.02	0.23
HMW adiponectin, ng/ml ‡§	3740	1.02	3620	1.02	3420	1.03	< 0.01
TNF-α, pg/ml ‡	5.81	1.02	5.72	1.02	5.62	1.02	0.37
IL-6, pg/ml ‡	3.07	1.04	2.86	1.05	2.79	1.05	0.56
hs-CRP, mg/l ‡|	1.13	1.03	1.12	1.03	0.99	1.03	< 0.01
HBCS, *n* = 1911							
Leptin, pg/ml ‡	11600	1.05	11700	1.05	12300	1.06	0.69
HMW adiponectin, ng/ml ‡§	4920	1.04	5030	1.04	4310	1.05	0.13
TNF-α, pg/ml ‡	8.83	1.05	8.70	1.05	8.56	1.07	0.55
IL-6, pg/ml ‡	19.9	1.12	23.0	1.12	18.6	1.15	0.43
hs-CRP, mg/l ‡|	1.54	1.05	1.49	1.05	1.28	1.06	< 0.01

* Values are means and SE.
† *P* for trend across quintile groups was assessed with linear regression using quintile median values as a continuous variable.
‡ Adjusted for age, sex, education, smoking, PA, intake of energy and WC.
§ Adjusted additionally for oral diabetes medication and for other markers of inflammation that were significantly associated with the BSDS in the age- and sex- adjusted model.
| Additionally adjusted for statin medication and for upstream inflammatory markers.

5.6 Incidence of T2D during 10 years of follow-up (V)

Among the 6745 participants, 541 new cases of T2D emerged during the 10-year follow-up period: 358 cases in the Health 2000 and 183 cases in the HBCS. In the longitudinal analysis, pooled HRs for the risk of T2D did not differ significantly between the BSDS quintiles measured at baseline (Table 16). No evidence emerged of heterogeneity between studies. Furthermore, exclusion of the first two years of follow-up, including only participants whose T2D status was confirmed at baseline with OGTT (in HBCS), or exclusion of energy under-reporters did not change the findings.

Table 16. Study-specific and pooled (HBCS and Health 2000) HRs for T2D according to the BSDS quintiles (V).

	BSDS quintiles *							
Model	**1 ref**	**3**	**95% CI**		**5**	**95% CI**		***P*** †
Health 2000								
Case *n*	79/1081	67/887			83/972			
BSDS range	1-9	12-13			17-25			
Model 1 ‡	1.00	0.89	0.64	1.23	0.88	0.64	1.20	0.66
Model 2 §	1.00	0.88	0.63	1.24	0.97	0.69	1.38	0.88
Methealth ≤ 2 ǀ								
Case *n*	36/881	32/712			34/764			
Model 3 §	1.00	0.89	0.53	1.47	0.85	0.50	1.45	0.77
Methealth > 2 ǀ								
Case *n*	43/200	35/175			49/208			
Model 3 §	1.00	0.89	0.56	1.40	1.04	0.65	1.66	0.77
HBCS								
Case *n*	41/354	28/334			30/382			
BSDS range	1-9	12-13			17-24			
Model 1 ‡	1.00	0.68	0.42	1.10	0.63	0.39	1.00	0.09
Model 2 §	1.00	0.70	0.42	1.15	0.72	0.42	1.30	0.24
Methealth ≤ 2 ǀ								
Case *n*	20/278	13/261			15/331			
Model 3 §	1.00	0.74	0.36	1.52	0.69	0.33	1.42	0.20
Methealth > 2 ǀ								
Case *n*	21/76	15/73			15/51			
Model 3 §	1.00	0.70	0.35	1.42	1.03	0.47	2.28	0.70
Pooled								
Case *n*	120/1435	95/1221			113/1354			
Model 1 ‡	1.00	0.80	0.62	1.02	0.82	0.65	1.04	0.08
Model 2 §	1.00	0.81	0.62	1.05	0.93	0.72	1.21	0.53
Methealth ≤ 2 ǀ								
Case *n*	56/1159	45/973			49/1095			
Model 3 §	1.00	0.84	0.55	1.26	0.79	0.51	1.22	0.29
Methealth > 2 ǀ								
Case *n*	64/276	50/248			64/259			
Model 3 §	1.00	0.83	0.56	1.22	1.04	0.69	1.56	0.65

* Values are HR and 95% CI.

† The *P*-value for trend across BSDS quintile median values was obtained from the Wald's test for the pooled risk estimates.

‡ Adjusted for age and sex.

§ Adjusted for age, sex, years of education, smoking, PA, intake of energy, intake of vitamin D and abdominal obesity.

ǀ A cumulative variable (range 0-4) of the following metabolic health variables: fasting plasma glucose > 5.6 mmol/l; triglyceride concentration > 1.7 mmol/l; HDL cholesterol concentration for men < 1.0 mmol/l and for women < 1.3 mmol/l; and hypertension as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg.

In stratum-specific analysis, participants were devided into those with ≤ 2 and > 2 metabolic disorders (described in Table 9) at baseline (Table 16). No modification by participants' metabolic health status was evident.

6 Discussion

Many studies have suggested that the Mediterranean diet promotes health, decreasing the risk of obesity and chronic diseases. However, differences in food cultures, local resources and ecological aspects, might make it difficult for other populations, such as Scandinavians, to adopt this diet. The research presented in this thesis examined the associations of the healthy Nordic diet with obesity and obesity-related risk factors. To measure adherence to the healthy Nordic diet, a dietary score was developed. The BSDS proved to be a useful tool to measure healthy nutrient intakes. Furthermore, participants adhering to the healthy Nordic diet, illustrated with the BSDS, were less likely to be abdominally obese or to have elevated hs-CRP concentrations. Despite these promising results, no association between adherence to the diet and T2D incidence during a 10-year follow-up period was found. The findings are mostly in line with the literature. However, because only a few epidemiological and clinical trial studies have so far examined the health effects of the Nordic diet, inconsistencies are apparent in the findings.

6.1 Nutrient intakes (I)

Macronutrients and fibre play key roles in diet quality. For instance, the amount of energy derived from fat associate with the risk of obesity and chronic diseases. Furthermore, fibre rich carbohydrates appear to associate inversely with obesity regadless of energy intake of an individual. Vitamins have antioxidant properties that may offer protection from developing CVD or T2D. Vitamin D, for which the daily average intake is too low in Finnish women, is known to affect bone health together with calcium (Helldán et al. 2013, Nordic Council of Ministers 2013). Furthermore, folate and iron are important from public health perspective since their intake among the Finnish population is too low in all age groups (Helldán et al. 2013). Sodium is also one major public health concern because of its blood pressure-

raising effect, and its intake has been too high in Finland for several decades (Laatikainen et al. 2006).

The results from cross-sectional sub-study I demonstrated that a higher BSDS was associated with a two-fold increase in fibre, and a one-third decrease in saturated fat (E%). Furthermore, the BSDS associated with a higher intake of food-derived vitamin D, folate and iron. These findings suggest that the BSDS could be used as a tool to measure the healthy dietary intake at the population level.

However, not all nutrients associated as expected with the BSDS. For example, participants with a higher BSDS had a higher intake of sucrose which is usually related to unhealthy features (Te Morenga et al. 2012). However, the source of sucrose can vary from natural sources (e.g. fruits) to artificially added sources (e.g. added "table" sugar, sweets, and soft drinks). Studies have often failed to distinguish which of these sources cause a risk of diseases (Te Morenga et al. 2012). In sub-study I, natural and artificial sources of sucrose were not separated from each other. In 2007, when the DILGOM study was conducted, about 20% of women's and about 16% of men's sucrose intake came from fruits (Paturi et al. 2008). Thus, it is possible that participants in the highest BSDS quintile obtained more sucrose because of a higher fruit intake.

The BSDS was also positively associated with a higher intake of sodium, although the increase was not substantial. This finding could be due to the high consumption of rye bread in the fifth BSDS quintile. The BSDS was also negatively associated with the PUFA intake, and the decrement in the total fat intake due to a higher BSDS is likely to be the cause of this result. Nevertheless, the ratio of PUFA to saturated and trans-fatty acids appeared to remain beneficial, as the intake of saturated fat displayed a steeper decrease than PUFA across the BSDS quintiles.

The impact of different cut-off strategies (quartile or median cut-offs) on the results was modest in sub-study I. This finding is generally supported by the literature since various dietary scores have successfully illustrated a healthy diet regardless of the cut-off method used (Bach et al. 2006, Wirt and Collins 2009, Benitez-Arciniega et al. 2011). In sub-study I, the median cut-off tended to produce slightly stronger associations than the quartile cut-offs, probably because of the

larger detection power due to the larger group size. The benefit of single cut-off value is that it is simpler to use. On the other hand, a single cut-off cannot distinguish between associations of the outcome variables for individuals with intermediate intake levels from those with extreme intake levels. Therefore, in the studies of this thesis, quartile cut-offs were used to precisely examine the different impact levels of the BSDS.

6.2 Obesity (II)

Excess abdominal fat is known to be more pathogenic than excess subcutaneous fat. Studies have shown that when abdominal obesity (measured as WC) is adjusted for general obesity (measured as BMI), it is more strongly associated with disease risk than either of these measures alone (Pischon et al. 2008). Thus, abdominal obesity adjusted for general obesity captures a specific effect of the abdominal fat mass. In sub-study II, participants with a high adherence to the healthy Nordic diet were less likely to be abdominally obese, for a given BMI, than the others. In other words, participants adhering to the healthy Nordic diet are less prone to abdominal fat accumulation.

Currently, no other large epidemiological studies have explored the association between the healthy Nordic diet and obesity measures. Nonetheless, randomized clinical trials supporting the results of this study have been conducted. In the Danish Nordic diet intervention, of those who completed the 26-week study, 91 participants in the intervention group had 3.2 kg greater weight loss than the 58 controls (Poulsen et al. 2014). Adamsson et al. (2011) also found a 4% decrement in weight among 44 participants following the healthy Nordic diet for 6 weeks compared to 42 controls. As a limitation to the study of Adamsson et al. (2011), the participants in the intervention group did not reach the level of energy intake that was set for them. Furthermore, no change in weight among 96 participants in the intervention group was found compared to the 70 controls over 18-24 weeks in a Nordic multicentre trial (Uusitupa et al. 2013). Other healthy diets, such as the Mediterranean diet, have been associated with a -1.75 kg greater weight loss and 0.42 cm lower WC among Western populations (Esposito et al. 2011, Kastorini et al. 2011), but the association

has been much stronger among Mediterranean populations than other European countries.

The association between the BSDS and abdominal obesity tended to be stronger among men than women in sub-study II. Randomized clinical trials on the healthy Nordic diet have not reported gender differences in their results (Adamsson et al. 2011, Poulsen et al. 2014). Furthermore, most Mediterranean diet studies report no differences in obesity according to the participants' sex, but in a cross-sectional study from the EPIC study, men with high MDS had lower likelihood of abdominal obesity compared to women with high MDS (Romaguera et al. 2009). These results may be explained to some extent by the higher susceptibility for abdominal obesity among men compared to women (Geer and Shen 2009). In addition, older women tend to be more prone to misreporting their dietary intake compared to men, which on the other hand may have weakened the observed association among women (Hirvonen et al. 1997, Kaartinen et al. 2012).

Sub-studies III-V examined whether obesity modulates the association of the BSDS with metabolic risk factors (e.g. inflammation and lipid fractions) and T2D. No statistically significant modification was evident in these studies. These results are in line with the randomized controlled trials, in which associations of inflammatory markers and lipid-fractions have been independent of weight change (Uusitupa et al. 2013), but in contrast, the change in fasting glucose concentration and insulin sensitivity has been dependent on the weight change (Adamsson et al. 2011, Poulsen et al. 2014).

6.3 Metabolic risk factors

6.3.1 inflammation (III, IV)

Low-grade inflammation, for which elevated hs-CRP is an important marker, is an independent risk factor for CVDs (Torres and Ridker 2003, Calabro et al. 2009). Individuals at high risk of CVD could benefit from a hs-CRP concentration of < 3.0 mmol/l regardless of their LDL cholesterol concentration. Sub-study III revealed an association between a high BSDS and a low risk of elevated hs-CRP independently

of socioeconomic and lifestyle factors, and BMI. Furthermore, the results of sub-study IV, including the DILGOM study and the HBCS, showed that the association between the BSDS and hs-CRP was linear and independent of upstream markers of inflammation, such as leptin, adiponectin, TNF-α and IL-6. Of the BSDS components, high intake of fruits, berries and of cereals, and low intake of red and processed meat as well as moderate intake of alcohol were associated with lower hs-CRP concentrations. Among the working-aged Finnish population, the intake of alcohol is especially substantial. Promoting the healthy Nordic diet, which recommends moderate alcohol intake, may therefore promote public health in Finland in terms of reducing inflammation.

Evidence for the association between the healthy Nordic diet and hs-CRP is inconsistent as one intervention study found decreased hs-CRP concentrations (de Mello et al. 2011), and another detected no changes in hs-CRP concentrations when comparing intervention group to the control group (Uusitupa et al. 2013). The authors explained this difference with thet higher intake of rye bread, berries and fatty fish in the study of de Mello et al. (2011) compared to the study of Uusitupa et al. (2013). Overall, only a few epidemiological studies have reported associations between healthy diet scores and markers of inflammation. For instance, in two small subsets of the NHS study (n = 690 and n = 1922), women in the highest quintile of the AHEI and the MDS had 24-41% lower CRP concentrations compared to women in the lowest quintile (Fung et al. 2005, Fargnoli et al. 2008). Moreover, only the study of Fargnoli et al. (2008) examined the possible modulation of upstream inflammatory markers. In contrast to the results obtained in sub-study IV, the association between AHEI and CRP disappeared after adjusting for upstream inflammatory markers.

6.3.2 Lipid fractions (III)

Dyslipidemias and hypertension are main risk factors for CVD. Sub-study III revealed that women who adhered to the healthy Nordic diet were more likely to have a low HLD cholesterol concentration. Furthermore, the number of men with an elevated LDL cholesterol concentration tended to increase across the BSDS

quintiles. In these results, the possibility of reverse causation occurred, because cases included medication users. They may have received dietary counselling as a part of their medical treatment (Working Group of the Finnish Medical Society Duodecim and Finnish Society of Internal Medicine 2013), and consequently changed their dietary habits, which may have confounded the results of sub-study III. In sensitivity analyses, when users of lipid-lowering medication were excluded, the trend between BSDS and the risk of an elevated LDL cholesterol concentration disappeared, but the association between the BSDS and the risk of a low HDL cholesterol strengthened. Thus, we cannot rule out the possibility that the diet may actually increase the risk of low HDL cholesterol concentration.

If true, the results regarding the lipid fractions partly conflict with the randomized controlled studies, in which positive changes in the LDL cholesterol concentration have been seen in the intervention groups compared to the controls (Adamsson et al. 2011, Uusitupa et al. 2013). In contrast, HDL cholesterol concentrations significantly decreased in the intervention group after following the healthy Nordic diet. However, at the same time, the LDL/HDL ratio changed beneficially (Adamsson et al. 2011). Unfortunately, sub-study III did not examine the LDL/HDL ratio, which would have aided the interpretation of the results regarding HDL cholesterol. Furthermore, assessing the association between the HDL particle size and type would had been useful, since a study of Lankinen et al. (2014) revealed that the healthy Nordic diet beneficially affected the HDL particle size, even though the total HDL cholesterol concentration remained stable.

6.4 T2D (V)

T2D is one of the fastest expanding chronic diseases and has been estimated to affect 328 million people around the world (Guariguata et al. 2014). A landmark clinical trial has demonstrated that the risk of T2D can be halved with lifestyle changes, such as diet and exercise (Tuomilehto et al. 2001). In the prospective sub-study V, adherence to the healthy Nordic diet did not significantly associate with T2D over 10 years of follow-up. The main reason why the associations were weakened was probably because each BSDS quintile had low numbers of T2D cases.

To obtain more T2D cases, a longer follow-up period may have been needed. Furthermore, since participants' lifestyle, anthropometric measures and dietary habits were measured only at the baseline health examination the unmeasured changes which occurred during follow-up, may have covered possible associations.

In comparing these results with other dietary scores (AHEI, DASH and MDS), the US cohort studies with a follow-up longer than 10-year have recorded a decreased risk of T2D among participants with a higher adherence to the pre-defined diet (de Koning et al. 2011, Chiuve et al. 2012). In Europe, these results have only been confirmed for MDS in a nested case-control study conducted on 16 154 participants of the EPIC study (InterAct Consortium et al. 2011).

In sub-study V, the baseline WC and metabolic status of the participants did not significantly modify the association between the BSDS and risk of T2D. Our results are partly consistent with Nordic diet trials which have shown that the healthy Nordic diet does not affect the fasting glucose concentration without weight reduction (Adamsson et al. 2011, Lankinen et al. 2011, Uusitupa et al. 2013, Poulsen et al. 2014). However, the diet improved the 2-hour glucose concentration among metabolically ill participants (Lankinen et al. 2011) and improved insulin sensitivity among participants with pre-diabetes (Poulsen et al. 2014).

6.5 The single foods and nutrients *vs.* whole-diet approach

The results of this thesis indicate that the whole diet described by a dietary score based on healthy Nordic foods may be an appropriate tool to assess healthy nutrient intake, as well as anthropometric and metabolic outcomes. The results also suggest that some single foods may have a stronger association with health outcomes, and the measurement of only these foods might be enough to assess the risk level. For instance, high consumption of Nordic cereals contributed the most to the inverse association between the healthy Nordic diet and abdominal obesity. This raises a question concerning whether the dietary score method adds any value to the traditional approach of studying single foods and nutrients.

Because foods and nutrients are always consumed in combination, the health effects of single food-items are always mixed, inhibited or cumulated. For example,

in the study of Mozaffarian et al. (2011), when food items were explored independently, the weight reduction for each additional daily serving was approximately < 300 g for each four-year period. When the cumulative effect of multiple healthy dietary changes was examined, the weight reduction was 1.8 kg for each four-year period. Thus, much information on the health effects of the diet is lost if only one food at a time is studied. In some cases, when a nutrient, such as beta-carotene, is separated from its natural environment an increment in disease risk may even occur (The ATBC Study Group 1994). Furthermore, like the BSDS, most dietary scores have been developed to illustrate a general healthy diet, and are therefore expected to have multiple beneficial effects on health. As the results in sub-studies II-IV demonstrated, other score components than the ones that predicted abdominal obesity proved to be more crucial when assessing inflammation. Thus, some single foods could be used to assess specific diseases, while a whole diet - based approach is a more useful tool to evaluate the impact of dietary components on overall health. Alternatively, a disease-specific score that includes dietary factors related to certain disease could be used to assess disease risks in a population.

6.6 Methodological issues

6.6.1 Participants and study design

The use of three independent datasets to explore associations can be seen as a major strength of this thesis. The DILGOM study and Health 2000 included large and representative samples of the Finnish population with a participation rate at an acceptable level. The HBCS provided data from a large and well-characterized cohort of elderly Finns born in the Helsinki area. However, the general phenomenon of health-conscious people tending to participate more often in health surveys may have diluted or even covered the results to some extent. Furthermore, the cross-sectional design does not allow any conclusions on causality to be drawn (sub-studies I-IV). Sub-study V provided an opportunity to assess causality to some extent. Nevertheless, the effect on the results of unmeasured changes in lifestyle,

weight or other health parameters after the baseline health examination could not be fully evaluated.

Some clues of the lifestyle changes during the follow-up period can be derived from the preliminary results of the follow-up study of the Health 2000, the Health 2011 survey. Based on the Health 2011 survey, the number of current smokers has reduced since 2000 (Heloma et al. 2012). This change has likely improved the health of participants in the lowest BSDS quintile who had the highest number of current smokers. Furthermore, the number of physically active individuals has reduced which, in contrast to smoking, may have had adverse effect on the health of the participants in the highest BSDS quintile who had the highest the number of physically active participants (Mäkinen et al. 2012). Consumption of rye bread was observed to decrease since 2000, which may have lowered adherence to the healthy Nordic diet to some extent in the higher BSDS quintiles (Männistö et al. 2012b). In addition, the effect of participants' age on the results should be noticed. Most of the participants in the higher BSDS quintiles were over 60 years old at the baseline. Because of their age, they were also more likely to get T2D during the 10-year follow-up compared to the under 40-year-old participants, whose number was highest in the first BDSD quintile. However, even though lifestyle changes have occurred at population level, whether these changes have been great enough to affect the risk of T2D at an individual level is debatable.

6.6.2 FFQ

The FFQ is considered to be a standard method for assessing long-term dietary intake in large epidemiological studies (Willett 2013). Furthermore, the FFQ has been shown to provide a valid estimate of diet quality as assessed by the dietary score (Benitez-Arciniega et al. 2011). One strength is that the DILGOM study, the Health 2000 and the HBCS used the same FFQ, which was originally validated for food and nutrient intakes and reproducibility against food diaries among healthy community controls for breast cancer patients (Männistö et al. 1996), and later on in the Health 2000 (Paalanen et al. 2006) and in the DILGOM study (Kaartinen et al.

2012). The same food composition database and nutrient intake calculation software were also used in the three studies.

As a limitation, nutrition research, including the FFQ, generally involves overestimation of healthy and underestimation of unhealthy food consumption. Health conscious people, women and overweight participants are especially prone to misreporting (Paalanen et al. 2006). This may have led to some misclassifications in the BSDS quintiles or dragged the BSDS cut-off points higher, which may have weakened the observed associations. Validation studies have revealed that the FFQ has a good ability to rank subjects according to their relative nutrient and food intakes (Männistö et al. 1996, Paalanen et al. 2006, Kaartinen et al. 2012). It also provides a fairly good estimate of the absolute intake. The most notable overestimate (2-fold difference between the FFQ vs 3-day food record) has been observed for the consumption of vegetables (Paalanen et al. 2006). Furthermore, the consumption of beef and pork was highly overestimated compared to the 3-day food record. Of the nutrient intakes, the FFQ most notably oversestimated the intake of PUFA and underestimated the intake of alcohol (E%) compared to the 3-day food record. Under-reporting of energy intake was controlled for in all studies by excluding participants with low energy intakes in relation to their estimated basic metabolic rate from the analyses. In most cases, the results did not change after controlling for under-reporting.

FFQ gives an estimate of long-term dietary exposure of an individual before the moment of assessment. In the DILGOM study, the HBCS and Health 2000, participants completed the FFQ only at baseline. Validity of using the baseline FFQ in T2D risk estimation over 10-year follow-up period is questionable since, undeniably, changes in the diet occur during such a long period. In principle, an individual can reduce his or her T2D risk considerably during 10 years with lifestyle changes such as diet (Tuomilehto et al. 2001). In the Finnish Diabetes Prevention Study, dietary changes such as decreasing total fat intake, increasing fibre intake and improving fat quality, decreased significantly the risk of T2D independently of other risk factors (Lindström et al. 2006). However, only 25% of the participants in the intervention group achieved the dietary goals despite all the support they received

(Tuomilehto et al. 2001). In the control group, the number of succeeders was only 12%. Thus in sub-study V, the chance that a high enough number of participants needed to impact the results, had achieved these kind of dietary changes, is debatable.

6.6.3 The Baltic Sea Diet Score

The strengths of the BSDS include its assessment of the diet's cumulative effect, which is overlooked in traditional nutrition research. The BSDS provides a tool for epidemiological studies to explore the associations between the healthy Nordic diet and disease. It takes into account the cultural and ecological aspects in constructing a healthy Nordic diet, which eases the practical implementation of the research results in Scandinavian countries.

A dietary score also has its weaknesses. Although a predefined score, such as the BSDS, better enables the capture of cumulative dietary exposure, some confounding due to correlations in the intake of various dietary factors still remains. Currently, there is no standard for creating dietary scores. Thus, the selection of the food groups and nutrients, and the scoring of the selected components are carried out through subjective decisions. Although subjective, the decisions concerning the BSDS components were made together with experienced nutrition researchers who were familiar with the healthy Nordic diet concept. Furthermore, selection of the BSDS components was carefully based on the Baltic Sea Diet Pyramid, and two different cut-offs methods were tested. Nevertheless, the inclusion of some components and their scoring can be questioned because of inconsistent evidence of their health effects. For instance, in the light of the newest Nordic nutrition guidelines, total fat intake could be excluded from the score and more weight could be given to the fat ratio (Nordic Council of Ministers 2013). Since many of the health effects of alcohol are specifically related to moderate intake, abstainers could be given fewer points than those with a moderate consumption of alcohol. Furthermore, to make the score simpler, the nutrient intake calculation software could be developed to facilitate the use of only food-based components, for example extraction of rapeseed oil from all vegetable oils.

The BSDS used population- and sex-specific consumption cut-offs, as do various other dietary scores. However, this method has been criticized for not giving a true estimate of the population's adherence to the predefined diet. For example, adherence to the Mediterranean dietary pattern has been observed to be lower among younger generations compared to the older generations (Leon-Munoz et al. 2012). This means that those who nowadays have the highest adherence to the MDS nevertheless have a much lower adherence compared to Mediterranean populations in the 1970s. A recent study by Roswall et al. (2014) revealed that of the traditional Nordic foods, only dark bread, root vegetables and fish were more consumed among Scandinavians than other Europeans. The consumption of berries, for example, did not differ between Scandinavia and other European countries. Consequently, the generally low adherence to the healthy Nordic diet among younger participants may have diluted the results to some extent.

6.6.4 Measurements and data handling

The DILGOM study, the HBCS and the Health 2000 conducted several measurements according to standardized protocols, which enabled robust and careful statistical testing. However, the possibility of residual confounding cannot be fully excluded. Furthermore, because some of the variables, for example physical activity, include measurement error, the strength of the associations may have led to conservative estimates.

Extensive laboratory analysis allowed the association of the BSDS with several biomarkers to be explored. However, differences between laboratories in the analytical methods applied resulted in unequal concentration levels, making direct comparison of the absolute concentrations impossible. Nevertheless, this affected neither the results nor the conclusions of this study, since the focus was solely on exploring associations. In addition, the meta-analysis technique was used to overcome differences in study design and laboratory assays. Moreover, even unlikely and unexpected variation in within-laboratory measurements may have led to the misclassification of some participants according to the international cut-offs, and affected the results to some extent.

Information on medication use and drug reimbursements was derived from nationwide registers, which have been proven reliable. However, identification of T2D cases solely based on registers in sub-study V led to conservative estimates, as individuals with undiagnosed diabetes at baseline were included among non-cases. This potentially attenuated the results. However, the baseline OGTT test conducted in the HBCS was used to confirm the results among participants who were known to not have undiagnosed diabetes. Furthermore, the result of stratified analysis including participants who had > 2 metabolic abnormalities did not differ from the main results. Regarding these results, the use of registers in T2D case identification did not affect the conclusions.

6.7 Implications for further research

The sub-studies of this thesis were among the first to explore the associations between the healthy Nordic diet and health outcomes in an epidemiological setting, using a dietary score method. Since the healthy Nordic diet is obviously not limited to Finland, the ability of the BSDS to reflect a healthy dietary intake should aditionally be examined in other Scandinavian populations.

To facilitate implementation of the BSDS to clinical practice and to studies that do not include extensive dietary assessment the BSDS should be transformed to a one-page, self-administered questionnaire. All components in the score should be food-based instead of nutrients (the fat ratio vs. rapeseed oil). Furthermore, the cut-off method could be developed so that it truly illustrates the desired adherence level to the healthy Nordic diet instead of population-specific cut-offs. Such information on satisfactory cut-offs could be derived, for example, from randomized clinical trials conducted on the healthy Nordic diet. With this type of development would eliminate the need to complete the FFQ and complex nutrient intake calculations.

The findings of this thesis study suggest that the healthy Nordic diet associates with a lower risk of abdominal obesity and inflammation, but with a higher risk of a low HDL cholesterol concentration. As all these findings were obtained in a cross-sectional design, to learn more about the causality of these associations, the studies should be replicated with longitudinal data. Such data will soon be available from all

three studies included in this thesis: The HBCS already has two follow-up measurements for the participants; the Health 2000 follow-up study, the Health 2011, was conducted during the preparation of this thesis and the resulting data are currently available for analyses; and the follow-up of the DILGOM study has just begun, and with the data expected to be ready for analyses in the 2015.

In this thesis, the association between the BSDS and T2D was assessed. Since the number of cases in each BSDS quintile was relatively low, replication of the study in a larger cohort with a longer follow-up would be needed to obtain stronger estimates. The association between the BSDS and other chronic diseases, such as CVD, could also be explored in longitudinal data. Lastly, randomized controlled studies with long follow-up times are needed to confirm possible causal associations between the healthy Nordic diet and chronic diseases.

7 Conclusions

A healthy diet composed of Nordic foods may prove useful in promoting overall health. The main conclusions of this thesis can be summarized as follows:

1. The BSDS shows associations with various nutrients, such as a higher intake of carbohydrates, fibre, vitamins and minerals, and a lower intake of saturated fatty acids and alcohol. The BSDS is a valid tool to indicate a healthy diet and can be utilized to assess diet-disease relationships in public health studies.

2. Participants who adhered to the healthy Nordic diet were less likely to be abdominally obese. Neither abdominal nor overall obesity modified the associations between the BSDS, low-grade inflammation, cardiometabolic risk factors and T2D. The diet could be used to promote normal waist circumference maintenance among population.

3. Participants with high adherence to the healthy Nordic diet had lower hs-CRP concentrations and were less likely to have hs-CRP concentrations ≥ 3.0 mg/l. Low-grade inflammation is known to increase the risk of chronic disease, which is why this finding may have relevance from the public health point of view.

4. High adherence to the healthy Nordic diet may place women at greater risk of low HDL cholesterol concentrations. The health consequences of this finding are controversial, because the causal relationship between the HDL cholesterol concentration and the risk of CVD is not clear.

5. Adherence to the healthy Nordic diet did not associate with the incidence of T2D during 10 years of follow-up.

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