A Healthy Nordic Diet and Cardiometabolic Risk Factors

*Intervention Studies with Special Emphasis on Plasma Lipoproteins*

VIOLA ADAMSSON
Abstract


A healthy diet is important in the prevention of cardiovascular disease (CVD). Several risk factors, modifiable by diet, are involved in the development of CVD, e.g. hyperlipidaemia, hyperglycaemia, insulin resistance, obesity and hypertension. Little data however exist on diets composed of foods originating from the Nordic countries, and their potential to reduce CVD risk.

This thesis aimed to investigate whether an ad libitum healthy Nordic diet (ND), either provided as a whole diet, or as a prudent breakfast (PB) alone, could influence CVD risk factors in healthy, mildly hypercholesterolemic men and women. Another aim was to describe the nutrient and food composition of the ND, both by using self-reported data and serum biomarkers of dietary fat quality.

The primary clinical outcome measure was LDL-cholesterol, and other cardiometabolic risk factors were secondary outcomes.

Two parallel, randomised, controlled intervention studies were conducted in free-living subjects. Clinical and dietary assessments were performed at baseline and at the end of dietary interventions. All foods were provided to subjects randomised to ND, whereas only breakfast items were supplied to subjects randomised to PB. Control groups followed their habitual diet/breakfast.

Compared with controls, ND reduced body weight and improved several CVD risk factors including LDL-cholesterol, insulin sensitivity and blood pressure. Several, but not all effects were probably partly mediated by diet-induced weight loss. ND accorded with Nordic nutrition recommendations and was defined as “a plant-based diet, where animal products are used sparingly as side dishes”. Compared with average Swedish diet, ND was high in dietary fibre, but low in sodium, meat, high-fat dairy products, sweets and alcohol. A decreased intake of saturated fat and increased intake of n-3 PUFA during ND was partly reflected in serum lipids. Eating a PB without other dietary changes did not improve lipid or glucose metabolism, but decreased markers of visceral fat and inflammation, without influencing body weight.

This thesis suggests that a whole ND, but not PB alone, promotes weight loss and improves multiple CVD risk factors in healthy subjects after 6 weeks. These results suggest that ND could have a potential role in the prevention of cardiometabolic diseases.
List of Papers

This thesis is based on the following Papers, which are referred to in the text by their Roman numerals:


III Adamsson V, Cederholm T, Vessby B, Risérus U. Influence of a healthy Nordic diet on serum fatty acid composition and associations with blood lipoproteins – results from the NORDIET study. In manuscript.


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### Abbreviations

<table>
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<tr>
<td>apoA1</td>
<td>Apolipoprotein A1</td>
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<td>apoB</td>
<td>Apolipoprotein B</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>CVD</td>
<td>Cardiovascular disease; <em>i.e.</em> an umbrella term encompassing diseases that affect the heart and blood vessels</td>
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<td>CHD</td>
<td>Coronary heart disease</td>
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<td>Hs-CRP</td>
<td>High sensitive C-reactive protein</td>
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<tr>
<td>DASH</td>
<td>Dietary Approach to Stop Hypertension</td>
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<tr>
<td>HDL-C</td>
<td>High density lipoprotein cholesterol</td>
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<tr>
<td>HOMA-IR</td>
<td>Homeostasis model assessment of insulin resistance</td>
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<tr>
<td>LDL-C</td>
<td>Low density lipoprotein cholesterol</td>
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<tr>
<td>MUFA</td>
<td>Monounsaturated fatty acid</td>
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<td>NCEP</td>
<td>National Cholesterol Education Program</td>
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<td>ND</td>
<td>Nordic Diet</td>
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<td>NNR</td>
<td>Nordic Nutrition Recommendations 2004</td>
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<tr>
<td>OECD</td>
<td>Organization for Economic Co-operation and Development</td>
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<tr>
<td>PUFA</td>
<td>Polyunsaturated fatty acid</td>
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<tr>
<td>SCD-1</td>
<td>Stearoyl coenzymeA desaturase-1</td>
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<tr>
<td>SFA</td>
<td>Saturated fatty acid</td>
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<tr>
<td>TNF-R2</td>
<td>Tumour necrosis factor receptor-2</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Prologue

During my years as a dietary manager for Swedish cross-country skiing, I packed oatmeal, lingon berry jam, hardbread, caviar, and whey into boxes and took them to the Olympics games, World Championships and World Cup competitions. I was a kind of traveller of Nordic food. Skiers' requests for familiar foods highlight that it is important that taste is recognised. In their case, it was mainly about being able to eat sufficient food to maintain energy balance before and after competitions and be able to perform to the best of their ability.

This insight of practical life was valuable when I started to seriously consider whether a Nordic diet could have similar effects on health, particularly in reducing the risk of cardiovascular disease for people in the north in the same way the Mediterranean diet has for people in the Mediterranean.

What instigated my desire to research this topic was the development in research on the Mediterranean diet, which I had followed closely for many years. An early inspiration, which was also the trigger for this thesis, was a Dutch study (Waijers PM et. al. Am J Clin Nutr. 2006 May;83(5):1170-6.) that suggested a healthy Dutch diet had greater health benefits for older Dutch women than the Mediterranean-like diet had. Researchers have for a long time looked at the health effects of individual components, but at the turn of the century, focus turned to looking at these individual components together as a whole for determining the health effects of individual foods and then of whole diets.

An important breakthrough was the study of a dietary portfolio, comprising a number of foods with cholesterol lowering properties that reduced LDL-C in a similar fashion as lipid-lowering drugs. In addition, another study showed that a strict low-fat diet could reduce plaque in blood vessels.

The concept of the whole being greater than individual parts and the possibility of influencing health through diet were important starting points for my research.

However, it is not just about the health effects of the food on one’s plate. Food and eating habits develop in conjunction with societal development. During the late 1990s and early 2000s, there were three parallel factors that caught the interest of consumers: a growing interest in locally produced foods, health concerns, and questions about how eating habits affected climate change.
If a Nordic diet could be shown to reduce the risk for cardiovascular disease in the same way as the Mediterranean diet does, this would be beneficial in several ways:

Firstly, we can confidently choose to eat well-known Nordic foods and not need to eat a more diverse diet.

Secondly, there may be environmental benefits from choosing locally produced foods, as this can encourage more agricultural variation and open countryside. Shorter transportation distances save energy and reduce emissions that contribute to the greenhouse effect.

Thirdly, more jobs would be created, in both agriculture and the subsequent processing, and therefore, a higher degree of self-sufficiency in terms of food production could be achieved.

As mentioned before, the trigger was Waijers et. al.

Viola Adamson
Introduction

A healthy lifestyle is important for the prevention of many lifestyle related diseases including cardiometabolic diseases (i.e. cardiovascular disease (CVD), obesity, metabolic syndrome, and type II diabetes). This thesis addresses potential effects of a healthy Nordic diet on cardiometabolic risk factors, especially CVD risk factors. The focus is on a whole diet, including fat- and carbohydrate quality, and the outcome focuses on plasma lipoproteins. A number of cardiometabolic risk factors are modifiable by diet; i.e. hyperlipidaemia, hyperglycaemia, insulin resistance, obesity (especially visceral obesity), and high blood pressure (1, 2).

Increased plasma low-density lipoprotein cholesterol (LDL-C) is an established risk factor for CVD (3, 4). The World Health Organisation (WHO) attributes 8.7% of the total burden of disease in the European region to high blood cholesterol levels (5). Controlled trials with LDL-C-lowering drugs show plaque regression and decreased CVD mortality (6). Due to the complexity of the disease a number of effects contribute to the prevention of CVD, for example decreased blood pressure, improved insulin sensitivity, increased physical activity, and perhaps lower inflammation (7). In addition to lipid-lowering drugs (8), several dietary factors also reduce LDL-C. These include dietary patterns that emphasise the intake of vegetables, fruits, and whole grains. Furthermore, increased intake of low-fat dairy products, poultry, fish, legumes, vegetable oils and nuts, and limited intake of sweets sugar-sweetened, beverages and red meat can also reduce LDL-C (1, 9). In contrast to drugs, dietary modifications reduce LDL-C without the risk of side effects. WHO estimates that 80% of all CVD could be avoided through changing lifestyle factors, among which diet is one of the most important factors (10). A diet low in saturated fatty acids (SFA) and high in dietary fibre can reduce total cholesterol by 20-30 % (11).

Within the OECD countries mortality from CVD varies considerably (12). Central and eastern European countries report the highest rates of CVD mortality. However, mortality rates from CVD have declined since 1980 in nearly all OECD countries. In the Nordic countries, i.e. Denmark, Norway, Sweden, Iceland, and Finland, the decline has been substantial (12-15). The lowest mortality rates are found in southern Europe, i.e. Portugal and the Mediterranean area including France, Spain, Israel, and Italy. The low mortality rates in southern Europe together with the highest rates in eastern Eu-
rope support the hypothesis that diet explains some of the difference in CVD mortality among countries (12).

The role of diet in CVD

A dietary pattern that emphasises the intake of vegetables, fruits, and whole grains as well as low-fat dairy products, poultry, fish, legumes, vegetable oils and nuts, and limits intake of sweets sugar-sweetened beverages and red meat is recommended by the American College of Cardiology/American Heart Association to adults who would benefit from lowering their LDL-C (1).

The Mediterranean diet

A traditional Mediterranean diet improves the CVD risk profile (16, 17). The pioneering Seven Countries Study (18) and numerous observational and interventional studies (19-22) have established the health benefits associated with adherence to the Mediterranean diet pattern. In a randomised controlled trial (16), the Mediterranean diet supplemented with olive oil or nuts had more beneficial effects on CVD risk factors than a low-fat diet. Adherence to the Mediterranean diet (17) consistently displays a reduced risk of developing the metabolic syndrome, type II diabetes, CVD, and some neurodegenerative diseases and cancers (17). The Mediterranean diet not only reduces LDL-C but also increases HDL-C (21). It has also been shown that adherence to Mediterranean-like pattern reduces mortality in elderly Swedish men (23). There is a strong link between the protective effects of the Mediterranean diet and reduced risk of coronary heart disease (CHD) (24).

The Mediterranean diet is described by both its food and nutrient content. On a food basis, Sofi et. al. (25) describe the Mediterranean diet to contain plenty of legumes, cereals, fruit, vegetables, and olive oil. At the same time it is low in meat and milk products. Willett et. al. (26) describe the traditional Mediterranean diet as the typical food pattern of the early 1960s in Crete, the majority of Greece, and in southern Italy. This included an abundance of plant food, olive oil as the principal fat, and low to moderate amounts of dairy products, principally yoghurt and cheese, moderate intake of red meat, but higher intake of poultry, fish, and eggs, and with wine in moderation during meals. Simopoulos et. al. (27) describe the traditional Greek diet by both its nutrient and food content being low in SFA, high in monounsaturated fat (MUFA), balanced in omega-6 and omega-3 fatty acids, high in fruits, vegetables and legumes, rich in antioxidants, moderate in amounts of cereals in the form of bread, usually sourdough bread. Bach-Faig et. al. (28) extended the description of the Mediterranean diet to include also the composition of the main meal and guidelines including amounts and servings of foods.
However, de Lorgeril et al. state the diet score usually used to assess conformity with the Mediterranean dietary pattern in epidemiological studies is simplistic and may not capture the various practical aspects of the traditional Mediterranean diets.

The DASH diet
The Dietary Approaches to Stop Hypertension trial (DASH-trial) is a randomised, controlled feeding study designed to compare the effect of three different dietary patterns on blood pressure among subjects with high, normal and mildly elevated blood pressure (30). The DASH diet is rich in fruits, vegetables, whole grain, nuts, legumes, and seeds that are good sources of potassium, magnesium, dietary fibre, and low-fat dairy products, fish, chicken, and lean meats to decrease SFA and increase protein and calcium (30). The control diet in the study was a typical American diet (30). The third dietary pattern was higher in fruit, vegetables and whole grain and lower in sweets, but had macronutrient content close to the control diet (30). The DASH diet could substantially lower elevated blood pressure in the absence of weight loss and sodium restriction (31) in different subgroups (32). When investigating the effect of a DASH diet reduced in sodium (33), systolic blood pressure was 7 mm Hg lower in subjects without hypertension, and 11.5 mm Hg lower in subjects with hypertension, when compared with the control diet high in sodium (33). In addition to lowering blood pressure, the DASH diet had beneficial effects on total cholesterol and LDL-C (34) and insulin (35). However, the DASH diet also reduces high-density lipoprotein cholesterol (HDL-C) which is negative as HDL-C is inversely associated with CVD risk (34). Similar findings are reported in other whole diet studies (36, 37).

The Portfolio diet
A vegetarian-based Portfolio diet including a combination of foods with cholesterol-lowering effect, such as plant sterols, vegetable protein, viscous dietary fibre and almonds, can reduce plasma LDL-C to similar levels as achieved by first-generation statins (38-40). After 2 weeks on the portfolio diet, LDL-C was reduced by 35%, compared to 12% in the control group (40), and after 12 months, in a long-term study, the reduction was still more than 20% (41). Jenkins et al. was the first to establish that dietary change, i.e. the portfolio diet, can reduce high sensitive C-reactive protein (CRP) (39, 42). They concluded that the combination of cholesterol-lowering foods in a complex diet (e.g., a dietary portfolio) rather than single food items has the potential to bridge the gap between drug therapy and dietary treatment (43).
The Nordic diet

The traditional Nordic dietary pattern seen in Denmark, Sweden, and Norway has previously been described on a food basis as being unhealthy (44), as it is known to be relatively high in potatoes and animal products and processed and sweetened/refined foods. The consumption of vegetables is reported to be similar to or below the overall mean in the European Prospective Investigation into Cancer and Nutrition project (EPIC) (44), and it is low in legumes and vegetable oil. Based on nutrient intake pattern, a high intake of retinol, vitamin D, and SFA and a low intake of beta-carotene, vitamin E and C, dietary fibre and iron is common among the Nordic countries, although there are some differences between the countries (45).

Nevertheless, the dietary pattern in the Nordic countries is healthier nowadays than in the past due to increased accessibility and consumption of fruit and vegetables and an improvement in fat quality (15, 46-50). In addition, public health programs with interventions on diet as a central component, has contributed to the positive dietary changes (51, 52). The positive change towards a healthier dietary pattern decreased the serum cholesterol levels in the Nordic countries during 1986-2004. This trend remained unchanged during 2004-2007 when the cholesterol levels began to rise (53), possible due to an increased SFA intake that was observed after 2002 (53).

Cardiovascular risk factors and the atherosclerosis process

Atherosclerosis is a process where fat and calcium accumulate in the intima of the blood vessel walls. The blood vessels become stiff and narrow slowing down the blood flow (54, 55). The atherosclerosis process most likely starts with the oxidation of lipids in LDL-C (54-56) followed by incorporation of cholesterol and cholesterol esters into the macrophages in the vessel wall (54, 55). The oxidised LDL activates NFκB-like transcription factors that induce gene expression. The protein products of these genes initiate an inflammatory response, initially leading to the development of “fatty streaks” (54, 55). Accordingly, at present the prevention and treatment of atherosclerosis are mainly directed towards lowering LDL-C, glucose, and insulin levels, reducing body weight and blood pressure, and to raising HDL-C which are risk factors modifiable by diet change (1). Other important risk factors are stopping smoking and increasing physical activity.

A risk factor is a characteristic, a condition, or behaviour that increases the possibility of a disease or injury (57). Biochemical risk factors, i.e. measurable in plasma and/or serum for CVD are high concentration of total cholesterol, LDL-C, apolipoproteinB (apoB), triglycerides, glucose, insulin, high LDL-C/HDL-C ratio, and apoB/apoA1 ratio and low levels of HDL-C,
apo-lipoproteinA1 (apoA1). Moreover, elevated serum concentrations of inflammatory mediators like CRP and tumour necrosis factor receptor-2 (TNF-R2) are associated to increase risk for CVD (58-60). Anthropometric risk factors are increased BMI and accumulation of visceral fat as measured by valid techniques such as sagittal abdominal diameter (SAD) or waist circumference. Smoking and high blood pressure are also established risk factor for CVD (1).

Blood lipids

Cholesterol is essential for normal body function and every cell in the body has cholesterol in its cell membranes. Cholesterol is needed to build up cellular membranes, and to form bile salts, vitamin D, and male and female sex hormones (androgens and estrogens), (54, 61). Cholesterol is transported in the circulation by lipoproteins. Too much cholesterol in the blood is a risk factor for CVD and could be caused by genetic or lifestyle factors (61).

Major lipoprotein classes are chylomicrons, very-low-density-lipoproteins (VLDL), LDL and HDL. Chylomicrons and VLDL are rich in triglycerides, whereas, LDL and HDL are rich in cholesterol (61). LDL-C is often referred to as the “bad cholesterol” as it carries and deposits cholesterol to all parts of the body. Conversely, HDL-C is often referred to as the “good cholesterol”, as HDL-C removes cholesterol from the artery walls and transports cholesterol back to the liver (62). HDL-C is associated with decreased risk of CVD. There are no good or bad cholesterols in the diet: “good” and “bad” cholesterol is merely a way of expressing the direction of cholesterol transportation by lipoproteins in the body.

Cholesterol and triglycerides are transported through the plasma in the core of the lipoproteins which are composed of free and esterified cholesterol, triglycerides and phospholipids (61). The protein part of lipoproteins is called apolipoproteins (apo), where apoA1 is the major protein in HDL-C and apoB is the major apolipoprotein in LDL-C (63). ApoA1 and apoB provides additional information to the assessment of LDL-C and HDL-C (63).

A 1 mmol/L statin-induced lowering of LDL-C reduces the risk of vascular events by 10% after 1 year, 25% after 2-3 years and about 30% after 4 years (6). In the JUPITER Study, a 50% risk reduction of vascular events was observed after 1-2 mmol/l drop in LDL-C (64). Genetic studies also support LDL-C as a causal risk factor of CVD, since genotypes that are associated with increased LDL-C levels was also independently associated with CVD (65). In addition, using meta-analyses of Mendelian randomisation studies it was shown that prolonged exposure of lower LDL-C early in lifespan was linked to markedly decreased risk of CHD (66).
Triglycerides

Triglyceride is an important risk factor of CVD (67). A reduction of 50% or more in triglyceride levels may be possible through lifestyle change where body weight reduction, decrease in added sugar and increased intake of unsaturated fatty acids are some factors (67). Hypertriglyceridemia, particularly in the non-fasting state is suggested as an important risk factor for CVD (68).

Glucose and Insulin

High blood glucose levels render the intima more vulnerable to injury and can initiate the atherosclerosis process (54). Insulin, as the regulator of glucose, has an indirect effect on the intima. Disturbance of insulin actions in glucose metabolism include reduced uptake and metabolism of glucose in insulin sensitive tissues, such as muscle and adipose tissue (69).

Inflammation

Oxidation of LDL-C triggers inflammatory processes that are related to CVD (55). CRP is a biomarker of systemic inflammation, CRP-levels between $\geq 3$ and $<10$ mg/L are denoted as low-grade inflammation, whereas, CRP-levels $\geq 10$ indicate acute inflammation not necessarily related to CVD risk. CRP-levels are influenced by changes in weight (2), i.e. increases in body fat are positively related to CRP. Furthermore, increased intake of dietary fibre is related to lower CRP (70, 71). There is a close link between visceral fat and low-grade systemic inflammation, providing a potential link between visceral fat and CVD (72). Other dietary components related to decreased risk may involve improved fat quality e.g. polyunsaturated fatty acids (PUFA), both n-3 and n-6 FA. Exchanging SFA with PUFA can reduce the visceral fat-to-subcutaneous fat ratio, and thus reduce inflammation markers, such as TNF-R2 (73).

Role of diet on anthropometric risk factors

Energy restriction, whether from caloric restriction or increased energy expenditure from exercise (74), affects weight and body mass index (BMI) and improves blood lipid profiles (75).

Blood pressure

High blood pressure (hypertension) is a major independent risk factor for CHD and stroke (1, 2, 76). Optimal blood pressure is defined as systolic blood pressure 120 mm Hg and diastolic blood pressure as 80 mm Hg (76).
Although 20-40% of the variation in blood pressure in a population may be due to genetic variations (76), lifestyle modifications such as dietary changes, are important options for reducing the risk (76). Reduced energy and sodium intake and a Mediterranean style or DASH diet are dietary options for reducing blood pressure (1, 76, 77). The replacement of carbohydrates with protein (half from plant sources) and MUFA may further lower blood pressure (78).

**Nutrients and CVD risk factors**

Early treatment in order to reduce LDL-C, either through diet or statins, is important for stopping the development of CVD (79). Dietary approaches to reducing LDL-C and increasing HDL-C levels are crucial for reducing the risk of CVD (1, 55). Several dietary options can improve the blood lipid profile and substantially contribute to reducing the inflammatory process.

**Fat quality and CVD risk factors**

In order to improve CVD risk, SFA intake needs to be reduced, however, the risk reduction depends on what replaces the SFA (80). Replacing SFA with unsaturated vegetable fats lowers LDL-C (81, 82), however, substituting MUFA or PUFA for SFA reduces LDL-C, but does not affect HDL-C (82). LDL-C decreases when SFA and trans-fatty acids are replaced by MUFA and or PUFA (82). The intake of trans-fatty acids, compared to SFA, increases LDL-C and decreases HDL-C (82). SFA myristic acid 14:0 and SFA palmitic acid 16:0 increase both LDL-C and HDL-C (82), whereas, eicospentaenoic acid (EPA) and docosahexaenoic acid (DHA) lower serum triglycerides (82). There is a little benefit from the HDL-C increase and LDL-C decrease when MUFA and PUFA replace carbohydrates (82), whereas, replacing SFA and trans fatty acids with PUFA and/or MUFA is beneficial for insulin sensitivity and is likely to reduce the risk of type II diabetes (83). To influence LDL-C/HDL-C ratio, changing the proportions of dietary fatty acids may be more important than restricting the total fat or SFA intake (84). PUFA linoleic acid improves insulin sensitivity, but the long-chain n-3 FA does not appear to improve insulin sensitivity or glucose metabolism (83).

When unsaturated fats replace SFAs and trans-fatty acids, the risk of CDH (85) and CVD (86) decrease, and replacing SFA with PUFA rather than MUFA or carbohydrate prevents CHD (87, 88).

Traditionally, the major sources of MUFA in Scandinavia (northern Europe) and United States are dairy products, meat, and partially hydrogenated oils (trans fatty acids) (89, 90).
Dietary cholesterol

Dietary cholesterol uptake from diet is strictly regulated, when dietary cholesterol intake increases the endogenously produced cholesterol decreases (91). In Sweden, diet contributes 263±123 mg cholesterol in women and 320±145 mg per day in men (90). In the Dietary guidelines for American (92) an intake of 300 mg or less cholesterol is recommended, whereas, NNR 2004 does not set an upper level for dietary cholesterol (93).

Carbohydrate quality and CVD risk factors

Traditionally, carbohydrates are classified as simple (mono- and disaccharides), or complex (oligosaccharides and polysaccharides (starch and dietary fibre)) in relation to their chemical structure. However, the nature of dietary carbohydrate appears to be an important determinant of health outcomes rather than the proportion of total energy derived from carbohydrate intake (94). Several characteristics are relevant for determining the effect of carbohydrate rich foods on CVD risk factors. Whole grain rather than refined grain and the structure of carbohydrate rich foods (intact, milled) have an impact on the glycaemic index or glycaemic load (95). In addition, the type, soluble or insoluble (96) and source of dietary fibre, the source of cereal dietary fibre (97), and the amount of dietary fibre (98) have an impact on CVD risk factors (99).

In the reduction of SFA intake, the improvements in CVD risk factors and diseases depend on what replaces the SFA (80). Triglycerides increase if SFA is replaced with carbohydrates (100, 101). When SFA is substituted with carbohydrates, the CHD risk decreases, whereas, if carbohydrates replace unsaturated fat, the risk increases (85). If carbohydrates replace SFA the benefits on myocardial infarction (MI) depends on the quality of the carbohydrates. Jakobsen et. al. (95) showed a non-significant inverse association between the substitution of carbohydrates with low-GI values for SFA. The risk of MI (hazard ratio (HR) per 5% increment of energy intake from carbohydrates is 0.8895% (CI: 0.72, 1.07). In contrast, there is a positive association between the substitution of carbohydrates with high-GI values for SFA and the risk of MI (HR: 1.33; 95% CI: 1.08, 1.64) (95). There is no association of carbohydrates with medium-GI values (HR: 0.98; 95% CI: 0.80, 1.21) and no effect by gender (95).

Whole grain

It is important to distinguish between whole grain and whole grain foods (102). Whole grain refers to the whole grain itself (as raw material) and whole grain foods are foods containing a defined amount of whole grain
There is no common definition for whole grain foods, including whole grain flour across countries (103).

A number of observational studies (104-108) have consistently suggested a lower risk of CVD and all-cause mortality with a high whole grain intake. However, short-term randomised controlled trials (RCT) have failed to show effects on CVD risk factors of whole grain foods from, for example, wheat when added to habitual diet (109, 110). Results from another RCT (111) indicated that none of three portions of whole grain foods, either wheat or oat based, substituted for refined grains reduce CVD risk through lipoprotein altering, but can reduce CVD risk in middle-aged people through blood pressure lowering mechanisms (112).

Consumption of foods rich in cereal fibre or mixtures of whole grains and bran is modestly associated with a reduced risk of obesity, type II diabetes, and CVD (113). The source of whole grain i.e. rye, oat, wheat or barley also has an impact on CVD risk factors (99, 104, 114). In a six week intervention trial (n=63), rye bread intake (70% of flour was whole grain rye) improved the oxidation resistance of LDL-C (115). Whole grain rye also has an effect on satiety (116).

Dietary fibre
LDL-C lowering effects may be achieved by increasing dietary fibre intake of water-soluble β-glucan rich cereals such as oats and barley (96-98, 117, 118). The major water-soluble fibre types, β-glucan, pectin psyllium, and guar gum effectively lower serum LDL-C concentrations, without affecting HDL-C or triglycerides concentrations (96). After intake of oats, a reduction of between 10% and 26% in total cholesterol is reported: the reduction is mainly in LDL-C fractions (96). The physiochemical properties of oat β-glucan should be considered when assessing the cholesterol-lowering effect of oat-products as the effect may depend on viscosity (119). The European Food Safety Authority (EFSA) panel has conclude there is a cause and effect relationship between oat and barley β-glucan and the lowering of blood LDL-C (120, 121).

Nordic foods and CVD risk factors
Fat and oil
In the Mediterranean diet olive oil is the main source of dietary fat (25, 26). In the Nordic area rapeseed oil is the corresponding oil. Compared to olive oil, rapeseed oil is high in PUFA, mainly 18:2n-6 (linoleic acid) and 18:3n-3 (α linolenic acid), and lower in MUFA and in SFA (Table 1).
Rapeseed oil has a similar effect on lipoprotein concentration and glucose tolerance as olive oil in hyperlipidaemic subjects (122) and can replace oils and fats high in PUFA e.g. sunflower oil in a lipid-lowering diet (123). In a dietary intervention study (124), a diet including rapeseed oil rich in both MUFA and PUFA (α-linolenic acid (ALA)) 18:3n-3) was compared to an olive oil diet rich in MUFA and low in ALA. Although systolic blood pressure, total cholesterol, and LDL-C, and insulin levels decreased in both the rapeseed oil and olive oil groups (P<0.05), after six months, the decrease in diastolic blood pressure with rapeseed oil was greater than with the olive oil diet (124). However, EFSA conclude that a causal relationship between the consumption of either rapeseed oil or olive oil and the lowering of blood LDL-C concentration and normal LDL-C and HDL-C levels has not been established beyond what could be expected from fatty acid composition of rapeseed oil or olive oil (125, 126).

Table 1. Fatty acid composition of rapeseed and olive oil1

<table>
<thead>
<tr>
<th>Fat total</th>
<th>SFA</th>
<th>MUFA</th>
<th>PUFA</th>
<th>16:0</th>
<th>18:0</th>
<th>16:1</th>
<th>18:1</th>
<th>18:2n-6</th>
<th>18:3n-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapeseed</td>
<td>100</td>
<td>7.1</td>
<td>61.3</td>
<td>26.9</td>
<td>4.3</td>
<td>1.6</td>
<td>0.2</td>
<td>59.3</td>
<td>18.8</td>
</tr>
<tr>
<td>Olive</td>
<td>100</td>
<td>14.3</td>
<td>72.6</td>
<td>8.8</td>
<td>11.1</td>
<td>2.7</td>
<td>1.2</td>
<td>70.7</td>
<td>8.1</td>
</tr>
</tbody>
</table>

1From: The National Food Administration's food database, version 05/08/2013.

Dairy products

A systematic literature review, conducted to evaluate common food-based dietary guidelines (127) conclude there is suggestive evidence (low grade) for dairy consumption to be associated with decreased risk of type II diabetes. However, there is no consistent evidence indicating dairy consumption is associated with an increased risk of CVD/CHD (127). In a prospective cohort study (128), milk fat were associated with increased risk of CVD, whereas, intake of fermented milk products may reduce the risk (129). High intake of cheese in woman, but not in men was related to lower incidence of CVD (129).

Fish

Fish is generally low in total fat, and cold-water fatty fish contributes the long-chain fatty acids EPA and DHA, which lower serum triglycerides in a dose-response relationship (130). EPA+DHA in doses of 0.7 and 1.8 gram reduce triglyceride levels by 8% and 11%. Herring, Baltic Herring, mackerel, salmon, and a selection of white fish contribute EPA and DHA. A modest consumption of fish, e.g. 1-2 servings per week, substantially reduces the risk of CHD death (131).
Nuts
There is a link between the consumption of nuts and reduced risk of CHD (24). The major fatty acid in hazelnuts and almond is oleic acid (18:1) (132). In 2003, the U.S. Food and Drug Administration approved a claim for nuts: “Scientific evidence suggests but does not prove that eating 1.5 ounces (42 g) per day of most nuts (including hazelnuts and almonds) as a part of a diet low in SFA and cholesterol may reduce the risk of heart disease” (133). Although several mechanisms for the decrease in LDL-C due to consumption of almonds have been suggested, the mechanism by which nuts reduces the risk of CHD cannot be attributed to a single component (133). Almonds contribute to a favourable fatty acid profile in the diet when MUFA and PUFA (132) replace foods high in SFA. The main bioactive compound in nuts associated with LDL-C reduction is phytosterol (134). Phytosterol competes with dietary cholesterol and bile acid uptake and interferes with cholesterol and bile acid absorption and reabsorption (132, 134), leading to LDL-C reduction.

Cereals
Cereals typical of the Nordic area are mainly rye, oats and barley. Cereals improve the carbohydrate quality of the diet as they include whole grain, dietary fibre, soluble dietary fibre (β-glucan), vitamins (folate and tocopherol), minerals (magnesium), and bioactive components (phytoestrogens, and plant sterols) (99, 135, 136). Nordic cereal products that improve carbohydrate quality are soft and hard bread rich in whole grain from rye and wheat, hot breakfast cereals (porridge) based on whole grain oat, rye, and barley), cold breakfast cereals based on whole grain and pearled oat and barley, and whole grain pasta as lunch-cereals. Cereals are usually part of breakfast and skipping breakfast affects the risk factors for CVD (137, 138)

Seeds
Linseeds (flax seeds) and psyllium provide soluble dietary fibre and lignans and have beneficial effects on blood lipids (139). Sunflower seeds contribute unsaturated fatty acids.

Fruits, berries, vegetables, root vegetables, potatoes and legume
A high intake of vegetable foods is recommended for adults who would benefit from LDL-C and decreasing blood pressure (1). Intake of fruit and vegetables is inversely associated with total mortality and coronary artery disease (107). There is a strong link between the protective effects of vegetables and reduced risk of CHD (24). The consumption of legumes more than 4 times a
week decrease risk of CHD by 11% (140), as these food groups contribute with dietary fibre, vegetable protein, vitamins, minerals and bioactive compounds to the diet.

Salt

There is evidence for a relation between salt (sodium chloride) intake and blood pressure. With an increased intake of sodium as sodium chloride, there is a dose dependent rise in blood pressure (141), although there is a substantial individual variation in sodium intake and blood pressure response (141). Chloride ion may also have a role in high blood pressure (142).

The major dietary sources of sodium are salt added during the processing of food (70-75%), salt added during cooking and at the table (10-15%) and sodium in unprocessed foods 10-15% (141). The mean daily sodium intake in Europe ranges from 3-5 gram per day (corresponding to about 8-11 g salt) (141). The intake of salt should be limited to about 5-6 g per day (1), which corresponds to 1.5 g sodium. The 2010 Dietary Guidelines for Americans calls for no more than 1.5 g sodium per day for African-Americans, people >51 years of age, and people with hypertension, diabetes mellitus, or chronic kidney disease, and no more than 2.3 g sodium per day for all others (143, 144).

Coffee

Coffee is an everyday habit in Scandinavia and the brewing method is important for the physiological effects. Coffee beans contain a terpenoid lipid, cafestol, which is one of the most cholesterol raising properties in the diet (10). The amount of cafestol in ready to drink coffee is dependent on the brewing method. One cup of traditionally brewed coffee (with filter), contains no cafestol, whereas, one cup of espresso contains 1 mg of cafestol and traditionally boiled Swedish coffee contains 7.2 mg cafestol.

Studies with emphasis on the Nordic diet

Recent studies show possibilities to use Nordic foods to create healthier Nordic diets e.g. to reduce cardiovascular risk. In the controlled long-term SYSDIET intervention study (18-24 weeks), a healthy Nordic diet was used to clarify whether Nordic alternative foods could have beneficial effects on CVD risk factors. Uusitupa et. al. (145) reported that the Nordic diet caused moderate improvements in lipid profile in weight-stable conditions in subjects with the metabolic syndrome. They also found that a healthy Nordic diet had a beneficial effect on the inflammatory marker IL1 receptor antagonist compared to a control diet (145)
From a 12 week, parallel design, dietary intervention trial (n=131) (The Sysdimet study) Lankinen et. al. reported that the combined effect of fatty fish, bilberries and whole grain products improve glucose metabolism and alter the lipidomic profile (146). The combination may also improve endothelial function and inflammation in overweight and obese individuals at high risk of developing diabetes (147). They also concluded that such a diet may have beneficial effects to prevent type II diabetes in high risk persons (146).

OPUS (Optimal well-being, development and health for Danish children through a healthy New Nordic Diet) is a 5-year multidisciplinary research project assessing the impact of serving school meals based on the New Nordic Diet (148, 149). The guidelines for OPUS are described in relation to the key principles; health, gastronomic potential, Nordic identity, and sustainability where the overall guidelines are; more calories from plant foods and fewer from meat, more foods from sea and lake, and from the wild countryside (150). As a part of OPUS, a 6 month randomised controlled trial, the health effects of the New Nordic Diet was investigated and show weight loss and blood pressure reduction in middle-aged, centrally obese subjects (151).

Nordic food Index

A healthy Nordic food index consisting of traditionally Nordic food items with expected health-promoting effects; i.e. fish, cabbage, rye bread, oatmeal, apples and pears, and root vegetables was extracted from the observational Danish prospective study - The Diet, Cancer and Health study. This index was shown to be associated with mortality (152): a 1-point higher index score was associated with a significant lower mortality rate for both men and women. Whole grain rye bread and cabbage could be considered among the healthiest food items within their respective food groups. Drake et. al. concluded that a recent developed tool, a Diet quality index, is useful to assess adherence to recommendations in Sweden (SNR) 2005 (153).

Foods

A systematic literature review was conducted to evaluate common food-based dietary guidelines (127). The scientific evidence on five key food groups; i.e. potatoes, berries, whole grain, milk and milk products and red meat and the relation to risk of diseases or intermediate biomarkers of these diseases was recently systematically reviewed. There was probable (moderate) evidence for whole grains to be associated with lower risk of type II diabetes and CVD. There was a suggestive evidence (low grade) for dairy consumption to be associated with decreased risk of type II diabetes. There was not enough evidence to draw any conclusions regarding the health impact of potatoes and berries based on present systematic review and there
were too few studies to draw any conclusions regarding red meat consumption and CVD risk (127).

Replacement of foods rich in SFA e.g. replacing dairy fat with rapeseed oil causes a rapid and clinically relevant improvement in serum lipoprotein profile, which includes lowering of triglycerides in hyperlipidaemic individuals (154).

Based on prospective cohort studies (i.e. epidemiological studies) recommendations in Scandinavia is four portions of whole grain per day, corresponding to 75 gram whole grain (raw material) per 10 MJ (155). According to Swedish National Food Agency women are recommended to consume about 70 gram whole grain (raw material) per day and men 90 gram per day (156). Data from one 24-h dietary recall, collected in 1995-2000 in the prospective Scandinavian cohort HELGA, was used to describe both the quantitative and qualitative intake of whole grain in Norway, Sweden and Denmark respectively (157). Kyrö et. al. suggests, on the basis of the HELGA cohort that between 16% and 35% of the population meet the recommendation of whole grain intake of 75 gram per 10 MJ. Qualitatively, rye contributed to the whole grain intake in Denmark, whereas in Norway wheat, and in Sweden rye and wheat did (157).

Alkylresorcinol is suggested to be a biomarker for whole grain intake (158), and a table has been established to be used to estimate the intake of dietary alkylresorcinol (159).

The draft 5th edition of the Nordic Nutrition Recommendations (NNR 2012) (160) sets the whole diet in focus while also setting recommended intake (RI) for macro- and micronutrients. Compared to NNR 2004 (93), RI for carbohydrate, fat and protein has a broader range, quality of fat and carbohydrates are emphasized, and RI for vitamin D and selenium has been increased (160).

Environment

Recently the role of food for sustainability has become an issue. For a new healthier and more environmental friendly Nordic diet, Bere and Brugs (161) suggest in consistency with the definition of a sustainable diet (162, 163), a focus on six ingredients: native berries, cabbage, native fish and other seafood, wild (and Pasteur-fed) land based animals, rapeseed oil and oat, barley and rye.
Hypothesis, aims, and outcomes

The hypothesis of this thesis was that a healthy diet based on foods originating from the Nordic countries improves cardiometabolic risk factors.

Aims

The overall aims were to determine whether a healthy Nordic diet (ND) based on foods originating from the Nordic countries, and/or a prudent breakfast (PB) alone affected CVD risk factors in healthy, mildly hypercholesterolaemic men and women. Furthermore, to describe the food and nutrient composition of a healthy Nordic diet. These aims were investigated through two randomised controlled intervention trials.

The specific aims were:

I. To investigate the effects of a healthy ND, eaten ad libitum, on CVD risk factors in healthy, mildly hypercholesterolaemic subjects (Paper I).

II. To describe and compare the food and nutrient composition of a healthy ND in relation to the intake of a Swedish reference population, and to the RI and AR, as described by NNR 2004 (Paper II).

III. To investigate the effects of a healthy ND on the FA composition of serum cholesterol esters (CE) (CE-FA) and to investigate associations between the changes in serum CE-FA composition during the intervention and changes in the blood lipoproteins (Paper III).

IV. To investigate whether the intake of a PB alone can reduce LDL-C levels and other cardiometabolic risk factors and improve fasting or postprandial glucose metabolism in healthy hypercholesterolaemic individuals (Paper IV).
Outcomes

Paper I
The primary outcome was the change in LDL-C after a healthy ND. Secondary outcome measures were changes in total cholesterol, HDL-C, apoA1, apoB, triglycerides, glucose and insulin sensitivity, CRP, weight, BMI, and blood pressure.

Paper II
The primary outcome was the actual consumption of foods and the nutrient intake in the ND.

Paper III
The primary outcome was the change in fatty acid (FA) composition in serum cholesterol esters (CE) (CE-FA) after ad libitum intake of healthy Nordic foods. Secondary outcome measures were associations between CE-FA and blood lipoproteins of relevance for the risk of CVD.

Paper IV
The primary outcome was the change in LDL-C after a PB. Secondary outcome measures were changes in total cholesterol, LDL-C, HDL-C, apoA1, apoB, triglycerides, glucose and insulin, high-sensitive CRP, TNF-R2, weight, BMI, SAD, and blood pressure.
Subjects

Papers I, II and III are based on subjects living in Bollnäs, Sweden. Paper IV is based on the second trial and subjects living in Uppsala, Sweden. No compensation was paid to the subjects and no one knew that the foods during the study were free of charge on participation in the study.

Subjects (Papers I, II, III)

Subjects living in the Swedish town Bollnäs were recruited through advertisements in the local newspaper during December 2007. Inclusion criteria were healthy (as assessed by a physician) Caucasian men and women between 25 and 65 years of age, plasma LDL-C $\geq 3.5$ mmol L$^{-1}$, body mass index $\geq 20$ and $\leq 31$ kg/m$^2$ and haemoglobin concentration $\geq 120$ g L$^{-1}$ for women and $\geq 130$ g L$^{-1}$ for men. The exclusion criteria were the use of lipid-lowering drugs for 2 months prior to screening and throughout the study, blood pressure $>145/85$ mmHg, plasma triglyceride concentrations $>4.5$ mmol L$^{-1}$, use of products or supplements fortified with plant sterols, n-3, n-6 or n-9 fatty acids intakes within 3 weeks before the baseline visit, allergy to certain foods, weight-loss diets or drugs, special diets (e.g. vegan and gluten free), and pregnancy or lactation. After screening of 212 subjects, 88 were eligible for the study and they visited the study clinic (Figure 1). The intervention was finalised in May 2008.
Figure 1. Flow chart of the phases of the RCT, the NORDIET study. Subjects were randomised to one of two groups, either control diet or to a Nordic diet (ND) group. After the end of the intervention, a subgroup of 11 subjects in the intervention group received the Nordic diet for an additional four weeks (Papers I, II, III).
Subjects (Paper IV)

Subjects were recruited by advertisements in local newspapers in Uppsala, Sweden, and the study was conducted between August 2009 and January 2010. The inclusion criteria were eating breakfast on a regular basis, 25-67 years of age, plasma LDL-C ≥3.0 mmol/L, body mass index (BMI) ≥25 and ≤31 kg/m, and haemoglobin concentration of ≥120 g/L for women and ≥130 g/L for men. The exclusion criteria were the use of lipid-lowering drugs, high blood pressure (defined as blood pressure >155/95 mmHg), regular use of dietary supplements fortified with plant sterols or PUFA (e.g., n-3), slimming or medically prescribed diet/medication, special diet (e.g., vegan or gluten-free), and aversion to eating porridge or herring or mackerel for breakfast for 12 weeks. After inclusion, 79 overweight and mildly hypercholesterolaemic but otherwise healthy men and women were included in the study and they visited the study clinic (Figure 2).

![Figure 2. Flow chart of the phases of the RCT, “Role of a prudent breakfast in improving cardiometabolic risk factors in subjects with hypercholesterolemia: a randomized controlled trial”. Subjects were randomised to one of two groups, either control breakfast or to a prudent breakfast (PB) group, (Paper IV).](image-url)
Methods

Design (Papers I, II, III)

The study was conducted in accordance with CONSORT guidelines (164). The protocol for this trial and supporting CONSORT checklist are available as supporting information. The study was a parallel, randomised, controlled, intervention study in free-living subjects (Figure 3) who were randomly assigned to a control diet (n=42) or an ad libitum healthy Nordic diet (n=44) for 6 weeks. Biochemical, anthropometric and dietary assessments were performed at baseline and after 6 weeks. (Figure 3 and Figure 4).

Extended intervention (Paper I)

In the ND group, the first randomly assigned subjects (n=11) entering the trial were offered the opportunity to continue the ND for an additional 4 weeks; that is, an extended intervention of 10 weeks was conducted in this subgroup (Figure 3).

![Figure 3. Study design for the RCT, the NORDIET study (Papers I, II, III).](image-url)
Figure 4. Dietary assessments in the RCT, the NORDIET study (Papers I, II, III). All subjects fulfilling the inclusion criteria completed a dietary history interview with trained dieticians. The first dietary history interview preceded the control diet and Nordic diet (ND) groups baseline visits. At six weeks, a second diet history interview was completed for the control diet group (n=42) to detect any changes from the first interview. Compliance to the ND in the ND group (n=44) at 6 weeks and for the extended intervention (n=11) at 10 weeks, was evaluated from daily study checklists (Figure 6).

Design (Paper IV)

The study was conducted in accordance with CONSORT guidelines (164). For the protocol for this trial the supporting CONSORT checklist, see Paper IV later in this thesis.

The study was a parallel, randomised, controlled, intervention study in free-living subjects (Figure 5) who were randomly assigned to one of two groups for 12 weeks: control breakfast or PB, e.g. PB is the breakfast included in the NORDIET study (Paper I). The sole intervention in this study was the instruction to eat a breakfast composed of healthy Nordic foods without other dietary changes. Biochemical, anthropometric and dietary assessments were performed at baseline and after 12 weeks (Figure 5).
Biochemical assessments (Papers I, II, III)

Blood samples were drawn from an antecubital vein through Vacutainer tubes. The samples were collected and handled according to the hospital routines of Bollnäs and Uppsala hospitals.

Blood lipids

Triglycerides, total cholesterol and HDL-C plasma concentrations were measured by enzymatic peroxidase reaction, with Cobas_6000 (c501module) Roche Diagnostics, Mannheim, Germany. Plasma LDL-C was calculated by Friedewalds formula (165), and apoA1 and apoB were measured by an immunoturbidometric method (166) at the Centre for Laboratory Medicine at Uppsala University Hospital, Uppsala, Sweden.

Glucose

Glucose was measured by UV test, an enzymatic hexokinase reference method, developed by Roche Diagnostics, Mannheim, Germany, with the Cobas_6000 analyzer.

Plasma insulin

Plasma insulin was measured by an enzyme-linked immunoassay kit (Mercodia AB, Uppsala, Sweden).
HOMA-IR
Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated as plasma insulin times glucose divided by 22.5 (167).

C-reactive protein
CRP was measured through immunological particle enhanced reaction, developed by Roche Diagnostics, Mannheim, Germany, with the Cobas 6000 analyzer.

Serum cholesterol ester fatty acids (Paper III)
CE-FA compositions in serum were measured at baseline and after 6 weeks in all subjects, and were determined by gas-liquid chromatography as previously described (168). The proportions of the separate CE-FAs were expressed as the percentage of all CE-FA analysed.

Stearoyl-CoA desaturase-1 (Paper III)
The activity of stearoyl-CoA desaturase-1 (SCD-1) was estimated by calculating the ratio between CE-16:1 and CE-16:0 (169).

Anthropometric assessments (Papers I, II, III)
Body weight, height and BMI
Subjects visited the clinic in the morning after a 12-h fast. Body weight was measured (kg) on a digital scale in light clothing without shoes. Height (cm) was measured without shoes. BMI was calculated as weight (kg) divided by height (m) squared.

Blood pressure (Paper I)
Blood pressure was measured manually with cuff and stethoscope while the subjects were in a sitting position on the right arm after a 5-min rest. Two measurements were taken with a 2-min interval, and the average value was calculated.
Biochemical assessment (Paper IV)

Blood samples were drawn from an antecubital vein with vacutainer tubes. The samples were treated according to sample treatment instructions provided by the Centre for Laboratory Medicine, Clinical Chemistry, at Uppsala University Hospital, where analyses were performed according to routine practice.

Blood lipids and glucose
Plasma LDL-C, total cholesterol, HDL-C, triglycerides, and glucose were measured by enzymatic reactions.

Oral glucose tolerance test
An oral glucose tolerance test (OGTT) was performed, e.g. 75 g glucose dissolved in 350 ml water. Plasma glucose and serum insulin were measured at 0, 30, 60, 90, and 120 minutes.

Area under the curve
The area under the curve (AUC) for insulin and glucose concentrations during the OGTT was calculated according to the trapezoid rule.

Serum insulin
Serum insulin was measured by a sandwich immunosorbent assay on a Cobas E601 immunology analyser from Roche Diagnostics, Mannheim, Germany.

HOMA-IR
Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) was calculated as plasma insulin times glucose divided by 22.5 (167).

CRP, apoA1 and apoB
CRP, apoA1 and apoB were measured by immunoturbidimetric assays and an Architect C 8000 instrument from Abbott (Abbott Park, Chicago, IL, USA).
TNF-R2
Soluble TNF-R2 (or Type A, type α, or 75 kDa) was measured in plasma by commercial sandwich ELISA (DY726, R&D Systems, Minneapolis, MN, USA). The concentrations in the samples were determined by comparing the optical density of the sample with the standard curve. The assay had a total coefficient of variation (CV) of approximately 7% calibrated against highly purified recombinant human peptides.

Anthropometric assessment (Paper IV)
Body weight, height and BMI
The subjects visited the clinic in the morning after a 12-h fast. Body weight was measured (kg) on a digital scale with subjects wearing light clothing and no shoes. Height was measured to the nearest 0.5 cm. BMI was calculated as weight (kg) divided by height (m) squared.

Sagittal abdominal diameter
SAD, a valid marker of visceral fat, (170) was measured to the nearest 0.1 cm with a ruler and water level at the level of the iliac crest and after normal expiration. The subject lying on a firm examination table in a supine position with bent legs (171).

Blood pressure (Paper IV)
Blood pressure was measured oscillometrically (Omron M4-1, Omron Healthcare Europe B.V, Hofddorp, The Netherlands) on the right arm while subjects were in a sitting position after a resting period of 3-5 min. blood pressure was calculated as the average of three measurements.

Dietary assessments
At baseline - Diet history (Papers I, II, III)
All subjects fulfilling inclusion criteria completed a diet history interview performed by trained dieticians. The first interview preceded the control diet and ND groups baseline visits (Figure 4). During the 1- to 2-h interview, subjects were asked about their habitual food intake with the intention of assessing habitual dietary intake for the preceding month. Subjects described average portion sizes of food items in terms of household measures, standard
weights of food items, and validated food portion photographs (172) of known weights. The diet history interview was chosen as the method has been shown to record average energy intake closer to the energy expenditure, compared with other methods (173).

At six weeks – Diet History and a Daily study checklist (Papers I, II, III)

At six weeks, the control diet group had a second diet history interview to determine any possible changes from the first diet history interview at baseline (Figure 4). In the ND group compliance with the ND was evaluated from the daily study checklists (Figure 6) (Paper I). The daily study checklist described the main meals for each day (i.e. which breakfast should be eaten, amount and type of snack, amount and type of bread and fruit). For every item consumed, subjects ticked the daily study checklist. Subjects were also asked to comment and describe any deviation from the menu. For one meal a week, except the week before visit at 6 weeks, the subjects had the opportunity to eat whatever they wanted: on the condition that they registered this in the daily study checklist. The daily study checklist was analysed at 6 weeks to estimate actual food and nutrient intake and to assess compliance with the intervention diet during the 6 weeks on ND.

At baseline and after 12 weeks (Paper IV)

As the study was not restricted to breakfast but also included a 3-day nutrient intake from the whole diet, both control breakfast and PB groups completed a 3-day food record in order to obtain data on the nutrient content of the whole diet at both baseline and after 12 weeks (Figure 6). The food record was a pre-coded menu book (172, 174) that has been evaluated by the National Food Administration in Sweden. It was supplemented with whole-grain and high-fibre products to suit the present study. To monitor compliance in the PB group, the subjects received a study diary that included a list and amounts of foods to be included in each PB. The subjects were asked to fill in the date, mark the foods they consumed, and record any possible failure to consume the food items in the PB.

Presentation of nutrient intake data (Papers I, II, III, IV)

In Paper I, the nutrient intake is presented to evaluate the difference in nutrient intake from baseline to 6 weeks within groups.

In Paper II, nutrient intake is presented and compared to RI and average requirement (AR). RI is defined as AR of a population plus a safety margin of 2 standard deviations (SD). AR is defined as the lowest long-term intake
level of a nutrient that will maintain a defined level of nutritional status in an individual. In the NNR 2004 (93), the AR value is used to define the level of a nutrient intake that is sufficient to cover the requirement for half of a defined group of individuals provided there is a normal distribution of the requirement (93). RI is used for planning diets and AR is appropriate when evaluating the nutritional intake of a group of people from dietary assessments. In Paper III, nutrient intake data, e.g. intake of dietary fatty acids, is used to investigate changes in corresponding serum CE-FA composition. In Paper IV, nutrient intake data is used to present the nutrient intake of the breakfast alone and of the whole day nutrient intake.

Dietist XP version 3.0, a computer program based on the Swedish National Food Administration database (2005-02-01), was used to plan the ND and to calculate the nutrient content of the ND (Papers I, II, III) and of the breakfast and the whole diet for control and PB groups (Paper IV). Dietist XP was supplemented with whole grain foods and sources of dietary fibre, i.e. fruit fibre, cereal fibre, vegetable fibre and legume fibre, and sources of cereal fibre i.e. oat, rye, barley, wheat.
Figure 6. The daily study checklist described the main meals for each day *i.e.* which breakfast should be eaten including the amount and type of snack, the amount and type of bread and fruit, and a suggested beverage. For every item consumed, subjects ticked the daily study checklist, and commented and described any deviation from the menu. The original daily study checklist is here presented in Swedish (Papers I, II, III).
Intervention (Papers I, II, III)

Planning the intervention diet

There were several phases in the planning of ND. First, the nutrient profile for the study was planned (Table 2). Second, a definition of foods to be included in ND was made. Third, the profile of food groups for the study was defined (Table 3). Fourth, a 21 day rotation menu was created, one example of a daily menu is presented (Figure 7). Fifth, recipes based on the nutrient and food profile were created. Sixth, recipes were tested. Seventh, the 21 daily menus, including new recipes, were nutritional calculated to fit into the nutrient profile of ND.

Nutrient profile

The nutrient profile for the study diet (Table 2) was based on daily RI, according to NNR 2004 (93), and inspired by earlier reports (25, 31, 33, 36, 43, 96, 118). The emphasis was on the quality of fat and carbohydrate, where the amount, quality and source of dietary fibre, refined cereals or whole grain cereals and the theory of glycaemic index was considered. The ND was calculated as isocaloric on a group level through validated formulas (93). The ND was given *ad libitum*, i.e. all subjects were provided with the same number of calories, but were at liberty to omit foods or request more to match individual energy needs.

Table 2. Nutrient profile of planned Nordic Diet

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal/day)</td>
<td>2200</td>
</tr>
<tr>
<td>Total protein (% of energy)</td>
<td>10–20</td>
</tr>
<tr>
<td>Carbohydrates (% of energy)</td>
<td>45–60</td>
</tr>
<tr>
<td>Dietary fibre (g/MJ)</td>
<td>&gt;3</td>
</tr>
<tr>
<td>β-glucan (g/day)</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Total fat (% of energy)</td>
<td>25–35</td>
</tr>
<tr>
<td>Saturated fatty acids (% of energy)</td>
<td>&lt;8</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids (% of energy)</td>
<td>5–10</td>
</tr>
<tr>
<td>Sodium (mg/day)</td>
<td>&lt;2161</td>
</tr>
</tbody>
</table>

Selection of food for the study diet

The definition for foods to be included in the NORDIET study was “*possible to cultivate, harvest and breed in the Nordic countries*” without the request that the foods actually had been cultivated, harvested or bred in the Nordic countries. When selecting foods for the NORDIET study the goal was that the intake of at least 80 % of the number of foods included should be reached. Foods included in ND should also be possible to obtain in the mar-
ket during the time of the study, as well as the habitual use of food items in the Nordic countries was considered. The selection of foods was based on nutritional value of the food, such as low in SFA, trans-fatty acids and sodium and high in MUFA and PUFA, dietary fibre, and whole grain (Table 3).

Important food items included in the food profile for the ND (Table 3) were, rapeseed oil rich in oleic, linoleic and α-linolenic acids (122, 154). Fish in general, especially fatty fish, was a natural ingredient in ND, and low-fat dairy products (milk and yoghurt and cheese for cooking (6, 10, 24), whole grain cereals (36, 104), and specific whole grain cereals based on oat and barley (118, 119) and rye (114, 152) were recommended. Processed β-glucan rich foods included in the ND and PB were analysed to secure intact molecular weight (175, 176).

However, some food items commonly regarded as traditional Nordic foods, such as butter and certain types of meat and hard cheese (could be used for cooking), were not included for general nutritional and metabolic reasons, e.g., LDL-C rising effects. As the short-term study did not include all seasons, it was not possible to include all types of foods that might otherwise have been included in a ND. As the study was conducted during wintertime some foods which might not be defined as possible to grow in the Nordic countries were included in the study.
Table 3. Food profile of ND. Description of food items, size of servings, and the contribution of the main nutrients within each food group in the planned ND in the NORDIET study. The nutrient contribution is presented in the order of why they were selected for the NORDIET study.

<table>
<thead>
<tr>
<th>Food group</th>
<th>Food items</th>
<th>Serving sizes</th>
<th>Nutrient contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat and oil</td>
<td>For bread, a vegetable low fat spread (38% fat) with no plant sterols added, and for cooking, a vegetable liquid margarine (80% fat): both based on vegetable oil (sunflower, linseed, and rapeseed oil). Rapeseed oil was used for dressing</td>
<td>5 gram low fat spread per slice of bread. 0.5 dl rapeseed oil for dressing per day</td>
<td>Fat quality: low in SFA and high in plant derived n-3 fatty acids, PUFA (linoleic acid, 18:2n-6, α-linolenic acid, 18:3n-3) and MUFA (oleic acid 18:1)</td>
</tr>
<tr>
<td>Dairy products</td>
<td>Low-fat drinking milk or fermented milk (0.5%). Cheese (&lt;17%) ≤ 5 dl per day. Cheese could be used for cooking as long as the total fat in the diet did not differ from RI</td>
<td>Minerals: calcium, magnesium. Vitamin: vitamin D</td>
<td></td>
</tr>
<tr>
<td>Fish</td>
<td>Herring, Baltic Herring, mackerel, salmon, and a selection of white fish</td>
<td>3-5 servings per week</td>
<td>Fat quality: long-chain n-3 fatty acids. Minerals: selenium, magnesium. Vitamin: vitamin D</td>
</tr>
<tr>
<td>Nuts</td>
<td>Mainly almonds</td>
<td>15 gram per day</td>
<td>Fat quality: low in SFA, high in MUFA and PUFA linoleic acid (18:2n-6)</td>
</tr>
<tr>
<td>Cereals and seeds</td>
<td>Cereals include soft and hard bread rich in whole grain from rye and wheat (50% whole grain as dry matter) and low in sodium, i.e. &lt;1% NaCl. Oat bran rusk were Beta-glucan rich food items to</td>
<td>Bread: 4-6 slices whole grain bread (50% whole grain as dry matter) per day.</td>
<td>Carbohydrate quality: cereals contributed the whole grain nutrient spectra, dietary fibre, insoluble and soluble dietary fibre (β-</td>
</tr>
</tbody>
</table>
recommended for snacks. For cold breakfast cereals, muesli and extruded oat bran were advocated, as was hot breakfast cereals such as porridge made of oat bran, oatmeal, or barley flakes.

Oat bran porridge was to be consumed for breakfast as a standard. As an option, when pearled oat or barley was included for lunch, any of the other breakfast alternatives could be consumed. Lunch and dinner cereals such as pearled barley and oat (Mathavre, Matkorn) were used instead of traditional rice. Whole grain pasta (50% whole grain per dry matter) or whole grain β-glucan enriched pasta were included. Seeds, such as linseed, psyllium, and sunflower seeds were included for breakfast.

<table>
<thead>
<tr>
<th>Fruits, berries, vegetables, root vegetables</th>
<th>Hot or cold as a snack, side dish or incorporated into the dish. Included rose hip, blueberry, lingonberry, apple, pear, prune, cabbage, cauliflower, brussel sprouts, broccoli, fennel, spinach, kohlrabi, viper’s grass, onion, leek, kale, sugar peas, turnip, carrot, parsnip, and beetroot</th>
<th>≥ 500 gram per day</th>
<th>Carbohydrate quality: dietary fibre. Vitamins: antioxidant vitamins Minerals: potassium, magnesium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potatoes</td>
<td>Mainly boiled</td>
<td></td>
<td>Vitamins, minerals</td>
</tr>
</tbody>
</table>
| Legumes               | N/A | No recommendations | Carbohydrate quality: dietary fibre.  
Protein quality: vegetable protein |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Meat</td>
<td>N/A</td>
<td>≤ 500 gram per week</td>
<td>Protein, vitamins, minerals</td>
</tr>
<tr>
<td>Poultry</td>
<td>N/A</td>
<td>≤ 300 gram per week</td>
<td>Could be included as long as the RI for dietary cholesterol was not exceeded</td>
</tr>
<tr>
<td>Eggs</td>
<td>N/A</td>
<td>For taste</td>
<td>Bioactive compounds: antioxidants</td>
</tr>
<tr>
<td>Herbs, spices and other</td>
<td>N/A</td>
<td>For taste</td>
<td></td>
</tr>
<tr>
<td>Sweets, desserts, coffee bread</td>
<td>N/A</td>
<td>At weekends</td>
<td>For taste</td>
</tr>
<tr>
<td>Beverages/liquids (non-alcoholic)</td>
<td>N/A</td>
<td>Free amount of tap water, tea, filtered (brewed) or instant coffee</td>
<td></td>
</tr>
<tr>
<td>Alcoholic beverages</td>
<td>N/A</td>
<td>The subjects’ habitual amount of alcoholic beverage</td>
<td>Subjects habitual amount</td>
</tr>
</tbody>
</table>
Figure 7. Example of the main meals, breakfast, lunch and dinner, included in ND (Papers I, II, III).
(Photographer Björn Lindberg)
Logistics (Papers I, II)

Throughout the study, all foods were prepared and supplied to subjects randomly assigned to the ND. In the ND group, all main meals were cooked, weighed and packed in meal boxes and labelled. The study diet were produced, weighed, packed and labelled at the “Hotel and restaurant programme” at “Torsbergs gymnasiesskola” in Bollnäs by seven students, their responsible teacher, and a representative of the research team.

However, beverages were not provided to the intervention group. Advice on suitable drinks was given (Table 4). The subjects were provided with a 21-day rotating menu plan, including breakfast, lunch, and dinner, and two snacks per day. Subjects collected cooler bags twice a week (Figure 8). The cooler contained up to eight food boxes for lunch and dinner. Staple foods for breakfast and snacks, such as cereals, bread, nuts, jam, margarine, biscuits, and snacks, were provided during the baseline visit. Subjects in the ND group received instructions on how to prepare their breakfast. In addition, subjects received daily study checklists (Figure 6) including menus for up to 4 days to monitor dietary compliance.

Figure 8. Subjects collected cooler bags twice a week. The cooler bag contained up to eight food boxes for lunch and dinner. Daily study checklists to monitor dietary compliance was also included in bags (Figure 6).

(Photographer Christer Vallstrand)
Table 4. Representative daily menu for the Nordic diet

**Breakfast**
- Hot or cold cereals: based on oat bran, oat meal or barley
- Psyllium and flaxseeds
- Milk products: low-fat milk or low-fat yoghurt
- Jam: blueberry\(^1\) or lingonberry\(^1\)
- Bread: whole grain\(^2\) (soft or hard)
- Margarine: rich in polyunsaturated fat\(^3\)
- Herring or mackerel, or turkey

**Lunch and dinner\(^4\)**
- Main dish: fish, chicken, meat or vegetarian
- Main meal starch: whole grain pasta, potatoes, pearled oat or barley
- Warm vegetables: such as broccoli, cauliflower, carrots or brussel sprouts
- Cold salad: such as cabbage or carrots
- Dressing: based on vegetable fat (rapeseed oil)
- Bread: whole grain\(^2\) (soft or hard)
- Margarine: rich in polyunsaturated fat\(^3\)

**Snacks\(^5\)** Almonds, oat bran rusks, and fruit

**Beverages\(^5\)** Unlimited amount of tap water, filtered (brewed) or instant coffee and tea. Limited amounts of fruit juice and low-fat milk. Low-alcohol beer. Avoid sugar-sweetened drinks including carbonated drinks

\(^1\)45 gram sugar per 100 gram jam. \(^2\)50% whole grain per dry matter. \(^3\)Based on vegetable fat. \(^4\)Vegetable oil (rapeseed) and liquid margarine used for cooking. \(^5\)To be consumed at any point during the day.

**Cooking methods**
Low-temperature cooking methods such as oven-baking and boiling were the main preparation methods recommended in the ND. For improving the taste of the study diet different spices were used as well as table salt with reduced sodium content.
The sole intervention in Paper IV, “Role of a prudent breakfast in improving cardiometabolic risk factors in subjects with hypercholesterolemia: a randomised controlled trial”, was the instruction to eat a breakfast composed of healthy Nordic foods, in accordance with NNR 2004 (Figure 9) (Table 5) without other dietary changes in subjects' habitual diet. All breakfast items were provided for subjects in the PB group, however, beverages were not provided but advice was given.

Figure 9. The prudent breakfast (PB) (Paper IV), included oat bran porridge with low-fat milk or yogurt, bilberry or lingonberry jam, soft or hard whole grain bread, low-fat spread, poultry or fatty fish, and fruit. (Photographer Björn Lindberg)
Table 5. Quantity and frequency of food items included in the prudent breakfast (PB)

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Porridge</strong></td>
<td></td>
</tr>
<tr>
<td>Oat bran. As an alternative to</td>
<td>40 g per serving (corresponding to 3 g β-</td>
</tr>
<tr>
<td>porridge, oat bran-enriched</td>
<td>glucan per day)</td>
</tr>
<tr>
<td>muesli could be eaten</td>
<td>Oat bran porridge: 5-7 days per week</td>
</tr>
<tr>
<td></td>
<td>Oat bran enriched muesli: Not more than 2 days per week</td>
</tr>
<tr>
<td>Low-fat milk or yogurt</td>
<td>Maximum amount of 4 dl</td>
</tr>
<tr>
<td></td>
<td>Each breakfast</td>
</tr>
<tr>
<td>Jam, raisins</td>
<td>1-2 tbsp. (17 g) of each</td>
</tr>
<tr>
<td></td>
<td>Each breakfast</td>
</tr>
<tr>
<td>Fresh or frozen fruit or berries</td>
<td>Corresponding to 1 fruit</td>
</tr>
<tr>
<td></td>
<td>Each breakfast</td>
</tr>
<tr>
<td>Psyllium</td>
<td>1.5 tsp. (7 g)</td>
</tr>
<tr>
<td></td>
<td>7 days per week</td>
</tr>
<tr>
<td>Linseed</td>
<td>1.5 tsp. (7 g)</td>
</tr>
<tr>
<td></td>
<td>7 days per week</td>
</tr>
<tr>
<td>Table salt</td>
<td>Do not exceed recipe on package</td>
</tr>
<tr>
<td></td>
<td>Use low-sodium table salt</td>
</tr>
<tr>
<td><strong>Sandwich</strong></td>
<td></td>
</tr>
<tr>
<td>Soft or hard whole-grain bread,</td>
<td>One soft slice (40 g) or two hard slices (24 g)</td>
</tr>
<tr>
<td>50% whole grain as dry matter</td>
<td>Each breakfast.</td>
</tr>
<tr>
<td></td>
<td>Bread was eaten until satiation. Subjects were allowed to have more or less bread to regulate satiety</td>
</tr>
<tr>
<td>Low-fat spread (38% fat)</td>
<td>5 g per slice of bread</td>
</tr>
<tr>
<td></td>
<td>Thin layer</td>
</tr>
<tr>
<td>Turkey meat</td>
<td>One slice (20 g)</td>
</tr>
<tr>
<td></td>
<td>4 days per week</td>
</tr>
<tr>
<td>Pickled herring or mackerel</td>
<td>Two to three pieces (10-15 g) of herring or</td>
</tr>
<tr>
<td></td>
<td>1 tbsp. mackerel</td>
</tr>
<tr>
<td></td>
<td>3 days per week</td>
</tr>
</tbody>
</table>
Statistics

Paper I
Data are presented as mean±SD. Per protocol analysis was used to assess effects on outcome measures. SPSS version 16.0 for Windows was used for statistical analyses.

Statistical analyses
Student’s paired t-test was used to assess change within groups and unpaired Student’s t-tests to compare mean changes between groups.
In secondary analyses, between-group differences in change during follow-up were tested with analysis of covariance (ANCOVA), with baseline values and weight change as covariates. Statistical tests were two-tailed, and \( p<0.05 \) was regarded as significant.

Power calculation
It was estimated that 92 subjects were required for 80% power with a type I error of 5% to detect a difference of 0.25 mmol L\(^{-1}\) in plasma LDL-C levels with an SD of ±0.56 mmol L\(^{-1}\).

Paper II
Statistical analyses
Student’s t-test was used to compare the mean food intake in the ND group with the mean food intake in a Swedish reference population. A two-tailed \( p<0.05 \) was regarded as significant. Food intake in Paper II is presented as actual amount consumed (mean gram/day). SPSS version 18 for Windows was used for the statistical analyses.
Paper III

Statistical analyses are based on per protocol analysis. To avoid chance findings due to the large number of analyses performed, only p-values less than 0.01 were considered statistically significant. Statistical analyses were performed with SPSS version 20 for windows.

Statistical analyses

Student’s two-sample t-test was used to compare changes between control diet and ND groups during the intervention period. Changes within groups were analysed with Student’s paired sample t-test. Pearson correlation coefficients were calculated with the ND and control diet groups combined. All P-values were unadjusted.

Paper IV

The data are expressed as mean±SD or standard error of mean (SEM), and median (interquartile range). All statistical analyses were based on intention-to-treat principles, with the exception of the area-under-the-curve for glucose and insulin where per protocol analyses were used. P<0.05 was considered statistically significant. Statistical analyses were with IBM SPSS version 19 for windows.

Statistical analyses

Differences between groups were analysed with an unpaired two-tailed t-test for normally distributed data and an independent-sample Mann-Whitney U-test for non-normally distributed data. A general linear model / univariate model for normally distributed variables (analysis of covariance (ANCOVA)) was used for differences in changes (X_{12 weeks}−X_{baseline}) between groups when adjusted for baseline. The AUC for insulin and glucose concentrations during the OGTT were calculated according to the trapezoid rule.

Correlations

Correlations were tested by Pearson’s correlation and by linear regression analyses. To avoid elevated CRP attributable to acute infection, subjects with CRP concentrations ≥10 mg/L at either baseline (n=7) or the end of the study (n=8) were excluded from the analysis of CRP and TNF-R2.

For nutrient data, paired t-tests were used to explore within-group changes between baseline and 12 weeks. Nutrients, not normally distributed after
logarithmically transformation data, are presented as median 25th and 75th percentiles.

Power calculation
The calculation of statistical power was based on dose-response studies with \( \beta \)-glucan and a previous trial where the present breakfast was included in a whole diet (98, 120). Based on a previous study (Paper I) with a comparable PB to the one used in this study, it was estimated that detecting a difference between groups in LDL-C of 0.4 mmol/L, with an estimated SD of 0.60, required \( n=36 \) subjects in each group with a power of 80\% (\( \alpha=0.05 \)).

Ethics and clinical trial registration

Papers I, II and III
Written informed consent was given by all subjects, and the study was approved by the regional ethical committee at Uppsala University (U-07-009). The trial was registered in the Current Controlled Trials database (http://www.controlled-trials.com); International Standard Randomized Controlled Trial Number (ISRCTN): 77759305.

Paper IV
Written informed consent was provided by all subjects, and the study was approved by the regional ethical committee in Uppsala. The trial was registered in the Current Controlled Trials database (http://www.controlled-trials.com); International Standard Randomized Controlled Trial Number (ISRCTN): 84550872
Results

Paper I

Of 88 subjects randomly assigned to the diet, 86 subjects completed the study (Table 6). The ND contained 27 % energy (E%) from fat, 52 E% carbohydrate, 19 E% protein and, 2 E% alcohol (Table 7). In the ND group, there was a decrease in total cholesterol (−16%, \( P < 0.001 \)), LDL-C (−21%, \( P < 0.001 \)), HDL-C (−5%, \( P < 0.01 \)), LDL-C/HDL-C (−14%, \( P < 0.01 \)), apoB/apoA1 (−1%, \( P < 0.05 \)) insulin (−9%, \( P = 0.01 \)) and systolic blood pressure by −6.6±13.2 mmHg (−5%, \( P < 0.05 \)) compared to the control diet group (Table 8). Despite the *ad libitum* nature of the ND, body weight decreased after 6 weeks, compared with the control diet group (−4%, \( P < 0.001 \)). After adjustment for weight change, the differences between groups remained for blood lipids, but not for insulin sensitivity or systolic blood pressure. There were no differences in diastolic blood pressure, triglyceride or glucose concentrations.

Individual changes in response to dietary treatments such as LDL-C, total cholesterol, HDL-C and LDL-C/HDL-C and weight, are presented in (Figure. 10 and Figure. 11).

All subjects in the extended subgroup (n=11) completed the additional 4-week intervention. This subgroup followed the ND for a total period of 10 weeks. In agreement with the total intervention group, the risk factors in the subgroup (n=11) reduced after 6 weeks and continued to decrease over the 10 weeks. Data for LDL-C, total cholesterol, LDL-C/HDL-C ratio, insulin, systolic blood pressure and body weight are presented in (Figure. 12). All values except apoB/apoA1 (p=0.09) differed significantly (\( P < 0.05 \)) from baseline to 10 weeks: LDL-C (-31%), total cholesterol (-24%), LDL-C/HDL-C (-25%), apoB/ apoA1 (-10%), insulin (-28%), Systolic blood pressure (-9%) and body weight (-6%) (Figure. 12).
Table 6. Baseline characteristics after randomisation to the different diets

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control diet (n=42)</th>
<th>Nordic diet (n=44)</th>
<th>P¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>53.4±8.1</td>
<td>52.6±7.8</td>
<td>0.63</td>
</tr>
<tr>
<td>Men/women</td>
<td>15/27</td>
<td>17/27</td>
<td>0.83</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>78.0±13.3</td>
<td>76.0±10.5</td>
<td>0.44</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.5±3.3</td>
<td>26.3±3.2</td>
<td>0.79</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129.8±13.6</td>
<td>127.9±12.4</td>
<td>0.50</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>83.4±9.3</td>
<td>80.8±7.5</td>
<td>0.16</td>
</tr>
<tr>
<td>Plasma glucose (mmol/l)</td>
<td>4.9±0.6</td>
<td>4.9±0.5</td>
<td>0.54</td>
</tr>
<tr>
<td>Plasma insulin (mU/l)</td>
<td>6.1±2.8</td>
<td>5.8±3.0</td>
<td>0.57</td>
</tr>
<tr>
<td>Insulin resistance (HOMA-IR)²</td>
<td>1.3±0.6</td>
<td>1.2±0.6</td>
<td>0.47</td>
</tr>
<tr>
<td>Plasma triglycerides (mmol/l)</td>
<td>1.4±0.8</td>
<td>1.6±0.8</td>
<td>0.32</td>
</tr>
<tr>
<td>Plasma cholesterol (mmol/l)</td>
<td>6.4±0.7</td>
<td>6.2±0.8</td>
<td>0.36</td>
</tr>
<tr>
<td>Plasma LDL cholesterol (mmol/l)</td>
<td>4.2±1.0</td>
<td>4.0±0.6</td>
<td>0.33</td>
</tr>
<tr>
<td>Plasma HDL cholesterol (mmol/l)</td>
<td>1.6±0.5</td>
<td>1.5±0.4</td>
<td>0.28</td>
</tr>
<tr>
<td>LDL-C/HDL-C ratio</td>
<td>2.8±0.9</td>
<td>2.9±0.8</td>
<td>0.80</td>
</tr>
<tr>
<td>Plasma apolipoprotein A1 (g/l)</td>
<td>1.5±0.3</td>
<td>1.5±0.3</td>
<td>0.76</td>
</tr>
<tr>
<td>Plasma apolipoprotein B (g/l)</td>
<td>1.1±0.2</td>
<td>1.1±0.2</td>
<td>0.85</td>
</tr>
<tr>
<td>ApoB/A1 ratio</td>
<td>0.8±0.2</td>
<td>0.8±0.2</td>
<td>0.77</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>1.5±1.4³</td>
<td>1.6±1.7</td>
<td>0.78</td>
</tr>
</tbody>
</table>

¹Differences between groups with unpaired two-tailed t-test. ²HOMA-IR = homeostasis model assessment-insulin resistance. ³n=40; subjects with baseline CRP >10 mg/l were excluded.
Table 7: Nutrient intake at baseline and at 6 weeks in the Control diet and Nordic diet groups

<table>
<thead>
<tr>
<th>Subjects, n</th>
<th>Energy (kcal/day)</th>
<th>Protein (g/day)</th>
<th>Alcohol (g/day)</th>
<th>Carbohydrates (g/day)</th>
<th>Dietary fibre (g/day)</th>
<th>β-glucan (g/day)</th>
<th>Fat (g/day)</th>
<th>Saturated fat (g/day)</th>
<th>Monounsaturated fat (g/day)</th>
<th>Polyunsaturated fat (g/day)</th>
<th>Dietary cholesterol (mg/day)</th>
<th>Sodium (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control diet</td>
<td>Baseline</td>
<td>42</td>
<td>2450±642</td>
<td>17±2.6</td>
<td>46±5.9</td>
<td>31±11</td>
<td>0.4±0.7</td>
<td>34±5.0</td>
<td>13±2.9</td>
<td>5.6±1.7</td>
<td>355±135</td>
<td>318±968</td>
</tr>
<tr>
<td>6 weeks</td>
<td>42</td>
<td>2517±642</td>
<td>17±2.6</td>
<td>33±5.6</td>
<td>31±11</td>
<td>0.4±0.7</td>
<td>34±5.0</td>
<td>13±2.9</td>
<td>5.6±1.7</td>
<td>355±135</td>
<td>318±968</td>
<td></td>
</tr>
<tr>
<td>Nordic diet</td>
<td>Baseline</td>
<td>42</td>
<td>2509±671</td>
<td>17±2.8</td>
<td>45±6.1</td>
<td>30±9.5</td>
<td>0.3±0.4</td>
<td>34±5.0</td>
<td>14±3.1</td>
<td>5.2±0.4</td>
<td>349±125</td>
<td>3517±969</td>
</tr>
<tr>
<td>6 weeks</td>
<td>42</td>
<td>1994±275</td>
<td>2.1±2.0</td>
<td>54±7.4</td>
<td>4.9±1.0</td>
<td>27±1.0</td>
<td>11±0.5</td>
<td>6.3±0.3</td>
<td>4.9±1.1</td>
<td>13±1.7</td>
<td>3727±1214</td>
<td></td>
</tr>
</tbody>
</table>

1 Assessed by diet history interview. 2 Difference within the group with paired sample t-test. 3 Assessed by daily study checklist. Percentage of daily energy intake. Could not be computed because the standard error of the difference is zero.
Table 8. Absolute and relative change in cardiovascular risk factors from baseline to week 6 in the control diet and Nordic diet groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control diet</th>
<th>Nordic diet</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, n</td>
<td>42</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>0.03±1.47 (0.04)</td>
<td>-3.00±1.86 (-4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)²</td>
<td>-0.01±0.51 (-0.04)</td>
<td>-1.04±0.60 (-4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>0.60±11.25 (0.5)</td>
<td>-6.55±13.18 (-5.0)</td>
<td>0.008</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>0.48±9.46 (0.6)</td>
<td>-2.99±8.90 (-4)</td>
<td>0.08</td>
</tr>
<tr>
<td>Plasma glucose (mmol/l)</td>
<td>0.05±0.34 (1)</td>
<td>0.00±0.41 (0)</td>
<td>0.52</td>
</tr>
<tr>
<td>Plasma insulin (mU/l)</td>
<td>0.90±2.88 (15)</td>
<td>-0.51±2.25 (-9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Insulin resistance (HOMA-IR)³</td>
<td>0.22±0.64 (17)</td>
<td>-0.11±0.51 (-9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Plasma triglycerides (mmol/l)</td>
<td>-0.03±0.40 (-2)</td>
<td>0.11±0.58 (7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Plasma cholesterol (mmol/l)</td>
<td>0.23±0.55 (4)</td>
<td>-0.98±0.75 (-16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Plasma LDL-C (mmol/l)</td>
<td>0.10±0.53 (2)</td>
<td>-0.83±0.67 (-21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma HDL-C (mmol/l)</td>
<td>0.11±0.19 (7)</td>
<td>-0.08±0.23 (-5)</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL-C/HDL-C ratio</td>
<td>-0.11±0.35 (-4)</td>
<td>-0.42±0.57 (-14)</td>
<td>0.003</td>
</tr>
<tr>
<td>Plasma apolipoprotein A1 (g/l)</td>
<td>0.11±0.14 (7)</td>
<td>-0.11±0.20 (-7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma apo B (g/l)</td>
<td>0.16±0.12 (14)</td>
<td>-0.09±0.15 (-8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apo B/A1 ratio</td>
<td>0.05±0.10 (7)</td>
<td>-0.01±0.13 (-1)</td>
<td>0.02</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>0.33±1.87 (20)</td>
<td>0.10±1.91 (6)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

¹Data are mean±SD (percentages from baseline). ²Differences between groups with Student’s unpaired t-test. ³HOMA-IR = homeostasis model assessment-insulin resistance.
Figure 10. Individual response to dietary treatment. Changes in LDL-C, total cholesterol and HDL-C from baseline to week 6 after a control diet and a healthy Nordic diet (n=86) (Paper I).
Figure 11. Individual response to dietary treatment. Changes in LDL/HDL ratio and weight (kg) from baseline to week 6 after a control diet and a healthy Nordic diet (n=86) (Paper I).
Figure 12. All subjects in the extended subgroup (n=11) completed the additional 4-week intervention. This subgroup followed the ND for a total period of 10 weeks (Paper I).
Paper II

Macro- and micronutrients

In the ND group after 6 weeks, the relative intake of protein, carbohydrate, total fat, SFA, MUFA and PUFA (Table 7) was in accordance with the planned nutrient profile (Table 2) and the RI of the NNR 2004 (93). The mean intake of total dietary fibre was approximately twice RI (Figure 13), (Table 7); the total dietary fibre comprised cereal 23 g, vegetables 15 g, fruits 5 g and legumes 5 g, (Paper II, table 3). β-glucan (4.9 g) and whole grain intake (111 g) (Paper II, table 3) were above the planned nutrient profile for the study (Table 2). The corresponding intake of vitamins A, D, E (tocopherol), thiamine, riboflavin, niacin, vitamins B6 and B12, folate, and vitamin C was above AR. The intake of minerals was above AR for calcium, phosphorous, magnesium, iron, zinc, potassium, and selenium. Sodium intake was below RI, according to NNR 2004 (Table 7) and (Paper II, table 3).

![Figure 13](image-url). When comparing nutrient intake in ND with average requirement (AR) from NNR 2004, ND represents a balanced nutrient intake that meet the recommendations at the time for the study. Intake presented as mean per day (Paper II).
Food items

After 6 weeks on the ND (n=44), the most apparent deviation from a Swedish reference population (Figure 14) was the higher absolute intake of fruits, berries, vegetables, root vegetables and potatoes, legumes, fish and egg, fat and oil, and lower intake of meat products and poultry, dairy products, sweets and desserts, and alcoholic beverages (p<0.001). The consumption of cereals and seeds was almost the same for both diets (p>0.3) (Figure 14). There was a change in carbohydrate quality (Figure 15).

*Figure 14. When comparing ND with the food intake of a Swedish reference population, ND is a more plant-based diet. Intake presented as mean, gram per day (Paper II).*
Figure 15. Relative change in intake of whole grain (raw material), total dietary fibre and sources of dietary fibre in ND, mean of 6 weeks (Paper II).

Paper III

In the ND group the total dietary SFA intake at the end of the study was one third of that at baseline (Table 7) with a minor decrease in dietary MUFA intake and an increase in total dietary PUFA. For intake of individual FA, there was a decrease in 18:2n-6 and increase in 18:3n-3 (Paper III, table 1).

There were differences between the two groups from baseline to 6 weeks (p<0.01) for serum CE-SFA 14:0, 15:0, 18:0 and 22:6n-3 with no differences between groups in other CE-FA (Paper III, table 2).

The relationship between the changes of CE-FA and blood lipids during the intervention period is presented in (Paper III, table 3). The changes in CE-SFA 14:0 were positively correlated to the changes in LDL-C (Figure 16), HDL-C, LDL-C/HDL-C, apoA1, and apoB (p<0.01), and changes in the marker for dairy fat intake, 15:0, were positively associated with changes in LDL-C (Figure 16) and apoB.

There were corresponding correlations for CE-SFA 18:0 with LDL-C, LDL-C/HDL-C, and apoB, whereas CE-PUFA 22:6n-3 was negatively correlated with LDL-C (Figure 16), HDL-C, apoA1, and apoB, but not with apoB/apoA1 (Paper III, table 1). The SCD-1 index was positively correlated with serum blood lipids, but the correlations were generally weaker than those of SFA (data are not shown).
Figure 16. Correlation of fatty acids in serum cholesterol esters (CE-FA) and LDL-C during the intervention period. The changes of CE-SFA 14:0 and 15:0 were positively correlated and changes of 22:6n-3 negatively correlated to the changes of LDL-C (Paper III).
Paper IV

Of the 79 subjects randomly assigned to control diet or PB groups (31 men and 48 women), one subject dropped out of the study (Figure 2). With the exception of apoA1 and serum insulin (AUC), no significant differences in clinical characteristics were found between the control breakfast and PB groups at baseline (Paper IV, table 2). Similarly there were no difference in HbA1c found between groups (p=0.92; data not shown).

When comparing breakfast intake at 12 weeks with breakfast intake at baseline, significant increases were observed in the intake of protein as a percentage of energy (E%), dietary fibre and β-glucan, and PUFA (p<0.05) (Paper IV, table 4). Significant decreases were observed in total fat, SFA, MUFA (E%), dietary cholesterol, and sodium (p<0.05). No differences in energy intake, carbohydrates (E%), and whole grain intake were observed. Significant changes in whole-day nutrient intake (Paper IV, table 3) were found with regard to alcohol and carbohydrates, dietary fibre, and β-glucan from baseline to 12 weeks in the PB group compared with the control group.

No significant changes in plasma LDL-C, total cholesterol, HDL-C, the LDL-C/HDL-C ratio, triglycerides, or the apoB/apoA1 ratio were found (Paper IV, table 5). No differences were observed between groups in body weight, plasma glucose, serum insulin, glucose and insulin AUC, HOMA-IR, or systolic and diastolic blood pressure (all p>0.18) (Paper IV, table 5). HbA1c was not influenced by the diets (data not shown).

SAD and plasma levels of CRP and TNF-R2 were significantly decreased by the PB compared with the control breakfast (p<0.05) (Paper IV, Figure 2a and 2b). The absolute changes in CRP and TNF-R2 between baseline and 12 weeks were 0.66±0.30 (+37%) for the control breakfast and -0.71 ± 0.27 (-30%) for the PB and 359±118 (+9%) for the control breakfast and 66±88 (+2%) for the PB, respectively. The change in CRP was weakly associated with the change in TNF-R2 (r=0.38, p <0.05, n=64).
Discussion

In this thesis, the impact of a healthy ND on CVD risk factors was investigated and the results presented in Paper I, II and III. In Paper IV the impact of a healthy Nordic breakfast on cardiometabolic risk factors was investigated and presented.

The four Papers are based on two randomised controlled trials. Papers I, II and III are based on 88 mildly hypercholesterolaemic but otherwise healthy men and women living in the Bollnäs, Sweden. Paper IV is based on 79 overweight and mildly hypercholesterolaemic but otherwise healthy men and women living in Uppsala, Sweden.

Principal findings

Paper I

In the first RCT, the results presented in Paper I suggested that a diet based on foods originating from the Nordic countries might be an option for lowering moderately raised cholesterol levels as well as lowering body weight, insulin resistance and blood pressure.

Paper II

At the time for the study, the ND fulfilled dietary recommendations regarding intake of macro- and micronutrients (Paper II). The ND was a plant-based diet, where animal products were only used sparingly as side dishes. Compared with food intakes in a Swedish reference population, the ND was higher in absolute intake of fruits, berries, vegetables, root vegetables, potatoes, legumes, vegetable fats and oils, fish and eggs, but lower in meat products, dairy products, sweets and desserts and alcoholic beverages. Intake of cereals in ND was equivalent to the intake in the Swedish reference population, although the carbohydrate quality in ND was higher, i.e. higher in dietary fibre from legumes, vegetables and cereals, and whole grains.
Paper III

After six week on ND, the decrease in dietary SFA and increase in dietary PUFA intake was reflected in corresponding changes in the CE-SFA 14:0, 15:0, 18:0 and CE-PUFA 22:6n-3 (Paper III, table 2). During the intervention, the changes in CE-SFA 14:0, 15:0 and 18:0 correlated positively with the changes in LDL-C, HDL-C, LDL-C/HDL-C, ApoA1 and ApoB (p<0.01), whereas the changes in CE-PUFA 22:6n-3 were negatively correlated with changes in the corresponding serum lipids. These relationships indicated the dietary fat composition of the healthy ND was linked to a change in blood lipids as supported by previous studies (11, 73, 81, 82).

Paper IV

The consumption a PB, without other dietary changes for 3 months did not influence blood lipids, body weight, or glucose metabolism but reduced markers of visceral fat and inflammation (Paper IV).
General discussion

Whole diet and risk factors

In the NORDIET study, an “ad libitum healthy ND, based on foods originating from the Nordic countries, improved CVD risk factors such as LDL-C, LDL-C/HDL-C ratio, insulin sensitivity and blood pressure to clinically relevant levels in mildly hypercholesterolaemic subjects” (Paper I). The NORDIET study was a short-term trial (6 weeks), however in a controlled long-term intervention study, the SYSDIET study, an iso-caloric healthy Nordic diet, caused moderate improvements in lipid profile after 18-24 weeks (145). There were significant decreases in LDL-C, apoB and total cholesterol in ND group compared to the control diet group. In SYSDIET there was a significant decrease in non-HDL-C and a non-significant decrease in LDL-C and apoB, and no effect on total cholesterol and apoA1. The reduction in LDL-C and apoB, and the reduction in LDL-C/HDL-C ratio, and apoB/apoA1 ratio was seen in both ND and SYSDIET. Anyhow, the reduction in HDL-C and apoA1 in ND was not seen in SYSDIET, where there was a trend toward elevated HDL-C, and no effect on apoA1. The difference in total fat intake (27 E% in ND and 32 E% in SYSDIET) could be one explanation for the difference. The reduced body weight in ND group, which was not seen in SYSDIET, could also explain some of the difference in lipid profile after the two diets as reduced body weight affects most CVD risk factors (74, 75). After adjustment for weight change, the effects on total cholesterol, HDL-C, LDL-C, apoA1, and apoB were independent of weight change in ND group (Paper I). Taken together, these improvements in blood lipid profile in ND and SYSDIET, supports favouring protections from CVD with a healthy diet based on Nordic foods.

Although dietary interventions low in fat, including ND (Paper I), decrease LDL-C, they may also decrease HDL-C (34, 37). The clinical relevance of HDL-C lowering in ND was probably minor as the LDL-C/HDL-C ratio decreased and according to some genetic data, and especially statin trials, LDL-C is to date a more robust risk factor than HDL-C (3, 4). However, a Mediterranean-style diet can increase HDL-C (21), and increasing total fat to 30-40 E% with high proportions of MUFA and PUFA has no HDL-C lowering effects (145, 154, 160).

In SYSDIET study (145), the iso-caloric healthy Nordic diet had a beneficial effects on low-grade inflammation marker IL 1 receptor antagonist
compared to a control diet (145). However, despite decreased LDL-C and weight loss in ND group, and improved quality of fat and carbohydrate in the ND, which are known factors for improving inflammatory markers (70, 71), no effect on the inflammatory marker CRP was identified (Paper I). However, in the 12-week PB study (Paper IV) there was no reduction in body weight, but a decrease in CRP and TNF-R2 after PB versus controls. PB reduced markers of visceral fat and inflammation, and the reduced levels of CRP and TNF-R2 might account for the reduction in SAD, as a link between visceral fat and low-grade inflammation is reported (72). The potential mechanisms for this effect are unclear, but may involve the improved fat quality of PB, e.g. PUFA (both n-3 and n-6) in place of SFA can reduce the visceral fat-to-subcutaneous fat ratio and reduce inflammation markers, such as TNF-R2 (73). The intake of dietary fibre, both from the breakfast alone, and from the whole day intake increased (Paper IV table 4, table 3). Therefore, another plausible mechanism involved in the reduction of CRP after PB is increased intake of dietary fibre, and dietary fibre from oat bran and rye bran as these affect CRP (70, 71). However, visceral fat and inflammatory risk factors were secondary outcomes.

The large reduction in systolic blood pressure seen in ND group was consistent with the reduction seen in the DASH diet (31) and the low sodium DASH diet (33). This might have been due to the low sodium content in ND or the dietary pattern in ND, supported by Appel et. al. (31). However, in ND the effect disappeared after adjustments for weight change (Paper I), it is unclear how much of the change in blood pressure was mediated by weight change.

Recently, a study on New Nordic Diet within the Danish OPUS-project (151) showed significant reductions in body weight (-4.7±0.5 kg) and blood pressure (-5.1 mmHg; 95% CI: -8.2, -2.1 mmHg) at similar magnitudes to those described in ND after 6 weeks (-3.0±1.86 kg and -6.55±13.8 mmHg) (Paper I). That study was however 6 month of duration and the subjects were moderately obese, but with slightly lower serum cholesterol levels compared with those in Paper I. Furthermore, an inverse association between n-3 PUFA and blood pressure is seen in 8-11 year-old children during an intervention with school meals based on the New Nordic diet (149). The overall guidelines for the New Nordic diet (150) are in line with the food composition of ND.

Impact of weight change on CVD risk factors in ND

Energy balance could not be maintained during ND, partly due to the high intake of dietary fibre from fibre rich foods such as cereals, fruits, vegetables, and legumes, (Paper I, II), and a weight loss of 3.0±1.86 (4%) was observed. As reducing body weight affects most CVD risk factors (74, 75)
ANCOVA was used to investigate the effect of weight change on the CVD risk factors investigated; baseline values and weight change were covariates. After adjustment, the effects on total cholesterol, HDL-C, LDL-C, apoA1, and apoB were independent of weight change (Paper I). Although Dattilo et al. (75), suggest weight reduction was associated with a decrease and correlation with both total cholesterol and LDL-C, the findings on total cholesterol, HDL-C, LDL-C, apoA1, and apoB in ND were independent of weight change (Paper I). The dietary pattern, including foods and nutrients with favourable effect on CVD risk factors in ND (Table 3) might be one explanation of the weight independent decrease in blood lipids. However, the effects on insulin sensitivity and blood pressure were statistically dependent on weight change in ND, but it remains unclear how much of the differences in insulin sensitivity and blood pressure were mediated by weight loss.

Foods and nutrients in ND
A healthy ND is “a plant-based diet, where animal products are used spar-
ingly as side dishes. ND has a favourable fat quality (low in saturated fat and trans fat, and high in unsaturated fat). ND has a favourable carbohy-
drate quality (i.e. rich in whole grains, fruits, berries, vegetables, root vege-
tables, potatoes, and legumes). Compared with the average Swedish diet, ND is low in sodium, and meat products, high-fat dairy products, sweets and desserts, and alcoholic beverages” (Paper II).

“At least part of the lipid-lowering effects observed after the ND appears related to the improved fat quality in ND, i.e. lower intake of high-fat dairy and meat products and higher intake of their low-fat counterparts, vegetable oils, and fatty fish” (Paper III).

This description of the dietary pattern in ND includes both its food and nu-
trient content, and ND is consistent with previously described dietary pat-
terns and the effects of whole diets on CVD risk factors investigated during observational and interventional studies (17, 22, 23, 25, 26, 30, 34, 43) and is supported by recent descriptions of healthy dietary patterns (1, 9, 28). Mozaffarian et. al. (9) highlights the role of cardio protective foods and dietary patterns, including the importance of favourable carbohydrate, fat quality and limited sodium intake. The dietary pattern in ND is also supported by NNR 2012 (160), which was released after the onset of this study.

Foods in ND
The food groups in the healthy ND described in this thesis (Table 3) are con-
sistent with previously described food groups in whole diets/food pattern
that improve CVD risk profile (16, 17, 22, 25, 26). However, the food items in ND were chosen from the definition “possible to cultivate, harvest and breed in the Nordic countries” without considering whether foods were actually cultivated, harvested or bred.

A combination of fatty fish, bilberries and whole grain products improve glucose metabolism, alter the lipidomic profile (147), and may prevent type II diabetes (146). The results from an evaluation of a healthy Nordic food-based index suggests intake of whole grain rye bread and cabbage were associated with a lower mortality rates in both men and women and can be considered among the healthiest food items (152). All foods mentioned in these previous studies (146, 147, 152) were included in the current ND: however, the study design did not allow any firm conclusions to be drawn on single foods with regard to the primary and secondary outcome measures. However, several correlations indicated changed fatty acid composition i.e. replacing SFA from milk fat (e.g. butter) with PUFA, mediated at least some of the lowering effects on LDL-C (Paper III).

Although there was a higher intake of fruit and berries, and legumes in ND than in a Swedish reference population (Paper II), the intake of cereals and seeds was similar in both the ND and in the Swedish reference population. The lack of difference between the intake of cereals and seeds in ND and in the Swedish reference population was a matter of quantity (intake as gram) (Figure 14), and the nutrient intake in ND highlighted an increase in whole grain and dietary fibre intake (Figure 15), suggesting improved carbohydrate quality in ND.

The whole grain intake of 111 gram per day (as whole grain raw material) in ND, was in line with actual recommendations (155, 156) and was above general whole grain consumption in Scandinavia (157). Oat, rye, wheat and barley comprised the mean daily whole grain intake over the 6 weeks in ND (Paper II). However, as sources of whole grain were calculated on dietary fibre intake, and oat bran porridge, which is not whole grain, was a main breakfast food item, oats might be overestimated as a source of whole grain in ND.

An evaluation of common food-based dietary guidelines suggest there is probable (moderate) evidence for whole grains to be positively associated with type II diabetes and CVD (127). Despite reported effects of whole grain from epidemiological studies (106-108), the EFSA panel does not accept a health claim concerning the consumption of whole grain and effects on e.g. blood cholesterol and CVD (103). This means whole grain is not characterised and a cause and effect relationship cannot be established between the consumption of whole grain and the claimed effects on i.e. blood cholesterol and CVD health (103). The biomarker alkylresorcinol could have been used to validate whole grain intake in ND, but as the main source of whole grains were oats and some barley (Paper II), this was not possible as alkylresorcinol is mainly found in wheat and rye (158, 159).
Fat and carbohydrate quality of ND

The change in fat- and carbohydrate quality from baseline to 6 weeks in ND might have contributed to the changes in CVD risk factors - a theory supported by other studies (81, 83, 85-87, 94, 95, 100, 101). During ND, the dietary changes included restricted intake of low-fat dairy products instead of a high intake of high-fat dairy products, use of vegetable fat and oil, an increase in fish intake, a decrease in meat intake, and the use of low-fat cooking methods such as oven-baking and boiling. These changes contributed to a decrease in SFA intake (from 14 E% at baseline to 5 E% after 6 weeks), and an increase in PUFA (from 5 E% at baseline to 6 E% after 6-weeks) (Paper I). The intake of 5 E% SFA in ND was consistent with recommendations for adults who would benefit from lowering LDL-C (1).

The reported intake of the decrease in dietary SFA and increase in dietary PUFA in ND (Paper I) was confirmed (Paper III, table 2) in the corresponding changes in CE-SFA 14:0 (found in butter and milk), 15:0 (a marker of dairy fat intake), and 18:0 (found in meat, milk, and butter), and CE-PUFA 22:6n-3 (a marker of fish intake). The increase in CE-FA, except for 16:0, in the whole group (n=86) was related to adverse changes in plasma lipoproteins, whereas, the change in CE-PUFA 22:6n-3 was inversely related to both LDL-C and HDL-C (Paper III). These results suggested that at least part of the lipid-lowering effects observed after the ND were related to the improvement in the quality of the dietary fat. These results were in agreement with a study by Iggman et. al. (154), where the replacement of dairy fat with rapeseed oil caused a rapid and clinically relevant improvement in serum lipoprotein profile in hyperlipidaemic individuals.

The high intake of dietary fibre (54 gram) after ND (Table 7) was a consequence of food choices when planning the ND, such as dietary fibre rich products, whole grain products and vegetables, for breakfast, lunch, dinner and snacks (Tables 3 and 4). Thus, there was no specific goal to reach the 54 gram of fibre intake. Part of the high fibre intake was the intake of β-glucan from oat and barley, which increased from 0.3 to 5 gram per day in ND. The high content of oat and barley products may contribute to a cholesterol lowering effect in ND (96, 97, 117, 120, 121).

Nutrient intake in ND

In the NORDIET study, previous dietary intake was investigated through the diet history interview in which all subjects habitual dietary intake for the previous month was assessed. After 6 weeks, the diet history interview was used to determine deviations from baseline in the control diet group. In the
ND group, the daily study checklist was used to calculate both nutrient and food intake after 6 weeks on ND.

At baseline, the diet history interview revealed high intake of SFA, and an intake of MUFA and PUFA in the low range of RI for both control diet and ND groups (Paper I) (93). Dietary fibre intake was in accordance with RI at baseline (Paper I) (93) for both control diet and ND groups. Sodium intake was above RI and above the intake of a Swedish reference population, in both groups. The reported high dietary fibre intake could be related to the reported high intake of energy at baseline. Habitual energy intake, calculated from the diet history, could be expected to be above the subjects’ habitual energy expenditure, as the subjects were slightly overweight at baseline (Paper I, table 1).

After 6 weeks, there were no changes in nutrient intake in the control diet group, but in ND, the changes in nutrient intake between baseline and 6 weeks were significant for all nutrients, except for alcohol (Table 7). The changes in nutrient intake in ND group was expected, as ND was planned with NNR 2004 (93) and inspired by other healthy diets (25, 31, 33, 36, 43, 96). The change in nutrient intake could be a consequence of the choice of foods with a focus on foods with high fat- and carbohydrate quality (Table 3), when planning the diet.

Validity of food and nutrient intake in ND

As there was no change in body weight or CVD risk factors from baseline to 6 weeks in the control diet group, it was assumed the reported dietary intake from the diet history interview was valid for the control diet group. In ND, the mean energy intake decreased by 522 kcal day\(^{-1}\) from baseline to 6 weeks, which corresponded to a weight loss of 3 kg after 6 weeks. The decrease in dietary SFA and increase in dietary PUFA intake in ND (Paper I) was reflected in corresponding changes in CE-SFA 14:0, 15:0, 18:0, and CE-PUFA 22:6n-3 (Paper III). With these findings, it was assumed that the dietary intake from dietary assessments used in ND was valid.

Side effects and sensory aspects of ND

There were no adverse events reported in either control diet or ND groups. The high content of dietary fibre in ND did cause flatulence and increased faecal quantity in some subjects, however after approximately 10 days, most subjects reported these effects subsided. The low salt content in the diet was less appreciated by some subjects, however, after 10 to 14 days several subjects reported an adaptation in taste to the low salt intake.
Why did not PB affect blood lipids?

“Eating a fibre-rich breakfast (porridge) without other dietary changes does not appear to lower blood lipids and body weight, or improve glucose metabolism, but it decrease markers of visceral fat and inflammation in healthy overweight subjects” (Paper IV).

Although the intervention breakfast in PB (Figure 9, Table 5), indicated changes in several nutrients from foods considered having an effect on CVD risk factors (96, 98), PB did not influence blood lipids, body weight, or glucose metabolism after 12 weeks (Paper IV, table 5). Thus, changing breakfast quality, without other dietary changes in the diet, did not affect blood lipids, body weight, or glucose metabolism in healthy overweight subjects who were all regular breakfast eaters at baseline.

The lack of effect on CVD risk factors after PB could be explained by several factors. First, subjects included in PB were already regular breakfast eaters as the aim was to investigate the role of breakfast nutrient quality. Previous studies explored the effect of eating breakfast per se on CVD risk factors, compared with skipping breakfast (137, 138).

Second, despite the change from baseline in β-glucan intake in the entire day’s nutrient intake (1.8 g from a 3-day food record and 2 g from the study diary), β-glucan intake did not reach the planned intake of 3 gram per day in the PB. The low β-glucan intake could be explained by low compliance to PB. The discrepancy of 0.2 gram could be explained by the two dietary assessment methods used, which were used for different purposes, to estimate the daily nutrient intake or the nutrient content of the breakfast eaten.

Third, despite the changes in nutrient intake from the breakfast, and some changes in overall nutrient intake for the whole day, there was no effect on LDL-C, which was the primary outcome of the study. The dietary changes in the breakfast might have been too small to influence LDL-C, as breakfast is only one part of the daily diet. A similar dietary intervention including all meals for the day, of which the PB represented the breakfast (Paper I), had profound effects on body weight, blood lipids and several other risk factors.

Fourth, as processing techniques may alter the molecular weight of the β-glucan and interfere with the viscosity and cholesterol lowering effect of β-glucan (119), processed β-glucan rich foods included in the ND and PB were analysed to determine intact molecular weight (175). Ten of eleven β-glucan rich foods in the ND, including oat bran porridge and oat bran-enriched muesli, which was included in PB, had a β-glucan molecular weight between $1.2 \times 10^6$ and $2.0 \times 10^6$ g/mol, and only one product (rusks used in the ND) had a molecular weight less than $1.0 \times 10^6$ g/mol (176).
ND and sustainability
The healthy ND is supported Bere and Brugs’ (161) proposal of six ingredients for a new healthier and more environmentally friendly Nordic diet, and is consistent with the definition of a sustainable diet suggested by Gussow and Clancy (162) and FAO 2010 (163).

Clinical implications of a healthy Nordic diet
The (-21%) LDL-C-lowering effect (-0.83 mmol/l) caused by the ND (Paper I), where PB was one part (Paper IV), was comparable to the effects of first-generation statins (8). A 1 mmol/l statin-induced reduction in LDL-C is suggested to reduce the risk of vascular events by 10% after 1 year, 25% after 2-3 years, and about 30% after 3 years (6). Thus, according to these numbers, the LDL-C lowering effect after ND may be of clinical relevance, although this remains to be investigated in larger trials with longer duration. The decrease in HDL-C after ND was probably due to a restricted fat intake (Paper I). However, improved LDL-C/HDL-C and apoB/apoA1 ratios suggest this effect alone is not of clinical relevance, as the overall risk profile improved. The decreased intake of SFA and increased n-3 PUFA intake in ND were partly reflected by changes in serum CE-FA composition, which were associated with an improved serum lipoprotein pattern (Paper III). However, the large reduction (nearly 7 mmHg) in systolic blood pressure after ND is clinically noteworthy. At a population level, this effect may correspond to an approximate 18% reduced risk of CVD mortality (77). In addition, the apparent satiating effect of the ND could be useful for managing overweight individuals and preventing obesity and the combined improvement in lipid and glucose metabolism and blood pressure may be clinically more important than improving single risk factors. Only changing the breakfast, without other dietary changes, does not appear to lower blood lipids and body weight, or improve glucose metabolism (Paper IV).

Strengths and limitations
The strengths of ND and PB include the randomised controlled design and that all food was provided for the ND group, and all breakfast items were provided for the PB group. The provision of the foods for the diet allowed the direct monitoring of compliance to the diet through daily study checklists on which uneaten foods were recorded: compliance in both the ND and PB groups were high. An important practical finding was the low dropout rate in both ND and PB groups, indicating good acceptance of the ND and PB.
The dietary history of food and nutrient intake was assessed through diet history interviews in ND. The advantages of the diet-history interview method are that relatively long periods can be studied, the levels of individual intake can be obtained through developing good communication with the subjects, and the interviewer can help to minimise the dropout rate. The diet history interview may also provide more valid data on intake as it records average energy intake closer to the energy expenditure than other methods (173). One limitation of this study was the use of different methods for dietary assessments at baseline and after 6 weeks in ND group (Papers I and II). However, the strength of the method used at 6 weeks in ND group was the knowledge that subjects had been provided with lunch- and dinner boxes and asked to comment and describe any deviation from the prescribed menu in a daily study checklist (Figure 6).

As de Lorgeril (29) comments in a review paper, diet scores usually used to assess conformity with the Mediterranean dietary pattern in epidemiological studies, may not capture the various practical aspects. The choice of cooking method used when preparing dishes is one practical aspect that may affect the final nutrient content of a food item or a dish. Cooking methods are not considered in scores used to assess compliance with the Mediterranean diet (17, 19, 29, 30); however, in ND, all cooking methods, recipes and menus were documented, which improve reproducibility of the study.

The change in dietary fatty acid intake in ND group is partly reflected in the change in serum CE-FA (Paper III), and could be used as a tool to validate the reported dietary fatty acid intake from the dietary assessments used in ND (Paper I). As the CE-FA composition in serum (Paper III) is given as relative amounts, this introduces the possibility that a result appearing to indicate an increase or decrease in a certain fatty acid is secondary to a pronounced increase in one or several other serum CE-FA present in high proportions. The change in dietary fatty acid intake in ND was partly reflected in the serum CE-FA, and as the change in body weight corresponded to the change in energy intake, the results from the dietary assessments used in ND are assumed valid.

There were limitations to ND and PB. ND was a controlled 6-week trial, in which subjects assigned to the ND were provided with all foods. Although the trial was not a long-term study, a subgroup was followed up for 10 weeks and presented a clear continuation of the favourable effects (Figure 12). This suggested the risk factor improvement might have been underestimated and that a steady state was not reached in the extended intervention of 10 weeks on the ND.

Physical activity was not monitored to assess differences between the groups in either ND or PB groups, although groups were encouraged to maintain their habitual lifestyle, including physical activity level, during the study.
Some foods (such as oranges, coffee, tea, almonds and psyllium), which might not comply with the definition of Nordic foods, were included in the study because of the time of the year, habitual use and cholesterol lowering effects. Typical Nordic berries e.g. cloudbERRIES, could have been used instead of oranges, but as cloudbERRIES are expensive, this might have taken the focus from an every-day menu. Another practical aspect was that subjects collected the cooler bags during their work time, therefore, it was not possible to include deep-frozen foods in the cooler bag, as they would thaw during the day.
Future perspectives

There are several possibilities for future research on healthy Nordic diet:

• To conduct additional interventional and epidemiological studies to translate the findings on CVD risk factors to potential effects on CVD hard outcomes.

• To investigate the environmental impact of choosing a healthy Nordic diet based on foods originating from the Nordic countries to fulfill the definition adapted from FAO/WHO (163) “Sustainable diet has a low environmental impact which contributes to food and nutrition security and to healthy life for present and future generations. Sustainable diets are protective and respectful of biodiversity and ecosystems, culturally acceptable, accessible, economically fair and affordable; nutritionally adequate, safe and healthy; while optimizing natural and human resources”.

• To investigate the effect on agricultural businesses if a healthy Nordic diet based on foods originating from the Nordic countries is chosen.

• To develop and improve the taste of the ND without impairing fat and carbohydrate quality.

• To improve the cooking methods, in order to optimise the health effects of a Nordic diet.
Conclusions

- An *ad libitum* healthy ND, based on foods originating from the Nordic countries, improves CVD risk factors such as LDL-C, LDL-C/HDL-C ratio, insulin sensitivity and blood pressure to clinically relevant levels in mildly hypercholesterolaemic subjects.

- The cholesterol lowering effect of ND was independent of weight loss, whereas the effects on insulin sensitivity and blood pressure appeared to be, at least partly, mediated by the ND-induced weight loss.

- It is possible to use foods originating from the Nordic countries to create a healthy ND in line with dietary recommendations and a prudent diet.

- By definition, ND is used in current studies is: “based on foods possible to cultivate, harvest and breed in the Nordic countries”.

- A healthy ND is “a plant-based diet, where animal products are used sparingly as side dishes”.

- ND “has a favorable dietary fat quality i.e. low in saturated fat and trans fat, and high in unsaturated fat. ND has a favourable carbohydrate quality i.e. rich whole grains, fruits, berries, vegetables, root vegetables, potatoes and legumes. In addition, as compared with the average Swedish diet, ND is low in sodium, and meat products, high-fat dairy products, sweets, desserts and alcoholic beverages”.

- The ND represents a prudent dietary pattern that has been consistently associated with decreased morbidity and mortality in prospective cohort studies.

- A healthy ND also considers healthy cooking methods such as low-temperature cooking methods *i.e.* oven baking and boiling.

- At least part of the lipid-lowering effects observed after the ND appear related to the improved fat quality in ND, *i.e.* lower intake of high-fat dairy and meat products and higher intake of their low-fat counterparts, vegetable oils, and fatty fish.
• Eating a fibre-rich breakfast (porridge) without other dietary changes does not appear to lower blood lipids and body weight, or improve glucose metabolism, but it decrease markers of visceral fat and inflammation in healthy overweight subjects.

• The results from this thesis suggest that a healthy diet based on foods originating from the Nordic countries has similar effects on plasma lipoproteins as a diet based on foods from Mediterranean countries, and may thus be an alternative in the treatment of mild hypercholesterolaemia in primary prevention.

• Additional interventional and epidemiological studies will be needed to translate the findings on CVD risk factors to potential hard outcomes effects on CVD.
Svensk sammanfattning

Medelhavskost är en kost som visats kunna förbättra den kardiovaskulära riskprofilen. I medelhavskost tar man inte enbart hänsyn till innehållet av näringsämnen utan också valet av livsmedel har betydelse.

Det övergripande syftet i avhandlingen är att i kontrollerade studier undersöka effekten av en hälsosam nordisk kost (ND) samt effekten av en nordisk frukost (PB) på kardioometabola riskfaktorer hos friska, milt hyperkolesterolemiska män och kvinnor. Ett andra syfte är att beskriva livsmedels- och näringsammansättning i ND. Ett tredje syfte är att undersöka hur ett förändrat intag av dietärt fett från ND påverkar fettsyrasammansättningen i serumkolesterolestrar och om det finns ett samband mellan dessa förändringar och förändringar i blodets lipoproteinprofil.


Metod och preliminära resultat

Artikel 1. I artikel 1, NORDIET-studien, har vi undersökt effekten av ND på kardiovaskulära riskfaktorer hos 88 friska försökspersoner med lätt förhöjda värden av low-density lipoprotein kolesterol (LDL-C) (4.0 mmol/l). ND var en hel kost som till största del bestod av traditionella livsmedel som har sitt ursprung och kan odlas, skördas och födas upp i de nordiska länderna. ND inkluderade livsmedel som har dokumenterade hälsoeffekter på kardiovaskulära riskfaktorer. ND gavs ad libitum och försökspersonerna informerades att studien inte var en viktminskningsstudie och uppmuntrades att äta tills mättnad. Försökspersonerna fick alla livsmedel för att tillaga frukost och mellanmål i hemmet. Lunch och middag tillhandahölls i färdiga matlådor.

Näringsprofilen för ND baserades på det dagliga rekommenderade intaget (RI) enligt Nordiska Näringsrekommendationer (NNR 2004), och har även inspirerats av tidigare studier av medelhavskost, DASH diet och portföljkost. Näringsprofilens fokus var fett- och kolhydratkvalitet. ND var en hel kost rik på frukt, bär, grönsaker, rottfakter, potatis, baljväxter, vegetabiliskt fettt och
oljor, fisk, med lågt innehall av köttprodukter, mejeriprodukter med högt fattinnehall, godis och desserter.

Den primära utfallsvariabeln i NORDIET-studien och frukoststudien var förändringen i LDL-C efter 6 respektive 12 veckor. De sekundära utfallsvariablerna var förändringar i övriga blodlipider, vikt, insulinåkänslighet, inflammationsmarkörer och blodtryck. ND förbättrade blodfettsprofilen och insulinåkänsligheten och sänkte blodtryck med kliniskt relevanta nivåer. Trots att ND serverades ad libitum, fann vi en minskning av kroppsvikten.


Artikel 3 är en delstudie baserad på NORDIET-studien där vi har undersökt hur förändringen av intaget av dietärt fett påverkat förändringen i fettsyresammansättning i serumkolesterolstr (CE-FA). Vi har sedan korrelerat förändringarna i CE-FA med förändringen av lipoproteiner i blodet. Resultaten visar att det minskade intaget av mättat fett och ökade intaget av fleromättat fett speglas i förändring av CE-FA mönstret. Således kan CE-FA användas som en objektiv markör för kostintaget av olika fetter som ingår i en nordisk kost. Resultaten visar även på ett samband mellan förändringar i CE-FA och det förbättrade lipoproteinmönstret. Detta tyder på att en del av de lipidsänkande effekter som observerats i ND verkar relaterade till den förbättrad fettkvaliteten i ND.

Artikel 4 är baserad på den andra genomförda RCT:n i avhandlingen, där kostinterventionen utgjordes av en nordisk frukost, PB, från NORDIET-studien. Vi undersökte effekten av PB på kardiometabola riskfaktorer hos 79 stycken redan frukostätande försökspersoner med lätt förhöjda värden av LDL-kolesterol. PB var rik på kostfiber och hade ett lågt fettinnehall.

Den primära utvallsvariabeln i PB var förändringen i LDL-C efter 3 månader. De sekundära utfallsvariablerna var förändringar i kroppsvikt, total cholesterol, HDL-C, LDL-C/HDL-C ratio, triglycerider apoA1 och apoB, apoB/apoA1 ratio, glukostolerns, insulinåkänslighet, sagittal abdominal diameter (markör för visceral fettansamling), tumor necrosis factor receptor-2 (TNF-R2) faktor, C-reactive protein (CRP), och blodtryck. Resultaten visar att PB inte påverkar blodfettern, kroppsvikt, och glukosmetabolismen, men minskade markörer för visceralt fett (SAD) och inflammation (CRP och
TNF-R2). Resultaten pekar på att kostråd om att enbart förbättra frukostvänorna ej är tillräckligt för att sänka lätt förhöjda värden av LDL-C eller förbättra glukosmetabolismen, men tycktes kunna sänka systemisk (låggradig) inflammation och reducera bukfettet, men de senare fynden behöver bekräftas i andra studier. 

Sammanfattningsvis föreslår denna avhandling att en hälsosam kost baserad på livsmedel med ursprung i de nordiska länderna kan förbättra blodfettprofilen, insulinänslighetens, minska kroppsvikten, sänka blodtrycket och kan därmed tänkas vara ett alternativ vid behandling av mild hyperkolesterolemi hos friska måttligt överviktiga personer. En del av de lipidsänkande effekter som observerats i ND verkar relaterad till den förbättrat fettkvaliteten i ND. En fiberrik frukost, utan andra ändringar i kosten, påverkade inte blodfetter, kroppsvikt, och glukosmetabolism men minskade markörer för visceralt fett och inflammation.
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