# The effect of heart-friendly nutritional advice on change in diet and cardiovascular disease risk factors in patients with inflammatory joint disease

Master thesis by

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**November 2016**

Year: 2016

Title: The effect of heart-friendly nutritional advice on change in diet and cardiovascular disease risk factors in patients with inflammatory joint disease

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Print: CopyCat®
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# Acknowledgement

The work included in this thesis would not been possible without the contribution from several persons to whom I am profoundly thankful.

First of all, I would like to thank my main supervisor Anne Grete Semb for all her support and for helping me together with Silvia Rollefstad to define the hypothesis of this master project. There have been of great value spending time and work with you, who possess so much research experience and knowledge. I am deeply grateful for your time reviewing my drafts and final manuscript and for giving important scientific feedback through the whole year I have been working with this thesis. I am especially grateful for all the time you have spent during the last days, helping me finish my manuscript. You have always had an optimistic and positive personality, which has given me confidence and belief in the work I have done.

I would also like to thank my co-supervisors, Silvia Rollefstad and Sissel Urke Olsen. You have both spend a lot of hours and even days evaluating all my material through the last year. I am so grateful for all support and feedback. You have given me important scientific input but also assisted with linguistic corrections and grammatical help. Silvia, thank you for all support with the statistical analyses.

I would also like to thank my third co-supervisors, Kirsten Bjørklund Holven, for reading through my finally manuscript and giving me some last feedback.

I am grateful to the statistician, Inge Christoffer Olsen, for answering all my statistical questions, help with power calculations and analyses. I am also thankful for the training in dual X-ray absorptiometry by Silje Halvorsen Sveaas. Your instructions were indispensable.

I want to thank all the persons at the Diakonhjemmet hospital, which have made it possible for me to perform a randomized clinical trial as my master project. It has been an incredibly exciting and instructive year.

I am deeply grateful to my family and close friends and especially my sister, Malene, for all supporting words and thoughtfulness through the whole year, but particularly during the last weeks of my work with my thesis. Finally, I would like to thank my outstanding boyfriend, Sindre, for his patience and care throughout this period. Thanks for taking care of our home and for serving me meals, while I spent all my time writing over the past few weeks.

# Summary

**Background**: Patients with inflammatory joint diseases (IJD) have an increased risk of atherosclerotic cardiovascular disease (CVD) compared to the general population. An increased presence of traditional risk factors combined with cardiovascular effects of chronic inflammation may be contributing factors. Nutritional advice has shown to influence CVD risk factors and may be essential in prevention of CVD in these patients.

**Objective**: To test in patients with IJD, whether an individually tailored, extended dietary counselling on cholesterol-lowering and heart-friendly diet had comparable effect on change of diet, lipids, blood pressure (BP), inflammatory markers and body composition, as a standardized brief advice on heart-friendly diet,

**Method**: Thirty one patients with IJD (rheumatoid arthritis (RA) n=16, Psoriatic Arthritis (PsA) n=7, Ankylosing Spondylitis (AS) n=8), aged 40-80 years, screened for CVD risk at the Preventive Cardio-Rheuma Clinic at Diakonhjemmet Hospital, received a brief standardized advice (3-4 minutes) on heart-friendly food by a physician and a written "shopping guide" for heart healthy food items. Sixteen patients were randomized to receive an individually tailored, extended dietary counselling (60 minutes), on heart-friendly and cholesterol-lowering diet (diet group [DG]), by a student in clinical dietetics. The remaining 15 patients (control group [CG]), received no further dietary information. Change in dietary habits, assessed by a validated questionnaire (SmartDiet), lipids, BP, C-reactive protein (CRP) and body composition, obtained by Bioelectrical impedance analysis (BIA) and Dual Energy X-ray Absorptiometry (DXA), were assessed after eight weeks of follow-up.

**Results**: Average increase in mean SmartDiet score were 5.1 points and 5.7 points in the DG and the CG, respectively after eight weeks follow-up (p=0.65). Eight weeks after intervention a more frequent use of vegetable oil/liquid margarine (p=0.04), bread high in fibre (p=0.04) and a less frequent use of butter/hard margarine (p=0.02) in the DG, compared to the CG was observed. LDL-cholesterol (LDL-c) and total cholesterol (TC) was reduced by 12.6 % and 2.4 % (p=0.05) vs.6.3 % and 0.4 % (p=0.19) in the DG and CG, respectively. There were no significant differences between the two groups in mean change in BP, lipids, CRP or body composition after eight weeks.

**Conclusion**: Our findings point to that the clinical effects of brief advice is comparable to an extended nutritional advice on cholesterol friendly food/diets in patients with IJD. This may be important in a clinical setting, with limited resources. Although, the extended dietary counselling seems to be superior to standardized brief advice in promoting heart-friendly food choices and possible in LDL-c- and TC-lowering effects. Nevertheless, both tailored, extended dietary counselling and brief advice showed equal improvement in SmartDiet score and there were no significant differences between the groups in either change in BP, CRP or body composition after eight weeks follow-up.

# Funding

The work included in this thesis was financed by the University of Oslo and Diakonhjemmet Hospital.

# Abbreviations

| | |
|---|---|
| ACR | American College of Rheumatology |
| ACPA | Antibodies to Citrullinated Protein Antigens |
| ALST | Appendicular Lean Soft Tissue |
| ANCOVA | Analysis of Co-variance |
| AS | Ankylosing Spondylitis |
| bDMARDs | Biologic Disease Modifying Anti-Rheumatic Drugs |
| BIA | Bioelectrical impedance analysis |
| BMI | Body Mass Index |
| BP | Blood pressure |
| CG | Control Group |
| CHD | Coronary Heart Disease |
| CK | Creatine Kinase |
| CRP | C-reactive protein |
| CV | Cardiovascular |
| CVD | Cardiovascular disease |
| DASH | Dietary Approaches to Stop Hypertension |
| DG | Dietary Group |
| DMARDs | Disease Modifying Anti-Rheumatic Drugs |
| DHA | Docosahexaenoic Acid |
| DXA | Dual Energy X-ray Absorptiometry |
| EAM | Extra-Articular Manifestation |
| EPA | Eicosapentaenoic Acid |
| ESR | Erythrocyte Sedimentation rate |
| EULAR | The European League Against Rheumatism |
| FFM | Fat Free Mass |
| FFMI | Fat Free Mass Index |
| FFQ | Food Frequency Questionnaire |
| FM | Fat mass |
| FMI | Fat Mass Index |
| HDL-c | High Density Lipoprotein Cholesterol |
| HLA | Human Leucocyte Antigen |
| IJD | Inflammatory Joint Disease |
| LM | Lean Mass |

| | |
|---|---|
| IFN | Interferon |
| IL | Interleukin |
| IQR | Interquartile Range |
| LDL-c | Low Density Lipoprotein Cholesterol |
| MD | Mediterranean diet |
| MDP | Mediterranean Diet Pattern |
| MI | Myocardial Infarction |
| MRI | Magnetic Resonance Imaging |
| MTX | Methotrexate |
| MUFA | Mono Unsaturated Fatty Acid |
| NSAIDs | Non-steroidal Anti-Inflammatory Drugs |
| PsA | Psoriatic Arthritis |
| PREDIMED | PREvención con DIeta MEDiterránea |
| PUFA | Polyunsaturated Fatty acid |
| RA | Rheumatoid Arthritis |
| RCT | Randomized Clinical Trial |
| SCORE | Systematic Coronary Risk Evaluation |
| SCS | Seven countries study |
| SD | Standard Deviation |
| sDMARDs | Synthetic Disease Modifying Anti-Rheumatic Drugs |
| SFA | Saturated Fatty Acid |
| SMC | Smooth Muscle Cell |
| SMM | Skeletal Muscle Mass |
| SMI | Skeletal Muscle Index |
| SPA | Spondyloarthritis |
| TC | Total Cholesterol |
| TIA | Transient Ischemic Attack |
| TG | Triglyceride |
| TNF | Tumor Necrosis Factor |
| WHO | World Health Organization |

# 1 Introduction

It has been established that patients with inflammatory joint diseases (IJD) as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) have an increased risk of atherosclerotic cardiovascular disease (CVD) compared to the general population (1-3). A combination of traditional risk factors and the cardiovascular (CV) effects of chronic inflammation might be contributing factors. For decades', dietitians have recommended diets to reduce joint pain in patients with IJD, even the evidence from human intervention studies are weak (4). However, the recommendations have changed due to new scientific knowledge. Today, effective anti-rheumatic treatments are in use (4). The effectiveness of newer anti-rheumatic drugs, may hypothetically outplay the importance of diet as a potential contributor in disease activity in patients with IJD. Nevertheless, diet will still be of considerable importance in prevention of comorbidity, as CVD, in these patients. Nutritional advice and guidance have been reported to influence CVD risk factors and have been shown to have beneficial effect on both prevention and treatment of CVD (5, 6). There is a knowledge gap on the effect of nutritional advice**,** on change in dietary habits and CVD risk factors in IJD patients.

# 2 Background

## 2.1 Inflammatory joint disease (IJD)

There are over 200 rheumatic diagnoses, with different manifestations, primarily affecting the musculoskeletal system. The majorities of the diagnosis are chronic, with persistent need for treatment. The disorders mainly involve pain and stiffness in muscles and joints, but may also afflict other organs (7). Rheumatic disorders are some of the main reasons why Norwegians search health care professionals and the leading cause of sick leave and seek disability benefits (8, 9), which not only affect the patient themselves, but also their families and the society. IJD is one out of four major groups among rheumatic disorders (10). RA and spondyloarthritis (SpA), as AS and PsA are the most common, which represent the three major IJD subtypes (3). IJD are characterized by chronic inflammation of joints and related tissues (3), leading to increased morbidity, comorbidity and mortality and often decreased quality of life, lost productivity and increased cost of health care. These may result in an economic- and social burden (11). Early diagnose and tailored treatment, combined with lifestyle changes, may provide better prognosis for the individual and possibly reduce the burden on healthcare system and the socio-economic costs.

### 2.1.1 Rheumatoid arthritis

RA is a chronic, autoimmune and progressive IJD, affecting mainly symmetrical peripheral joints with erosive synovitis that causes functional disability (12). Extra-articular manifestations (EAM), such as subcutaneous nodules, vasculitis, pericarditis, pulmonary nodules or intestinal fibrosis may occur (11). The disease cause varying degrees of joint destruction, inflammation of the synovium or lining of the joint, which lead to pain, stiffness, swelling, joint damage, and loss of function (13). Despite fluctuating course with both remission and aggravation of the disease, most RA patients need ongoing medical treatment.

There are no separate diagnostic criteria for RA, but RA has been classified and often diagnosed, according to the 1987 American College of Rheumatology (ACR) classification criteria for RA (table 1) (14). These classification criteria from 1987 have been criticized for their lack of sensitivity in early disease (15). Therefore, new classification criteria were developed by working groups from the ACR and The European League against Rheumatism (EULAR) in 2010 (15). In the new set of criteria (table 2), which are based on number and size of the joints

with synovitis, serological test, acute phase reactants and duration of symptoms, scores between 0-10 are given. A patient with score > 6 will be classified with the disease. This new classification system focuses on features in RA at earlier stages of disease, rather than symptoms occurring at a late-stage of the course.

**Table 1** The 1987 ACR classification criteria for rheumatoid arthritis, a simplified version after Arnett et al. (14)

| **The 1987 revised criteria for the classification of rheumatoid arthritis** | |
|---|---|
| **Classification criteria for RA**<br>• **At least 4 out of 7 criteria.**<br>• **Criteria 1-4 must have been present for at least 6 weeks** | **Definition** |
| **1. Morning stiffness** | Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement |
| **2. Arthritis of 3 or more joints areas** | At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints |
| **3. Arthritis of hand joint** | At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint |
| **4. Symmetric arthritis** | Simultaneous involvement of the same joint areas (as defined in 2 ) on both sides of the body (bilateral involvement of PIPS, MCPs, or MTPs is acceptable without absolute symmetry) |
| **5. Rheumatoid nodules** | Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions,<br>observed by a physician |
| **6. Serum rheumatoid factor** | Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the<br>result has been positive in 4 % of normal control subjects |
| **7. Radiographic changes** | Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist<br>radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify) |

ACR, American College of Rheumatology; RA, Rheumatoid Arthritis; PIP, Proximal Interphalangeal Joints; MCP, Metacarpophalangeal Joints; MTP, Metatarsophalangeal Joints

**Table 2** The 2010 ACR/EULAR classification criteria for rheumatoid arthritis, a simplified version after Aletaha et al. (15)

| The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis | |
|---|---|
| **Target population, patients who:**<br>1. **Have at least 1 joint with definite clinical synovitis**<br>2. **With a synovitis not better explained by another diseases** | Score |
| **Classification criteria for RA**<br>**(score based algorithm, a score ≥ 6/10 are needed)** | |
| **A. Join involvements** | |
| **1 large joint** | 0 |
| **2-10 large joints** | 1 |
| **1-3 small joints (with or without involvement of large joints)** | 2 |
| **4-10 small joints (with or without involvement of large joints)** | 3 |
| **> 10 joints (at least 1 small joint)** | 5 |
| **B. Serology (at least 1 test result is needed for classification)** | |
| **Negative RF and negative ACPA** | 0 |
| **Low-positive RF or low-positive ACPA** | 2 |
| **High-positive RF or high-positive ACPA** | 3 |
| **C. Acute-phase reactants (at least 1 test result is needed for classification)** | |
| **Normal CRP and normal ESR** | 0 |
| **Abnormal CRP or abnormal ESR** | 1 |
| **D. Duration of symptoms** | |
| **< 6 weeks** | 0 |
| **≥ 6 weeks** | 1 |

ACR, American College of Rheumatology; EULAR, European League against Rheumatism; RA, Rheumatoid Arthritis; RF, Rheumatoid factor; ACPA, Antibodies to Citrullinated Protein Antigens; ESR, Erythrocyte Sedimentation rate; CRP, C-reactive protein

## Epidemiology

The prevalence of RA in developed populations have been reported to be 0.5-1 % of the adult population (16), although the overall prevalence varies between ethnic groups and geographical areas (17). In European and Scandinavian countries, the prevalence of RA ranges from 0.4-3.0 %, while in Norway, the prevalence has been estimated to 0.5 % (12, 17). Genes, environment and culture have also been proposed to account for this diversity. The incidence rates have been reported to range from 9-45 per 100 000 cases annually in Europe, while new cases in Norway has been reported to be between 20-25 per 100 000 annually (12, 18). In light of the earlier classification criteria, establishing an early diagnosis of RA has been challenging, and has resulted in that only few studies have addressed the incidence rate of RA (11). Both incidence and prevalence of RA generally increase with age, but decline after 70 years of age (19). There is a female preponderance in RA, with a female to male ratio of 2-3:1 (11, 20, 21).

**Pathogenesis**

The global variation observed between prevalence and incidence, indicate different genetic risks and environmental exposure (21). Genetics contribution has been attributed to 50 % of the risk of developing RA. While smoking is the leading environmental risk factor, which doubles the risk of developing RA if one is genetically disposed (21). The cause of RA is unknown (11), although, inflammation is an essential part of the pathogenesis and several inflammatory cascades, including overexpression of tumor necrosis factor (TNF) and overproduction of a variety of cytokines (such as interleukin (IL)-1 and IL-6), promote synovial inflammation and joint destruction (21). The female preponderance in RA, makes it hypothetically likely that hormones, menstrual- and reproductive factors are of importance (11). Pregnancy is strongly associated with remission in female RA patients and clinical trials have shown protection or a postponed development of severe RA in female users of contraceptives (22, 23). RA is characterized as an autoimmune disease and the most specific biomarker of RA is antibodies to citrullinated protein antigens (ACPA), which are present in approximately 60 % of all RA patients, compared to only 2 % of the general population (24). ACPA is added to the new classification criteria from 2010, in addition to rheumatoid factor (RF). The latter is a less specific biomarker of RA (15). Clinical trials distinguish between autoantibody-positive and autoantibody- negative RA patients, were autoantibody-positive patients seems to have a more severe course of the disease with more extensive joint damage and low remission rates (21).

**Treatment**

In the last two decades, pharmacological treatments for rheumatic diseases have evolved remarkably and is required to reduce or reverse signs and symptoms as pain, systemic inflammation, large-scale cartilage breakdown, joint deformities and severe functional disabilities (25). The management of RA has primarily relied on the use of disease modifying anti-rheumatic drugs (DMARDs) (25). Biologic DMARDs (bDMARDs) have been of significant importance for disease outcome and have been mentioned as a “therapeutic revolution” (21). Low disease activity and remission is the therapeutic goal for RA (25). Today Methotrexate (MTX) is the routine drug of choice in newly diagnosed RA patients (eventually combined with short-term low dose glucocorticoids), but if low disease activity or remission is not reached on MTX, other synthetic DMARDs (sDMARD) or bDMARD (most commonly a TNF-α inhibitor or T-cell stimulation modulators, B-cell inhibitors or IL-6 inhibitors) are usually added (25). Patients with RA have a high risk of comorbidities that need treatment, which may

lead to polypharmacy (21). Supportive non-pharmacological treatments as exercise, patient's education and psychological support is also of importance (21).

### 2.1.2 Ankylosing spondylitis

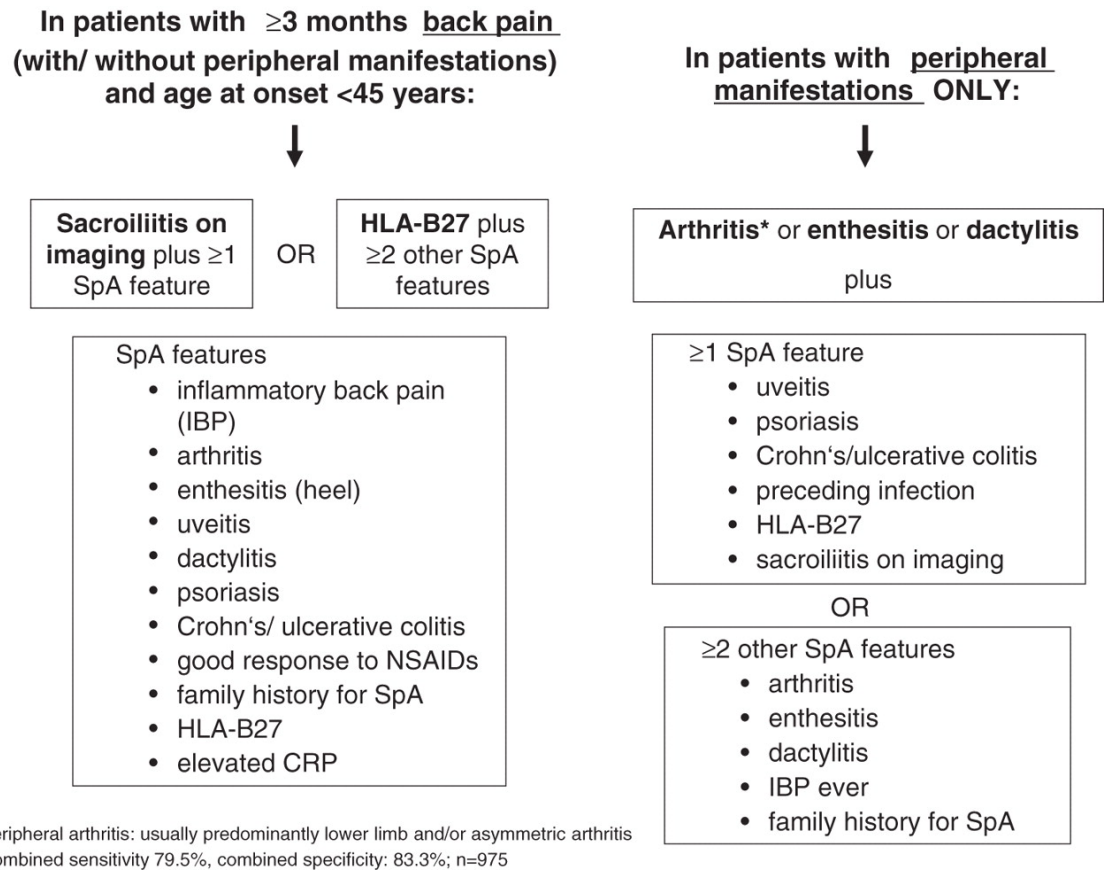
AS (also known as Bechterew´s disease) is a common inflammatory rheumatic disease and the major subtype of SpA (26). AS generally affects the axial skeleton, were inflammation, especially in the sacroiliac joint (sacroiliitis), structural changes and damage of the spine give rise to back pain, spinal stiffness and loss of mobility (26). Peripheral asymmetrical oligoarthritis, primarily in the lower limbs and EAMs like uveitis and/or gastroenterological involvement may also be present in AS patients (26, 27).

Traditionally, the 1984 modified New York criteria have been widely used to classify AS (table 3) (28), but these were replaced in 2009 by the Assessment of Ankylosing Spondylitis (ASAS) criteria for axial SpA, which were developed to detect early disease (29). In 2011 the ASAS criteria for peripheral SpA were published (figure 1) (30).

**Table 3** Modified New York criteria for ankylosing spondylitis (28)

| **Modified New York criteria for ankylosing spondylitis** |
|---|
| **A. Diagnosis**<br>**1. Clinical criteria**<br>a) **Low back pain and stiffness for more than 3 months which improves with exercise, but is not relieved by rest.**<br>b) **Limitation of motion of the lumbar spine in both the sagittal and frontal planes.**<br>c) **Limitation of chest expansion relative to normal values corrected for age and sex**<br>**2. Radiologic criteria**<br>a) **Sacroiliitis grade ≥ 2 bilaterally or sacroiliitis grade 3-4 unilaterally** |
| **B. Grading**<br>**1. Definite ankylosing spondylitis if the radiologic criterion is associated with at least 1 clinical criterion**<br>2. **Probable ankylosing spondylitis if:**<br>a) **Three clinical criteria are present.**<br>b) **The radiologic criterion is present without any signs or**<br>**c) symptoms satisfying the clinical criteria. (Other causes of sacroiliitis should be considered.)** |

**Figure 1.** Assessment of Spondyloarthtitis international Society (ASAS) criteria for axial spondyloarthritis (SpA) and the ASAS criteria for peripheral SpA.




Rudwaleit M, van der Heijde, D, Landewe R Et al.Ann Rheum Dis 2011;70:25-31
HLA, Human Leucocyte Antigen; CRP, C-reactive protein; NSAIDs, Non-steroidal Anti-Inflammatory Drugs.



## Epidemiology

AS generally occurs in young people and approximately 80 % of affected patients develop symptoms before the age of 30 (26). The prevalence of AS is associated with prevalence of the Human Leukocyte Antigen (HLA)-B27 allele (27) and 90-95 % of AS patients seem to carry this allele (31). Generally, the prevalence of AS is approximately between 0.1 and 1.4 % (26), but with great variety by geographical distribution (27, 32, 33). The prevalence of AS in Norway has been reported to be 0.4-1.8 (27).

The incidence of AS is associated with HLA B27 as well. In population with lower prevalence of HLA B27, the incidence rates of AS have been shown to be lower compared to regions with higher prevalence of HLA B27. Overall, the incidence of AS has been estimated to be 0.5-14 per

100 000 person years (26), while high rates of AS have been observed in the Nordic countries and in North America (incidence rates between 6.9-10.6 per 100 000 person years). The lowest incidence rates were found in Greece and Japan, with rates of 1.5 and 0.5 per 100 000 person years, respectively (27). In Norway, the incidence rate of AS has been reported to be 10.6 per 100 000 person years (27). There is a male preponderance in AS, with a male to female ratio of approximately 2:1 (26).

**Pathogenesis**

The underlying cause of AS remains unknown, but inflammation and new bone formation are two main features in the disease (26). It has been hypothesized that the geographical variety in prevalence and incidence of AS are due to genetic and environmental differences. Environmental factors are supposed to explain approximately 10 % of the disease susceptibility, while entirely 90 % seems to be explained by genetic factors (34). Approximately 1/3 of the genetic effect is related to the HLA B27 genotype, which is the most important gene predisposing for AS (35). The association is still unknown. Both gastrointestinal bacterial species and Chlamydia trachomatis, infecting the genitourinary tract, are potentially environmental triggers in AS (34). An association between HLA B27 and some gastrointestinal bacterial species have been observed, which may partly explain the link between Crohn´s disease and AS (26). It has been reported that 54 % of HLA B27 positive patients with Crohn´s disease develop AS, while only 2,6 % of HLA B27 negative Crohn´s patients do the same (26). Mechanical stress at the enthesesis is another apparent environmental factor in AS, which may cause inflammation and bone erosion (34). However, underlying triggers of inflammation in AS are not entirely explained, and pathways including IL-17 and IL-23 seem to be involved (35). Inflammation may initiate new bone formation (35). Both abnormal bone formation, together with bone destruction are contributors to structural damage in the skeleton of patients with AS (35).

**Treatment**

The primary recommended goal of treatment in AS is; “to maximize long-term health related quality of life and social participation through control of signs and symptoms, prevention of structural damage, normalization or preservation of function, avoidance of toxicities and minimization of comorbidities” (36). Furthermore, remission or minimal disease activity are the main treatment target in AS patients, with use of a combination of non-pharmacological- and pharmacological approaches (36, 37). Both education and regular exercise are essential features

of the non-pharmacological part of the treatment. Exercise may reduce inflammation in AS patients and have been shown to decrease disease severity scores and improve joint mobility (38). Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) is approved as first-line drug treatment, while TNF α–inhibitors should be given to patients with high disease activity (37). Contrary to RA, DMARDs, including MTX, have not shown to be effective in treating AS patients (37).

### 2.1.3 Psoriatic arthritis

Like AS, PsA is included in the group of SpA (39). PsA is a seronegative IJD, associated with psoriasis and a diversity of musculoskeletal, extra-articular features and comorbidities (39). The disease is characterized by spondylitis, enthesitis and dactylitis (40, 41).

Moll and Wrights classification criteria from 1973 (42) have, despite criticism for low sensitivity for detecting milder forms for PsA, been widely used in trials and clinical practise over many years (39). The Moll and Wrights criteria have been updated by various diagnostic- and classification criteria (39). In 2006, the Classification Criteria for Psoriatic Arthritis (CASPAR) were published (table 4) (43). These criteria are also appropriate for use in the diagnostic processes of PsA (44).

**Table 4** CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria, a simplified representation after Taylor et al. (43)

| The CASPAR criteria for psoriatic arthritis | |
|---|---|
| **To meet the CASPAR criteria, a patients must have inflammatory articular disease (joint, spine, or entheseal) with ≥ 3 points from the following 5 categories:** | |
| 1. | 1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis |
| 2. | **Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination.** |
| 3. | **A negative test result for the presence of rheumatoid factor by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.** |
| 4. | **Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.** |
| 5. | **Radiographic evidence of juxtaarticular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.** |

**Epidemiology**

Estimation of prevalence and incidence of PsA has been challenging before the CASPAR criteria, due to lack of consensus regarding classification-and diagnostic criteria (40). The prevalence of PsA in population-based trials has been estimated to vary from 0.01 % to 0.47 %, while the incidence has been reported between 3.02-23.00 per 100 000 persons per year (45). PsA has been shown to be prevalent worldwide, but with variation between geographic location and distinct ethnic groups. Europe may have the highest prevalence of PsA, while publications from West Africa and Japan have reported the lowest prevalence (45). A study from Western Norway reported in 2005 a PsA prevalence of 0.2 %. (41). These variations may likely be explained by variety of genetic and environmental factors, but may also be related to differences in study design and methodological quality (39, 40, 45). Approximately 70 % of the PsA patients develop psoriasis before articular involvement and the majority experience onset of the disease between the age of 30-55 (39). The disease is equally frequent in males and females (39).

**Pathogenesis**

PsA is a disease of unknown aetiology, but it is believed that both genes and environmental factors in combination with immunologic mechanisms are of importance in the development of the disease (39, 45). Both infiltration of activated T-cells and T-cell derived cytokines, as IL-1, -2 and -10 and TNF-$\alpha$, are all essential determinants in the pathogenesis (39). A higher accumulation of PsA in some families suggests that heritability is of significance. High-frequent alleles as HLA B38 and B39 are associated with increased susceptibility for PsA with peripheral arthritis and PsA with spondylitis, respectively, while HLA B27 is associated with axial PsA (39). Physical traumas and infections have been identified as potential environmental triggers (39, 45). Smoking is a risk factor for development of both psoriasis and PsA (45).

**Treatment**

Initially, the management of PsA was primary based on experience and research in RA patients, but has during the last few years, been replaced by evidence based knowledge founded on examination of PsA patients (46). In 2016, updated recommendations for management of PsA were published by EULAR (47). The primary goal is "to maximise health-related quality of life, through control of symptoms, prevention of structural damage, normalisation of function and social participation" Remission or minimal disease activity are the main treatment target in PsA

patients, with reversal of inflammation as crucial element to attain this target (47). To alleviate musculoskeletal signs and symptoms, NSAIDs may be used, possible in combination with use of corticosteroids (47). Both conventional sDMARDs and/or bDMARDs (often TNF-inhibitor) should be considered in patients with insufficient response to other treatment (47).

## 2.2 Cardiovascular disease (CVD)

Worldwide, it has been estimated that CVDs are accountable for approximately 17.5 million deaths per year, which represent 31 % of all global deaths and make it the number one cause of death (48). The World Health Organization (WHO) defines CVD as follows "is caused by disorders of the heart and blood vessels, and includes coronary heart disease (CHD) (myocardial infarction [MI]), cerebrovascular disease (stroke), raised blood pressure (BP) (hypertension), peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure." (49). Despite the fact that CVD mortality has decreased since 1970s, CVD remains the leading cause of death in Norway (50). Closely 330 000 CVD events were registered in Norway in 2014, of which approximately 11 700 were fatal (51, 52). The leading lifestyle related causes of CVD are tobacco use, physical inactivity, harmful use of alcohol and unhealthy diet, which may manifests as hypertension, hyperlipidemia, raised blood glucose and/or overweight and obesity in the individual (49).

### 2.2.1 Atherosclerotic disease

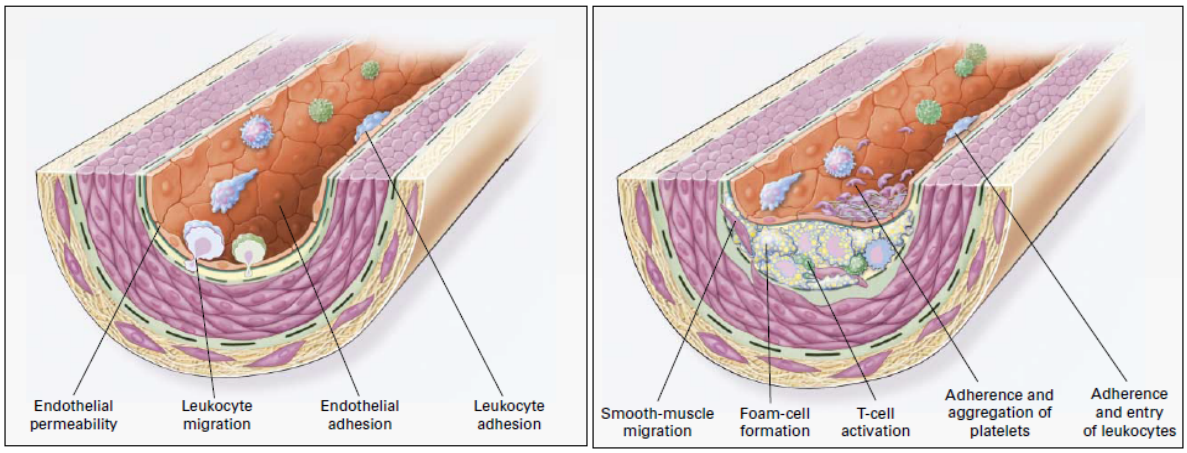
CVD can be divided in to two different groups according to aetiology (53). Ischemic heart disease, CHD, cerebrovascular disease and diseases of the aorta and arteries, including hypertension and peripheral vascular disease, arise from atherosclerosis, while the rest of the CVDs have secondary aetiology and will not be paid further attention to in this thesis.

**Pathogenesis of atherosclerosis**

Atherosclerosis is an inflammatory pathological process, which develops in the wall of blood vessels, (figure 2 and 3), starting asymptomatically in childhood and adolescence and progress into clinical events in the middle age (54). Acceleration of the atherosclerotic development depends on presence of different risk factors (53). Endothelial function has been shown to be central to the atherosclerotic development, apparently due to its importance in regulation of the vascular homeostasis (54). The atherosclerotic process, starts with a formation of an atheroma or

a plaque, and formation of fatty streaks (accumulation of lipids and leukocytes in tunica intima of the vessel wall) and endothelial dysfunction develops (55, 56). Endothelial dysfunction may be induced by numerous factors such as hypertension, increased levels of low density lipoprotein cholesterol (LDL-c) and homocysteine, free radicals caused by cigarette smoking, diabetes mellitus, genetic alterations, contagious microorganisms or inflammation (54, 57). A dysfunctional endothelium becomes more permeable, allowing LDL-c infiltration of the arterial wall, causing lipid retention and accumulation (57). LDL modification (e.g. oxidation) in the intima media of the vessel wall, inducing secretion of bioactive mediators which may activate the endothelium, leading to expression of various types of adhesions molecules (58). Recruitment and adherence of leukocytes (T- lymphocytes and monocytes) results in trans-endothelial migrating of leukocytes into the intima media (57).

**Figure 2**. Endothelial dysfunction (left image) and formation of fatty streaks (right image), the initiating step of atherosclerosis.

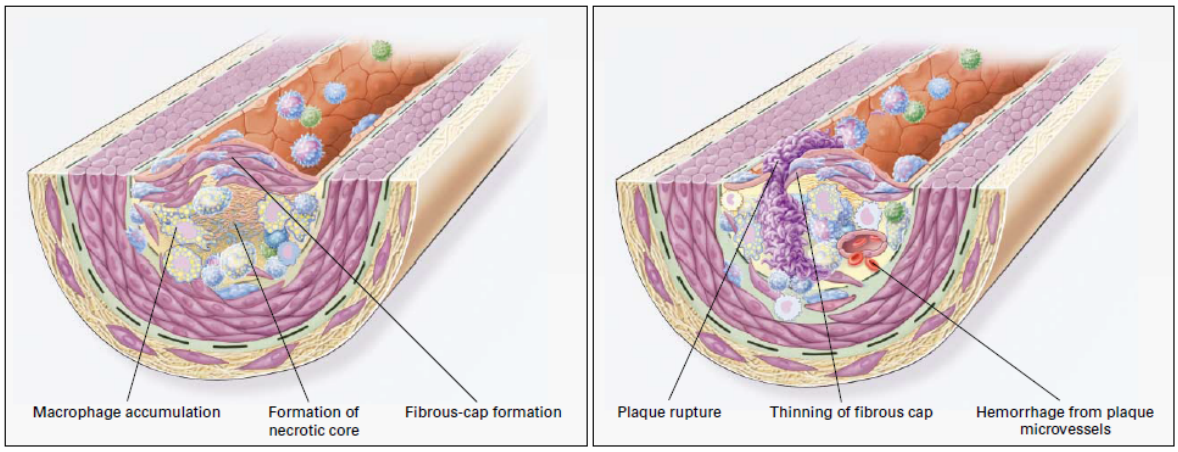



Reproduced with permission from Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med. 1999 Jan 14;340(2):115-26. © Massachusetts Medical Society

Monocytes in the intima media differentiate into macrophages, engulfing oxidized LDL-c and becoming foam cells (59). The activated macrophages (foam cells) release several signal molecules as pro-inflammatory cytokines (such as TNF-α and IL-1), growth-regulating molecules (e.g. platelet-derived growth factor) and proteolytic enzymes (such as metalloproteinases), of which some promote recruitment of additional inflammatory cells, some stimulate T-cell activating and others are of importance for cell survival, apoptosis or replication (57). Smooth muscle cells (SMC) proliferate and immigrate from tunica media to tunica intima (59). They are stimulated by e.g. cytokines and growth factors released from activated platelets, adhered to the dysfunctional endothelium (57). An accumulation of activated platelets, together

with foam cells and activated T-cells, contribute to advancement of the plaque. Over time, growth of the plaque leads to apoptosis and cell death of foam cells and SMCs. A necrotic core of accumulating lipids from the dying cells creates in the center of the advancing plaque (56, 59). A fibrous cap covers the atherosclerotic plaque, which consist of matrix molecules, as collagen, produced by the SMC (56, 57).

**Figure 3.** Formation of atherosclerotic plaque, (left image) and atheromatous plaque with unstable, fibrous cap and rupture (right image)




Reproduced with permission from Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med. 1999 Jan 14;340(2):115-26. © Massachusetts Medical Society

Despite arterial thickening and narrowing of the vessel, even large plaque may be asymptomatic. Acute events as MI or ischemic stroke seem to appear after plaque rupture and formation of a thrombus (58). Several molecules, produced by immune cells in the inflammatory activated plaque, contribute in destabilization and rupture of the lesion through inhibition of cap formation and degradation of the fibrous cap. Exposure of thrombogenic plaque content, stimulate coagulation factors and platelets, which initiate thrombosis (58). Complete occlusion of a vessel will lead to ischemia and subsequent necrosis and may be fatal if it occurs in coronary arteries or in arteries supplying the brain.

## 2.3 CVD and IJD

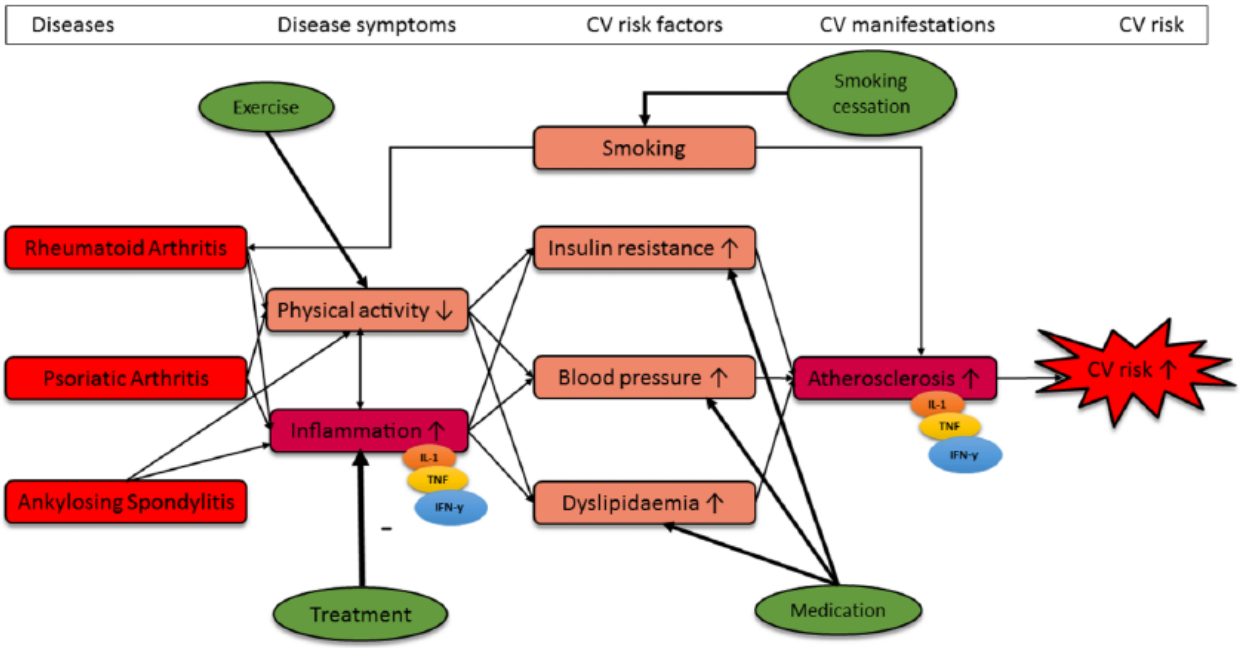
Patients with IJD are in high risk for CVD-related morbidity and mortality compared to the general population, where atherosclerotic events are the major cause of premature death (1-3). The majority of research has been performed on individuals diagnosed with RA, but similar

results have been shown for patients with PsA and AS (2, 60, 61). Patients with RA have 2-3 times more asymptomatic cholesterol plaques in the carotid artery compared to the general population (62). In addition, RA patients have an increased risk of MI and sudden death (63-65). Based on this knowledge, is therefore important to implement CVD preventive measures in patients with IJD.

## 2.4 CVD risk factors in IJD patients

An increased presence of traditional risk factors, combined with the CV effects of chronic inflammation may be contributing factors in the increased CVD risk (figure 4) (3).

**Figure 4** The association between inflammatory joint disorders and cardiovascular risk.




R Agca, S C Heslinga, V P van Halm, M T Nurmohamed Heart 2016;102:790-795.
CV, Cardiovascular; IL, Interlekine; TNF, Tumor Necrosis Factor; IFN, Interferon



Whether traditional CVD risk factors have the same influence on CVD morbidity in IJD patients compared to the general population or whether IJD patients have higher prevalence of these traditional risk factors, remain controversial (2, 66, 67). Han and co-workers reported a significant increased prevalence of hypertension and hyperlipidaemia in patients with AS and a

significant higher prevalence of hypertension, hyperlipidaemia and type II diabetes in patients with PsA and RA, compared to healthy controls (61). In a review published in 2013, a higher rate of cigarette smoking, less physical activity, a higher prevalence of insulin resistance and abnormal fat distribution were registered among patients with RA, compared to the general population (67). There is inconsistent data regarding the prevalence of hypertension, dyslipidaemia or diabetes in patients with RA (67). Peters and co-workers reported an increased prevalence of hypertension among patients with AS compared to the general population, but the study lacked evidence of smoking habits (2). The lipid profile in PsA- and AS patients has been reported to vary, depending on disease activity and presence of anti-rheumatic therapy (2).

### 2.4.1 Hypertension

Hypertension is a leading risk factor for CVD. Elevated BP cause impairment of the endothelium and accelerates development of atherosclerosis. It may further cause an increased risk of stroke and MI, as well as heart failure, renal impairment and damage of retinal blood vessels (53, 59, 68). Globally, elevated BP has been estimated to cause 7.5 million deaths (53). Hypertension is defined as systolic BP > 140 mmol/l and/or diastolic BP > 90 mmol/L, while a systolic- and diastolic BP < 120 and < 80 respectively, are assessed optimal. In patients with hypertension, a combination of non-pharmacological treatment (dietary intervention, increased physical activity, weight control) and pharmacological treatment are recommended (69).

### 2.4.2 Smoking

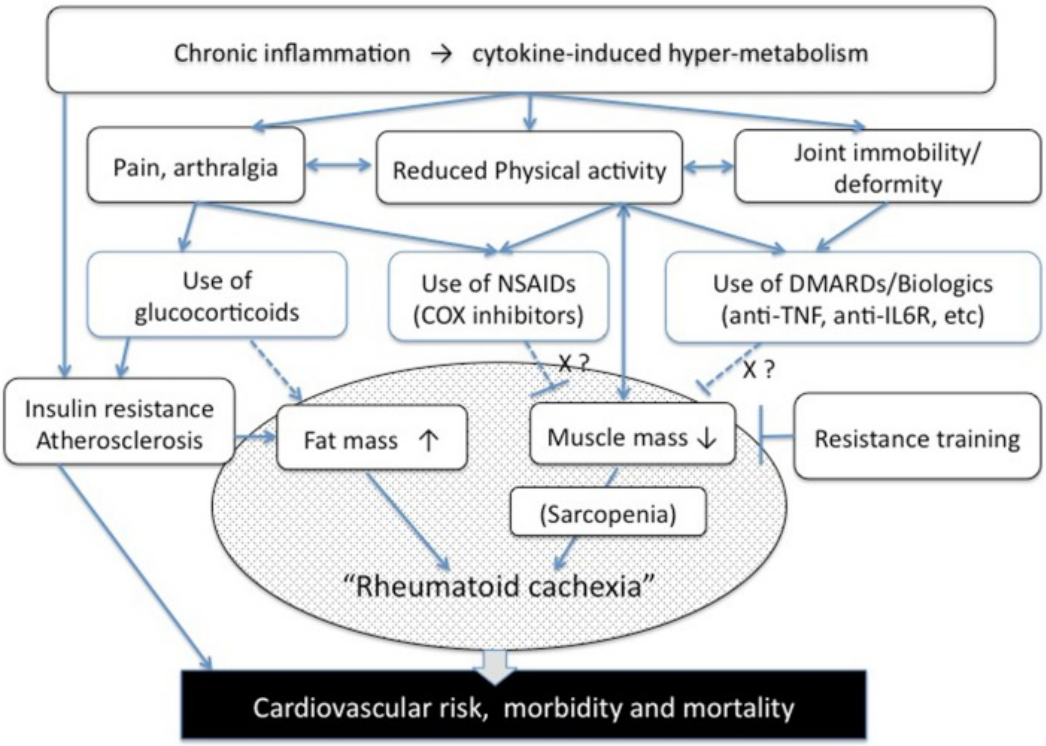
Smoking has been estimated to explain nearly 10 % of CVD and both tobacco use and passive smoking are contributors to increase the risk of CVD (53). Cigarette smoking accelerates the development of atherosclerosis and is associated with endothelial dysfunction, thrombosis, inflammation and altered lipid profiles (70). Additionally, Cigarette smoking has a synergistically effect on other risk factors, like diabetes and hyperlipidemia, contributing to a further increased risk (71). A meta-analysis reported a 50 % increased risk of a CVD event in smokers with RA, compared with non-smoking RA patients (66). In epidemiological studies, smokers have higher levels of triglycerides (TG) and LDL-c, while high density lipoprotein cholesterol (HDL-c) concentration decreases compared to non-smokers. An increased LDL-c/HDL-c ratio, confer higher risk of CVD and the ratio has been reported to be elevated by 15-20 % in smokers (72). Smoking cessation decreases both the risk of CVD morbidity and mortality and is strongly recommended, both as primary and secondary prevention of CVD (71).

### 2.4.3 Overweight, obesity and rheumatoid cachexia

BMI is a commonly used marker for adiposity (73). According to the WHO criteria, overweight and obesity are defined as BMI 25.0-29.9 kg/$m^2$ and ≥ 30 kg/$m^2$ respectively (74). Overweight and obesity are a result of lasting imbalance between energy intake and energy expenditure, often caused by a combination of too high food consumption and low physical activity. Prospective observational studies display persistent evidence of an association between high BMI and increased CVD risk, where The Framingham study was one of the first to demonstrate this relation (48, 53, 75). Overweight and obesity have unfavorable metabolic effects and are strongly related to other CVD risk factors like hypertension, dyslipidemia and insulin resistance (76). The fat distribution is of importance and intra-abdominal fat has an additional adverse effect on CVD risk compared to subcutaneous adipose tissue (76). Visceral abdominal fat is an endocrine and metabolic active tissue, which secretes proinflammatory adipokines, as TNF-α, IL-6 and C-reactive protein (CRP), which all have an atherosclerotic enhancing effect through contributing in low-grade inflammation and endothelial dysfunction (77, 78)). Waist circumference is a measurement for intra-abdominal fat mass (FM) which is unrelated to height and correlates with BMI (76). Higher waist circumference is followed by an increase in risk factors associated with CVD. Risk of metabolic complication(s) has been shown to be increased when WC is ≥ 94 cm in men and ≥ 80 cm in women, and substantially increased when WC is ≥102 cm and ≥ 88 cm in men and women respectively (76).

In patients with inflammatory diseases, overproduction of the cytokines IL-1β, IL-6 and TNF- α are a part of the pathogenesis of the joint disease. A chronic overproduction of these pro-inflammatory mediators may lead to an alteration in body composition as muscle wasting combined with increased adipose tissue and additionally loss of bone mass. Despite these changes in body composition, the body weight often remain stable (79, 80). Increased adipose tissue, may amplify the adverse effect through further pro-inflammatory cytokine production. The accelerating loss of muscle mass in combination with normal or increased fat mas (FM), is known as rheumatoid cachexia and has been reported to be present in two thirds of RA patients (80). There is presently no consensus of clinical criteria for rheumatoid cachexia (81). The loss of lean mass (LM) is primarily attributed to cytokine - driven hypermetabolism and protein degradation (figure 5). The use of high-dose steroids, diet and level of physical activity may also influence the body composition (80).

**Figure 5.** A hypothetical pathogenesis of rheumatoid cachexia




Masuko, K. Rheumatoid cachexia revisited: a metabolic co-morbidity in rheumatoid arthritis. Front Nutr. 2014 Nov 24;1:20
NSAID, Non-steroidal Anti-Inflammatory Drugs; COX, Cyclooxygenase-2; DMARS, Disease Modifying Anti-Rheumatic Drugs TNF, Tumor Necrose Factor; IL, Interleukin



### 2.4.4 Physical inactivity

The relationship between inactivity or low physical activity and risk of CVD has been known since the first studies from the 1950s were published (48). Inactivity is the fourth leading risk factor for mortality, and increase the risk of death with 20-30 % (53). Daily physical activity is important in prevention of lifestyle-related diseases as CVD, and it has been reported that even activity of moderate intensity has beneficial effects on risk factors for CVD (82). The present Norwegian recommendation for physical activity have been based on international recommendations. Adults are recommended to be physical active at least 150 minutes of moderate intensity, or at least 75 minutes of high intensity every week. Less than one third of the Norwegian population has been reported to accommodate these recommendations (83). Patients with IJD are less physical active compared to healthy controls, due to pain and fatigue, making it difficult to exercise (80, 84, 85). Low aerobic fitness and low muscle mass will be a

consequence of prolonged inactivity and predicts all-cause mortality and CVD-mortality in both healthy and ill men and women (80, 86). Despite this, a meta - analysis did not find any higher risk of CVD morbidity in inactive RA patients compared with physically active RA patients (66). However, patients with IJD may have additional benefits of increased physical activity related to improved functional ability and prevention of loss of muscle mass (80). Increased exercise and regular physical activity are recommended as primary and secondary prevention of CVD and have been reported to reduce overall risk of CVD events by up to 50 % (87). Anti-atherosclerotic effects like improved lipid profile, increased insulin sensitivity, reduced inflammation, BP and adiposity in addition to increased cardiorespiratory function have been reported, which all are factors of importance in CVD prevention (87).

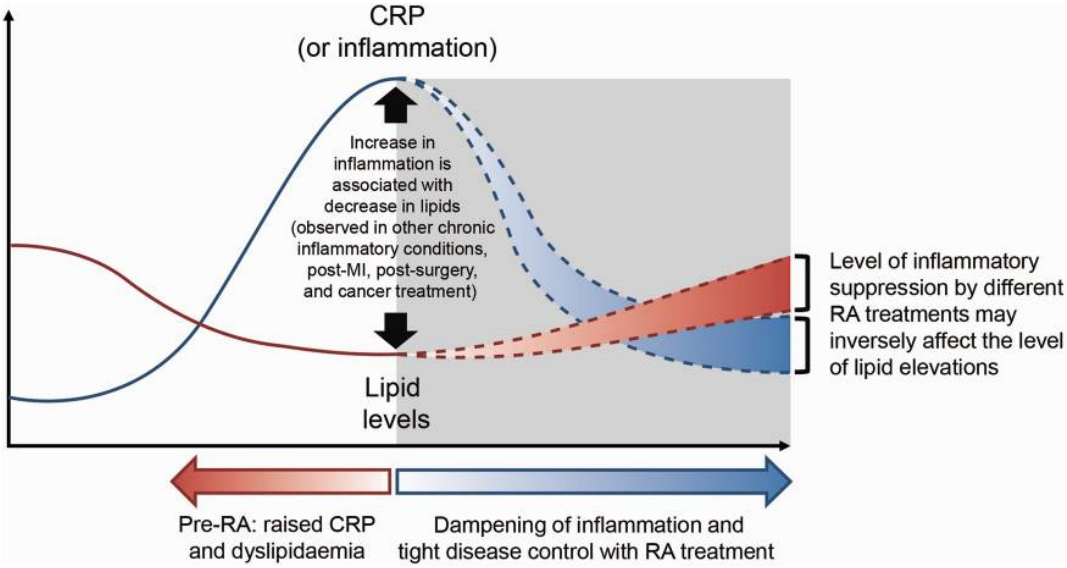
### 2.4.5 Lipids

Dyslipidemia is traditionally associated with an increased risk of CVD in the general population and is estimated to cause > 30 % of ischemic heart disease globally (53, 88). Evaluating the lipid profile, including total cholesterol (TC), LDL-c, HDL-c and TG, is standard in CVD risk assessment. TC or TC/HDL-c ratio are incorporated in the SCORE (Systematic Coronary Risk Evaluation) calculator, a widely used algorithm for estimating the risk for a fatal atherosclerotic event within the next coming 10 years (89). The various lipid fragments affect CVD risk differently. LDL-c may directly accelerate atherosclerosis through infiltration and retention in the arterial wall and further promote endothelial cell activation and inflammation, while HDL-c has a protective function, preventing inflammation and oxidative stress through promoting cholesterol efflux (55). Cholesterol level in plasma may be influenced by several factors, like gender, age, diet, physical activity and genetic conditions (69). In primary prevention, TC < 5 mmol/L and LDL-c < 3 mmol/L is recommended, while HDL-c > 1.0 mmol/L and > 1.2 mmol/L for men and women respectively are associated with lower CVD risk. There is no target for TG, but levels < 1.7 mmol/L is associated with reduced CVD risk (90).

In patients with active rheumatic disease, the association between lipids and CVD seems to be more intricate compared to the general population (figure 6). Despite lower lipoprotein levels in patients with RA, it has been shown that these patient have a higher risk of both MI and ischemic cerebral stroke (64, 91-93). Additionally, patients with high-grade inflammation and elevated CRP levels, shows a decreased lipid levels (3, 64, 94). A resolution of inflammation and a decrease of CRP levels through anti-rheumatic treatment, seems to increase or normalise

the lipids levels (3, 95). This inverse association between decreased lipid levels and CVD risk has been termed the "the lipid paradox" (64, 94). However, dyslipidemia is prevalent in RA patients and has been reported to affect 55-60 % of the patients (96). In a meta-analysis comparing RA patients with and without hypercholesterolemia, a 73 % increased risk of CVD morbidity was reported in RA patients with hypercholesterolemia (66).

**Figure 6.** Description of the inverse relationship between reversal in inflammation and lipid levels




Choy E, Ganeshalingam K, Semb AG, Szekanecz Z, Nurmohamed M Rheumatology (2014) 53 (12): 2143-2154.
CRP, C-reactive protein; MI, Myocardial Infarction; RA, Rheumatoid Arthritis.
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## 2.4.6 Inflammation

Chronic systemic inflammation is an independent CVD risk factor and of importance for both initiating and development of atherosclerosis (3, 96). A synergistic effect of inflammation on traditionally CVD risk factors in developing atherosclerosis has been proposed (2). A prospective cohort study from 2009 found an increased CVD risk in patients with RA even after adjusting for traditionally risk factors. The inflammatory component in IJD may explain this association (97).

### 2.4.7 Diet

A healthy diet, low in processed high-energy food ("fast food") including sugary beverages , corresponding with energy expenditure, will prevent overweight and obesity and therefore contribute in promoting a good CV health (53). There is currently scientific evidence that diet recommendations; as more fruit and vegetables, unsaturated fat and fish oils, fiber and lean dairy and meat products as well as low intake of saturated fat, trans fatty acids and reduced salt consumption have positive effects on CVD risk factors (53, 98-100). Worldwide, approximately 2,8 % of deaths may be attributed to low consumption of fruit and vegetables (53), which is an important contributor of dietary fibre, antioxidants, vitamins and minerals, but still low in energy, and therefore promoting weight control (101). The high nutrient density of phytonutrients, potassium and fibre are of particular importance for CV health (102).

Prospective trials have demonstrated inconsistent findings in respect to the relationship between intake of dietary fat and the risk of CVD (103-106). However, replacing saturated fatty acids (SFA) and trans fatty acids (TFA) with a combination of monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), has shown decrease in CVD risk through a more favorable lipid profile (104, 105) and a significantly reduction in CVD events (107). According to national recommendations, the intake of SFA should be limited and not exceed 10 energy percent (E %) in the general population, and be less than 7 E % for high-risk groups (102)

The average Norwegian eats 10 g salt/day, which is twice the recommendations (108). Clinical trials have shown a reduction in BP in both normotensive and hypertensive by a limited salt intake (109). A reduction of salt by 4.6 g/day, has been shown to decrease BP in persons with hypertension by 5.0 and 2.7 mmHg for systolic and diastolic BP, respectively (110). A reduction of 10 mmHg and 5 mmHg systolic and diastolic BPs respectively, has been related to a reduction in the risk of stroke by 50-60% and the risk of MI by 40-50% in hypertensive persons (111).

## 2.5 Nutrition and diets in prevention and treatment

### 2.5.1 Diets and treatment of IJD

Nutrition and diet has played a therapeutic role in the management of different diseases throughout the history. Patients seek alternative and complementary therapies to traditional therapies when they encounter disease, especially in severe and long-lasting or chronic

diagnosis. The role of food in the management of RA is controversial, despite this, RA patients has been reported to regard food to be of importance in relation to their symptom severity and were willing to change their diet in an attempt to decrease their suffering (112).

Different hypothesis regarding the importance of diet in IJD patients have been proposed, and indicates that diet and lifestyle may play a role in both the development of and the course of rheumatic disease (113, 114). Laboratory studies in animals, suggest that dietary intake may have an impact on disease activity in IJD patients, though human studies are still scarce (4). However, the evidence from human intervention studies are small and consists of single trials with a high risk of bias (115), mostly published in the 1990s and early in the 20th century (4). Various dietary patterns, interventions and nutrients have been tested throughout the previous decades (4, 116). Vegetarian- or vegan diets (117), elemental- or elimination diets (118-120) and the Mediterranean diet (MD) (121, 122) are the most frequently investigated diets, but also periods of fasting (122) has been tested. Disease activity (e.g. swollen joints, pain score, morning stiffness, grip strength, CRP) were frequently common outcome measures in these trials. However, the effects by adherence to these diets or dietary changes, were shown to be uncertain and potentially biased due to significant weight differences and high drop-out rates among the patients (115).

The potentially effect of dietary changes in IJD patients, compared to an ordinary diet are still questionable. Today, effective anti-rheumatic treatments (sDMARDs/bDMARDs) exist (4). This may lead to a less importance of diet as a potential contributor to disease activity. Nevertheless, diet will still be of considerable importance related to other aspects of IJD. Ensuring adequate and proper nutrition may be essential for further prognosis and in prevention of comorbidities. The increased CVD risk in IJD patients makes prevention of comorbidities of especially importance. Nutritional advice and guidance have been shown to influence CVD risk factors and provide beneficial effects in both prevention and treatment (5, 6). CVD preventive treatment as alteration of modifiable risk factors, such as diet and lifestyle, is recommended to be initiated before starting pharmacological medication (90).

## 2.5.2 Diets and nutrients in prevention of CVD

CVD, along with a number of other non-communicable metabolic diseases, have shown an increased prevalence globally during the last few years. Probably a result of an ageing population in combination with urbanization and an unhealthy lifestyle (5, 123). Different nutrients, diets and dietary patterns have been promoted and recommended in prevention of CVD, with various nutritional quality and evidence. Recently there has been an increased focus on the impact of food patterns, rather than the effect of single nutrients (124). Many weight-loss diets, as Atkins and low-carbohydrate diets have become popular and promoted through media and other social media channels in recent years. Some of the health benefits observed in these diets, as normalizing BP, improved glycaemia and/or lipids could be attributed to the weight loss itself, while the long-term effects are more uncertain (125). However, a recent meta-analysis showed that previously healthy persons on a low-carbohydrate diet, increased their levels of LDL-c, despite of greater weight reduction, compared to persons on a low-fat diet (126). Nevertheless, diets as vegetarian diet, low-sodium diet; Dietary Approaches to Stop Hypertension (DASH) diet and the MD have shown beneficial health effects and are associated with improvement in several CVD risk factors (5).

**Vegetarian diet**

A plant-based vegetarian diet is rich in fruit and vegetables, contribute with several vitamins, minerals, phytochemicals, antioxidants and fibre. These are components which have shown beneficial effects on CVD risk factors as BP, weight-regulation, lipids and insulin sensitivity (123). Several epidemiological studies have revealed that following a vegetarian diet are related to lower mortality rate from both CVD and cerebrovascular disease, compared to omnivores (eating food of both plant and animal origin) (123). There is general agreement that a vegetarian diet protect against CVD (127), despite that some studies have reported higher levels of TG and reduced HDL-c in vegetarians, probably a result of a higher intake of refined carbohydrates and fructose (5). Although, following a vegetarian diet may result in micronutrient deficiency and low intake of omega-3 PUFA (123).

**Dietary Approaches to Stop Hypertension (DASH) diet**

The DASH diet includes a high intake of fruit, vegetables and whole grains, but also fish, some meat and poultry. The consumption of total fat intake, and especially SFA, should be limited, through implementing low-fat dairy products and lean meat choices. Sugar-sweetened

beverages, sweets and sodium should be limited (128). This dietary pattern aims to prevent and reduce hypertension (129). A meta-analysis of 17 randomized clinical trials (RCTs) from 2014 concluded that the DASH diet had an advantageous effect on both systolic- and diastolic BP in adults, and especially in subgroups of patients with hypertension and in men (129). Previous trials have reported conflicting results of the DASH diet´s effect in normotensive persons (130, 131). It has been questioned whether the reduction in BP can be attributed to other lifestyle changes, as increased exercise, or as a result of energy-restriction and weight loss rather than the DASH diet itself (129, 132). However, following a DASH-like diet, would be rich in antioxidants and contain high levels of potassium and low levels of sodium, where the last-mentioned are in accordance with recommendations from WHO, to prevent raised BP and reduce CVD risk (133).

**The Mediterranean diet**

The phrase "Mediterranean diet" (MD) mainly refers to traditional food patterns of populations in the Mediterranean regions back in the early1960s (134). This diet was primarily characterized by a daily high consumption of fruit, vegetables (including legumes) and complex carbohydrates, with a moderate weekly consumption of fish, (and low intake of red meat). MD contains low-to-moderate consumption of dairy products, like cheese and yoghurt. While olive oil was their main source of fats and a low-to-moderate amount of red wine was served by some of the meals (134-136).

As early as in the end of the 1950s, Ancel Keys and his co-workers initiated a cross-cultural prospective study, the Seven Countries Study (SCS), with the aim of investigating the associations between diet, particularly fat composition, besides other risk factors, and the incidence of CVD, among different populations (137). Sixteen cohorts of men between 40-59 years, from seven countries (USA, Finland, Netherlands, Italy, Greece, Japan and Yugoslavia) were investigated. This 15-year follow-up study revealed that populations from Mediterranean countries showed lower mortality from CVD compared with non-Mediterranean European populations. (137). Results from several observational cohort studies have also been consistent with these findings and has demonstrated an inverse association between compliance to a MD and CVD-risk (124, 135, 138).

Adopting a Mediterranean diet pattern (MDP) has been associated with advantageous effects on CVD risk factors such as BP, lipids and blood glucose (139-142) and have revealed preventive

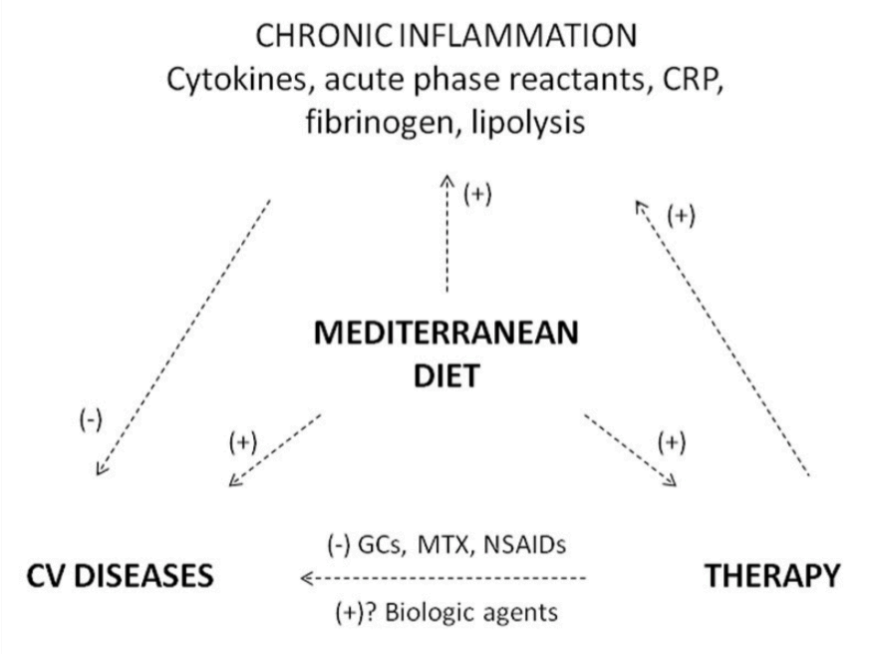
effects in both primary and secondary CVD (143, 144). The Lyon Diet Heart Study was a secondary prevention RCT (143). Patients who had survived a first MI were randomized either to follow a MD, enriched with α-linoleic acid, or to follow a prudent Western diet. After 4 years of follow-up, adherence to a MDP showed a significant reduction in all-cause- and CVD morbidity and mortality (145). The PREDIMED-trial (PREvención con DIeta MEDiterránea), revealed cardioprotective effects in high-CVD risk persons without established CVD assigning to a MD. The MD was supplemented with extra-virgin olive oil or nuts, while the controls were only advised to reduce their dietary fat consumption. The MD group compared to a control group, showed a 30 % decrease in relative risk for major CVD events (144). In a systematic review from 2009, the association between dietary patterns and CVD were examined. There was reported that a MDP or a "prudent" dietary pattern (characterized by a high intake of vegetables (including legumes), fruit, whole grains and fish and other seafood), had a protective effect on CVD risk, contrary to a "western" dietary pattern (characterized by a high intake of processed meat, red meat, butter, high-fat dairy products, eggs and refined grains) (146).

**The Mediterranean diet and IJD**

Patients with IJD may have advantage from a MD considering their increased risk of CVD (122) and other health benefits as well (121). The MD constitutes components which may have anti-inflammatory- and anti-oxidative effects, having advantageous impact on chronic inflammation, CVD risk and the treatment of IJD patients (figure 7) (122).

In 2003 a RCT was conducted, where a total of 56 RA patients were allocated to either 12 weeks of a Cretan MD or 12 weeks of an ordinary western diet (121). After three months, a significant reduction in pain (measured by visual analogue scale (VAS) was reported in the MD group. Neither improvement in morning stiffness nor in physical function (HAQ score) was revealed (121). Nevertheless, a significant change in physical function was reported from baseline to follow up in the MD group.

**Figure 7.** Description of how the Mediterranean diet may affect chronic inflammation, therapy and cardiovascular disease in IJD patients.




Francesca Oliviero, Paolo Spinella, Ugo Fiocco, Roberta Ramonda, Paolo Sfriso, Leonardo Punzi: How the Mediterranean diet and some of its components modulate inflammatory pathways in arthritis Swiss Med Wkly. 2015;145:w14190. www.smw.ch
CRP, C-reactive protein; CV, Cardio Vascular; GC, Glucocorticoid; MTX, Methotrexate; NSAIDs, Non-steroidal Anti-Inflammatory Drugs.



**Nutrients, food items- and groups**

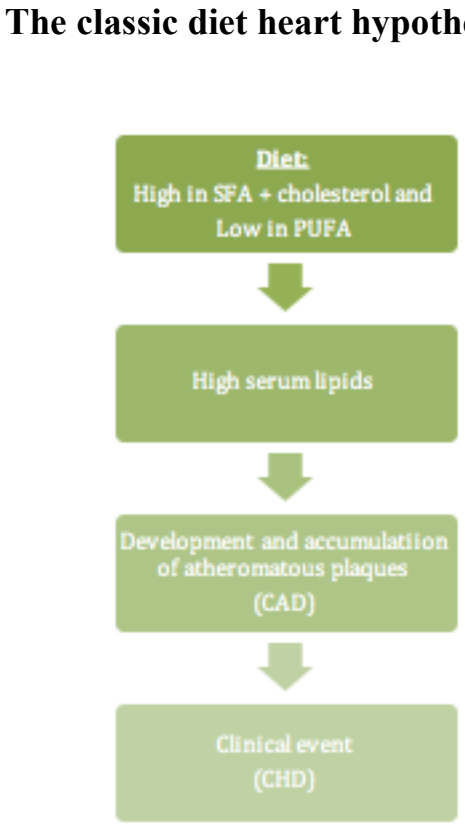
Much of the research that exists about diet and CVD are based on studies done on single dietary components or nutrients. This is challenging because nutrients are consumed as complex foods and meals rather than single nutrients in a pure chemical form and potentially synergistic or antagonistic effects depending on the diet's composition may therefore not be excluded (125, 147).

**Dietary fats**

Over the previous decades, it has been encouraged from national authorities, to reduce total intake of fat, in promotion of general health and preventing CVD (148). Although, reports suggest that type and quality of fat have a higher impact in lowering CVD risk, compared to the total fat intake (149). The assumption that type and quality of fatty acids in the diet is of importance in developing CVD is largely relied on former ecological studies (137), as well as

prospective epidemiological studies (150). The association between dietary fat and increased CVD risk may be explained by the classic "diet-heart" hypothesis (151) (figure 8), which indicates that a low intake of PUFA combined with high intake of SFA and dietary cholesterol, will increase the level of serum cholesterol, followed by formation- and accumulation of atherosclerotic plaques and further development of CVD (147). However, this theory has been criticized for being an oversimplification of the relation between diet and CVD risk because other dietary components may affect the lipid profile as well (147). There is broad consensus that dietary fat influences blood lipids (90), and there has been shown that some SFA, are more potent (152).

**Figure 8.** The classic diet heart hypothesis, reproduced after Sherwin et al. (151)




SFA: saturated fatty acids, PUFA: Polyunsaturated fatty acids, CAD: coronary artery disease, CHD: Coronary heart disease

Despite replacing SFA with PUFAs has shown to decrease CVD morbidity and mortality (153), the association between intake of dietary SFA and CVD risk has been inconsistent (154, 155). Nevertheless, several observational studies and clinical trials have demonstrated that there exists

evidence of the importance of dietary fat in CVD risk (103, 104, 156, 157). The Norwegian Directorate of Health recommend a daily intake of total 25-40 E % from fat, of which maximum 10 E % from SFA, 10-20 E % from MUFA and 5-10 E % from PUFA. The essential PUFA, linoleic acid and α-linolenic acid, should be a minimum of 3 E %, where at least 0.5 E % from α-linoleic acid (158). Although, diets with a total of 25-35 % fat and less than 7 E % from SFA has been demonstrated to reduce the risk of CVD (69)

Inclusion of dietary omega-3 PUFA may be of additional importance to patients with IJD, which is characterized by inflammation as a result of proinflammatory mediators as arachidonic acid (AA) -derived eicosanoids and cytokines. Consumption omega-3 found in fatty fish and fish oil, may inhibit AA metabolism by competing for the same enzymes and consequently inhibit production of pro-inflammatory eicosanoids and cytokines, and instead produce less potent mediators as $PGE_3$ and $LTB_5$ (159). Trials with consumption of omega-3 PUFA from both low- and high doses of fish oil supplementation has reported a decreased synthesis of IL-1β and TNF-α (160). Goldberg and Lee with co-workers showed that high-dose supplementation (≥2,7 g/d) of omega-3 PUFAs significant decreased consumption of NSAIDs in RA patients (99, 161). Goldberg reported significant reduced number of minutes with morning stiffness, reduced joint pain intensity and tender joints as well, while Lee and with co-workers saw trends, but no significant effects.

**Carbohydrates and dietary fibre**

The association between carbohydrates and CVD, seems to be indirectly attributed to total energy consumption and overweight/obesity, along with an effect on plasma lipids, especially TG and glycaemic control (162). Trials have reported elevated plasma TG in participant's with increased consumption of energy from refined carbohydrates (163, 164). An increased intake of dietary fibre, a heterogeneous group of indigestible polysaccharides and lignin, has in several trials showed an opposing effect and is associated with lipid lowering effects (165). Water-soluble fibre, especially oat fibre is inversely associated with TC and LDL-c levels (166). High intakes of fibre from whole grain were in the Nurses' Health Study reported to be associated with reduced risk of CVD (167). The same result was reported in the Health Professionals Follow-up Study, where a high fibre intake was inversely associated with CVD risk, independent of fat intake (168). Additionally, a high fibre intake has been associated with reduced incidence of hypertension (169). Li and co-workers investigated the effect of replacing SFA with PUFA and/or different sources of carbohydrates. Replacing 5 E % of energy intake from SFA with

similar energy intake from whole grain carbohydrates found an association with 9 % decreased CVD-risk, while replacing SFA with refined starches or added sugars, did not show any significant changes in CVD risk (170). Norwegian health authorities recommend, according to Nordic Nutrition Recommendation, an intake of 25-35 g fibre/day or equally 3g/MJ (158).

## 2.6 Dietary assessment methods

Diet is a major lifestyle-related risk factor for CVD, which makes it important to find an appropriate way to obtain valid information about a person's diet and dietary habits, which often be challenging. There are several different dietary assessment methods, each with inherent strengths and limitations (171). Dietary information may be obtained by either retrospective or prospective methods and there can be differentiated between open- and closed methods, depending on all kind of food are included in the assessment or just selected food items (172). Among the prospective methods are weighed dietary registration and food dairies, which are associated with high validity and accuracy, and thus often considered as a reference method in validation studies (173). Although, they are expensive, time-consuming and provide a large respondent burden (171). Additionally, the prospective methods may influence the behaviour and dietary habits in the respondent and the registered food may not be representative for the habitual diet.

Retrospective dietary assessment methods include 24-hours dietary recall, dietary history and food frequency questionnaire (FFQ). These are often less expensive and time consuming and provide a minor respondent-burden (171). Although, they may be less precise compared to prospective methods and recall bias may be a limitation. FFQ are frequently used method in epidemiological studies (172), but may also be a tool in assessment of diet in clinical trials. The FFQ can be both self-administered or used as an interview, where the latter is more resource-demanding and increases the risk of pleasing bias, but minimize the risk of misinterpretations related to the questionnaire. Nevertheless, use of FFQ is generally cost-effective and timesaving and assess usual dietary intake, providing quantitative and/or qualitative information about an individual's dietary habits (171). The general value by using FFQ in dietary research has been supported by correlations analysis, where the method has been compared to a presumable superior method or biomarkers (174). Although, food trends, personal preferences and food supply are in constant change and a questionnaire that reflects the population to be tested, will be of important for the validity of the results.

# 3 Objective and hypothesis

Since there currently is little knowledge about how alteration in lifestyle-related CVD risk factors may be affected in patients with IJD, the main aim of this study was to test whether an individually tailored, extended dietary counselling on cholesterol-lowering and heart-friendly diet (intervention) had comparable effect on change of diet, as a standardized brief advice on cholesterol-lowering diet, given by a physician (control). Secondly we aimed to compare the effect of the extended counselling to the controls, on changes in 1) lipids, 2) CRP, 3) BP and 4) body composition.

## 3.1 Research questions

1. Is there a difference in change in diet, assessed by the validated questionnaire SmartDiet (appendix 1), between IJD patients receiving an individually tailored, extended dietary counselling compared to IJD patients receiving a standardized brief advice on cholesterol-lowering and heart-friendly diet, from baseline to eight weeks-follow up?

2. Is there a difference in change of lipid levels, CRP or BP between IJD patients receiving an individually tailored, extended dietary counselling, compared to IJD patients receiving a standardized brief advice on cholesterol-lowering and heart-friendly diet?

3. Does individually tailored, extended dietary counselling, compared to brief advice on cholesterol-lowering and heart-friendly diet, have an impact on body composition measured by bioelectrical impedance analysis (BIA) and dual energy X-ray absorptiometry (DXA), in IJD patients?

4. Are there any in-between group differences in change of diet, biomarkers (lipids, CRP), BP or body composition, in IJD patients receiving an individually tailored, extended dietary counseling, compared to IJD patients receiving a standardized brief advice on cholesterol-lowering and heart-friendly diet?

# 4 Methods

## 4.1 Study population/subjects

Patients with IJD referred for CVD risk stratification at the Preventive Cardio-Rheuma clinic, department of rheumatology, Diakonhjemmet Hospital, from the rheumatology outpatients clinic at Diakonhjemmet Hospital or from primary care physicians, were screened for inclusion to the study and were requested to participate by the physician during the consultation. Before signing a written consent (appendix 2), all patients were informed orally and in writing about the study design and of the right for the participant to withdraw from the study at any time, and for whatever reason. All study participants were recruited continuously from January-June 2016.

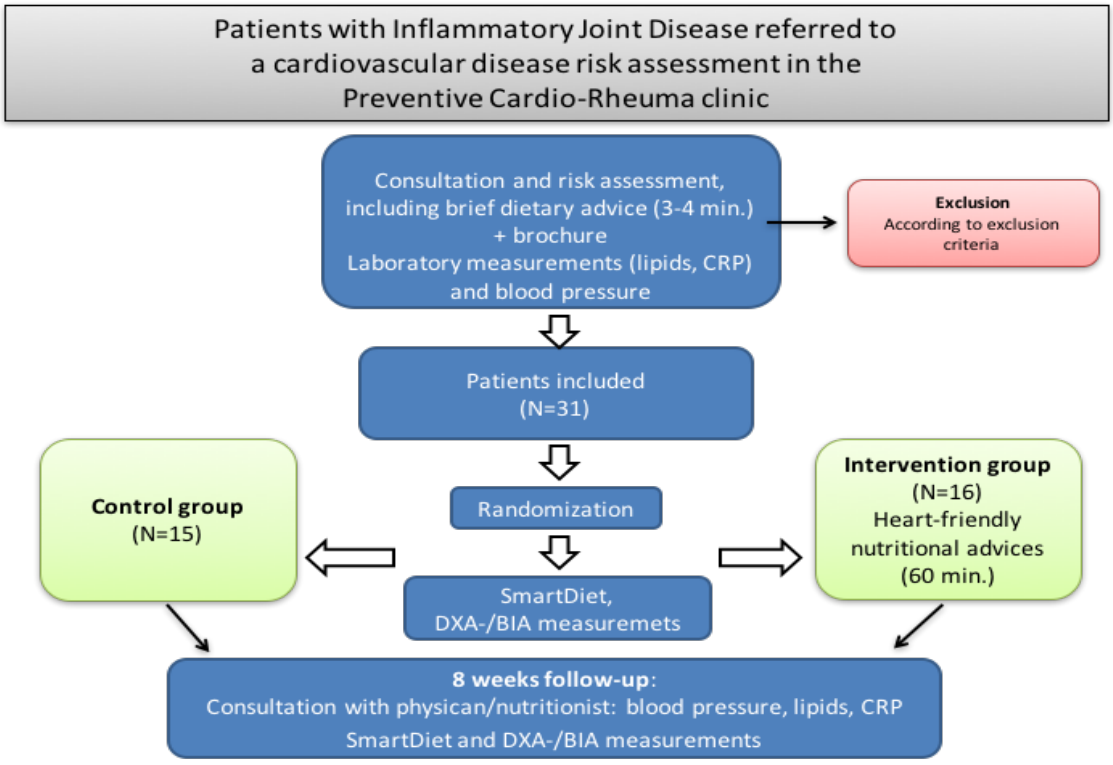
Patients with a diagnosis of RA, PsA or AS were eligible to participate. Other inclusion criteria were age between 40 and 80 years, being statin-naïve with an indication for statin therapy as in primary or secondary prevention for CVD. Exclusion criteria were: 1) diagnosed atherosclerotic CVD as MI, coronary intervention as c coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), transient ischemic attack (TIA)/ischemic stroke, >50 % stenosis of the carotid artery, atherosclerosis in the carotid artery together with focal neurological symptoms, 2) BP >160/100 mmHg and/or medically treated hypertension or 3) familial hypercholesterolemia (TC >7.5 mmol/L and LDL-c >4.9 mmol/L).

## 4.2 Design

The study was an open RCT with two treatment groups (figure 9 and 10). During the first consultation with a physician, all the participants received a brief standardized advice (3-4 minutes) about heart-friendly food. Further they received a brochure, "Innkjøpsguiden for hjertevennlige matvarer", a shopping guide for heart healthy food items, developed by dieticians at Diakonhjemmet Hospital (appendix 3). This guide gives an overview of selected recommended heart-friendly groceries, in various food groups, as well as an overview of less favourable groceries. Half of the enrolled participants was then randomized to an extended nutritional counsellingof 60 minutes, hereafter termed the dietary group (DG). These patients received a thorough individually tailored, extended counselling in heart-friendly and cholesterol-lowering diet (by MGF, hereafter termed the nutritionist), where individual needs and

preferences were based on their response of the questionnaire, SmartDiet. The remaining other half, called the control group (CG), received no further dietary information.

**Figure 9** Flowchart of study design

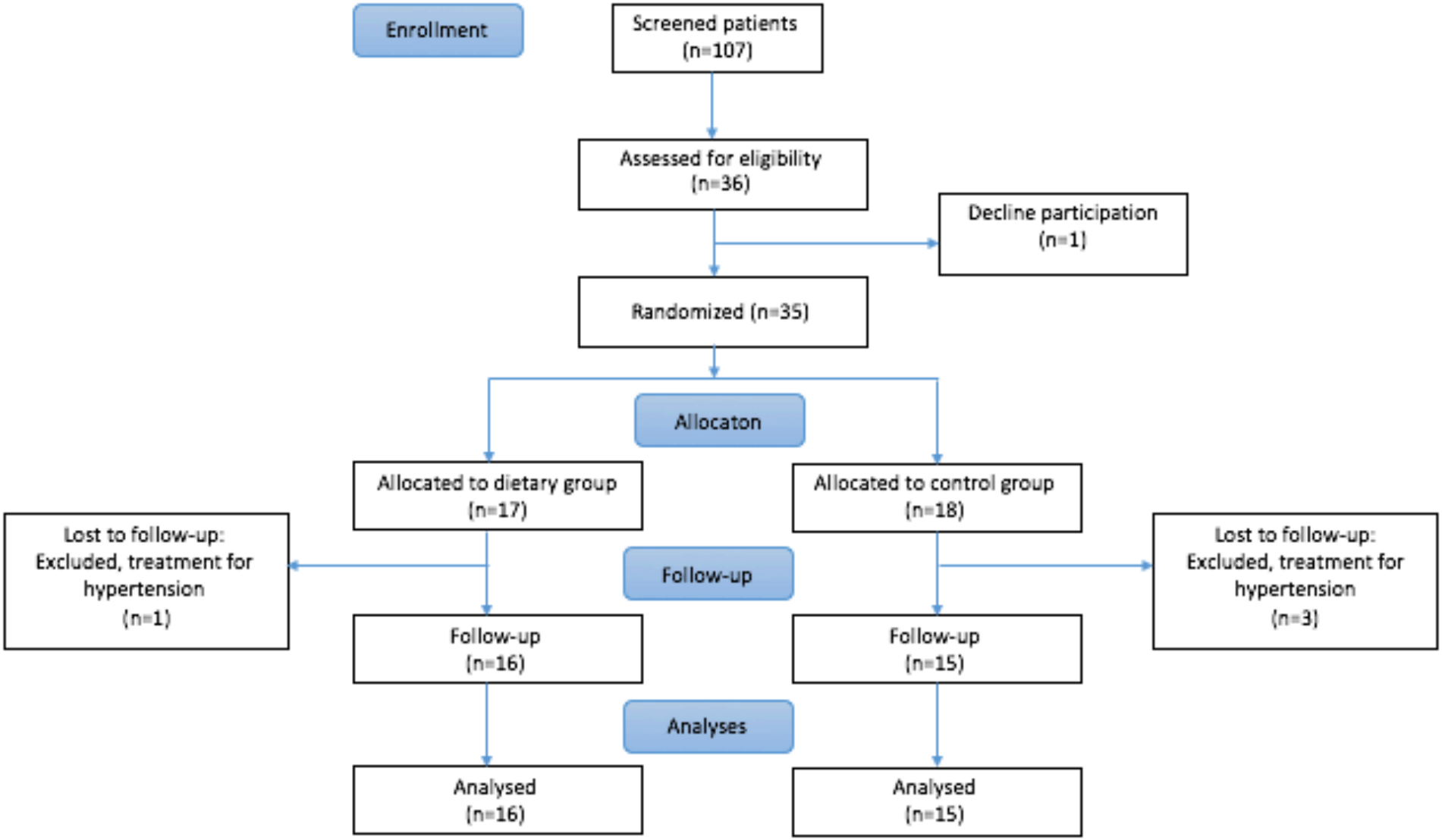



CRP, C-reactive Protein; BIA, Bioelectrical Impedance Analyses; DXA, Dual-Energy X-ray absorptiometry

**Randomization**

An independent statistician made the final randomization list. Two independent secretaries compiled randomization envelopes, which was based on the randomization list. Inside the envelope a sheet describing the allocated treatment group was inserted into a dyed sheet, too further ascertain the blindness of the randomization. It was not possible to reveal the treatment group without opening the envelope. Patients in the study were assigned randomization numbers sequentially. Randomization number and treatment group was recorded in each Case Report File.

**Figure 10** Flow chart of study participants



## 4.3 Data collection

### 4.3.1 Medical consultation

All the participants followed standard procedure for CVD risk evaluation, which could be divided into the following;

**Prior to the consultation**

Within one week prior to the medical consultation, the patients gave standardized blood samples, including lipids and inflammatory markers. The patient also brought with them a completed questionnaire on CVD risk factors, symptoms of CVD, established CVD and familial CVD, as well as demographic data, information about co-morbidity and use of medication. The answers in the questionnaire were quality assured by the consulting physician.

**During the consultation**

Brachial BP was measured and a 12 lead electrocardiogram (ECG) was recorded digitally and evaluated during the consultation. A trained sonographer performed the B-Mode ultrasound examination of the carotid arteries. Waist circumference was measured of all patients. Further, the patient received a brief (3-4 minutes) standardized advice about heart-friendly foods and cholesterol-lowering diet, including receiving the brochure "Innkjøpsguiden". The value of physical activity and smoking cessation were also discussed with the patient.

**CVD risk evaluation**

The patients were categorised into three CVD risk groups; **1) Very high risk:** when the patient had established atherosclerotic CVD, and/or an estimated 10 year risk of CVD by the Systematic Coronary Risk Evaluation (SCORE) (89) ≥10% and LDL-C >1.8 mmol/L, **2) High risk: when the** estimated 10 year risk of CVD ≥ 5 % and LDL-C > 2.5 mmol/L **3) Moderate-low risk:** estimated risk < 5 %

**After the consultation**

Following the medical consultation, all recruited patients filled out SmartDiet. If they had questions or found anything difficult, the participants had assistance in filling out SmartDiet. The questionnaires was reviewed and checked for errors by MGF. The following evaluations and measurements were performed by one person (MGF); Body composition and body

weight were measured by use of BIA and the participants heights were measured by a wall mounted stadiometer (height measure tape KaWe REF 44 444). Measurement of body composition by DXA was performed in the afternoon/evening, due to logistical challenges in the outpatient clinic.

### 4.3.2 Dietary counselling

Participants in the DG received a tailored, expanded dietary counselling for approximately 60 minutes including individually tailored dietary advice about heart-friendly and cholesterol-lowering diet, which was related to the answers obtained in the SmartDiet questionnaire. Despite individualization, the same standardized main topics were discussed with all participants, in a greater or lesser extent depending on already present dietary habits, personal preferences or other special needs. The topics that were emphasized was; Importance of limiting and replacing saturated fat from full-fat dairy products, various animal products, snacks, pastries and chocolate, by unsaturated fat from marine sources, such as oily fish, and vegetable sources such as, oils, nuts, almonds and avocado. The participants were encouraged to use low-fat dairy products or products where saturated fat was replaced by unsaturated fat, such as products from ”Vita Hjertego"”. The patients were further encouraged to use lean meat products for dinner and spreads, and reduce use of processed minced meat and sausage products for the advantage of unprocessed lean meat and poultry. Before cooking, visible fat and skin was encouraged to be removed

Fish and oily fish in particular, was highlighted as good sources of the essential long chain omega-3 fatty acids, emphasizing the positive effects of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) on CVD health (100). Oily fish is also a good source of vitamin D, which is essential for absorption of calcium and hence for good bone health. This is especially important in patients using corticosteroids, a risk factor for development of osteoporosis (175). Patients was encouraged to use more fish, in all forms (except deep-fried), also as spreads.

Importance of type of fat, rather than amount of fat, was consistently emphasised. The use of spreadable plant-based margarine instead of butter or hard margarine was recommended. For frying and baking, oils and liquid margarine was advocated, while extra virgin oils were recommended for vinaigrette and dressings. Those who frequently used margarine or butter as spread, was introduced for margarine added plant sterols. Plant based fat sources were

exemplified as healthy food choices. Furthermore, mayonnaise and mayonnaise-based salads, caviar and remoulade were highlighted as good sources of healthy fat, but to be used in moderation. The participants were encouraged to limit sugar-rich foods and beverages and attempt to find alternatives and possibly use fruit and berries as a substitute for sweets. They were informed about the overall high salt consumption in the Norwegian population, and the positive health effects by salt reduction (108, 109).

The benefit of increasing intake of fibre through whole-grain cereals and a high consumption of fruits, berries, vegetables including legumes (176, 177), were underlined as well. Oats was highlighted as a particularly favourable choice because of its content of beta-glucans (soluble fibre) and it´s favourable effect on cholesterol (165, 166). Further, the patients were introduced for "*Brødskalaen*", a bread scale (figure 11), which is a voluntary labelling system developed by Næringslivets Hovedorganisasjon Mat og Drikke og Baker- og Konditorbransjens Landsforening, in cooperation with Forbrukerrådet (the Consumer Council), Helsedirektoratet (the Norwegian Directorate of Health) and Mattilsynet (The Norwegian Food Safety Authority) in 2006 (178). The labelling system is a visual tool, which is intended to make it easier for the consumers to choose a healthier bread. The scale is divided into four categories based on the percentage of the whole wheat content. White bread: semi-dark bread, dark bread, and whole wheat.

**Figure 11** "Brødskalaen" (The bread scale)


Published with permission from Opplysningskontoret for Brød og korn.
(http://www.matportalen.no/merking/tema/merking_av_mat/bruk_brodskalan)

Another labelling system which was emphasized during counselling, was "*Nøkkelhullet*", ("the Keyhole"), which is a voluntary labelling system that authorities in Norway, Denmark, Sweden and Iceland have developed (figure 12). In Norway, the Norwegian Directorate of Health and The Norwegian Food Safety Authority are responsible for the labelling. Groceries with the keyhole symbolize a healthier food choice compared to similar groceries within the

same food group. The labelled food shall fulfil at least one of the four of the following demands: less sugar, less salt, less fat and saturated fat or more fibre and whole grain, compared with similar foods in the same food group (179). The labelling system includes pre-packaged foods as well as fruits, berries, vegetables and potatoes, bread, cheese, meat fish and seafood, none of which are wrapped.

**Figure 12** "Nøkkelhullsmerket" ("The Keyhole")

Published with permission from Avdeling for ernæring og forebygging i helsetjenesten, Helsedirektoratet (http://www.matportalen.no/merking/tema/nokkelhullet/)

Coffee habits were requested and discussed with the participant if they reported frequently use of an unfavorable brewing method. Depending on brewing method, there is a varying content of diterpens in coffee, which has shown a cholesterol promoting effect (180). Additionally, the new "coffee trends" may increase the consumption of full-fat milk, through high intake of Caffelatte, cappuccino, cortado e.g. Alcohol consumption was assessed and discussed in general and more thoroughly if the patient had a high alcohol consumption (>7 unit/week in women and > 14 units/week in men) or if the participant showed TG values > 1.7 mmol/L.

The participants were not encouraged to take other supplements than cod liver oil ("tran") or similar omega-3 supplements, which is recommended for the general population. Persons who claimed to already take supplements, were not asked to stop this.

**The control group**

The patients in the (CG) received no further diet or grocery information until the 8 weeks follow-up. After the follow-up session, the patients in the CG were offered a similar 60 minutes individually tailored, extended dietary counselling as the patients in DG received 8 weeks earlier.

### 4.3.3 Eight weeks follow-up

After eight weeks, the participants in both groups was contacted for follow-up. They went through medical consultation, where a physician assessed the need for initiation of cholesterol-lowering drugs, based on blood samples collected within one week prior to the consultation, in addition to the already comprehensive CVD risk evaluation done at baseline. The medical consultation was followed by new measurements of BP, waist circumference, body weight and body composition, performed by MGF. The participants again completed SmartDiet, for assessment of changes in diet and lifestyle habits.

### 4.3.4 Diet – SmartDiet

Dietary data were collected by SmartDiet at baseline and after eight weeks follow-up, for use in assessment of alteration in diet- and lifestyle habits in the participants. The SmartDiet was developed by the Lipid Clinic, Oslo University Hospital, to efficiently evaluate diet- and lifestyle habits in clinical practice (181). The third revision of the form, released in May 2009, was used. SmartDiet was validated in 2002 and provides a good estimate of dietary fat and fibre, while estimated intake of fish, vegetables and snacks were appraised to be of minor precision (181). The form contains a total of 26 questions, of which 21 are qualitative or quantitative questions about average use of different food groups and beverages; milk and dairy products, meat, fish and eggs, fat sources, cereals, fruits/vegetables/berries, legumes, potatoes/rice/pasta, nuts/almonds/avocado and olives, sweet spreads/sweet beverages, chocolate/cakes/biscuits/snacks and coffee and alcohol. The form had 4 additional questions, which record meal pattern, diet supplementation, smoking habits and physical activity, besides self-reported height and weight and potential desirable weight reduction.

Out of the 26 questions, fifteen were point scoring. Each of these questions showed three or four response categories, each giving a score of 1, 2 or 3. A total score between 15 and 45 points were possible to obtain. 27 points or less indicates that the diet should be improved in several areas to become more heart-friendly (”Du bør forbedre kostholdet ditt på mange punkter, for å gjøre det mer helse- og hjertevennlig”), 28-35 points indicates that the diet still needs for improvements to become more heart-friendly (”Du kan forbedre kostholdet ditt på en del punkter, slik at det blir mer helse- og hjertevennlig”), while a total score of $\geq$ 36 points consider the participant to have healthy dietary habits (”Du har sunne kostholdsvaner”). Total score obtained from the form was used to measure change in diet habits. A clinically

meaningful change in SmartDiet score has previously been described to be at least 3 points (181). Additionally, the answers in the SD questionnaire provided a basis for the individual tailored, extended dietary counselling at baseline in the DG and for the CG after 8 weeks follow up.

### 4.3.5 Lipids

Assessment of the lipids was part of the standard CVD risk evaluation. Blood samples was taken from the vein in the arm and the tapping was carried out according to procedures for blood sampling of qualified health personnel. All blood samples were measured at the Diakonhjemmet hospital laboratory (European standard Accredited 2009) by routine procedures in a COBAS 600 modular and Cobas 8000 modular, delivered by Roche Diagnostics Norge AS.

Laboratory tests included TC, HDL-c, TG, LDL-c, liver enzymes, creatine kinase (CK), creatinine, glomular filtration rate and haemoglobin. LDL-c was calculated using Friedwalds equation, assumed TG < 4.4 mmol/L (182). When TG > 4.4 mmol/L, a blood sample was sent to Oslo University Hospital, Rikshospitalet for direct measurement of LDL-c. Blood samples were collected at baseline and after 8 weeks follow-up

### 4.3.6 Inflammatory markers

Measurement of the inflammatory cursor, CRP, was standard procedure, and a marker for disease activity in IJD patients (183) and an individually CVD-risk factor (184). Analyses was based on the same blood samples collected to measure lipids in blood, and will therefore be obtained by same procedures. In cases where the levels of CRP were measured < 1 mg/L, the value 0.001 was recorded for use in all statistical analysis.

### 4.3.7 Blood pressure

Measurement of BP was performed as a standard part of CVD risk evaluation. Two validated and calibrated apparatuses, Omron® 7 series BP device with comfit ™ cuff, model BP760 and Welch Allyn® ProBP 3400 Series BP device with FlexiPort® BP cuffs were used. BP was measured after at least 5 minutes rest in supine position, using an automated BP cuff, according to the appliance's manual (185). If BP was > 140/90 mmHg, two more BP

measurements were performed, where the average of the two last measurements were used as variable in the statistical analyses.

### 4.3.8 Body composition

**Body mass index**

Body mass index (BMI) is a simple and commonly used tool to assess nutritional status. BMI is defined as a person's weight in kilograms, divided by the square of the person's height in metres ($kg/m^2$). See table 5 for cut off points, according to WHOs classification of BMI ranges (74).

**Table 5**. Cut off points for body mass index, according to WHO standard for international classification (74).

| BMI ($kg/m^2$) | Nutritional status |
|---|---|
| **< 18.5** | Underweight |
| **18.5–24.9** | Normal weight |
| **25.0–29.9** | Pre-obesity |
| **30.0–34.9** | Obesity class I |
| **35.0–39.9** | Obesity class II |
| **> 40** | Obesity class III |

BMI, Body Mass Index

**Waist circumference**

Waist circumference is an intensive measure of visceral adiposity and useful in detecting changes in adiposity and as supplement to BMI, when assessing for obesity-related health risks (186). Waist circumference was measured by a standard measuring tape (in cm). A physician performed the measurement (in supine position) during the medical consultation at baseline. At eight weeks follow-up, the same person who performed the nutritional counselling (MGF) performed measurements of waist circumference). The measurements were performed in according to recommended procedure (187), with the patients in the standing position, with the measuring tape placed in a horizontal plane midway between the lower ribs and upper part of the hipbone. The results were assessed according to WHOs cut off points (table 6) (186).

**Table 6** Cut off values for waist circumference in adults, according to WHOs definitions on overweight and obesity (186)

| | Men | Women |
|---|---|---|
| **Overweight** | > 94 cm | > 80 cm |
| **Obesity** | > 102 cm | > 88 cm |

WHO, World Health Organization

**Dual-Energy X-ray absorptiometry**

Measurements of FM, and LM (muscle, organs and body fluids) were obtained by the Hologic Discovery™ QDR series DXA system. This is a valid and reliable method used in clinical practice and which commonly is referred to as the "gold standard" within the measurements of body composition (188, 189). The method is based on measurement of body absorption of X-rays at two different energies, and utilize that FM, bone mass and LM have different absorption properties. Results from DXA measurement provides a detailed evaluation of the patient's nutritional status and provide information about metabolic- and CVD risk (189).

The examination was performed barefoot, in underwear or with only light cloths, all loose items of metal, as pieces of jewellery, watches e.g., were removed prior to the examination. Calibration of the equipment, performance of the examination and analysis of the results were conducted according to the procedures and guidelines specified by the manufacturer (190) and were performed at the rheumatology outpatient clinic, Diakonhjemmet hospital. The DXA-examinations were performed in the evenings, on average 2.4 days after inclusion, and 1.7 days after the follow-up consultation after 8 weeks. In the cases where the DXA-examination was done in the evening or on another day, a new examination by BIA was performed at the same time. This ensured uniform measurement conditions for both examinations and made the comparison of the two methods (BIA/DXA) more valid.

**Bioelectrical Impedance Analyses**

We used a Tanita® Professional Body Composition scale - type BC-418 MA" in the bioelectrical impedance analysis. The scale measures body weight and estimates body fat percentage (fat mass (kg)/ body weight (kg) * 100), fat free mass (FFM) (muscle, bone, tissue, water and all other components of FFM in the body), impedance (reflects the body´s inherent resistance to an electrical current), total body water (TBW) (the amount of water) and BMI. The analysis were collected barefoot, in underwear or only with light cloths and

otherwise in accordance with the procedures and guidelines specified by the manufacturer (191).

The participants had no restrictions (e.g. performance of vigorous exercise, alcohol consumption or intake of excessive amounts of food or beverages) prior to the measurements of body composition (obtained by both BIA and DXA). This may have affected quantity or distribution of body water and further estimation of FM/FFM/LM.

**Fat mass and fat percentage**

FM makes up the most variable component of the body composition and varies according to gender and age (table 7). The body fat percent of the participants was evaluated against the cut of point reported by Gallagher et al. (192). Classification of overweight and obesity based on fat percentage are recommended rather than use of BMI, because use of body fat ranges and not BMI, takes in to account differences in gender, age, and body composition.

**Table 7.** Cut off values for body fat ranges (%) in adults, men and women, to determine the appropriate body fat percentage.

| | **Men** | | | **Women** | | |
|---|---|---|---|---|---|---|
| **Age** | **Underweight** (fat %) | **Healthy** (fat %) | **Overweight** (fat %) | **Underweight** (fat %) | **Healthy** (fat %) | **Overweight** (fat %) |
| **20-39** | < 8 | 9-19 | 25 | < 21 | 22-33 | > 39 |
| **40-59** | < 11 | 12-21 | 28 | < 23 | 24-34 | > 40 |
| **60-79** | < 13 | 19-24 | 30 | < 24 | 25-36 | > 42 |

As reported by Gallagher D, Heymsfield SB, Heo M et al. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. Am J Clin Nutr. 2000 Sep;72(3):694-701.

**Lean mass and fat free mass**

Skeletal muscle mass (SMM) is the major constitute of LM/FFM in the human body (193). The proportion of SMM provides information about a person's health and are important for nutritional processes and needs in the body and therefore of clinical importance. It is currently possible to measure SMM directly using computed axial tomography (CT) or magnetic resonance imaging (MRI), but both are expensive methods and therefore not available in general practice (193). Instead, SMM may be estimated using equations, based on the more accessible measurement techniques; BIA (194) and DXA (193).

Calculation of SMM obtained by BIA

A cross-validated equation (figure 13) was applied for prediction of total body SMM, obtained by BIA (194). The equation has been shown to rapidly and precisely estimate complete SMM in adult Caucasian populations, having a high correlation (r=0.86) with MRI-measurement of SMM. The validity of the use of this equation in patients with altered hydration status or the sensitivity of the method in detecting changes in SMM in response to nutritional interventions are still not investigated (194).

**Figure 13** BIA equation for predicting total-body skeletal muscle mass (194)

$$SMM\ (kg) = ((Ht^2/R \times 0.401) + (gender \times 3.825) + (\ age \times -0.071) + 5.102)$$

SMM, Skeletal Muscle Mass, Ht; height (cm), R; BIA resistance (ohms), gender; men=1 and women=0, age; (years).

Calculation of SMM obtained by DXA

A validated equation has been developed for prediction of SMM, obtained by DXA (figure 14) (193). The equation has been shown to provide reliable and precise estimates for SMM in healthy adults with different ethnicity in both genders, showing a highly correlation ($r \geq 0.97$) with MRI-measurement of SMM (193).

**Figure 14** DXA equation for predicting total-body skeletal muscle mass (193)

$$SMM\ (kg) = (1.13 \times ALST) - (0.02 \times age) + (0.61 \times sex) + 0.97$$

SMM, Skeletal Muscle Mass, ALST; appendicular lean soft tissue (kg), age; (years), sex

**Assessment of muscle mass**

An unfavourable body composition including low muscle mass (with or without increase in FM), has been reported to be prevalent among patients with IJD (195-198). These are features characteristic for the conditions sarcopenia/sarcopnic obesity and rheumatoid cachexia, which have been discussed in the literature throughout the years (199-202). However, studies evaluating body composition in patients with IJD are limited. In this study, we decided to consider the patients' muscle mass in light of sarcopenia and rheumatoid cachexia. Additionally, we compared FFM/LM with cut off-values for low muscle mass.

Sarcopenia

Sarcopenia is a condition characterized by progressive loss of muscle mass in combination with physical disability. At present there is lack of common diagnostic criteria and a clinical definition of sarcopenia (203). In this thesis, cut points for high-risk sarcopenia (skeletal muscle index (SMI) < 8.50 kg/$m^2$ in men and SMI < 5.75 kg/$m^2$ in women) (204) have been used for categorization of patients with sarcopenia and have been reported to be used in determination of sarcopenia in RA patients (197). These cut-off points for classification of sarcopenia in this study, correspond with other cut-off points used in classification of sarcopenia, in previous studies (204, 205). SMI is muscle mass normalized for height (SMM (kg) /height $(m)^2$).

Rheumatoid cachexia

Rheumatoid cachexia is a complex metabolic syndrome associated with underlying illness, characterized by loss of muscle mass, with or without loss of FM and associated with normal or increased BMI (BMI ≥ 25.0) (206). There is no agreed diagnostic criteria for rheumatoid cachexia (206) and various definitions have been suggested (199, 200, 207). In this thesis, cut of values for fat free mass index (FFMI, fat free mass (kg) / height $(m)^2$) and fat mass index (FMI, fat mass (kg) / height $(m)^2$) have been used in categorization of patients as rheumatoid cachectic (207). The cut off values was defined as FFMI < the 25th percentile (FFMI 14.7-15.4 < kg/$m^2$ for women and < 17.6-18.4 kg/$m^2$ for men, depending on age) combined with FMI > the 50th percentile (FMI > 5.5-9.3 kg/$m^2$ for women and > 4.0-5.7 kg/$m^2$ for men, depending on age (208)).

Low muscle mass

The cut-off values described by Elkan et al. (199) when evaluating low muscle mass and were defined as FFMI < the 10th percentile (FFMI < 13.7–14.7 kg/$m^2$ for women and < 16.9–17.6 kg/$m^2$ for men, depending on age (208).

## 4.4 Statistical analyses

All statistical analysis presented in this thesis were performed using the Statistical Package for Social Science for Mac (IBM® SPSS® Statistics) version 23. The level of statistical significance was set at a p-value of $\leq 0.05$ for all analyses.

### 4.4.1 Power calculation

With an estimated difference between the groups of three points (obtained by SmartDiet) and a standard deviation (SD) of 2.69 for change from baseline to follow-up, at least 13 patients were calculated to be needed in each group, to show a statistical difference (two-sided t-test, 5% level) between the groups at 80% strength. The corresponding count for 90 % strength was 17 patients completed in each group.

### 4.4.2 Examination of data

All continuous variables were plotted for normality. The descriptive data of the continuous variables were presented with mean and SD and median and interquartile range (IQR) for variables with a normal and non-normal distribution, respectively. Categorical data was presented as numbers and percentages.

### 4.4.3 Univariate regression analyses

Outcomes were presented as crude and adjusted data with 95% confidence intervals, and all hypotheses were tested using a 5 % two-sided significance level.

**Group comparisons**

Variables with a normal distribution were analysed with Students T-test (Independent samples t-test) and Analysis of Co-variance (ANCOVA), for group comparisons, with baseline values as covariates. A supplementary model including baseline values, BMI, SBP and DBP as covariates was conducted. The model fit was tested by checking residuals and homogeneity of variance. For variables with a non-normal distribution (TG and CRP), log-transformation (ln) was performed to obtain normality. Percent change in mean values for lipids was calculated from the provided end-point and baseline values. An independent sample T-test was conducted to compare the percent change in TC, LDL-c, and TG, between the DG and the CG, after checking for normality distribution. When a variable did not have a normal distribution for example HDL-c, a Mann-Whitney U test was conducted to compare percent

change in HDL-c between the two groups. When analysing dichotomous variables, the Chi-Square test was applied, except when the number in at least one cell was < 5 or > 20 % of the cells had an excepted value < 5, the Fisher test was applied.

**In-between group differences**

Paired-samples t-test was applied when examining in-between differences in the two groups, from baseline to 8 weeks follow-up.

### 4.4.4 Correlations

To investigate the relationship between two independent methods for measuring body composition, DXA and BIA, Pearson product-moment correlation coefficient was applied. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity.

### 4.4.5 Missing data

The primary static analyses follow the intention-to-treat principle (209). Missing data was handled using pairwise deletion. Analysis with all cases in which the variables of interest are present. Cases (patients) were only excluded if they were missing the data required for the specific analysis and were still included in any of the analyses for which they had the necessary information.

## 4.5 Ethical aspects

The data collection in this RCT fulfilled the conditions of privacy and information security according to the Helsinki Declaration (210). The study was approved by the South East Health Authority Ethical Committee for Medical Research (nr. 2015/2087). The patient data was anonymised. The link between study number and the name of the respectively patient was kept separately and stored in a locked fire safe cabinet from the patient data. Only the project manager and her co-workers had access to this. Data collected were only used as described in the purpose of the study.

Start of cholesterol-lowering medication was postponed by eight weeks in our study. This was considered clinically safe, taking into account that the development of atherosclerotic disease is a prolonged process. In addition, according to national guidelines, change in diet and

lifestyle, are recommended to be tried before starting preventive medication. Patients assessed with high CVD-risk and an immediate need for preventive drug therapy, were considered not suitable for participation in the study, which was stated in the exclusion criteria.

## 4.6 Literature search

To collect information on related literature and results for use in this thesis, literature searches in PubMed were performed.

# 5 Results

## 5.1 Patient characteristics

Baseline characteristics are shown in table 8. A total of 31 patients with IJD (RA n=16, PsA n=7, AS n=8) were included in the study, of whom 16 were randomized to the DG. In both groups, there were mostly women and there were no sex differences between the groups. Participants in the DG had lower BMI (p=0.03), waist circumference (p=0.002), FM (measured by BIA or DXA, p=0.01 and 0.02, respectively) and body fat percentage (measured by BIA or DXA, p=0.02 and 0.03, respectively) at baseline, compared to the (CG). The groups were comparable with regard to LM. The lipid profile in the two groups was similar and median CRP was < 5 mg/L in both groups. Systolic (p=0.04) and diastolic (p=0.04) BP was higher among patients in the CG compared to those in the DG, which probably can be seen in the context of higher BMI and waist circumference in the CG. The reminding CVD risk factors were comparable between the groups, except for more patients in the DG with physical activity ≥ 3 times per week (p=0.05). Among patients in the CG, 40.0 % were classified being hypertensive (systolic BP > 140 mmHg) compared to 12.6 % of the patients in the DG (p=0.09). Diabetes mellitus was not present in any of the groups. In the DG and the CG, 6.3 % and 14.3 % had combined dyslipidaemia (TG > 2 mmol/L and HDL-c < 1) (p=0.59), while 56.0 % and 33.3 % had hyperlipidaemia (TC > 5 mmol/L), respectively (p=0.20). A high number of the included patients had atherosclerotic plaque(s) (DG: 81.3 %, CG: 86.7 %) (p=1.00). There were no significant differences in medication use between the groups. Among the patients in the DG, 81.3 % was using bDMARDS, compared to 53.3 % of the patients in the CG (p=0.14), while 43.8 % and 60.0 % of the patients was using sDMARDs (p=0.37), respectively. Current prednisolone medication was present in 6.3 % and 20.0 % amongst the DG and the CG patients, respectively (p=0.33).

**Table 8.** Baseline characteristics

| | All patients, n=31 | Diet group, n=16 | Control group, n=15 | p value* |
|---|---|---|---|---|
| Diagnosis RA/PsA/AS n (%) | 16 (51.6) / 7 (22.6) / 8 (25.8) | 7 (43.8) / 4 (25.0) / 5 (31.3) | 9 (60.0) / 3 (20.0) / 3 (20.0) | 0.72[b] |
| Sex male/female n (%) | 13(41.9) / 18 (58.1) | 7 (43.8) / 9 (56.3) | 6 (40.0) / 9 (60.0) | 0.83[a] |
| Age mean ± SD | 54.94 ± 9.96 | 53.38 ± 10.36 | 56.60 ± 8.91 | 0.36 |
| **CV risk factors** | | | | |
| **Lipids** | | | | |
| TC (mmol/L) mean ± SD | 5.88 ± 0.84 | 6.10 ± 0.85 | 5.64 ± 0.78 | 0.13 |
| HDL-c (mmol/L) mean ± SD | 1.48 ± 0.42 | 1.46 ± 0.47 | 1.50 ± 0.38 | 0.82 |
| LDL-c (mmol/L) mean ± SD | 3.71 ± 0.83 | 3.90 ± 0.95 | 3.52 ± 0.66 | 0.21 |
| TG (mmol/L) median (IQR) | 1.29 (1.08) | 1.29 (0.98) | 1.29 (1.23) | 0.91 |
| **Blood pressure, mean ± SD** | | | | |
| Systolic (mmHg) | 129.06 ± 17.11 | 122.96 ± 14.30 | 135.57 ± 17.89 | 0.04 |
| Diastolic (mmHg) | 80.85 ± 9.80 | 77.34 ± 10.16 | 84.60 ± 8.14 | 0.04 |
| **Antropomethry, mean ± SD** | | | | |
| Weight (kg) | 81.04 ± 12.26 | 76.43 ± 15.89 | 85.95 ± 13.35 | 0.08 |
| BMI (kg/m2) | 27.56 ± 4.89 | 25.76 ± 1.19 | 29.49 ± 1.13 | 0.03 |
| Waist circumference (cm) | 96.48 ± 11.44 | 90.69 ± 9.94 | 102.67 ± 9.78 | 0.002 |
| **Body composition** | | | | |
| **BIA, mean ± SD** | | | | |
| Body fat mass (kg) | 26.44 ± 10.02 | 22.22 ± 8.99 | 21.92 ± 8.76 | 0.01 |
| Body fat percent (%) | 32.22 ± 8.93 | 28.78 ± 8.25 | 28.73 ± 8.02 | 0.02 |
| Fat free body mass (kg) | 54.60 ± 11.35 | 54.21 ± 11.97 | 53.41 ± 10.68 | 0.85 |
| **DXA, mean ± SD** | | | | |
| Body fat mass (kg) | 27.32 ± 10.07 | 23.34 ± 8.69 | 22.21 ± 7.99 | 0.02 |
| Body fat percent (%) | 33.01 ± 8.44 | 29.94 ± 7.48 | 28.91 ± 7.40 | 0.03 |
| Lean body mass (kg) | 52.17 ± 10.61 | 51.61 ± 11.17 | 51.60 ± 10.28 | 0.76 |
| **Smoking habits n (%)** | | | | |
| Daily smoking | 7 (22.6) | 3 (18.8) | 4 (26.7) | 0.69[b] |
| Social smoking | 2 (6.5) | 2 (12.5) | 0 (0.0) | 0.48[b] |
| **Physical activity habits, n (%)** | | | | |
| Never or < 1 time per week | 8 (25.8) | 3 (18.8) | 5 (33.3) | 0.43[b] |
| 2-3 times per week | 13 (41.9) | 5 (31.3) | 8 (53.3) | 0.29[a] |
| ≥ 3 times per week | 10 (32.3) | 8 (50.0) | 2 (13.3) | 0.05[b] |
| **Comorbidities n (%)** | | | | |
| Combined dyslipidaemia (TG > 2 mmol/L, HDL-c < 1 mmol/L) | 3 (9.7) | 1 (6.3) | 2 (14.3) | 0.59[b] |
| Hyperlipidaemia (TC > 6 mmol/L) | 14 (45.2) | 9 (56.3) | 5 (33.3) | 0.20[a] |
| Hypertension (SBP > 140 mmol/L) | 8 (25.81) | 2 (12.6) | 6 (40.0) | 0.09[b] |
| Diabetes | 0 (0.0) | 0 (0.0) | 0 (0.0) | - |
| Plaque i a. Carotid | 26 (83.9) | 13 (81.3) | 13 (86.7) | 1.0[b] |
| Gastric ulcer | 1 (3.2) | 0 (0.0) | 1 (6.7) | 0.48[b] |
| Crohn's disease | 0 (0.0) | 0 (0.0) | 0 (0.0) | - |
| Ulcerative colitis | 2 (6.5) | 1 (6.3) | 1 (6.7) | 1.0[b] |
| **Inflammation biomarkers, median (IQR)** | | | | |
| CRP (mg/L) | 2.00 (4.00) | 2.00 (4.00) | 3.50 (5.25) | 0.15 |
| **Medication n (%)** | | | | |
| Prednisolone | 4 (12.9) | 1 (6.3) | 3 (20.0) | 0.33[b] |
| NSAIDs | 12 (38.7) | 6 (37.5) | 6 (40.0) | 0.89[a] |
| sDMARDs | 16 (51.6) | 7 (43.8) | 9 (60.0) | 0.37[a] |
| bDMARDs | 21 (67.7) | 13 (81.3) | 8 (53.3) | 0.14[b] |

*Differences between the diet group and the control group at baseline, analyzed with independent samples t test
[a]Pearson Chi-Square,
[b]Fisher´s Exact Test
RA, Rheumatoid Arthritis; PsA, Psoriatric Arthritis; Ankylosing Spondylitis; SD, Standard Deviation; TC, Total cholesterol; HDL-c, High Density Lipoprotein Cholesterol; LDL-c, Low Density Cholesterol; TG, Triglycerides; IQR, interquartile Range; BMI, Body Mass Index; BIA, Bioelectrical impedance analysis; DXA, Dual Energy X-rays Absorptiometry; a. Carotid, arteria Carotid; CRP, C-reactive Protein; NSAIDS, Non-steroidal Anti-Inflammatory Drugs, sDMARDs, Synthetic Disease-modifying Anti-rheumatic Drugs; bDMARDs, Biologic Disease-modifying Anti-rheumatic Drugs

**Table 9.** Effect of extended and individually tailored nutritional consultation, compared to a standardized brief advice, on diet, lipids, inflammatory markers, blood pressure and body composition.

| | Diet group, n = 16 | | Control group, n = 15 | | Unadjusted mean group difference (95 % CI)[b] | p value[a] | Estimated mean group difference (95 % CI)[b] | p value[c] | Estimated mean group difference (95 % CI)[b] | p value[d] |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | 8 weeks | Baseline | 8 weeks | | | | | | |
| **Diet** | | | | | | | | | | |
| SmartDiet score, mean ± SD | 28.25 ± 2.89 | 33.31 ± 2.73 | 25.60 ± 4.63 | 31.27 ± 5.08 | -0.60 (-3.29, 2.09) | 0.65 | 0.46 (-2.19, 3.10) | 0.73 | 1.55 (-1.24, 4.34) | 0.26 |
| **Lipids** | | | | | | | | | | |
| Total cholesterol (mmol/L), mean ± SD | 6.10 ± 0.85 | 5.73 ± 1.12 | 5.64 ± 0.78 | 5.55 ± 0.58 | -0.28 (-0.81, 0.25) | 0.29 | -0.15 (-0.69, 0.38) | 0.56 | -0.13 (-0.76, 0.51) | 0.68 |
| HDL-cholesterol (mmol/L), mean ± SD | 1.46 ± 0.47 | 1.51 ± 0.54 | 1.50 ± 0.38 | 1.48 ± 0.28 | 0.07 (-0.13, 0.26) | 0.50 | 0.06 (-0.13, 0.25) | 0.53 | 0.05 (-0.19, 0.28) | 0.70 |
| LDL-cholesterol (mmol/L), mean ± SD | 3.89 ± 0.95 | 3.42 ± 1.04 | 3.52 ± 0.66 | 3.36 ± 0.47 | -0.31 (-0.71, 0.08) | 0.11 | -0.23 (-0.62, 0.16) | 0.23 | -0.26 (-0.71, 0.19) | 0.25 |
| Triglycerides (mmol/L), median (IQR) | 1.29 (1.86, 0.88) | 1.62 (2.08, 0.84) | 1.29 (2.05, 0.82) | 1.36 (1.91, 0.86) | 1.06 (0.84, 1.35) | 0.63 | -0.06 (-0.18, 0.29) | 0.62 | 0.06 (-0.23,0.35) | 0.67 |
| **Inflammation biomarkers** | | | | | | | | | | |
| C- reactive protein (mg/L), median (IQR) | 2.00 (4.00, 0.00) | 2.00 (4.75, 1.00) | 3.50 (7.25, 2.00) | 4.00 (8.00, 2.00) | 1.28 (0.30, 79.45) | 0.25 | 0.18 (-2.08, 2.43) | 0.87 | 1.08 (-1.50, 3.67) | 0.40 |
| **Blood pressure** | | | | | | | | | | |
| Systolic blood pressure (mmHg), mean ± SD | 122.96 ± 14.30 | 121.81 ± 12.39 | 135.57 ± 17.89 | 130.03 ± 13.39 | 4.38 (-3.67, 12.43) | 0.28 | -0.80 (-7.84, 6.23) | 0.82 | 0.07 (-7.20, 7.35) | 0.98 |
| Diastolic blood pressure (mmHg), mean ± SD | 77.34 ± 10.16 | 77.78 ± 7.56 | 84.60 ± 8.14 | 82.87 ± 7.90 | 2.17 (-3.71, 8.05) | 0.46 | -1.65 (-6.79, 3.50) | 0.52 | -0.65 (-6.27, 4.97) | 0.81 |
| **Body composition** | | | | | | | | | | |
| Weight (kg) | 76.43 ± 15.89 | 75.31 ± 14.50 | 85.95 ± 13.35 | 84.59 ± 13.69 | 0.24 (-1.75, 2.23) | 0.81 | -0.30 (-2.33, 1.73) | 0.76 | -0.39 (-2.72, 1.95) | 0.71 |
| BMI (kg/m2) | 25.76 ± 4.76 | 25.38 ± 4.28 | 29.49 ± 4.38 | 29.03 ± 4.52 | 0.07 (-0.61, 0.76) | 0.83 | -0.15 (-0.88, 0.57) | 0.67 | -0.16 (-0.96,0.64) | 0.68 |
| Waist circumference (cm) | 90.69 ± 9.94 | 89.03 ± 8.63 | 102.67 ± 9.78 | 101.07 ± 10.08 | -0.06 (-3.03, 2.92) | 0.97 | -1.66 (-5.04, 1.72) | 0.32 | -0.41 (-3.67, 2.86) | 0.80 |
| **BIA** | | | | | | | | | | |
| Body fat mass (kg) mean ± SD | 22.22 ± 8.99 | 21.92 ± 8.76 | 30.94 ± 9.29 | 29.97 ± 9.41 | 0.91 (-0.09, 1.90) | 0.07 | 0.74 (-0.38, 1.86) | 0.19 | 0.82 (-0.43, 2.07) | 0.19 |
| Body fat percent (%) mean ± SD | 28.78 ± 8.25 | 28.73 ± 8.02 | 35.89 ± 8.36 | 35.29 ± 8.60 | 0.54 (-0.82, 1.90) | 0.43 | 0.36 (-1.14, 1.87) | 0.63 | 0.80 (-0.86, 2.47) | 0.33 |
| Fat free body mass (kg) mean ± SD | 54.21 ± 11.97 | 53.41 ± 10.68 | 55.03 ± 11.05 | 54.65 ± 11.07 | -0.43 (-2.46, 1.61) | 0.67 | -0.50 (-2.43, 1.44) | 0.61 | -0.94 (-3.29, 1.40) | 0.42 |
| **DXA** | | | | | | | | | | |
| Body fat mass (kg) mean ± SD | 23.34 ± 8.69 | 22.21 ± 7.99 | 31.88 ± 9.85 | 30.03 ± 9.50 | -0.06 (-1.69, 1.58) | 0.94 | -0.68 (-2.39, 1.03) | 0.42 | -0.74 (-2.83, 1.34) | 0.47 |
| Body fat percent (%) mean ± SD | 29.94 ± 7.48 | 28.91 ± 7.40 | 36.51 ± 8.34 | 35.98 ± 8.50 | -0.48 (-1.79, 0.84) | 0.46 | -0.73 (-2.16, 0.71) | 0.31 | -0.96 (-2.68, 0.77) | 0.26 |
| Lean body mass (kg) mean ± SD | 51.61 ± 11.17 | 51.60 ± 10.28 | 51.35 ± 9.11 | 50.66 ± 8.91 | 0.69 (-0.61, 1.99) | 0.29 | 0.71 (-0.49, 1.90) | 0.24 | 0.90 (-0.50, 2.30) | 0.20 |

[a]Differences from pre- to post intervention (8 weeks) values, between the groups, analyzed with independent samples t test
[b]Estimated regressions coefficients
[c]Estimated mean group difference values, analyzed with ANCOVA, with baseline values as covariates
[d]Estimated mean group difference values, analyzed with ANCOVA, with baseline, BMI, SBP, DBP values as covariates
SD, Standard Deviation; TC, Total cholesterol; HDL-c, High Density Lipoprotein Cholesterol; LDL-c, Low Density Cholesterol; TG, Triglycerides; IQR, interquartile Range; BMI, Body Mass Index; BIA, Bioelectrical impedance analysis; DXA, Dual Energy X-rays Absorptiometry; BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure

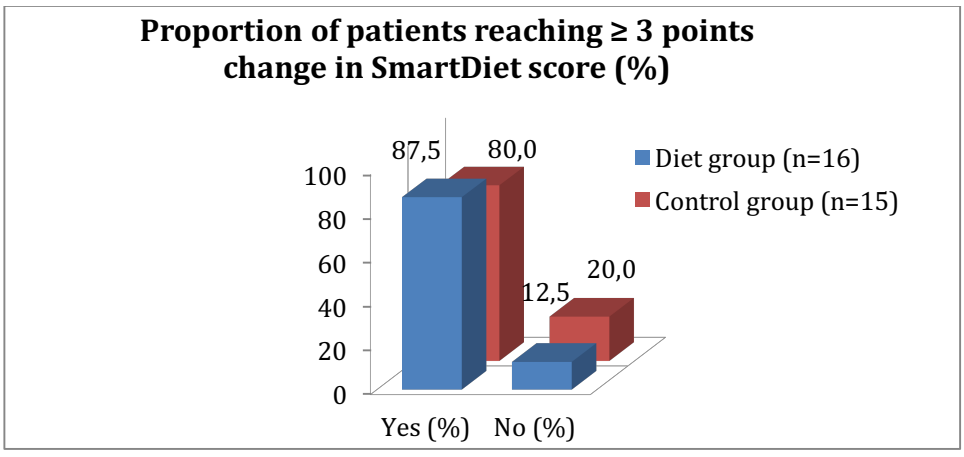
## 5.2 Main results

Group differences (both unadjusted and adjusted) between the DG and the CG, concerning SmartDiet score, lipids, BP and body composition are summarised in table 9.

### 5.2.1 Diet

The questionnaire SmartDiet measured dietary habits, and an increased sum score by at least 3 points implied clinically significant improvement of the diet. A 3 point SmartDiet score improvement was obtained by 87.5 % ($p<0.001$) and 80.0 % ($p<0.001$) in the DG and in the CG, respectively (figure 15). From baseline to eight weeks follow-up, there was an increase in mean sum SmartDiet score of 5.1 points ($p <0.001$, data not shown) in the DG and 5.7 points ($p <0.001$, data not shown) in the CG. There were no significant differences in change in sum SmartDiet score from baseline to post-intervention, between the DG and the CG ($p=0.65$) and no further change was observed after adjusting for baseline SmartDiet score, BMI and BP ($p=0.26$) (table 9).

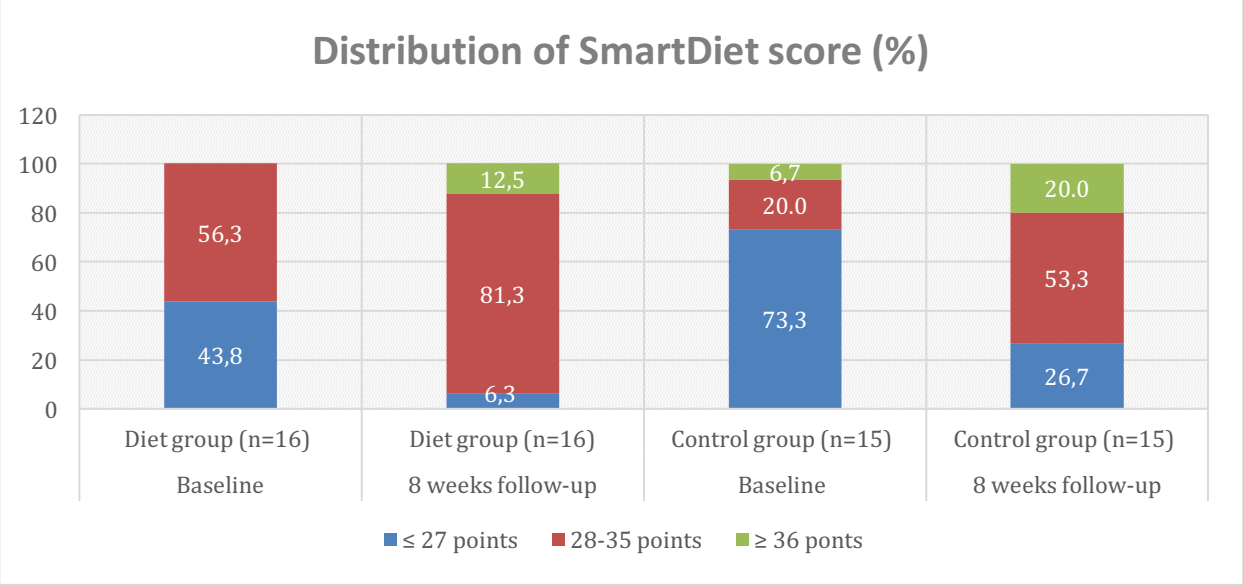
**Figure 15**. Proportion of patients reaching ≥ 3 points change in SmartDiet score




The sum score obtained from the SmartDiet showed that 73.3 % of the patients in the CG had a poor diet (sum score ≤ 27) at baseline. In comparison, 43.8 % of the patients in the DG showed a similar low total score ($p=0.95$) (Figure 16). The proportions with score < 27 points were improved to 6.3 % and 26.7 % in the DG and the CG, respectively ($p=0.17$), after eight weeks. There was a significant difference between the proportion of patients in the DG (56.3 %) and the CG (20.0 %) which obtained a sum score between 28 and 35 point at baseline ($p=0.04$). The difference was 81.3 % vs 53.3 %, respectively, after eight weeks ($p=0.14$). Only one patient in the CG had a satisfying diet at baseline (sum score ≥ 36 points), compared to none in the DG

(p=0.48). After eight weeks, 12.5 % and 20.0 % had obtained a sum score ≥ 36 points in the DG and in the CG, respectively (p=0.57). The increase in SmartDiet score from pre-intervention to post-intervention test, reflects several changes in dietary habits (table 10a and 10b).

**Figure 16**. Distribution of total score obtained by SmartDiet.




Twenty-seven points or less indicates that the diet should be improved in several areas, 28-35 points indicates that the diet still could be improved to become more heart-friendly, while a total score of ≥ 36 points indicates that the dietary habits to be heart-friendly and healthy

**Milk- and dairy products**

There were no significant differences between the groups in choice of milk (p=0.17), use of dairy products for cooking (p=0.38) or selection of cheese (p=1.00) at baseline, or after the follow-up (p=0.31, p=1.00, p=0.40). Post-intervention test showed an increase by 6.6 % in the proportion of patients who reported most frequent use of low-fat milk in the CG and 6.3 % increase in the proportion of patients who reported most frequent use of skimmed milk in the DG. Forty percent of the patients in the CG reported a use of less than one litre milk per week at both first and last consultation. In comparison, there was a minor reduction (6.2 %) observed in the DG. No patients in the DG reported use of full-fat milk at any time, while the reported consumption in the CG was reduced from 13.3 % to 6.7 % from first to last consultation.

The proportion of patients most frequently using lean varieties (< 10 % fat) of cream, sour cream, crème fraiche etc. increased at the last consultation by 31.3 % in the DG and by 20 % in the CG, while frequent use of whole fat varieties was reduced after eight weeks follow-up in

both groups, compared to baseline. None of the participants in either group, reported using low- or medium fat cheese before inclusion. At the last consultation, this proportion was increased to 56.3 % and 60.0 % in the DG and in the CG, respectively.

**Meat and fish products**

There was no significant difference between the groups in use of meat spreads (cold cuts) at baseline (p=1.00) or after eight weeks (p=0.53). Although, a significant lower proportion of patients in the DG reported consumption of processed high-fat meat (for dinner) at baseline, compared to the proportion of patients in the CG (p=0.02). The difference was not present eight weeks after intervention (p=0.20). A greater proportion of patients in both groups reported frequent use of lean varieties of cuts for dinner after eight weeks follow up, compared to baseline (DG: 93.8 % vs 68.8) (CG: 73.3 % vs 53.3 %). Corresponding observation was observed in use of cold cuts.

There was no significant difference between the groups in use of fish (spreads) on bread at baseline (p=0.90) or after eight weeks (p=0.36). Nevertheless, the consumption of ≥ 5 slices of bread with fish per week, was decreased by 18.7 % in the DG group, while this consumption remained stable in the CG. A greater, but non-significant proportion of the patients in the DG replied a more frequent use of fish (> 2 times per week) compared to patients in the CG, both at baseline (87.6 % vs 66.7 %) (p=0.60) and after eight weeks follow-up (87.6 vs 73.3 %) (p=0.39). There was only a minor increase in the proportion of patients in the CG who reported use of fish > two times per week, while the reported consumption remained constant in the DG. Reported use of dietary supplements, as cod liver oil and omega 3 supplements was unchanged in the CG (40 %), while a minor reduction was observed in the DG. No significant differences were observed between the groups at baseline (p=0.62) or after eight weeks (p=0.76) for cod liver oil and omega 3 supplements.

**Fat sources**

Fifty % and 73.3 % of the patients in the DG and the CG, reported most frequently using butter or hard margarine for bread at baseline. Although, there was no significant difference in selection of fat source (for bread) between the two groups at baseline (p=0.37). After eight weeks, a significant greater proportion of patients in the CG reported more frequent use of butter or hard margarine for bread, compared to the DG (46.7 % vs 6.7 %) (p=0.02). However, there were no differences in use of soft margarine (e.g. Soft flora, soy margarine, olive margarine)

(p=0.10) or margarine with high content of unsaturated fat (e.g. Vita, Vita light, Vita Pro-active) (p=0.69), between the groups after the follow-up. No one of the participants in the DG reported using margarine added plant sterols at baseline, compared to 6.7 % in the CG (p=0.48). After eight weeks, the proportion in the DG was increased to 37.0 %, while the proportion in the CG was increased to 26.7 % (p=0.70).

No differences were revealed between the groups in selection of fat source for cooking at baseline (p=0.09). Although, significant difference was observed in use of vegetable oil/liquid margarine for cooking, between the groups after eight weeks (p=0.04). The proportion of patients who answered most frequent use of vegetable oil or liquid margarine for cooking war increased from 56,3 % to 93.8 % and from 20.0 % to 60.0 % in the DG and CG, respectively. A non-significant difference was observed in use of butter or hard margarine between the groups after the follow-up (p=0.08), despite only 6.3 % of the patients in the DG compared to 33.3 % of the patients in the CG, answered using butter/hard margarine for cooking after eight weeks.

**Fruit, vegetables and nuts**

No significant differences in consumption of fruit and vegetables were observed between the DG and the CG at baseline (0.50) or after the follow-up (p=1.00). Although, after eight weeks twice as many of the patients in the DG (25.0 %) and three times as many of the patients in the CG (20.0 %), reported eating ≥ four portions of fruit and vegetables per day compared to what they did at baseline. Simultaneously, in the DG at follow up compared to baseline, there was a decrease (31.3 % to 18.8 %) in the proportion of patients who answered that they had a consumption of less than two servings of fruits and vegetables per day. In comparison, after the eight weeks in the CG, there was a decrease from 53.3 % to 26.7 % in consumption of less than two servings of fruit and vegetables daily.

There was no significant difference in weekly consumption of avocado between the groups at baseline (p=0.85). Although, the proportion which replied a weekly consumption of avocado was barely significant higher in the DG, compared to the CG, after the follow-up (p=0.05). The consumption was increased by 25.0 % in the DG and decreased by 6.7 % in the CG after the follow-up. No significant differences between the groups were detected in consumption of nuts at baseline (p=0.21) or after eight weeks (p=0.11). No changes in consumption of nuts were observed in the DG from first to final consultation, but a decrease (6.7 %) was observed among patients in the CG at the follow-up.

**Bread**

No differences were observed between the DG and the CG in selection of bread at baseline (p=0.07). A significant difference in selection of bread high in fibre was revealed (p=0.04) after eight weeks, where 93.8 % of the patient in the DG and 60.0 % of the patients in the CG reported a frequent consumption of bread high in fibre. This corresponds to an increase of approximately 30 % from baseline, in both groups. The consumption of bread low in fibre, was significant lower in the CG compared to the DG after the follow-up (p=0.04).

**Sweet beverages, chocolate, snacks and cakes**

The frequency of chocolate-, snack- and cakes consumption between the groups at baseline (p=0.35) and after the follow-up (p=0.37) were similar. Although, a lower frequency of consumption of chocolate, snacks, cakes and similar products was reported in the DG and in the CG, at the final consultation, compared to baseline. In the DG, 50.0 % of the patients answered that they usually ate sweets 0-1 time per week at the final consultation, while 73.3 % of the patients in the CG replied the same.

No significant differences were reported in consumption of sweet spreads and sweet beverages between the DG and the CG at baseline (p=0.30) or after eight weeks (p=0.10).
All of the patients in the DG reported an intake of sweetened beverages, including fruit juice and sweet spreads, no more than once per day after the follow-up and 80.0 % of the patients in the CG answered the same.

**Alcohol consumption**

Alcohol consumption was comparable in the DG and the CG at baseline (p=1.00) and after eight weeks (p=1.00). Most of the patients in both groups reported a usually consumption of 1-7 alcohol units per week at baseline (DG: 78.6 % CG: 76.9 %) and after eight weeks (DG:64.3 % CG:57.1 %). In the DG, there was observed an increase by 14.3 % in the proportion of patients who replied a weekly consumption of 8-14 units of alcohol, from first to last consultation. A greater proportion of the patients in the CG answered that they usually consumed less than one unit per week at eight weeks follow-up, compared to what was reported at baseline (35.7 % vs 15.4 %). In comparison, 14.3 % of the patients in the DG reported an alcohol consumption of less than one unit per week, which was held constant during the study time.

**Table 10a**. Description of food habits in the study population at first and last consultation.

| | DG (n=16) Baseline | CG (n=15) Baseline | p value[1] | DG (n=16) 8 weeks follow-up | CG (n=15) 8 weeks follow-up | p value[1] |
|---|---|---|---|---|---|---|
| **Milk (%):** | | | 0.17 | | | 0.31 |
| ≤ 1 litre per week | 25,0 | 40.0 | | 18,8 | 40,0 | |
| Whole fat milk | 0,0 | 13,3 | | 0,0 | 6,7 | |
| Low-fat milk | 62,5 | 26,7 | | 62,5 | 33,3 | |
| Skimmed milk | 12,5 | 20,0 | | 18,8 | 20,0 | |
| **Dairy products (%):** | | | 0.38 | | | 1.00 |
| Cream, sour cream etc. (whole fat) | 18,8 | 33,3 | | 12,5 | 13,3 | |
| Cream, sour cream etc. low fat) | 62,5 | 40,0 | | 31,3 | 33,3 | |
| Cream, sour cream etc. (< 10 % ) | 0,0 | 13,3 | | 31,3 | 33,3 | |
| **Cheese (%):** | | | 1.00 | | | 0.40 |
| ≤ Once per week | 6,3 | 0,0 | | 0,0 | 0,0 | |
| Whole fat | 93,8 | 100,0 | | 43,8 | 40,0 | |
| Medium-fat ( 17 %) | 0,0 | 0,0 | | 50,0 | 33,3 | |
| Low-fat cheese (< 10 %) | 0,0 | 0,0 | | 6,3 | 26,7 | |
| **Meat (as cold cuts) (%):** | | | 1.00 | | | 0.53 |
| ≤ Once per week | 18,8 | 26,7 | | 25,0 | 40,0 | |
| Fat meat | 25,0 | 20,0 | | 12,5 | 0,0 | |
| Lean meat (< 10 %) | 56,3 | 53,3 | | 62,5 | 60,0 | |
| **Meat (for dinner) (%):** | | | 0.02* | | | 0.20 |
| ≤ Once per week | 0,0 | 6,7 | 0.48 | 0,0 | 6,7 | |
| High fat cuts* | 0,0 | 33,3 | 0.02* | 0,0 | 0,0 | |
| Medium-fat cuts | 31,3 | 6,7 | 0.17 | 6,3 | 20,0 | |
| Lean cuts | 68,8 | 53,3 | 0.40[2] | 93,8 | 73,3 | |
| **Fish (on bread) (%):** | | | 0.90 | | | 0.36 |
| ≤ 1 slice/week | 56,3 | 46,7 | | 50,0 | 40,0 | |
| 2-4 slices/week | 18,8 | 26,7 | | 43,8 | 33,3 | |
| ≥ 5 slices/week | 25.0 | 26.7 | | 6.3 | 26.7 | |
| **Fish (for dinner) (%):** | | | 0.60[2] | | | 0.39 |
| ≤ 1 times/week | 12,5 | 33,3 | | 12,5 | 26,7 | |
| ≥ 2 times/week | 87,6 | 66,6 | | 87,6 | 73,3 | |

*p < 0.05
[1]Differences between the diet group and the control group, analyzed Fisher´s Exact test
[2]Pearsons Chi-square
[3]Independent samples t test
DG, Dietary Group; CG, Control Group

**Table 10b**. Description of food habits in the study population at first and last consultation.

| | DG (n=16) Baseline | CG (n=15) Baseline | p value[1] | DG (n=16) 8 weeks follow-up | CG (n=15) 8 weeks follow-up | p value[1] |
|---|---|---|---|---|---|---|
| **Fat source on bread (%):** | | | 0.37 | | | 0.04* |
| Usually no butter/margarine | 0,0 | 0,0 | | 0,0 | 0,0 | |
| Butter/hard margarine | 50,0 | 73,3 | | 6,3 | 46,7 | 0.02* |
| Soft margarine | 25,0 | 6,7 | | 62.5 | 33,3 | 0.10[2] |
| Margarine with highly unsaturated fat | 25,0 | 20,0 | | 31,3 | 20,0 | 0.69 |
| Margarine added plant sterols | 0,0 | 6,7 | 0.48 | 37,0 | 26,7 | 0.70 |
| **Fat source for cooking (%):** | | | 0.09 | | | 0.04* |
| Usually no fat source | 0,0 | 0,0 | | 0,0 | 0,0 | |
| Butter/hard margarine | 37,5 | 66,7 | | 6,3 | 33,3 | 0.08 |
| Soft margarine | 6,3 | 13,3 | | 0,0 | 6,7 | 0.48 |
| Vegetable oil/liquid margarine | 56,3 | 20,0 | | 93,8 | 60,0 | 0.04* |
| **Bread (%):** | | | 0.07 | | | 0.04* |
| Do not eat bread/grain products | 0,0 | 6,7 | | 0,0 | 0,0 | |
| Low in fibre | 37,5 | 66,7 | | 6,3 | 40,0 | 0.04* |
| High in fibre | 62,5 | 26,7 | | 93,8 | 60,0 | 0.04* |
| **Fruit, vegetables and nuts (%):** | | | 0.50 | | | 1.00 |
| < 2 portion/day (< 300 g) | 31,3 | 53,3 | | 18,8 | 26,7 | |
| 2-4 portion/day (300-600 g) | 56,3 | 40,0 | | 56,3 | 53,3 | |
| ≥ 4 portion/day (> 600 g) | 12,5 | 6,7 | | 25,0 | 20,0 | |
| Legumes (weekly consumption) | 56,3 | 60,0 | 0.83[2] | 68,8 | 53,3 | 0.40[2] |
| Nuts/almonds (weekly consumption) | 68,8 | 46,7 | 0.21[2] | 68,8 | 40,0 | 0.11[2] |
| Avocado (weekly consumption) | 50,0 | 46,7 | 0.85[2] | 75,0 | 40,0 | 0.05*[2] |
| **Sweet beverages or sweet spreads (%):** | | | 0.30 | | | 0.10[2] |
| ≥ 3 times/week | 0,0 | 13,3 | | 0,0 | 0,0 | |
| 2 times/week | 6,3 | 13,3 | | 0,0 | 20,0 | |
| 0-1 times/week | 93,8 | 73,3 | | 100,0 | 80,0 | |
| **Chocolate, snacks, biscuits and cakes (%):** | | | 0.35 | | | 0.37[2] |
| ≥ 3 times/day | 37,5 | 13,3 | | 25,0 | 6,7 | |
| 2 times/day | 31,3 | 40,0 | | 25,0 | 20,0 | |
| 0-1 times/day | 31,3 | 46,7 | | 50,0 | 73,3 | |
| **Diet supplementation (%):** | | | 0.62 | | | 0.76 |
| Uses cod liver oil/omega-3 supplementation | 43,8 | 40,0 | | 38,0 | 40,0 | |
| **Alcohol habits (%):** | | | 1.00 | | | 0.32 |
| < 1 unit/week | 14,3 | 15,4 | | 14,3 | 35,7 | |
| 1-7 units/week | 78,6 | 76,9 | | 64,3 | 57,1 | |
| 8-14 units/week | 7,1 | 7,7 | | 21,4 | 7,1 | |
| **Egg, mean ± SD** | 3.06 ± 2.09 | 2.60 ± 1.50 | 0.56[3] | 3.34 ± 2.18 | 2.93 ± 1.65 | 0.59[3] |

*$p < 0.05$
[1]Differences between the diet group and the control group, analyzed Fisher´s Exact test
[2]Pearsons Chi-square
[3]Independent samples t test
DG, Dietary Group; CG, Control Group

### 5.2.2 Lipids

At baseline and after eight weeks blood samples were obtained for comparisons of lipid levels in the DG and the CG. TC (p=0.13), LDL-c (p=0.21), HDL-c (p=0.82) and TG (p=0.91) was comparable in the DG and the CG at baseline. Eight weeks after inclusion no significant mean differences were observed between the groups for either change in TC (p=0.29), LDL-c (p=0.11), HDL-c (p=0.50) or TG (p=0.63) (table 9). Adjusting for baseline values, BMI and BP did not change the outcome (table 9). Although, mean percent change in LDL-c from baseline to eight weeks follow up was significant higher in the DG compared to the CG (p=0.05) (figure 17).

**Total cholesterol**

Both the DG and the CG showed an average decrease in TC from first to last consultation, but only a minor reduction of ~0.1 mmol/L was observed in the CG (p=0.97, data not shown), compared to ~0.4 mmol/L reduction in the DG (p=0.04, data not shown). However, no significant difference in percent change was observed between the groups from first to last consultation (p=0.19).

**LDL Cholesterol**

Patients in the DG showed a mean reduction in LDL-c of ~0.5 mmol/L form first to last consultation (p=0.001, data not shown), while patients in the CG showed a mean reduction in LDL-c of ~0.2 mmol/L (p=0.32, data not shown). These findings correspond with a mean percent reduction of 12.6 % and 0.4 % in the DG and CG (p=0.05), respectively.

**HDL cholesterol**

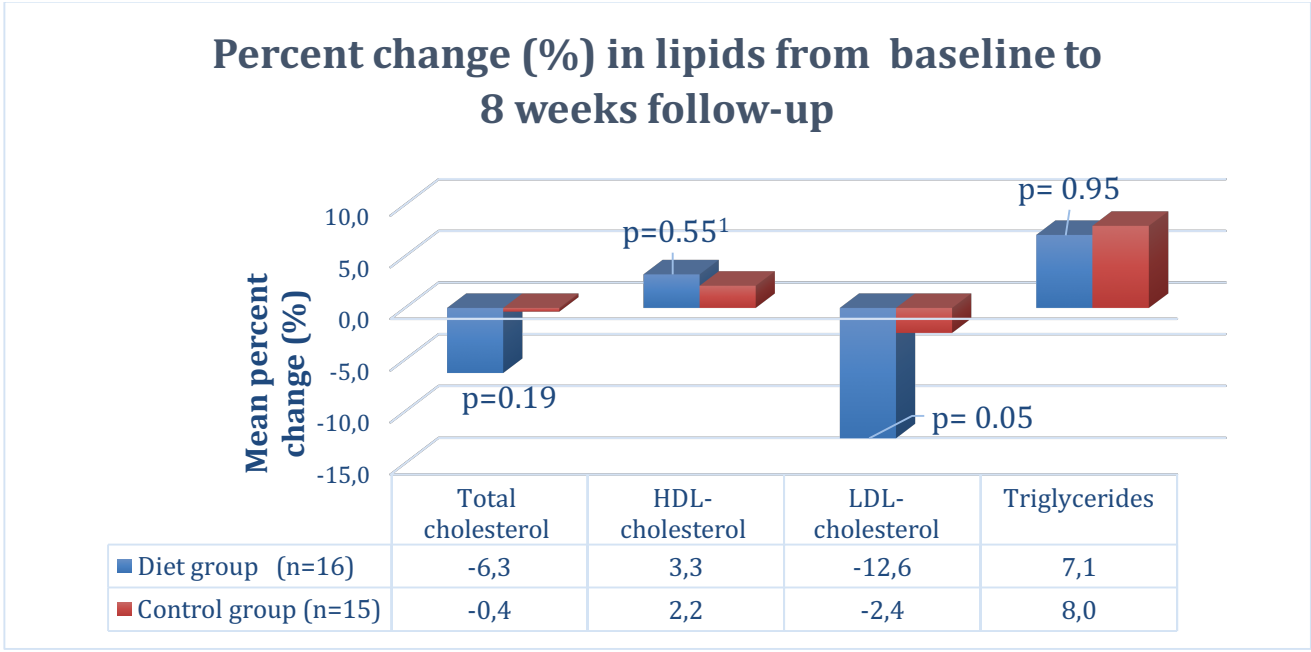
HDL-c were on average increased by ~0.05 mmol/L in the DG (p=0.48) and decreased by ~0.02 mmol/L in the CG (p=0.80) from first to last consultation. There were a mean percent change of 3.3 % and 2.2 % in the DG and the CG, respectively (p=0.55).

**Triglycerides**

A median increase in TG was observe in both the DG and the CG. There was a similar mean percent change in TG in both groups [7.1 % and 8.0 % in the DG and the CG (p=0.95), respectively]. In spite of the increase in TG, the median TG was still < 1.7 mmol/L in both groups at the end of the study.

The proportion of patients with hyperlipidaemia was reduced by 56.3 % to 33.3 % in the DG from first to final consultation. In comparison, there were no decline in number of cases with hyperlipidaemia in the CG (data not shown). A total of 6.3 % and 14.3 % of the patients in the DG and the CG, respectively, were classified with combined dyslipidaemia at baseline. At the final consultation, the proportion of patients with combined dyslipidaemia was increased to 12.6 % in the DG, while no cases of combined dyslipidaemia were found among the patients in the CG (data not shown).

**Figure 17**. Percentage change in lipids from baseline to 8 weeks follow-up in the diet- and control group.




| | Total cholesterol | HDL-cholesterol | LDL-cholesterol | Triglycerides |
|---|---|---|---|---|
| Diet group (n=16) | -6,3 | 3,3 | -12,6 | 7,1 |
| Control group (n=15) | -0,4 | 2,2 | -2,4 | 8,0 |

Differences between the diet group and the control group, analyzed with independent samples t test
[1]Man-whitney U test

### 5.2.3 Blood pressure

BP was measured at first and final consultation. There were no significant mean differences in change in systolic BP or diastolic BP between the DG and the CG after eight weeks follow-up (p=0.28, p=0.46) (table 9). Adjusting for baseline values, BMI and BP did not change the outcome (table 9). Both groups showed a decline in systolic BP from baseline to the final consultation, though a modest reduction was observed in in the DG (1.15 mmHg) In comparison, the patients in the CG showed a reduction in systolic BP of 5.53 mmHg. Diastolic BP was in

average increased by 0.44 mmHg and decreased by 1.73 mmHg in the DG and the CG, respectively.

The BP in the CG patients was consistently higher compared to BP in the DG patients. Six out of 15 patients in the CG were classified as hypertensive (systolic BP > 140 mmHg) at baseline, compared to 2 out of 16 patients in the DG (p=0.09). After eight weeks follow-up, four of the patients in the CG were still classified as hypertensive, while none of the patients in the DG were hypertensive at the final consultation (p=0.43).

### 5.2.4 Inflammatory markers

Change in inflammation was analysed by use of CRP levels from blood samples at baseline and after eight weeks follow-up. No differences were observed in change in CRP from first to final consultation, between the DG and the CG (p=0.25) (table 9). Adjusting for baseline values, BMI and BP did not change the outcome (table 9). Median CRP was unaltered (2.0 mg/L) from first to last consultation in the DG, while a modest increase from median 3.5 mg/L to 4.0 mg/L were found in the CG patients after eight weeks.

### 5.2.5 Body composition

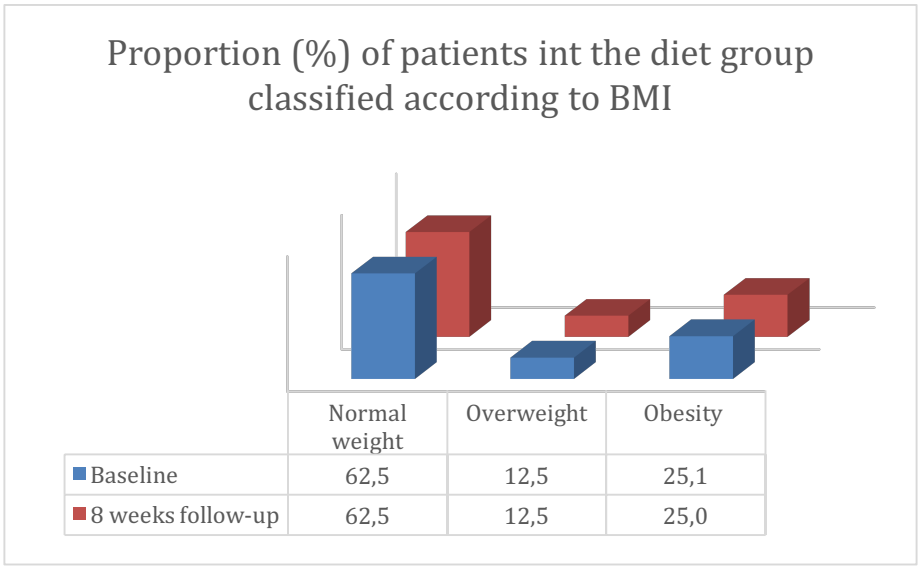
Information about body composition (FM, fat percent, FFM/LM) was obtained by two different methods, BIA and DXA at baseline and at follow up. No significant differences in change from baseline to follow up in FM (p=0.07 vs p=0.94)), fat percent (p=0.43 vs p=0.46) or FFM/LM (p=0.67 vs p=0.29) were detected between the DG and the CG. Neither was any differences in change in body weight (p=0.81) nor BMI (p=0.83) observed between the two groups. Adjusting for baseline values, BMI and BP did not change these results. Mean decrease in body weight at follow-up was 1.12 kg in the DG, compared to 1.36 kg in the CG.

**Fat mass**

According to BMI classification, 37.5 % of the patients in the DG and 86.7 % of the patients in the CG, were overweight or obese at baseline (figure 18a and 18b). The BMI algorithm do not include sex, age or the distribution of body mass, therefore, the patients were also assessed on the basis of their proportion of body fat mass (figure 19a and 19b). Estimated fat percent obtained at baseline by use of BIA, classified 37.5 % and 86.7 % of the patients in the DG and the CG with overweight or obesity, respectively. In comparison, when fat percentage was

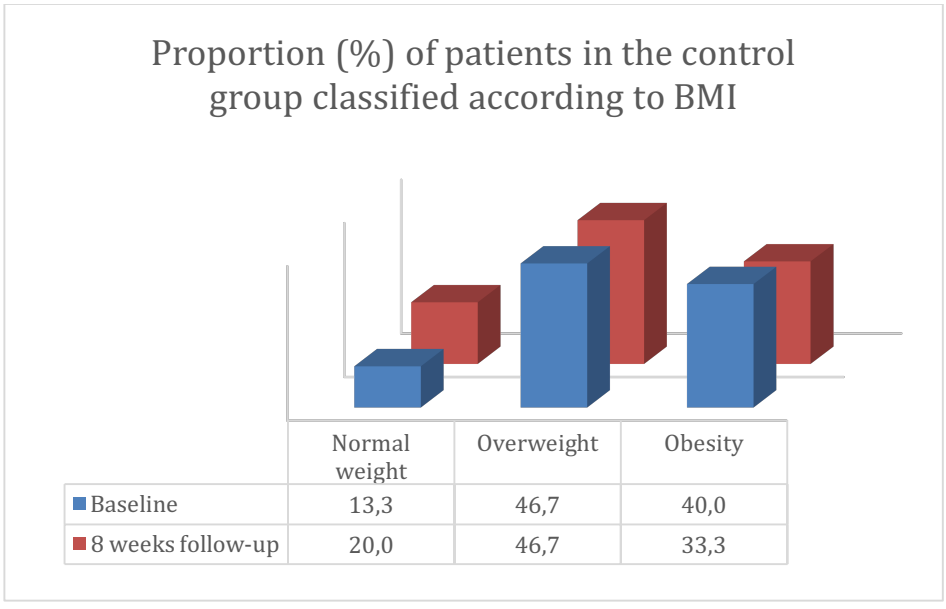
estimated by DXA, 43.8 % and 85.7 % of the patients in the DG and CG were overweight or obesity at baseline. Using the WHO´s cut off values for waist circumference, 62.5 % and 86.7 % of patients in the DG and CG were defined as overweight or obese at baseline, respectively (data not shown).

**Figure 18 a**. Classification of normal weight, overweight and obese patient in the diet group, according to BMI




BMI, Body Mass Index

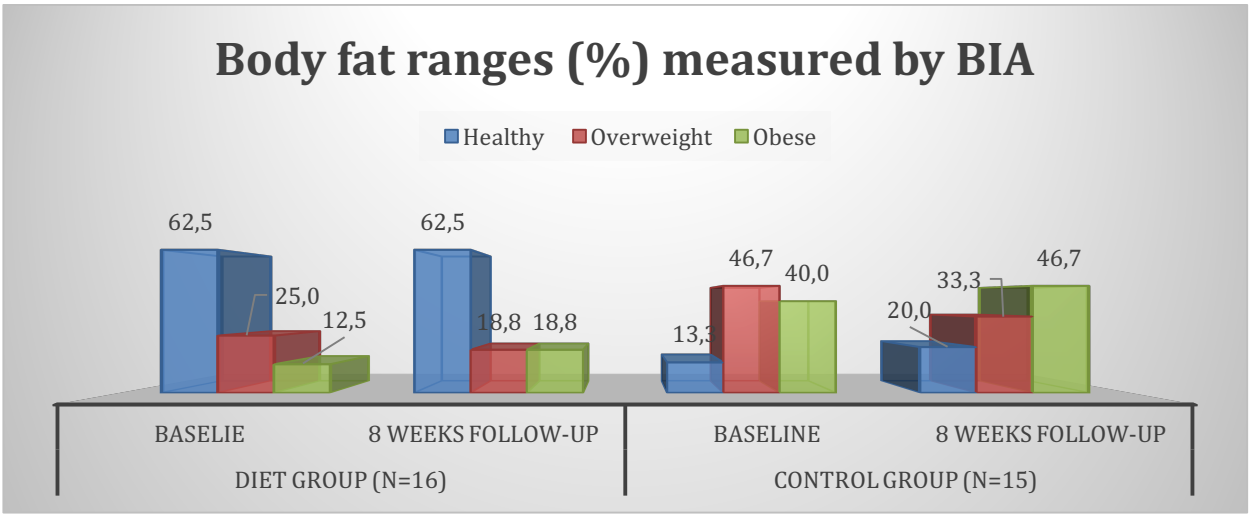
**Figure 18 b**. Classification of normal weight, overweight and obese patients in the control group, according to BMI




BMI, Body Mass Index

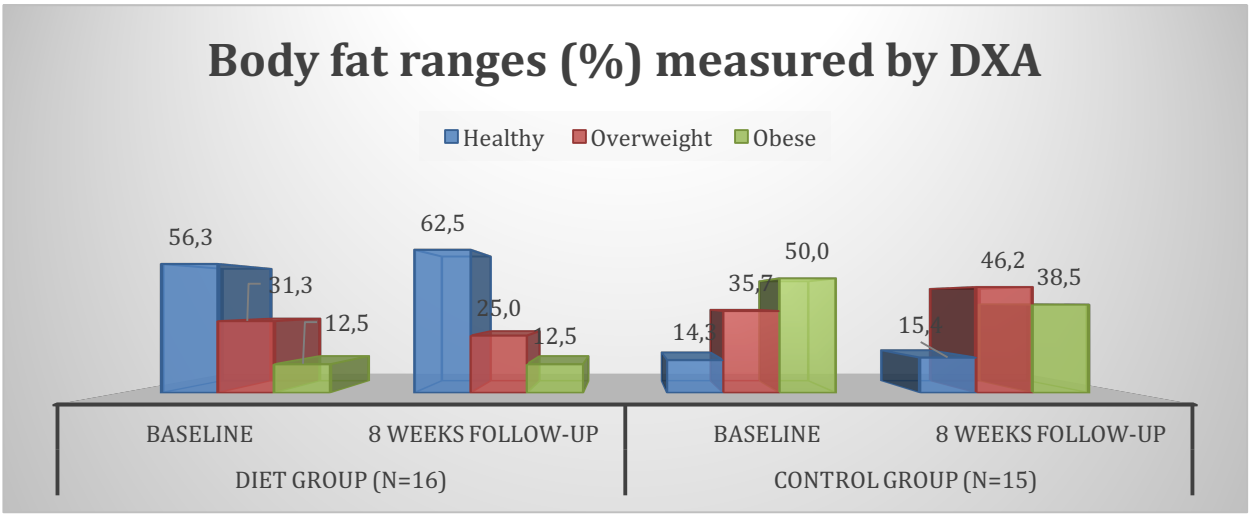
At baseline 56.3 % and 62.5 % of the patients in the DG were defined healthy based on their FM, measured by DXA and BIA, respectively. In comparison, 13.3 % to 14.3 % of the patients in the CG had a FM corresponding to a healthy body composition when they were included. Depending on whether BIA or DXA were used, an average reduction from baseline to eight weeks follow-up in FM of 0.30 kg and 1.13 kg (DG), and of 0.97 kg and 1.85 kg (CG), respectively, were observed-(table 9). The proportion of patients in the DG classified as overweight was decreased by approximately 6 % (independent of measuring by BIA or DXA). The patients classified as obese (DG) was unchanged (measured by DXA) and increased by approximately 6 % when measuring FM by BIA. Among the patients in the CG, measurements obtained by BIA showed a reduction in patients with overweight of 13.4 % from baseline to eight weeks follow-up. Patients with obesity was increased by 6.7 % in the CG. An opposite outcome was observed for measurements obtained by DXA, where patients with-overweight was increased by 10.5 % during the study. The proportion of patients in the CG classified with obesity was reduced by 11.5 % during the same period.

**Figure 19 a**. Classification of healthy, overweight and obese patients, by body fat ranges, measured by BIA.




BIA, Bioelectrical Impedance Analyses

**Figure 19 b.** Classification of healthy, overweight and obese patients, by body fat ranges, measured by DXA.




DXA, Dual-Energy X-ray absorptiometry

**Fat free mass/Lean mass**

Mean reduction in FFM/LM, from intervention start, measured by DXA and BIA were estimated to be 0.01 kg and 0.8 kg in patients in the DG, and 0.4 kg and 0.7 kg in patients in the CG. The proportion of patients classified with low muscle mass, according to FFMI values below the 10$^{th}$ percentile (FFMI < 14.1-17.6 kg/m$^2$, depending on age and sex), were 12.5 % (BIA) and 31.3 % (DXA) in the DG at baseline (data not shown). In comparison, low muscle mass was present at baseline in the CG in 0.0 % (BIA) and 14.3 % (DXA) (data not shown). At eight weeks follow-up, the corresponding estimates of patients with low muscle mass were 18.8 % (BIA) and 31.3 % (DXA) in the DG and 0.0 (BIA) and 15.4 % (DXA) in the CG (data not shown).

**Correlation between BIA/DXA**

FM was consistently estimated to be somewhat higher when using the DXA method, compared to BIA, while FFM/LM were consistently estimated to be lower using DXA compared to BIA. The relationship between FM, fat percent and LM measured by DXA compared to BIA, was evaluated by using Pearson product-moment correlation coefficient. There was a strong positive correlation between the variables, $0.90 > r < 0.98$ (data not shown).

**Sarcopenia**

Figure 20 shows the proportion of patients classified with sarcopenia (women with SMI < 5.75 kg/m$^2$ and in men < 8.50 kg/m$^2$) in each group. The classification of sarcopenia was based on measurements obtained by BIA and DXA. There were no differences in change in estimated SMM (obtained by BIA, p=0.60, obtained by DXA, p=0.52) or SMI (obtained by BIA, p=0.61, obtained by DXA, p=0.49) between the groups after eight weeks (table 11).

At baseline**,** 43.8 % (DXA) and 68.8 % (BIA) of the patients in the DG and 28.6 % (DXA) and 53.3 % (BIA) of the patients in the CG, were classified with sarcopenia There were no significant differences between the two groups in the proportion of patients classified with sarcopenia, neither at baseline (DXA, p=0.40, BIA, p=0.40) nor after eight weeks follow-up (DXA, p=0.69, BIA, p=0.90) (data not shown). The proportion classified with sarcopenia, was consistently higher based on measurements obtained by BIA, compared to measurements obtained by DXA. This can be due to the estimates of TSMI, which are based on different equations depending on whether DXA or BIA has been used as measuring method.

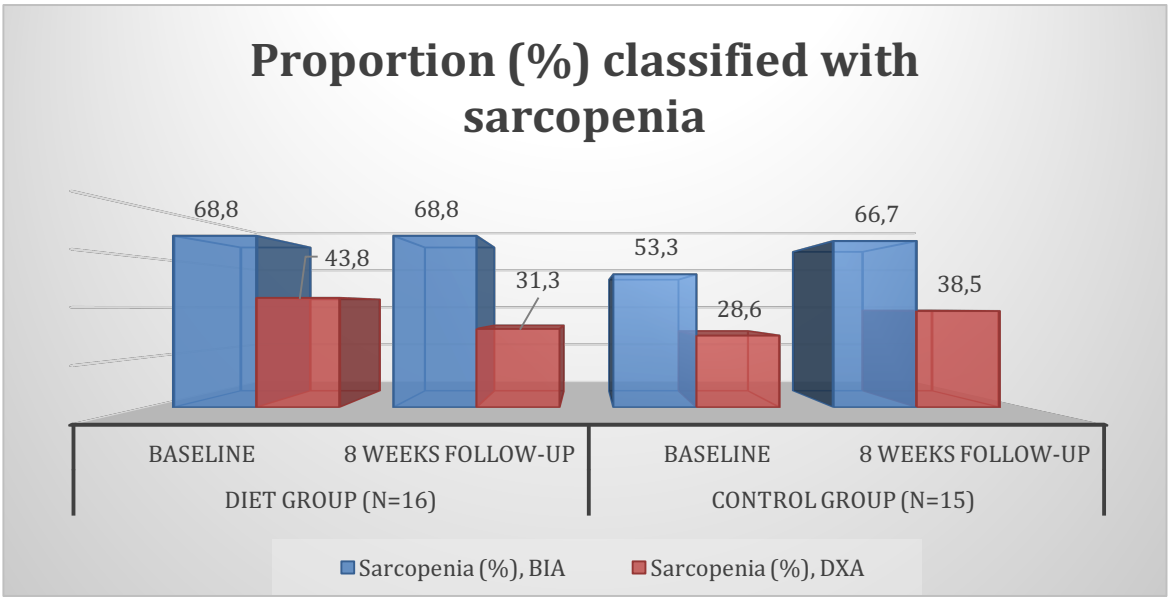
**Table 11.** Estimated total skeletal muscle mass and skeletal muscle index (based on measurements obtained by BIA and DXA) in the patients at baseline and after eight wees follow-up

| | Diet group, n = 16 | | Control group, n = 15 | | Unadjusted mean group difference (95 % CI) | p value[a] | Estimated mean group difference (95 % CI)[b] | p value[c] |
|---|---|---|---|---|---|---|---|---|
| | Baseline | 8 weeks | Baseline | 8 weeks | | | | |
| **BIA** | | | | | | | | |
| Estimated SMM (kg) mean ± SD | 23.26 ± 6.16 | 22.87 ± 5.39 | 22.73 ± 5.93 | 22.61 ± 5.93 | -0.31 (-1.49, 0.88) | 0.60 | -0.80 (-2.18, 0.58) | 0.25 |
| Skeletal muscle index mean ± SD | 6.70 ± 1.47 | 6.59 ± 1.21 | 6.61 ± 1.52 | 6.57 ± 1.53 | -0.09 (-0.43, 0.26) | 0.61 | -0.23 (-0.63, 0.17) | 0.26 |
| **DXA** | | | | | | | | |
| Estimated SMM (kg) mean ± SD | 25.67 ± 6.45 | 25.21 ± 6.10 | 25.29 ± 6.03 | 23.77 ± 5.87 | 0.33 (-0.71, 1.38) | 0.52 | 0.07 (-1.12, 1.25) | 0.91 |
| Skeletal muscle index mean ± SD | 7.39 ± 1.52 | 7.27 ± 1.43 | 7.35 ± 1.49 | 6.91 ± 1.43 | 0.10 (-.020, 0.41) | 0.49 | 0.03 (-0.32, 0.34) | 0.86 |

[a]Differences from pre- to post intervention (8 weeks) values, between the groups, analyzed with independent samples t test
[b]Estimated regressions coefficients
[c]Estimated mean group difference values, analyzed with ANCOVA, with BMI, DBP, SPB as covariates

BIA, Bioelectrical Impedance Analyses; DXA, Dual-Energy X-ray absorptiometry; SMM, Skeletal Muscle Mass; BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure

**Figure 20**: Percentage of the study population classified with sarcopenia (women with SMI < 5.75 kg/m$^2$ and in men < 8.50 kg/m$^2$) at baseline and after 8 weeks follow-up.




SMI, Skeletal Muscle Index; BIA, Bioelectrical Impedance Analyses; DXA, Dual-Energy X-ray absorptiometry

**Rheumatoid cachexia**

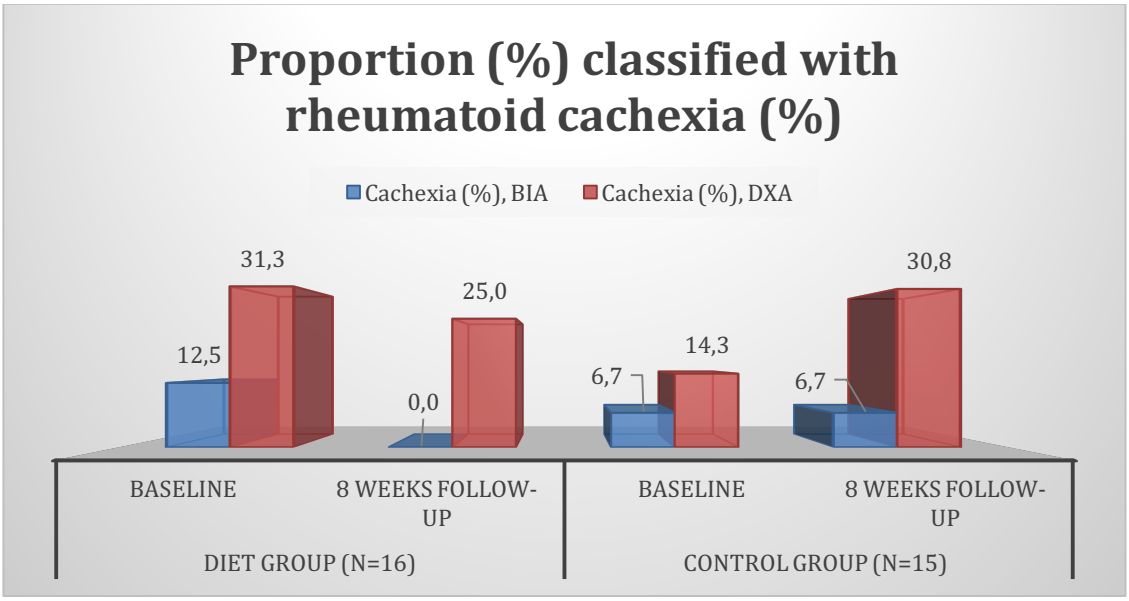
Figure 21 shows the proportion of patients classified with rheumatoid cachexia in each group at baseline and after eight weeks follow-up. The patients were classified according to FFMI and FMI (data not shown). There was a great disparity in the proportion of patients classified with rheumatoid cachexia, depending on whether BIA or DXA were used as measuring method for obtaining information about FM, FFM and LM.

In the DG, 12.5 % (BIA) and 31.3 % (DXA) of the patients were classified with rheumatoid cachexia at baseline. In comparison, 6.7 % (BIA) and 14.3 % (DXA) of the patients in the CG were classified with rheumatoid cachexia. There were no significant differences between the groups at baseline (DXA, p=0.40, BIA, p=1.00) or after eight weeks follow-up (DXA, p=1.00, BIA, p=0.48) (data not shown).

In total, 22.6 % (DXA) and 9.7 % (BIA) of the included patients were classified with rheumatoid cachexia. Of those who were classified with cachexia by BIA, all had a BMI within the normal range (18.5-24.9 kg/m$^2$). Of those who were classified with cachexia by DXA, approximately 70

% of the patients had BMI within the normal range, while the remaining proportion of the patients had BMI as overweight (25.0-29.9 kg/m$^2$) (data not shown).

**Figure 21.** Percentage of patients in the intervention group and in the control group, classified with rheumatoid cachexia (FFMI 14.7-15.4 < kg/m$^2$ for women and < 17.6-18.4 kg/m$^2$ for men and FMI > 5.5-9.3 kg/m$^2$ for women and > 4.0-5.7 kg/m$^2$ for men) at baseline and after eight weeks follow-up.




FFMI, Fat Free Mass Index; FMI, Fat Mass Index; BIA, Bioelectrical Impedance Analyses; DXA, Dual-Energy X-ray absorptiometry

## 5.2.6 Outliers

One patients in the DG, showed a weight loss of >11 kg during the follow-up period of eight weeks. Excluding this person from the analysis did not change any of the outcomes, except a significant difference in weight between the two groups at baseline (p=0.03).

# 6 Discussion

## 6.1 Discussion of main findings

Our findings point to that the clinical effects of brief advice are comparable to an extended nutritional advice on cholesterol friendly food/diets in patients with IJD. This may be important in a clinical setting, with limited resources**.**

### 6.1.1 Diet

No differences were revealed between the DG and the CG regarding change in SmartDiet score (5.1 vs 5.7) after eight weeks follow-up. In addition, the study was successful in improving dietary habits (> 3 points increase in SmartDiet score) were obtained by both intervention groups (87.5 % and 80 % in the DG and CG, respectively). These findings indicated that even brief, standardised advice combined with a written nutritional purchase guide, may be sufficient to improve dietary habits in a heart-friendly direction and support the current procedure at the Preventive Cardio-Rheuma Clinic, Department of Rheumatology at Diakonhjemmet Hospital, where brief advice on heart-friendly diet with a brochure is a part of the standardized routine during CVD risk evaluation in IJD patients. After eight weeks, significant differences between the groups in choice of heart-friendly food items was revealed, as well as a significantly greater change in LDL-C.

There were no significant differences in the mean SmartDiet score between the groups at baseline. However, significant more of the DG patients, compared to the CG patients, obtained a SmartDiet score between 28 and 35 points at baseline, while more of the CG patients obtained a SmartDiet score ≤ 27 points, compared to DG patients at baseline. Thus, the patients in the CG might have had a greater potential to make dietary changes compared to DG patients. The effect of the dietary interventions may depend on the pre-intervention dietary status. However, supplemental analyses, adjusting for baseline SmartDiet score and BMI, did not influence the results. The patients in the CG compared to the DG had higher BMI and waist circumference, which may be related to a less healthy diet among CG patients. This assumption was further supported by a difference in consumption of meat products, where patients in the CG had a higher consumption of processed high fat meat (farce/sausage) (33.3 vs 0.0 %) compared to the DG. This implies a higher consumption of fat, including SFA by patients in the CG.

At the end of the study, further differences in dietary habits were demonstrated between the two groups. A higher proportion of CG patients used butter/hard margarine compared to the DG patients, while significantly more DG patients used olive oil/liquid margarine/vita. Additionally, the use of high fibre content bread was higher in DG compared to CG. On this basis, is it likely to assume that patients in the DG consume less SFA and more PUFA and dietary fibre, compared to patients in the CG. These observations may indicate a better compliance to the dietary advice given by the nutritionist, compared to advice given by the physician. Further suggesting a superior effect in dietary changes obtained by a tailored, extended dietary counselling compared to a brief advice.

Few studies compare the effectiveness of tailored dietary counselling given by nutritionists and brief advice given by physicians. Although, one study compared the effectiveness of receiving a general dietary counselling by a physician and an additional detailed counselling by a dietitian (6). A total of 136 hypercholesterolemic patients went through a consultation (30 minutes), including physical examination and brief dietary advice given by a physician together with a written nutritional information. The patients were advised to select lean meat/poultry/fish and low-fat dairy products, limit sugar, margarine and egg, and they were encouraged to increase consumption of fruits and vegetables. After 3 weeks, 70 of the participants were randomized to further two to four additionally dietary sessions (over three months) by a registered dietitian. These counsellings included more thorough and precise dietary recommendations. After three months, a significantly greater mean reduction in LDL-c was observed in the dietitian group compared to the physician group (12 % vs 7 %, respectively). However, the observed effect did not sustain after one year (6). The main conclusion from this study may be that the effect on diet change and on LDL reduction after advice by dietitian or brief advice from a physician are comparable after 1 year, which further supports our results.

Another recently published study investigated the effectiveness of a brief dietary intervention on CVD risk factors in 39 patients with hyperlipidaemia (211). The patients received a tailored dietary counselling (single session of 45 minutes), mainly based on the MD diet and the Portfolio diet (212), combined with a nutritional educational manual (e.g. food guides and recipes). Pre to post intervention changes in diet and lipid profile were analysed after six weeks. A significant reduction in energy-dense/nutrient poor foods were demonstrated. These results further support the suitability of a brief and single dietary counselling.

A common feature in these studies, including our own, were that all the patients received some kind of written information, in addition to the oral advises and counselling. Of medical information communicated by a health professional, 40-80 % is forgotten immediately. In addition, about half of what is actually remembered, is misunderstood (213). It is likely that patients in our study may have become anxious after the information about their increased CVD risk and indication for cholesterol-lowering treatment. Stressed patients have been reported to remember less information given by health personnel (213), supporting the importance of written material. However, we were not able to assess how much of the observed effect in our study that could be attributed to the written information, compared to what was orally communicated. It is likely to assume that "Innkjøpsgudien" have been of importance for the improvement observed in dietary habits and SmartDiet score.

Professor Ingar Hjermann has been a pioneer within dietary research and prevention of CVD. He and his co-workers initiated in the 70s a 5-year intervention trial (The Oslo Diet and Antismoking study) where healthy, normotensive 40-49 years old men at high risk of CVD, were advised to change diet habits (30 minutes). Primarily through lowering their consumption of SFA and increase their intake of PUFA, increase consumption of fish, vegetable products and fibre rich bread, while over-weight participants and participants with hypertriglyceridemia were advised to reduce total energy-intake, sugar and alcohol consumption as well (153). Additionally, the intervention consisted of advice in smoking cessation. There were follow-up examinations every 6 months (intervention group) and every 12 months (control group, not receiving any dietary counselling), which included a short examination and a registration of diet- and smoking habits. During five years TC was on average decreased by 13 % more in men which had received dietary advice, compared to the controls. Furthermore, the incidence of fatal- and non-fatal MI was reduced by 47 % in the intervention group, compared to the control group (153). A 20-year follow-up showed that men in the intervention group still had a more conscious approach to diet and lifestyle, and ate less SFA and cholesterol and more PUFA, compared to men in the control group (214). This suggests that diet counselling may result in permanent change in dietary habits. A recently 40-year follow-up of this study, showed a sustained significantly decrease in risk of MI in the intervention group, compared to the control group (215). Consequently, the Oslo study demonstrated that making lifestyle interventions, as diet counselling, provides evident and lifelong effects.

An important component in this study, which may explain some of the successful improvement in diet, may have been the involvement of the participants' spouses, because they received group based dietary information. Both men and women increasingly share responsibility for the household, including cooking, and thus the involvement of spouses may have influenced the result. In addition, to obtain a lasting change in dietary habits, involvement of the whole family and/or life partner is may be of great importance. Thus, we emphasized in our study that generally recommendations in heart-friendly food choices which were given during the extended counselling, advantageously also could be followed by the rest of the family. We also emphasized that the advices which were given, was meant to be lasting habitual dietary changes and not a short-timed diet.

The Oslo Study included a smoking cessation program in addition to dietary intervention. Therefore, it was not possible to distinguish between the effect of smoking cessation and change in dietary habits on CVD mortality (215). Patients in our study who smoked, were also encouraged to quit smoking. However, there was no change in smoking habits in either groups after 8 weeks. Therefore, smoking cessation did not influence our results.

For some patients, a brief advice can be sufficient to achieve change in dietary habits and lifestyle, as demonstrated in the Oslo study, but obtaining lasting lifestyle changes have often shown to be difficult and time consuming (216). To achieve long-lasting dietary alterations, a requirement of counselling on several occasions with intensified dietary-and lifestyle guidance have shown to be necessary (217) and most studies which have investigated the effect of behavioural counselling in improvement of dietary habits and other CVD risk factors, have been intensive interventions, often by multiple contacts and sessions (on average 5 to 16) over an extended period (on average 9 to 12 months), frequently combined with physical activity and/or weight reduction (217).

A previous review showed that medium (31-360 minutes) to high intensity (> 360 minutes) diet counselling resulted in improvements of several important CVD risk factors, as reduction in levels of TC and LDL-c and decrease in BP after 12-24 months (218). Corresponding findings was reported for improvement in diet intake (objectively measures and self-reported dietary consumption). Overall, Lin and co-workers concluded that intensive, combined lifestyle interventions did not decrease CVD events or mortality at up to 10 years, which is in contrast to what was observed in the Oslo study (215). However, results from The Oslo study (219) were

not included in this review by Lin and co-workers, because the main outcomes were published before 1990 (218).

Despite several of these intensive lifestyle interventions have shown to be effective, many would require great resources, which may not be available in current health systems. There is a knowledge gap regarding the effectiveness of less intensive counselling in relation to the minimum of and/or the duration of sessions needed to obtain alteration in dietary habits which have clinically important effects CVD-risk factors (217). However, we have during our study, compared the effects obtained by a tailored, extended dietary counselling and a standardized brief advice, which has contributed in enlightening these gab. Although, further studies are needed.

### 6.1.2 Lipids

**Cholesterol**

There were no differences in mean change over 8 weeks in either TC, LDL-c or HDL-c between the two groups. However, the reduction of both TC and LDL-c were greater in the DG compared to the CG and barely significant for LDL-c. These findings insinuate a superior cholesterol-lowering effect obtained by tailored counselling compared to the effects obtained by standardised brief advice, but due to the small sample size, caution in interpretation of the findings are needed and further studies are warranted. However, our findings are in accordance with previous studies (6, 101, 212). A decrease in TC and LDL-c levels has been associated with reduced CVD risk. LDL-c has been considered the major target regarding lipid-lowering therapy and has been used as a response marker in most trials with lipid-lowering therapy (220). A reduction in LDL-c, corresponding to 1.0 mmol/L, has been associated with a reduction in CVD morbidity and mortality by 22 %, even in persons at less than 10 % predicted 5-year absolute CVD risk (220). Data from 10 prospective cohorts showed that 10 % reduction in TC, corresponded to an average reduction of 0.6 mmol/L, and was associated with 19 % to 54 % decreased incidence of ischaemic heart disease, depending on age (221). Heart-friendly dietary habits have demonstrated a reduction in LDL-c from 5 % to 30 % (10 % on average) (101, 212).

Although, the response of lipid levels following alterations in dietary habits, also depends on the influence of other factors as cholesterol levels before the dietary changes, the cause of increased levels of cholesterol, adherence to the dietary modification (222), as well as dietary habits prior

to the cholesterol-lowering diet (6). A significant greater proportion of the patients in the DG showed a SmartDiet score between 27 and 35 points at baseline, which indicate that more of the patients in the DG had a more healthy diet before the study, compared to the patients in the CG. Thus, patients in the CG may have had a greater potential for change in diet and thus possibly alteration in cholesterol. Despite this, a small reduction in TC and LDL-c was observed in the CG. This support a superior cholesterol-lowering effect by an extended counselling with a nutritionist compared to standardized brief advice by a physician, which is in accordance with what has been reported previously (6).

Nevertheless, the differences observed in mean percentage change in LDL-c levels between the two groups may be attributed to a more unfavourable choice of fat sources in the CG. More of the patients in this group reported a frequent consumption of butter/hard margarine and lower consumption of vegetable oil/liquid margarine, indicating a more unfavourable SFA:PUFA ratio, which has been associated with a more adverse lipid profile (223). It is likely to assume that patients in the CG consumed less fibre, compared to the patients in the DG, due to the lower consumption of wholemeal bread. Fibre has cholesterol –lowering properties (224) and thus high dietary fibre consumption has been suggested to be an important dietary constituent in prevention of CVD, independent of fat intake (165, 168). Results from a prospective cohort study found that replacing 5 % of energy intake from SFA with an equivalent energy intake from PUFAs or whole grain was associated with a 25 % and 9 % decrease in CVD risk, respectively (170). Overall, epidemiologic observations imply that even small improvements in CVD risk factors (e.g. lipid levels) reduce the risk for heart disease and stroke in persons at increased CVD risk (225).

Only minor and non-significant alterations were observed in HDL-c in both groups. Although, mean percent change revealed that patients in the DG and CG had an increase in HDL-c of 3.3 % and 2.2 %, respectively. Low plasma levels of HDL-c have been associated with increased CVD risk and has been associated with anti-atherogenic properties, mainly through reduced reverse cholesterol transport (226). Nevertheless, recent studies have reported that these anti-atherogenic properties may be independent of the plasma levels of HDL (226) and there is currently no distinct evidence that an increase in HDL-C have a protective effect against CVD risk (90).

**Triglycerides**

Despite that no significant differences were observed between the groups in change in TG, both the CG and the DG increased their TG levels by 8.0 % and 7.1 %, respectively. This was a surprising observation because dietary interventions with replacement of SFA with PUFA have been associated with hypotriglyceridemic effects (90). Therefore, our results were in contrast to what has been shown in prior dietary interventions (153, 217). Hjermann and co-workers demonstrated a 20 % lower fasting TG levels and a 25 % non-fasting TG levels in the dietary intervention group, compared to the control group(153). Although, other diet interventions have resulted in minor and non-significant changes in TG levels (6).

Several lifestyle factors may influence TG levels. Weight reduction may induce-20 % to 30 % of the observed reduction in TG (90). We did not observed any significant weight reduction in our study. A high consumption of carbohydrates, notably refined carbohydrates (90) and regular consumption of substantial amounts of fructose (> 10 % energy) may increase TG (164). Although, only minor changes were demonstrated in consumption of refined foods and beverages (sweets, and sweet beverages, including fruit juice and white bread) and can probably not explain the observed increase in TG in either groups in our study.

Alcohol consumption is another important component influencing the TG level (227). The proportion in the DG which reported alcohol consumption between 8 to 14 units per week, was increased at follow-up, compared to baseline (7.1 % vs 21.4 %), while no corresponding changes were observed in the CG. On the other hand, there was an increase in the proportion of patients in the CG who reported consumption of less than one unit per week. In general, one has to drink excessive amounts of alcohol before harmful effects on TG levels would appear. Although, in patients with already established hypertriglyceridemia, only small amounts of alcohol could cause additional increase of TG level and potentially unfavourable effects (90). Despite the increase in TG levels in our study, the levels were still < 1.7 mmol/L in both the DG and the CG, which is not associated with any increased CVD risk (90).

### 6.1.3 Blood pressure

Hypertension is reported to be prevalent in IJD patients (37 % -73 %) (228, 229). Despite that patients with BP >160/100 mmHg were excluded from participating in this study, 25.8 % of the recruited patients were still classified as hypertensive (SBP >140), with a greater proportion in

the CG than in the DG (40.0 % vs 12.6 %, respectively). This may be seen in context of more unfavourable anthropometric measurements and possible a more overall unhealthy lifestyle in the CG, compared to the DG. Especially overweight and elevated BMI are correlated with BP (230). Nevertheless, after the follow-up, significant less patients were hypertensive in the DG compared to the CG.

We observe no significant differences between the DG and the CG in change in SBP or DBP after 8 weeks of follow-up. A clinical important reduction in SBP was observed in the CG (5.53 mmHG), but not in the DG. However, even a small reduction in SBP/DBP (approximately 2 mmHg/ 1 mmHg) may cause reduction in CVD morbidity and mortality (231). Corresponding assumptions has been proposed from epidemiologic data, were a reduction in SBP (2 mmHg) has been associated with a decline in risk of CVD by 6 % or a cerebrovascular accident by 16 % (225).

A high consumption of sodium is a well-known risk factor for hypertension (232), and sodium restriction is therefore frequently included in diet interventions. Reduction in salt consumption was discussed with the patients in the DG during their dietary counselling and the patients were encouraged to limit use of processed meat and snacks, to choose unsalted nuts and use "Nøkkelhullet" as a guide during purchase. However, SmartDiet does not give the opportunity to evaluate salt intake, although questions in SmartDiet related to processed meat and snacks (often with a high content of salt), may be an indicator of salt consumption.

The proportion of patients, who reported frequent use of processed meat with high fat content, was reduced from 33.3 % to 0.0 % in the CG after eight weeks. Concurrently, CG patients more often (20.0 %) chose lean cuts for dinner, which indicating a major dietary change. Additionally, the proportion who said they ate chocolate/snack/cakes over 3 times per week, was halved in the CG, while there was a considerably increase (26.6 %) in the percentage who reported a consumption between 0 to 1 times per week. Altogether, these changes in diet may contributed to a reduction in salt intake. Equivalent dietary findings were observed in the DG, although, corresponding differences in BP were not observed. This may be explained by a significantly lower BP at baseline in the patients in the DG, compared to the patients in the CG Adjusting for BP, did not influence the results. Forty % of the patients in the CG were hypertensive, compared to only 12.6 % of the patients in the DG. In addition, almost 90 % of the patients in the DG were

normotensive (SBP ≤ 140 mmHg). In a recent review Kelly and co-workers concluded that sodium modification in normotensive patients did not significantly alter BP (233).

Several lifestyle-related factors may affect BP. A review reported a mean reduction in SBP of 5.0 mmHg by an overall improvement of diet, while interventions of alcohol- and sodium restriction reduced SBP by 3.8 mmHg and 3.6 mmHg, respectively, in hypertensive patients (234). Most of the diet interventions included in this review also encouraged to weight reduction, while others gave advice on exercise as well, which made the interpretations challenging (234). The weight reduction observed in our study where not significant in either the DG (1.1 %) or the CG (1.7 %), but even weight loss between 0-2.5 % has been reported to significantly reduce both DBP and DBP (235). Thus, the possibility that even the minor weight reduction in our study may be of clinical importance, and should therefore not be omitted. Although, further studies are warranted to elucidate this.

However, Conlin and co-workers demonstrated a significant reduction in BP (SPB: 11.4 mmHg, DBP: 5.5 mmHg) in hypertensive participants, receiving a combination diet (DASH) for eight weeks, where body weight was held constant (236). The all food and meals were supplied throughout the study. Therefore, any habitual behavioural changes were not required. This is a limitation for generalising the result to the general population. A Cochrane review recently concluded that there was lacking support for individual dietary advice as a method to achieve reduction in salt consumption (237). However, it was reported that advice on salt reduction to hypertensive persons resulted in a significant mean decrease of 4.14 mmHg in SBP, while no significant differences were found in DBP. In normotensive, only a non-significant and minor mean reduction was observed in SBP (1.15 mmHg) (237). Corresponding findings are reported in a previous review (238), where the effect of giving dietary advice on reduction of salt consumption in general practice were investigated. They concluded that brief advices advice on salt-lowering diet were probably not enough to reduce salt consumption, and that more intensive intervention was needed (238). This was consistent with later findings reported by Lin and co-workers who concluded that medium (31-360 minutes) to high-intensity (> 360 minutes) combined lifestyle counselling in patients with certain CVD risk factors (including hypertension), reduced SBP and DBP by an average of 2.03 mmHg and 1.38 mmHg, respectively (218).

An increase in consumption of fruit and vegetables is another diet factor that has been associated with reduction in BP (102, 236, 239). After the follow-up in our study, there was a substantial increase of average intake of fruit and vegetables > 600 g/day by 13 % in both groups. Our findings indicate that at least 25 % (DG) and 20 % (CG) of the patients accommodate the recommendation of minimum 500 g fruit and vegetables per day. In comparison, only 12.5 % (DG) and 6.7 % (CG) did the same before the intervention.

Excessive alcohol consumption is also related to increased risk of hypertension (240) and a limited consumption is recommended. We observed an increase in alcohol consumption among the DG patients, while the CG patients demonstrated a decrease in consumption after eight weeks follow-up. Despite of this, none of the patients in the DG were hypertensive after the follow-up, while the proportion of hypertensive patients in the CG was decreased.

### 6.1.4 Inflammatory markers

The concentration of CRP in plasma has been considered important in the pathogenesis of the development of CVD (241) and has been shown to be an important predictor of CVD death in patients with IJD (242). No significant changes in CRP levels was observed between the two groups after eight weeks follow-up. Previous studies have shown that dietary intervention may affect inflammation, but weight loss seems to be of more importance (243). Findings from an RCT in 52 female patients with metabolic syndrome showed that lifestyle changes resulted in a mean reduction in CRP level of 58 % after 6 months (244). This study used an intensive lifestyle intervention with follow-up sessions several times per week, over a six months period, where exercise, nutrition and weight loss were important components. Average weight loss in the intervention group was 8.1 %. Because CRP levels has been shown to correlate with BMI and obesity (245), the decrease in CRP levels observed in these patients, may be seen in the context of their weight-loss. However, there was no significant weight loss in our study.

Several studies have demonstrated anti-inflammatory effects by intake of omega-3 long-chain PUFA (n-3 LC-PUFA) (246). RA is one of several inflammatory diseases, where a number of trials has been performed with omega-3 long-chain PUFA. Beneficial effects on duration of morning stiffness, number of tender/swollen joints, time to fatigue, joint pain or use of NSAIDs (247-250) has been reported, in addition to a reduction in production of inflammatory biomarkers as eicosanoids and cytokines (79). Such favourable effects are common findings in

studies providing high-dose supplementation (2.2 to 5.5 g / day or 30-40 mg / kg) of EPA and/or DHA (247-251). Other studies with lower doses of omega-3 fatty acids, have not found similar beneficial effects (252). We did not encourage omega-3 supplements in our study, because we aimed evaluate the effect of an overall dietary counselling on change in CRP and not investigate potential effects of supplementation of single nutrients. It is therefore less likely that the intake of omega-3 LC-PUFA have been high enough to provide a noticeable anti-inflammatory effect in our study. The supplementation of cod-liver oil or omega-3 were relatively stable in both groups, approximately 40 %, both at baseline and after the follow-up, and was therefore not likely affecting the results of this study.

Traditional assays identify elevated CRP concentration in the range 5-300 mg/L (242), while use of high-sensitivity CRP assays defines CRP levels of < 1, 1 to 3 and > 3 mg/L as low, moderate and high-risk groups for future CVD events (184). In this study the median CRP were measured to 2 mg/L, both at baseline and after eight weeks in the DG, while median CRP was increased from 3.5 to 4.0 mg/L in the CG after eight weeks. The increase was not statistically significant. These values display a relatively low disease activity and systemic load in the patients, despite the median CRP values in the DG and CG corresponds with moderate- and high risk of future CVD in the general population, respectively. In recent years, new medications have contributed to a better disease control and to lower inflammation in IJD-patients (21, 25, 36). The majority of patients in this study was treated with potent anti-inflammatory medication as well, which may explain the absence of alterations in CRP-levels.

### 6.1.5 Body composition

No significant differences were detected in change in FM, fat percent or FFM/LM between the DG and the CG, after the period of follow-up. Mean reduction in body weight were 1.12 kg and 1.36 kg in the DG and the CG, respectively. The dietary intervention was not intending to achieve weight loss. Although, it is reasonable to assume that compliance to the given dietary advice potentially could result in a weight reduction for several of the patients. Nevertheless, weight reduction became a natural part of the conversation with the patients in the DG, who were overweight or obese. Despite this, no significant differences in weight reduction was observed between the groups.

The enrolment of patients lasted from January to June 2016, with the last follow-up in the end of August. Yet, over 40 % of the patients were recruited in May and June. A number of the patients therefore had their follow-up immediately after, or during their summer vacation. Summer vacation consumption habits are commonly different compared to that of the everyday life. The level of physical activity may be different during the vacation. It is likely to assume that this may have resulted in a lower weight loss than otherwise could be expected and also led to minor changes in body composition as well.

The same person (MFG) accomplished the examinations of body composition in both groups, who also performed the tailored, extended dietary counselling in the DG at baseline. This may have result in an increased attention to diet and focus on nutrition in the patients in the CG, although additionally guidance to these patients was not given until the end of the study. The knowledge that body composition and body weight would be examined after eight weeks, may have motivated for lifestyle changes in both groups. This may account for why no differences in body composition were observed between the DG and the CG.

**Overweight and obesity**

In general, a high body mass, with a great proportion of body fat, were observed among the patients at baseline. Average BMI in both the DG and the CG corresponded to overweight (> 25 $kg/m^2$). While mean BMI in the CG was close to 30 $kg/m^2$, which corresponds to obesity (74). Regardless of whether the patients were classified according to BMI or body fat percentage, more than twice as many of the patients in the CG were overweight or obese, compared to patients in the DG. These findings may be seen in context of a potentially more unfavourable lifestyle among the patients in the CG at baseline, compared to the patients in the DG. A lower mean SmartDiet score was obtained in the CG. Additionally, a greater proportion of the patients in the CG seemed to be less physical active compared to the patients in the DG. Significantly more patients in the DG reported to be physically active more than three times per week (50.0 % vs 13.3 %), compared to patients in the CG.

Overweight and obesity is associated with unfavourable metabolic alterations as insulin resistance, diabetes and hypertension (253). In this study, mean waist circumferences were ~ 91 cm and ~ 103 cm in the DG and CG, respectively, which signalled a high degree of abdominal adiposity among the patients. The INTERHEART study has demonstrated a strong association between waist circumference and risk of MI and concluded that waist-to-hip-ratio may be a

better indicator of MI than BMI (254). This may be of especially importance in IJD-patients, because an altered and unfavourable body composition not necessarily would be detected by assessing BMI (255, 256). RA patients have been shown to have more visceral fat (adipose tissue deposited around the mesentery and omentum) compared to non-RA controls, despite comparable BMI and waist circumference (198), which is highly associated with increased CVD risk (257). Visceral fat promotes secretion of pro-inflammatory cytokines (258), which has been hypothesised to stimulate breakdown of muscle mass (203). This condition with concurrently decrease in muscle mass combined with increase in FM is in the literature named sarcopenic obesity (203).

**Muscle mass and sarcopenia**

There is still no standardized clinical definition, diagnostic criteria or treatment guidelines for sarcopenia (203). However, three consensus papers have proposed a definition, which all include either the combination of low or loss in muscle mass in combination with low muscle strength (e.g. handgrip) or muscle performance (e.g. walking speed) (259, 260). In our study, neither muscle strength nor performance was measured. Therefore, the evaluation of sarcopenia was examined according to cut-off values for SMI (SMI < 5.75 kg/$m^2$ (women) and < 8.50 kg/$m^2$(men)) (204), based on calculated estimates of total SMM, determined after examination of body composition by BIA and DXA.

Due to lack of agreement in diagnostic criteria, a variety of prevalence of sarcopenia has been reported (261). However, RA patients are more likely to be sarcopenic compared to age-matched controls (196, 197). Similar findings have been reported in patients with SpA (195). In our study there was a large discrepancy in the proportion of patients classified with sarcopenia at baseline (43.8 % to 68.8 % in the DG vs 28.6 % to 53.3 % in the CG), depending on whether DXA or BIA were used in examination of body composition. The BIA examinations consistently demonstrated a higher proportion of patients with sarcopenia. This large range in prevalence of sarcopenia may be seen in context of the calculations of SMM, which were derived from two different, but validated equations (193, 194). Age, height and sex were included in both equations, while whole body impedance and appendicular lean soft tissue (ALST) (the sum of the LM in the limbs) were included in the determination of SMM, based on BIA and DXA, respectively. The large divergence in prevalence of sarcopenia was a challenge in interpretation of the results.

Examination by BIA showed a general a higher LM compared to DXA, there was therefore unexpected greater proportion of the patients classified with sarcopenia by BIA compared to DXA. The validity of these results may therefore be uncertain. In comparison, a lower proportion of the patients in both groups were classified with low muscle mass (207). The proportion of patients defined by low muscle mass, were as expected, consistently higher by use of DXA compared to BIA. Nevertheless, the results indicate that sarcopenia is a current condition among the patients in this study, regardless method. This is an important observation which supports previous findings that sarcopenia is a prevalent problem in IJD patients (195, 197).

**Rheumatoid cachexia**

The characteristic condition with the combination of increased FM and decreased muscle mass, is in the literature referred to as rheumatoid cachexia (262), although both sarcopenia and cachexia result in loss of muscle mass. It may therefore be difficult to distinguish in clinical practice between the two - sarcopenia and rheumatoid cachexia. Sarcopenia is a multifactorial condition, which is influenced by factors such as age, sedentary lifestyle and malnutrition, but additionally also by inflammatory diseases, such as IJD (202). In comparison, cachexia is described as a complex metabolic syndrome with primary illness and inflammation as the underlying main components (202).

Nevertheless, at present there is neither a consensus in determinable methods for identifying patients with rheumatoid cachexia (256), nor specific cut-off values for diagnosis (81), but Engvall et al. (200) and Elkan et al. (207) have defined rheumatoid cachexia by different criteria. This lack of agreement results in a wide range in reported prevalence, from of 10 % (263) to 67 %. (264). Elkan and co-workers reported a prevalence of 18 % and 26 %, in women and men, respectively (207). However, it is reasonable to assume that studies conducted in recent years, have reported a lower prevalence of rheumatoid cachexia, as a consequence of better treatment options for patients with IJD.

Thus, our findings at baseline, where in accordance with previously reported prevalence of rheumatoid cachexia. However, twice as many cachectic patients were observed in the DG as in the CG, based on examinations obtained by DXA. A lower proportion was classified cachectic by BIA, although, still twice as many in the DG. This was as expected because examinations performed by DXA consistently demonstrated lower LM and higher FM compared to

measurements obtained by BIA, despite the examinations were obtained at the same time under similar conditions. The concordance between body composition evaluated by DXA and BIA has been examined by several researchers, and it seems to be an agreement that BIA in general overestimate FFM and underestimate FM (188, 265-267). Due to practical constraints, BIA is often the only available option for body composition assessment in clinical routine practice, but the described over- and underestimation should be taken in consideration during evaluations of measurements examined by BIA.

Chronic inflammation is associated with activation of the nuclear kappa beta (NF-$\kappa\beta$) pathway (268), through activation by TNF and IL-1 (269, 270). Such inflammatory biomarker may trigger metabolic changes resulting in breakdown of lean tissue and especially muscle mass (262), which is the hallmark in cachexia (270). Results obtained from a cross-sectional study showed an inverse association between acute phase response and LM in female patients with RA (271), which may lead to disability, increased weakness and metabolic abnormalities (201, 272). A low muscle mass combined with a reduction in physical activity and an increased sedentary lifestyle, will contribute to further reduction of muscle mass, often in combination with increased FM (273). Altered body composition (low LM and high FM) have been observed among RA patients in several studies (199, 200, 255, 262), and also in early RA (disease duration ≤ 12 months) (274). However, contradictionary results in early RA were changes in LM and FM over a period of 2 years were significantly less pronounced compared to changes in age- and sex-matched controls. New and enhanced forms of medical treatment, including use of sDMARDs/bDMARDs and a decline in use of steroids might contribute in maintenance of LM in RA patients (275, 276). Even low-dose glucocorticoids have been reported to correlate with FM and may contribute in gain of adiposity (277). However, a small proportion (12.9 %) of all the patients in our study was treated by prednisolone, while a greater proportion was treated by sDMARDs (51.6 %) and bDMARDs (67.7 %). Yet we observed a large proportion of patients with an unfavourable body composition, particularly in terms of high FM, either alone or in combination with low LM/FFM.

Inadequate nutrition has been shown not to be a contributing factor in the development of rheumatoid cachexia (275), although a variety of amino acids supplementation have been tested in reversing cachexia in RA patients (278). Dietary intake among RA patients seems to be adequate, considering protein- and energy intake, and is reported not to be distinct from healthy controls (262, 279). Inflammation has been associated with an increased resting metabolism in

RA patients, which may cause cachexia (280). However, due to lower physical activity and a reduction in LM, total energy expenditure seems to be lower in RA patients compared to healthy controls (281), which also suggest a reduction in total energy requirement. To our knowledge, little research have been accomplished in this field, but it is not unlikely that patients suffering from rheumatoid cachexia may have a greater protein requirement than the general population, despite of a lower overall energy requirement.

## 6.2 Methodological considerations

### 6.2.1 Study design

In this RCT we have investigated whether a tailored, extended dietary counselling on cholesterol-lowering and heart-friendly diet had comparable effect on change in diet and other CVD risk factors, as a standardized brief advice on cholesterol-lowering diet. The participants were recruited from the Preventive Cardio-Rheuma Clinic, Department of Rheumatology at Diakonhjemmet Hospital from January to June 2016.

Measuring the outcomes of nutritional intervention can be challenging, and it is important to be aware of the limitations that are present in the collection of dietary information by questionnaires. Recall bias will potentially cause in low accuracy and lead to an incomplete and mistaken description of the person's dietary habits, e.g. through incorrect estimation of frequency of food consumption by the responder (172). SmartDiet was used to evaluate changes in dietary habits in the participants. The questionnaire has been used in other studies (282, 283) and has also become a model in development of a Canadian Version questionnaire (284). How healthy and heart-friendly the diet was, were assessed by a total score ranged from 15 to 45 points, where a sum score < 27 points assumed as least healthy and > 35 points as most healthy (181). Because of this wide range, an increase of at least 3 points has been set as premise to denote an improvement in diet. These assumptions are based on an inverse correlation showed between sum SmartDiet score and intake of SFA, but the assessment of point score has never been documented (181). Nevertheless, the questionnaire has been validated against a 7-day "weighed food consumption record" (181). Yet there are some limitations. There will always be a risk that the patients answered the questionnaire according to how they wished they ate or according to what they thought was the "right" answer, instead of reporting what they actually used to eat. In this study, the patients had access to guidance by a nutritionist when answering the questionnaire, which may have increased the risk of pleasing bias (172).

Weight and body composition were measured at baseline and after eight weeks follow-up. Thus, it is likely to assume that this may have influenced the participants' motivation to make lifestyle-related changes, both in diet and physical activity. Most of the participants returned to the outpatient clinic a second time, for DXA-measurements. This may have been regarded as an additional "follow-up session" and reminded the patients about their dietary advice and increased the awareness of the study participation. This may have contributed in counterbalancing possibly differences between the two groups.

There were no standardized guidelines prior to the examination of body composition, which may have reduced the validity of the results. Both DXA and BIA have been showed to be sensitive to hydration status (285). A high/low consumption of food and/or beverages or level of physical activity prior to the examination were not standardised. These could have influenced the validity of the results. Although, these factors were considered to be randomly distributed and thus be of less importance compared to systematic errors. However, dehydration will give a false low body fat percentage and relatively higher LM, while over-hydration will give the opposite effect. Both BIA and DXA are reported to be associated with greater errors in examinations of overweight persons (285, 286) Additionally, physical limitations that make obese patients too wide to receive a whole body DXA scan has also been reported (285). These limitations may have affected our results, because a great proportion of the participants were overweight or obese.

Waist circumference was measured by different persons at first and last consultation. Baseline measurements were performed by a physician during the medical consultation, in a supine position, without specifying a more precise site of the measurement. In comparison, the measurements after eight weeks were performed in standing position, at the midpoint between the distal border of the lowest rib and the superior border of the iliac, by a nutritionist. Measurement of waist circumference at different sites have been reported to affect the detection of abdominal obesity (287). Thus, comparisons and interpretation of these results were challenging.

Blood samples were basically obtained fasting and within a week prior to consultation at the outpatient clinic. In the cases where this was not performed (n=2) and where it was not possible to obtain new samples, the last blood samples from the patient's journal were used in the analysis. These blood samples may therefore vary from the actual levels at baseline. Whether the patients met fasting for blood sampling or not, were not recorded. Patients who were lacking

blood samples when included at baseline, were asked to obtain new samples within the same day, even these became non-fasting. These samples may have affected the levels of TG (288).

There is also important to consider that the follow-up period spanned through the summer for a large proportion of the participants, which is a time of the year where it is likely to assume that several change their dietary habits. This may have contributed in reduced compliance to the dietary advice and further a minor effect in lipids, BP, CRP and body composition than probably expected. However, there is not likely that this have affected the difference between the groups.

### 6.2.2 Study population

A total of 31 participants were included in this study, which was half of what was stipulated (60 patients) in the protocol. An important reason for the difficultness in recruiting participants may be related to the exclusion criteria. A large proportion of the referred patients already used lipid-lowering (statins) and/or antihypertensive medication. This combined with a limited time (6 months) available for enrolment explain the relatively low number of patients in the study. Although, to obtain 80 % strength, a priori power calculations estimated that a minimum of 13 patients was necessary in each group. Despite randomization, the small sample size resulted in a significant difference between the groups, in BMI, FM and BP at baseline.

However, a strength in this study is the high response rate, only one patients abstained from participating in the study, which minimize the risk of extern selection bias and increase the generalisability. The high response rate may be due to recruiting patients from an outpatient clinic. The patients which were asked to participated, had just been told there was need for cholesterol-lowering medication, which for most of the patients were a tough message. Thus, there is likely to assume that the possibility to participate in a study where the purpose was to lower cholesterol levels through changes in dietary habits, seemed to be a desirable choice too many. Another strength was the low missing. No patients were lost to follow-up, although, two patients were lacking their last DXA measurement.

It was a higher proportion of patients with RA (51.6%) compared to those suffering from AS (25.8%) and PsA (22.6). Because of a female preponderance in RA, the higher proportion of women observed (58.1%) was expected. There were no patients with diabetes mellitus in the study. This may be seen in context of the exclusion criteria, many diabetic patients use

antihypertensive and/or lipid-lowering medications, which made them not suited for participating. There was not adjusted for education level or socioeconomic status in this study, which is a limitation, though, the hospital has regional responsibility, which make it reasonable to assume some heterogeneity in the study population.

# 7 Conclusion

In this following section the answers to the predefined research questions are presented.

1. **Is there a difference in change in diet, assessed by the validated questionnaire SmartDiet, between IJD patients receiving an individually tailored, extended dietary counselling compared to IJD patients receiving a standardized brief advice on cholesterol-lowering and heart-friendly diet, from baseline to eight weeks-follow up?**

   We observed no significant difference in change in diet measured by SmartDiet score between patients receiving a tailored, extended counselling versus the controls, who received standardized brief nutritional advice, from first to final consultation. However, when evaluating the different food groups, patients in the intervention group (DG) consumed more "heart-friendly" groceries than controls after 8 weeks, e.g. higher fiber consumption and less butter/hard margarine.

2. **Is there a difference in change of lipid levels, CRP or BP between IJD patients receiving an individually tailored, extended dietary counselling, compared to IJD patients receiving a standardized brief advice on cholesterol-lowering and heart-friendly diet?**

   There were no significant differences in change in mean group change in lipid levels, CRP or BP between the two groups. However, the mean percentage change in LDL-c was significantly higher in the DG compared to the CG.

3. **Does individually tailored, extended dietary information, compared to brief advice on cholesterol-lowering and heart-friendly diet, have an impact on body composition measured by bioelectrical impedance analysis (BIA) and dual energy X-ray absorptiometry (DXA), in IJD patients?**

   The change in FM, fat percent or FFM/LM measured by BIA and DXA, were not significantly different between the intervention group and controls.

4. **Are there any in-between group differences in change of diet, biomarkers (lipids, CRP), BP or body composition, in IJD patients receiving an individually tailored, extended dietary counseling, compared to IJD patients receiving a standardized brief advice on cholesterol-lowering and heart-friendly diet?**

It was observed a significant improvement in diet measured by SmartDiet score, in both the DG and the CG, after 8 weeks of follow-up. Post-intervention test of lipids, showed that LDL-c and TC were significantly reduced by in average 0.5 mmol/L and 0.4 mmol/L, respectively, compared to the pre-intervention tests in the DG. No significant reductions in lipids were found in the CG. Patients in the CG had a non-significant, but clinically important, reduction in SBP (5.5 mmHg) from first to final consultation. Concerning CRP, BP and body composition, no significant changes in-between the groups were observed.

## 7.1 Clinical implications and future perspectives

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CVD is the major cause of death in industrialised countries (48). A large proportion of CVD events have been shown to be attributable to modifiable risk factors (98). Thus, a heart-friendly diet is of importance to prevent CVD morbidity and mortality. The IJD diagnoses are associated with an increased risk of CVD (3). However, the effect of dietary advice on various outcomes has not previously been investigated in this patient population. In clinical practice it is essential to find simple, but functional methods for communicating heart-friendly and cholesterol-lowering dietary advice to patients with a high risk of CVD. Our results are the first step in the evaluation of different approaches to achieve dietary changes in patients with IJD.

At present, the current practice at the Preventive Cardio-Rheuma Clinic at Diakonhjemmet Hospital is to give brief advices on heart-friendly diet. Results from this study showed that a standardized brief advice, as well as an extended tailored dietary counselling, improved the patients' dietary habits. The tailored counselling seemed to result in dietary habits which included less SFA, more PUFA and a higher content of fibre, compared to the dietary habits after the brief advice, which all are important components in a heart-healthy and cholesterol-lowering diet. Furthermore, it appears that the tailored dietary counselling had a superior cholesterol-lowering effect, especially concerning LCL-c. The results from our study have not provided sufficient evidence to change current clinical practice, considering a small sample size and a short follow-up. Further studies are needed to elucidate whether an tailored, extended dietary counselling is needed to decrease cholesterol levels over time and have effects on CVD outcome in patients with a high risk of CVD.

In a health-economic perspective, it would be an advantage if standardized and brief cholesterol-lowering dietary advice, also provided by other health professionals than clinical dietitians, proves effect on reduction in CVD risk factors and eventually CVD outcome. On the other hand, it may be speculated that a LDL-c lowering effect of the tailored, extended dietary counselling in some patients will allow a dose reduction of statins, with following economic consequences and less dose dependent adverse events. If the difference in the effect of tailored, extended dietary counselling versus brief advice is modest, it is not likely that an extended dietary counsellingwill be offered to all patients with IJD, from a health-economical point of view. Therefore, it will be of great importance to accomplish additional research, with a larger sample size and longer follow-up, to illuminate which IJD patients that will benefit the most from a tailored, extended dietary counselling.

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# Appendix I

The SmartDiet questionnaire

# SmartDiet™

## 26 spørsmål om ditt kosthold og din livsstil



**Les spørsmålene og de angitte svarmulighetene nøye!**

**Sett kryss ved det svaret som passer best med det du *vanligvis* spiser.**

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**Kommentarer:**

Antall poeng: _____

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**Kostholdsvurdering**

| | |
|---|---|
| 27 poeng eller mindre: | Du bør forbedre kostholdet ditt på mange punkter, for å gjøre det mer helse- og hjertevennlig. |
| 28-35 poeng: | Du kan forbedre kostholdet ditt på en del punkter, slik at det blir mer helse- og hjertevennlig. |
| 36 poeng eller mer: | Du har sunne kostholdsvaner. |

Navn: .....

Fødselsdato: ..... Dato for besvarelsen: .....

Navn på fastlege: .....

Adresse til fastlege: .....

Sett ett kryss til hvert spørsmål ved å krysse av i sirkelen ved det alternativet som passer best med det du vanligvis spiser.
Vær oppmerksom på at spørsmålene veksler mellom å spørre etter daglig og ukentlig forbruk.

**1. Melk (sur/søt) og yoghurt**

**Hvor mange glass melk drikker/bruker du daglig som drikke, i matlagingen, på gryn, i grøt, i dessert, i kaffe/te o.l.?** Antall:....

**Hvor mange små beger med yoghurt (ca 1 dl) spiser du i løpet av en uke?** Antall:....

**Hvilken type melk bruker du oftest?**

Helmelk • Kulturmelk • Kefir • Kaffemelk 5 % fett .....

Lettmelk • Cultura • Biola naturell lettmelk • Ekstra Lett melk • Melk med smak .....

Skummet melk • Skummet kultur melk • Biola bærdrikk 0,1 % fett .....

Drikker/bruker mindre enn 1 liter melk i uken eller bruker aldri .....

**2. Fløte, rømme o.l.**

**Hvilken type bruker du oftest i matlagingen, i dressing, i dip, i kaker, i kaffe/te o.l.**

Kremfløte • Crème Fraiche • Seterrømme • Pisket krem .....

Matfløte • Lettrømme • Crème Fraiche lett .....

Kaffefløte • Ekstra lett rømme • Vikingmelk • Kesam • Matyoghurt • Crème Fraiche 10 % fett .....

Bruker ikke dette ukentlig eller bruker aldri .....

**3. Ost på brødmaten, i matlaging, på pizza o.l.**

**Hvor mye ost som pålegg, regnet i osteskiver eller i spiseskjeer (for smørbar ost), spiser du daglig?** Antall: ....

**Til hvor mange middager per uke bruker du ost? (eks pizza, lasagne, i saus, i salat o.l.)** Antall: ....

**Hvilken type ost bruker du oftest?**

Hvitost • Nøkkelost • Gudbrandsdalsost (G35) • Ekte geitost • Fløtemysost • Edamer • Gråddost • "Dessert oster" • Smørbare fete oster • Mozzarella • Revet pizza-/pastaost • Taffelost • Burgerost • Snøfrisk • Parmesan .....

Lettere hvitost • Lettere nøkkelost • Lettere fløtemysost • Lettere Gudbrandsdalsost • Lettere smørbare oster • Mozzarella • Fetaost • Prim med vaniljesmak .....

Ost med raps- og solsikkeolje (Vita Gul o.l.) • Cottage cheese • Gammalost • Pultost • Mager mysost • Prim • Mager prim • "Så lett" ost 10 % fett .....

Bruker ost kun en gang i uken eller bruker aldri .....

**4. Kjøttpålegg**

**Hvilken type kjøttpålegg bruker du oftest?**

Salami • Lett salami • Servelat • Fårepølse • Stabburpølse • Morrpølse • Haugpølse • Reinsdyrpølse • Falukorv • Fleskepølse • Sylte • Lammerull • Paté • Fenalår • Leverpostei (vanlig) .....

Kokt/rimet skinke • Hamburgerrygg • Krydderskinke • Pastramiskinke • Roastbiff • Bankekjøtt • Kylling- og kalkunpålegg • Lett servelat • Kalverull • Spekeskinke uten fettrand • Oljebaserte postei er (Vita, Mills, Delikat, Gilde) • Mager leverpostei .....

Bruker kjøttpålegg kun en gang i uken eller bruker aldri .....

**5. Kjøtt til middag**

**Hvilken type kjøtt bruker du oftest?**

Familiedeig • Medisterdeig • Grillpølse • Wienerpølse • Kjøttpølse • Medisterpølse • Knakkpølse • Nakkekoteletter med fettrand • Lammekoteletter • Medisterkake • Wienerschnitzel • Bacon • Flesk • Grillbøn • Fårekjøtt .....

Kjøttdeig (svine-, lam) • Kyllingpølse • Leverpølse • Kjøpte karbonader • Hamburger • Kebabkjøtt • Kjøttkaker • Kjøttpudding • Kamkoteletter med fettrand • Nakkekoteletter uten fettrand • Kylling, kalkun og høne med skinn • Bayonneskinke med fettrand • Hamburgerrygg med fettrand .....

Karbonadedeig • Kjøttdeig (svin, kylling) • Biff • Filet (kylling, svin, okse, lam) • Viltkjøtt • Stek uten fettrand • Bogskinke • Kamkoteletter uten fettrand • Kjøtt uten synlig fett • Kylling, kalkun og høne uten skinn • "Go og mager" pølser • Vita pølser .....

Spiser kjøtt kun en gang i uken eller spiser aldri .....

**6. Fiskepålegg**

**Hvor ofte har du fisk som pålegg eller i salater til lunsj?**

*Eksempel: Laks • Makrell • Sild • Sardiner • Brisling • Tunfisk • Reker • Krabbe • Crab-sticks • Fiskepudding • Fiskekaker o.l.*

**På inntil 1 brødskive i uken eller aldri** .....

På 2-4 brødskiver i uken .....

**På 5 eller flere brødskiver per uke** .....

**7. Fisk til middag**

**Hvor mange ganger i uken spiser du fisk, fiskemat og/eller fiskeretter?**

Inntil en gang i uken eller aldri .....

2 ganger i uken .....

3 eller flere ganger i uken .....

**Til hvor mange av disse middagene spiser du fet fisk ukentlig?** Antall:....

*Eksempel: Ørret • Laks • Makrell • Kveite • Sild*

**8. Majones, remulade og kaviar**

**Hvor ofte bruker du majonesprodukter, remulade og/eller kaviar på brødmaten?**

*Eksempel: Majones • Rekesalat • Italiensk salat • Crab-stick salat • Skagensalat • Frokostsalat • Remulade • Kaviar/kaviarmix o.l.*

På inntil 1 brødskive i uken eller aldri .....

På 2-7 brødskiver i uken .....

På 8 eller flere brødskiver per uke .....

**9. Smør eller margarin på brødmaten**

**Hvilken type bruker du oftest?**

Meierismør og alle andre typer smør • Smøregod • Bremyk • Brelett • Brelett Oliven • Melange margarin • Per margarin • Soft margarin uten salt og melk • Letta .....

Soft Flora (beger) • Soft Light • Soya margarin • Soya lett margarin • Oliven margarin • Olivero • Solsikke margarin • Sott Ekstra • Brelett omega-3 margarin .....

Vita • Vita lett • Vita Pro-aktiv • Becel Pro-activ • Münsterland Organic Margarin .....

Bruker vanligvis ikke smør eller margarin på brødmaten .....

**10. Plantesteroler**

**Bruker du et produkt som inneholder plantesteroler?**

*Eksempel: Vita Pro-aktiv • Becel Pro-aktiv* ◯ Ja ◯ Nei

**11. Fett i matlagingen**

**Hvilken type fett bruker du oftest til steking, baking, i saus, som dressing o.l.**

Meierismør og alle andre typer smør • Bremyk • Smøregod • Melange margarin (kube) • Per margarin • Soft Flora stekemargarin (kube) • Soya stekemargarin • Palmeolje .....

Soft Flora (beger) • Soya margarin • Solsikke margarin • Oliven margarin • Olivero • Soft Ekstra .....

Olje • Flytende margarin • Vita .....

Bruker vanligvis ikke fett i matlagingen .....

**12. Brød, knekkebrød og andre kornprodukter**

**Hvor mange skiver brød, rundstykker eller knekkebrød spiser du daglig?** Antall:....

**Hvor mange porsjoner havregrøt, kornblanding eller andre typer frokostblandinger spiser du ukentlig?** Antall:....

**Hvilken type brød og kornprodukter spiser du oftest?**

Kneippbrød • Firkornbrød • Landbrød • Jegerbrød • Loff • Fine rundstykker • Baguetter • Ciabatta • Lyst knekkebrød • Riskaker • Puffet ris • Cornflakes • Havrenøtter • Frokostkorn (med sjokolade, honning, sukker) o.l. .....

Rugbrød • Pumpernikkel • Bakers havre-, spelt- og byggbrød • Vita brød • Goman havrebrød • Mesterbakeren grovbrød • Birkebeinerbrød • Mørke knekkebrød • Rugspro • Fibemik • Havregryn • Weetabix • Havretras • Shredded wheat o.l. .....

Spiser ikke brød, knekkebrød eller andre kornprodukter .....

**13. Grønnsaker, frukt og bær**

**Hvor mange porsjoner grønnsaker, frukt og bær spiser du daglig?**

*1 porsjon = 150 g som tilsvarer ca 2 gulrøtter eller ca et stort eple*

Mindre enn 2 porsjoner (< 300 g) .....

2-4 porsjoner (300-600 g) .....

Mer enn 4 porsjoner (> 600 g) .....

**Hvor mange av disse porsjonene er grønnsaker?** Antall:....

**Hvor mange ganger i uken spiser du salat til lunsj?** Antall:....

**14. Sott pålegg og søt drikke**

**Hvor ofte bruker du søtt pålegg eller søt drikke med sukker eller fruktsukker?**

*Eksempel: Syltetøy • Marmelade • Prim • Geitost • Sjokoladepålegg • Honning • Brus • Saft • Fruktjuice/juice • Nektar o.l.*

0-1 ganger daglig .....

2 ganger daglig .....

3 eller flere ganger daglig .....

**15. Sjokolade, snacks, kaker, kjeks o.l.**

**Hvor ofte spiser du snacks?**

*Eksempel: Sjokolade • Fløteis • Potetgull • Ostepop • Baconcrisp • Tortilla chips • Kaker • Kjeks • Smågodt o.l.*

0-1 ganger ukentlig .....

2 ganger ukentlig .....

3 eller flere ganger ukentlig .....

**Totalt antall poeng:** =====

**16. Belgvekster**

**Spiser du belgvekster ukentlig?** ◯ Ja ◯ Nei

*Eksempel: Hvite tørrbønner • Brune bønner • Kikerter • Linser • Erter • Sukkererter o.l.*

**17. Potet, ris og pasta**

**Hvor mange porsjoner poteter, ris og/eller pasta spiser du daglig?**

*En porsjon tilsvarer 2 poteter eller 2 dl kokt ris eller 2 dl kokt pasta/spaghetti*

◯ Spiser ikke ◯ 0-1 porsjon ◯ 2 porsjoner ◯ 3 porsjoner eller fler

**Hva spiser du oftest?** ◯ Potet ◯ Ris ◯ Pasta

**18. Nøtter, mandler o.l.**

**Spiser du nøtter/mandler ukentlig?** ◯ Ja ◯ Nei

**Spiser du avokado eller oliven ukentlig?** ◯ Ja ◯ Nei

**19. Kaffe**

**Drikker du kaffe?** ◯ Ja ◯ Nei

Hvis ja, hvilken type? .....

*Eksempel: Cappuccino • Café latte • Presskannekaffe • Kokekaffe • Traktekaffe • Pulverkaffe o.l.*

**20. Alkohol**

**Drikker du alkohol?** ◯ Ja ◯ Nei

Hvis ja, hvor mange enheter drikker du til sammen per uke?

◯ Mindre enn 1 ◯ 1-7

◯ 8-14 ◯ 15 enheter eller flere

*1 enhet =*
*1 glass vin (125 ml)*
*1 glass øl (0.33 l)*
*4 cl brennevin*

**21. Egg**

**Hvor mange egg, inkludert i matlaging, spiser du per uke?** Antall.....

**1. Måltidsmønster**

**Hvor mange måltider, inkludert mellommåltider, spiser du daglig?**

◯ 1-2 måltider ◯ 3 måltider

◯ 4 måltider ◯ 5 eller flere måltider

**2. Høyde, vekt og midjemål**

Høyde: ..... cm Vekt: ..... kg

**Ønsker du å gå ned i vekt?** ◯ Nei ◯ Ja

Hvis ja, hvor mange kilo ønsker du å gå ned i vekt? ..... kg

Midjemål: ..... cm (Fylles ut av helsearbeider)

**3. Røyk/snus**

**Røyker du?** ◯ Nei ◯ Ja ◯ Ja, selskapsrøyker

Hvis ja, hvor mange sigaretter/piper røyker du i gjennomsnitt per dag? Antall .....

**Snuser du?** ◯ Nei ◯ Ja

Hvis ja, hvor mange porsjoner snuser du i gjennomsnitt per dag? Antall .....

**4. Mosjon**

**Hvor ofte mosjonerer du i minst 30 minutter slik at du blir lett andpusten eller svett?**

*Eksempel: Rask gange • Løping • Skigåing • Svømming • Sykling o.l.*

◯ Sjeldnere enn 1 gang per uke eller aldri

◯ 1 til 2 ganger per uke

◯ 3 eller flere ganger per uke

**Hvilken type mosjon bedriver du?** .....

**5. Kosttilskudd**

**Bruker du kosttilskudd?**

◯ Nei ◯ Tran ◯ Fiskeoljekapsler/omega3-kapsler

◯ Multivitaminpreparat ◯ Annet .....

# De gode rådene finner du her

**Mettet fett er kolesteroløkende. Reduser derfor inntaket av matvarer med mye mettet fett. Velg i stedet matvarer med umettet fett som kan senke kolesterolet.**

Drikk mager melk, ½ liter skummet, søt eller sur, daglig. Dersom du ikke drikker melk daglig, kan det føre til et for lavt inntak av kalsium.

Alle fløte- og rømmetyper inneholder mye mettet fett og anbefales ikke i hverdagskostholdet. Cultura, skummet kultur, lettmelk, ekstra lett melk, skummet melk, yoghurt, mager Créme Fraiche (10 % fett) og Kesam (1 % fett) kan brukes i matlaging, til sauser og dressing.

Ost er en kilde til store mengder mettet fett. Velg lettere eller mager ost (ost med mindre enn 10 % fett) til hverdags. Ikke bruk lettere ost som pålegg på mer enn en tredel av dagens brødskiver. Vær også oppmerksom på mengde og type ost du bruker i matlagingen. Velg gjerne planteoljebaserte oster som pålegg og i matlagingen.

Fett kjøtt er også en kilde til store mengder mettet fett. Velg kjøtt med mindre enn 10 % fett både som middagsmat og som pålegg. Skjær bort alt synlig fett, og spis minst mulig oppblandede kjøttprodukter. Velg for eksempel karbonadedeig eller kylling-/ svinekjøttdeig fremfor kjøttdeig. Fjern skinnet på kylling, kalkun og annet fjærkre. Velg skinkeprodukter som pålegg fremfor salami, fårepølse og lignende.

Spis alle typer fisk til middag flere ganger i uken. Fet fisk som makrell, sild, laks og ørret inneholder umettet fett (omega-3) og er derfor spesielt gunstig. Spis fisk som pålegg daglig. Ta i tillegg 1 skje tran, eventuelt 2 fiskeoljekapsler, daglig året rundt.

Bruk gjerne majonespålegg daglig, men i moderate mengder. De fleste majonesprodukter inneholder mye olje og derfor mye fett (og kalorier), men fettet er umettet og derfor gunstig.

Myk plantemargarin er en god kilde til umettet fett. Velg typer med mer enn 70 % umettet fett. Velg gjerne margarin med plantesteroler. Plantesteroler er gunstig for kolesterolet. Ved bruk av medikamentet Ezetrol® (ezetimib) forventes imidlertid ikke plantesteroler å gi noen ytterligere kolesterolreduksjon.

Bruk gjerne olje, flytende eller myk plantemargarin i matlagingen (velg typer med mer enn 70 % umettet fett). Spis mindre stekt mat. Velg heller kokt eller ovnsstekt mat, da vil behovet for fett i matlagingen reduseres.

Grove kornprodukter er viktig i hverdagskostholdet. Spis mye av alle sorter fiberrike kornprodukter. Havre er spesielt gunstig og bør brukes regelmessig. Brødet bør inneholde mer enn 6 gram fiber pr 100 gram brød. Se også etter Brødskala'n på emballasjen.

Husk "5-om-dagen". Spis minst tre porsjoner grønnsaker og to porsjoner frukt hver dag. Fyll halve middagstallerkenen med grønnsaker, både rå og lettkokte. Spis frukt og grønnsaker som mellommåltid, som pålegg og som pynt på pålegget. Vær raus med porsjonene. Erter, bønner og linser kan med fordel spises ofte.

En porsjon poteter, ris eller pasta daglig er et fint tilbehør til middagen.

Bruk minst mulig sukker, sukkerholdig mat og drikke, som kjeks, kaker, is, søtt pålegg, sukkergodt, sjokolade, juice, nektar, saft og brus. Med unntak av fruktjuice gir disse produktene ingen eller få næringsstoffer, men kan bidra til økt vekt. Sukker (inkludert fruktsukker) kan også øke triglyseridverdiene.

Nøtter og mandler inneholder gunstig umettet fett, men er veldig kaloririke. Bruk det derfor gjerne, men i begrenset mengde. Kokosnøtten og chillinøttene inneholder mye mettet fett og bør derfor unngås.

Kaffebønnen inneholder fettstoffer som øker kolesterolet. Velg derfor pulverkaffe (inneholder ikke fett) eller kaffe som blir filtrert, da filteret fjerner det meste av fettstoffene. Husk at kaffe tilsatt melk (for eksempel café latte, cappuccino) kan være en kilde til mettet fett avhengig av melketypen som brukes og mengde kaffe som drikkes.

Alkohol inneholder mye kalorier og kan derfor føre til vektøkning. Alkohol kan også øke triglyseridverdiene.

Eggeplommen inneholder mye kolesterol. Begrens inntaket til to eggeplommer per uke. Den største årsaken til økning av kolesterolet i blodet er likevel matvarer rike på mettet fett.

Spørreskjemaet vil ikke nødvendigvis gi et komplett bilde av ditt kosthold. Du kan få mer informasjon om kostholdet i heftet "Kostbehandling ved høye blodlipider hos voksne" (Lipidklinikken 2006).

Spørsmål 1-15 med unntak av spørsmål 10 er evaluert i forhold til veid kostholdsregistrering.

Kilde: Svilaas A, Strøm EC, Svilaas T, Borgejordet Å, Thoresen M, Ose L. SmartDietTM, a health educational tool. Reproducibility and validity of a short food questionnaire for assessment of dietary habits. Nutr Metab Cardiovasc Dis 2002; 12: 60-70. Tredje revidering av skjemaet utgitt i mai 2009.

74841 Ullern AS, Porsgrunn

# Appendix II

Study information provided to the participants

Diakonhjemmet Sykehus

## FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET:

## EFFEKTEN AV KOSTHOLDSINFORMASJON PÅ RISIKOFAKTORER VED HJERTE-KARSYKDOM HOS PASIENTER MED REVMATISK LEDDSYKDOM

I forbindelse med at du har revmatisk leddsykdom og er henvist til den Forebyggende Hjerte-Revma klinikken for en vurdering av din risiko for fremtidig hjerte-karsykdom, har du fått påvist forhøyet risiko for hjerte-karsykdom kommende 10 år, og det er indikasjon for forebyggende tiltak. De rådende anbefalinger for forebyggende hjerte-karsykdom er å starte med kolesterolvennlig kostholds veiledning før oppstart av kolesterolsenkende medikamentell behandling. Du vil derfor bli spurt om å delta i dette studiet hvor vi vil undersøke om det er nødvendig med en utvidet versus en kort standardisert informasjon om hjertevennlige matvarer/kosthold for å påvirke endring i dine kolesterolverdier, ditt blodtrykk, din kroppsmassesammensetning, i tillegg til en betennelsesmarkør kalt C-reaktivt protein (CRP).

### HVA INNEBÆRER PROSJEKTET?

Det å samtykke i deltagelse til dette prosjektet innebærer at du må besvare et spørreskjema omhandlende mat- og livsstilsvaner (SmartDiet) to ganger under besøket på Forebyggende Hjerte-Revma klinikk ved Revmatologisk Avdeling her på Diakonhjemmet sykehus. Alle pasientene fyller ut SmartDiet skjema etter legekonsultasjonen på den Forebyggende Hjerte-Revma klinikken. Alle pasientene vil få en kort (ca. 3 min) standardisert informasjon om kolesterolvennlige matvarer/kosthold med en brosjyre av lege. Deretter vil halvparten av pasienten bli trukket ut til å få en utvidet klinisk ernærings fysiologisk samtale/informasjon (ca. 60 min).

I tillegg til standard målinger av kolesterol, betennelsesprøver (CRP) og blodtrykk, vil vi på 2 måter måle din kroppsmasse sammensetning ved å måle fettprosent og muskel masse. Alle målinger vil bli tatt ved studiestart og ved avslutning av studiet etter 8 uker. Etter at SmartDiet spørreskjemaet igjen er besvart ved studiens slutt, vil du få en ny konsultasjon hos lege og en klinisk ernærings fysiologisk samtale hvor du vil bli informert om resultatene av blodprøver, blodtrykk og kostholds registrering. Du vil så få informasjon om og resept på en kolesterolsenkende medisin dersom det er indikasjon for dette.

I prosjektet vil vi innhente opplysninger om deg, og følgende informasjon vil registreres: alder, kjønn, resultatet av spørreskjemaet SmartDiet, blodprøvesvar, blodtrykk, høyde, vekt, BMI, muskelmasse og fettprosent.

### HENSIKTEN MED STUDIET

Hensikten med studiet er å undersøke om hvilken grad av kostveiledning som nødvendig, dvs om det er nødvendig med en utvidet ernæringsfysiologisk samtale/informasjon, eller om det holder med en kort målrettet informasjon med brosjyre, for å oppnå endringer i kosthold, kolesterolverdier, betennelse, blodtrykk, BMI, muskelmasse og fettprosent.

VI vil også sammenligne målemetodene for kroppsammensetning: DEXA som er gullstandard og Bioimpedanse målemetoden.

### MULIGE FORDELER OG ULEMPER

Studiedesignet følger rådende anbefalinger for forebyggende tiltak for hjerte-karsykdom.

Fordeler med å delta i studien er at du vil bli bedre fulgt opp enn ved en vanlig konsultasjon og du vil således ha større mulighet for å kunne oppnå en positiv endring av ditt kosthold i retning av mer hjertevennlig.

Ulempen er at du vil bruke noe mer tid på dette, sammenliknet med en standard konsultasjon.

Vi tror at sammenlagt vil fordelen ved studiedeltagelse være større enn ulempene. I tillegg vil du ved å delta bidra til økt kunnskap om hvor mye informasjon som er nødvendig for å oppnå gunstig effekt på kolesterolverdier, blodtrykk, betennelse og kroppsmasse sammensetning.

## FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side og du vil samtidig godkjenne at blodprøvene tatt av deg før denne lege konsultasjonen og før du signerte samtykke om deltagelse kan brukes i denne studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for din videre behandling. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte (Anne Grete Semb, telefon nummer 22454076, Silvia Rollefstad, Silvia.Rollefstad@diakonsyk.no, telefon nummer 22454244, eller Sissel Urke Olsen, sisselurke.olsen@diakonsyk.no, telefon nummer 2245 4470, Maria Grorud Fagerhøi, telefon nummer 97168724, maria.g.fagerhoi@hotmail.com )

## HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.

Alle opplysningene vil bli behandlet avidentifisert, dvs uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Denne oppbevares adskilt fra dataene og er nedlåst.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Informasjon om deg vil bli avidentifisert og slettet senest 10 år etter prosjektslutt (2026).

## OPPFØLGINGSPROSJEKT

Det er foreløpig ikke planlagt videre oppfølging. Vi ønsker imidlertid å ha muligheten til å ta kontakt med deg igjen, dersom dette er aktuelt på et senere tidspunkt.

# SAMTYKKE TIL DELTAKELSE I PROSJEKTET

## JEG HAR MOTTATT INFORMASJON OM PROSJEKTET OG ER VILLIG TIL Å DELTA I PROSJEKTET

---

Sted og dato

Deltakers signatur

---

Deltakers navn med trykte bokstaver

Sted og dato……..

Prosjektansvarlig Signatur……

Prosjektansvarliges navn med trykte bokstaver:……..

# Appendix III

“Innkjøpsguiden”

# INNKJØPSGUIDE - hjertevennlig kosthold

## ANBEFALES

### GRØNNSAKER, FRUKT og BÆR
Linser, bønner, kikerter, erter, grønnsaker, potet, frukt, bær. Ingen restriksjon unntatt varer notert i høyre kolonne.
Frukt og bær: 200-300 g per dag
Grønnsaker: 300-500 g per dag (utenom potet)
Avokado: maks 1 stk per dag
Oliven: maks 5-10 stk per dag
Tørket frukt: maks 50 g per dag
Lettere syltetøy og annet søtt pålegg: helst ikke daglig og ikke mer enn 1-2 ss pr dag

### NØTTER og FRØ
Ca 10-20 stk per dag (1-2 håndfuller) uten salt og sukker: mandler, peanøtter, valnøtter, pistasienøtter, hasselnøtter, cashewnøtter, paranøtter, pekannøtter, macadamianøtter, gresskarfrø, solsikkefrø, linfrø, sesamfrø ol

### FETT og OLJER - 2 ss pr dag
Steking/baking: olivenolje, rapsolje, peanøttolje, Vita hjertego', flytende margarin
Kalde retter/dressing: kaldpresset olje, ekstra jomfruolivenolje, nøtteoljer, linfrøolje, sesamolje
Brødskive: Soft flora original + lett + oliven, Vita hjertego' original + lett + proaktiv, Brelett oliven + original
Annet: Vita hjertego' lett majones, lett majones, remulade, majonesbaserte salater

### EGG
Et moderat inntak av eggeplommer anbefales. Dette tilsvarer 3-4 egg pr uke medregnet det som brukes i matlaging. Ingen begrensning på eggehvite.

### DRIKKEVARER
Vann, Olden, First Price vann m/kullsyre, Bonaqua m/kullsyre. Begrens inntaket av melk og juice til maks 2 glass pr dag totalt. Sukkerfri brus/saft kan drikkes med måtehold.

### SØTSAKER, DESSERT og SNACKS
**Inntaket begrenses til 1-2 porsjoner pr uke**
**1 porsjon = cirka 100-150 g**
Popkorn/potetgull laget på olivenolje/nøtteolje, ubehandlede nøtter, fruktis, lettis, soyais, risis, havreis, vegetabilsk fløte, sorbét, gelé, mørk sjokolade minst 70 % kakao, sukkerfri sjokolade og godteri, marsipan, gummigodteri, skumgodteri, gjærbakst uten krem/fyll, nøttekaker og fruktkaker uten krem/fyll.

Siktet mel kan delvis eller helt erstattes med sammalt/grovt mel, mandelmel, kokosmel, andre nøttemel ol. Smør kan erstattes med rapsolje/margarin. Sukrin, Sukrin +, Sukrin Gold, Tagatose, Canderel, Splenda, Stevia, Natren ol kan brukes i stedet for sukker. H-melk kan byttes ut med ekstra lettmelk/lettmelk. Kesam, skyr, jogurt og cottage cheese kan gjerne brukes i bakst.

**Frukt, bær og grønnsaker kan spises som dessert/snacks/mellommåltid daglig.**

## BEGRENS

### GRØNNSAKER, FRUKT og BÆR
Pommes frites, friterte potetkuler, potetmos laget med fløte/H-melk/smør, gratinerte poteter/grønnsaker
Tørket frukt med sjokoladetrekk og/eller yoghurttrekk

### NØTTER og FRØ
Salte nøtter, chillinøtter, brente mandler, nøtter/frø med sjokoladetrekk og/eller yoghurttrekk

### FETT og OLJER
Meierismør, Melange, Per, Linnea, Bremykt, Soft folie, Delfia, Flott, frityrolje, palmeolje, delvis herdet fett/olje, palmekjerneolje, kokosolje, margarin med transfett og/eller palmefett

Solsikkeolje, soyaolje og/eller maisolje anbefales ikke til steking eller annen bruk pga høyt innhold av omega 6. Ekstra jomfruoljer tåler dårlig oppvarming over 100-120 grader. Kaldpressede oljer tåler dårlig temperaturer over 180 grader. Peanøttolje tåler oppvarming til 220 grader.

### DRIKKEVARER
Sukkerholdig saft og brus. Juice og melk som tørstedrikk. Farris og bris (mye salt). Store mengder og regelmessig inntak av alkohol. Mer enn 1 liter kaffe per dag er ikke anbefalt. Kokekaffe og espressokaffe kan øke kolesterolet noe hos noen, mens filterkaffe, kapselkaffe og frysetørret ikke gjør det.

### SØTSAKER, DESSERT og SNACKS
Inntaket bør begrenses til kun spesielle anledninger og ikke oftere enn ett par ganger pr uke. Unngå spesielt produkter med mye tilsatt sukker og mye fett (spesielt transfett, herdet fett, palmeolje og smør).

### SALT
Inntaket bør begrenses til 1 ts pr dag (5 g). Unngå hel- og halvfabrikata (posesupper, ferdigmat, posesauser, hermetikk og lignende). Smak på maten før du salter den. Bruk saltefrie eller saltreduserte krydder og urter. Vær obs på at mange krydderblandinger inneholder mye salt.

**Nøkkelhullsmerking:** Myndighetene i Norge, Sverige og Danmark har valgt nøkkelhullet som symbol på sunnere matvarer. Matvarer merket med nøkkelhullet har mindre fett, sukker og salt og mer fiber enn andre produkter i sin kategori. Produktet kan ikke inneholde kunstig søtstoff.

Diakonhjemmet sykehus, utarbeidet av kliniske ernæringsfysiologer
Redigert september 2015

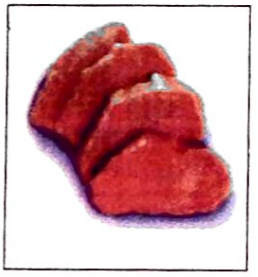
# INNKJØPSGUIDE - hjertevennlig kosthold

## ANBEFALES

### MEIERIPRODUKTER
~~Melk/drikke: ekstra lett- eller skummet melk, Biola,~~ skummet kultur, Cultura
Yoghurt: 0.1 % yoghurt, mild og lett yoghurt, dobbel 0% yoghurt, Skyr, 14-serien fra Tine, Go'morgen Zero
Matlaging: lettmelk, yoghurt naturell, Crème fraiche lett, lett matfløte, matyoghurt med og uten smak, rømme ekstra lett, kesam (mager)
Melkefrie alternativer: lettere kokosmelk, soyamelk, rismelk, havremelk, soyafløte, havrefløte, soyarømme, soyayoghurt
Ost (maks 17 % fett): Synnøve Lett, Så lett gulost, Arla Finello light, Kavli skivet ost, Norvegia lettere, Jarlsberg lite, Nøkkelost lettere, lettere hvitost/gulost/mysost, lettere fetaost/mozzarella/camembert, mager smøreost/smelteost, prim (mager), gammelost, pultost, cottage cheese (mager) med og uten smak,
Dessert: vaniljekesam (mager), lettere dessertfløte, lettere iskrem, Skyr
Annet: produkter fra Vita hjertegod

### KJØTT og KJØTTPÅLEGG
Velg rent kjøtt uten synlig fett. Maks 10 % fett. Maks 500 g ferdig tilberedet rødt kjøtt pr uke.

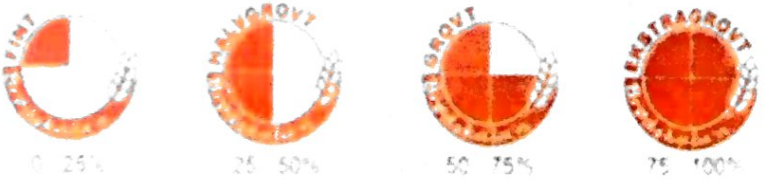
Svinekjøtt: flatbiff, indrefilet, ytrefilet, koteletter uten fettrand, bog, knoke, renskåret svinekjøtt, svinekjøttdeig, Finsbråten Mersmak pølser, Gilde Go'og mager pølser, Gilde Go' og mager bacon, Grilstad filetbacon (skjær bort fettrand)
Storfekjøtt: indrefilet, ytrefilet, mørbrad, flatbiff, rundstek, bankekjøtt, bog, høyrygg, karbonadedeig
Annet: rent lammekjøtt, lammefilet, kyllingkjøttdeig, kalkun/kylling uten skinn, kyllingpølser, kalkunpølser, reinsdyr, hjort, elg, hval
Pålegg: hamburgerrygg, kokt skinke, pastrami, provenceskinke, pepperskinke, roastbiff, kyllingpostei, Vita hjertego` leverpostei, Gilde Go`og mager leverpostei, Finnsbråten Mersmak postei.



### FISK og FISKEPÅLEGG
Ingen restriksjon unntatt varer notert i høyre kolonne. Velg blandingsprodukter med minst 50 % fisk, gjerne mer. Se etter nøkkelhullsmerket.
Pålegg: fiskekaker, fiskeboller, fiskekarbonader, fiskepudding, makrell i tomat, tunfisk, skalldyr, kabaret, sardiner, brisling, laks i rapsolje, peppermakrell

### BRØD og KORNPRODUKTER
Ekstra grove brød og knekkebrød, Rugsprø, Fiberrik, fullkornspasta, naturris, villris, helkorn, frokostblandinger med lite sukker og mye fiber (se etter nøkkelhullsmerke, eks 4-korn, Go`dag, musli, havregryn, havregrøt med kli, Vita hjertego flerkornsflak, Weetabix, Rugfras, Havrefras, Speltfras), kli

**Brødskala'n** viser hvor mange prosent hele korn, sammalt mel og kli det er i brød/knekkebrød - regnes som grovt hvis det er over 50 %. Det anbefales helst ekstra grove brød/knekkebrød til hverdags (mer enn 10 g fiber pr 100 g).




## BEGRENS

### MEIERIPRODUKTER
~~Melk/drikke: H-melk, Kefir, Kulturmelk~~
Yoghurt: helfet yoghurt, Nyt yoghurt, gresk yoghurt 10%, L'amour
Matlaging: seterrømme (35 % fett), lettrømme (20 % fett), Crème fraiche (35 % fett), matfløte (22 % fett), kremfløte (38 % fett)
Ost (over 17 % fett): helfet myk, helfast og fast ost, muggost, mysost, Norvegia, Jarlsberg, Synnøve, Nøkkelost, Normanna, Norzola, Gräddost, Ridderost, Mozzarella, fetaost, Chevre, Cheddar, Brie, Camembert, Parmesan, kremost, Snøfrisk, Port Salut, Sveitser, Nordbo, Taffelost, Edamer, Prim vanilje
Dessert: vaniljesaus, vaniljekrem, kremtopp, fløteiskrem
Annet: kaffefløte (10 % fett)

### KJØTT og KJØTTPÅLEGG
Kjøtt med synlig fett. Skinn.

Svinekjøtt: nakkekoteletter, kotelettkam, svinekoteletter med fettrand, ribbe, spareribs, fleskebein, sideflesk, medisterdeig, medisterfarse, medisterkaker
Storfekjøtt: oksebryst, bibringe, entrecôte, kjøttdeig, kjøttfarse, pølser, middagspølser,
Lam: lammekoteletter, lammebog, fårikål, pinnekjøtt, lammelår, lammeribbe, lammedeig
Annet: familiedeig, kalkunkorv, kyllingskinn, kalkunskinn, steaklets, kjøttboller/pudding, and, gås, kyllinglår med skinn, kyllingnugetts
Pålegg: fårepølse, fleskepølse, gjesterull, lett salami, morrpølse, ribberull, lammerull, salami, servelat, sylte, tunge, helfet leverpostei, paté, dansk salami, stabburspølse, spekemat med synlig fett.

Begrens inntaket av saltet kjøtt og kjøttpålegg til 1-2 ganger pr uke.

### FISK og FISKEPÅLEGG
Panert fisk, frityrstekt fisk, torskelever

Begrens inntaket til 1-2 ganger pr uke pga høyt saltinnhold: sursild, ansjos, røkt makrell, røkelaks, gravlaks, røkt ørret, fiskepaté og kaviar, reker (i lake), annen røkt og saltet fisk

### BRØD og KORNPRODUKTER
Loff, kornprodukter med lite hele korn og fiber, lyse baguetter/ciabatta/rundstykker, pølsebrød, hamburgerbrød, frokostblanding med mye sukker og lite fiber (Honni Korn, Honey nut, Solfrokost, Cherrios, Frosties, Coco pops, Nesquick)