The relationship between nutrition and fatigue in patients diagnosed with inflammatory rheumatic disease

A study on patients' nutritional status, dietary intake, and other potential predictors of fatigue

This dissertation is submitted as part fulfilment of the master degree in Clinical Nutrition

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Abstract

Background: Fatigue in patients with inflammatory rheumatic disease (IRD), is one of the most common and challenging symptoms experienced. It is described by many as a feeling of intense tiredness, exhaustion and lack of energy not relived by resting. The cause of fatigue is unknown but thought to be multifactorial involving psychosocial, physiological, behavioural, and biological mechanisms. Little is known about how dietary intake and nutritional status affect fatigue in IRD. Hence, the purpose of this study was therefore to gain more knowledge about self-reported fatigue and nutrition in this patient group.

Aim: The main aim of this study was to investigate the relationship between nutritional status and dietary intake on fatigue levels in IRD. The secondary objective was to examine if psychosocial and behaviour characteristics predict fatigue in this patient group.

Methods: This study was an observational cross-sectional study that looked at baseline data of outpatients recruited at the Rheumatology ward at Haukeland University Hospital. Nutritional status was assessed by measuring waist circumference (WC), hand grip strength (HGS) and body composition. Dietary intake was assessed using 24-hour recall and 7-day food records. Clinical parameters such as laboratory data, disease activity, bone mineral density and blood pressure were also included as potential predictors of fatigue. Fatigue was assessed by self-reported fatigue questionnaires. Psychosocial and behaviour characteristics were assessed by self-reported questionnaires. Statistical analysis included correlation and multiple linear regression analysis with significance set at $p<0.05$.

Results: There were 31 patients included in the study. Anthropometrics and body composition were not associated with fatigue. Higher unsaturated fat intake such as omega-3 (r -0.364, p=0.036), and omega-6 (r -0.388, p=0.038) and polyunsaturated fat (PUFA) (r -0.421, p=0.023) from 24-hour recall, correlated with lower fatigue scores, and high saturated fat (r 0.411, p=0.027) intake correlated with higher fatigue score. However, the result was inconsistent. Only pain remained significant (β 0.624, p=0.029) with fatigue in multiple regression when significant predictor variables (pain, sleep, saturated fat, disease activity, PUFA and blood pressure) from correlation analysis were included in the analysis.

Conclusion: Pain was associated with fatigue scores to a greater extent than other variables included in this study. These findings suggest that nutritional status and dietary intake do not associate with fatigue in our study population. Additional research and randomized controlled trials in IRD patients are required to fully assess the role of nutrition in fatigue management.

Table of content

List of abbreviations

AS	Ankylosing Spondylitis
AX-SPA	Axial Spondyloarthritis
ASDAS	Ankylosing Spondylitis Disease Activity Score
BASDAI	Bath Ankylosing Spondylitis Disease Activity Score
BIA	Bioelectrical Impedance Analysis
BMD	Bone Mineral Density
BMI	Body Mass Index
BMR	Basal Metabolic Rate
BRAF-MDQ	Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire
CHO	Carbohydrates
CRP	C-Reactive Protein
DAPSA	Disease Activity Index for Psoriatic Arthritis
DAS28	Disease Activity Score 28 joint count
DBP	Diastolic Blood Pressure
DEXA	Dual Energy X-ray Absorptiometry
DMARD	Disease-Modifying Anti-Rheumatic Drug
EI	Energy Intake
E%	Energy percent
ESR	Erythrocyte Sedimentation Rate
FM	Fat Mass
FFM	Fat Free Mass
FFMI	Fat Free Mass Index
FMI	Fat Mass Index
FT4	Thyroxine
HDL	High Density Lipoprotein
HGS	Hand Grip Strength
HUH	Haukeland University Hospital
IRD	Inflammatory Rheumatic Diseases
LDL	Low Density Lipoprotein
MHAQ	Modified Health Assessment Questionnaire
MMA	Methylmalonic acid
NSAID	Non-Steroidal Anti-Inflammatory Drug
PAL	Physical Activity Level
PGA	Patient Global Assessment
PSA	Psoriatic Arthritis
PUFA	Poly Unsaturated Fatty Acids
RA	Rheumatoid Arthritis
RAID	Rheumatoid Arthritis Impact of Disease
RAND 12	The 12-Item Short Form Health Survey
SBP	Systolic Blood Pressure
SFA	Saturated Fatty Acids
SLE	Systemic Lupus Erythematosus
SPA	Spondyloarthritis
TAG	Triglycerides
WC	Waist Circumference

1 Introduction

1.1 Inflammatory rheumatic diseases

Rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (ax-SpA) are the most common inflammatory rheumatic diseases (IRD) in ordinary outpatient clinics in Norway.[1] Both PsA and ax-SpA is part of the group spondyloarthritis (SpA). Furthermore ax-SpA is the most common form of spondyloarthritis and is divided into radiographic (also known as ankylosing spondylitis) and nonradiographic disease. IRDs have many overlapping characteristics, and can be described as autoimmune systemic conditions, with the presence of inflammation, that mainly affects the joints. The chronic inflammation is mainly present in the joints and commonly causes joint destruction and deformities in all groups. However, inflammation can also be present in other organs, with the most common being the lungs, intestines, eyes, and skin.[2,3] IRDs are differentiated by the signs and symptoms of the disease, pathogenic mechanisms, and primary population that is affected. In addition to clinical signs and symptoms, RA, PsA, and ax-SpA are associated with impaired physical function, fatigue, pain and stiffness that can decrease health-related quality of life.[3] Patients with RA, PsA and ax-SpA also have an increased risk of comorbidities such as cardiovascular disease, depression, anxiety, cancer, and are prone to developing infections. [3, 4, 5, 6]

1.1.1 Prevalence

IRDs are relatively common conditions that often debut between early and middle adulthood in which lifelong therapy is often necessary. It has been estimated that 1 in 12 women and 1 in 20 men will develop an IRD during their lifetime.[7] The prevalence for the different rheumatic diseases varies, but in Norway it is estimated that 0,5–1 % of the population suffers from RA, and 0,1–0,2 % are diagnosed with PsA, while around 0,15 – 0,5 % have ankylosing spondylitis (AS). [1,2] Worldwide the estimated prevalence of RA is 0.5%–1.0%, with an observable reduction from north to south (in the northern hemisphere) and from urban to rural areas.[4, 8] It is estimated that the prevalence of RA is higher in women than men with a sex ratio of 3:1, and increases with age,[3] with peak onset in the fifth to sixth decade of life.[9] Furthermore, an assessment of patients from 7 European and North American countries found that around 30% of the patients with psoriasis also had PsA.[10] It has been estimated that onset of PsA can typically occur 8–10 years after the onset of psoriasis. Furthermore, the estimated prevalence of PsA is approximately the same for both women and men.[3] Ax-SpA is

underdiagnosed, and diagnosis is often delayed, therefore true prevalence is difficult to assess. However, in the United States the estimate ranges from 0.9–1.4%, and debut age typically occurs before patients are 45 years of age. Recent evidence also suggests that the prevalence is the same for both women and men.[3]

1.1.2 Pathophysiology

IRDs are known as autoimmune conditions where the body's own immune system is overactive and therefore gets activated by mistake to attack the body's own tissue or proteins. This process causes inflammation to be formed at the site of tissue damage caused by the autoimmunity.[11] Hence, the purpose of medications, used to treat IRD is to stop the inflammatory process. When the immune system does not repair acute inflammation, chronic inflammation develops that can last for months and years. In rheumatic diseases, chronic inflammation is usually seen at the onset of disease where destruction and repair of tissue is seen simultaneously. If the stimulating agent of the innate immune system is not removed, hence the autoimmunity, it will lead to further inflammation by production of proinflammatory cytokines and activation of the specific adaptive immune system. Cytokines are signalling molecules in the form of proteins that can be pro- or anti-inflammatory and are therefore important for the innate immune system. Pro-inflammatory cytokines include TNF-alpha, interferon gamma and granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-1 (IL-1), IL6, IL12, IL18, that are produced from T cells, macrophages, and dendritic cells. Inhibition of pro-inflammatory cytokines are therefore important mechanisms in the treatment of IRD.[11]

The cause of IRDs is complex and to this date not fully understood, but it is thought that both genetic and environmental factors play a role. Early diagnosis is important for optimal therapeutic success, and complete remission is typically not sustained without continuing treatment.[4]

1.1.2.1 Rheumatoid arthritis

RA is one of the most common IRD in which abnormal activation of B cells, T cells, and innate immune effectors occurs.[9] Although the aetiology is still unknown, development is associated with genetics and environmental factors contributing to disease susceptibility. Having family members with RA increases the risk around 3-4 times of developing the disease,[4] Genome-wide association studies have identified more than a hundred loci associated with RA susceptibility, with the majority implicating immune mechanisms.[4] The genetic factors thought to be of major influence in RA susceptibility are the specific human leukocyte antigen (HLA) alleles. They have been associated with disease severity in rheumatoid arthritis, with patients homozygous for disease-associated alleles having the most severe disease.[9]

Furthermore, infections with bacterial and viral pathogens, such as Escherichia coli, Epstein-Barr virus, and Porphyromonas gingivalis (a bacterium frequently found in periodontitis) being some examples, have been linked to initiation of RA in susceptible individuals. However, proposed mechanisms remain unclear.[4,9] There is significant evidence supporting a role for autoimmunity in generating the rheumatoid arthritis phenotype including seropositivity for autoantibodies such as IgG referred to as rheumatoid factor (RF) and citrullinated peptides (ACPAs). These autoantibodies are present in 50-75% of patients at diagnosis, and appear to be a marker of a more destructive and aggressive RA phenotype.[4,9] In addition, smoking is associated with a higher risk of developing the disease.[2,4]

RA is characterised by several inflammatory cascades eventually causing persistent synovitis, damaging the cartilage in joints and underlying bone.[4] In RA, most of the inflammatory activity is seen in the joint synovium. Joint involvement is predominantly symmetric in RA, hence affecting the same joints on each side.[12] The typical RA patient presents with swollen and tender joints, morning joint stiffness, abnormal laboratory tests such as high erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP).[4]

There are well-defined classification criteria that are used to diagnose RA. In 2010, a new ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) classification criteria was presented.[2] Classification criteria as seen in Table 1,[13] include number of swollen or tender joints involved, serology of negative or positive test result for RF and ACPA, normal or abnormal acute-phase reactants such as CRP and ESR and duration of symptoms lasting <6 weeks or ≥6 weeks. A score of ≥6/10 is needed for classification of a

patient as having definite RA.[13] The key clinical characteristic is the confirmation of definite, persistent, clinical synovitis in at least one joint.[12]

Table 1. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis

A. Joint involvement (0-5 points)	
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 (0-3 points)	
Negative RF *and* negative ACPA	0
Low-positive RF *or* low-positive ACPA	2
High-positive RF *or* high-positive ACPA	3
C. Duration of symptoms (0-1 points)	
<6 weeks	0
>6 weeks	1
D. Acute-phase reactants (0-1 points)	
Normal CRP *and* normal ESR	0
Abnormal CRP *or* abnormal ESR	1

Classification criteria for RA; add score of categories A–D. Table adapted from Aletaha et al.[13]

1.1.2.2 Psoriatic Arthritis

PsA is an immune mediated inflammatory disease that affects both the axial and peripheral skeleton and is frequently associated with the skin condition psoriasis. PsA presents with many different clinical symptoms and is therefore difficult to define.[3,5] As symptoms are also similar to other IRDs such as RA, there is a risk of misdiagnosis. However, one differentiation between PsA and RA is that the inflammation of affected joints in PsA is often asymmetrical (involving different joints on each side of the body), and patients are mostly seronegative for RF.[3] In both RA and PsA, most patients have polyarthritis (≥5 involved joints), although joint involvement can be oligoarticular (≤5 involved joints) or polyarticular (≥5 involved joints).[12]

Key features of PsA are synovial membrane inflammation contributing to joint damage. Formation of osteoclasts leads to bone resorption and eventually causing bone erosion, joint deformity, and loss of function. The inflammation can also occur in the connective tissue between tendon or ligament and bone, referred to as enthesis. Many of the other common clinical features of PsA include nail and skin changes, inflammation of uvea (uveitis), finger and toe tendons and joints (dactylitis).[5] PsA symptoms may occur alone or in combination

and can range from mild to very severe.[3] Another differentiating feature of PsA is inflammation of the axial skeleton, that is estimated to occur in up to half of the patients with PsA. In comparison, inflammation in the axial skeleton is not present in RA other than cervical spine involvement.[12]

The precise mechanism of pathogenesis of PsA is complex and not fully understood and involves genetics, environmental factors, and immune-mediated inflammation.[5] Different HLA gene variants have been associated with different clinical features of PsA. The HLA-B27 gene, as found in many patients with AS, is associated with axial skeletal involvement in psoriatic arthritis. Studies also suggest involvement of other genes,[5] however due to the complexity of the topic, an analysis is beyond the scope of this study.

Environmental factors have been implicated in triggering development of PsA in people that are already genetically susceptible to developing the disease. Such factors include stress, infections, obesity, trauma, and smoking.[5] The streptococcus bacterium is linked to the triggering of psoriasis and to post-streptococcal reactive arthritis.[14] Furthermore, an increase in the prevalence of streptococcal antibodies found in patients with PsA indicates a role for infection as a gene–environment interaction. [5] However, the mechanism behind an infectious agent as a potential trigger of PsA is unclear.

PsA can be diagnosed according to the CASPAR (Classification criteria for PsA) criteria with ≥3 points from the following 5 categories: 1. Evidence of current psoriasis, family history of psoriasis or personal history of psoriasis. 2. Physical examination showing typical psoriatic nail dystrophy. 3. Negative serology test for RF. 4. Current dactylitis or a history of dactylitis. 5. Juxtaarticular new bone formation as shown by radiography.[15]

1.1.2.3 Axial Spondyloarthritis

Ax-SpA is the most common form of SpA and is characterised by chronic inflammation mainly affecting the axial skeleton. The term covers both the non-radiographic and radiographic axial spondyloarthritis. Radiographic ax-SpA, also known as ankylosing spondylitis (AS), refers to development of structural damage in the sacroiliac joints or spine visible on X-ray or CT scans. Non-radiographic refers to the patient group with no structural changes and damage in the sacroiliac joints.[3,6] Clinical presentation includes chronic back ache typically caused by inflammation as the leading symptom of ax-SpA. Stiffness of lower

back and pelvis is also common. However, any part of the spine might be involved. Around 30 to 50 % of the patients present with arthritis and enthesitis as the most common peripheral manifestations, and the joints are usually swollen and painful. Inflammation of the uvea is also typically common in this patient group. Furthermore, dactylitis, psoriasis, and inflammatory bowel disease are also associated with ax-SpA.[3,6]

Pathogenesis is poorly understood, but as suggested for the other IRDs the pathogenesis of ax-SpA appears to be the result of genetic, immunological, and environmental factors. It has been estimated that 95% of the patients with AS have the HLA-B27 gene, hence the presence of this gene has been reported to associate with susceptibility and disease activity of AS.[2, 6] However, the pathogenic role of HLA-B27 is not clear and there are many other genes that still needs to be identified.[6]

Ax-SpA can be diagnosed according to the ASAS criteria as seen in Table 2. The criteria include age of onset less than 45 years and having had back pain for 3 months with the presence of radiographic sacroiliitis or active inflammation of sacroiliac joints on magnetic resonance imaging, plus at least one typical SpA feature. According to the criteria, ax-SpA can also be diagnosed by having the HLA-B27 gene plus at least two other SpA features.[16]

Table 2. The ASAS classification criteria for axial spondyloarthritis

In patients with back pain ≥3 months and age at onset <45		
Sacroiliitis on imaging plus ≥one feature of SpA	or	HLA-B27 plus ≥two other features of SpA
SpA features:		
• Arthritis		
• Inflammatory back pain		
• Enthesitis (heel)		
• Dactylitis		
• Psoriasis		
• Uveitis		
• Crohn's/colitis		
• Good response to NSAIDs		
• HLA-B27		
• Elevated CRP		
• Family history of SpA		

Adapted from Rudwaleit et al.[16] Abbreviations; NSAIDs= Non-steroidal anti-inflammatory drugs

1.1.2.4 Treatment

Treatment of IRD focuses on inducing remission by reducing inflammation and thereby reducing the risk for joint damage, hence alleviating joint pain and other common symptoms. Treatment includes use of medications that reduce symptoms such as pain killers and nonsteroidal anti-inflammatory drugs (NSAIDs). Other medication used include corticosteroids and disease modifying antirheumatic drugs (DMARDs) such as sulfasalazine, methotrexate and leflunomide.[2,4] Corticosteroids have quick acting symptomatic and disease modifying effects, but its use is associated with serious long-term side effects.[4] DMARDs are immunosuppressive and target inflammation. They are classified as either synthetic or biological DMARDs. Synthetic DMARDs are further defined as conventional synthetic or targeted synthetic. The mode of action of conventional synthetic DMARDs is still largely unknown, while targeted synthetic DMARDs are highly specific and target a specific pathway of the immune system. An example includes the Janus kinase inhibitors, such as tofacitinib.[2,4] Biological DMARDs include TNF inhibitors, which is the most important group. Examples include etanercept, infliximab, and adalimumab. Although, these drugs have a high likelihood of achieving benefit in patients, their use is limited due to being costly and can cause side effects such as drug-associated toxicity.[9]

1.1.3 Fatigue

1.1.3.1 Rheumatic Diseases and Fatigue

Fatigue has been reported to be one of the most challenging and common symptoms in patients with IRD that may worsen manifestation of pain and physical disability and affect quality of life. Furthermore, fatigue is also an independent predictor of job loss and disability in patients with IRD. Fatigue can therefore affect a person's ability to function and carry out daily activities. [17, 18, 19]

Studying fatigue is difficult since it is a complex multifaceted phenomenon that is determined by a subjective feeling. Hence, it is difficult to measure as no objective marker exists. Furthermore, since fatigue is a subjective feeling, it makes it difficult to define. Conceptually, no consensus exists on the definition of fatigue.[17] However, many describe it as a feeling of intense tiredness, exhaustion and lack of energy not relived by resting. [19] A recent review of fatigue in IRD written by Davies and her colleagues proposed the following definition of

fatigue: “A multi-dimensional phenomenon in which the biophysiological, cognitive, motivational and emotional state of the body is affected resulting in significant impairment of the individual’s ability to function in their normal capacity.” [17]

Fatigue can be experienced as acute or as chronic. Acute fatigue typically decreases as the effect of the triggering factor gradually diminishes to restore a normal homeostatic balance, while chronic fatigue is fatigue that persists for 6 months or longer. Furthermore, fatigue severity can also range from mild to severe.[20] Shared predictors of fatigue have been identified across different diseases with pain and depression often being the strongest predictors.[17] Other often reported predictors include anxiety, sleep disturbance, physical inactivity and obesity. [17, 19, 21, 22] Furthermore, there are some indications that the prevalence is higher in women and people with lower social economic status.[23]

The prevalence of fatigue varies significantly within different rheumatic diseases.[20] Fatigue is also difficult to measure since it is a subjective feeling and multiple tools have been used to assess fatigue. However, an international study with over 6000 patients found that 41–51% of the patients with RA, PsA and ax-SpA reported severe fatigue. [18, 23] Measurement of reliable and accurate estimates of fatigue is challenging and depends on the use of self-reported questionnaires. Furthermore, there are no agreed upon golden standard method for what fatigue questionnaire to use, making comparison to other studies difficult.[17]

1.1.3.2 Pathogenesis of fatigue

1.1.3.2.1 Physiological and biological factors

To this date there is no clear understanding of what causes fatigue in IRD. However, the cause is believed to be multidimensional [17, 20] combining psychosocial, physiological, and biological mechanisms such as pain, anxiety, inflammation, and the central nervous system (CNS). However, these mechanisms are complex and thought to interact with each other. [17] The different suggested factors and mechanisms thought to be involved in fatigue will be briefly discussed below.

Inflammation is considerably one of the most studied mechanisms of fatigue and it is believed by many researchers that the activation of the immune system and production of type I interferons and pro-inflammatory cytokines such as IL-6, IL-1 and TNF- α is thought

to play a role in fatigue by inducing a sickness behaviour characterized by fatigue, lethargy, fever and coldness, numbness, increased sensitivity to pain, depression, isolation, changed sleeping pattern and inability to concentrate. This behaviour is thought to be an adaptive response in animals and the human body, increasing chances of survival.[17, 18, 24] Sickness behaviour therefore works as an adaptive program used during immune activation, and when switched on for too long, believed to happen in chronic conditions like IRD, it can become dysfunctional potentially leading to long-term changes in energy availability of single cells and energy distribution between organs in the body.[24] However, mechanisms remain unclear.

Studies have shown associations between inflammation and fatigue prognosis. A meta-analysis found that anti-TNF agents and other biologic DMARDs reduced fatigue in patients with RA compared with placebo.[25] Furthermore, a study by Van Steenberg et al, done in patients with RA, showed that the association between inflammation and fatigue was statistically significant but effect sizes were small.[26] However, a study showed that although many RA patients achieved clinical remission using anti-TNF drugs, many did not achieve complete remission of fatigue. [27] It is now recognised that fatigue often persist despite patients receiving treatment aimed at reducing disease activity and pro-inflammatory cytokines. This suggests that non-inflammatory pathways mediate fatigue as well.[17, 19, 26]

Even though inflammation does not seem to directly cause fatigue an alternative pathway through the CNS has been suggested. A review by Korte et al [24] proposed that inflammation in chronic inflammatory diseases negatively affect neurotransmitters functioning in various areas in the CNS, leading to an overlap in fatigue, pain and depression.[24] The CNS is thought to play a role in fatigue as cognitive impairment and lack of motivation are common symptoms in IRD patients suffering from fatigue.[17] Inflammation may cause alterations to neural chemistry and functional connectivity in the brain which in turn may contribute to the development of fatigue.[24] However, direct evidence of metabolic and pro inflammatory changes in the CNS remains challenging to find and the involvement of the CNS requires further research.[17]

Neuroendocrine disturbance such as dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis may contribute to fatigue through its involvement in the stress response, energy utilization and metabolism where cortisol production is implicated. Persistent inflammation seen in chronic inflammatory diseases, might reduce the response of the HPA axis.[17] Studies have showed that cortisol concentration in RA patients compared to healthy subjects is

similar, but the ACTH/cortisol hormone secretion is inadequate in relation to inflammation due to ratio of serum cortisol to serum cytokines being much lower in RA patients compared to healthy subjects.[28] Nevertheless, more research is needed to determine a causative relationship between neuroendocrine disturbance and fatigue.[17]

The autonomic nervous system (ANS) plays an important role in response to stressors such as inflammation. The sympathetic and parasympathetic nervous system are part of the ANS, and imbalances characterized by sympathetic overactivity and low vagal tone may influence fatigue.[17, 20] The association between fatigue and ANS needs further investigation.

Metabolic disturbances such as oxidative stress, an imbalance between free radicals and antioxidants, have been associated with fatigue along with overproduction of nitric oxide. Inflammation is a key contributor to oxidative and nitrosative stress.[17, 29]

Patients with RA have reported sleep disturbances such as poor quality of sleep, feeling fatigued and unrested after sleep and having issues with falling asleep. Studies have confirmed this by showing that RA patients have lower overall sleep efficiency and more awakenings.[30] The relationship between fatigue and sleep is not fully understood, but it is believed that poor sleep leads to fatigue experienced during the day which again will lead to sleep disturbances during the night.[17] Furthermore, inflammation interacts with the synthesis of neuroendocrine mediators such as melatonin (the sleep hormone), growth hormones, prolactin, and monoamines, and all these mediators can affect sleep. Circulating concentrations of cortisol also affects sleep, and sleep disturbances are associated with altered HPA axis and cortisol production.[17,31]

Reduced physical activity has been associated with fatigue in people with rheumatic diseases.[32] A meta-analysis showed that an aerobic exercise program was associated with improved fatigue levels in RA patients, but the effects were small.[33] Furthermore, physical inactivity correlates with obesity in RA patients and obesity is another reported predictor of fatigue in patients with IRD such as RA, in which the mechanism between this association remains unclear.[17, 22] Body composition might affect fatigue indirectly, through loss of lean body mass as seen in rheumatoid cachexia. This can lead to reduced muscle strength which can influence physical disability. Obesity is also linked to sleep disorder,[22] and it has been reported that excessive dietary intake, particularly high fat consumption, may alter sleep parameters, resulting in fatigue.[34] Other possible mechanisms include altered energy metabolism and mitochondrial dysfunction, which is also associated with oxidative stress.

Nevertheless, obesity is multifactorial with many determinants, hence the link between fatigue and obesity is complex.[17]

1.1.3.2.2 Behavioural and psychosocial factors

Depression has been associated with fatigue in RA patients, and a systematic review found depression to be more prevalent among RA patients.[35] However, it is important to recognise that fatigue is included as a symptom in diagnostic criteria for depression[19] and many patients with fatigue do not have depression. Fatigue is therefore often a feature and not the primary symptom of depression.[17] Inflammation has also been associated with depression and it has been hypothesised that there is an overlap between the mechanisms underlying some of the symptoms of depression and fatigue such as dysregulation of monoamine metabolism in CNS, however the mechanism remains unclear.[24]

Another important predictor of fatigue in many IRD patients is self-reported pain.[17, 18, 19] In a study done in patients with RA receiving DMARDs and anti-TNF treatment, fatigue reduction was linked to improvements in pain, and it was suggested that this association was more important than reductions in disease activity when considering fatigue management. [36]

Furthermore, psychosocial factors such as socioeconomic status, reduced social support, and life stress have been associated with fatigue in RA patients.[18, 20, 37] Cognitive therapy has been shown to be a promising treatment option for fatigue management in patients with RA, but the potential mechanisms linking these psychosocial factors to fatigue development have however not been identified.[17, 32]

In summary, inflammation and the immune system are key contributors in IRD and seem to be the underlying driver of fatigue through various complex and not fully understood interconnecting mechanisms involving psychological, biological, and physiological factors. Furthermore, potential long-term consequences of these interconnecting mechanisms are alteration to the human body's natural physiological response that causes them to become maladaptive. This again can perpetuate fatigue and explains why removing inflammation alone does not get rid of fatigue. Moreover, fatigue is experienced both mentally and physically with individual differences in perceived fatigue, hence the contribution of the different mechanisms likely varies.[17]

Figure 1. Hypothesized mechanisms involved in pathogenesis of fatigue

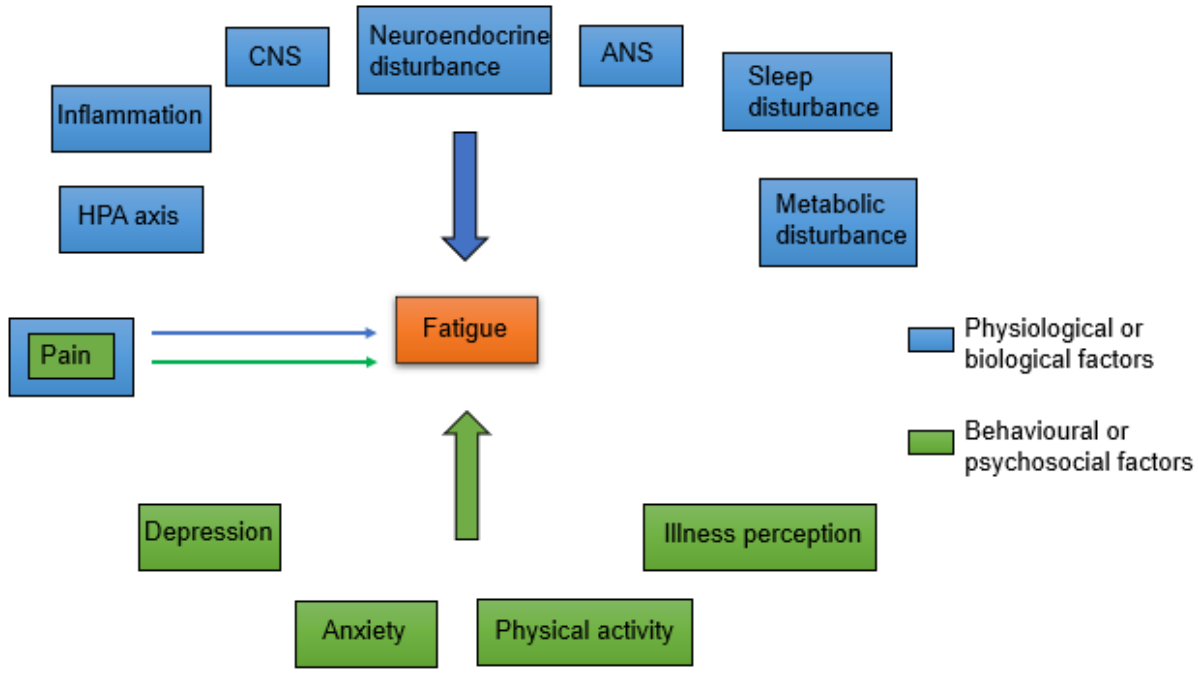


Figure 1. A theoretical model showing the relationship between proposed mechanisms of fatigue in patients with IRD. Pain is thought to affect fatigue involving both physiological or biological and behavioural or psychosocial factors. Model adapted from Davies et al.[17]

1.1.4 Nutrition and Fatigue

The role of dietary interventions on influencing disease activity and related symptoms in patients with RA is now more widely researched, with fish oil supplements and the Mediterranean diet (MD) being the most promising.[38, 39] However, a literature search shows that only a few studies have looked at the relationship between diet, nutritional status, and fatigue symptoms in patients with IRD. Three intervention studies were identified in RA patients that investigated the effect of omega-3 supplementation, MD, and herbal supplements. The MD and omega-3 interventions showed statistically significant improvements in vitality fatigue scores, but herbal supplement compared to placebo had no effect on fatigue.[40, 41, 42] Furthermore, a study from 2020 investigated the effect of the MD on fatigue in RA using a questionnaire measuring perceived RA impact of disease (RAID) including fatigue as one of the outcome measures, and found no significant association between MD and the fatigue domain of RAID.[43]

An intervention study done in PsA patients found that weight loss after 6 months with weight loss treatment led to improvement in fatigue scores.[44] There has also been done some studies on association between vitamin D status and fatigue in rheumatic diseases, but no clear link has yet been found.[21, 45]

More studies concerning nutrition and fatigue have been done in other patient groups such as chronic fatigue syndrome (CFS), multiple sclerosis (MS), and fibromyalgia. Systematic reviews, done in CFS, and fibromyalgia patients concluded that there is little evidence for a relationship between vitamin and mineral deficiencies and supplementation on fatigue.[46, 47] It is more likely that the diet as a whole or different food groups can influence fatigue. One systematic review found the potential for a low-fat, starchy plant-based diet to improve self-reported fatigue levels in patients with multiple sclerosis (MS).[48] Some clinical studies have found an association between foods rich in omega-3, whole grains high in fibre and polyphenol-rich vegetables and improved fatigue symptoms in breast cancer patients.[49] However, the research is more indicative, than evident and more research is needed in patients with IRD.

1.1.4.1 Malnutrition and fatigue

In a meta-analysis up to 32% of patients with RA experienced rheumatoid cachexia (RC).[50] RC is characterized by changes in body composition involving reduction of fat-free mass, with or without loss of fat mass (FM), resulting in no or limited changes in body mass index (BMI).[50] Metabolic changes caused by the inflammatory nature of the disease, activates nuclear factor kappa-B (NF-κβ) that can lead to depletion of lean tissue.[51, 52] Furthermore, malnutrition and BMI decrease in RA patients have been found to be a predictor of poor prognosis in terms of functioning and life expectancy. Chronic fatigue along with depression, inflammation, pain, and other common complaints in RA patients may have an indirect effect on energy intake by supressing appetite and limit food intake, which again affects nutritional status.[52, 53]

Therefore, nutritional status is hypothesised to impact fatigue scores in patients with rheumatic diseases. However, to current knowledge and as previously mentioned very few studies have investigated the relationship between nutritional status and fatigue in patients with rheumatic diseases. However, some studies have looked at nutritional status as mediator

of fatigue in older people as fatigue is highly frequent in the elderly. Nevertheless, little is in fact known about the association between malnutrition and fatigue in elderly.[54] One study looked at patient reported factors affecting food intake in older people recruited from Aarhus University Hospital, Denmark, and found that the presence of fatigue after discharge from hospital was associated with reduced food intake, that lead to weight loss and readmission to hospital. Furthermore, it was stated that fatigue can be an early sign of deterioration in health status among malnourished elderly patients that had newly been discharged from hospital.[54]

Loss of weight and muscle mass which reflects malnutrition, has been linked with fatigue and predicts quality of life. Furthermore, severity of weight loss has been found to reflect fatigue scores in elderly, with weight loss correlating with worse fatigue scores at discharge from hospital. Fatigue has also been frequently linked with cancer and cachexia, where impaired nutritional status plays a role.[55] At last, a single study also looked at the relationship between hand grip strength and fatigue and found an association between right- and left-hand grip strength and fatigue in patients with RA.[56]

Hence, we know little about how nutritional status affects fatigue in IRD and the purpose of this study is therefore to gain more knowledge about self-reported fatigue and nutrition in IRD. Furthermore, we hope this study can help identify more factors that affect fatigue so that the treatment options can be improved and more tailored to combat fatigue symptoms in this patient group.

2 Aims and objectives

The main aim of this study was to investigate the relationship between nutritional status and dietary intake on fatigue sores in patients with RA, PsA and ax-SpA, assessed by anthropometry, laboratory measurements, clinical parameters, and fatigue questionnaires. However, secondary objective was to examine psychosocial and behaviour characteristics as potential predictors of fatigue, as suggested in the literature.

2.1 Hypothesis

RA, PsA and ax-SpA patients that meet the Norwegian Dietary Guidelines and have a good nutritional status as indicated by anthropometrics, body composition, laboratory, and bone mineral density data, experience significantly less fatigue.

3 Materials and methods

3.1 The EROM project

Patients with RA and SpA are at risk of developing malnutrition and can experience nutritional challenges due to the many symptoms associated with IRD. A study done at Haukeland University Hospital (HUH) in 2020, found high prevalence of abdominal obesity and low-fat free mass index (FFMI) in patients with RA and SpA,[57] which formed the basis for the Nutrition in Rheumatic Diseases (EROM) study.

The EROM study is an ongoing study with start date in December 2020 at HUH. The EROM study aims to investigate the effect of improved dietary intake, with focus on increasing consumption of oily fish, on disease activity in patients with RA and SpA. Furthermore, the EROM study will also look at the effect of omega-3 supplementation in this patient group with emphasis on disease activity.

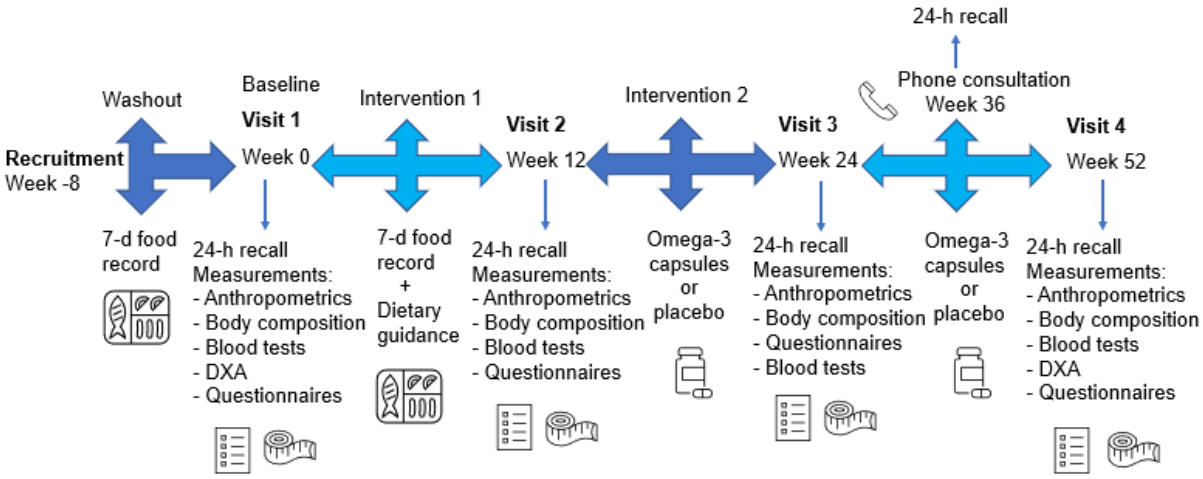
3.1.1 EROM project study design

The patients recruited into the EROM study are followed for 12 months and data collected at baseline (week 0) and every scheduled follow up interval after 12, 24, 36 and 52 weeks. Hence, the study consists of 4 visitations along with one consultation/check-up over the phone. Visit 1 during week 0, visit 2 during week 12, visit 3 during week 24 and visit 4 during week 52. The phone interview takes place during week 36.

Anthropometrical and body composition measurements are collected at each visit (total of 4 visits). Blood tests were taken at visit 1,2,3 and 4. Dietary data from the last 24 hours are collected at each interval, but a self-registered 7-day food record is filled out before visit 1 and 2. Furthermore, data regarding bone mineral density, measured by dual-energy X-ray

absorptiometry (DXA), is collected at visit 1 and 4. See figure 2 for an overview of the study design.

Figure 2. Timeline for washout, intervention 1 and intervention 2 with last visitation in week 52.



The EROM study is twofold with two interventions:

Intervention 1 involves dietary guidance of the patient group where they receive advice on how to increase intake of oily fish and make healthier food choices. They also receive a booklet with recipes that contain a high omega-3 content. Furthermore, they gain access to a dietary course consisting of 4 sessions. During this intervention period there is no control group. Participants must avoid use of omega-3 supplements for 8 weeks before the start of the study and should also not take omega-3 supplements during the study.

After intervention 1 the participants will receive either omega-3 capsules or placebo for 6 months in intervention 2. Intervention 2 is double-blinded, and the patients are randomized to take either 3 grams of omega-3 or placebo daily (capsules with soya oil), divided into 4 capsules per day. Omega-3 high concentrate from GC Rieber VivoMega AS is used. Patients are asked to sustain from use of other Omega-3 supplements during the intervention 2 period.

3.1.2 My role in the EROM project

As a master student of Clinical Nutrition, I joined the EROM study at the end of August 2021 as part of my master project for 2021/2022. My role was to assist PhD student and dietician Marie Njerve Olsen with patient consultations that included collecting anthropometric and body composition data along with information concerning dietary intake.

Hence, I contributed to data collection during the different visitations that the patients had to attend (visit 1, 2, 3 and 4). My participation in data collection took place when I joined the project late August to December before the Christmas vacation in 2021.

During the visitations attended by the patient, I conducted dietary intake interviews regarding their dietary intake the previous 24 hours. Furthermore, I collected anthropometric data by measuring the patient's height, waist circumference and hand grip strength. I also operated a body composition scale used to take measurements such as fat mass and muscle mass. After the measurements had been completed, the data (measurements) was explained to the patient during the consultation.

Apart from the consultations and data collection, I helped to create food recipes that was used for a dietary booklet that the patients received on their first visit. This was to help give them ideas on how to increase their omega-3 intake through food. When creating the recipes, I used the tool "Kostholdsplanleggeren" (dietary planner) to estimate that the patient would receive roughly 3 g of omega-3 from the dish.

All data collected from the different visitations I helped plotting and enter in the statistical software platform SPSS. Furthermore, I analysed the DXA data including bone mineral density such as X-rays taken of the hip and femur and plotted the patients' T and Z-scores into SPSS. The data concerning; DXA, blood pressure, and blood tests were taken from the patient journal system called DIPS before it was entered in SPSS. The data which I participated in collecting will be explained in greater detail below in the method section.

In summary, the EROM project is an intervention study looking at the effect of dietary guidance and omega-3 supplementation on disease activity in patients with rheumatic inflammatory diseases. In comparison, my master project looked at the baseline data collected from the EROM study before start of the interventions, to investigate potential predictors of fatigue in this patient group using all the raw data. This will be discussed in greater detail in the sections below.

3.2 Master project

3.2.1 Study Design

This study was an observational cross sectional study part of the EROM project where I looked at the baseline data collected at week 0. The cross-sectional study was conducted at HUH in the Rheumatology Department from December 2020 to December 2021.

The data was collected by PhD student Marie Njerve Olsen, master students' Kirsten Sletholen, Kristine Teigland, consulting rheumatologist and study nurses. Blood samples were collected and analysed at HUS.

3.2.2 Study Population

Participants recruited included patients enrolled at HUH outpatient clinic participating in rehabilitation programmes or receiving infusions with biological disease-modifying anti-rheumatic drugs (bDMARDs). They were recruited by the rheumatologist in the outpatient clinic of the Department of Rheumatology. Furthermore, patients were also recruited via rheumatologists working at private clinics in Bergen, and from ads posted in local newspapers and local rheumatism association. Since the study was conducted at HUS and the participants had to arrange own transportation to the hospital, participants that were included in the study lived near Bergen city in Norway.

The inclusion criteria for the study included patients diagnosed with RA using the ACR/EULAR 2010 criteria, PsA using CASPAR-criteria, and ax-SpA including both the ankylosing spondylitis (AS) and non-radiographic ax-SpA, using ASAS criteria. Furthermore, the participants recruited were between 18 and 75 years, had been diagnosed with the disease for 6 months or longer, and no change in medication the last 12 weeks. Participants also had to speak Norwegian and give consent.

The exclusion criteria to the EROM study and thus to this study included patients unable to consume omega-3 capsules and follow dietary interventions. Contraindications also included use of anticoagulants, pregnancy/breastfeeding, allergy against soy/fish proteins, mental or severe physical illness like liver disease or insulin-dependent diabetes.

3.2.3 Data Collection

After recruitment and washout period, participants were invited for their first visit where baseline data was collected. Baseline data included demographics, behaviour characteristics, dietary data, anthropometrical measurements, analysis of body composition, blood tests, blood pressure, and disease activity measurements.

3.2.3.1 Methods

3.2.3.1.1 Participant characteristics

Demographics were collected by a self-reported questionnaire (see Appendix III), and included household income, education, and work. Behaviour characteristics such as alcohol consumption, use of supplements and physical activity were also included in the questionnaire that the participants filled out during the consultation. All participants had to state their age before being included in the study as it was one of the inclusion criteria.

Rheumatic disease specific factors and use of drugs was determined by the treating rheumatologist. Participant characteristics related to the study was also obtained from the participant's patient journal in DIPS.

3.2.3.1.2 Estimation of nutritional intake

3.2.3.1.2.1 24-hour recall

Dietary intake was assessed during the first consultation through an interview referred to as a 24-hour recall. In the 24-hour recall the patient was interviewed by a master student in clinical nutrition or PhD candidate, asking open questions about the patient's exact food intake during the last 24-hour period, hence the day before the consultation. Questions asked included information about all types of food and drinks consumed, portion size and quantity, what type of food was consumed. Examples include type of butter or bread, or percentage fat of the milk, and how the food was prepared. All the information were written down on a printed sheet (Appendix II) that also included reminder notes for the interviewer to double check that all the information needed had been gathered. Furthermore, the participants were

asked if they were currently taking any supplements and if the 24-hour recall day was a typical day for them, hence if the recall day landed on a Sunday, would this normally represent a typical day of the week.

3.2.3.1.2.2 7-day food record

Since a 24-hour recall is not sufficient alone to describe a person's usual dietary intake, participants were asked to fill out a 7-day food record a week prior to the first study visit. The 7-day food record was then collected at the beginning of the consultation or emailed to the PhD student prior to the consultation. In the food record the patient was supposed to write down detailed description of all the different foods and drinks that had been consumed each day, at what time, quantity and type of food/drinks consumed and possibly, brand name. In mixed dishes like pizza or soups, the different ingredients and amount used plus quantity consumed, had to be written down. Furthermore, all components of the meal had to be registered, including use/type of butter on bread, type of bread – white bread or wholemeal and how coarse the bread is. It is important to note that the 7-day food record was self-reported and therefore prone to individual inaccuracy and errors.

3.2.3.1.2.3 Analysis

After the dietary intake from the 7-day food record and 24-hour recall had been collected, all the dietary information was entered into "Kostholdsplanleggeren". This is a dietary tool that has been developed by the Norwegian Directorate of Health and the Norwegian Food Safety Authority. A profile was created for each patient ID and then the different food items, dishes and drinks that had been consumed by the patient were added to the patient's profile. After all the desired food and drink items had been added to the patient profile, the tool calculates the sum of the nutrient content of the registered foods for the 24-hour recall and the average intake for the 7-day food record and compare it with Norwegian recommendations for intakes of macro and micronutrients.

The calculated average dietary intake for the 7-day food record and 24-hour recall were then plotted into SPSS for statistical analysis. Table 3 shows all the nutrients that were chosen for analysis in SPSS.

Table 3. Nutrients included for analysis in SPSS.

Energy giving	Fats	Carbohydrates	Fat-soluble vitamins	Water soluble vitamins	Minerals
Kilocalories	Saturated fat	Total carbohydrates	Vitamin A	Thiamine	Calcium
Fats	Cis-monounsaturated fatty acids	Fibre	Vitamin D	Riboflavin	Iron
Carbohydrates	Cis-polyunsaturated fatty acids	Added sugar	Vitamin E	Niacin	Salt
Protein	Omega-3	Starch		Vitamin B6	Sodium
	Omega-6			Folate	Potassium
				Vitamin B12	Magnesium
				Vitamin C	Zinc
					Iodine
					Selenium

3.2.3.1.2.4 Goldberg cut-off for underreporting

To estimate underreporting of dietary intake, the revised Goldberg cut offs method was used.[58] The method allows for an estimation of whether reported energy intake equals actual energy intake during the investigation period. This is done by calculating confidence limits for the relationship between reported energy intake (EIrep)/estimated basal metabolic rate (BMRest) and physical activity level (PAL). If the EIrep:BMRest value is below the cut off value calculated for each individual then it can be said that the participant has underreported. The equations on how this is calculated can be seen in the appendix (Appendix IV). PAL values were determined based on the self-reported questionnaire (Appendix III). BMR was measured using a calibrated professional medical scale, that measured body composition by BIA, but also estimated the patient's BMR.

3.2.3.1.3 Body weight, height, and BMI

To assess nutritional status, we measured anthropometrics including height (cm), weight (kg), and BMI; (kg/m^2). The height of the participant was measured in standing position using a free-standing stadiometer. The participant was asked to remove shoes and socks and any head accessories that could affect the accuracy of the measurement. Furthermore, the participant was told to stand straight with feet together, knees straight and shoulder blades, heels and

buttocks touching the stadiometer. The head also had to be in the Frankfurt plane position with eyes looking straight ahead and arms relaxed to the sides.

The weight of the participant was measured using the calibrated professional TANITA medical scale. The participant had to remove shoes and socks and 1 kg was subtracted from the body weight to account for the clothes. All the participants were told to be fasting before measuring their weight, and weight measurements were taken before 10.00 in the morning for most patients. Weight to height ratio was calculated for all the patients using BMI. This was calculated as weight (kg)/height $(m)^2$. The BMI of the patient was then categorized according to the WHO BMI scale,[59] see Table 4 below.

Table 4. Nutritional status and BMI categories

Nutritional status	BMI kg/m^2
Underweight	Below 18.5
Normal weight	18.5–24.9
Pre-obesity	25.0–29.9
Obesity class I	30.0–34.9
Obesity class II	35.0–39.9
Obesity class III	Above 40

3.2.3.1.4 Waist circumference (cm)

Waist circumference was measured using a "waist watcher tape" that is a measuring tape that can be made into a loop and fitted around the waist with a pushbutton that can be pressed to tighten the tape firmly around the waist. To measure waist circumference, the patient was told to either remove clothing around the torso or lift the clothes up to expose the skin. Then the mid-point between the upper hip bone (iliac crest) and lowest rib margin was measured and marked on both sides with a marker pen. The tape was positioned around the participant's waist by using the marking points as guidance and measured during calm exhalation. The patient was asked to be fasting before the measurement took place. Table 5, shows reference values used.[60]

Table 5. WHO reference values for waist circumference.

	Men	Women
Moderately increased	94-101 cm	80-87 cm
Significantly increased	≥ 102 cm	≥ 88 cm

3.2.3.1.5 Hand grip strength (HGS)

HGS can be used as a measure of skeletal muscle function, and even though HGS did not capture RA and SpA patients with malnutrition in the study from 2020 at HUH,[57] it was included as a variable to investigate if it could correlate with fatigue levels in this patient group. HGS was measured using a Jamar dynamometer (kg) according to a standardised protocol.[61] The arm was positioned at the side of the torso and the hand gripping the dynamometer in a 90-degree angle. The participant was then asked to grip the dynamometer as hard as possible for a few seconds. Measurements were repeated 3 times in both dominant and non-dominant hand. Each participant was asked if they were able to perform the HGS test before the measurements in case of arthritis in the hand/fingers or if they were receiving infusion in one of the arms. If they were unable to do the HGS test due to arthritis in hands the data would be missing, or if they received infusion in one arm, the measurement would be taken with opposite hand. However, if the participant stated that it was okay to perform the HGS test in both hands, the test would be performed according to procedure.

3.2.3.1.6 Body composition and bone mineral density

Since BMI alone cannot provide any information regarding body fat and muscle content, we measured body composition using the calibrated professional medical scale from TANITA, by performing BIA and using dual energy X-ray absorptiometry (DXA), standardised by health care professionals.

The BIA analysis took place during the consultation and was performed by either the PhD or master student. The participant had to remove shoes and socks before stepping on the scale. The participant was asked if they had a pacemaker, any metal fitted in their body or was pregnant, which was considered exclusion criteria for this study. In most cases the body composition was measured in the morning and the patient had been told to fast overnight. Before the patient stepped on the scale, one kg was subtracted from body weight to account for the clothes. The patient was told to step barefoot on the scale where the electrode platform was marked, then the patient's gender, age, and height was entered in the control unit on the scale before the readings could begin. After the personal information was entered, the patient had to hold two handlebars down to the sides while both body impedance and segmental impedance were measured. The measurement took less than 30 seconds and result could be

seen on the control unit screen of the scale or on the laptop that was connected to the scale. Fat free mass index (FFMI) and fat mass index (FMI) were derived as fat-free mass (kg) and body fat (kg), respectively, and divided by height (m) squared (kg/m^2).

The DXA measurements were taken either before or after the patient had performed the BIA analysis, this was due to the DXA measurement being performed by a study nurse and took place in a different room at a scheduled appointment time. Therefore, the measurements that was taken during the consultation had to be worked around the scheduled appointment time for the DXA measurement. DXA measurements included both body composition and bone mineral density (BMD) measurements. BMD measurements included T and Z-scores for the femoral neck, total hip and lumbar column (L1-L4). BMD was measured because we wanted to check for osteopenia or osteoporosis and if there was a correlation between T-scores or Z scores and fatigue. The DXA data were analysed and taken from the patient journal DIPS. Table 6 shows body composition measurements and BMD included in analysis.

Table 6. Measurements of body composition and BMD included in the analysis.

BIA	DXA
Fat mass (kg and %)	Fat mass (kg and %)
Fat-free mass (kg and %)	Fat-free mass (kg and %)
Muscle mass (kg and %)	Muscle mass (kg and %)
	Bone mineral density (T and Z-scores)

3.2.3.1.7 Clinical parameters

Blood samples were taken by the study nurses and analysed at HUH before consultation with the PhD or master student. All the measurements, including blood samples, were taken in the morning, after fasting overnight. Biomarkers included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), LDL (mmol/L), HDL (mmol/L), triglycerides (mmol/L), cholesterol (mmol/L), vitamins and hormones.

Blood pressure was measured by the study nurse or during the patient's appointment with the rheumatologist after consultation with the PhD or master student. The blood pressure was

measured as systolic and diastolic blood pressure (mmHg). See table 7, for full list of clinical parameters measured.

Table 7. Clinical parameters measured.

Inflammatory markers	Lipids	Nutritional status	Hormones	Blood pressure
CRP	Cholesterol	Haemoglobin (Hb)	TSH	Systolic BP
ESR	HDL	Homocysteine	Thyroxin (Ft4)	Diastolic BP
	LDL	Methylmalonic acid (MMA)		
	Triglycerides	Cobalamin		
		Folate		
		Ferritin		
		Albumin		
		Vitamin D		
		Glucose		

3.2.3.1.8 GoTreat IT (GTI)

We used an electronic monitoring tool called “Go treat it” for rheumatology. It is a tool where data collected can be recorded so that the patients' disease progression can be monitored over time. The patients can fill out web-based forms or questionnaires regarding self-assessment of disease activity on various health aspects. Health care professionals can also enter patient related data into the system. Data regarding some of the fatigue and disease activity scores was collected using this monitoring tool and will be discussed further below.

3.2.3.1.9 Assessment of Fatigue

All participants were asked to fill out fatigue questionnaires (Appendix V) usually at the beginning of the consultation, or while waiting for the doctor’s appointment. There were 4 questionnaires included in the study, and 3 of them included subcategories used to measure fatigue. The Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ) specifically measures fatigue in patients with RA, while the other two questionnaires also measure fatigue, but include other questions regarding function and other physical and mental aspects used to assess quality of life. For the analyses regarding fatigue, the subcategories specifically asking questions on fatigue where used.

3.2.3.1.9.1 BRAF-MDQ

The main self-reported questionnaire used in the study to assess fatigue was the BRAF MDQ which measures fatigue experienced the last 7 days. BRAF-MDQ has 20 questions distributed across 4 categories: physical fatigue (e.g., have you, living with fatigue (e.g., has fatigue affected your social life?), cognitive fatigue (e.g., have you forgotten things because of fatigue?), and emotional fatigue (e.g., have you felt down or depressed because of fatigue?). For the first 3 questions, the response options are numerical or categorical such as "how many days did you experience fatigue in the past 7 days?" (0-7). For the rest of the questions there are 4 response options: "Not at all," A little," "Quite a bit," to "Very much."

The score of each of the 5 categories are combined to create a total score, where higher scores indicate a higher grade of fatigue. If question 1 and 2 had not been answered and more than one question for each category had been left unanswered, the questionnaire would not be valid. If a question had not been answered, then the missing question score would be replaced with the average score for that category. If there was a missing value for the "physical fatigue" category, the value of the 3 answered questions would be added and divided by the total max possible score for those 3 questions. Then the sum of those questions was multiplied by the maximum score possible for all 4 questions.

3.2.3.1.9.2 RAID

RAID (Rheumatoid Arthritis Impact of Disease) is a questionnaire that measures self-reported perceived impact of disease on health, including fatigue and was therefore included in the study. RAID was developed as a questionnaire for patients with RA, but was used for all the patients in this study. RAID has 7 questions about pain, physical disability, fatigue, sleep, physical well-being, emotional well-being, and coping. Each question estimates severity score from 0-10 during the last 7 days, where a higher score indicates worse perceived disease impact. In this study the fatigue category for RAID was used to measure fatigue scores. However, pain and sleep disturbance scores were also included in analysis.

3.2.3.1.9.3 RAND 12

RAND 12 (short form health survey) measures health-related quality of life and includes some questions regarding fatigue and was therefore also considered useful for this study. RAND 12 has 12 questions and was filled out by the patients electronically in GTI. Furthermore, RAND-12 has 8 categories: PF (physical functioning), RP (role physical), BP

(bodily pain), GH (general health), VT (vitality (energy/fatigue)), SF (social functioning), RE (role emotional), MH (mental health). However, in this study the VT (fatigue) category was chosen as one of the measures to estimate fatigue scores with. The scores were automatically calculated in the GTI programme. The VT scores range from 0 to 100, with higher scores indicating less fatigue. A VT score of ≤35 was used as an estimate of severe fatigue.

3.2.3.1.9.4 MHAQ

MHAQ (Modified Health Assessment Questionnaire) was another self-reported questionnaire that was included in the study as it measures physical function or disability. It includes questions regarding function, pain, fatigue and joint problems and was developed for patients with RA but is also used for patients with other rheumatic diseases. MHAQ has 8 questions, and each question gives a score from 0-3 (0 = no problems, 3 = impossible to complete). The average of all 8 questions is calculated, but at least 6 questions must be completed. This questionnaire was not used to estimate fatigue score, but was used to estimate if physical function correlates with fatigue.

In summary, no cut off values have been identified for fatigue scores obtained from BRAF-MDQ and RAID. Hence, the fatigue score interpretation from these questionnaires is that higher scores reflect greater severity of fatigue.

3.2.3.1.10 Assessment of Disease Activity

Assessment of disease activity is important when evaluating the impact it has on fatigue scores of the patients. The assessment was done by the treating rheumatologist and data was entered in GTI and then plotted in SPSS.

DAS28 (Disease Activity Score 28-joint count) is an instrument that measures disease activity score which includes examination of 28 joints. DAS28 was developed for patients with RA, but may also be valid in patients with PsA, however DAS28 might not capture all the joints commonly affected in PsA.[62] In this study DAS28 was measured for both RA and PsA patients. To calculate DAS28, the number of swollen and tender joints out of 28 examined joints are measured and registered by the rheumatologist. Furthermore, measurements of disease activity also often include DAS28 combined with CRP (mg/dL) and patients' own assessment of disease activity often referred to as patient global assessment (PGA), where degree of disease activity is marked on a scale from 0-100 mm. The assessment is done by the treating rheumatologist and entered in GTI which automatically

calculates a score. Higher values indicate a higher disease activity and if the score is below 2.6 it is considered remission of the disease.[4] In this study 3 measurements of DAS28 was included; DAS28 (joint count only), DAS28-CRP(3) (includes CRP, but not PGA), and DAS28-CRP(4) (includes CRP and PGA).

DAPSA (Disease Activity Index for Psoriatic Arthritis) is a measure of disease activity in patients with PsA and consists of 5 variables. Information collected includes number of swollen and tender joints, patient perceived pain and patient perceived disease activity or overall health.[62] An automatic score is calculated once the information is entered in GTI.

Disease activity in ax-SpA patients is normally measured by ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score) and BASDAI (Bath Ankylosing Spondylitis Disease Activity Index). BASDAI is a questionnaire that the patient fills out in GTI and includes 6 questions regarding fatigue, pain, and morning stiffness during the last week. Each question has a score of 0-10 and the total score is calculated by adding the score of question 1-4 with the average score of question 5 and 6, the added score is then divided by 5. Higher scores indicate higher disease activity. In comparison to ASDAS-CRP, BASDAI has no validated cut-off values for disease activity status, however a study by Kwon et al,[63] suggested cut off scores corresponding to ASDAS-CRP scores which can be seen in Table 8.

The ASDAS score is calculated based on the patient's own assessment of disease activity and inflammatory markers such as CRP or ESR, [64] but in this study only CRP was included in analyses. The patient assessment is based on questions from the BASDAI questionnaire. The score for both ASDAS and BASDAI can be calculated automatically in GTI, and higher scores indicate higher disease activity.

Table 8. Instruments used to measure disease activity

Components		Remission	Low disease activity	Moderate disease activity	High disease activity
DAS28[4]	Tender joint count (of 28), swollen joint count (of 28)	<2.6	2.6 to 3.2	>3.2 to ≤5.1	>5.1
DAS28-CRP[4]	Tender joint count (of 28), swollen joint count (of 28), CRP, patient assessment of disease activity (PGA)	<2.6	2.6 to 3.2	>3.2 to ≤5.1	>5.1
DAPSA[62]	Swollen joint count, tender joint count, patient pain, patient global assessment, CRP	≤4	>4 to ≤14	>14 to ≤28	>28
ASDAS-CRP[64]	Patient-reported disease activity, and CRP	<1.3	≥1.3 to <2.1	≥2.1 to ≤3.5	>3.5
BASDAI[63]	Patient-reported disease activity based on 6 questions from questionnaire	<1.9	≥1.9 to < 3.5	≥3.5 to ≤4.9	>4.9

3.2.3.1.11 Other potential predictors of fatigue

In addition, as a lot of fatigue research in rheumatic diseases has involved identifying other potential predictors of fatigue including, pain, disability, sleep and sometimes age,[17, 65] I also wanted to investigate this relationship. Pain, sleep, and physical disability were assessed by RAID and MHAQ self-reported questionnaires.

3.3 Ethics

The EROM study was approved Norwegian "Regional Committees for Medical and Health Research Ethics" and registered in clinical trials (NCT04586933). Participation in the study had no effect on receiving any other treatment and participants could withdraw at any time. Written informed consent was obtained from all the participants at the first consultation (See appendix I). The storage of participant's personal data and health research data is in accordance with Haukeland hospital's privacy policy and is anonymised on the research server operated by the hospital's ICT (information and communication technology).

3.4 Statistical Analysis

Statistical analyses were performed using SPSS version 16.0 (SPSS Inc, Chicago, IL, USA). The threshold for significance was set at $p<0.05$ and p-values <0.01 were also highlighted. Descriptive analyses were given as total number and percentages (%) for categorical variables and mean with standard deviation (SD) and minimum and maximum values for continuous variables.

The Shapiro–Wilk test was used to check for normality of the continuous variables as it is recommended for a sample size of less than 50. Tests for homoscedasticity and linearity of data was also performed. As some of the variables showed skewness and were not normally distributed, the non-parametric Spearman correlation test was used to analyse the relationship between non-normally distributed continuous variables whereas Pearson correlation test was performed on the continuous variables that showed normal distribution. To check for any differences between mean fatigue scores of categorical variables, one way ANOVA analysis was performed with Welch's Test for Unequal Variances accounting for unequal samples.

Furthermore, multiple linear regression was performed with independent predictors significantly associated with fatigue scores ($p <0.05$). The assumption of multiple linear regression is that the data is normally distributed. Due to some of the dependent variables being non-normally distributed and unable to be transformed into normally distributed variables, multiple regression analysis was performed using *"total score"* of BRAF-MDQ and RAID "*fatigue"* category as dependent variables as they were all normally distributed. The impact of each variable was expressed with regression coefficients with 95% confidence intervals.

4 Results

4.1 Study population

Participant characteristics is described in Table 9. The total amount of participants that met study criteria and were recruited into the study were 31 persons. Female participants comprised 24 (77 %) of sample size and 7 (23 %) were males, with mean ± SD age of 50.3 ± 10.8 years for all participants. All the included participants were non-Hispanic whites and 6 (19 %) of them were currently smoking.

Furthermore, 18 (58 %) of the patients recruited had RA, while 8 (26 %) and 5 (16 %) had PsA and ax-SpA respectively. The median duration of disease from date of diagnosis to study inclusion was 11 (0.5 – 22) years.

Use of medication included DMARDs either conventional or biologic, steroids and NSAID. A combination of use of both biologic and conventional DMARDs were the most frequent drugs used and was used by 10 (32 %) of the participants. Conventional DMARDs only, was used by 6 (19 %) of the participants while 8 (26 %) used biologics only, with 17 (59%) patients using folic acid. Furthermore, 5 (16 %) of the patients used corticosteroids and NSAID was used by 17 (55%) of the participants. Antidepressants and sleeping agents were used by 6 (21 %) and 2 (7 %) of the patients respectively.

Table 9. Participant characteristics, n=31.

	n (%)
Demographics	
Age (years)	50.3 ± 10.8 (30 – 73)*
Sex (women)	24 (%)
Non-Hispanic white	31 (100)
Disease specific factors	
RA	18 (58)
PsA	8 (26)
Ax-SpA	5 (16)
Disease duration (years)	11 (0.5 – 22) †
Drugs	
cDMARD	6 (19)
bDMARD	8 (26)
Combination	10 (32)
Corticosteroids	5 (16)
NSAID	17 (55)
Folic acid	17 (59)
Calcigran Forte	8 (28)
Antidepressants	6 (21)
Sleeping agents	2 (7)
Other	
Smoking, current	6 (19)

* Values are the mean with SD and range. † Values are the median (min-max). *Abbrevations*: RA=rheumatoid arthritis, PsA=psoriatic arthritis, ax-SpA =Axial spondyloarthritis. cDMARD=conventional disease-modifying anti-rheumatic drugs, bDMARD=biologic disease-modifying anti-rheumatic drugs, NSAID=non-steroidal anti-inflammatory drugs. Smoking includes all types of tobacco used.

4.1.1 Behaviour characteristics

Out of the 28 participants that answered the questionnaire regarding education, 15 (53 %) reported that they had studied at a college or university <4 years, of whom 8 (29 %) patients reported lower educational level, while 5 (18 %) had studied more than 4 years at college or university as seen in Table 10.

Furthermore, 10 (35 %) of the study participants reported a household income higher than >1 000 000 NOK. Alcohol consumption was also reported to be relatively frequent, with 12 (44%) of the participants reporting that they drink every week.

Physical activity level was reported to be quite high among the study participants with as many as 24 (80 %) being physically active several times per week. Only 3 (10 %) people reported to work out less than once per week.

Table 10. Behaviour characteristics of study population with frequency and percentages reported, n=30.

		Total n (%)
Education	Primary or high school, or certificate of apprenticeship	8 (29)
	College/university < 4 years	15 (53)
	College/University, > 4 years	5 (18)
Household income (NOK)	250 000 - 450 000	3 (11)
	451 000 -750 000	7 (25)
	751 000- 1 000 000	8 (29)
	>1 000 000	10 (35)
Physical activity	<1 times/week	3 (10)
	1 time/week	3 (10)
	2-3 times/week	14 (47)
	Almost every day	10 (33)
Alcohol*	Rarely	7 (26)
	1-3 times/month	8 (30)
	1 time/week	8 (30)
	Several times/week	4 (14)

* Alcohol represents individual consumption.

Table 11 shows the distribution of self-reported supplements used by study participants. There were 22 (76 %) participants that reported use of supplements, and the most frequently used supplement was folic acid, by 10 (34 %) out of 29. Furthermore, 7 (24 %) participants also reported to use vitamin D, calcium, and fish oils.

Table 11. Self-reported use of supplements in the study population shown as frequency and percentage, n=29.

Supplements	n (%)
Taking supplements	22 (76)
Vitamin D	7 (24)
Calcium	7 (24)
B vitamins	3 (10)
Iron	1 (3)
Folic acid	10 (34)
Vitamin C	3 (10)
Vitamin E	2 (7)
Fish oils	7 (24)
Multivitamins	1 (3)

4.2 Assessment of Fatigue Scores

In the total study population, 2 (6 %) participants did not fill out the RAID and BRAF-MDQ questionnaires, while 3 (10 %) participants had not filled out the RAND 12 questionnaire. For the RAID questionnaire, the mean ± SD fatigue scores were 3.8 ± 2.2, as seen in Table 12. BRAF-MDQ and its categories also showed mean ± SD scores below half of the maximum score for that category. Physical fatigue had a mean ± SD score of 9.1 ± 5.4, living with fatigue; 4.2 ± 3.1, cognitive fatigue; 3.6 ± 3.1, emotional fatigue; 2.4 ± 2.5 and total fatigue; 19 ± 12. For RAND 12, the VT (fatigue) mean ± SD score in study population was less than half the maximum possible score; 30 ± 19, indicating worse overall fatigue levels.

Furthermore, Table 12 also shows how many of the participants received a fatigue score that was either equal to or above half of the maximum score, hence indicating more severe fatigue. For the VT category (fatigue), a lower score below or equal to 35 indicated severe fatigue. For the RAID fatigue questionnaire, 11 (38%) reported fatigue scores ≥ 5.

For BRAF-MDQ, 3 (10 %) of the participants reported scores above or equal to half of the maximum score. It was the physical fatigue category where most participants had the highest fatigue scores, with 9 (31%) of the participants having a fatigue score ≥11.

For the RAND 12 VT (vitality/fatigue) category, 23 (82 %) of the participants had scores equal to or below 50, while 15 (54%) of the participants had scores ≤35, indicating severe fatigue. No participant scored the maximum fatigue score for any of the fatigue questionnaires and its sub-categories.

Table 12. Fatigue scores as reported by RAID, BRAF-MDQ and RAND12.

		N	Mean ± SD	Min–Max *	Max score**	≥ half of max score (%)	Severe fatigue
RAID	Fatigue	29	3.8 ± 2.2	0 – 8	10	11 (38)	
BRAF-MDQ	Physical	29	9.1 ± 5.4	0 – 18	22	9 (31)	
	Living	29	4.2 ± 3.1	0 – 10	21	0 (0)	
	Cognition	29	3.6 ± 3.1	0 – 12	15	2 (7)	
	Emotion	29	2.4 ± 2.5	0 – 9	12	3 (10)	
	Total	29	19 ± 12	0 – 40	70	3 (10)	
							Score ≤35
RAND 12	VT	28	30 ± 19	0 – 60	100	5 (18)	15 (54)

*Min-Max score represents the lowest and highest patient reported fatigue score. ** Max score represents the maximum score that is possible to obtain for each fatigue category. VT= vitality/fatigue, a lower score means better vitality. For RAID/BRAF-MDQ a higher fatigue score indicates more severe fatigue.

Table 13 compares the validity and correlation between each questionnaire used to measure fatigue in patients with IRD. All the different questionnaire categories used in this study statistically significantly correlated. Hence, as the fatigue score of one questionnaire increased, so would the score from the other fatigue questionnaire it was compared to. Furthermore, as the score for the VT category would decrease, indicating worse fatigue, the score of the other questionnaires would increase. Hence, indicating a strong relationship between the fatigue questionnaires used. Furthermore, the BRAF-MDQ physical fatigue category correlated almost perfectly (r 0.909, p=0.000) with the scores from the RAID fatigue category. The BRAF-MDQ total fatigue category also strongly correlated (r 0.880, p=0.000) with fatigue for RAID.

Table 13. Correlation coefficients between the different fatigue questionnaires used in this study to measure fatigue, n=28

		RAID	**RAND12**	**BRAF-MDQ**				
		Fatigue	VT	Physical	Living	Cognition	Emotion	Total
RAID	Fatigue	-	-0.581**	0.909**	0.756**	0.680**	0.685**	0.880**
	p value	-	**0.002**	**0.000**	**0.000**	**0.000**	**0.000**	**0.000**
RAND 12	VT	-0.581**	-	-0.679**	-0.484*	-0.471*	-0.473*	-0.625**
	p value	**0.002**	**-**	**0.000**	**0.012**	**0.015**	**0.015**	**0.001**
BRAF-MDQ	Physical	0.909**	-0.679**	-	-	-	-	-
	p value	**0.000**	**0.000**	-	-	-	-	-
	Living	0.756**	-0.484*	-	-	-	-	-
	p value	**0.000**	**0.012**	-	-	-	-	-
	Cognition	0.680**	-0.471*	-	-	-	-	-
	p value	**0.000**	**0.015**	-	-	-	-	-
	Emotion	0.685**	-0.473*	-	-	-	-	-
	p value	**0.000**	**0.015**	-	-	-	-	-
	Total	0.880**	-0.625**	-	-	-	-	-
	p value	**0.000**	**0.001**	-	-	-	-	-

P (p-value). ** Correlation is significant at the 0.01 level (2-tailed).* Correlation is significant at the 0.05 level (2-tailed).

4.3 Assessment of Nutrient Intake

Results for calculation of energy and nutrient intake from 24-hour recall and 7-day food record compared with recommendations for healthy people are seen in Table 14, along with the number of participants that did not meet the recommended reference values. As men normally consume more calories than women and have different reference values for some of the nutrients, separate mean values were calculated for both genders. For the 24-hour recall, data was collected from 31 participants, while for the 7-day food record that the patient's had to fill out and hand in, only 20 participants completed a food record for 7 consecutive days. The 24-hour recall mean ± SD intake for saturated fat was 32 ± 11 g (15 E%) for females and 34.3 ± 21.0 (13 E%) for males, mean ± SD salt intake was 6.7 ± 2.1 g for females and 7.2 ± 2.0 g for males, and mean ± SD sodium intake was 2704 ± 821 mg for females and 2960 ± 828 mg for males.

The 7-day food record mean ± SD intake for saturated fat was 29 ± 8 g (15 E%) for females and 41 ± 13 (16 E%) for males, salt mean ± SD intake was 6.8 ± 2.1 g for females and 10.1 ± 3.9 g for males, and sodium mean ± SD intake was 2663 ± 779 mg for females and 4077 ± 1550 mg for males. The mean ± SD intake of these nutrients from both 24-hour recall and 7-day food record was higher than the recommended reference values for females and males.

Furthermore, males had a higher than recommended mean ± SD sugar intake from 24-hour recall; 79.2 ± 79 g (14 E%) and 7-day-food record; 66 ± 68 g (12 E%) than females from 24-hour recall; 28 ± 31 g (6 E%), and 7-day-food record; 23 ± 15 g (5 E%).

The mean ± SD intake of nutrients from the 24-hour recall was lower than recommended for the following nutrients; fibre intake in females; 21 ± 5.7 g and 21 ± 5.8 g in males, vitamin D intake; 4.1 ± 2.6 µg in females and 7.1 ± 8.2 µg in males, vitamin A intake; 672 ± 322 µg in females and 454 ± 206 µg in males, and folate intake; 248 ± 82 µg in females and 205 ± 76 µg in males. The mean ± SD nutrient intake of the nutrients listed above were also lower than recommended from the 7-day food record; fibre intake in females; 20 ± 5 g and 16.4 ± 1.4 g in males, vitamin D intake; 4.1 ± 2.4 µg in females and 5.7 ± 2.9 µg in males, vitamin A intake; 585 ± 209 µg in females and 825 ± 263 µg in males, and folate intake; 230 ± 78 µg in females and 215 ± 29 µg in males.

The males had a lower vitamin C mean ± SD intake from 24-hour recall; 60 ± 57 mg and 7-day food record; 65 ± 35 mg than recommended reference values. Females had a lower than recommended ± SD intake of iron for the 24-hour recall; 8.7 ± 2.7 mg and 7-day food record; 8.6 ± 1.9 mg. Males also had a lower than recommended mean ± SD iron intake from the 7-day food record; 8.0 ± 0.8 mg. Furthermore, females had lower than recommended mean ± SD calcium intake for the 7-day food record; 782 ± 251 mg. Saturated fat intake was higher than recommended for 27 (87 %) of the participants for the 24-hour recalls and 19 (95 %) of the intakes from the 7-day food records.

All the participants, except 1 (3%) patient from the 24-hour recall, had low vitamin D intakes. Furthermore, 13 (42 %) from the 24-hour recall and 8 (40 %) of the participants from the 7-day food record had low calcium intake. For iron intake age specific recommended reference values was used for each participant, and intake was low in 24 (77 %) of the participants from 24-hour recall and 17 (85 %) from the 7-day food record. Fibre intake was low in 22 (71 %) and 16 (80 %) of participants from 24-hour recall and 7-day food record respectively.

Iodine intake was low in 21 (68 %) and 13 (65 %) of participants from 24-hour recall and 7-day food record respectively. Only 1 (3 %) had low B12 intake for the 24-hour recall and none for from 7-day food record.

Table 14. Nutrient intake from 24-hour recall (n=31) and 7-d-food record (n=20) compared to reference values for healthy females and males.

Nutrients		24-hour recall, mean ± SD	E%	< ref (%)	> ref (%)	7-d food record mean ± SD	E%	< ref (%)	> ref (%)	Reference
Calories (kcal)	F	1880 ± 400	-	-	-	1790 ± 298	-	-	-	– kcal
	M	2226 ± 648	-			2291 ± 541	-			
Fat (g)	F	84 ± 28	39	1 (3)	14 (45)	77 ± 19	39	0 (0)	8 (40)	25-40 E%
	M	94.0 ± 39.9	37			100 ± 20	41			
Saturated fat (g)	F	32 ± 11	15	4 (13)	27 (87)	29 ± 8	15	1 (5)	19 (95)	<10 E%
	M	34.3 ± 21.0	13			41 ± 13	16			
MUFA (g)	F	31 ± 13	15	4 (13)	4 (13)	28 ± 8	14	0 (0)	0 (0)	10-20 E%
	M	36.7 ± 14.7	14			36.3 ± 6.5	14			
PUFA (g)	F	13.0 ± 7.2	6	12 (39)	3 (61)	12 ± 4	6	5 (25)	0 (0)	5-10 E%
	M	15.8 ± 7.1	6			13.7 ± 3.7	5			
Omega-3 (g)	F	2.2 ± 1.2	1	17 (55)	14 (45)	2.6 ± 1.2	1	8 (40)	12 (60)	1 E%
	M	3.2 ± 2.5	1			2.7 ± 0.9	1			
Omega-6 (g)	F	10.6 ± 6.1	5	18 (58)	13 (42)	9.7 ± 2.7	5	14 (70)	6 (30)	5 E%
	M	12.2 ± 5.7	5			10.5 ± 2.4	4			
CHO (incl fibre) (g)	F	203 ± 55	43	16 (52)	0 (0)	194 ± 31	42	11 (55)	0 (0)	45-60 E%
	M	270 ± 82	49			243 ± 92	41			
Starch (g)	F	110 ± 39	-	-	-	102 ± 27	-	-	-	–
	M	116 ± 25	-			121 ± 22	-			
Sugar (g)	F	28 ± 31	6			23 ± 15	5			<10 E%

	M	79.2 ± 79	14	23 (74)	8 (26)	66 ± 68	12	16 (80)	4 (20)	
Fibre (g)	F	21 ± 5.7	-	22 (71)	0 (0)	20 ± 5	-	16 (80)	0 (0)	25 – 35 g
	M	21 ± 5.8	-			16.4 ± 1.4	-			
Protein (g)	F	79.5 ± 19	16	2 (6)	4 (13)	82 ± 18	19	0 (0)	3 (15)	10-20 E%
	M	82.2 ± 29	14			88 ± 14	16			
Salt (g)	F	6.7 ± 2.1	-	12 (39)	19 (59)	6.8 ± 2.1	-	9 (45)	11 (55)	<6 g
	M	7.2 ± 2.0	-			10.1 ± 3.9	-			
Vitamin A (RAE)	F	672 ± 322	-	23 (74)	8 (26)	585 ± 209	-	13 (65)	7 (35)	700 RAE
	M	454 ± 206	-			825 ± 263	-			900 RAE
Vitamin D (µg)	F	4.1 ± 2.6	-	30 (97)	1 (3)	4.1 ± 2.4	-	20 (100)	0 (0)	10 µg
	M	7.1 ± 8.2	-			5.7 ± 2.9	-			
Vitamin E (alfa-TE)	F	13.6 ± 7.3	-	5 (16)	26 (84)	11.8 ± 3.3	-	1 (5)	19 (95)	8 alfa-TE
	M	13.7 ± 5.3	-			14.2 ± 3.0	-			
Thiamine (mg)	F	1.55 ± 0.9	-	11 (35)	20 (65)	1.3 ± 0.3	-	3 (15)	17 (85)	1.1 mg [a]
	M	1.5 ± 0.7	-			1.5 ± 0.2	-			1.3 mg [a]
Riboflavin (mg)	F	1.6 ± 0.5	-	7 (23)	24 (77)	1.5 ± 0.4	-	5 (25)	15 (75)	1.2 mg [b]
	M	3.1 ± 2.6	-			2.9 ± 1.8	-			1.5 mg [b]
Niacin (mg)	F	14.8 ± 5.8	-	-	-	16.5 ± 4.6	-	-	-	–
	M	33 ± 32	-			31 ± 21	-			
Vitamin B6 (mg)	F	1.3 ± 0.4	-	11 (35)	20 (65)	1.4 ± 0.4	-	8 (40)	12 (60)	1.2 mg [c]
	M	2.1 ± 1.3	-			1.9 ± 0.8	-			1.5 mg [c]
Folate (µg)	F	248 ± 82	-	22 (71)	9 (29)	230 ± 78	-	18 (90)	2 (10)	300 µg
	M	205 ± 76	-			215 ± 29	-			
Vitamin B12 (µg)	F	5.2 ± 2.4	-	1 (3)	30 (97)	5.3 ± 2.1	-	0 (0)	20 (100)	2 µg
	M	8.7 ± 5.8	-			7.9 ± 3.6	-			
Vitamin C (mg)	F	104 ± 73	-	14 (45)	17 (55)	85 ± 53	-	10 (50)	10 (50)	75 mg
	M	60 ± 57	-			65 ± 35	-			
Calcium (mg)	F	868 ± 354	-	13 (42)	18 (58)	782 ± 251	-	8 (40)	12 (60)	800 mg
	M	875 ± 360	-			948 ± 403	-			
Iron (mg)	F	8.7 ± 2.7	-	24 (77)	7 (23)	8.6 ± 1.9	-	17 (85)	3 (15)	15 mg [d]
	M	9.2 ± 4.0	-			8.0 ± 0.8	-			9 mg [d]
Sodium (mg)	F	2704 ± 821	-	9 (29)	22 (71)	2663 ± 779	-	6 (30)	14 (70)	<2300 mg
	M	2960 ± 828	-			4077 ± 1550	-			
Potassium (mg)	F	3071 ± 783	-	19 (61)	12 (39)	3049 ± 887	-	13 (65)	7 (35)	3100 mg
	M	3338 ± 1066	-			2887 ± 469	-			3500 mg
Magnesium (mg)	F	301 ± 77	-	13 (42)	18 (58)	294 ± 70	-	8 (40)	12 (60)	280 mg
	M	304 ±119	-			283 ± 24	-			350 mg
Zinc (mg)	F	10.2 ± 3.3	-	7 (23)	24 (77)	9.6 ± 2.2	-	1 (5)	19 (95)	7 mg
	M	10.7 ± 5.2	-			10.5 ± 2.2	-			9 mg
Selenium (µg)	F	55 ± 43	-	20 (65)	11 (35)	52 ± 21	-	10 (50)	10 (50)	50 µg
	M	54 ± 29	-			56 ± 16	-			60 µg
Iodine (µg)	F	199 ± 202	-	21 (68)	10 (32)	153 ± 111	-	13 (65)	7 (35)	150 µg
	M	100 ± 51	-			164 ± 47	-			

Table shows mean with standard deviation and percentage of nutrient intake contributing to energy intake shown as E%. The table shows reference values for all age groups except for [a, b, c, d] are reference values for 31-60 years.[66] *Abbreviations*: Monounsaturated fat (MUFA), polyunsaturated fat (PUFA), CHO= carbohydrates, retinol activity equivalent (RAE). 1 RAE = 1 µg retinol. Above or below reference is referred to as > or < ref and includes both genders.

4.3.1 24-hour recall and fatigue scores

To test for any correlation between nutrient intake and fatigue, correlation coefficients were calculated for all the nutrients included in the 24-hour recall with fatigue scores from RAID, BRAF-MDQ and RAND 12. Only the nutrients that showed a statistically significant correlation with one or more of the fatigue scores were included in Table 15. A complete list of correlation coefficients for all nutrients can be found in the Appendix VI. Calculations were done for genders combined due to small differences in intake and low sample size for the males (n=7).

There was a statistically significant positive correlation between RAID fatigue scores and percentage saturated fat intake (r 0.374, p=0.046). There was a statistically significant negative correlation between fatigue score from RAID with intake of PUFA (r -0.421, p=0.023), omega-3 (r -0.364, p=0.036), and omega-6 (r -0.388, p=0.038), suggesting that lower intakes of these unsaturated fatty acids is associated with higher fatigue scores. No statistically significant correlations were seen between RAND 12 vitality/fatigue score and nutrient intake from the 24-hour recall.

There was a statistically significant positive correlation between saturated fat in grams (r 0.387, p=0.038), and as percentage of energy intake (r 0.465, p=0.011) for the emotional fatigue category, and total fatigue score for percentage saturated fat intake (r 0.411, p=0.027) of BRAF-MDQ. Hence, suggesting that high saturated fat intake is associated with higher fatigue scores. Increased intake of PUFA also significantly correlated with decreased BRAF-MDQ score for physical fatigue (r -0.422, p=0.023) and living with fatigue (r -0.384, p=0.040). While omega-3 (r -0.378, p=0.043) and omega-6 (r -0.379, p=0.043) intake also showed negative correlation with physical fatigue.

Furthermore, carbohydrate intake negatively correlated with cognitive fatigue (r -0.513, p=0.01), and physical fatigue (r -0.392, p=0.035) and starch intake also negatively correlated with physical fatigue (r -0.378, p=0.043), suggesting there might be a relationship between low carbohydrate intake and higher fatigue score. Furthermore, sodium (r 0.383, p=0.040) and zinc (r 0.516, p=0.004) intake positively correlated with cognitive fatigue. Iodine negatively correlated with BRAF-MDQ scores for emotional fatigue (r -0.405, p=0.029), suggesting that a low intake correlates with higher fatigue scores.

Table 15. Correlation coefficients for RAID and BRAF-MDQ scores with nutrient intake from 24-hour recall in study population, n=29.

		RAID	BRAF-MDQ				
		Fatigue	Physical	Living	Cognition	Emotion	Total
Saturated fat (g)	r	0.199	0.128	0.176	0.303	0.387*	0.302
	p	0.302	0.508	0.360	0.110	**0.038**	0.111
Saturated fat E%	r	0.374*	0.335	0.340	0.333	0.465*	0.411*
	p	**0.046**	0.076	0.071	0.078	**0.011**	**0.027**
PUFA (g)	r	-0.421*	-0.422*	-0.384*	-0.053	-0.064	-0.342
	p	**0.023**	**0.023**	**0.040**	0.785	0.743	0.069
Omega-3 (g)	r	-0.391*	-0.378*	-0.308	-0.005	-0.163	-0.321
	p	**0.036**	**0.043**	0.104	0.978	0.399	0.090
Omega-6 (g)	r	-0.388*	-0.379*	-0.361	-0.042	-0.077	-0.305
	p	**0.038**	**0.043**	0.054	0.829	0.690	0.108
Carbohydrates (g)	r	-0.298	-0.392*	-0.326	-0.196	-0.141	-0.275
	p	0.116	**0.035**	0.085	0.307	0.466	0.149
Carbohydrates E%	r	-0.180	-0.275	-0.245	-0.513**	-0.339	-0.351
	p	0.351	0.149	0.200	**0.004**	0.072	0.062
Starch (g)	r	-0.309	-0.378*	-0.200	-0.135	-0.079	-0.241
	p	0.102	**0.043**	0.299	0.484	0.684	0.208
Sodium (mg)	r	-0.024	-0.129	-0.017	0.383*	0.254	0.054
	p	0.904	0.505	0.931	**0.040**	0.183	0.779
Zinc (mg)	r	0.185	0.075	0.293	0.516**	0.350	0.346
	p	0.336	0.698	0.122	**0.004**	0.063	0.066
Iodine (µg)	r	-0.139	-0.012	-0.249	-0.078	-0.405*	-0.163
	p	0.471	0.950	0.193	0.689	**0.029**	0.399

P (p-value). ** Correlation is significant at the 0.01 level (2-tailed).* Correlation is significant at the 0.05 level (2-tailed). *Abbreviations*: Poly unsaturated fatty acids (PUFA).

4.3.2 7-day food record and fatigue scores

Correlation coefficients were calculated for all nutrients from the 7-day food record that correlated with one or more categories of the fatigue questionnaires, seen in Table 16. There was a statistically significant negative correlation between RAID fatigue score and protein (r -0.478, p=0.039). Furthermore, fatigue scores from RAND 12 negatively correlated with omega-3 (r -0.594, p=0.007), vitamin D (r -0.503, p=0.028) and selenium intake (r -0.460, p=0.047), indicating that a low intake of these nutrients are associated with better overall fatigue scores, which is contradictory to the findings from the 24-hour recall.

BRAF-MDQ physical fatigue scores had a statistically significant negative correlation with saturated fat intake (g) (r -0.507, p=0.027). These findings correlated with data from the 24-hour recall. Fibre (r -0.458, p=0.049), protein (r -0.494, p=0.032), potassium (r -0.521, p=0.022), magnesium (r -0.515, p=0.024) and zinc (r -0.496, p=0.031) had a statistically significant negative correlation with "living with fatigue" category. Suggesting that a low

intake of these nutrients is associated with higher fatigue scores, however in the 24 hour-recall, high zinc intake was associated with higher fatigue scores. Furthermore, potassium intake had a statistically significant negative correlation with emotional fatigue (r -0.504, p=0.028), and iodine intake with total fatigue (r -0.473, p=0.041)

Table 16. Correlation coefficients for RAID, BRAF-MDQ and RAND 12 with nutrient intake from 7-day food record in study population, n=19.

		RAID	BRAF-MDQ				RAND 12
		Fatigue	Physical	Living	Emotion	Total	VT
Saturated fat (g)	r	-0.433	-0.507*	-0.277	-0.042	-0.308	-0.255
	p	0.064	**0.027**	0.250	0.888	0.199	0.716
Omega-3 (g)	r	-0.039	0.083	-0.034	0.016	0.091	-0.594**
	p	0.873	0.734	0.891	0.948	0.710	**0.007**
Fibre (g)	r	-0.229	-0.180	-0.458*	-0.212	-0.303	0.045
	p	0.346	0.462	**0.049**	0.384	0.207	0.856
Protein (g)	r	-0.478*	-0.353	-0.494*	-0.233	-0.369	-0.109
	p	**0.039**	0.138	**0.032**	0.337	0.120	0.656
Vitamin D (µg)	r	-0.430	-0.321	-0.166	0.150	-0.211	-0.503*
	p	0.066	0.181	0.497	0.539	0.385	**0.028**
Potassium (mg)	r	-0.323	-0.235	-0.521*	-0.504*	-0.434	0.083
	p	0.177	0.334	**0.022**	**0.028**	0.063	0.736
Magnesium (mg)	r	-0.387	-0.337	-0.515*	-0.426	-0.408	0.000
	p	0.101	0.158	**0.024**	0.069	0.083	0.998
Zinc (mg)	r	-0.312	-0.367	-0.496*	-0.107	-0.344	-0.001
	p	0.193	0.122	**0.031**	0.664	0.149	0.995
Selenium (µg)	r	-0.164	-0.092	0.008	0.002	0.044	-0.460*
	p	0.503	0.708	0.972	0.994	0.858	**0.047**
Iodine (µg)	r	-0.347	-0.340	-0.447	-0.443	-0.473*	-0.035
	p	0.146	0.155	0.055	0.057	**0.041**	0.886

P (p-value). ** Correlation is significant at the 0.01 level (2-tailed).* Correlation is significant at the 0.05 level (2-tailed).

4.3.3 Underreporting

The revised Goldberg cut offs was used to determine the number of participants that underreported or overreported their energy intake as assessed by 24-hour recall or the 7-day food record. PALs ranging from 1.4 – 1.7 (low to higher activity levels) were used depending on the patients self-reported perception of activity level.

As seen in Table 17, there were 5 (16%) participants that underreported energy intake from 24-hour recall as in comparison to 11 (55%) participants underreporting from the 7-day food record. Furthermore, 26 (84 %) of the participants' dietary intake from the 24-hour recall was found to be plausible, while only 45% of reported dietary intake from the 7-day food record

was found to be plausible. In addition, none of the participants were found to have overreported dietary intake for any of the two methods used.

Table 17. Assessment of participants underreporting or overreporting dietary intake using revised Goldberg cut offs.

	24-hour recall n (%)	7-day food record n (%)
Under-reporters	5 (16)	11 (55)
Plausible reporters	26 (84)	9 (45)
Over-reporters	0 (0)	0 (0)

4.4 Anthropometric Measurements

The mean ± SD height and weight of the participants were; 171.2 ± 8.5 cm and 87.8 ± 17.2 kg respectively, with a mean ± SD BMI of 29.9 ± 5.1 (kg/m^2), seen in Table 18. In the total study population, 26 (84 %) participants were classified as overweight with a BMI over 25 kg/m^2, and no participants were considered underweight. Furthermore, 29 (94 %) of all the participants had a waist circumference (cm) above reference value and only 2 (6 %) met the reference criteria.

For the handgrip strength 5 females and 2 males were unable to perform the test due to arthritis in the hand/fingers or they received infusion. Furthermore, males had an overall higher HGS mean ± SD in dominant; 38.6 ± 13.3 kg, and non-dominant hand; 38.5 ± 14.1 kg than females who had a HGS mean ± SD of 23.4 ± 4.4 kg for dominant and 22.9 ± 5.8 kg for non-dominant hand.

Furthermore, 6 (25 %) participants had below reference value for HGS in dominant hand and 7 (30 %) participants had lower than recommended value for HGS in the non-dominant hand. Furthermore, there was no statistically significant difference between mean handgrip strength of the dominant compared to non-dominant hand ($p > 0.05$, CI 95% -0.82, 1.80).

Table 18. Anthropometric measurements in study population with number of participants above or below reference values.

	Sex	*N*	Mean ± SD	Min–Max	Reference Value	Below Reference *n* (%)	Above Reference *n* (%)
Height (cm)	All	31	171.2 ± 8.5	159 – 193	-	-	-
Weight (kg)	All	31	87.8 ± 17.2	53.2 – 131.9	-	-	-
BMI (kg/m^2)	All	31	29.9 ± 5.1	19.4 – 39.9	18.5–24.9	0 (0)	26 (84)
WC (cm)	M	7	105 ± 10.2	87 – 117.5	<94	1 (14)	6 (86)
	F	24	96.8 ± 13.4	69 – 130.5	<80	1 (4)	23 (96)
HGS dominant hand (kg)	M	5	38.6 ± 13.3	25.5 – 58.7	≥30[a]	2 (40)	3 (60)
	F	19	23.4 ± 4.4	12.7 – 30.2	≥20[b]	4 (21)	15 (79)
HGS non-dominant hand (kg)	M	5	38.5 ± 14.1	25.2 – 61.1	≥30[a]	2 (40)	3 (60)
	F	19	22.9 ± 5.8	10.2 – 31.1	≥20[b]	5 (26)	14 (74)

Mean with standard deviation and minimum and maximum values. *N*=sample size. *Abbreviations*: Waist circumference (WC), Handgrip strength (HGS), Body Mass Index (BMI). a Handgrip strength below 30 kg was considered below reference for males. b Handgrip strength below 20 kg was considered below reference for females.[67]

There was no correlation found between BMI, waist circumference and self-reported fatigue scores from RAID, BRAF-MDQ and RAND 12 as seen in Table 19. Males and females have different reference values for WC and HGS. Correlation coefficients were therefore calculated separately for gender, however due to low sample size for the males (n=7 for WC, n=5 for HGS) analyses that included both genders were also included.

Table 19. Correlation coefficients for RAID, BRAF-MDQ and RAND-12 scores with anthropometric measurements in study population.

			BMI (kg/m^2)	WC (cm)	HGS dominant Hand (kg)	HGS non-dominant hand (kg)
		Sex	**r**	**r**	**r**	**r**
RAID	Fatigue	F	-0.222	-0.125	0.131	0.216
		M	-0.130	0.130	0.266	0.339
		All	-0.188	-0.059	0.102	0.167
BRAF-MDQ	Physical	F	-0.216	-0.105	0.255	0.357
		M	-0.209	-0.036	0.564	0.564
		All	-0.158	-0.019	0.219	0.274
	Living	F	-0.047	0.030	0.168	0.150
		M	0.027	0.054	0.200	0.200
		All	-0.043	0.065	0.141	0.119
	Cognition	F	-0.218	-0.139	0.226	0.414
		M	-0.019	-0.111	0.051	0.051
		All	-0.224	-0.160	0.161	0.260
	Emotion	F	-0.216	-0.201	0.244	0.358
		M	0.123	-0.019	-0.224	-0.224
		All	-0.156	-0.098	0.172	0.261
	Total	F	-0.222	-0.142	0.316	0.463
		M	0.036	-0.036	0.200	0.200
		All	-0.181	-0.84	0.241	0.329
RAND 12	VT	F	0.175	-0.138	-0.071	-0.109
		M	-0.062	-0.309	-0.949	-0.949
		All	0.118	-0.191	-0.171	-0.235

Abbreviations: Waist circumference (WC), Handgrip strength (HGS), Body Mass Index (BMI). ** Correlation is significant at the 0.01 level (2-tailed).* Correlation is significant at the 0.05 level (2-tailed). HGS (females n=19, males, n=5), BMI (n=31), WC (females n=19, males n=7)

4.5 Body Composition Measurements

The participants in the study had their body composition measured by BIA and DXA as seen in Table 20. There was no missing data for the BIA measurements, but one male participant missed his DXA appointment.

BIA measurements showed that males had lower mean ± SD body fat percentage (M: 29.6 ± 9.0 %, F: 36.1 ± 5.7 %) and higher FFM mean ± SD (M: 71.4 ± 10.2 kg, F: 52.6 ± 6.3 kg), hence giving a slightly lower FMI mean ± SD (M: 17.1 ± 7.4 kg/m^2, F: 18.4 ± 5.7 kg/m^2), but higher FFMI mean ± SD (M: 39.0 ± 3.8 kg/m^2, F: 31.3 ± 3.5 kg/m^2) than females.

DXA measurements showed similar findings to BIA, hence males had a lower mean ± SD body fat percentage (M; 36.6 ± 10.3 %, F; 44.0 ± 5.9 %), higher mean ± SD muscle mass (M; 62.2 ± 8.2 kg, F; 44.9 ± 5.4 kg) and hence a lower FMI mean ± SD (M; 20.7 ± 8.6 kg/m^2, F;

21.7 ± 6.1 kg/m^2) and higher FFMI mean ± SD (M; 36.0 ± 2.8 kg/m^2, F; 28.2 ± 3.1 kg/m^2) than females.

The DXA measurements compared to BIA, showed higher FM (kg) and body fat percentage mean values, and lower FFM and muscle mass mean values. A paired sample t-test (not seen in table) showed a statistically significant difference between mean values of the DXA and BIA measurements of body fat percentage ($p<0.01$, 95% CI -8.5, -6.8), FM ($p<0.01$, 95% CI -6.5, -4.8), FFM ($p<0.01$, 95% CI -6.4, -4.5), and muscle mass ($p<0.01$, 95% CI -6.1, -4.3).

Table 20. Measurement of body composition by BIA and DXA in males and females.

		BIA			DXA		
	Sex	***N***	**Mean ± SD**	**Min–Max**	***N***	**Mean ± SD**	**Min–Max**
Fat mass (kg)	M	6	30.9 ± 12.5	16.5 – 52.7	7	37.4 ± 14.9	18.4 – 56.8
	F	24	30.9 ± 9.8	12.3 – 55.5	24	36.4 ± 10.5	15.8 – 61.9
Body fat percentage	M	6	29.6 ± 9.0	19.5 – 47.2	7	36.6 ± 10.3	22.6 – 52.1
	F	24	36.1 ± 5.7	23.1 – 45.1	24	44.0 ± 5.9	30.3 – 52.1
Muscle mass (kg)	M	6	67.8 ± 9.7	55.9 – 85.2	7	62.2 ± 8.2	52.2 – 73.8
	F	24	49.9 ± 6.0	38.8 – 64.1	24	44.9 ± 5.4	36.3 – 56.9
FFM (kg)	M	6	71.4 ± 10.2	58.9 – 89.6	7	65.6 ± 8.6	55.0 – 78.0
	F	24	52.6 ± 6.3	40.9 – 67.5	24	47.3 ± 5.6	38.5 – 59.5
FMI (kg/m^2)	M	6	17.1 ± 7.4	9.0 – 31.3	7	20.7 ± 8.6	10.0 – 33.7
	F	24	18.4 ± 5.7	7.4 – 31.6	24	21.7 ± 6.1	9.6 – 35.3
FFMI (kg/m^2)	M	6	39.0 ± 3.8	34.9 – 46.4	7	36.0 ± 2.8	32.6 – 40.4
	F	24	31.3 ± 3.5	24.4 – 38.4	24	28.2 ± 3.1	22.3 – 33.9

Data shown as mean with standard deviation and maximum and minimum values. *Abbreviations*: Fat free mass (FFM), Fat mass index (FMI), Fat free mass index (FFMI).

Furthermore, as seen in Table 21, none of the participants were categorized as malnourished according to body mass composition. For the female participants, 23 (96 %) had a high FMI according to BIA measurements, and all female participants had high FMI according to data from DXA measurements.

All males also had FMI above reference values for both BIA and DXA measurements, but there was one missing value for the DXA data. However, the missing data was from a male participant that had very high values for both FMI and FFMI from BIA, it can be assumed that he would meet the same criteria for the DXA measurements. All participants were considered to have very high FFMI values.

Table 21. Body composition measured as low, normal, high, and very high fat mass index (FMI; kg/m2), and fat-free mass index (FFMI; kg/m2) by BIA and DXA in males and females.

		FMI BIA (%)	FMI DXA (%)	FFMI BIA (%)	FFMI DXA (%)
Women	Low	0 (0)	0 (0)	0 (0)	0 (0)
	Normal	1 (4)	0 (0)	0 (0)	0 (0)
	High	4 (17)	1 (4)	0 (0)	0 (0)
	Very High	19 (79)	23 (96)	24 (100)	24
Total		24	24	24	24
Men	Low	0 (0)	0 (0)	0 (0)	0 (0)
	Normal	0 (0)	0 (0)	0 (0)	0 (0)
	High	0 (0)	0 (0)	0 (0)	0 (0)
	Very High	7 (100)	6 (86)	7 (100)	6 (86)
Total		7	6	7	6

Low FMI: <1.8 (M), <3.9 (W). Normal FMI: 1.8–5.1 (M), 3.9–8.1 (W). High FMI: 5.2–8.2 (M), 8.2–11.7 (W). Very high FMI: ≥8.3 (M), ≥11.8 (W). Low FFMI: <16.7 (M), <14.6 (W). Normal FFMI: 16.7–19.7 (M), 14.6–16.7 (W). High FFMI: 19.8–21.6 (M), 16.8–18.1 (W). Very high FFMI ≥21.7 (M), ≥18.2 (W).[68] Fat free mass (FFM), Fat mass index (FMI), Fat free mass index (FFMI).

No statistically significant correlation between fatigue and body composition was found except for FFM, muscle mass (kg), and FFMI in males for the VT category of the RAND 12 questionnaire (r -0.894, p=0.041) as shown in appendix VII. However, the sample size for males was very low (n=5).

4.6 Clinical parameters

Blood tests and blood pressure measurements are shown in Table 22. There was one missing value for haemoglobin and cholesterol due to invalid test values, and one participant did not have their blood pressure recorded.

None of the participants had blood test values below reference for albumin, B12, glucose, ESR, or thyroxine hormone (fT4). One (4 %) female had below reference value for haemoglobin and 2 (8 %) females, independent of the female with low haemoglobin level, had low ferritin levels.

Furthermore, 10 (32 %) participants had vitamin D levels below reference and 3 (10 %) had low folate levels. For total cholesterol and LDL, 21 (70 %) and 23 (74 %) participants respectively, had higher than recommended levels. The reference values used were values considered as increasing the risk for cardiovascular diseases. In addition, 14 (47 %)

participants had high SBP and 13 (43 %) had high DBP. CRP and ESR was high in 7 (23 %) and 2 (8 %) participants respectively.

The mean ± values of cholesterol, LDL, SBP, and DBP were higher than reference values; 5.3 ± 0.7 mmol/L, 3.5 ± 0.7 mmol/L, 125 ± 13 mmHg, and 82 ± 9 mmHg respectively.

Table 22. Measurement of clinical parameters in study population including blood tests and blood pressure.

	Sex	*N*	Mean ± SD	Min–Max	Reference Value	Below Reference *n* (%)	Above Reference *n* (%)
Haemoglobin	M	7	15.0 ± 1.4	13.5 – 17.6	13,4 - 17,0	0 (0)	1 (14)
	F	23	13.3 ± 1.0	11.1 – 15.1	11,7 - 15,3	1 (4)	0 (0)
Ferritin	M	7	255 ± 127	51 – 461	34 – 300	0 (0)	3 (43)
	F	24	93.8 ± 50.8	10 – 196	18–240	2 (8)	0 (0)
ESR (mm/t)	M	7	5.0 ± 3.7	1 – 11	1–20 [a]	0 (0)	0 (0)
	F	24	14.3 ± 9.2	2 – 34	1–30 [a]	0 (0)	2 (8)
CRP (mg/L)	All	31	3.84 ± 4.0	1 – 19	< 5	-	7 (23)
Homocysteine (µmol/L)	All	31	10.9 ± 3.1	5.3 – 20.2	< 15	-	2 (6)
MMA (µmol/L)	All	31	0.16 ± 0.08	0.1 – 0.49	< 0.26	-	2 (6)
TSH (mIU/L)	All	31	1.73 ± 0.97	0.36 – 4.57	0,40-4,50 [b]	1 (3)	1 (3)
fT4 (pmol/L)	All	31	16.2 ± 2.9	11.7 – 25.2	9,5-22,0 [c]	0 (0)	2 (6)
Albumin (g/L)	All	31	44.4 ± 3.2	40 – 57	39 – 50 [d]	0 (0)	1 (3)
Glucose (mmol/L)	All	31	5.5 ± 0.6	4.3 – 6.7	4,0 - 6,0	0 (0)	4 (13)
Cholesterol (mmol/L)	All	30	5.3 ± 0.7	4.1 – 7.2	< 5 [f]	-	21 (70)
HDL (mmol/L)	M	7	1.4 ± 0.4	1 – 1.9	0,8 - 2,1	0 (0)	0 (0)
	F	24	1.66 ± 0.4	0.8 – 2.8	1,0 - 2,7	0 (0)	1 (4)
LDL (mmol/L)	All	31	3.5 ± 0.7	2.3 – 5.3	< 3 [f]	-	23 (74)
TAG (mmol/L)	All	31	1.37 ± 0.7	0.59 – 3.23	< 1,7 [f]	-	8 (26)
25-OH-vit D	All	31	59.0 ± 20.6	22.0 – 111.0	50–113	10 (32)	0 (0)
Folate (nmol/L)	All	31	24.5 ± 14.1	4.8 – 45.3	< 10	3 (10)	-
B12 (pmol/L)	All	31	435 ± 165	256 – 1024	175 – 700 [e]	0 (0)	2 (6)
SBP (mmHg)	All	30	125 ± 13	105 – 150	≤ 120	-	14 (47)
DBP (mmHg)	All	30	82 ± 9	70 – 98	≤ 80	-	13 (43)

Data shown as mean with standard deviation and minimum and maximum values with number of participants below or above reference values. An age-specific references exist, here all age groups considered. b/c Reference values >20 år. d Age-specific references exist, here all age groups considered. e. Reference value ≥18 år. f. For cholesterol values, risk of cardiovascular disease reference values has been used. *Abbreviations*: fT4=free thyroxine, MMA=methylmalonic acid. Vitamin D=25-OH-vit D, TSH=thyroid stimulating hormone. LDL=low density lipoprotein, HDL=high density lipoprotein, TAG=triglycerides, SBP=systolic blood pressure, DBP=diastolic blood pressure. Reference values taken from "Analyseoversikten".[69]

There was no statistically significant correlation between any of the clinical parameters and fatigue scores from the RAID questionnaire and the "physical", "cognitive", and "emotional" fatigue category of BRAF-MDQ. Hence, the correlation coefficients for these categories were not included in Table 23, but can be seen in **appendix VIII**.

Vitamin D significantly correlated with fatigue scores of the RAND 12 VT category (r -0.546, p=0.003). For scores reported from BRAF-MDQ, there was a negative statistically significant correlation between "living with fatigue" (r -0.431, p=0.020) and HDL, suggesting that low serum HDL is associated with higher fatigue scores. Furthermore, there was a negative statistically significant correlation between SBP (r -0.383, p=0.044) for total fatigue of BRAF-MDQ, suggesting that as blood pressure increases total fatigue decreases.

Table 23. Correlation coefficients for BRAF-MDQ and RAND 12 scores with clinical parameters in study population, n=29.

		BRAF-MDQ		RAND 12
		Living	Total	VT
Haemoglobin	r	0.103	0.059	-0.079
Ferritin	r	-0.040	-0.046	-0.065
ESR (mm/t)	r	-0.200	-0.142	0.087
CRP (mg/L)	r	-0.153	-0.151	-0.256
Homocysteine (µmol/L)	r	-0.197	-0.329	0.090
MMA (µmol/L)	r	-0.011	-0.006	-0.041
TSH (mIU/L)	r	0.076	0.139	0.176
fT4 (pmol/L)	r	-0.028	-0.038	-0.338
Albumin (g/L)	r	0.182	0.231	0.014
Glucose (mmol/L)	r	0.047	-0.022	0.057
Cholesterol (mmol/L)	r	0.060	-0.127	0.284
HDL (mmol/L)	r	-0.431*	-0.348	0.131
	p	**0.020**	0.064	0.507
LDL (mmol/L)	r	0.151	-0.054	0.243
TAG (mmol/L)	r	0.243	0.155	0.034
25-OH-vit D	r	-0.161	-0.023	-0.546**
	p	0.403	0.905	**0.003**
Folate (nmol/L)	r	-0.041	0.177	-0.154
B12 (pmol/L)	r	0.200	0.170	-0.089
SBP (mmHg)	r	-0.332	-0.383*	0.103
	p	0.084	**0.044**	0.610
DBP (mmHg)	r	-0.085	-0.126	-0.127

** Correlation is significant at the 0.01 level (2-tailed).* Correlation is significant at the 0.05 level (2-tailed). *Abbreviations*: p=p-value, fT4=free thyroxine, MMA=methylmalonic acid. Vitamin D=25-OH-vit D, TSH=thyroid stimulating hormone. LDL=low density lipoprotein, HDL=high density lipoprotein, TAG=triglycerides, SBP=systolic blood pressure, DBP=diastolic blood pressure.

4.7 Bone Mineral Density using DXA

Bone density was measured in the femoral neck, total hip and lumbar column (L1-L4). T-score ≤ -2.5 in lumbar spine, femoral neck or total right and left hip with DXA was diagnostic for osteoporosis. A T-score of -1,0 to -2,5 was classified as osteopenia. A Z-score compares BMD with a reference population with the same age, and gender, and a Z-score ≤ -2.0 were used for patients who were under 50 years of age.

In Table 24, there were 30 (97 %) patients out of 31 total participants that had a DXA scan, and 11 (37 %) had osteopenia, and 1 (3 %) participant that had osteopenia also had osteoporosis. No participants under the age of 50 had a Z-score ≤ -2.0.

Table 24. Bone mineral density in the lumbar spine, femoral neck, and total hip, and incidence of osteopenia and osteoporosis in the study population, n=30.

BMD		Median (min-max)	Osteopenia n (%)	Osteoporosis n (%)
Z-score	Spine L1- L4	0.05 (-1.5 to 2.6)	-	-
	Left femoral neck	0.2 (-1.7 to 1.4)	-	-
	left hip	0.45 (-1.7 to 2.4)	-	-
	right femoral neck	0.05 (-1.5 to 1.4)	-	-
	right hip	0.1 (-1.5 to 2.2)	-	-
T-score	Spine L1- L4	-0.35 (-2.5 to 1.9)	5 (17)	1 (3)
	left femoral neck	-0.65 (- 2.4 to 0.8)	9 (30)	0 (0)
	left hip	-0.2 (-1.9 to 1.5)	6 (20)	0 (0)
	right femoral neck	-0.8 (-2.1 to 1.3)	10 (33)	0 (0)
	right hip	-0.1 (-1.4 to 1.7)	6 (20)	0 (0)
Total			10 (33)	1 (3)

T-scores were used to determine the number of participants with osteopenia and osteoporosis.

Low BMD was defined as meeting criteria for either osteopenia or osteoporosis and in Table 25, self-reported use of vitamin D supplements or use of Calcigran forte with patient's BMD is listed. Two of the participants that reported use of vitamin D supplements had also been prescribed Calcigran Forte. However, for the rest of the study population self-reported use of vitamin D did not coincide with Calcigran Forte use or there was missing data preventing comparison of the supplement use and prescribed medication.

Out of the 10 patients with low (<50 nmol/L) serum 25(OH)vitamin D, only one patient had low BMD and did not report use of supplements. Out of 18 people that had normal serum 25(OH)vitamin D, there was a higher number of patients that reported use of supplements with low BMD (5 vs 4) as compared to those that did not report use of supplements.

Furthermore, 9 out of the 10 people that had low serum 25(OH)vitamin D, had not been prescribed Calcigran Forte, but had however, normal BMD. Out of the 10 Calcigran Forte users that had normal 25(OH)vitamin D levels, 5 (50 %) had low BMD. Furthermore, 4 (50 %) of the 8 patients that did not use Calcigran Forte, but had normal vitamin D levels, had low BMD.

Table 25. Self-reported use of vitamin D supplements and Calcigran Forte compared with vitamin D blood levels and Bone Mineral Density in study population, n=28.

Vitamin D level		Normal BMD	Low BMD
	Self-reported use:		
<50 nmol/L	Does not use supplements	8	1
	Use supplements	1	0
≥50 nmol/L	Does not use supplements	7	5
	Use supplements	2	4
	Calcigran Forte use:		
<50 nmol/L	No	9	1
	Yes	0	0
≥50 nmol/L	No	4	4
	Yes	5	5

To check for a difference in fatigue scores between patients with normal BMD and low BMD, a one-way ANOVA test was run with Welch test accounting for the unequal sample. Fatigue scores from RAID was used as the dependent variable. As shown in Table 26, the difference was significant, however the mean ± SD fatigue score was higher for the group with normal BMD; 4.3 ± 2.2 score, than low BMD; 2.6 ± 1.8 score, suggesting that fatigue is not affected by BMD.

Table 26. Bone Mineral Density of participants using Fatigue scores from RAID questionnaire.

		N	**Mean ± SD**
DXA	Normal	18	4.3 ± 2.2
	Low BMD	10	2.6 ± 1.8
p-value	0.036		

N: sample size.

To further test the association between BMD and fatigue, correlation coefficients were calculated from converting the raw BMD (T-scores) data and fatigue scores into statistical T-scores and performing the Pearson and Spearman's correlation test in SPSS, depending on which variable was normally distributed or not. However no statistically significant correlation was found between any of the variables as seen in Table 27.

Table 27. Correlation coefficients for T-scores with RAID, BRAF-MDQ, and RAND-12 scores in the study population, n=28.

			T-score				
			Spine L1-L4	Left femoral neck	Left hip	Right femoral neck	Right hip
RAID	Fatigue	r	0.151	0.233	0.195	0.292	0.252
BRAF-MDQ	Physical	r	0.095	0.213	0.210	0.288	0.242
	Living	r	0.099	0.181	0.194	0.167	0.209
	Cognition	r	-0.106	0.011	0.010	0.066	0.057
	Emotion	r	-0.041	0.128	0.129	0.145	0.162
	Total	r	0.049	0.185	0.188	0.227	0.220
RAID 12	VT	r	-0.059	0.116	0.061	0.003	-0.030

4.8 Disease Activity Measurements

Table 28 shows mean ±SD values for disease activity measures for RA, PsA and ax-SpA with reference values for what is considered remission or active disease activity. In total study population, DAS28 and DAS28-CRP(3) was measured in 25 (81 %) patients, with one missing data record for each measurement. All DAS28 measurements including CRP and PGA was measured in both RA and PsA patients. DAS28-CRP(4) including PGA, was measured in 23 (74 %) of the total 31 patients, with 3 missing records.

Furthermore, in the total study population 8 (26 %) PsA patients had DAPSA measured, and 5 (16 %) ax-SpA patients had ASDAS-CRP and BASDAI measured. Data from DAS28 and DAS28-CRP showed that 13 (52 %) patients had remission and 12 (48 %) active disease.

When DAS28-CRP(4) with PGA (patient's own perception of pain) was considered, the number of patients with remission was decreased to 11 (48 %), while 12 (52 %) had active disease. Furthermore, 6 (75 %) DAPSA and 4 (80 %) ASDAS-CRP and BASDAI measurements showed active disease.

Table 28. Measurement of disease activity in study population and number of participants in remission.

	N	Mean ± SD	Min–Max	Reference Value	Remission n (%)	Active disease n (%)
DAS28	25	2.6 ± 1.0	0.7 – 4.0	<2.6	13 (52)	12 (48)
DAS28-CRP(3)	25	2.5 ± 0.9	1.4 – 4.9	<2.6	13 (52)	12 (48)
DAS28-CRP(4)	23	2.7 ± 1.0	1.2 – 5.5	<2.6	11 (48)	12 (52)
DAPSA	8	17.1 ± 14.5	1.8 – 47.4	≤4	2 (25)	6 (75)
ASDAS-CRP	5	2.4 ± 0.8	1.1 – 3.3	<1.3	1 (20)	4 (80)
BASDAI	5	4.1 ± 2.8	0.8 – 8.2	<1.9	1 (20)	4 (80)

Mean values with standard deviation and minimum and maximum values. DAS28 is measurement of disease activity counting tender and swollen joints only. DAS28-CRP(3) includes swollen and tender joint counts and CRP. DAS28-CRP(4) also includes PGA=patient global assessment.

In Table 29, the correlation coefficients for the different disease activity measurements and fatigue scores were calculated. Furthermore, in this analysis, pain scores that were self-reported from the RAID questionnaire were included to test the strength of the relationship with disease activity and for comparison with fatigue scores.

DAS28 that measures tender and swollen joints only, did not correlate with fatigue scores. DAS28-CRP(3) had significant positive correlations with pain (r 0.601, p=0.003) and living with fatigue (r 0.458, p=0.028) from BRAF-MDQ. DAS28-CRP(4), showed a stronger correlation and had lower p value for pain (r 0.726, p=0.000), and living with fatigue (r 0.562, p=0.008), than DAS28-CRP(3).

Furthermore, DAS28-CRP(4) showed significant correlations with physical fatigue (r 0.562, p=0.008), and total fatigue (r 0.485, p=0.026) of BRAF-MDQ. DAS28-CRP(4) also correlated with RAID fatigue scores (r 0.542, p=0.011) and RAND12 VT (-0.566, p=0.005).

DAPSA measurements correlated statistically significant with BRAF-MDQ “living with fatigue” (r 0.744, p=0.034) and pain scores (r 0.771, p=0.025). ASDAS-CRP had high correlation coefficients for fatigue scores, however they were not statistically significant. Furthermore, BASDAI scores did not correlate with any of the fatigue scores, but very strongly correlated with pain (r 0.918, p=0.028).

Table 29. Correlation between disease activity and RAID, BRAF-MDQ, and RAND 12 in study population.

			DAS28	DAS28-CRP (3)	DAS28-CRP (4)	DAPSA	ASDAS-CRP	BASDAI
			n=25	n=25	n=23	n=8	n=5	n=5
RAID	Pain	r	0.232	0.601**	0.726**	0.771*	0.822	0.918*
		p	0.147	**0.003**	**0.000**	**0.025**	0.088	**0.028**
	Fatigue	r	0.006	0.380	0.542*	0.631	0.844	0.799
		p	0.979	0.074	**0.011**	0.094	0.072	0.105
BRAF-MDQ	Physical	r	0.073	0.384	0.562**	0.656	0.793	0.746
		p	0.740	0.070	**0.008**	0.078	0.109	0.148
	Living	r	0.106	0.458*	0.562**	0.744*	0.536	0.421
		p	0.630	**0.028**	**0.008**	**0.034**	0.351	0.480
	Cognition	r	0.053	0.175	0.222	0.671	0.783	0.447
	Emotion	r	0.063	0.201	0.303	0.590	0.632	0.316
	Total	r	0.022	0.345	0.485*	0.702	0.739	0.599
		p	0.922	0.107	**0.026**	0.052	0.154	0.285
RAND12	VT	r	-0.207	-0.397	-0.566**	-0.642	-0.866	-0.577
		p	0.422	0.055	**0.005**	0.086	0.058	0.308

P (p-value). ** Correlation is significant at the 0.01 level (2-tailed).* Correlation is significant at the 0.05 level (2-tailed).

4.9 Other potential predictors of fatigue

In Table 30, other potential predictors of fatigue were analysed by calculating Pearson and Spearman's correlation coefficients. Age did not significantly correlate with any of the fatigue scores reported in the table. MHAQ scores had a positive significant correlation with RAID fatigue (r 0.432, p=0.019) and physical fatigue (r 0.442, p=0.016), suggesting that patients that are more physical disabled also have higher fatigue scores.

Furthermore, pain correlated with RAID fatigue (r 0.534, p=0.003), physical fatigue (r 0.489, p=0.008), living with fatigue (r 0.417, p=0.027), total fatigue (r 0.393, p=0.038) and VT (fatigue) (r -0.483, p=0.014). Sleep was found to correlate with all the fatigue scores, except cognitive fatigue. Sleep also showed the strongest overall correlations with fatigue; RAID fatigue (r 0.540, p=0.003), BRAF-MDQ "physical" (r 0.606, p=0.001), "living" (r 0.654, p=0.000), "emotional" (r 0.555, p=0.002), and "total fatigue" (r 0.620, p=0.000), RAND 12 (r -0.402, p=0.046).This suggests that patients with high pain scores and sleep disturbances have higher levels of fatigue.

Table 30. Other factors including age, and correlation coefficients for fatigue scores from RAID, BRAF-MDQ and RAND 12, n=28.

			MHAQ	Pain	Sleep	Age
RAID	Fatigue	r	0.432*	0.534**	0.540**	-0.316
		p	**0.019**	**0.003**	**0.003**	0.095
BRAF-MDQ	Physical	r	0.442*	0.489**	0.606**	-0.352
		p	**0.016**	**0.008**	**0.001**	0.061
	Living	r	0.218	0.417*	0.654**	-0.169
		p	0.257	**0.027**	**0.000**	0.380
	Cognition	r	0.053	0.210	0.363	-0.208
	Emotion	r	-0.001	0.222	0.555**	-0.237
		p	0.996	0.257	**0.002**	0.215
	Total	r	0.230	0.393*	0.620**	-0.276
		p	0.229	**0.038**	**0.000**	0.148
RAND12	VT	r	-0.145	-0.483*	-0.402*	-0.007
		p	0.470	**0.014**	**0.046**	0.973

P (p-value). ** Correlation is significant at the 0.01 level (2-tailed).* Correlation is significant at the 0.05 level (2-tailed).

In Table 31, mean ± SD fatigue scores for variables categorized into groups based on education, physical activity, household income, and medication were calculated. Welch's Test for Unequal Variances was used to test for any significant differences. However, no statistical difference was seen.

Table 31. Mean difference between fatigue scores based on education, physical activity, household income, and medication in study population.

			RAID	BRAF-MDQ	
		N	**Fatigue**	**Physical**	**Total**
Education	Primary or high school, or certificate of apprenticeship	8	4.3 ± 2.3	10.4 ± 5.4	22.2 ± 11.4
	College/university < 4 years	15	3.5 ± 2.4	7.6 ± 5.7	17.9 ± 14.3
	College/University, > 4 years	4	4.3 ± 2.4	11 ± 5.4	18.8 ± 10.3
Physical Activity	1 time/week or less	6	3.8 ± 3.3	8.8 ± 8.0	18.8 ± 17.5
	2-3 times/week	13	3.8 ± 1.9	9.6 ± 4.5	19.0 ± 9.4
	Almost every day	10	3.9 ± 2.3	8.5 ± 5.3	19.7 ± 13.4
Household Income	≤ 750 000 NOK	10	3.5 ± 2.1	8.4 ± 4.2	22.1 ± 12.4
	> 750 000 NOK	17	4.0 ± 2.4	9.3 ± 6.3	17.6 ± 12.9
Medication	No DMARDs	5	4.0 ± 1.9	8.4 ± 5.0	23.6 ± 15.7
	cDMARD	6	4.0 ± 2.4	9.4 ± 5.0	15.4 ± 8.9
	bDMARD	8	3.6 ± 3.1	9.5 ± 7.4	19.1 ± 14.8
	Both	10	3.9 ± 1.8	9.0 ± 4.1	19.9 ± 10.1

Abbreviation: cDMARD= conventional disease-modifying antirheumatic drugs. bDMARD= biologic disease-modifying antirheumatic drugs

Furthermore, the Eta Coefficient test, that measures the strength of a relationship when one of the variables is categorical was also performed. Eta correlation value ranges from zero, which means no association, to one which means perfect or strong association. Hence, eta calculation showed no strong relationship between physical activity (0.026), income (0.107), and medication (0.070) with fatigue scores for RAID.

4.10 Multiple linear regression

Multiple linear regression analyses included predictor variables significantly associated with the fatigue scores in correlation analyses. Since disease activity and pain were found to correlate with fatigue scores, the relationship between these predictors were investigated in a multi-variable analysis in Table 32. DAS28-CRP(3) without PGA was included as the measure of disease activity due to bigger sample could be included in analysis.

When both disease activity and pain were included as independent predictors of fatigue, only pain remained statistically significant with fatigue measured with RAID (β 0.707, p=0.003) and total fatigue from BRAF-MDQ (β 0.621, p=0.010). Furthermore, when investigating the effect of disease activity (β 0.398, p=0.020) and fatigue (β 0.529, p=0.003) as independent predictors of pain, both remained statistically significant in the multiple regression model, indicating an interconnecting relationship between pain and fatigue, pain, and disease activity, but not between fatigue and disease activity.

Table 32. Investigating the relationship between fatigue, disease activity and pain, n=22

Fatigue (RAID)		**BRAF-MDQ (Total)**		**Pain**	
Variable	**β (p-value)**	**Variable**	**β (p-value)**	**Variable**	**β (p-value)**
Adjusted r^2 = 0.409		Adjusted r^2 = 0.0.330		Adjusted r^2 = 0.558	
Pain	0.707** **(0.003)**	Pain	0.621* **(0.012)**	Fatigue	0.529** **(0.003)**
DAS28-CRP	-0.042 (0.843)	DAS28-CRP	-0.010 (0.966)	DAS28-CRP	0.398* **(0.020)**

Adjusted r^2: adjusted for the number of predictors in the model. ** Correlation is significant at the 0.01 level (2-tailed).* Correlation is significant at the 0.05 level (2-tailed). Pain was measured using the RAID questionnaire. For disease activity DAS28-CRP(3) was used without the patient perceived pain assessment.

4.10.1 All predictors and fatigue

At last, a multiple linear regression model was created with all the identified predictor values of fatigue that could be used in a regression model in Table 33. Predictors from the 24-hour recall were used in preference of 7-day food record due a larger sample size and coinciding data with the 7-day record, as some of the 24-hour recall days represented the last day of the 7-day food record. Hence, combining the data would lead to inaccuracy in the regression model.

In the multiple regression model PUFA intake was used to represent omega-3 and omega-6 intake as adding all the three variables together would result in high multicollinearity (the predictors are too highly correlated) making the model inaccurate.

For the fatigue scores from the RAID questionnaire, pain was the only variable that remained significantly associated with fatigue (β 0.624, p=0.029). For the total fatigue score from BRAF-MDQ questionnaire, none of the variables remained significant.

Table 33. Investigating the relationship between all the predictor variables on fatigue, n=21.

Fatigue (RAID)		**BRAF-MDQ (Total)**	
Variable	**β (p-value)**	**Variable**	**β (p-value)**
Adjusted r^2 = 0.324		Adjusted r^2 = 0.308	
Pain	0.624* (**0.029**)	Sleep	0.449 (0.065)
DAS28-CRP	-0.176 (0.511)	Saturated fat E%	0.073 (0.742)
Sleep	0.152 (0.497)	Pain	0.223 (0.447)
Saturated fat E%	0.083 (0.698)	SBP	-0.279 (0.204)
Polyunsaturated fat	-0.202 (0.341)	DAS28-CRP	0.059 (0.839)

Adjusted r^2: adjusted for the number of predictors in the model. ** Correlation is significant at the 0.01 level (2-tailed).* Correlation is significant at the 0.05 level (2-tailed). Pain and sleep were measured using the RAID questionnaire. For disease activity DAS28-CRP(3) was used without the PGA.

5 Discussion

The main aim of this study was to investigate if there is a relationship between dietary intake, nutritional status, and fatigue in patients with IRD. Although, unsaturated fat intake such as omega-3, omega-6 and total polyunsaturated fat correlated with less fatigue, and high saturated fat intake correlated with more fatigue, it was contradictory to findings from 7-day food record. Furthermore, correlations did not remain significant in multiple regression analysis, indicating less of a role of dietary intake in fatigue or flaws in data collection methods. Furthermore, anthropometrics and body composition were not associated with fatigue, arguably due to skewed sample size and absence of malnutrition. Although, not consistent across analyses, there seems to be a trend towards pain being associated with fatigue to a greater extent than other variables included in this study, such as nutrients, disease activity, and sleep as shown in multiple linear regression. The variables found to be significant in correlation analysis, including disease activity, sleep, saturated fat, and PUFA became non-significant when included in multiple linear regression analysis. Furthermore, the finding that pain often remained statistically significant in multiple regression analyses suggests that it is independently associated with fatigue. The identified predictors of fatigue from correlation and multiple regression analyses will be discussed further below.

5.1 Discussion of Methods

HGS has been found to correlate with functional ability and upper limb and hand function in patients with RA,[70] however it was not a reliable measurement in this study due to some patients suffering from arthritis in their hands, pain or were receiving infusion in their arm. Hence, all these factors may have affected performance along with the repeated HGS measures done, hence only one measurement should have been conducted.[71]

Furthermore, when considering body composition, the differences seen between BIA and DXA measurements indicates that BIA underestimates fat mass and overestimates fat free mass.[72] Hence, DXA was a more reliable measure that was used when investigating relationship between body composition and fatigue.

The 24-hour recall was not a reliable enough method to assess whether dietary intake was associated with fatigue, as one day is not representable of a patient's total dietary intake and

risk of recall bias. In addition, 7-day food record was not an accurate dietary assessment method, due to underreporting and variation in patient reported intake. Underreporting was calculated to represent 16 % of the dietary intake from the 24-hour recall in comparison to 55 % of dietary intake from 7-day food record. Hence, dietary intake from 24-hour recall was a more accurate and reliable measurement than the 7-day food record. Similar finding was found in a systematic review evaluating dietary assessment methods. Underreporting was common for all methods, but 24-hour recalls showed lowest level of variation and underreporting ranging from 8-30 %, as compared to 11–41% for food records.[73] Therefore, when interpreting the result from nutrient intake, more weight was put on data from the 24-hour recall. Nevertheless, dietary intake measured over 4-7 days is recommended as it reflect dietary intake more accurately.[74] Therefore, more precise guidelines on how to record 7-day food intake should have been given to the participants. To improve data collection a reminder should have been sent out to each participant a week before submitting the 7-day food record.

Many of the patient consultations landed on a Monday, meaning data from 24-hour recall would be from Sunday, usually not a representative day of the week for most people. The 24-hour recall included a question whether the recall was a representative day of the week, however it was not always asked and therefore not included in the analysis. Furthermore, "kostholdsplanleggeren" lacked many of the food items consumed, making it hard to find replacements and do accurate estimations of nutrient intake.

5.2 Limitations

The study sample size and missing data are considered a big limitation. Analyses for body composition and anthropometrics had to be split into gender, and in combination with missing data for these measurements, it lowered the sample size even further. Any significant result for gender may therefore have been missed. In addition, no control group was included in study population.

Furthermore, it is possible that our study population is not a representative population of fatigue and malnutrition in IRD as inpatients were not included. Participants included in the study were recruited for the EROM project that lasts for one year, with many measurements and interventions, hence the patient burden is high. Therefore, the patients included in the study may have had better overall health compared to patients that decided not to participate.

Hence, patients with severe fatigue and disease activity may not be represented in this study as supported by the findings found from reported fatigue scores from BRAF-MDQ as only 3 (10%) reported total fatigue scores ≥ 35. When considering that severe fatigue was present in 41 to 57 % of rheumatic disease patients in the international study by Overman et al,[23] that included more than 6000 participants, and has also been reported to be present in as many as 80 % of RA patients.[20] Our study population may not be representative of fatigue in IRD. However, 11 (38 %) had RAID fatigue scores ≥ half of the max score, while 15 (54 %) were classified as having severe fatigue from RAND 12, hence there were great variances in fatigue scores depending on which questionnaire that was used.

It was a limitation that the dietary intake assessments, anthropometric and body composition measurements were conducted by three different people. Furthermore, fasting overnight was considered important before measuring blood lipid profile and was not properly controlled for. Hence, the impact non-fasting may have had on blood tests is unclear.

5.3 Discussion of Results

5.3.1 Dietary intake, nutritional status, and fatigue

In correlation analysis, higher saturated fat intake from 24-hour recalls correlated with lower fatigue scores for both the RAID questionnaire and BRAF-MDQ physical and total fatigue. Furthermore, lower fatigue scores correlated with higher intake of unsaturated fats such as PUFA, omega-3, and omega-6, although findings were not consistent across analysis. Although direct comparisons cannot be made, one study by Wahls et al,[75] found that use of low saturated fat diet or Palaeolithic elimination diet in MS patients, where processed foods are eliminated, were associated with within-group reduction in fatigue. Both the diets are low in saturated fats and high in unsaturated fats and suggests that alerting dietary nutrient content such as reducing saturated fat and increasing unsaturated fat intake can reduce MS related fatigue.[75] Future studies might want to investigate the effect of similar diets on fatigue scores in patients with IRD.

When considering omega-3 intake, one study looked at the effect of a daily intake of 3 grams of omega-3 for 12 weeks along with use of 75 mg indomethacin, a NSAID, while another

control group received indomethacin only. The omega-3 plus indomethacin treated group achieved a better improvement in terms of reducing disease activity than the control group along with improvements seen for pain score and in fatigue/vitality (VT) category for SF-36 measuring fatigue. However, both treatment and control group had improvements in disease activity, fatigue/vitality, and pain scores between baseline and at 12 weeks interval, but improvements were significantly better for the treatment group. Hence, this suggests a potential relationship between fatigue, disease activity, pain and omega-3 intake.[41] In my multiple linear regression analyses, pain was found to be associated with fatigue rather than disease activity, and when all the potential predictors of fatigue were included in the analysis only pain remained statistically significantly. Hence, it is possible that it was reduction in pain score that influenced fatigue rather than omega-3 intake, in the study by Das Gupta et al.[41]

Carbohydrate intake from 24-hour recall, including starch, correlated with lower fatigue scores for the physical and cognitive fatigue category of BRAF-MDQ. In one study done in people doing shift work found that increased fatigue and longer sleep durations were associated with higher intakes of fat. Furthermore, lower fatigue was associated with higher carbohydrate intakes.[76]

When considering the hypothesis that a diet high in saturated fat can increase fatigue, a potential explanation and suggested mechanism can be through the association between saturated fat and oxidative stress. As explained by Davies et al,[17] metabolic disturbances such as oxidative stress has been associated with fatigue. Dietary fatty acids are a good source of oxidisable lipids and can lead to activation of mitochondrial metabolism and to the formation of reactive oxygen species (ROS). Furthermore, overnutrition can lead to increased free fatty acid loads in cells which in turn might lead to overproduction of free radicals in the electron transport chain. Some fatty acids, notably saturated fat, can also directly activate the ROS-producing NADPH oxidase. These events are also involved in pro-inflammatory processes.[77]

Furthermore, the biomarker plasma F_2-isoprostane, used to measure oxidative stress, independently correlated with fatigue levels in systemic lupus erythematosus (SLE) patients.[78] Supplementation with antioxidants such as N-acetylcysteine has shown to improve muscle fatigue, which may indicate some involvement of metabolic disturbances in fatigue pathogenesis, however no precise mechanisms have been identified. [79] No current studies have been identified investigating the relationship between oxidative stress and fatigue in RA

and SpA patients. Considering that antioxidant intake in this study did not correlate with any of the fatigue measures, the relationship between oxidative stress and fatigue remains unclear.

Nutritional status, as determined by blood tests, anthropometric and body composition measurements were not associated with fatigue in IRD. Some studies have however found associations between obesity and fatigue in rheumatic diseases.[17, 22, 44, 65] In one study, including data collected during a single home visit, obesity as defined by measured BMI was associated with fatigue in RA in bivariate analysis, but did not remain significant in multiple regression analysis when other potential fatigue predictors were included.[22] However, in the current study neither BMI, body fat percentage or calculated FMI from BIA nor DXA significantly correlated with fatigue scores.

5.3.2 Disease activity, pain, and fatigue

DAS28 and serum CRP when measured separately, did not correlate with fatigue scores in this study. However, when CRP was included as part of DAS28 measurement (DAS28-CRP(3)), it became significant and correlated with "living with fatigue". Furthermore, when all of the clinical (DAS28 + CRP) and subjective (PGA) parameters were combined and used to measure DAS28-CRP(4), it showed a stronger significant positive correlation with both RAID fatigue scores and BRAF-MDQ total fatigue scores, indicating that the patient's own perception of disease affects fatigue. Furthermore, disease activity did not remain significant in multiple linear regression analyses.

Since it has been hypothesized that inflammation and production of pro-inflammatory mediators play a role in fatigue, medications are expected to reduce fatigue as it reduces inflammation and an overactive immune system.[17] However, as previously mentioned despite RA patients achieving clinical remission with anti-TNF treatment, many do not achieve remission of their fatigue. Furthermore, those who continued to experience fatigue after disease remission also report poorer scores for pain and had poorer scores for other reported health status variables.[27,36] Therefore, fatigue experienced by participants may reflect pain and not disease activity, as supported by the findings that disease activity mainly only significantly correlated with fatigue when PGA was included in the assessment.

Furthermore, the multiple regression analyses, although not consistent, showed that pain rather than disease activity predicts fatigue, suggesting that fatigue is caused by another mechanism than inflammation alone.[17, 80] Nevertheless, decreasing inflammation may have an indirect effect on fatigue in IRD by reducing pain as pro-inflammatory cytokines have a direct action on pain via sensory neurons or indirectly via prostaglandins.[81] Potential mechanisms are unclear and need to be further investigated.

5.3.3 BMD, serum vitamin D and fatigue

To current knowledge, no studies have been done in patients with IRD and the effect of bone mineral density on fatigue scores. There have been notably more studies done in MS patients and predictors of fatigue. One study by Cleland et al,[82] investigated predictors of reduced BMD in people with MS and found that symptomatic fatigue along with physical activity, depression, disability, and inflammation contributed independently to decreased femoral neck BMD. Furthermore, fatigue was one of the greatest predictors of low BMD along with physical activity and depression. However, in my study no association was found between BMD and fatigue scores.[82]

Low vitamin D levels can affect BMD and impact our immune system by potentially contributing to increased activation, suggesting a role in pathogenesis of RA.[21] However, in my study low serum vitamin D was not associated with low BMD.

There have not been many studies investigating the relationship between vitamin D concentration and fatigue in patients with IRD. However, in the studies that investigated this has either shown little or no effect. The study by Jelsness-Jørgensen et al, found that fatigue in RA did not differ across patients with varying levels of serum vitamin D. [21] This was also confirmed in another study where there were no significant differences between vitamin D levels and measures of both disease activity and fatigue in RA.[83] Only one study by Khoja et al, found that supplementation of vitamin D was associated with significant improvement in the RA patients' fatigue scores and other parameters such as pain, physical disability, and quality of life.[84] However, the reductions seen in fatigue could have been caused by improvements in pain scores, which was not investigated in the study. Whether vitamin D status is linked to fatigue in IRD is still not known, however in this study no associations

were found even though 32 % of the participants had levels below 50 nmol/L. In fact, lower vitamin D levels unexpectedly correlated with better vitality/fatigue scores from RAND 12.

5.3.4 Clinical parameters and fatigue

A significant negative correlation between SBP and total fatigue score from BRAF-MDQ, suggests that high blood pressure was associated with lower fatigue scores. However, the association did not remain significant in multiple regression analysis. Furthermore, blood pressure was only measured at one time interval, hence the positive correlation is difficult to interpret without having monitored blood pressure and fatigue over time, including matched controls, to observe if measurements remain constant or show variability.

A study done in patients with RA, found that a history of hypertension was more prevalent in those who did not achieve partial remission of fatigue with anti-TNF treatment.[27] It has been hypothesised that one potential mechanism which could give rise to both fatigue and blood pressure dysregulation is dysfunction of the hypothalamic-pituitary-adrenal axis.[85]

Furthermore, participants blood lipid profile including concentrations of total cholesterol, LDL, and triglycerides showed no correlations with fatigue scores except from HDL. To current knowledge no studies have looked at fatigue and blood lipid levels in patients with IRD. However, a study done by Maxwell et al in a cohort of MS patients found that after dietary intervention, increased HDL and changes in total cholesterol were associated with improved fatigue scores. [86] In comparison, only higher HDL levels correlated with lower fatigue scores for the BRAF-MDQ living with fatigue category, and since our study was not an intervention study and associations were found in MS patients, true comparisons cannot be made.

5.3.5 Other predictors of fatigue

In this study I was unable to show whether education, physical activity, household income, and medication have an impact on fatigue in IRD, possibly due to small sample size. Hence, differences between the groups were not large enough to be of any significance.

Furthermore, age was found to have no correlation with fatigue in this study. It has been hypothesised that decreasing lean muscle mass, that is a result of both malnutrition and as a result of aging could lead to fatigue in patients with RA.[52] However, neither muscle weakness as measured by HGS nor FFM or muscle mass correlated with fatigue scores in our study population. Other studies have also found no significant correlations between fatigue and age in IRD.[36, 65] Additionally, in our study population, none of the participants had low FFMI, hence making it hard to evaluate any true relationship between FFM and fatigue scores.

In our study there was a strong correlation between sleep score and fatigue across all measured fatigue categories except from cognitive fatigue. This supports previous findings from other studies. In other cross-sectional studies, correlations between reported sleep disturbance and fatigue scores have been consistently observed. The evidence for longitudinal correlations is less clear.[65]

The MHAQ questionnaire score was found to positively correlate with the fatigue scores for RAID and physical fatigue category for BRAF-MDQ, hence indicating that patients with IRD who experience more fatigue, are also more disabled. Other studies have found similar correlations. [87] In cross-sectional studies, associations between fatigue scores and low physical functioning were significant in all but two studies. The median correlation was 0.49 which compares to findings from this study where the correlation for RAID fatigue was 0.43 and 0.44 for physical fatigue.[65]

5.4 Clinical Relevance

More research is now showing that fatigue needs to be managed by a multidisciplinary team using both pharmacological and non-pharmacological methods.[18] Strengths of this study includes the fact that we included a lot of different measurements, hence making it possible to estimate fatigue predictors across a broad spectrum of variables. This can help identify better methods to manage fatigue in IRD. It is also a strength that 3 different questionnaires were used to measure fatigue, making it easier to identify fatigue in this patient group.

Additionally, this study provides an overview of dietary intake and nutritional status of RA and SpA patients. As IRD patients are likely to experience nutritional challenges, including obesity,[57] participating in this study may have contributed to patient awareness of own health, reducing risk of cardiovascular disease or other co morbidities commonly associated with IRD.[88]

Hopefully, this study can contribute to new studies being designed investigating the relationship between dietary components and fatigue in more depth. At last, this study adds to the growing evidence-based research suggesting that pain is an important contributor to fatigue.[36, 65, 87]

5.5 Future Research

This study was a cross-sectional study in nature part of the larger EROM study, hence it only included participants attending one outpatient clinic, and I therefore believe the findings in this study require reproduction in other centres and in a prospectively recruited cohort measuring fatigue and potential predictors of fatigue over time. This study only included "between patients" correlations and differences, hence future studies should also include "within patient" differences and associations with fatigue. This is important since factors associated with fatigue, such as behavioural and psychosocial factors depend on the individual, hence one treatment option working for a patient might not work for the other patient due to individual differences. Furthermore, intervention studies or cross-sectional studies should include many different patient groups suffering from chronic fatigue such as MS, CFS and cancer, to investigate if potential predictors of fatigue vary or remain constant across different patient groups. There is also a need to identify specific biomarkers for fatigue other than having to rely on self-reported fatigue via questionnaires. In the future, larger

sample sizes will contribute to better precision and accuracy of the result when calculating significant values. There is also a need for a consensus on how to define fatigue and how to measure it using standardized accepted fatigue questionnaires, so that comparison between study results is more efficiently accomplished. Furthermore, more dietary interventions lasting longer than 12 weeks should investigate the relationship between nutrient intake and fatigue in IRD as such studies are currently lacking.

5.6 Conclusion

The main aim of this study was to investigate the effect of nutritional status on fatigue however, the findings suggest that fatigue scores in IRD are more strongly associated with patient perceived pain. Although not consistent across analyses, high dietary saturated fat intake and low CHO and unsaturated fat intake correlated with higher fatigue scores, but in multiple regression analysis this association did not remain significant. Furthermore, anthropometrics and body composition were not associated with fatigue scores. Hence, these findings suggest that dietary intake and nutritional status are not associated with fatigue in this study population. However, bearing in mind the limitations of the dietary assessment methods and malnutrition not being identified in the study population, the relationship between nutrition and fatigue in IRD remains unclear. There is currently a need for additional research exploring this relationship, hence dietary intake and nutritional status cannot yet be excluded as predictors of fatigue. Further research and randomized controlled trials are required to fully assess the role of dietary intake and fatigue. Future studies should include participants that meet criteria for both over and undernutrition so that biomarkers for malnutrition can be tested for any correlation with fatigue scores. Furthermore, when investigating the secondary outcomes of this study, correlations between disease activity and fatigue seem to be mainly mediated by patient perceived pain as shown in multiple regression analyses. This cross-sectional study contributes to the growing body of research that indicates that the aetiology of fatigue is multifactorial and complex, and most likely results from a cluster of many different, but related factors.

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7 Appendix

7.1 Appendix I

HELSE BERGEN
Haukeland Universitetssjukehus

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET VED HAUKELAND UNIVERSITETSSYKEHUS

ERNÆRINGSINTERVENSJON VED REVMATISK SYKDOM

- EFFEKT AV MARINE OMEGA-3 FETTSYRER OG KOSTVEILEDNING

Dette er et spørsmål til deg om å delta i et forskningsprosjekt med formål å undersøke om omega-3 fettsyrer og et kosthold som forbedrer ernæringsstatusen kan påvirke sykdomsaktiviteten hos pasienter med revmatoid artritt, psoriasisartritt og Bekhterevs sykdom.

Du får spørsmålet om å delta fordi du er pasient ved Revmatologisk avdeling på Haukeland Universitetssykehus, og har en inflammatorisk leddsykdom.

Studien gjennomføres av en prosjektgruppe ved Revmatologisk avdeling, Haukeland Universitetssykehus som er tilknyttet Universitetet i Bergen. Haukeland Universitetssykehus er ansvarlig for prosjektet.

HVA INNEBÆRER PROSJEKTET?

Deltakelse i forskningsprosjektet vil ikke påvirke din ordinære behandling.

Kostholdsintervensjonen innebærer:

1. Fem individuelle konsultasjoner og oppfølgingssamtaler på telefon med klinisk ernæringsfysiolog.
2. Kosttilskudd i form av fire tabletter omega-3 fettsyrer, eller placebo (soyaolje), daglig i 24 uker.
3. Tilgang til kostholdskurs på internett med klinisk ernæringsfysiolog.

Hvis du allerede bruker omega-3 tilskudd vil du bli bedt om å ikke innta dette i en periode på 8 uker før første samtale med lege og klinisk ernæringsfysiolog. Du vil bli

bedt om å ikke bruke andre omega-3 tilskudd under hele prosjektperioden.

Under samtaler med lege og klinisk ernæringsfysiolog ved Revmatologisk avdeling på Haukeland Universitetssykehus vil følgende data bli samlet: vekt, høyde, midjemål, håndgripestyrke, blodprøver sykdomsaktivitet og analyse av kroppssammensetning.

Det vil bli samlet inn informasjon om ditt kosthold og din ernæringsstatus ved fem konsultasjoner før, under og to ganger etter en periode med omega-3 tilskudd/placebo. Placebo er kapsler uten virkestoff som brukes for å undersøke effekt av omega-3. I denne studien inneholder placebokapslene soyaolje.

Du vil bli bedt om å registrere følgende:

1. Alt du drikker og spiser i løpet av 7 dager (kostregistrering).
2. Alle relevante medisiner du bruker, som Ibux, Voltaren eller Naproxen (medikamentregistrering).

Følgende opplysninger vil bli hentet fra din journal: alder, sykdomsdebut, bruk av sykdomsmodifiserende medisiner, svar på blodprøver samt score på sykdomsaktivitet.

MULIGE FORDELER OG ULEMPER

Deltakelse vil ikke påvirke den ordinære behandlingen din. Deltakelse vil kunne medføre ekstra kontroll på poliklinikken.

Noen kan oppleve det som ubehagelig å innta fire til fem tabletter med omega-3 fettsyrer og perioden på 24 uker kan oppleves lang.

Kostveiledning: I tillegg til den ordinære behandlingen din vil du få tilbud om fem timer individuell kostveiledning av klinisk ernæringsfysiolog. Dette vil skje samtidig med dine planlagte kontroller eller på et annet tidspunkt som passer. Du vil få utdelt et helsekort med opplysninger om din ernæringsstatus.

Konsultasjon: Antatt varighet av kostveiledning og undersøkelse ved visitt kan ta inntil 120 minutter. I tillegg kan det ta inntil 10 minutter å fylle ut et spørreskjema. I tilfeller der konsultasjon ikke kan legges til dine vanlige kontroller kan det bli nødvendig med en ekstra tur til sykehuset.

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. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for din ordinære 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-Kristine Halse, 55975387, anne.kristine.hjortesth.halse@helse-bergen.no.

HVA SKJER MED OPPLYSNINGENE OM DEG?

Opplysningene som registreres om deg skal kun brukes slik som beskrevet i formålet med prosjektet. 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. Du har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode (koblingsnøkkel) knytter deg til dine opplysninger gjennom en navneliste. Koblingsnøkkelen er lagret på et passordbeskyttet området som kun prosjektleder Anne-Kristine Halse har tilgang til.

Koblingsnøkkelen vil bli slettet innen 2030.

HVA SKJER MED PRØVER SOM BLIR TATT AV DEG?

Prøvene som tas av deg skal oppbevares i en forskningsbiobank tilknyttet prosjektet. Prøver som vil bli lagret er blodprøver til Vestnorsk Forskningsbiobank for Revmatiske sykdommer, Haukeland Universitetssykehus. Bjørg-Tilde Fevang er ansvarshavende for biobanken.

Prøvene vil bli lagret permanent.

I forbindelse med dette prosjektet vil noen av prøvene bli sendt til Skottland for analyse av fettsyrenivå i blod. Materialet vil bli destruert ved prosjektslutt.

FORSIKRING

Ved deltakelse i studien har du standard rettigheter som pasient etter Pasientsikkerhetsloven, og Produktansvarsloven.

ØKONOMI

Dette prosjektet får økonomisk støtte fra GC Rieber Oils som bidrar med kapsler med omega-3 fettsyrer og placebo. GC Rieber Fondene dekker lønn til klinisk ernæringsfysiolog (PhD kandidat) i minimum ett år. Revmatologisk avdeling ved Haukeland Universitetssykehus dekker utgifter til studiesykepleier og lege.

Ut over dette er det ingen interessekonflikter i prosjektgruppen. Det vil bli søkt om forskningsmidler på vanlig måte.

GODKJENNING

Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning [79907].

Etter ny personopplysningslov har Haukeland Universitetssykehus og prosjektleder Anne-Kristine Halse et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et

lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6a og artikkel 9 nr. 2 og ditt samtykke.

Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet.

KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet kan du ta kontakt med Anne-Kristine Halse, tlf: 55975387, anne.kristine.hjortesth.halse@helse-bergen.no, eller Marie Njerve Olsen, tlf: 95802404, marie.njerve.olsen@helse-bergen.no

Personvernombud ved institusjonen er Christer Kleppe, 55975558, personvernombudet@helse-bergen.no

JEG SAMTYKKER TIL Å DELTA I PROSJEKTET OG TIL AT MINE PERSONOPPLYSNINGER OG MITT BIOLOGISKE MATERIALE BRUKES SLIK DET ER BESKREVET

Sted og dato

Deltakers signatur

Deltakers navn med trykte bokstaver

7.2 Appendix II

24h kosthistorie EROM

ID:

Dato/dag: **Er dette en typisk dag? (Hvis nei, hvorfor?)**

Kosttilskudd? **Allergier? Andre ting som påvirker matinntak?**

Tid (00-24)	Type mat/drikke Detaljert beskrivelse av all mat og drikke. Husk ingredienser i blandet mat og merkevarenavn:	Mengde/ porsjonsstr:

Tid (00-24)	Type mat/drikke Detaljert beskrivelse av all mat og drikke. Husk ingredienser i blandet mat og merkevarenavn:	Mengde/ porsjonsstr:

Sjekkliste:

1. Be pasienten redegjøre
2. Be om detaljer
   - Frokost
   - Lunsj
   - Middag
   - Kvelds
   - Mellommåltider
3. Drikke til/utenom måltider?
4. Berikning?
   Dressing, rømme, smør, fløte/annet tilbehør middag?
5. Snacks? Nøtter, mellombar?
6. Kosttilskudd?
7. Spising på natt
8. **Aktivitetsnivå/PAL?**

Kommentarer/vurdering:

- Hvor utfyllende svar har du fått?
- Hvor fullstendig/nøye er informasjonen du har fått?

7.3 Appendix III

Ernæringsintervensjon ved revmatiske sykdommer (EROM).

Pasient ID: _____

1. Vekt og høyde

Vekt: _____kg Vekten din for 5 år siden?	 _____kg vet ikke◯
Er du fornøyd med vekten din nå?	Ja◯ Nei, for lett◯ Nei, for tung◯
Har du hatt ufrivillig vekttap de siste 3 mnd? - Ja - Nei - Vet ikke	 ◯ ◯ ◯
Hvis ja, hvor mange kilo har du gått ned?	_____kg
Hvor mye har du spist den siste uken?	Mer enn normalt ◯ Normalt ◯ Litt mindre enn normalt ◯ Mindre enn halvparten av normalt ◯ Mindre enn en fjerdedel av normalt ◯
Jeg har spist mindre fordi: - Ikke matlyst - Er kvalm - Har ikke klart å lage/handle mat - Har problemer med å tygge/svelge - Er utmattet - Annet:	 ◯ ◯ ◯ ◯ ◯ _____
Din høyde som ung voksen?	____cm Vet ikke◯

2. Kosthold og spisevaner

Har du noen gang deltatt på kurs om kosthold og revmatisk sykdom? - Ja, i regi av Lærings og Mestringssenteret ved Haukeland Universitetssykehus - Ja i regi av annet sykehus - Ja, i regi av annen organisasjon/privat - Nei.	 ◯ ◯ ◯ ◯
Har du noen gang endret kostholdet ditt, med tanke på din revmatiske sykdom?	Ja ◯ Nei ◯
Føler du at kosthold/diett påvirker din revmatiske sykdomstilstand/aktivitet - Ja, i stor grad - Ja, i noen grad - Nei, ikke i det hele tatt.	 ◯ ◯ ◯

Hvis ja, hvordan mener du at kostholdet påvirker din revmatiske sykdomstilstand? - Mindre smerte generelt - Mindre morgenstivhet - Færre vonde ledd - Bedre fysisk funksjon - Annet: _____	◯ ◯ ◯ ◯ ◯ ◯
Har du noen gang utelatt/begrenset matvarer i ditt kosthold, på grunn av din revmatiske sykdom?	Ja◯ Nei◯
Hvis ja, hvilke matvarer har blitt utelatt/begrenset? - Tomat/ tomatbaserte produkter - Produkter med svinekjøtt - Produkter med rødt kjøtt - Meieriprodukter - Alkohol - Sjokolade - Søtsaker/ salt snacks - Produkter med gluten - Produkter med hvete - Produkter med laktose - Salt - Karbohydratrike matvarer - Annet: _____ _____ _____	◯ ◯ ◯ ◯ ◯ ◯ ◯ ◯ ◯ ◯ ◯ ◯
Har du prøvd noen av følgende kosthold/dietter for din revmatiske sykdom? - Middelhavskosthold - Vegetarisk kosthold (ikke kjøtt/fisk) - Vegansk kosthold (ikke animalske matvarer som egg/melk) - Faste i perioder, og i så fall hvor lenge - Annet: _____	◯ ◯ ◯ ◯ ◯ _____lengde (timer) ◯
Bruker du kosttilskudd?	Ja◯ Nei◯

Hvis ja, hvilke? - Tran og/eller omega 3 kapsler - Vitamin og/eller mineraltilskudd - Antioksidant tilskudd - Vitamin-E tilskudd? - Vitamin D tilskudd - B-vitaminer (flere b-vit i samme tabl) - Kalsium tilskudd (eks Calcigran). - Vitamin C - Jern tilskudd - Folat (folsyre) - Heelsekostpreparat som ingefær, gurkemeie o.l. - Annet: _____	◯ ◯ ◯ ◯ ◯ ◯ ◯ ◯ ◯ ◯ ◯ ◯ ◯				
Har du brukt omega-3 tilskudd eller tran før du ble med i studien?	◯ Ja, men det er mer enn 8 uker siden ◯ Ja, inntil nylig ◯ Nei				
Hvis ja, hvor stor dose har du tatt?	◯ Vanlig dose med tran: _____ ◯ Omega-3 kapsler, antall: _____ ◯ Høykonsentrert omega-3 kapsler, antall: ___ ◯ Annet_____				
Har du fått råd om å ta kosttilskudd av helsepersonell? Har du fått råd om å ta kosttilskudd pga medisinbruk?	Ja ◯ Nei◯ Ja ◯ Nei ◯				
Hvor mange måltider spiser du hver dag?	_____-Antall				
Hvor ofte spiser du vanligvis disse matvarene? (sett ett kryss per linje) - Sjokolade/smågodt/chips…… - Kokte poteter…… - Pasta/ris…….. - Kjøttdeig, pølser, hamburger og lignende - Hvitt, rent kjøtt(kylling, kalkun)…….. - Rødt rent kjøtt (storfe, svin, lam, vilt) - Mager, ren fisk (torsk, sei)…….. - Fet fisk…….. (laks, ørret, sild, makrell, uer som pålegg eller middag)	0-3 ganger per mnd ◯ ◯ ◯ ◯ ◯ ◯ ◯ ◯	1-3 ganger per uke ◯ ◯ ◯ ◯ ◯ ◯ ◯ ◯	4-6 ganger per uke ◯ ◯ ◯ ◯ ◯ ◯ ◯ ◯	1 gang per dag ◯ ◯ ◯ ◯ ◯ ◯ ◯ ◯	2 ganger el mer pr dag ◯ ◯ ◯ ◯ ◯ ◯ ◯ ◯
Hvor mange glass drikker du vanligvis av følgende? (0.5L = 3 glass)	Sjelden eller aldri	1-6 gl per uke	1 gl per dag	2-3 glass	4 gl eller

				per dag	mer per dag
- Vann, farris……	◯	◯	◯		
- Helmelk……..	◯	◯	◯	◯	◯
- Annen melk……..	◯	◯	◯	◯	◯
- Brus/saft med sukker……	◯	◯	◯	◯	◯
- Brus saft uten sukker…….	◯	◯	◯	◯	◯
- Juice eller nektar	◯	◯	◯	◯	◯
- Kaffe……..	◯	◯	◯	◯	◯
				◯	◯

Hvor ofte spiser du følgende måltider i løpet av en uke?	Aldri/ Sjelden	1-2 ganger pr uke	3-4 ganger pr uke	5-6 ganger pr uke	Hver dag
- Frokost	◯	◯	◯	◯	◯
- Formiddagsmat/ lunsj	◯	◯	◯	◯	◯
- Middag	◯	◯	◯	◯	◯
- Kveldsmat	◯	◯	◯	◯	◯

Hvor mange ganger i løpet av dagen pleier du å spise et eller annet utenom hovedmåltidene?	
- Sjelden	◯
- 1 g om dagen	◯
- 2g om dagen	◯
- 3-4g om dagen	◯
- Mer enn 4 g om dagen	◯

	Mindre enn 1	1	2	3	4	5+
Hvor mange porsjoner grønnsaker (utenom potet) spiser du vanligvis per dag?	◯	◯	◯	◯	◯	◯
Hvor mange frukt spiser du vanligvis per dag	◯	◯	◯	◯	◯	◯

3.1 Bruk av alkohol

Omtrent hvor ofte har du iløpet av de siste 12 mnd drukket alkohol	
- 4-7g per uke	◯
- 2-3g per uke	◯
- Ca 1g per uke	◯
- Ca 1g per mnd	◯
- Ca 2-3g per mnd	◯
- Noen få ganger per år	◯
- Aldri siste år	◯
- Aldri drukket alkohol	◯

3.2 Tobakk/snus:

Røyker du selv? Nei, jeg har aldri røykt Nei, jeg har sluttet Ja, av og til(fest/ferie, ikke daglig) Ja, daglig	 ◯ ◯ ◯ ◯
Hvor mange sigaretter røyker eller røykte du daglig?	**_____antall**
Bruker du, eller har du brukt snus? Nei, aldri Ja, av og til (fest/ferie, ikke daglig) Ja, men har sluttet Ja, daglig	 ◯ ◯ ◯ ◯
Hvor mange bokser snus bruker du per mnd?	**_____antall**

3. **Fysisk aktivitet/mosjon**

Hvor ofte mosjonerer du? - Aldri - Sjeldnere enn en gang i uka - En gang i uka - 2-3g i uken - Omtrent hver dag	 ◯ ◯ ◯ ◯ ◯
Dersom du mosjonerer, hvor høy intensitet har du? - Rolig, uten å bli andpusten og svett - Så hardt at jeg blir andpusten og svett - Tar meg helt ut	 ◯ ◯ ◯
Hvor lenge holder du på hver gang? - Mindre enn 15 min - 15-30 min - 30-60 min - Mer enn 60 min	 ◯ ◯ ◯ ◯
Har du vanligvis minst 30 minutter fysisk aktivitet på arbeid eller/og på fritiden din?	Ja ◯ Nei ◯

4. Arbeid

Er du i lønnet arbeid? Er du i ulønnet arbeid?	Ja ◯ Nei ◯ Ja ◯ Nei ◯
Hvis du er i lønnet eller ulønnet arbeid hvordan vil du beskrive arbeidet ditt?	

- For det meste stillesittende arbeid (f.eks skrivebordsarbeid) - Arbeid som krever at du går mye (f.eks ekspeditørarbeid, undervisning) - Arbeid hvor du løfter og går mye (f.eks postbud, pleier, bygningsarbeid) - Tungt kroppsarbeid (f.eks skogsarbeid, tungt bygningsarbeid)	◯ ◯ ◯ ◯
Hvis du ikke er i heltids arbeid, er det på grunn av: - Arbeidsløshet/permittering - Pensjon eller trygd/sykemelding - Utdanning eller militærtjeneste - Annet	 ◯ ◯ ◯ ◯

5. <u>Utdanning og inntekt.</u>

Hvilken utdanning er den høyeste du har fullført? - Grunnskole - 1-2årig videregående skole - 3 år i videregående skole - Fagbrev eller svennebrev - Høyskole/universitet, mindre enn 4 år - Høyskole/universitet, 4 år eller mer	 ◯ ◯ ◯ ◯ ◯ ◯
Hva er din husstands samlede inntekt siste år? Ta med alle inntekter fra arbeid, trygder, sosialhjelp og lignende - Under 250 000 - 250 000- 450 000 - 451 000- 750 000 - 751 000 – 1 000 000 - Over 1 000 000 - Vet ikke/Ønsker ikke å svare	 ◯ ◯ ◯ ◯ ◯ ◯

7.4 Appendix IV

The following equations taken from Black[58], have been used to determine lower and upper cut off values:

$$\text{EIrep: BMRest} > \text{PAL x } e\left[SDmin\ x\ \frac{S}{100}/\sqrt{n}\right]$$

And for upper cut offs:

$$\text{EIrep: BMRest} < \text{PAL x } e\left[SDmax\ x\ \frac{S}{100}/\sqrt{n}\right]$$

In the equation:

PAL: is estimated physical activity level for the study population. This was determined from self-reported questionnaire that the participants filled out during first visitation at the hospital.

SDmin: is -2 for the 95% lower confidence limit.

SDmax: is +2 for the 95% upper confidence limit.

n: is the number of study participants

S: is the coefficient variation (***CV***) of PAL when considering the variability in energy intake and BMR.

Furthermore, the **S** value is calculated by using the following equation:

$$S = \sqrt{[\frac{CV_{wEI}^2}{d} + CV_{wB}^2 + CV_{wP}^2]}$$

CV_{wEI} is within-patient variation in energy intake. The revised factor by Black, **23%** is applied to the equation.

d is the number of days of dietary assessment, hence in my study it is 1 day for the 24-h recall and 7 days for the 7 day-food record.

CV_{wB} is the within-patient variation in repeated BMR measurements or precision of estimated BMR compared to measured BMR. The revised factor by Black, **8.5%** is applied to the equation.

CV_{tP} is the total between and within patient variation in PAL. The revised factor by Black, **15%** is applied to the equation.

With the information already at hand S can be calculated for 24-hour recall:

$$S = \sqrt{[\frac{23^2}{1} + 8.5^2 + 15^2]} = \sqrt{529 + 72.25 + 225} = \sqrt{826.25} = \mathbf{28.7}$$

And 7-day food record:

$$S = \sqrt{[\frac{23^2}{7} + 8.5^2 + 15^2]} = \sqrt{75.57 + 72.25 + 225} = \sqrt{826.25} = \mathbf{19.3}$$

The individual EIrep:BMRest ratio values of each participant was then compared to the calculated lower and upper cut off values for under and overreporting. Hence if the participant's EIrep:BMRest ratio is below the lower cut off value, then the participant has underreported. However, if the EIrep:BMRest ratio is above the upper cut off value then the participant has overreported. All participant EIrep:BMRest ratios that falls within the lower and upper intervals of the cut offs, are considered plausible reporters.

7.5 Appendix V

Navn..... **Dato**.....

Bristol flerdimensjonal spørreundersøkelse om utmattelse hos pasienter med revmatoid artritt (BRAF-MDQ)

Vi vil gjerne vite hvordan utmattelse har påvirket deg de siste 7 dagene.
Vennligst svar på alle spørsmålene. Ikke tenk for lenge og hardt, bare gi oss din første reaksjon – det finnes ingen riktige eller gale svar!

1 Sett en ring rundt det tallet som viser ditt gjennomsnittlige nivå av utmattelse i løpet av de siste 7 dagene.

Ingen utmattelse 0 1 2 3 4 5 6 7 8 9 10 Totalt utslitt

****

På hvert av de neste spørsmålene: kryss av for det ene svaret som passer best for deg.

2 Hvor mange dager opplevde du utmattelse i løpet av den siste uken (7 dager)?

0	☐	4	☐
1	☐	5	☐
2	☐	6	☐
3	☐	Hver dag	☐

3 Hvor lenge, i gjennomsnitt, varte hver episode med utmattelse i løpet av de siste 7 dagene?

Mindre enn en time ☐

Flere timer ☐

Hele dagen ☐

Vennligst bla om .....

Norwegian for Norway

BRAF-MDQ
V1 27.08.10

	I løpet av de siste 7 dagene	Ikke i det hele tatt	Litt	Nokså mye	Svært mye
4	Har du manglet *fysisk* energi på grunn av utmattelse?	-----	----	-----	-----
5	Har utmattelse gjort det vanskelig for deg å bade eller dusje?	-----	-----	-----	-----
6	Har utmattelse gjort det vanskelig for deg å kle deg?	-----	-----	-----	-----
7	Har utmattelse gjort det vanskelig for deg å utføre arbeidet ditt eller andre daglige aktiviteter?	-----	-----	-----	-----
8	Har du unngått å legge planer på grunn av utmattelse? f.eks. planer om å gå ut eller jobbe i huset eller i hagen	-----	-----	-----	-----
9	Har utmattelse påvirket ditt sosiale liv?	-----	-----	-----	-----
10	Har du avlyst planer på grunn av utmattelse, f. eks. planer om å gå ut eller jobbe i huset eller hagen?	-----	-----	-----	-----
11	Har du avslått invitasjoner på grunn av utmattelse? f.eks. til å møte en venn	-----	-----	-----	-----
12	Har du manglet *mental* energi på grunn av utmattelse?	-----	-----	-----	-----
13	Har du glemt ting på grunn av utmattelse?	-----	-----	-----	-----
14	Har utmattelse gjort det vanskelig å tenke klart?	-----	-----	-----	-----
15	Har utmattelse gjort det vanskelig å konsentrere seg?	-----	-----	-----	-----
16	Har du gjort feil på grunn av utmattelse?	-----	-----	-----	-----
17	Har du følt at du har mindre kontroll på områder i livet ditt på grunn av utmattelse?	-----	-----	-----	-----
18	Har du følt deg flau på grunn av utmattelse?	-----	-----	-----	-----
19	Har utmattelsen gjort at du har følt deg opprørt?	-----	-----	-----	-----
20	Har du følt deg nedfor eller deprimert på grunn av utmattelse?	-----	-----	-----	-----

Norwegian for Norway

BRAF-MDQ
V1 27.08.10

Bristol Rheumatoid Arthritis Fatigue scales (BRAFs): Scoring

BRAF-Numerical Rating Scales V2 revised: Three NRS give 3 separate answers from 0-10 where high is worse

BRAF Multidimensional Questionnaire (BRAF-MDQ): 20 items are combined to create 5 scores, high is worse:

Total fatigue score	0-70	Items 1-20 summed
Physical (severity) subscale	0-22	Items 1-4 summed
Living with fatigue subscale	0-21	Items 5-11 summed
Cognitive fatigue subscale	0-15	Items 12-16 summed
Emotional fatigue subscale	0-12	Items 17-20 summed

Subscale		Question	Range	Score
Physical	1	NRS fatigue	0-10	
	2	How many days?	0-7	
	3	How long on average has each episode of fatigue lasted?	0-2	
	4	Have you lacked physical energy because of fatigue?	0-3	
		Physical severity total	**0-22**	
Living	5	Has fatigue made it difficult to bath or shower?	0-3	
	6	Has fatigue made it difficult to dress yourself?	0-3	
	7	Has fatigue made it difficult to do your work or other daily activities?	0-3	
	8	Have you avoided making plans because of fatigue?	0-3	
	9	Has fatigue affected your social life?	0-3	
	10	Have you cancelled plans because of fatigue?	0-3	
	11	Have you refused invitations because of fatigue?	0-3	
		Living with fatigue total	**0-21**	
Cognition	12	Have you lacked mental energy because of fatigue?	0-3	
	13	Have you forgotten things because of fatigue?	0-3	
	14	Has fatigue made it difficult to think clearly?	0-3	
	15	Has fatigue made it difficult to concentrate?	0-3	
	16	Have you made mistakes because of fatigue?	0-3	
		Cognitive fatigue total	**0-15**	
Emotion	17	Have you felt you have less control because of fatigue?	0-3	
	18	Have you felt embarrassed because of fatigue?	0-3	
	19	Has being fatigued upset you?	0-3	
	20	Have you felt down or depressed because of fatigue?	0-3	
		Emotional fatigue total	**0-12**	
		BRAF-MDQ total score	**0-70**	

Missing BRAF-MDQ data

- Questions 1 and 2 must be completed to be valid
- Only 1 question may be missing from each dimension (maximum of 3 in the overall BRAF-MDQ).
- Replace the missing question score with the average score for that dimension
- For the **Physical Fatigue** dimension, a weighted average score is used to account for the varying score ranges in the 4 items. First, sum the 3 completed items, then divide by the total max possible score for those 3 questions, then multiply by the maximum score possible for all 4 questions (ie 22).

Eg: Q1 is 10/10, Q2 is 6/7, Q3 is missing, Q4 is 2/3, summed to give 18
Divide by total max possible for those 3 questions (10+7+3 = 20) thus 18/20 = 0.9 weighted average
Multiply by the max possible score for all 4 questions (22) ie 0.9 x 22 = 19.8
Physical score would therefore be imputed as 19.8

RAID

Smerte

Sett ring rundt det tallet som best beskriver smerten du kjente pga din leddgikt i løpet av den siste uken:

0	1	2	3	4	5	6	7	8	9	10

Ingen smerte Ekstrem smerte

Måling av fysisk funksjon

Sett ring rundt det tallet som best beskriver vanskeligheten du hadde med å gjøre daglige fysiske aktiviteter pga din leddgikt i løpet av den siste uken.

0	1	2	3	4	5	6	7	8	9	10

Ingen vanskelighet Ekstrem vanskelighet

Fatigue/utmattelse

Sett ring rundt det tallet som best beskriver hvor mye fatigue/utmattelse du kjente pga din leddgikt i løpet av den siste uken.

0	1	2	3	4	5	6	7	8	9	10

Ingen fatigue Totalt utmattet

Søvn

Sett ring rundt det tallet som best beskriver søvnvansker (hvile om natten) du følte pga din leddgikt i løpet av den siste uken.

0	1	2	3	4	5	6	7	8	9	10

Ingen vansker kstreme vansker

Fysisk velvære

Tatt i betraktning din leddgikt generelt, hvordan ville du gradere nivået av fysisk velvære i løpet av den siste uken? Sett ring rundt det tallet som best beskriver nivået av fysisk velvære.

0	1	2	3	4	5	6	7	8	9	10

Veldig bra Veldig dårlig

Følelsesmessig velvære

Tatt i betraktning din leddgikt generelt, hvordan vil du gradere nivået av følelsesmessig velvære i løpet av den siste uken.
Sett ring rundt det tallet som best beskriver nivået av følelsesmessig velvære.

0	1	2	3	4	5	6	7	8	9	10

Veldig bra Veldig dårlig

Mestring

Tatt i betraktning din leddgikt generelt, hvor bra mestret (taklet, styrte, kontrollerte) du din sykdom i løpet av den siste uken?

0	1	2	3	4	5	6	7	8	9	10

Veldig bra Veldig dårlig

RAND-12 Din helse

Spørsmålene under handler om hvordan du oppfatter helsen din. Disse opplysningene vil hjelpe oss til å forstå hvordan du føler deg og hvor godt du er i stand til å utføre dine vanlige aktiviteter.

Hvert spørsmål skal besvares ved å sette et kryss (X) i den boksen som passer best for deg.

1. Stort sett, vil du si at helsen din er:

Utmerket	Veldig god	God	Nokså god	Dårlig
☐	☐	☐	☐	☐

2. De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er helsen din slik at den begrenser deg i utførelsen av disse aktivitetene nå? Hvis ja, hvor mye? [Kryss (X) en boks på hver linje.]

		Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
a	**Moderate aktiviteter** som å flytte et bord, støvsuge, gå en spasertur eller drive med hagearbeid	☐	☐	☐
b	Gå opp trappen **flere** etasjer	☐	☐	☐

3. I løpet av de siste fire ukene, har du hatt noen av de følgende problemene i arbeidet ditt eller i andre daglige aktiviteter på grunn av din fysiske helse?

		Ja	Nei
a	**Fått gjort mindre** enn du ønsket	☐	☐
b	Vært begrenset i type **arbeidsoppgaver** eller andre aktiviteter	☐	☐

4. I løpet av de siste fire ukene, har du hatt noen av de følgende problemene i arbeidet ditt eller i andre daglige aktiviteter på grunn av følelsesmessige problemer (som å føle seg engstelig eller deprimert)?

		Ja	Nei
a	**Fått gjort mindre** enn du ønsket	☐	☐
b	Utført arbeid eller andre aktiviteter **mindre grundig** enn vanlig	☐	☐

5. **I løpet av de siste fire ukene, hvor mye har smerter påvirket det vanlige arbeidet ditt (gjelder både arbeid utenfor hjemmet og husarbeid)?**

Ikke i det hele tatt	Litt	Moderat	Ganske mye	Ekstremt mye
☐	☐	☐	☐	☐

6. **De neste spørsmålene handler om hvordan du føler deg og hvordan du har hatt det i løpet av de siste fire ukene. For hvert spørsmål, ber vi deg velge det svaret som best beskriver hvordan du har følt deg.**

Hvor ofte i løpet av de siste fire ukene:

		Hele tiden	Mesteparten av tiden	En god del av tiden	Noe av tiden	Litt av tiden	Aldri
a	Har du følt deg rolig og avslappet?	☐	☐	☐	☐	☐	☐
b	Har du hatt mye overskudd?	☐	☐	☐	☐	☐	☐
c	Har du følt deg nedfor og deprimert?	☐	☐	☐	☐	☐	☐

7. **I løpet av de siste fire ukene, hvor mye av tiden har den fysiske helsen din eller følelsesmessige problemer påvirket dine sosiale aktiviteter (som å besøke venner, slektninger osv.)?**

Hele tiden	Mesteparten av tiden	En del av tiden	Litt av tiden	Aldri
☐	☐	☐	☐	☐

MHAQ

Navn: ..... nr. ..... Dato: .....

SPØRRESKJEMA – UTDELES OG UTFYLLES VED KLINISK UNDERSØKELSE

SPØRSMÅL OM FUNKSJON, SMERTE, TRETTHET OG LEDDPLAGER

I LØPET AV SISTE UKEN, KUNNE DU:	UTEN problemer	med VISSE problemer	med STORE problemer	kunne IKKE
Kle på deg selv, inkl. å knytte skolisser og å kneppe knapper?	☐	☐	☐	☐
Komme opp i og ut av sengen?	☐	☐	☐	☐
Løfte en full kopp eller et fullt glass til munnen?	☐	☐	☐	☐
Gå utendørs på flat mark?	☐	☐	☐	☐
Vaske og tørke deg over hele kroppen?	☐	☐	☐	☐
Bøye deg for å ta opp klær fra gulvet?	☐	☐	☐	☐
Skru vanlige kraner opp og igjen?	☐	☐	☐	☐
Komme inn og ut av en bil?	☐	☐	☐	☐

7.6 Appendix VI

Correlation coefficients for RAID and RAND 12 scores with nutrient intake from 24-hour recall in study population.

		RAID	**RAND 12**
		Fatigue	VT
Kilocalories	r	-0.166	-0.132
Fat (g)	r	-0.065	-0.229
Fat E %	r	0.009	-0.222
Saturated fat (g)	r	0.199	-0.290
Saturated fat E %	r	0.374*	-0.359
	p	**0.046**	0.060
MUFA (g)	r	-0.107	-0.224
PUFA (g)	r	-0.421*	0.107
	p	**0.023**	0.588
Omega-3 (g)	r	-0.391*	0.133
	p	**0.036**	0.499
Omega-6 (g)	r	-0.388*	0.076
	p	**0.038**	0.700
Carbohydrates (g)	r	-0.298	0.145
Carbohydrates E %	r	-0.180	0.187
Starch (g)	r	-0.309	0.194
Sugar (g)	r	-0.042	0.113
Fibre (g)	r	-0.051	-0.123
Protein (g)	r	0.073	0.072
Protein E %	r	0.297	0.152
Salt (g)	r	-0.048	0.175
Vitamin A (RAE)	r	0.215	-0.134
Vitamin D (µg)	r	-0.361	-0.066
Vitamin E (α-TE)	r	-0.124	-0.165
Thiamine (mg)	r	0.119	-0.057
Riboflavin (mg)	r	0.089	0.189
Niacin (mg)	r	0.072	-0.089
Vitamin B6 (mg)	r	-0.046	-0.161
Folate (µg)	r	0.135	-0.121
Vitamin B12 (µg)	r	-0.220	0.347
Vitamin C (mg)	r	0.298	-0.256
Calcium (mg)	r	0.002	0.176
Iron (mg)	r	-0.123	-0.077
Sodium (mg)	r	-0.024	0.171
Potassium (mg)	r	-0.238	-0.102
Magnesium (mg)	r	-0.287	0.065
Zinc (mg)	r	0.185	0.017
Selenium (µg)	r	0.040	0.054
Iodine (µg)	r	-0.139	0.235

Monounsaturated fat (MUFA), polyunsaturated fat (PUFA), carbohydrates include fibre (CHO). P (p-value). Pearson correlation coefficients (r) were calculated for RAID fatigue while Spearman's (ρ) correlation coefficients (r) were calculated for RAND12 VT. ** Correlation is significant at the 0.01 level (2-tailed).* Correlation is significant at the 0.05 level (2-tailed).

Correlation coefficients for BRAF-MDQ scores with nutrient intake from 24-hour recall in study population

		BRAF-MDQ				
		Physical	Living	Cognition	Emotion	Total
Kilocalories	r	-0.211	-0.146	0.071	-0.020	-0.031
Fat (g)	r	-0.070	-0.010	0.264	0.206	0.114
Fat E %	r	0.054	0.102	0.307	0.331	0.185
Saturated fat (g)	r	0.128	0.176	0.303	0.387*	0.302
	p	0.508	0.360	0.110	**0.038**	0.111
Saturated fat E%	r	0.335	0.340	0.333	0.465*	0.411*
	p	0.076	0.071	0.078	**0.011**	**0.027**
MUFA (g)	r	-0.043	0.047	0.240	0.191	0.125
PUFA (g)	r	-0.422*	-0.384*	-0.053	-0.064	-0.342
	p	**0.023**	**0.040**	0.785	0.743	0.069
Omega-3 (g)	r	-0.378*	-0.308	-0.005	-0.163	-0.321
	p	**0.043**	0.104	0.978	0.399	0.090
Omega-6 (g)	r	-0.379*	-0.361	-0.042	-0.077	-0.305
	p	**0.043**	0.054	0.829	0.690	0.108
Carbohydrates (g)	r	-0.392*	-0.326	-0.196	-0.141	-0.275
	p	**0.035**	0.085	0.307	0.466	0.149
Carbohydrates E%	r	-0.275	-0.245	-0.513**	-0.339	-0.351
	p	0.149	0.200	**0.004**	0.072	0.062
Starch (g)	r	-0.378*	-0.200	-0.135	-0.079	-0.241
	p	**0.043**	0.299	0.484	0.684	0.208
Sugar (g)	r	-0.081	-0.075	-0.203	-0.106	-0.014
Fibre (g)	r	-0.163	-0.155	0.023	-0.156	-0.118
Protein (g)	r	0.099	0.091	0.288	0.000	0.207
Protein E %	r	0.364	0.255	0.185	-0.038	0.284
Salt (g)	r	-0.143	-0.042	0.367	0.208	0.034
Vitamin A (RAE)	r	0.185	0.271	0.221	0.234	0.262
Vitamin D (µg)	r	-0.293	-0.274	0.031	-0.150	-0.257
Vitamin E (α-TE)	r	0.018	-0.030	0.186	0.104	0.045
Thiamine (mg)	r	0.025	-0.018	0.129	-0.029	0.044
Riboflavin (mg)	r	-0.018	-0.028	-0.248	-0.132	0.094
Niacin (mg)	r	-0.024	0.023	0.162	0.155	0.131
Vitamin B6 (mg)	r	-0.081	-0.113	0.016	-0.084	0.005
Folate (µg)	r	0.112	0.093	0.035	-0.079	0.080
Vitamin B12 (µg)	r	-0.186	-0.207	-0.116	-0.245	-0.121
Vitamin C (mg)	r	0.330	0.132	0.080	0.191	0.223
Calcium (mg)	r	0.032	0.055	0.048	0.071	0.081
Iron (mg)	r	-0.270	-0.034	0.107	-0.11	-0.063
Sodium (mg)	r	-0.129	-0.017	0.383*	0.254	0.054
	p	0.505	0.931	**0.040**	0.183	0.779
Potassium (mg)	r	-0.198	-0.314	-0.094	-0.255	-0.241
Magnesium (mg)	r	-0.276	-0.314	-0.010	-0.245	-0.236
Zinc (mg)	r	0.075	0.293	0.516**	0.350	0.346
	p	0.698	0.122	**0.004**	0.063	0.066
Selenium (µg)	r	0.125	-0.167	0.067	-0.271	-0.031
Iodine (µg)	r	-0.012	-0.249	-0.078	-0.405*	-0.163
	p	0.950	0.193	0.689	**0.029**	0.399

Monounsaturated fat (MUFA), polyunsaturated fat (PUFA), carbohydrates (CHO). P (p-value). ** Correlation is significant at the 0.01 level (2-tailed). Pearson correlation coefficients (r) were calculated for BRAF-MDQ physical, living and total fatigue. Spearman's (ρ) correlation coefficients (r) were calculated for cognitive and emotional fatigue. * Correlation is significant at the 0.05 level (2-tailed).

Correlation coefficients for RAID and RAND 12 scores with nutrient intake from 7-day food record in study population

		RAID	**RAND 12**
		Fatigue	VT
Kilocalories	r	-0.404	-0.009
Fat (g)	r	-0.336	-0.142
Fat E %	r	0.028	-0.255
Saturated fat (g)	r	-0.433	0.089
Saturated fat E %	r	-0.294	0.105
MUFA (g)	r	-0.236	-0.149
PUFA (g)	r	-0.121	-0.333
Omega-3 (g)	r	-0.039	-0.594**
	p	0.873	**0.007**
Omega-6 (g)	r	-0.143	-0.108
Carbohydrates (g)	r	-0.299	0.123
Carbohydrates E %	r	0.067	-0.255
Starch (g)	r	-0.317	0.266
Sugar (g)	r	-0.199	-0.148
Fibre (g)	r	-0.229	0.045
Protein (g)	r	-0.478*	-0.109
	p	**0.039**	0.656
Protein E %	r	-0.194	-0.058
Salt (g)	r	-0.027	0.157
Vitamin A (RAE)	r	-0.189	0.048
Vitamin D (µg)	r	-0.430	-0.503*
	p	0.066	**0.028**
Vitamin E (α-TE)	r	-0.074	-0.309
Thiamine (mg)	r	0.017	0.099
Riboflavin (mg)	r	-0.270	0.075
Niacin (mg)	r	-0.286	-0.187
Vitamin B6 (mg)	r	-0.241	-0.219
Folate (µg)	r	-0.217	0.132
Vitamin B12 (µg)	r	-0.232	-0.313
Vitamin C (mg)	r	-0.124	0.132
Calcium (mg)	r	-0.428	0.223
Iron (mg)	r	-0.271	0.254
Sodium (mg)	r	-0.108	0.288
Potassium (mg)	r	-0.323	0.083
Magnesium (mg)	r	-0.387	0.000
Zinc (mg)	r	-0.312	-0.001
Selenium (µg)	r	-0.164	-0.460*
	p	0.503	**0.047**
Iodine (µg)	r	-0.347	-0.035

Monounsaturated fat (MUFA), polyunsaturated fat (PUFA), carbohydrates include fibre (CHO). P (p-value). Pearson correlation coefficients were calculated for RAID fatigue while Spearman's (ρ) correlation coefficients were calculated for RAND12 VT. ** Correlation is significant at the 0.01 level (2-tailed).* Correlation is significant at the 0.05 level (2-tailed).

Correlation coefficients for BRAF-MDQ and nutrient intake from 7-day food record in study population, n=19.

		BRAF-MDQ				
		Physical	Living	Cognition	Emotion	Total
Kilocalories	r	-0.444	-0.240	-0.305	-0.076	-0.300
Fat (g)	r	-0.358	-0.207	-0.045	0.130	-0.216
Fat E %	r	0.026	0.011	0.216	0.166	0.083
Saturated fat (g)	r	-0.507*	-0.277	-0.171	-0.042	-0.308
	p	**0.027**	0.250	0.728	0.888	0.199
Saturated fat E %	r	-0.368	-0.238	-0.086	-0.034	-0.209
MUFA (g)	r	-0.228	-0.159	-0.062	0.090	-0.181
PUFA (g)	r	-0.143	0.094	0.177	0.166	0.049
Omega-3 (g)	r	0.083	-0.034	0.149	0.016	0.091
Omega-6 (g)	r	-0.190	0.046	0.090	0.182	-0.033
Carbohydrates (g)	r	-0.398	-0.110	-0.344	-0.012	-0.229
Carbohydrates E %	r	-0.053	0.185	-0.206	0.049	0.010
Starch (g)	r	-0.410	-0.275	-0.229	-0.069	-0.321
Sugar (g)	r	-0.303	0.163	0.050	0.451	-0.027
Fibre (g)	r	-0.180	-0.458*	-0.024	-0.212	-0.303
	p	0.462	**0.049**	0.922	0.384	0.207
Protein (g)	r	-0.353	-0.494*	-0.083	-0.233	-0.369
	p	0.138	**0.032**	0.737	0.337	0.120
Protein %	r	0.040	-0.361	0.012	-0.404	-0.146
Salt (g)	r	-0.181	-0.277	0.003	-0.047	-0.158
Vitamin A (RAE)	r	-0.286	-0.168	-0.111	-0.194	-0.204
Vitamin D (µg)	r	-0.321	-0.166	0.160	0.150	-0.211
Vitamin E (α-TE)	r	-0.031	0.068	0.032	0.094	0.003
Thiamine (mg)	r	-0.044	0.122	-0.071	0.179	0.077
Riboflavin (mg)	r	-0.355	-0.202	-0.362	-0.392	-0.215
Niacin (mg)	r	-0.304	-0.198	-0.062	-0.187	-0.154
Vitamin B6 (mg)	r	-0.160	-0.285	0.015	-0.166	-0.115
Folate (µg)	r	-0.221	-0.357	-0.211	-0.152	-0.298
Vitamin B12 (µg)	r	-0.224	-0.198	-0.058	-0.169	-0.132
Vitamin C (mg)	r	-0.099	-0.205	-0.216	-0.162	-0.228
Calcium (mg)	r	-0.399	-0.441	-0.249	-0.231	-0.409
Iron (mg)	r	-0.385	-0.444	-0.050	-0.139	-0.375
Sodium (mg)	r	-0.286	-0.295	-0.163	-0.143	-0.243
Potassium (mg)	r	-0.235	-0.521*	-0.225	-0.504*	-0.434
	p	0.334	**0.022**	0.354	**0.028**	0.063
Magnesium (mg)	r	-0.337	-0.515*	-0.224	-0.426	-0.408
	p	0.158	**0.024**	0.356	0.069	0.083
Zinc (mg)	r	-0.367	-0.496*	-0.125	-0.107	-0.344
	p	0.122	**0.031**	0.609	0.664	0.149
Selenium (µg)	r	-0.092	0.008	0.167	0.002	0.044
Iodine (µg)	r	-0.340	-0.447	-0.297	-0.443	-0.473*
	p	0.155	0.055	0.216	0.057	**0.041**

Table 17. Saturated fat (SFA), monounsaturated fat (MUFA), polyunsaturated fat (PUFA), carbohydrates include fibre (CHO). P (p-value). Pearson correlation coefficients were calculated for BRAF-MDQ physical, living and total fatigue. Spearman's (ρ) correlation coefficients were calculated for cognitive and emotional fatigue. ** Correlation is significant at the 0.01 level (2-tailed).* Correlation is significant at the 0.05 level (2-tailed).

7.7 Appendix VII

Correlation coefficients for RAID, BRAF-MDQ and RAND 12 scores with body composition measurements in study population using DXA.

		Sex	Body fat %	Fat mass (kg)	FFM (kg)	Muscle mass (kg)	FMI (kg/m2)	FFMI (kg/m2)
			r	r	r	r	r	R
RAID	Fatigue	F	-0.115	-0.188	-0.234	-0.243	-0.186	-0.244
		M	0.028	0.122	0.467	0.448	0.018	0.403
		All	0.000	-0.084	-0.087	-0.095	-0.105	-0.149
BRAF-MDQ	Physical	F	-0.294	-0.263	-0.093	-0.101	-0.279	-0.130
		M	0.111	0.264	0.591	0.571	0.139	0.549
		All	-0.039	-0.090	-0.067	-0.073	-0.122	-0.127
	Living	F	-0.008	-0.103	-0.229	-0.234	-0.083	-0.199
		M	0.468	0.518	0.213	0.196	0.450	0.150
		All	0.164	0.018	-0.217	-0.222	0.036	-0.230
	Cognition	F	-0.164	-0.247	-0.329	-0.344	-0.270	-0.396
		M	0.152	0.152	0.395	0.395	0.152	0.395
		All	-0.096	-0.203	-0.316	-0.324	-0.225	-0.352
	Emotion	F	-0.247	-0.326	-0.385	-0.394	-0.312	-0.398
		M	0.555	0.555	0.185	0.185	0.555	0.185
		All	-0.088	-0.167	-0.302	-0.309	-0.159	-0.302
	Total	F	-0.165	-0.231	-0.261	-0.266	-0.223	-0.256
		M	0.133	0.215	0.411	0.397	0.120	0.322
		All	0.017	-0.104	-0.172	-0.178	-0.109	-0.222
RAND 12	VT	F	-0.032	0.063	0.341	0.361	0.075	0.306
		M	-0.112	-0.112	-0.894*	-0.894*	-0.112	-0.894*
		p	0.858	0.858	**0.041**	**0.041**	0.858	**0.041**
		All	0.020	-0.027	0.180	0.194	-0.006	0.152

P (p-value), ** Correlation is significant at the 0.01 level (2-tailed).* Correlation is significant at the 0.05 level (2-tailed). Fat free mass (FFM), Fat mass index (FMI), Fat free mass index (FFMI).

7.8 Appendix VIII

Correlation coefficients for RAID and RAND 12 scores with clinical parameters in study population.

		RAID	**RAND 12**
		Fatigue	VT
Haemoglobin	r	0.165	-0.079
Ferritin	r	0.055	-0.065
ESR (mm/t)	r	-0.162	0.087
CRP (mg/L)	r	-0.193	-0.256
Homocysteine (µmol/L)	r	-0.260	0.090
MMA (µmol/L)	r	0.123	-0.041
TSH (mIU/L)	r	0.174	0.176
fT4 (pmol/L)	r	-0.076	-0.338
Albumin (g/L)	r	0.321	0.014
Glucose (mmol/L)	r	-0.054	0.057
Cholesterol **(**mmol/L)	r	-0.117	0.284
HDL **(**mmol/L)	r	-0.206	0.131
LDL **(**mmol/L)	r	-0.087	0.243
TAG **(**mmol/L)	r	0.156	0.034
25-OH-vit D	r	-0.032	-0.546**
	p	0.871	**0.003**
Folate **(**nmol/L)	r	0.234	-0.154
B12 **(**pmol/L)	r	0.044	-0.089
SBP (mmHg)	r	-0.370	0.103
DBP (mmHg)	r	-0.054	-0.127

** Correlation is significant at the 0.01 level (2-tailed).* Correlation is significant at the 0.05 level (2-tailed).
Abbreviations: p (p-value), fT4 (free thyroxine), MMA (methylmalonic acid). Vitamin D (25-OH-vit D), TSH (thyroid stimulating hormone) Cholesterol (Chol). LDL (low density lipoprotein), HDL (high density lipoprotein), TAG (triglycerides), SBP (systolic blood pressure), DBP (diastolic blood pressure).

Correlation coefficients for BRAF-MDQ scores with clinical parameters in study population

		BRAF-MDQ				
		Physical	Living	Cognition	Emotion	Total
Haemoglobin	r	0.099	0.103	-0.129	0.024	0.059
Ferritin	r	0.006	-0.040	-0.122	-0.094	-0.046
ESR (mm/t)	r	-0.053	-0.200	-0.041	-0.220	-0.142
CRP (mg/L)	r	-0.140	-0.153	0.036	-0.052	-0.151
Homocysteine (µmol/L)	r	-0.306	-0.197	-0.302	-0.349	-0.329
MMA (µmol/L)	r	0.140	-0.011	-0.237	-0.185	-0.006
TSH (mIU/L)	r	0.174	0.076	0.160	0.186	0.139
fT4 (pmol/L)	r	-0.117	-0.028	-0.012	0.104	-0.038
Albumin (g/L)	r	0.318	0.182	0.121	0.251	0.231
Glucose (mmol/L)	r	-0.150	0.047	-0.088	0.123	-0.022
Cholesterol **(**mmol/L)	r	-0.220	0.060	-0.370	-0.195	-0.127
HDL **(**mmol/L)	r	-0.280	-0.431*	-0.200	-0.336	-0.348
	p	0.141	**0.020**	0.245	0.120	0.064
LDL **(**mmol/L)	r	-0.136	0.151	-0.306	-0.072	-0.054
TAG **(**mmol/L)	r	0.123	0.243	-0.026	0.201	0.155
25-OH-vit D	r	0.048	-0.161	0.076	-0.067	-0.023
Folate **(**nmol/L)	r	0.051	-0.041	0.335	0.152	0.177
B12 **(**pmol/L)	r	-0.015	0.200	0.034	0.177	0.170
SBP (mmHg)	r	-0.313	-0.332	-0.328	-0.359	-0.383*
	p	0.105	0.084	0.794	0.672	**0.044**
DBP (mmHg)	r	0.016	-0.085	-0.222	-0.117	-0.126

** Correlation is significant at the 0.01 level (2-tailed).* Correlation is significant at the 0.05 level (2-tailed).
Abbreviations: p (p-value), fT4 (free thyroxine), MMA (methylmalonic acid). Vitamin D (25-OH-vit D), TSH (thyroid stimulating hormone) Cholesterol (Chol). LDL (low density lipoprotein), HDL (high density lipoprotein), TAG (triglycerides), SBP (systolic blood pressure), DBP (diastolic blood pressure).