Diet as a complementary therapy in Rheumatoid Arthritis

On the menu: An anti-inflammatory portfolio diet

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Cover illustration: *The Three Graces* by Peter Paul Rubens (1577-1640), Public domain, via Wikimedia Commons.

The cover illustration is a clipping from the painting *The Three Graces* (1638). This painting is considered artistic evidence for the existence of rheumatoid arthritis before the first known description of the disease by Augustin Jacob Landré-Beauvais during his doctoral dissertation in 1800. The joints of the hand of the woman to the left are damaged in a way that is typical for the disease.

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"The content of a book holds the power of education and it is with this power that we can shape our future and change lives."

- Malala Yousafzai

ABSTRACT

Over the last two decades, pharmacological treatment in rheumatoid arthritis (RA) has evolved remarkably and is essential to suppress disease progress. Still, it often fails to provide satisfactory symptom relief suggesting a need for complementary treatment. The aim of this thesis was to evaluate the effects of a proposed anti-inflammatory portfolio diet on RA symptoms, and to investigate the patients' habitual energy and nutrient intake.

The thesis was based on the crossover trial ADIRA (Anti-inflammatory Diet In Rheumatoid Arthritis). The intervention diet was rich in whole grain, fatty fish, fruit, berries, vegetables, and probiotics, and low in red meat, while the control diet was similar to the general Swedish diet.

Results from **paper I** indicated modest beneficial effects on disease activity of the intervention diet. Results from **paper II** indicated that the intervention diet improved physical functioning but no other aspects of health-related quality of life. In both papers, these results were primarily obtained among participants with stable pharmacological treatment. **Paper III**, using dietary biomarkers and food records, indicated high compliance to instructions on whole grain, seafood, red meat, and overall fat quality. **Paper IV** showed that habitual intake of saturated fatty acids was high, while intake of fiber and several micronutrients, especially vitamin D, was low.

These findings suggest that a proposed anti-inflammatory diet has modest beneficial effects on RA symptoms and are consistent with previous research showing inadequate nutrient intake in these patients. Further research in the real-world clinical setting is required to investigate the feasibility of the dietary treatment more thoroughly. Yet, the results of the thesis indicate that dietitian involvement in RA management may be important to optimize these patients' nutrient intake. The dietitian could also further advice dietary modifications to induce weight reduction among overweight patients and reduce the risk of comorbidities.
Keywords: dietary intervention, diet, nutrition, rheumatoid arthritis

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Sammanfattning på svenska

Reumatoid artrit (RA), eller ledgångsreumatism som det ofta kallas, är en kronisk, inflammatorisk sjukdom som 0,7 % av Sveriges befolkning idag lever med. Sjukdomen orsakar inflammation i lederna men patienterna har också en ökad risk för andra sjukdomar, bland annat hjärt-kärlsjukdom. Den medicinska behandlingen har utvecklats enormt de senaste decennierna men många patienter har ändå kvarstående sjukdomssymtom så som smärta och trötthet. Därför finns ett stort behov av att finna en effektiv komplementär behandling. Enskilda studier har visat symtomlindring av olika kostmönster och kostkomponenter men många av dessa studier är små och av låg kvalitet. Trots att det idag inte finns några starka evidens för symtomlindring provar många patienter olika dieter på egen hand. Näringsintaget i patientgruppen har i flera studier visat sig vara bristfälligt men det saknas moderna, omfattande studier av svenska patienter med RA. Den här avhandlingen har undersökt effekterna av en kost innehållandes livsmedel och kostkomponenter med föreslagna anti-inflammatoriska egenskaper på sjukdomsaktivitet och hälsorelaterad livskvalitet vid RA, samt det habituella energi- och näringsintaget i patientgruppen.

Avhandlingen baserades på behandlingsstudien ADIRA (Anti-inflammatorisk kost vid reumatoid artrit) där 50 deltagare slumpades till att börja med en kost rik på fullkorn, fet fisk, frukt, bär, grönsaker och probiotika, eller en kontrollkost som var lik den generella kosten i Sverige. Deltagarna åt varje kost i tio veckor. Studien försedde deltagarna med mat motsvarande ~50 % av deras dagliga intag och för övriga måltider fick de instruktioner om att äta på ett liknande sätt. Deltagarna uppmanades vara viktstabila under studiens gång och följsamhet till studiekosterna undersöktes med biomarkörer i blodet samt kostdagböcker.

Resultatet visade måttliga förbättringar i sjukdomsaktivitet vid RA av den föreslagna anti-inflammatoriska kosten. Detta var tydligast hos deltagare som inte ändrade sin anti-reumatiska medicinering under studietiden. Vidare sågs betydelsefulla förbättringar i den fysiska funktionen och även dessa förbättringar var tydligast hos deltagare med stabil medicinering. Inga övriga undersökta aspekter av livskvalitet, så som mental och social funktion, förbättrades. Studiedeltagarna var viktstabila och hade god följsamhet till studiekosterna avseende instruktioner om intag av fullkorn, fisk och rött kött, samt fettkvalitet.

Slutligen visade avhandlingens resultat att patienternas habituella intag av mättat fett var högt medan intaget av fiber samt flertalet mikronutrienter, särskilt vitamin D, var lågt.

Avhandlingens resultat talar för att dietisten har en viktig roll i vården av dessa patienter i syfte att optimera näringsintaget. En kostbehandling skulle dessutom kunna inducera viktnedgång vid övervikt, minska risken för samsjuklighet, och möjligtvis även förbättra sjukdomssymtomen. Koststudier tenderar att attrahera personer med ett visst intresse av kost och hälsa, personer som gör medvetna kostval, och man kan därför tänka sig att patientgruppen i allmänhet har ett ännu sämre näringsintag än vad avhandlingens resultat visade. Detta betonar ytterligare vikten av en dietist. Framtida studier bör undersöka kostbehandlingens genomförbarhet och effekter i den verkliga kliniska verksamheten där patienter endast får kostråd och inte kostnadsfri hemleverans av mat.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Vadell AKE**, Bärebring L, Hulander E, Gjertsson I, Lindqvist HM, Winkvist, A (2020). Anti-inflammatory Diet In Rheumatoid Arthritis (ADIRA) – a randomized, controlled crossover trial indicating effects on disease activity.
Am J Clin Nutr 2020;111:1203-1213.
https://doi.org/10.1093/ajcn/nqaa019.

II. **Turesson Wadell A**, Bärebring L, Hulander E, Gjertsson I, Hagberg L, Lindqvist HM, Winkvist, A (2021). Effects on health-related quality of life in the randomized, controlled crossover trial ADIRA (Anti-inflammatory Diet In Rheumatoid Arthritis).
PLoS ONE 16(10): e0258716. https://doi.org/10.1371/journal.pone.0258716.

III. **Turesson Wadell A**, Bärebring L, Hulander E, Gjertsson I, Landberg R, Lindqvist HM, Winkvist A (2023). Dietary biomarkers and food records indicate compliance to study diets in the ADIRA (Anti-inflammatory Diet In Rheumatoid Arthritis) trial.
Front. Nutr. 10:1209787. doi: 10.3389/fnut.2023.1209787

IV. **Turesson Wadell A**, Bärebring L, Hulander E, Gjertsson I, Lindqvist HM, Winkvist A (2022). Inadequate Dietary Nutrient Intake in Patients With Rheumatoid Arthritis in Southwestern Sweden: A Cross-Sectional Study.
Front. Nutr. 9:915064. doi: 10.3389/fnut.2022.915064.

Contents

Abbreviations

AA	Arachidonic acid
ACR	American College of Rheumatology
ADIRA	Anti-inflammatory Diet In Rheumatoid Arthritis
ALA	α-linolenic acid
BMI	Body mass index
CRP	C-reactive protein
CVD	Cardiovascular disease
DAS28	Disease activity score-28
DHA	Docosahexaenoic acid
DMARD	Disease modifying anti-rheumatic drug
DPA	Docosapentaenoic acid
E%	Energy percent
EPA	Eicosapentaenoic acid
ESR	Erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology
FFQ	Food frequency questionnaire
HAQ	Health assessment questionnaire
HrQoL	Health-related Quality of Life

IL	Interleukin
kcal	kilocalories
LA	Linoleic acid
LI	Lower intake level
MUFA	Monounsaturated fatty acids
NNR	Nordic nutrition recommendations
OPLS	Orthogonal projections to latent structures
OPLS-DA	OPLS with discriminant analysis
OPLS-EP	OPLS with effect projections
PG-VAS	Patient global visual analogue scale
PUFA	Polyunsaturated fatty acids
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
RI	Recommended intake
SCFA	Short-chained fatty acid
SF-36	36-item short form survey
SF-36 PF	SF-36 physical functioning
SFA	Saturated fatty acids
SRQ	Swedish Rheumatology Quality Register
TNF	Tumor necrosis factor
VAS	Visual analogue scale

Definitions in short

Dietary biomarker	A biochemical indicator of actual dietary intake or of the result of metabolism of dietary intake
Dietary fiber	Carbohydrates in plants which cannot be metabolized by human digestive enzymes, but only through anaerobic fermentation by the gut microbiome
Fatigue	A tiredness that is constant and does not diminish by rest or sleep.
Habitual dietary intake	Usual, long-term energy and nutrient intake
Health-related quality of life	The patient's perception of well-being related to or affected by illness and/or treatment (1)
Microbiome	All microbial organisms that naturally exist within the gastrointestinal tract
Prebiotics	A substrate that is selectively utilized by host microorganisms conferring a health benefit (2)
Portfolio diet	A combination of individual food items with suggestive effects on rheumatoid arthritis symptoms
Probiotics	Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (3)
Remission	Absence of (measurable) disease activity

Preface

One can say that it began about 230 million years ago: the history of rheumatoid arthritis may have started with the dinosaurs. In 2016, researchers found, for the first time, septic arthritis in bones from a hadrosaur[1]. The poor dinosaur was probably suffering a lot since septic arthritis causes joint pain and fever and, if untreated, may cause substantial damage of the joint. But what could she do, antibiotics was first discovered million years later…

We fast-forward some hundred million years. The first known description of rheumatoid arthritis was by Augustin Jacob Landré-Beauvais during his dissertation in 1800[2]. Landré-Beauvais met several patients, primarily poor women, with severe joint pain. The symptoms these patients suffered from were however not like the ones of other known diseases of the joints. Gout had been discovered and acknowledged, and Landré-Beauvais believed that some form of gout was the cause of these people's illness. Almost 100 years later, after the disease had been clearly distinguished from gout, the physician Archibald Garrod named it "Rheumatoid arthritis"[3].

Garrod claimed that this disease was far older than 90 years, that ancient bone findings demonstrated damage alike such stemming from rheumatoid arthritis. This claim became questioned, and rheumatoid arthritis was generally said to be *a disease of the modern era*. However, it is also said that the Greek physician and the "Father of medicine" Hippocrates, who lived around 400 BC, described a patient with rheumatoid arthritis in one of his texts[3]. Whether this disease can be described as a new or old disease has been debated for quite some time, and it is an important debate and research field. Knowledge on this matter can provide important clues about the etiology of the disease.

Besides meeting patients with rheumatoid arthritis (possibly…), Hippocrates is often ascribed the famous quote "*Let food be thy medicine, and medicine be thy food*". Although the true origin and meaning of that quote may not be as is generally believed[4], we do know today that what we eat can indeed affect both incidence and symptoms of several diseases. So, I and many other researchers thus ask ourselves: can food be medicine also for people suffering from rheumatoid arthritis?

[1] Anné J, Hedrick BP, Schein JP. First diagnosis of septic arthritis in a dinosaur. R Soc Open Sci. 2016;3(8):160222.

[2] Landré-Beauvais AJ. The first description of rheumatoid arthritis. Unabridged text of the doctoral dissertation presented in 1800. Joint Bone Spine. 2001;68(2):130-43.

[3] Entezami P, Fox DA, Clapham PJ, Chung KC. Historical perspective on the etiology of rheumatoid arthritis. Hand Clin. 2011;27(1):1-10.

[4] Cardenas D. Let not thy food be confused with thy medicine: The Hippocratic misquotation. e-SPEN journal. 2013;8(6):e260-e2.

Introduction

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is an autoimmune, chronic disease primarily affecting the joints of the body. The global prevalence is estimated to be ~0.5% (4) and in Sweden about 0.7-0.8% of the adult population has a RA diagnosis (5). The pathophysiology involves an activation of the immune response resulting in inflammation at the synovial membrane (6). The cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6 are among the most important mediators of the inflammatory processes in RA (6). Swelling, tenderness and erythema are consequences of the synovitis (7). Further, the inflammation causes stiffness and pain, and if the disease is left untreated, joint destruction and deformities will emerge. The patients' physical ability is often negatively affected and usual daily activities such as dressing, eating, showering and grocery shopping, can be difficult (8). Although the impact on physical health is larger, RA also impair mental and social functioning (9). Fatigue and work disability are common consequences of the disease. It is estimated that about 40-70% of all patients suffer from fatigue; a kind of tiredness that is constant and does not diminish by rest or sleep (10). The pain and negatively affected physical functioning as well as the general inflammation and pharmacological treatment are all possible disease-related reasons for the fatigue. However, non-disease-specific factors, such as depression, obesity, and low physical activity, may be even more important predictors (10). Patients report fatigue to be one of the most important disease symptoms and it negatively affect their daily living and social life and induce work disability (11). A study investigating the work disability rates among ~8000 patients with RA in 32 countries concluded that about one third of all patients <65 years of age became work-disabled due to their RA (12).

Both genetic and environmental factors are involved in the pathogenesis of RA. The risk of developing RA is significantly higher if there is a family history of the disease (7). The autoantibodies rheumatoid factor (RF) and anti-cyclic citrullinated peptides (ACPA) occur in about 60-70% of all patients with RA, and the disease pathogenesis differs between seropositive RA (presence of RF or ACPA) and seronegative RA (neither RF nor ACPA) (7, 13). The most important environmental factor in the pathogenesis of RA is smoking

which in a Swedish study was shown to account for 35% of all ACPA-positive RA (14) and seemed to have a greater influence in men compared to women (14, 15). High body mass index (BMI) is also a risk factor (16, 17), while a moderate alcohol intake has been shown to protect against RA development (17, 18). The possibly protective role of alcohol could be due to the polyphenolic compound resveratrol which is antioxidative and anti-inflammatory through its inhibiting effect on the nuclear factor kappa-B (NF-κB), thus reducing the inflammatory gene expression (19). Resveratrol also suppresses cyclooxygenase -2, an enzyme involved in the conversion of omega-6 fatty acids into inflammatory mediators such as prostaglandins. The role of diet in the etiology of RA is however not fully established but some studies have shown protecting effects of fish and vegetables, and a Mediterranean dietary pattern (20).

Although the disease occurs also in younger individuals, incidence peaks around ages 50 to 70 years (21, 22). RA is more common among women than men with ~3/4 of patients being female. The difference in incidence between females and males is higher in younger individuals but decreases with age (22). Also, women have a worse disease prognosis (23, 24). The reason behind the sex differences is not fully understood but sex hormones are most likely involved. During pregnancy, disease activity often ameliorates and early menopause seems to increase the risk to develop the disease (25). Just as with female sex, seropositive RA is also associated with a more aggressive course of the disease compared to seronegative RA. However, a recent meta-analysis found that males were more likely to be seropositive than were females (26).

As mentioned, RA primarily affects the joints. However, it is considered a systemic disease, i.e., other organ systems may also be affected by the inflammation (7). Examples of extraarticular manifestations are vasculitis (inflammation of the blood vessels), rheumatic nodules (limps under the skin), anemia and interstitial lung disease (27). Also, patients with RA have a higher risk for several comorbidities such as cardiovascular disease (CVD), osteoporosis, bacterial infections and depression. About half of all patients suffer from comorbidity, with anxiety disorders and hypertension being the most common (28). The rate of CVD in this patient group is high and this can be attributed to both the systemic inflammation and side effects of the pharmacological treatment, primarily glucocorticoids and non-steroidal anti-inflammatory drugs (29). Traditional risk factors also play a role. Hypertension, dyslipidemia, smoking, and obesity are all well known risk factors for CVD and are commonly reported in patients with RA (30, 31). Nevertheless, even when accounting for traditional

risk factors, patients with RA still have an increased risk for CVD, i.e., the disease per se seems to be a risk factor, but the reason for this is not fully understood (32). Osteoporosis and bacterial infections are also comorbid conditions in RA and result from both inflammation and side effects of pharmacological treatment, primarily glucocorticoids and immunosuppressive medications (29, 33). Further, about 30% of the patients have a depression (34). Systemic inflammation, pharmacological treatment, pain, fatigue, and sedentary behavior due to reduced physical function, are all possible reasons for the high depression rate (35). Finally, the mortality rate is higher in this patient group compared to the general population (34) with the risk of CVD mortality being 50% higher (36).

Disease activity

As previously mentioned, disease symptoms in RA include e.g., inflammation, swollen and tender joints, pain, stiffness (especially morning stiffness) and fatigue. The disease is characterized by flares, i.e., periods of higher disease activity alternates with periods of lower, or even absent, disease activity, i.e., remission (37). An RA disease flare has previously been described and defined by Bingham et al. (38) as:

> A flare occurs with any worsening of disease activity that would, if persistent, in most cases lead to initiation or change of therapy; and a flare represents a cluster of symptoms of sufficient duration and intensity to require initiation, change or increase in therapy. (p. 2339)

Five disease activity measurements in RA are recommended for clinical use (39). The Clinical Disease Activity Index (CDAI) includes both provider and patient reported variables, the Simplified Disease Activity Index (SDAI) includes provider and patient reported variables as well as lab results, and the Patient Activity Scale-II as well as the Routine Assessment of Patient Index Data 3 (RAPID3) include only patient reported variables.

The recommended index most used both in the clinic as well as in clinical trials is the Disease Activity Score-28 (DAS28) (40). This is a composite score including erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), tender and swollen joint count (out of 28 joints), and patient perception of general health (41). When these variables are combined, it results in one single continuous measure of disease activity, ranging from 0-9.4 (42). DAS28 is further divided into four levels of disease activity: remission, low, moderate, and high disease activity (41, 43) as described in Table 1.

Table 1. Categorization of disease activity

Disease activity	DAS28-ESR
Clinical remission	<2.6
Low	2.6–≤3.2
Moderate	>3.2–5.1
High	>5.1

Categorization according to van Gestel (43) and van Riel et al (41). DAS28-ESR, Disease activity score-28 using erythrocyte sedimentation rate

DAS28 was first developed using ESR as the inflammation measure, but it was later shown that also CRP could be used (44). However, both scoring and interpretation differ depending on the inflammation marker chosen. CRP reflects more acute, short-time changes in inflammation compared to ESR. Also, ESR is a non-specific measure of inflammation and is affected by factors like age, shape and size of erythrocytes, and plasma protein, in particular immunoglobulins (45). Importantly, DAS28-CRP in general scores 0.2 units lower than DAS28-ESR (46). Joints of the fingers, wrists, elbows, shoulders, and knees are included in the 28 joint count (Figure 1).

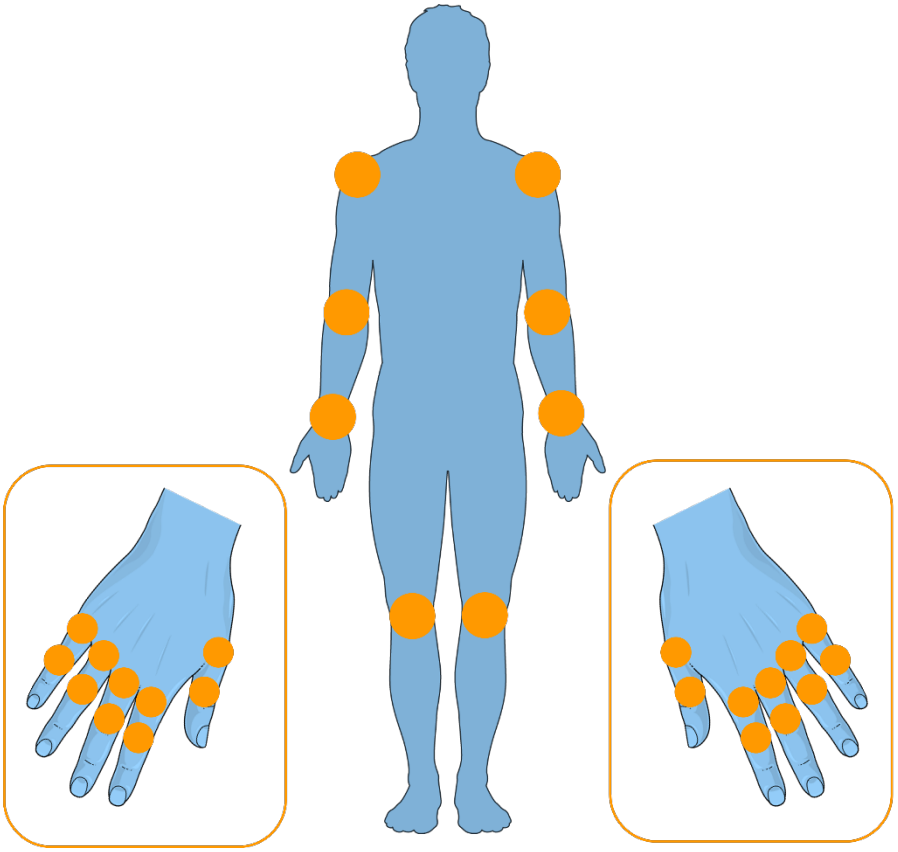

Figure 1. Joints included in the assessment of tender and swollen joints in Disease Activity Score-28.
The figure was partly generated using "Outlines" and "Hand" from Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license (https://creativecommons.org/licenses/by/3.0/).

The patient perception of general health included in DAS28 is assessed using a 100 mm (best to worst) visual analogue scale (VAS). This VAS is called a "Patient Global Visual Analogue Scale" (PG-VAS), Figure 2 (47).

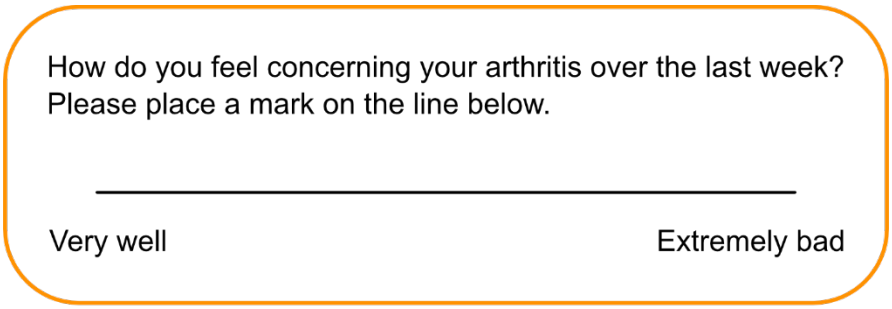

Figure 2. Example of a Patient Global Visual Analogue Scale.

The wording is retrieved from French T, Hewlett S, Kirwan J, Sanderson T. Different wording of the Patient Global Visual Analogue Scale (PG-VAS) affects rheumatoid arthritis patients' scoring and the overall Disease Activity Score (DAS28): a cross-sectional study. Musculoskeletal Care. 2013;11(4):229-37.

Exact wording of the PG-VAS differs between studies, which has shown to affect the DAS28 outcome (47). There is no consensus on what exact phrase to use or what exactly the question is supposed to capture. The example in Figure 2 focuses on the arthritis, but it could also aim to target patients' perception of his/her general health (47). In the description of the development of the DAS28, a PG-VAS with a question concerning general health was included, but it was not further specified (48).

According to the American College of Rheumatology (ACR), the following formula should be used to calculate DAS28-ESR (39) :

$$0.56 \times \sqrt{(Tender\ joint\ count)} + 0.28 \times \sqrt{(Swollen\ joint\ count)} + 0.70 \times \ln(ESR) + 0.014 \times (VAS)$$

For DAS28-CRP, the following formula is recommended (39):

$$0.56 \times \sqrt{(Tender\ joint\ count)} + 0.28 \times \sqrt{(Swollen\ joint\ count)} + 0.36 \times \ln(CRP + 1) + 0.014 \times (VAS) + 0.96$$

The patient reported variables in the DAS28 (i.e., tender joints and general health) contribute the most to the final score, while the inflammation marker contributes the least (49).

DAS28 is a further development of Disease Activity Score (DAS) which also includes ESR or CRP and patient perception of general health, but the painful joint count is calculated using a specific index called Ritchie Articular index, and the swollen joint count include 44 joints (41). But as it was shown that a joint count including only 28 joints often affected by the disease was as valid as the more comprehensive joint count, DAS28 was developed and validated in a study including ~1000 patients with recent-onset RA in the Netherlands (48, 50).

Pharmacological treatment

The pharmacological treatment for patients with RA has evolved tremendously during the last decades (51). Together with more knowledge about the disease pathogenesis and thus earlier diagnoses and treatment, this has resulted in less joint destruction and deformities, and thus a higher functional ability for the patients in general. Also, even though being higher compared to the general population, the mortality rate has decreased over the last 50 years (34, 52). The European Alliance of Associations for Rheumatology (EULAR) regularly provides recommendations for the management of rheumatic diseases and the Swedish Society for Rheumatology provides national guidelines for medical treatment.

It has been recognized that earlier diagnosis and medication improve the prognosis (53). The majority of the patients with RA are prescribed Disease Modifying Antirheumatic Drugs (DMARDs), which most often include methotrexate (54, 55). DMARDs are immunosuppressive drugs that reduce both inflammation and risk of organ damage as well as provide symptom relief. These drugs are divided into synthetic conventional DMARDS (e.g., methotrexate), targeted synthetic DMARDs (e.g., janus kinase (JAK)-inhibitors) or biological DMARDs (e.g., TNF-inhibitors) (54). Methotrexate has several disease modifying properties. Among them, it is a folic acid antagonist meaning that it inhibits the work of folic acid in e.g., cell division and DNA synthesis. Thus, supplemental folic acid should accompany methotrexate treatment to reveal possible side effects (e.g., nausea, mouth sores) of the folic acid inhibition (54).

Notably, the effect of DMARDs is not instant. Therefore, bridging therapy with glucocorticoids (per oral or as injections) is used at diagnosis or during

disease flares (54, 56). Although glucocorticoids are highly effective in preventing joint destruction, they have many side effects. The risk of both diabetes mellitus and CVD has been shown to increase if glucocorticoids are used during a longer period of time. Osteoporosis, depression, increased appetite and weight gain are other known side effects, and some can occur already at very low doses. Due to the osteoporosis risk, supplemental calcium and vitamin D are recommended if the patient is treated with glucocorticoids (56).

To evaluate the effectiveness of the pharmacological treatment, EULAR response criteria can be used (43). It was primarily developed for use in clinical trials to compare different treatments and includes both changes in DAS28 as well as the baseline DAS28, i.e., the DAS28 before starting the treatment. The patient is then classified as having no, moderate, or good response to the treatment. Details of the response criteria are displayed in Figure 3.

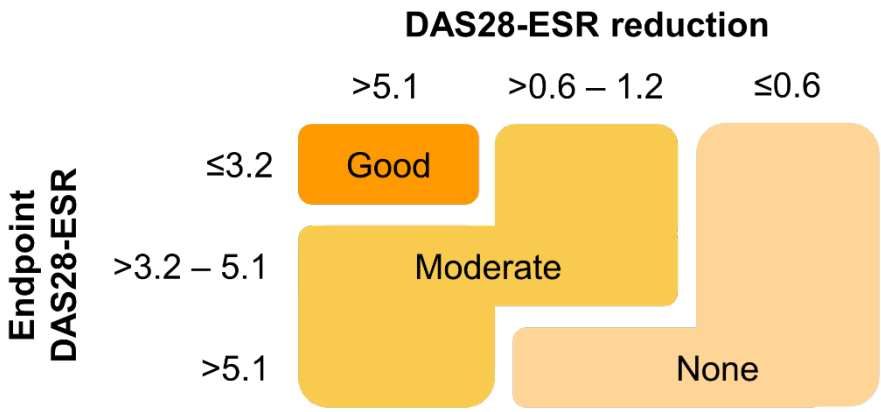

Figure 3.The scoring of EULAR response criteria which measures the response to rheumatoid arthritis treatment. DAS28-ESR, Disease activity Score-28 erythrocyte sedimentation rate.

Complementary treatment

EULAR also includes some lifestyle factors in their recommendations on management of RA and other rheumatic diseases. They conclude that improvements in some lifestyle factors are an important part of the disease management, but only as a complement and not as a replacement for the medical treatment (57). Since exercise is beneficial in general and it has been shown to

reduce pain and increase the physical ability and health-related quality of life (HrQoL), regular exercise is recommended; aerobic exercise at a moderate intensity for 150 min/week and muscle-strengthening exercise two times/week. Health professionals should encourage and help patients to adapt exercise to their own ability and state of disease. Further, striving towards a healthy weight through a healthy diet and physical activity is recommended. Lifestyle factors also include alcohol intake and smoking habits. EULAR recommend health professionals to encourage and support the patients to stop smoking due to overall negative health effects and disease specific negative effects on disease activity, effectiveness of DMARDs and risk of comorbidities.

As for dietary recommendations from EULAR, they conclude that the evidence for dietary effects on the disease is low due to low quality studies with few participants (57). However, the patients should be educated of the importance of a generally healthy diet (high in fruits and vegetables, legumes, and seafood, while low in saturated fats [SFAs] and sugars) to reduce the risk of obesity and other diseases. They should also be informed that specific diets probably do not reduce disease symptoms to any greater extent.

The ACR also published recommendations on lifestyle factors recently. They recommend against adherence to a certain diet except the Mediterranean diet (the concept of this diet is described in the "Diet" section further ahead), which they *conditionally* recommend (58). They base this recommendation on e.g., low to moderate level of evidence of improvement in pain but no change in physical ability or disease activity and the possible patient burden of following such a diet. They also *conditionally* recommend following established US dietary recommendations without dietary supplements. The recommendation is conditional due to e.g., very low to moderate level of evidence and possible harm.

The Mediterranean diet is recommended also by the French Society for Rheumatology (59). Primarily due to the positive effects on cardiometabolic risk factors, they state that this diet could be proposed to patients with RA. Yet, as the general population in France are recommended to eat a Mediterranean-like diet as well, this is in fact not a disease-specific recommendation. However, the French Society for Rheumatology also recommends that because of its proved symptom relieving effects, a supplemental 2-3 g of omega-3 fatty acids/day (fish oil) could be suggested to patients with RA (59). No other specific diets or food components are generally recommended to patients with RA.

These are a few examples of current dietary recommendations from different rheumatology societies. The Swedish Society for Rheumatology does not provide specific dietary guidelines for patients with RA but instead refer the patients to the general Swedish dietary recommendations (60). Further, in their recommendations on CVD prevention in inflammatory rheumatic diseases they state, without providing further details, that dietary habits should be considered (61).

Treatment goals

A treat-to-target approach is recommended for the management of RA with the goal being remission or, for some patients, a low disease activity level, and to prevent joint destruction (54, 62). As mentioned previously, the treatment has evolved and improved, and patients today are diagnosed earlier and thus start treatment in an early stage of the disease. In general, joint deformities as well as some of the previously common comorbidities are less common. Still, most patients do not reach sustained remission (63, 64). Sustained remission can be defined as DAS28-ESR <2.6 on at least two consecutive occasions for ≥6 months (64), but also other definitions are used (63). Male sex, low disease activity at baseline and a combination of DMARDs as initial treatment are some examples of predictors for both temporary and sustained remission (63). Further, patients with obesity have in some studies been shown to have higher disease activity levels and to not reach remission to the same extent as those with lower BMI (63, 65, 66).

Despite reaching remission or having a good response to the treatment, many patients still suffer from remaining symptoms such as fatigue and pain (67-70). Also for fatigue, obesity predicts higher levels and less reduction with treatment (65).

DIET

General dietary recommendations

According to the World Health Organization (WHO), "*Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*" (71) (p. 1). Dietary habits have a significant role in achieving this state of well-being. A healthy diet prevents malnutrition and reduces the risk for several diseases such as CVD and diabetes (72). About every ten years, the Nordic Council of Ministers updates the Nordic Nutrition

Recommendations (NNR), which include dietary reference values for the Nordic countries, and in the 2023 version, also the Baltic countries (73). The nutrition recommendations include recommended intake ranges and levels for macronutrients and micronutrients, respectively. Recommended intake ranges for macronutrients are based on reduced disease risk as well as an adequate nutrient intake (74). The recommended intake (RI) of micronutrients is set to meet the need of nearly all individuals in the general population while the average requirement (AR) should cover the requirements for half of the population. The lower intake level (LI) marks the level of intake below which most individuals would develop clinical deficiency symptoms. Except for the nutrient recommendations, the NNR also include recommendations on healthy dietary patterns (74).

The current dietary guidelines for the general population in Sweden were developed by the Swedish Food Agency and are based on NNR 2012 (74, 75). In the development of these guidelines, several factors were taken into consideration: the nutrient recommendations from NNR 2012, the actual dietary intake in Sweden, and also environmental aspects (75). Further, they were based on evidence from both observational and intervention studies. The current Swedish dietary guidelines in short are displayed in Figure 4 but during 2024, new dietary guidelines, based on NNR 2023, are planned to be presented.

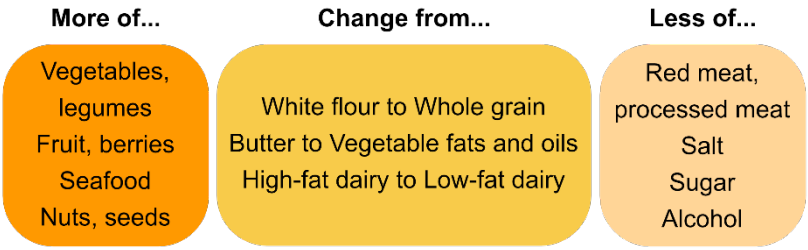

Figure 4. Dietary recommendations to the general population in Sweden, developed by the Swedish Food Agency (Livsmedelsverket. De svenska kostråden - Hitta ditt sätt - Att äta grönare, lagom mycket och röra på dig. Livsmedelsverket; 2022.).

Anti-inflammatory effects of diet

While diet cannot replace the pharmacological treatment, there are many indications that certain diets or dietary components as an addition to medication could possibly further alter disease activity and symptoms in RA (19). Except from the well-known dietary effects on weight and blood lipid profile, diet can also affect the immune system, directly and indirectly, and thus inhibit inflammation.

The omega-6 fatty acid arachidonic acid (AA) is a precursor for inflammatory eicosanoids (76). Long-chained **omega-3 fatty acids,** which are abundant in **fatty fish**, or can be supplied through supplements, decrease this eicosanoid production and inhibit production of inflammatory cytokines (76). Also, the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have the ability to reduce the inflammatory gene expression by inhibiting the activation of the NF-κB (76). **Walnuts** and **rapeseed oil** are plant-based sources of the shorter omega-3 fatty acid α-linolenic acid (ALA) which are converted to primarily EPA in the human body (76, 77). **Olive oil,** an important component of the Mediterranean diet, contains the antioxidant vitamin E and several phenolic compounds with antioxidative properties (19). The phenolic compounds in olive oil have been shown to inhibit the activation of the NF-κB (78). The production of reactive oxygen species, a subgroup of free radicals, are increased in RA and when too much of these species are produced, and the body cannot eliminate enough of these, oxidative stress occurs (79). The oxidative stress can activate NF-κB and lead to increased

production of TNF-α and other inflammatory cytokines. Antioxidants neutralize the reactive oxygen species and reduce free radicals and thus reduce the oxidative stress (80). Also **spices**, such as **ginger, cinnamon, garlic**, and **turmeric**, contain phenolic compounds (81). Extracts from several spices have in both in vitro and in vivo studies been shown to inhibit the activation of the NF-κB and to regulate production of inflammatory mediators (81). For example, curcumin in turmeric binds to cyclooxygenase-1 and lipoxygenase and thus disturb the AA metabolism leading to a reduced inflammatory eicosanoid production (81). In addition, spices can also affect the gut microbiota due to polyphenols and prebiotic components (81). Finally, certain **vitamins and minerals** have anti-inflammatory effects. **1,25-dihydroxyvitamin D**, which is the active form of vitamin D, has a modulating role in both the innate and adaptive immune system and exert anti-inflammatory effects e.g., through inhibition of the NF-κB (82). In the diet, vitamin D_2 or D_3 is found in fatty fish, egg yolk and enriched dairy products/dairy alternatives and is after consumption and absorption further metabolized to 1,25-dihydroxyvitamin D by primarily the liver and kidney (73). Further, **β-carotene** (a pro-vitamin A carotenoid), **vitamin C**, **vitamin E**, **selenium**, and **zinc** are all nutrients with antioxidative effects (73, 83, 84). **Selenium**, which are abundant in especially seafood but also egg, dairy, meat, and cereals grown in selenium-rich soil, also seems to inhibit NF-κB and reduce the production of inflammatory mediators (85).

The gut microbiota and permeability of the intestinal barrier seem to play a role in the development of inflammatory diseases, and patients with RA have been shown to have an altered and less diverse microbiota compared to healthy individuals (86). The microbiota is involved in the regulation of the immune response. A diverse, rich microbiota leads to an increased production of short-chained fatty acids (SCFAs) which can improve the intestinal barrier and thus prevent toxins from entering the bloodstream and triggering an inflammatory response (87). SCFAs also affect several immune cells, e.g., T cells which are part of the adaptive immune system. In RA, T cells are infiltrated in the synovial membrane where they activate cells initiating inflammation (88). Plant-based diets and the Mediterranean diet are rich in **dietary fiber (prebiotics)** which function as "food" for the microbiota and increases both amount and activity of the bacteria (88). The human digestive enzymes cannot metabolize these dietary fibers and thus they are transported to the colon where they are fermented by the gut bacteria. During gut microbiota fermentation of dietary

fiber, SCFAs are produced. **Probiotics** are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (3) (p. 507). They have the ability to improve the gut microbiota and thus reduce the activity of inflammatory cytokines, modulate the inflammatory gene expression through inhibition of the NF-κB complex, and strengthen the intestinal barrier (89). Probiotics are available as supplements in the form of capsules, pills and tablets, or specific strains added to sour milk and juice. Potentially healthy microorganisms can be found naturally in fermented foods too, but not all are proven probiotic (90). In contrast, **an unhealthy diet rich in added sugar and SFAs** has been shown to increase levels of the microbe *Prevotella copri*, which in some studies has been associated with early RA symptoms, and to increase the permeability of the intestinal barrier (91).

There could also be an anti-inflammatory effect of *not* eating. When **fasting**, the body produces ketone bodies which have inhibiting effects on the inflammatory cytokine IL-17 (92). Other explanations for the anti-inflammatory effect of fasting could be an altered gut microbiota and decreased intestinal permeability (93, 94). In addition, since fasting is very calorie-restricted it should induce weight loss which by itself also could be anti-inflammatory, at least in overweight and obese individuals (95).

Rheumatoid arthritis and diet

Effects of diet on disease symptoms

The effects of diet and dietary components on RA disease activity and other symptoms have been investigated in several studies. The different study types used in dietary interventions are further described in the section Dietary interventions (page 19). The traditional **Mediterranean diet** is well known for its potential to lower the risk of CVD (96) and includes a high amount of olive oil, nuts, vegetables and legumes, fruit, and whole grain cereals, a moderate amount of dairy, fish and red wine, and a low amount of red meat and sweets (97). In patients with RA, interventions with the Mediterranean diet have lowered disease activity, increased physical ability, and reduced pain (98-101). However, a non-randomized allocation of study participants to the different treatment arms could have induced bias such as confounding, possibly having an impact on the results (99, 100).

As for the Mediterranean diet, **plant-based diets** have also been associated with a reduced risk for several diseases such as CVD (102). The studies investigating the effect of plant-based diets on RA symptoms have often included a fasting period before the vegetarian diet period (103-106), and/or has the vegetarian diet been very restricted in different ways (living food (107), gluten-free (108, 109), free from certain fruit or vegetables (109), soy free (109), etc.). In addition, some studies investigating fasting and/or a vegetarian diet have not randomized their study participants into the different treatment arms (99, 104, 110, 111) inducing risk of bias. Improvements in disease activity and/or pain and morning stiffness have been shown in some patients consuming a vegetarian diet (103, 104, 107-109, 112). A recently performed study on 7-days of fasting followed by a plant-based diet with anti-inflammatory herbs and spices, rich in prebiotics, and with restrictions on the timing of eating, showed within-group improvements in both disease activity and physical ability (105). Importantly, there were no significant differences compared to the control group who consumed a diet with low levels of AA according to general dietary guidelines and who also improved their disease symptoms. Further, significant weight reduction could possibly explain some of the symptom relief in these studies (103, 105-107, 109, 112, 113). Other studies investigating the effects of **5–7 days of fasting** have also seen positive effects on disease activity, physical functioning, and quality of life (99, 106, 110, 111, 114). However, it is important to bear in mind that such strict fasting (200-800 kilocalorie (kcal) per day), despite its possible positive effects, cannot be implemented for a longer period of time and thus is not an appropriate long-term dietary treatment.

Elemental diet is an artificial, hypoallergenic diet consisting of no whole protein, but instead amino acids, mono- and disaccharides, medium- and long-chain triglycerides, vitamins, and minerals (115). Two randomized and controlled pilot studies concluded improvements from the diet in a few aspects of disease activity (115, 116). In another randomized controlled trial (RCT) using an elemental diet, within-group differences in pain and physical ability were obtained but neither pain nor physical ability differed from the control group who continued their regular diet (117). Further, there have been RCTs investigating effects also of other types of hypoallergenic diet, or **exclusion diets**. These diets exclude certain food groups such as meat, gluten, dairy, egg, and additives (118-120). Excluded food groups have varied between studies, and so has the results. However, some improvements in RA symptoms have been reported (118, 121).

One RCT in RA investigated the effects of **a diet with <90 mg/day of AA and supplemental omega-3 fatty acids** (122). The combination of low AA and high omega-3 fatty acid intake had more pronounced effects on disease activity, compared to only low AA intake or a western diet supplemented with omega-3 fatty acids. Further, a proposed **anti-inflammatory diet** (rich in fish, vegetables, fruit, olive and canola oil, and whole grain, and low in red meat, SFAs, and refined carbohydrates) with the addition of **flaxseeds** daily was compared to a regular diet with the addition of flaxseeds and to a regular diet with the addition of roasted wheat (123). Only the regular diet with flaxseed improved disease activity, while pain was reduced in both flaxseed groups. Several aspects of quality of life were also improved in the flaxseed groups compared to the wheat group (123).

All these examples of dietary interventions have investigated possible effects of whole diets: the Mediterranean diet, plant-based diets, fasting, an elemental diet, exclusion diets and two "anti-inflammatory" diets. However, there are also several studies investigating the effects of certain food items, food components or nutrients. **Blue mussel** intake has in one RCT reduced disease activity and pain, and increased several aspects of quality of life (124). In a cross-sectional study, higher **fish intake** was associated with lower disease activity (125). Further, the effects of intake of **pizza** on disease activity was evaluated in a cross-sectional study including Italian patients with RA (126). High-frequency consumers reported lower disease activity, and the **mozzarella cheese** on the pizza seemed to be responsible for that. However, the contribution of tomato sauce could not be analyzed. Within the same cohort**,** associations between **olive oil** and **nuts**, and disease activity were studied. Here, some analyses resulted in significant associations between a higher intake of olive oil and lower disease activity, but significant associations between nut intake and disease activity were only obtained among seropositive patients and patients with a longer disease duration (127).

Gioxari and co-authors included 20 RCTs in a meta-analysis and concluded that **omega-3 fatty acids** can alter some aspects of disease activity in RA, e.g., early morning stiffness, pain, and physical ability (128). They also concluded an improved lipid profile. Most of the included trials used EPA+DHA supplements (a few used ALA) and not foods rich in omega-3 fatty acids. Further, the study periods lasted from 12 to 72 weeks and the doses ranged from 0.3 g/day through 9.6 g/day. In contrast to this, a more recent meta-analysis found no significant differences between omega-3 fatty acid supplementation and placebo and concluded only small gains of supplementation use (129).

Zeng and co-authors reviewed ten RCTs on **probiotics** in RA and performed a meta-analysis that, despite individual studies reporting beneficial effects on several aspects of disease activity such as DAS28 and pain, resulted only in reduced CRP (89). The authors stated that evidence was not sufficient for a general recommendation on probiotic use in this patient group. Another meta-analysis included studies on **prebiotics, probiotics and synbiotics** (mix of pre- and probiotics) (130). Twelve RCTs were included, and the analysis resulted in a decrease in DAS28 and a slight improvement in physical ability (borderline significant), and it also confirmed the CRP lowering effects of probiotics. Levels of other inflammatory markers were also reduced.

Effects of **curcumin** on several aspects of RA disease activity were recently evaluated by Kou and co-authors. A total of ten RCTs were included, and the authors reported positive effects on both inflammatory markers, DAS28 and pain (131). The symptom alleviating effects of supplemental **ginger**, **cinnamon**, **saffron** and **garlic** have also been studied. Through a systematic review of six RCTs, Letarouilly and co-authors concluded possible positive effects on e.g., disease activity, pain, and inflammatory markers of these spices, but considered the evidence too low to provide a recommendation (132).

A systematic review and meta-analysis of the effects of 15 different types of dietary polyphenols on RA symptoms was recently performed (133). Except for some of the already mentioned spices or spice extract, RCTs investigating effects of **cranberry extract, pomegranate extract, olive oil, sesamin** (a lignin in sesame seeds), **resveratrol** (present in, for example, red wine), **quercetin** (flavonoid in several fruits and vegetables), and **hesperidin** (flavonoid in citrus fruit), among others, were included. For some of these polyphenols, only one single study could be evaluated, or studies could not be combined for a meta-analysis. Still, the authors concluded beneficial effects on disease activity, inflammatory markers and pain of several of these polyphenols (133).

Supplementation with nutrients such as **vitamin D**, **vitamin E** and **selenium** have also been studied in patients with RA. Al-Saoodi and co-authors concluded no effects of vitamin D on ESR, CRP, and physical ability when a total of eleven RCTs were summarized (82). However, DAS28 and pain were significantly lower after supplementation of vitamin D compared to control group (e.g., placebo pills or lower doses). Still, the authors concluded that the evidence for these effects was low due to few data. Nguyen and co-authors included only two RCTs in a meta-analysis of the effects of vitamin E supplementation which resulted in no significant differences in disease activity and

pain (134). Further, although significantly higher physical ability and less pain followed selenium supplementation compared to placebo in a recent RCT (135), results from a 2007 systematic review as well as another recently performed RCT indicate that selenium supplementation is ineffective regarding RA symptoms (83, 136). One trial investigating **a combination of selenium, zinc, vitamin A, C and E**, resulted in reduced CRP levels as well as DAS28, but this study did not contain any control group (137). Finally, a pilot study provided margarine enriched with **vitamin E** and different carotenoids and supplemental **vitamin C**. A reduction in DAS was obtained but also here a control group was lacking (138).

Despite the many interventions using whole diets, food items or supplement with food components, there is still only sufficient evidence to recommend patients with RA the Mediterranean diet for some symptom relief as well as reduction of CVD risk. Further, the ability of the Mediterranean diet to affect more aspects of disease activity than pain is uncertain (58). Trials investigating dietary effects in RA have been of low quality and have had a high risk of bias due to small sample sizes, lack of blinding, uncertainties in the randomization process, et cetera (139). The lack of blinding is even more problematic when outcomes are subjective as often is the case in RA studies. When study results have been summarized to evaluate overall effects, heterogeneity due to e.g., different outcome measures, pharmacological treatment, and study population, and a lack of studies with longer duration, have made it difficult to draw firm conclusions (139). Further, reported effect sizes have often been small and thus the clinical relevance of the effects could be questioned (57).

Also, a dietary intervention suffers from certain issues that a pharmacological study does not have to consider. The intake of a studied drug is zero at baseline. That is most often not the case when it comes to dietary components (81). Further, at baseline and before that, the intake amount of the studied food or food component often differ among the study participants. In addition, both cooking methods and the rest of the dietary intake can affect the bioavailability of the food component (81). This also means that a single food item or component may not have the same health benefits when isolated in a supplement as when incorporated into the whole diet (140).

Dietary intake

Despite low certainty of the scientific evidence for symptom alleviating effects of diet, many patients with RA report that they experience positive and negative effects of certain foods on their disease symptoms (141-147). Blueberries,

strawberries, and fish have been reported by patients to alleviate symptoms, while soda (with or without sugar), alcoholic beverages, and red meat have been reported to worsen RA symptoms (141, 144, 145). Further, many change their diet after diagnosis and try different diets such as fasting or non-meat, vegetarian, and vegan diets (141, 142, 145, 147). A Swedish study reported that female patients with RA consumed less red meat than did healthy controls (148). Although receiving general dietary advice from the rheumatologist, it is rare that the patients consult with a dietitian for personalized advice (145, 149). Still, it is well-known that long-term dietary restrictions may lead to an inadequate nutrient intake. Several studies have shown high intakes of SFAs (149-154) and low intake of fiber (151, 153-155) in patients with RA. Further, a low intake of several vitamins and minerals have been reported (151, 155-161).

DIETARY INTERVENTIONS

Study types

The dietary effects on health can be investigated using different types of studies. The nutritional observational epidemiologic studies are useful to examine the effects of diet or dietary components on long-term health and disease incidence (162). Here, many participants are included, they live their life "as usual" and can be followed up several years later. However, to study dietary effects in such studies comes with several issues. Large epidemiologic studies include hundreds or thousands of participants, which means that the dietary assessment method needs to be rather brief and inexpensive to make it possible to analyze the food- and nutrient intake for all participants. An even more serious problem is all other factors, often lifestyle factors, that are associated with and "disturb" the relation between food and health. Hence, it is difficult to isolate dietary effects in these studies. The results of observational epidemiologic studies can form the basis for further, more controlled, interventions which allow for evaluation of a true causal relationship between dietary patterns, certain foods or nutrients, and health.

The studies deemed to have the best chance to be of a high quality and thus may draw conclusions regarding causal relationships between diet and health, are the RCTs (163). In these studies, the participants are randomized to one of two or more groups where the intervention group(s) receives the diet/food/other aimed to be studied and the control group(s) receives another diet/food/other or continue eating as usual. In RCTs with a crossover design the participants receive both intervention and control diet/treatment with a

wash-out period in between. When investigating supplements, the participants can be blinded to what treatment they receive since the control group can receive placebo pills. However, blinding is difficult when whole dietary patterns are being studied (164). The possibly disturbing features of the factors mentioned previously should be absent from RCTs, since the participants are randomized, i.e., the disturbing factors are also distributed randomly among the groups (162). Long-term randomized controlled dietary interventions may be challenging to perform, but to investigate dietary effects on disease risk factors as well as symptom relief in already ill patients is possible with a shorter study duration. Although these studies cannot include as many participants as in the epidemiologic studies, there still need to be a certain number of participants included to have the ability to obtain statistically significant results, i.e., to have "statistical power" (165, 166). Exact number of participants needed is calculated before participant recruitment using established formulas for power calculation including information on the desired significance and power level and the expected effect size. With a crossover design, the number of participants can be decreased due to reduced inter-variability (163).

Dietary assessment methods

Regardless of study type, to be able to draw conclusions on the health effects of diet demands a high-quality method to capture the dietary intake. The method must be valid and thus capture what it is intended to capture, e.g., the habitual dietary intake, the intake over a specific day or the intake of certain foods or nutrients depending on the study aim (167, 168). It must also measure the *true* intake. If the measurement tool is valid, it does not contain any random or systematic errors, or at least these are limited. An example of a random error is the difference between the habitual dietary intake and the intake during that specific day when the assessment was performed. This is due to the day-to-day variation in an individuals' food intake and this variation should not be reduced. Instead, random errors can, in this case, be reduced by increasing the number of assessed days (167). Systematic errors could be that questions about a certain food group are missing in a questionnaire aimed to capture the whole dietary intake or if the participants are interviewed about their diet and the interviewer is not the same person for all participants leading to differently asked questions or difference in interpretation of the answers. Random errors lead to imprecise results, while systematic errors lead to bias (167). Further, a valid method should also be reliable, meaning that the results should be consistent over time (provided that the true dietary intake is kept unchanged) (167).

Some examples of dietary assessment methods are 24-h recall, food frequency questionnaire (FFQ), and food records. The 24-h recall aims to capture the exact food-and drink intake during the preceding 24 hours through an interview. This method can capture the habitual dietary intake on a group level provided the number of participants is large enough, or on an individual level providing there are several 24-h recalls performed in different days and seasons of the year for each individual (167).

FFQs can be either qualitative or semi-quantitative. A qualitative FFQ includes questions on consumption frequency of certain foods or food groups during a specified time period (167). This FFQ type does not provide enough information to calculate energy- and nutrient intakes, but only intake frequency. The FFQ becomes quantitative when questions on portion sizes are added to those about frequency. Using this type of FFQ, energy- and nutrient intake can be estimated (169). An FFQ can include questions aimed to capture the whole dietary intake, but it can also be specified to capture intake of a certain nutrient. For example, it could focus on seafood, dairy and margarine intake if the studied nutrient is vitamin D (170). FFQs are often used in epidemiological studies (162).

Food records are registrations of all food and drinks consumed, at the time of consumption, performed by the study participant. Weighed food records are considered the "golden standard" among the different dietary assessment methods and is the most precise method to capture dietary intake in individuals (167). Here, the participants weigh all food items and drinks consumed, while for estimated food records, the participant estimates the intake using household measuring cups etc. Number of registration days varies and depends on number of participants as well the within-subject variation in food and nutrient intake (167). However, weekend days should be included in the recording period since food intake may be different during these days compared to weekdays (167, 171). When performing a weighed food record, the participant should be as precise as possible when describing the foods and drinks consumed. For example, the brand name of a certain food or the recipe of a dish could be recorded if feasible.

To obtain information on energy and nutrient intake, the completed 24-h recalls, FFQs and food records need to be analyzed using, for example, nutrition analysis software including food databases with nutrient information.

These dietary assessment methods have some common limitations, e.g., they are all subjective measures of dietary intakes, and they are all prone to bias; mainly underreporting meaning a reported smaller energy intake than the true intake (172). There could also be selective misreporting inducing social approval or social desirability bias (173). This is the case when the respondent report what he/she thinks is the "right" way to eat. This can lead to underreporting of less healthy and overreporting of more healthy food items. Besides the risk for misreporting, the assessment methods perform differently depending on the study aim. Weighed food records are burdensome for the participant to perform and for the study personnel to analyze. Also, it may be difficult to capture the dietary intake over a longer period and thus the variation in intake. The 24-h recall method is more convenient for the participant but as it relies on memory, it is prone to recall bias. Also, it is crucial for the interviewers to capture *all* intake in their questions which may be difficult. FFQs are also prone to recall bias and cannot provide as exact energy and nutrient intakes as the other methods.

Dietary biomarkers

Dietary biomarkers are biochemical indicators of recent or long-term dietary intake (174). They indicate either actual dietary intake or the result of metabolism of dietary intake Thus, dietary biomarkers have the potential to function as an *objective* way to measure dietary intake and can be used to e.g., validate the subjective dietary assessment methods, to assess recent or long-term dietary intake to estimate disease risk or to assess compliance in dietary interventions (175, 176).

In 2017, Gao and co-authors proposed a classification scheme for different types of dietary and health biomarkers (177). They proposed three major types of dietary and health biomarkers:

1. Exposure and intake biomarkers
2. Effect biomarkers
3. Susceptibility biomarkers

Exposure biomarkers indicate which type and level of dietary and food compounds the individual have been exposed to. These biomarkers are often reported as concentration in blood or as intake rate. Effect biomarkers show how the body respond to the nutritional exposure, e.g., plasma glucose response. Susceptibility biomarkers are those that show the effect of the individual susceptibility to the exposure, i.e., these predict exposure effects on the individual

or define the susceptibility to develop a disease. One biomarker could belong to one or more of these classes. For example, the same biomarker could be used to assess the dietary intake of a specific nutrient (exposure biomarker) as well as to evaluate the nutrient status of an individual and thus the risk for e.g., deficiency (susceptibility biomarker).

Further, Gao and co-authors proposed that the major types of biomarkers should be further classified into subtypes (177). For example, exposure biomarkers were proposed to be divided into:

1. Food compound intake biomarkers
    i. Nutrient intake biomarkers
    ii. Non-nutrient intake biomarkers
2. Food or food component intake biomarkers
3. Dietary pattern biomarkers

Food compound intake biomarkers are biomarkers reflecting the nutrient- or non-nutrient intake over a specified period of time, while food or food component intake biomarkers refer to the intake of certain foods rather than nutrients (177). Non-nutrients could be, for example, toxicants or phenolic compounds. When the aim is to study whole dietary patterns, often in long-term studies, a combination of food or food component intake biomarkers can be used (177, 178). These are classified as dietary pattern biomarkers.

Although this thesis to some extent also includes established health biomarkers such as CRP and certain blood lipids, the focus of this section will be on the dietary biomarkers and more specifically on the food or food component intake biomarkers.

To accurately measure the intake of a certain food, the biomarker must be sensitive and specific to intake, i.e., measure what it is supposed to measure, be sensitive to important changes, and not be present in any other food (179). More, bioavailability and factors not related to the diet but still affecting the biomarker status must be considered. For example, carotenoids are biomarkers for vegetable and fruit intake, but the bioavailability of certain carotenoids differs depending on e.g., what fruit is consumed, particle size, or whether fat was added to the meal or not (180). Thus, two people consuming the same amount of fruit and vegetables could still differ in plasma carotenoid concentration. In addition, non-dietary factors such as smoking, cholesterol level, sex and BMI may also affect the biomarker concentration (181, 182). Finally, dietary

biomarkers can reflect both short-, medium- and long-term dietary intake (179). If the outcome of interest is compliance to a dietary intervention, probably the use of short- or medium-term biomarkers would be the most accurate. Contrary, when evaluating dietary intake in relation to disease risk, long-term dietary intake is often more important, and results could be misleading if assessing biomarkers of short-term intake (162). The pharmacokinetics of the biomarker (absorption, metabolism, excretion etc.) and the biologic specimen used when measuring the biomarker decide whether it reflects short- or long-term dietary intake: adipose tissue has a slow turnover rate and biomarker concentration collected from this specimen can reflect the intake during a longer period of time, while biomarkers in plasma and serum generally reflect more recent intake (162).

Using metabolomics, it is possible to identify and quantify small molecule metabolites in the metabolome, which is defined as "[…] the collection of all small molecule metabolites or chemicals that can be found in a cell, organ or organism" (183) (p. 482). As parts of the metabolome are related to food consumption, metabolomics can be used to explore the response and consequences of food intake. In this way, it may be possible to identify a metabolic profile related to a certain dietary pattern as well as to detect possible biomarkers of food intake (178, 183). The use of metabolomics in nutrition science and dietary biomarker research is promising but within the scope of this thesis, metabolomics is not further used or discussed.

Table 2 shows the biomarkers used and discussed in this thesis.

Table 2. Examples of established biomarkers for different foods.

Food	Biomarker	Biological specimen	Ref.
Fish (primarily fatty fish)	omega-3 fatty acids EPA and DHA	Plasma, serum	(184, 185)
Fruit and vegetables	Carotenoids	Plasma, serum	(186, 187)
Whole grain wheat and rye	Alkylresorcinols	Plasma, urine	(188-193)

DHA, Docosahexaenoic acid; EPA, Eicosapentaenoic acid.

HEALTH-RELATED QUALITY OF LIFE

When studying the effect of diet on disease incidence or symptoms, the subjective nature of the dietary assessment methods often is a problem. However, subjectiveness is not always negative. How the patient her-/himself perceives the effect of a treatment can be argued to be if not more, at least as important as the more objective outcomes such as inflammation, CVD risk factors, nutrient status etc. Only the patients themselves can decide and evaluate how much pain they have, how tired they are, and how sad they feel. In research such outcomes are referred to as patient- or person-reported outcome measures and they reflect individual dimensions that contribute to the quality of life or HrQoL (194).

Although often used interchangeably, quality of life and HrQoL have different meanings. The definition of HrQoL is not clear and both its definition and the common use of the term have been challenged (195). It could be described as one part of the broader term quality of life focusing on self-perceived well-being of illness or treatment (1, 194). There are many established instruments (e.g., questionnaires) to use when measuring HrQoL. These can include global questions on the overall HrQoL but also single-item questions or multi-item scales on different dimensions (i.e., aspects) of HrQoL (194). Some instruments contain both. Dimensions measured when evaluating HrQoL could be both psychological, physical, and social; emotional

functioning, cognitive functioning, physical functioning, social well-being, etc. (194). Further, there are disease-specific instruments as well as generic instruments. The latter has the advantage of making it possible to compare the results of the studied patient group with those of the general population (194). Also, the instruments could be dimension specific, meaning that they focus only on one of the dimensions of quality of life, such as cognitive functioning.

What constitutes a high quality of life is different for different people, and it could even differ for the same person depending on when the question is asked. A patient suffering from a disease may state her overall quality of life as very low when she becomes ill. As time goes, the disease may not improve but still the patient rates her quality of life as better than before. This could be due to her getting used to the symptoms, coping, or comparing herself to other patients who are even more sick (196). It could also be due to a shift in what dimensions she believes are more important for the concept of quality of life; perhaps family relations become more important than physical functioning when you are ill. The phenomenon of these changes in perceived HrQoL is called "response shift" (196).

Just as for the dietary assessment methods, it is important that the instruments used to measure HrQoL are valid (measure what they are intended to measure), reliable (can reproduce the results when repeated under the same conditions), sensitive (can detect a difference between the studied groups) and responsive (can identify clinically relevant changes within an individual over time) (194). Also, unless the patient is cognitively impaired or very young, it is crucial that it is the patient her-/himself that answers the questions, and not a relative, physician or other healthcare professional (194).

In two studies on HrQoL in the general Swedish population, reported HrQoL varied depending on several factors, e.g., women reported lower quality of life than men, and lower educational level and income, smoking and sedentary behavior were all associated with lower quality of life (197, 198). Further, being diagnosed with a disease was also associated with lower scores in these two studies which used two different HrQoL-instruments.

Globally, the most frequently used HrQoL instrument in population-based studies is the generic 36-item Short Form Health Survey (SF-36) (199). Table 3 provides examples of established HrQoL-

instruments, what they intend to measure and whether they are domain-specific, disease-specific, or generic.

Table 3. Examples of health-related quality of life instruments and their characteristics.

Instrument	Type	Outcome	Dimensions	Ref.
EQ-5D (EuroQol five dimensions)	Generic	General health status	Mobility, self-care, usual activities, pain/discomfort, anxiety/depression	(200)
Fatigue Severity Scale	Domain-specific	Fatigue	Fatigue	(201)
HADS (Hospital Anxiety and Depression Scale)	Domain-specific	Anxiety, depression	Anxiety, depression	(202)
HAQ (Health Assessment Questionnaire)	Disease-specific (or possibly generic (203))	Functional ability in rheumatoid arthritis	Physical functioning	(203)
RSCL (Rotterdam Symptom Checklist)	Disease-specific	Quality of life in patients with cancer	Physical symptom and psychological distress, activity level, overall global quality of life	(204)
SF-36 (36-item Short Form Health Survey)	Generic	General health status	Physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health	(205)

Rheumatoid arthritis and health-related quality of life

Patients with RA report a lower HrQoL than the general population and, compared to male patients, female patients tend to report a lower HrQoL for the mental functioning dimensions (9, 206, 207). However, the physical aspects of quality of life seem to be worse than the mental aspects for these patients, regardless of sex.

There are likely dietary effects on certain aspects of HrQoL in RA. In some studies, the Mediterranean diet has improved functional ability and reduced pain and stiffness (98, 100, 146). Further, also omega-3 fatty acid supplementation may reduce pain and improve physical ability (128). Seafood intake possibly affect HrQoL as well. A frequent fish intake has been negatively associated with depression score (208) and functional ability (209), and an RCT investigating effects of blue mussel intake resulted in better mental health and less pain and fatigue in the intervention group (124). A meta-analysis of RCTs on supplemental prebiotics, probiotics and synbiotics concluded a borderline significant effect on functional ability, but no effect on pain (130). Further, another meta-analysis investigating effects of Mediterranean, vegetarian, vegan, and ketogenic (very low in carbohydrates and high in fat, leading to production of ketones) diets revealed improvements in both pain and functional ability (210). However, since HrQoL outcomes are highly subjective and dietary interventions seldom are blinded, the results from such studies can merely indicate rather than determine dietary effects on HrQoL.

As previously mentioned, the ACR conditionally recommend adherence to a Mediterranean-style diet due to improvements in a patient-reported outcome focusing on one dimension of HrQoL: a low to moderate certainty of evidence that this diet can reduce pain, together with e.g., the patient's perspective of adherence to such a diet (58).

THE NEED FOR FURTHER RESEARCH

The potential of certain foods or dietary patterns to exert anti-inflammatory effects is of great interest for many researchers, treating physicians and patients around the world. Not least for those in the search of the optimal RA treatment. Despite highly effective pharmacological treatment and despite often reaching the main goal of disease remission (i.e., low DAS28) many patients still suffer from disease symptoms such as pain and fatigue, and thus there is a need for effective complementary treatment. In addition, the patients seek ways to be

more active in their disease management and recently, recommendations on implementations of self-management strategies were developed by EULAR (211). Thus, to engage the patients themselves in the management of their disease is considered an important part of the RA treatment. Regarding dietary modifications, the Mediterranean diet can be recommended to these patients due to the well-known beneficial effects on cardiometabolic health, which is a common comorbidity in patients with RA, and due to low to moderate certainty of evidence for its effects on pain. However, the effect on other symptoms is uncertain. Further, previous studies have shown inadequate nutrient intakes in this patient group emphasizing the importance of dietitian involvement in RA management. Yet, up-to-date research on the nutrient intake in Swedish patients with RA is lacking which indicates the need for new studies focusing also on this aspect of the disease.

Few interventions have investigated the symptom alleviating effects of whole diets appropriate for long-term use. More common, isolated food components or very restricted diets have been studied. Isolated food components possibly do not produce the same biological response as does the whole diet where the individual food components may potentiate each other's effects on health. Very restricted diets are likely inappropriate as long-term treatment. Further, most dietary interventions in RA have been of low quality and heterogeneity makes it difficult to draw firm conclusions. Thus, there is a need for high quality studies investigating possible symptom reducing effects of whole diets that include the food components with suggestive anti-inflammatory effects.

Aim

The overall aim of this thesis was to evaluate the effects of a proposed anti-inflammatory portfolio diet on disease symptoms and health-related quality of life in patients with rheumatoid arthritis. Further, it also aimed to study the habitual nutrient intake in this patient group.

The specific aims of each paper were:

I. To investigate the effects of a proposed anti-inflammatory diet on disease activity measured as DAS28 in patients with rheumatoid arthritis.

II. To investigate the effects of a proposed anti-inflammatory diet on health-related quality of life in patients with rheumatoid arthritis.

III. To evaluate compliance to the intervention and control diet in the ADIRA trial using dietary biomarkers and food records.

IV. To investigate the habitual energy and nutrient intake in patients with rheumatoid arthritis residing in Southwestern Sweden

Patients and Methods

SELECTION OF PARTICIPANTS

The recruitment of participants was performed mainly through the Swedish Rheumatology Quality Register (SRQ), but also through posters at the Department of Rheumatology, Sahlgrenska University Hospital, Gothenburg, Sweden.

In the SRQ, 1091 patients with an RA diagnosis and listed at Sahlgrenska University Hospital were identified. Because the study food was to be delivered directly to the participants' homes by a home delivery food chain, residing in their delivery area was a criterion. Of the 1091 identified patients, 774 patients were sent an invitation letter to participate in the study. Of these, 113 patients expressed interest, and, after a telephone pre-screening, 66 patients met the inclusion criteria of being aged 18-75 years old and having a disease duration of ≥2 years. These patients were invited to a screening visit (Figure 5).

At the screening visit, inclusion criteria were DAS28 ≥2.6 and a clinically stable RA with no change in DMARDs during the preceding 8 weeks. Exclusion criteria were pregnancy or lactation, intolerances or allergy to non-exchangeable foods, and inability to understand the study information which was given in Swedish.

In Paper I, II and III, all patients who met the criteria for inclusion and completed at least one diet period, were included in the analyses. In Paper IV, all patients who attended the screening visit, regardless of inclusion in the trial, and who completed at least one food record were included in the analyses (Figure 5).

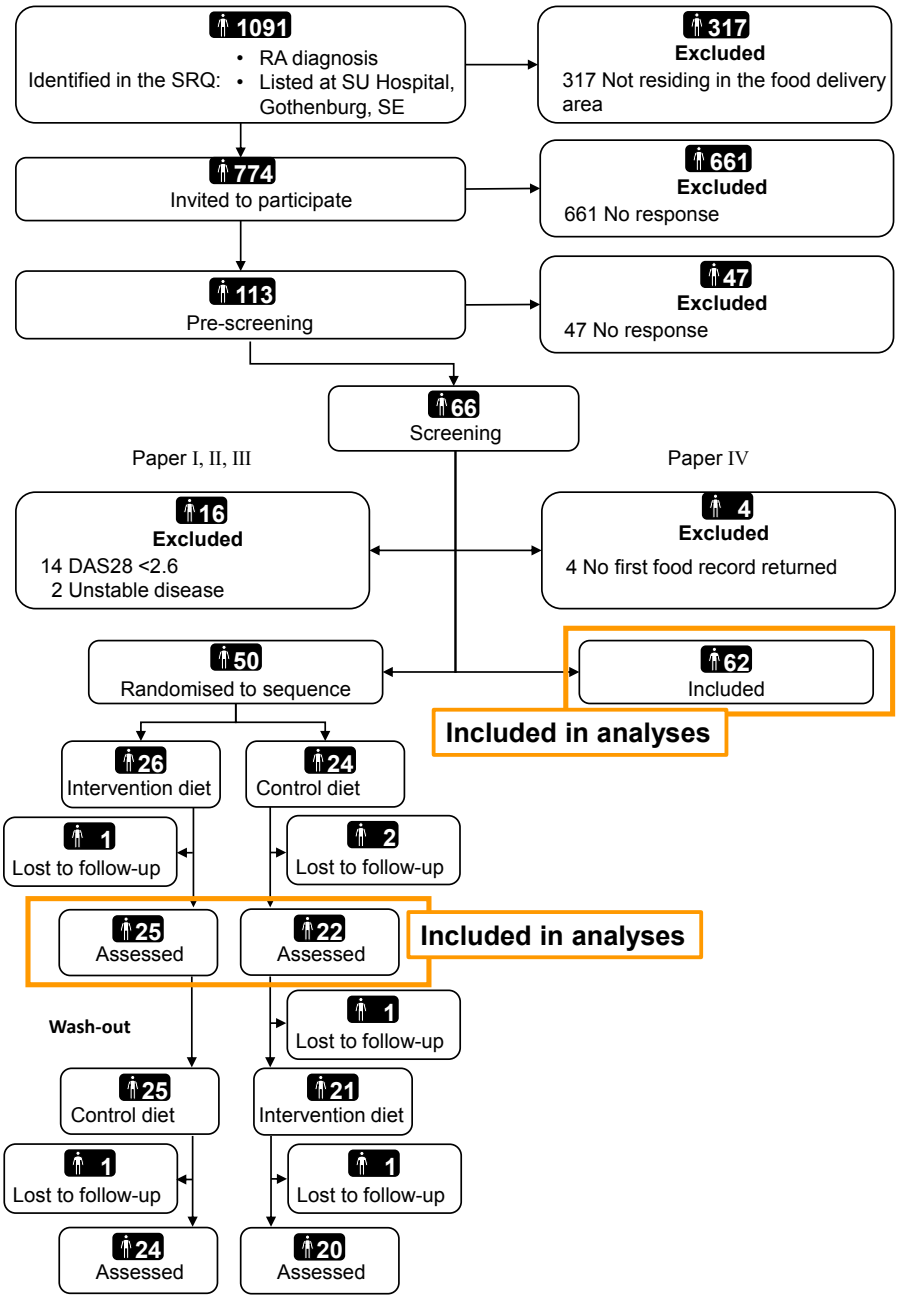

Figure 5. Participant flow in the ADIRA trial. DAS28, Disease activity score-28; RA, Rheumatoid arthritis; SRQ, Swedish Rheumatology Quality Register; SU, Sahlgrenska University

STUDY DESIGN

The ADIRA trial had a crossover design, i.e., half of the included participants were randomized to begin with the intervention diet period for ten weeks, followed by a wash-out period, and then change to the control diet for ten weeks. The other half of the participants began with the control diet period, followed by the wash-out period, and then changed to the intervention diet.

The randomization of included participants was made by a computer-generated list with an allocation ratio of 1:1.

There were five study visits for each participant during the trial: the screening visit, before each diet period and after each diet period. These took place at the Clinic of Rheumatology at the Sahlgrenska University Hospital, Gothenburg. In addition, once each diet period, the participants were interviewed about their compliance over a phone call. In Figure 6, all assessments for each visit are listed.

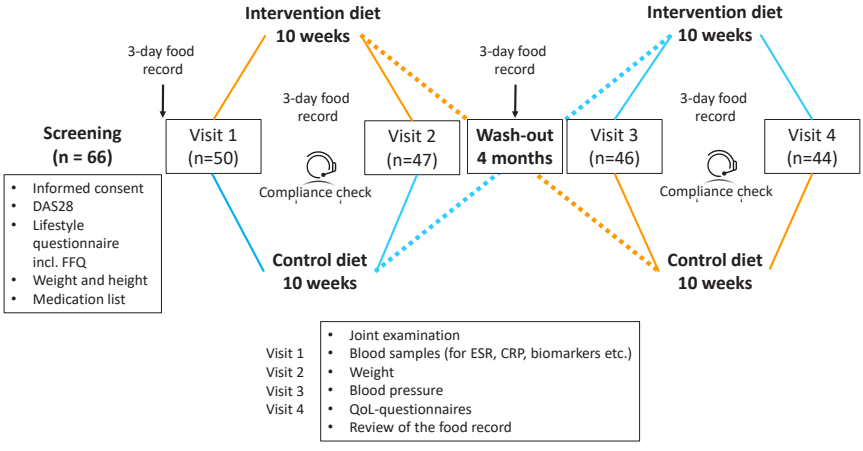

Figure 6. Study design of the ADIRA trial. CRP, C-reactive protein; DAS28, Disease activity score-28; ESR, Erythrocyte sedimentation rate; FFQ, Food frequency questionnaire; QoL, Quality of life.

Participants were instructed to fast overnight before visit 1, 2, 3 and 4, but there were no further restrictions on time for the last meal/drink the day before.

STUDY DIETS

The study provided the participants with breakfast, one main meal and one snack per day for five days per week. Before each diet period, the participants were also provided with three different weekly menus which were repeated three or four times during the ten weeks. The main meal was either easy to prepare (recipe was included in the menu), a ready-to-eat meal, or a mix of both.

The food provided by the study corresponded to ~1100 kcal/day, i.e., about 50% of daily needs. In this thesis, the foods provided by the study are referred to as the "intervention diet" and "control diet". For the remaining meals, the participants were free to choose foods and cooking methods themselves, with some specific restrictions for each diet period which are listed below. These foods were bought and paid for by the participant. In this thesis, when referring to the "the intervention diet period" or "control diet period", *all* foods consumed are included.

In an attempt to blind the participants, investigators and study material referred to the intervention diet as "the fiber diet", and the control diet as "the protein diet".

Nutritional supplements were not allowed during the trial unless prescribed by physician. Changes in medication use was allowed (see further details below).

Intervention diet period

The intervention diet was a portfolio diet combining food items/-components which in previous studies have shown promising effects on RA symptoms. It was hypothesized that by combining these foods, they would potentiate each other's functions and thus result in a more pronounced effect on disease activity and symptoms.

There were three different breakfasts in the intervention diet:

- Sour milk, plain, 0.5% fat (enriched with probiotics: *Lactobacillus [L.] acidophilus LA-5®*, *Bifidobacterium [B.] lactis BB-12®* and *L. casei F19®*)
- Granola/muesli with rolled oats and nuts.
- Frozen blueberries or pomegranate
- Probiotic juice drink (*L. plantarum 299v*)

or

- Oat porridge with extra fiber
- Walnuts
- Milk, 0.5% fat
- Frozen blueberries or pomegranate
- Probiotic juice drink (*L. plantarum 299v*)

or

- Yoghurt, plain, 0.5% fat
- Granola/muesli with rolled oats and nuts.
- Frozen blueberries or pomegranate
- Probiotic juice drink (*L. plantarum 299v*)

As a snack, participants were provided with two fruits per day: banana, apple and/or pear.

The main meals in the intervention diet consisted of

- Protein: Fish (3-4 times/week) or legumes (1-2 times/week)
- Carbohydrates: Potatoes, whole grain cereals (pasta or wheat berries) or bulgur
- Vegetables: Large amount, e.g., spinach, ruccola, pepper, green onion, green peas, broccoli.
- Sauce: Mainly yoghurt (10% fat) or low-fat Crème Fraîche
- Cooking fat: Mainly rapeseed oil
- Flavoring: Soy sauce, lime, ginger etc.

For the whole intervention diet period, the participants were instructed to:

- Limit red meat intake to ≤3 times/week.
- Eat ≥5 portions/day of fruit, berries, and vegetables.
- Use oil or margarine as cooking fat.
- Use low-fat dairy such as low-fat milk and margarine.
- Choose bread and other cereals based on whole grain.

The food components with proposed anti-inflammatory effects included in the ADIRA diet are listed in Table 4.

Table 4. The food components with proposed anti-inflammatory effects included in the ADIRA diet.

Food item	Anti-inflammatory components
Fatty fish	Omega-3 fatty acids (EPA, DHA, DPA), vitamin D, selenium
Rapeseed oil	Omega-3 fatty acids (ALA)
Walnuts	Omega-3 fatty acids (ALA)
Probiotic juice	Probiotics
Probiotic-enriched sour milk	Probiotics
Whole grain	Fiber/Prebiotics
Fruit, berries, and vegetables	Fiber/Prebiotics, antioxidants
Legumes	Fiber/Prebiotics, antioxidants

ADIRA, Anti-inflammatory Diet In Rheumatoid Arthritis; ALA, Alpha-linolenic acid; DHA, Docosahexaenoic acid; DPA, Docosapentaenoic acid; EPA, Eicosapentaenoic acid.

Control diet period

The diet during the control diet period was intended to be nutritionally like a typical Swedish diet, i.e., high in SFAs, low in polyunsaturated fatty acids (PUFAs) and low in fiber. More specifically, the control diet was designed to correspond to the macronutrient intake of Swedish adults 45-64 years of age according to the Swedish Food Agency's nationwide dietary survey Riksmaten 2010-11: 17 energy percent (E%) protein, 34 E% total fat, 43 E% carbohydrates and 13 E% SFAs.

There were two different breakfasts in the control diet:

- Mix of quark and yoghurt, sugar-sweetened, 2% fat

- Corn Flakes
- Orange juice

or

- White bread
- Sandwich spread based on mainly butter, 75% fat.
- Cheese, 28% fat
- Orange juice

As a snack, they were provided with either quark, protein pudding or protein bar.

The main meals in the control diet consisted of

- Protein: Red meat (3-4 times/week) or chicken (1-2 times/week)
- Carbohydrates: Potatoes or white rice
- Vegetables: Mainly canned tomatoes and mushrooms, small amount of other vegetables, e.g., pickled beetroots and haricots verts.
- Sauce: Mainly cream or coconut milk/-cream
- Cooking fat: Mainly butter (but the ready-to-eat meals contained mainly rapeseed oil)
- Flavoring: Broth, jelly, vinegar etc.

For the whole control diet period, the participants were instructed to:

- Eat red meat ≥5 times/week.
- Limit intake of fruit, berries, and vegetables to ≤5 portions/day
- Limit intake of seafood to ≤1 time/week
- Use butter as cooking fat.
- Use high-fat dairy such as whole milk and butter-based sandwich spread.
- Not use any probiotics

The intervention and control diet were isocaloric, but the intervention diet had a higher nutrient density and contained more of, for example, total fat, monounsaturated fatty acids (MUFAs), PUFAs, omega-3- and omega-6 fatty acids, fiber, β-carotene, retinol equivalents, vitamin D, vitamin E, vitamin B12,

magnesium, potassium, and selenium (Table 5). In contrast, the control diet contained more of, for example, protein, SFAs, vitamin C and zinc (Table 5).

Table 5. Nutrient content of the ADIRA diets

	Intervention diet		**Control diet**	
		E%		E%
Energy, *MJ*	4.62		4.60	
Energy, *kcal*	1105		1098	
Protein, *g*	45.8	16.8	62.3	23.0
Total fat, *g*	43.5	34.8	34.5	27.8
SFA, *g*	11.8	9.4	16.4	13.2
MUFA, *g*	14.3	11.4	11.4	9.2
PUFA, *g*	13.5	10.8	3.84	3.1
Palmitic acid (16:0), *g*	6.21	5.0	7.07	5.7
Stearic acid (18:0), *g*	1.85	1.5	2.66	2.1
LA (18:2, n-6), *g*	9.31	7.5	2.99	2.4
ALA (18:3, n-3), *g*	1.24	1.0	0.74	0.6
AA (20:4, n-6), *g*	0.22	0.2	0.05	0.0
EPA (20:5, n-3), *g*	0.74	0.6	0.01	0.0
DPA (22:5, n-3), *g*	0.39	0.3	0.02	0.0
DHA (22:6, n-3), *g*	1.14	0.9	0.01	0.0
Carbohydrates, *g*	119	43.7	129	47.6
Fiber, *g*	23.9	4.1	8.26	1.4
Vitamin C, *mg*	75.5		102	
Iron, *mg*	8.44		6.72	

Calcium, *mg*	477		443	
β-carotene, *μg*	2347		645	
Retinol equivalents, *RE*	317		238	
Vitamin D, *μg*	9.39		1.33	
Vitamin E, *mg*	10.8		4.70	
Thiamin, *mg*	0.96		0.86	
Riboflavin, *mg*	0.87		1.30	
Niacin equivalents, *NE*	21.3		25.8	
Vitamin B6, *mg*	1.74		1.54	
Vitamin B12, *μg*	4.47		2.74	
Phosphorus, *mg*	934		794	
Magnesium, *mg*	282		149	
Potassium, *mg*	2374		1847	
Zinc, *mg*	5.24		6.15	
Folate, *μg*	224		197	
Selenium, *μg*	42.1		26.7	

AA, Arachidonic acid; ADIRA, Anti-inflammatory Diet In Rheumatoid Arthritis; ALA, Alpha-linolenic acid; DHA, Docosahexaenoic acid; DPA, Docosapentaenoic acid; E%, Energy percent; EPA, Eicosapentaenoic acid; kcal, kilocalorie; LA, Linoleic acid; MJ, Megajoule; MUFA, Monounsaturated fatty acids; PUFA, Polyunsaturated fatty acids; SFA, Saturated fatty acids

DIETARY ASSESSMENTS

Food Frequency Questionnaire

At the screening visit, the participants responded to a non-quantitative FFQ aimed to assess frequency of intake of different foods during the last twelve months. Examples of foods included were different kinds of bread, sandwich

spread, cooking fat, vegetables, fruit, nuts and seeds, pasta, rice, meat, processed meat, oily fish, lean fish, poultry, cheese, snacks, candy, bakery products, coffee, tea, and alcoholic beverages. There were six frequencies to choose from: *less than one time/month or never* up to *three times/day or more*. For bread and alcohol, participants were also asked to report number of slices per week and number and amount of different drinks per week (for example "Number of glasses of wine (15 cl)"), respectively. For bread, rice, pasta, bulgur, and couscous there were also questions regarding whole grain product intake.

The FFQ was primarily used to examine the quality of the participants' habitual dietary intake, and for this purpose a dietary quality index based on the FFQ was calculated. This index was developed by the Swedish Food Agency and adapted by Bärebring et al (212). Participants obtaining 0-4 points were considered to have a poor dietary quality, 5-8 points were considered a fair dietary quality, and 9-12 points a high dietary quality. For this thesis, this index was only used to describe the study population at baseline (Paper I and II) and as a covariate in some of the statistical models (Paper I and III).

Food Records

Right before and in the end of each diet period, i.e., a total of four times, the participants performed a 3-day food record. They were instructed to preferably weigh all food items, and if unable to do so, to use household measuring cups instead. When also such tools were unavailable, as when eating outside home, they were advised to estimate the amount themselves and express as dL /tbsp/tsp or refer to pictures on portion sizes included in the food records. Further, they were instructed to be detailed in their reporting, such as to report fat percent (e.g., for milk, yoghurt), possible enrichments of the products (e.g., for plant-based milk), and if the food was cooked or raw when weighed. Finally, the participants were encouraged to note the brand name of the product, especially for bread and granola/muesli.

The food records were completed on three consecutive days: Thursday, Friday and Saturday, or Sunday, Monday, and Tuesday. All four food records for each participant were completed on the same days.

At each study visit, a dietitian (the author of this thesis) reviewed the food record together with the participant. By using *Portionsguide* (213), with images on food items and dishes served in different portion sizes, the participant could specify estimated amounts further.

All food records were analyzed by the same dietitian using The Swedish Food Composition Database 2017-12-15 in Dietist Net Pro version 18.12.16 (Kost och Näringsdata AB). For eight food items not included in the Swedish database, the Finnish food database Fineli 2018-02-28 was used instead. Tap water and salt was not included in the analyses.

In paper I, the food records completed in the end of each diet period were used as compliance assessment, i.e., to investigate if the nutrient intake during the diet periods differed as could be expected.

In paper III, the food records completed during each diet period were used. Daily intake of fruit, berries and vegetables, seafood, and red meat (in gram) were manually extracted from the food records and, together with the previously analyzed intake of whole grain and fatty acids, used to assess compliance to the study diets.

In paper IV, the food records before each diet period (i.e., if both food records were performed and valid, a total of six days reported), and the food records performed by participants attending the screening visit but then excluded from the trial (i.e., three days reported) were used to evaluate habitual dietary intake. Except from reporting median intake of energy and several macro- and micronutrients, the intake was also compared to NNR 2012 on E%, RI, AR, and LI.

DISEASE ACTIVITY

Disease activity was measured using DAS28-ESR and DAS28-CRP.

In paper I, the primary outcome was differences in DAS28-ESR between the intervention and control diet period. Differences in DAS28-CRP, ESR, CRP, tender joint count, swollen joint count and VAS for general health between the diets were secondary outcomes.

In paper II, III and IV, DAS28-ESR was only used to describe the study population at baseline.

Within two weeks before the screening visit, participants provided blood samples for analysis of ESR and CRP. This was done prior to the visit to be able to calculate DAS28 at the screening visit, due to it being a factor for inclusion/exclusion. For visit 1 (i.e., baseline) we used the DAS28 calculated at screening. At visit 2, 3 and 4, new blood samples for analysis of serum ESR

and CRP were provided. The samples were directly centrifuged at 2200 *g* for 10 min and then routinely analyzed at the laboratory for Clinical Chemistry at the Sahlgrenska University Hospital, Gothenburg, Sweden.

Two trained research nurses at the Clinical Rheumatology Research Centre, Clinic of Rheumatology, obtained the blood samples and performed the examination of the joints (screening and visit 2-4). The nurses were blinded to the treatment periods.

The VAS for general health used for obtaining the participants' own estimation of their health contained the question: *How have you been feeling in general over the last week, concerning your rheumatic disease?* Participants were instructed to place a mark on the 100-mm horizontal line, where 0 mm corresponded to "*completely fine*" and 100 mm corresponded to "*worst imaginable*", to indicate their feeling.

The previously described formulas for calculation of DAS28-ESR and DAS28-CRP, recommended by the ACR, were used (39). Disease activity was categorized and defined as in Table 1 in the Background section of this thesis.

To further evaluate response to the study diets, EULAR response criteria developed for comparison of treatments in clinical trials, was used (43).

HEALTH-RELATED QUALITY OF LIFE

In paper II, the effects on HrQoL were studied. Outcomes evaluated were HAQ (203), SF-36 (205, 214), VAS for pain, fatigue and morning stiffness, and duration of morning stiffness.

HAQ measures daily functional ability during the past week by asking 20 questions regarding dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. Each question has six possible answers ranging from *Without any difficulty* through *Unable to do*. Two of these answers address the need for aiding devices or assistance from someone else. All answers are summed up to a HAQ disability index which ranges from 0-3, where 3 indicates complete disability. The Swedish HAQ has been validated for use in patients with RA (215).

SF-36v2® standard contains 36 items about both physical ability and physical, social and mental well-being. Thirty-five of the items are divided into the

following health domains: physical functioning (PF), role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. The scoring scale ranges from 0-100 for each scale, where 100 corresponds to best health state. The domains can be summed up to summary scores: physical component summary and mental component summary. Optum1PRO CoRE Smart Measurement1 System Version 1.5.7240.26936 (Optum, Inc) with the Missing Data Estimation Method, was used to calculate the scores. One question in the SF-36 asks about the difference in general health compared to one year ago but is not included in any of the eight domains. The responses to this question were not analyzed nor presented at all in paper II. The Swedish version of SF-36 has been validated for use in the Swedish adult population (198, 216).

Three different VAS were used to evaluate pain, fatigue, and morning stiffness. Participants were asked "*During last week, how much pain/fatigue/morning stiffness at wake-up have you suffered from because of your rheumatic disease"* and instructed to place a mark on the 100-mm horizontal line, where 0 mm corresponded to "*No pain/fatigue/stiffness*" and 100 mm corresponded to "*worst imaginable pain/fatigue/stiffness*", to indicate their feeling.

In addition, a scale measuring duration of morning stiffness was created for the ADIRA trial (Figure 7).

The questionnaires for HrQoL were performed at study visits 1-4.

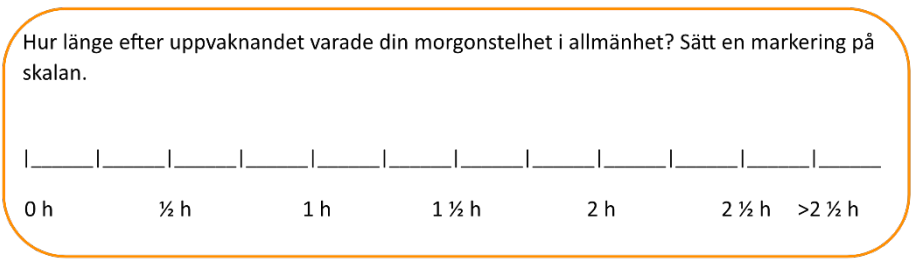

Figure 7. Scale for morning stiffness duration.

COMPLIANCE

In papers I and II, a scoring system developed specifically for the ADIRA trial was used to measure compliance to the study diets.

Also, in paper I, the food records were used to investigate if the nutrient intake during the diet periods differed as could be expected between the diets.

In paper III, dietary biomarkers and food records were used to also objectively evaluate compliance to the study diets. In addition, the results of the biomarkers and the reported dietary intake were compared to the results of the study-specific scoring system.

The ADIRA-specific self-reported compliance scoring system

At middle of each diet period, a telephone administered interview was performed by a dietitian (the author of this thesis). The primary aim of this interview was to assess compliance to the study food. However, this was also a chance to motivate the participants to continue with the study and help them with a proper exchange of food items if needed. Further, possible adverse effects of the study food were also reported during this conversation.

The form in Figure 8 was used to assess compliance. In this figure, the form has been translated to English.

Meal/Consumption	Entire meal	Part of the meal	No part of the meal
Breakfast (of 5)	*[Number of meals: 0–5]*	*[Number of meals: 0–5]*	*[Number of meals: 0–5]*
Main meal (of 5)	*[Number of meals: 0–5]*	*[Number of meals: 0–5]*	*[Number of meals: 0–5]*
Snack (of 5)	*[Number of meals: 0–5]*	*[Number of meals: 0–5]*	*[Number of meals: 0–5]*

Figure 8. The form used to assess compliance (translated from Swedish)

From this form, a compliance scoring system was developed. Entire meal consumed equaled 2 points, part of the meal consumed equaled 1 point and no part of the meal consumed equaled 0 points. Thus, maximum points were 30 (2 points x 3 meals x 5 days). Participants receiving ≥24 points (80%) were considered compliant to the diet period.

Reported dietary intake

Compliance was also measured using reported intake from the 3-day food records. How the food records were performed and analyzed for nutrient content have already been described.

Due to the intended differences in food intake between the intervention- and control diet periods, also the nutrient intake could be expected to differ between the diet periods. The most pronounced expected differences are displayed in Table 6.

Further, the intake of specific food items was extracted from the food records. Intake of whole grain, fruit, berries and vegetables, seafood and red meat were chosen to be used as a compliance measure.

The daily intake of whole grain (g) could be extracted directly from the nutrient analyses data, but the other food items had to be manually extracted. Included in the food categories were:

- *Fruit, berries and vegetables*: fresh, frozen, dried or canned (incl. canned and puréed tomatoes) fruit, berries, vegetables, root vegetables, mushroom, olives, legumes, lemon-/lime juice. Excluded were jam and jelly, broth, fresh herbs, nuts, and juice- and other fruit-based beverages.
  An additional variable where also juice- and other fruit-based beverages were included was created.
- *Seafood*: fresh, frozen, or smoked fish, shellfish, and roe. Broth was excluded.
- *Red meat*: fresh, frozen, smoked, or dried beef, pork, lamb, game meat. Poultry and broth were excluded.

These foods were reported primarily as intake in g/day but also of portions/day or portions/week depending on how the instruction to the participants appeared.

Table 6. Nutrients that could be expected to differ between the diet periods.

	Intervention diet period		Control diet period	
Saturated fatty acids	Lower	Less meat, lean dairy, oil/margarine	Higher	More meat, high-fat dairy, butter
Polyunsaturated fatty acids	Higher	More seafood, nuts, oil/margarine	Lower	Less seafood, butter
Omega-3 fatty acids	Higher	More oily fish, walnuts, rapeseed oil/margarine	Lower	Less oily fish, butter
Fatty acid pattern	Healthy	Less meat, more seafood, lean dairy, nuts, oil/margarine	Unhealthy	More meat, less seafood, high-fat dairy, butter
Fiber	Higher	Whole grain and more fruit and vegetables	Lower	Refined grains and less fruit and vegetables
Vitamin C	Higher	More fruit and vegetables	Lower	Less fruit and vegetables
Vitamin D	Higher	More oily fish, margarine	Lower	Less oily fish, butter
Selenium	Higher	More seafood, nuts	Lower	Less seafood

Dietary biomarkers

Dietary biomarkers were used for objective evaluation of compliance. Plasma concentrations (nmol/L) of alkylresorcinol homologues C17:0, C21:0, C23:0, C25:0, the sum of these, and the ratio C17:0/C21:0 were used as biomarkers for whole grain wheat and rye intake.

Serum concentrations (μmol/L) of carotenoids lutein + zeaxanthin, b-cryptoxanthin, lycopene, α-carotene, β-carotene, the sum of these, and the sum minus lycopene, were used as biomarkers for intake of fruit, berries, and vegetable.

Plasma concentrations (% of total fat) of individual fatty acids were used as biomarkers for intake of margarine/oil (linoleic acid [LA] and ALA) and seafood (EPA, docosapentaenoic acid [DPA] and DHA).

Finally, the plasma fatty acid pattern (each individual fatty acid as % of total fat) was used as a marker for the difference in dietary fat quality of the diets.

The laboratory analyses of each biomarker are thoroughly described in paper III.

OTHER ASSESSMENTS

Anthropometrics

Height was measured to the closest 0.5 cm at screening, using a wall-mounted stadiometer, and without shoes. At screening and each study visit, weight was measured to the closest 0.1 kg in light clothing and without shoes. To account for the weight of the clothes, 1 kg was subtracted. If the participant was unable to remove the shoes, 1.5 kg was subtracted.

Sociodemographic factors

At screening, all participants answered a questionnaire regarding sociodemographic factors, i.e., questions about education, work hours, parent's birthplace, and nicotine use. Education was divided into *No education*, *Primary school* (a total of nine years), *2-year upper secondary school* (a total of eleven years), *3-year upper secondary school* (a total of twelve years), and *University degree or equal*. Work hours were divided into *Not working*, *≤15 hours/week*, *16-30 hours/week*, *31-40 hours/week*, and *>40 hours per week*. The question about parent's birthplace was categorized as *Europe*, *Middle East*, *Africa*, *Asia*, *North America*, and *South America*. Nicotine use was divided in *Yes* and *No*, with a follow-up question about type: *Cigarettes*, *Snuff*, *Nicotine gum* or *Nicotine patches*.

Pharmacological treatment

At the screening visit, the participants provided their medication list. At visit 1 and 3, i.e., before each diet period, they were provided a form to note any changes in their medication; if they stopped or started using any medication, and any temporarily used medication during the diet period. They also filled in any health care visits.

In papers I and II, data on pharmacological treatment were used to describe the study population at baseline. Also, in sensitivity analyses, the data on changes in pharmacological treatment were used. In these analyses, only participants without changes in DMARDs or glucocorticoids were included.

STATISTICAL ANALYSES

Power analysis

To detect a change in DAS28-ESR of ≥0.6 units with 90% power and a significance level of 0.05, 38 participants were needed. To account for dropouts, a sample size of 50 were considered appropriate.

Main analyses

In papers I, II and III, a linear mixed model was used to analyze differences in disease activity, HrQoL, plasma and serum biomarkers and reported dietary intake, within and between the diet periods. The model included treatment, period, sequence and baseline variable as fixed effects, and subject as random effect. However, tender and swollen joint count yield discrete data (0-28) and there were few numbers represented in our study population, i.e., the variance was small. Thus, a generalized logistic mixed model was used instead (paper I). Fixed and random effects were the same as for the linear mixed model. Variables with skewed residuals were transformed before analysis (square root or log10).

More, in paper I, to evaluate response to treatment using the EULAR response criteria, the chi-square test was performed. Further, it was hypothesized that DAS28-ESR and dietary quality before the intervention diet period may have affected the treatment response. Thus, the Mann Whitney U-test was used to statistically analyze the difference in median DAS28-ESR and dietary quality index pre intervention diet period.

In addition to investigating mean differences using linear mixed models in each dietary biomarker when evaluating compliance in paper III, we also explored differences in the plasma fatty acid patterns and the fatty acid pattern from reported intake between the diet periods. For this, Orthogonal Projections to Latent Structures (OPLS) models were used. Background variables such as BMI, age, sex, ESR and dietary quality, were included as y-variables and their influence on the data was tested. The variables were included in the final model if CV-ANOVA p was <0.05. OPLS with effect projections (OPLS-EP) and OPLS with Discriminant Analysis (OPLS-DA) were used to separate classes according to classification of diet (intervention or control). In OPLS-EP, post-values from the diet periods were used and only participants completing both diet periods/food records were included, while in OPLS-DA delta values (post-pre) for the diet periods were used and all participants who completed at least one diet period or completed both food records for at least one diet period were included. Those fatty acids with the six highest VIP-scores among fatty acids with loadings $w \geq \pm 0.1$ were regarded as the most discriminating fatty acids for each diet period.

Paper IV was merely descriptive and no statistical tests were performed. Results on the nutrient intake of the reported days (i.e., the median intake of three or six days) were stratified by sex and compared to gender- and age-specific reference values for nutrient intake according to NNR 2012 (74). For nutrient recommendations where menopause rather than age is the depending factor, 52 years was set as the age of menopause (217).

Confounding factors

Our participants were randomized to which diet period to begin with, and due to the crossover design, each participant was his/her own control. Thus, confounding should not be a major problem. Still, it was hypothesized that age, sex, BMI at baseline, education, nicotine use, and dietary quality at baseline may had confounding effects and therefore these variables were evaluated in relation to DAS28-ESR and its components. Only dietary quality exhibited confounding effects (change in the β-estimate of $\geq 10\%$) and only for tender and swollen joint count. Dietary quality was therefore added to the model as a fixed effect for these two outcomes.

Due to lack of confounding factors for most of the variables and outcomes in paper I, we did not explore or include any of these variables as confounders for remaining papers and analyses. However, previous publications from the ADIRA study have indicated changes in inflammation and blood lipids during

the trial (218, 219). Since both alkylresorcinols and carotenoids are transported by lipoproteins in the body, the level of triglycerides and cholesterol may affect the level of these biomarkers. In addition, it has been shown that inflammation affect the plasma and serum level of β-carotene. Thus, these variables were evaluated for possible confounding effect for all plasma alkylresorcinols (triglycerides and total cholesterol), serum carotenoids (triglycerides, total cholesterol, low-density lipoprotein and high-density lipoprotein) and serum β-carotene (CRP). Results are displayed in Table 7. Variables which exhibited confounding effects were included in the model as fixed effects.

Table 7. Variables tested for confounding effects.

	Triglycerides	Total cholesterol	LDL	HDL
AR				
Total AR	x	-		
C17:0	x	x		
C19:0	x	-		
C21:0	x	-		
C23:0	x	-		
C25:0	-	-		
C17:0/C21:0	x	-		
Carotenoids				
Lutein + zeaxanthin	-	x	x	x
β-cryptoxanthin	-	-	-	-
Lycopene	x	-	-	x
α-carotene	-	-	-	-
β-carotene	x	x	x	x
Total carotenoids	x	-	x	x
Total carotenoids minus lycopene	-	x	x	x

Grey = not tested, x = exhibited confounding effect (change in β-estimate ≥10%), - = exhibited no confounding effect. AR, alkylresorcinols

Sensitivity analyses

We performed several sensitivity analyses in papers I and II. The following were performed for all outcomes: 1) only including those who completed both diet periods (per-protocol analyses), 2) only including those diet periods deemed to have been performed with good compliance according to the scoring system (per-protocol analyses), 3) only including participants without changes in DMARD or glucocorticoid use (per-protocol analyses), and 4) including all randomized participants with missing post-values imputed in three different ways (intention-to-treat-analyses): *a*) for the control diet period: median change during the control diet period added to the pre-value in the same diet period, for the intervention diet period: median change during the intervention diet period added to the pre-value, *b*) for the control diet period: same as in *a*, for the intervention diet period: Q1 change added to the pre-value (worst-case-scenario), *c*) for the control diet period: same as in *a*, for the intervention diet period: Q3 change added to the pre-value (best-case-scenario). Post-values were only imputed if there was a pre-value for the diet period (i.e., if the participant had dropped out during the first diet period or wash-out, no values were imputed for the second diet period. The same models as for the main analyses were used.

In paper II, we also did a fifth sensitivity analysis using a generalized logistic mixed model for all outcomes (per-protocol analyses). This was due to most data originally being categorical. We dichotomized the variables to <median and ≥median values. The same fixed and random effects as for the main analyses were used.

In paper I, the Wilcoxon signed rank test was performed as a supporting analysis for all continuous outcome variables due to originally skewed data. For the variables tender and swollen joint count, the chi-square test was used instead.

ETHICAL CONSIDERATIONS

The ADIRA trial was approved by the regional ethical review board in Gothenburg (registration number 976-16, November 2016, and supplements T519-17, June 2017 and T878-17, October 2017), and the study was conducted according to the Declaration of Helsinki (220). All participants provided written and informed consent.

Participation in the ADIRA trial may have been burdensome for some participants. The diet periods maintained for a total of 20 weeks, and for the participant, the dietary intake during one of the diet periods was possibly vastly different from the habitual intake. Eating habits are affected by several factors: preferences and perceptions, the social and cultural context, economics etc., and thus a change in dietary habits may be difficult (221). The participants were informed that participation was voluntarily and that they could discontinue their participation at any time without providing a reason. They did not receive any payment, but food corresponding to half of their daily intake delivered to their homes for 20 weeks at no cost could perhaps serve as a form of compensation for their participation. Further, the participants were provided with their individual results on disease activity, blood lipids, blood pressure and inflammation markers. If any lab results deviated from the normal range the investigators forwarded it to a rheumatologist involved in the study for further evaluation. Participants were also provided with information on their individual BMI and body composition as well as the calculated nutrient intake from the food record performed at baseline.

Although some of the foods included in the intervention diet may cause some gastrointestinal discomfort if not used to eating it (e.g., legumes), no risk of the study food to cause any serious harm to the participants existed. The Swedish dietary recommendations are based on e.g., scientific evidence of the impact of food and nutrients on health with possible food-related risks also being considered (222). The control diet in the ADIRA did not correspond to these recommendations which could be considered unsafe. However, the nutrient content of the control diet period was intended to be similar to the general intake in the Swedish population. Further, although the instructions on e.g., red meat intake transcended the recommendations on a maximum of 500 g/week (in the trial, participants were instructed to consume at least 5 portions/week, i.e., 635 g/week if one portion=125 g), the control diet period lasted only for ten weeks which, in this aspect, is a relatively short period.

Results

Detailed descriptions of the results are found in the published papers. In this chapter, a summary of the results is presented.

STUDY PARTICIPANTS

Of the 66 participants attending the screening visit, 50 met the inclusion criteria and were included in the ADIRA trial. Of these 50 participants, 47 completed the first diet period, and 44 completed both diet periods. The reasons for drop-out were not related to the study food.

Of the 47 participants who completed at least one diet period and therefore were included in the main analyses in papers I, II and III, median (IQR) age was 63 (54, 71) years old and 77% were women. About half of the participants (49%) were highly educated with a university degree or equal and parental birthplace was for most participants in Europe (94%). Overweight and obesity were common, with the mean ± SD BMI being 27.6 ± 5.4 and 32% having a BMI corresponding to obesity. Duration of the RA was median (IQR) 19.2 (19.6, 28.2) years and median (IQR) DAS28-ESR was 3.7 (3.0, 4.6). DAS28-ESR corresponded to a moderate disease activity for 57% of the participants and to a high disease activity for 9%.

Almost all participants used immunosuppressive treatment; DMARDs were used by 89% of the participants completing at least one diet period and 26% used glucocorticoids. Twenty-three percent used both DMARDs and glucocorticoids. Twenty-two participants made changes in these medications during the study and thus were excluded from the sensitivity analyses where only participants without pharmacological changes were included.

In paper IV, 62 participants were included. The excluded participants in this paper (n=4) were excluded due to not returning any food record at all. The 12 participants excluded after the screening visit, completed only the first food record and the 50 participants who were included in the ADIRA trial would ideally have performed two food records each (before visit 1 and visit 3). However, drop-outs and invalid food records resulted in 44 participants with two 3-day food records (i.e., six reported days) and 18 participants with one 3-day

food record, to include in the analyses. The baseline characteristics in paper IV did not differ substantially from those in papers I-III.

Minor adverse effects were reported by 29% of the participants during the intervention diet period (e.g., stomachache, diarrhea, nausea.) and by 9% during the control diet period (e.g., constipation, bloating).

PAPER I

The main outcome of the ADIRA trial was changes in disease activity measured as DAS28-ESR, which was investigated in paper I. DAS28-CRP as well as each component of the DAS28-ESR were secondary outcomes in this paper.

The mean (95% CI) difference in DAS28-ESR between the intervention and control diet period favored the intervention diet period but were non-significant at -0.29 (−0.65, 0.08), $P = 0.162$. However, within the intervention diet period DAS28-ESR was significantly reduced (mean difference: −0.37, 95% CI: -0.63, −0.11). This was not the case for the control diet period (mean difference: −0.08, 95% CI: −0.34, 0.17).

No other outcomes differed significantly between or during the diet periods, except for DAS28-CRP, which was reduced with a mean of −0.46 (95% CI: −0.70, −0.21) during the intervention diet period. Still, as for DAS28-ESR, there was no significant difference between the diet periods.

In sensitivity analyses including only participants without changes in DMARDs or glucocorticoids, the difference between the diet periods were larger and with a trend towards significance for several outcomes. The mean difference (95% CI) in DAS28-ESR was −0.44 (−0.92, 0.03), $P = 0.067$.

When missing values were imputed as a best-case scenario, the mean difference (95% CI) in DAS28-ESR between the diet periods was borderline significant at -0.34 (-0.69, 0.01), $P = 0.057$.

Response to the dietary treatment was also evaluated using EULAR response criteria. No significant difference in percent of participants with no, moderate, or good response between the diet periods could be seen. However, responders had a higher DAS28-ESR before starting the intervention diet period than had non-responders ($P = 0.001$).

PAPER II

There were no significant differences between the diet periods for any of the outcomes (HAQ, SF-36, VAS pain, VAS fatigue, VAS morning stiffness and duration of morning stiffness) in the main analyses.

Within the intervention diet period, physical functioning according to SF-36 (SF-36 PF) improved significantly with a mean difference of 5.79 (95% CI: 1.58, 10.01).

In sensitivity analyses where participants without changes in DMARDs or glucocorticoids were included, a borderline significant difference was seen for HAQ (mean: -0.14, 95% CI: -0.27, 0.00, $P = 0.051$). For SF-36 PF, the difference between the diet periods was significant with a mean (95% CI) of 7.90 (0.56, 15.24), $P = 0.036$.

In the sensitivity analyses where missing values were imputed as a best-case scenario, there was a significant difference in SF-36 PF between the diet periods (mean: 5.71, 95% CI:0.10, 11.32), $P = 0.046$.

PAPER III

The plasma concentrations of the alkylresorcinol homologues C21:0 and C23:0, and the fatty acids LA, EPA and DHA were all significantly higher after the intervention diet period compared to after the control diet period (AR: $P = <0.05$, fatty acids: $P = <0.001$). Total AR was borderline significantly higher after the intervention diet period compared to after the control diet period ($P = 0.052$). Unexpectedly, the serum concentration of several of the carotenoids were significantly lower after the intervention diet period compared to after the control diet period ($P = <0.05$ and <0.001).

The reported intake of whole grain, fruit, berries and vegetables, and seafood were significantly higher during the intervention diet period ($P = <0.001$) and the reported meat intake was lower ($P = <0.001$) compared to during the control diet period.

The overall plasma fatty acid pattern as well as the fatty acid pattern from reported dietary intake differed as intended between the diet periods. Further, almost all individual diet periods were classified into the correct diet period in the OPLS-DA analyses.

Overall, results from biomarkers and reported intake were consistent with the results from the ADIRA-specific self-reported compliance scoring system.

PAPER IV

For 95% of the participants, the intake of SFAs exceeded the recommendations. Females had a median (IQR) intake of 15 (13, 17) E% and males 15 (12, 17) E%. For fiber, 89% had an intake below recommendations (median [IQR] intake among females: 17 [13, 21] g, and males: 19 [15, 21] g). The other macronutrients were within or just slightly beyond recommendations.

Median intake of several micronutrients was below the RI for both females and males. Vitamin D, thiamin, vitamin A, riboflavin and iron had the most salient discrepancies from the recommendations; 36-82% of the participants did not reach AR for these nutrients. About 15% did not reach LI for vitamin A, and ~10% of the female population did not reach LI for vitamin D, calcium, and riboflavin.

Discussion

The main aim of the ADIRA trial was to test the hypothesis that a proposed anti-inflammatory diet rich in fatty fish, healthy fats, fruit and vegetables, whole grain, and probiotics, compared to a diet corresponding to the average Swedish nutrient intake, would reduce disease activity and improve quality of life in patients with RA. Further, the compliance to the study diets were evaluated using 3-day food records and established biomarkers, and the habitual energy and nutrient intake of patients residing in Southwestern Sweden were investigated.

In addition, the ADIRA trial also aimed to investigate changes in inflammatory markers and blood lipids. Differences in body composition following the intervention and control diet have also been explored in the study. These results have been published (218, 219, 223) but fall outside the scope of this thesis. In short, the proposed anti-inflammatory diet improved the blood lipid profile, i.e., a higher level of favorable blood lipids and a lower level of unfavorable blood lipids were seen after the intervention diet period compared to after the control diet period (218). Further, ESR was reduced in patients deemed to be compliant, while several other inflammatory markers were lower following the intervention diet period compared to the control diet period when all study participants were included in the analysis (219). CRP did not differ between the diet periods at all. Body composition changed to a more favorable composition with a larger fat free mass and smaller fat mass during both diet periods but there was no difference between the diet periods. (223)

The dietary effects on disease activity and HrQoL, compliance to the study diets and the participants' habitual nutrient intake are further discussed in the respective sections below.

DISCUSSION OF THE RESULTS

Modest beneficial effects on disease activity

We found no significant effects on DAS28-ESR, any of its components or DAS28-CRP in the main analyses. There was a significant reduction of DSA28-ESR and DAS28-CRP during the intervention diet period alone (but

not compared to the control diet period) as well as in unadjusted analyses. Further, there was a trend (i.e., a p-value slightly above the predetermined significance level) towards a reduction in disease activity in patients who did not change their DMARD and glucocorticoid use during the study. However, all these reductions were small, less than 0.6 units, and therefore of uncertain clinical relevance.

The ADIRA intervention diet can be described as a Nordic version of the Mediterranean diet with the addition of probiotics. Nordic due to e.g., rapeseed oil instead of olive oil, farmed salmon, Nordic fruits and berries such as apples, pears and blueberries, oatmeal, and wheat berries. Sköldstam and co-authors also investigated the effects of a Swedish version of Mediterranean diet (98). However, no probiotics were included in that diet and the control group continued eating their regular diet. Contrary to the ADIRA trial, the study of Sköldstam and co-authors reached a statistically and clinically significant reduction in DAS28 during the intervention diet as well as between the intervention and control group. Despite several similarities between these studies such as the diet, a Swedish study population, similar median age, BMI, and female:male ratio, there were also important differences. Our study population had a lower disease activity at baseline, and we allowed participants to make changes in their medications if needed. In the Sköldstam study, the participants were only allowed to adjust the non-steroidal anti-inflammatory drug dose but not the DMARD or corticosteroid doses. Since we obtained other results when excluding all patients who did any changes in their medication (new medication, change of dose or discontinuing a medication), it is likely that the difference in the pharmacological treatment between the studies could partly explain the disparate results. Further, when using another exclusion criteria, i.e., only excluding participants who *started* or *discontinued* DMARD or glucocorticoid treatment from the analysis, it was found that the DAS28-ESR was statistically significantly lower after the intervention diet period compared to the control diet period (224). Finally, the study participants in Sköldstam's intervention group had a significant weight reduction during the study, which was not the case for the control group, and not the case in the ADIRA trial. Weight loss by itself could possibly improve disease activity in RA (113), although Sköldstam and co-authors, in a study pooling data from three dietary interventions, claimed that this was not the reason behind the symptom reductions (225).

Further, in an RCT aiming for weight loss among overweight and obese patients with RA, Sadeghi and co-authors obtained a significantly lower DAS28 after a Mediterranean diet compared to both a low-fat diet and a "regular" diet,

despite non-significant differences in weight loss (101). This indicates probable effects of such a diet regardless of weight loss. The Mediterranean diet in that study consisted of olive and canola oil, nuts, and legumes every day, low-fat dairy, and only 150 g red meat/month. From this description of the diet, it seemed similar to the ADIRA diet (except the probiotics) but as this was performed in Iran, the diets likely differed in food items. Further, the consumption of seafood was not described in the article, but the participants consumed fish oil supplements two times per week which was not the case in ADIRA. The low-fat group consumed a diet with only 20% fat and the control group continued with their regular diet. The Mediterranean diet group reduced their DAS28 with 1.5 units, i.e., considerably more than in our study. But since the Sadeghi study was a weight loss study, it is difficult to make a fair comparison. Further, the DAS28 constituents and calculations differed, and so did the study design.

We labelled the ADIRA intervention diet "an anti-inflammatory diet" due to the content of food components which have previously been shown to affect RA disease activity positively. Adam and co-authors also investigated the effects of a diet they called "an anti-inflammatory diet" (122). Patients were allocated to either this diet or to continue their usual intake (a western diet). Within these groups, the participants were randomized to start with fish oil supplements or placebo (corn oil) for three months, followed by two months wash-out, and then they switched supplement. The anti-inflammatory diet was described as a modified lacto-vegetarian diet. Further, the participants consumed only vegetable fats. This was also encouraged in ADIRA but in Adam's study, the participants were not supposed to consume fish at all but were instead given fish oil supplements (during half of the study period). These supplements corresponded to 30 mg omega-3 fatty acids per kg of body weight, thus around 2.1 g per day (if 70 kg body weight). This amount is approximately the same as in the ADIRA intervention diet, but in our study, the participants consumed it through fish intake instead of supplementation. An AA intake of <90 mg/day in the study by Adam and co-authors was received through a maximum intake of 240 g meat/day. Our study allowed slightly more meat, and the intervention diet contained 220 mg AA per day but overall, the diets were similar. Adam and co-authors did not evaluate DAS28 but concluded positive effects on disease activity measured as, for example, number of swollen joints, and the patient's and physician's global assessments of disease activity, with greater changes compared to the control diet + fish oil supplement. Contrary, the ADIRA intervention diet did not reduce the number of swollen joints, nor did it improve the patient's global assessment. One explanation for the

different results could be the different instruments used. ADIRA used the 28-joint count while Adam used the 66-joint count. Further, Adam and co-authors did not report the exact phrase of the patient's global assessment. As results are dependent on the phrasing (47), this could also explain the different results.

The power calculation for the ADIRA trial was based on a change of 0.6 units in DAS28, which is considered a clinically relevant improvement (98). The recruitment was successful ending up with the number of participants we accounted for, but we did not achieve a clinically relevant reduction in DAS28. One explanation for this could be that most participants had only a low or moderate disease activity at baseline. As mentioned, the baseline disease activity in ADIRA was lower than in the study by Sköldstam and co-authors (98). This could be due to the evolvement and the now more intense use of the anti-rheumatic medications compared to when that study was performed in early 2000s. Beginning a treatment with an already low disease activity would most likely result only in small improvements. This was also something we could see when response to the dietary treatment was evaluated using EULAR response criteria. The baseline DAS28-ESR was significantly higher in responders compared to in non-responders. On the other hand, RA is characterized by its periods of flares followed by periods of remission, i.e., if the patient has a high disease activity at first, most likely the disease activity is lower the next time he/she is examined, regardless of the intervention being effective or not (i.e., "regression to the mean"). The very small improvement in DAS28 could possibly further be explained by the dietary intervention being insufficiently intense. We provided the participants with only 50% of their daily dietary intake, five days per week. Possibly, the effect would have been more pronounced if food corresponding to 100% of daily intake were provided. However, this would most likely have resulted in more dropouts since the study participation would be much more of an effort for the participants.

Beneficial effects on physical functioning

Physical functioning was significantly improved only during the intervention diet period and between the diet periods in those patients who did not change their DMARD or glucocorticoid use. No other aspects of HrQoL were significantly reduced, but overall, reductions were larger in patients who did not change their anti-rheumatic medication.

The improvement in physical functioning among the subgroup of participants who did not change their medication was shown as a significant increase of 7.3 units in SF-36 PF during the intervention diet period and a difference of 7.9

units after the intervention diet period compared to after the control diet period. Also, this subgroup reduced their HAQ during the intervention diet period and had a 0.14 units lower HAQ after the intervention diet period compared to after control diet period. However, the meaningfulness of the size of the improvement, i.e., the clinical relevance, may be difficult to interpret. There are several ways to evaluate clinically relevant changes in these outcomes; through use of reference values from the population or the patients' description of what change they find important, or statistically through data derivation of effect sizes (194). Kosinski and co-authors evaluated important changes in SF-36 and HAQ using changes in disease severity measured as both the patient's and physician's estimation of global health, pain assessment and swollen and tender joints (226). They categorized the improvements in each of these assessments to three different levels. The mean change at one level of improvement in disease severity was between 6.4 and 8.4 units (average 7.7 units) for SF-36 PF and between -0.13 and -0.24 units (average -0.19 units) for HAQ. Using these numbers, the obtained improvement in physical functioning during the ADIRA trial seems to be of clinical relevance. Nonetheless, clinical relevance of changes in HrQoL is highly subjective and individual. Ideally, trials including these outcomes should also further explore whether the changes were meaningful to the participants or not. One way to explore this could be by simply asking a question about the importance of the changes directly after the original HrQoL question (194).

In the previously discussed study by Sköldstam and co-authors, the participants in the intervention group obtained a significantly higher physical ability measured as HAQ compared to the control group (-0.15 vs. no change) and the intervention group significantly increased the SF-36 vitality domain with 11.3 units (98). Further, pain measured on a VAS was reduced in the intervention group but not in the control group, and the difference was statistically significant between the groups. Once again, the differences in medication changes could possibly explain the disparate results between that study and ADIRA. When including only the participants who did not change their medication, the between-period difference in HAQ were of the same size and borderline significant also in ADIRA. However, despite our participants having a slightly higher SF-36 PF at baseline, the ADIRA diet seemed to have a greater effect on SF-36 PF than did the Mediterranean diet in the Sköldstam study. This could partly be due to the more intense dietary intervention in AIDRA. On the other hand, improvements in both SF-36 vitality domain and pain were larger in the study by Sköldstam. Adam and co-authors also investigated the effects on VAS pain (122). The magnitude of reduction, in terms of mm on the scale, was not

reported but the anti-inflammatory diet with the addition of fish oil significantly reduced pain. Further, after three months, the participants had significantly less pain compared to those consuming their regular diet + fish oil. Overall, as the studies differ in their design, some differences must be expected. Still, the absence of improvement in morning stiffness were the same in all three studies.

Although the ADIRA diet resulted in some improvements in the physical aspects of HrQoL, the trial failed to improve aspects of mental health, pain, and fatigue. In the general Swedish population, females in the age group 45-64 years old have a mean SF-36 score ranging from 68 through 88 (out of 100) in the domains covering aspects of mental health (198). Unsurprisingly, the domains covering physical health were rated lower in our study population, who consisted mostly of females with a median age of 63 years old, but the mental health domains were rated higher or the same (except from the vitality domain). Mean scores in another Swedish population with RA six years after diagnosis were reported to be 37 for the physical component summary score and 52 for the mental summary score (227). Our study population had slightly higher summary scores. The female:male ratio in that study differed from ours, our population had a higher mean age and a longer disease duration. However, HrQoL relates to more than age, sex and having a chronic disease or not; also factors such as education and employment are important (198). Almost half of the ADIRA participants were unemployed (for most probably due to retirement), but the educational level was high, with 49% having a university degree or equivalent. The employment and educational status were however not reported in the other study.

Conclusively, the mental health components scored high in the ADIRA study population and thus, the possibility of further improvements may be lower. A study that investigated the effects of blue mussel intake, significantly improved the mental component summary score of SF-36 and reduced both pain and fatigue (124). This study sample had lower SF-36 mental health summary scores and higher pain and fatigue score at baseline than did our study population. This further strengthens the theory of our participants having a too good mental health to obtain further improvements through dietary change.

As for pain, our population reported pain corresponding to 43 mm on a VAS at baseline. In contrast, in a 2022 report by the SRQ, Swedish patients reported pain corresponding to 20-30 mm one year after diagnosis (228). In a previous study evaluating minimal important differences in VAS pain, a score of >33.4

was considered severe pain and improvement of around 10 mm was considered an important change (229). The Mediterranean have previously been shown to reduce pain further in patients with only moderate pain (98) but the ADIRA diet did not induce any clinical or significant improvement in pain despite most participants suffering from severe pain. On the other hand, VAS pain is a highly subjective measure. We tried to blind participants to the diets by referring to "the fiber diet" and "the protein diet" instead of intervention and control diets. We also did not communicate which diet we believed would reduce disease symptoms. Sköldstam and co-authors did not perform any blinding and therefore their significant reductions in pain, as well as in the other HrQoL-outcomes (98), may have been overestimated.

Participants were compliant to the study diets

Through analyses of biomarkers and food records, we found that the participants were compliant to our overall dietary instructions regarding intake of whole grain, cooking fat, seafood, and red meat, and overall dietary fat quality. Thus, the participants changed their whole diets and did not just consume the food provided by the study. This validates our study results and indicates that such a diet is feasible for this patient group.

Unexpectedly, the level of serum carotenoids was higher during the control diet period compared to during the intervention diet period. Still, the 3-day food records displayed a markedly higher intake of fruit, berries, and vegetables during the intervention diet period; the participants consumed almost three portions more per day (~300 g) during this diet period compared to the control diet period. The discrepancies between the biomarkers and food records could be due to what type of fruit and vegetables the participants consumed. They were provided with two fruits per day, but these consisted of only bananas, apples, and pears - all fruits that are not particularly rich in carotenoids (180). Further, the control diet consisted of daily intake of orange juice, which has an abundance of β-cryptoxanthin and is one of the primary sources of this carotenoid in several European countries (180), and several main meals contained canned tomatoes which are especially rich in lycopene (180). Although carotenoids are a commonly used biomarker for fruit and vegetable intake, several studies have reported only moderate correlation between serum/plasma carotenoids and fruit and vegetable intake (186, 230). Also, it has been shown that carotenoids perform better as a biomarker for fruit and vegetables when lycopene is excluded (230, 231). In the analysis where we removed lycopene from total carotenoids, the difference in plasma level between the intervention diet

period and the control diet period were smaller and no longer statistically significant. Also, when juice was added to the variable *Fruit, berries and vegetables*, we could see that although the reported total intake was still higher during the intervention diet period, the difference between the periods was smaller and the reduction in fruit and vegetable intake during the control diet period was no longer significant. Thus, the daily juice intake and the many meals with canned tomatoes possibly explain some of the higher plasma carotenoid levels during the control diet period. This confirms the importance of using food records as a complement to established biomarkers when investigating compliance, at least in dietary intervention studies that provides or recommends specific food items.

Fatigue, pain and stiffness could make activities of daily living difficult (8), and such activities may include grocery shopping and food preparation. Further, previous studies with a whole diet intervention who have provided the participants with the food have reported good compliance (232-234). Thus, home delivery of foods and easy-to-cook/ready-to-eat meals likely contributed to the good compliance in the ADIRA trial. Also, to perform dietary interventions where the individual's whole dietary pattern may be changed and for a rather long time, demands motivated participants. If there is a belief that the diet has effects on the disease symptoms, the motivation is probably higher. Most likely, the participants in ADIRA were interested and believed in dietary treatment, and thus were motivated to change their dietary patterns. On the other hand, this could have resulted in low compliance to the control diet if they did not believe it would have any effect or maybe even make symptoms worse. However, we communicated to the participants that we were investigating effects of both diets and that both diets could be effective. Further, the food records showed a significantly reduced intake of whole grain, fruit, berries, vegetables, and seafood and a significantly increased intake of red meat during the control diet period, i.e., participants seemed to be compliant also to the control diet. Of the biomarkers, only plasma EPA and DHA were significantly reduced during the control diet period but since the control diet was intended to correspond to a typical Swedish nutrient intake, a major change in dietary intake was not expected during this period.

In a study investigating the effects on physical functioning and quality of life of a Mediterranean diet in patients with RA (results not published yet), Raad and co-authors asked a group of participants which factors enabled adherence and which did not (235). Based on their answers, it seems that the study food needs to be easily available in both grocery stores and restaurants and, due to

pain, the food should be easy to prepare. Further, planning and preparation were considered time consuming and thus, already planned and prepared meals would be convenient and enable adherence. More, continuously support from both family and a dietitian, as well as lessons on how to cook the study food seem to be important. Finally, the economic aspects were also mentioned and thus food to a reduced cost would probably promote compliance. The ADIRA trial had all these features and this likely contributed to the high compliance.

Poor habitual nutrient intake

When exploring the habitual nutrient intake, we also included those patients who, due to unstable disease or remission, were excluded from the ADIRA trial. We concluded that the patients had high intakes of SFAs and low intakes of carbohydrates and fiber. In both females and males, the median intake of most micronutrients was lower than RI but reached AR. However, for vitamin D, median intake was very low and 12% of the females did not even reach LI. Also, in the male study population, the intake of thiamin and riboflavin did not reach AR. Further, despite the median intake being above AR, about one third of the females had a very low thiamin and iron intake, and half of the males had a low vitamin A intake.

There seems to be few other studies that have investigated the nutrient intake in Swedish patients with RA but those existing have displayed an overall macronutrient distribution slightly different from what we saw (150, 236, 237) but with similarities in the energy adjusted intake of SFAs and fiber (150, 237). The intake of micronutrients also differs. Andersson and co-authors used food records to examine nutrient intake in elderly female patients (237). These patients had a lower than recommended mean intake of vitamin D, vitamin E, iron, folate, and selenium. Except from the vitamin E intake which was according to recommendations in the female population of the ADIRA trial, the same could be seen in our study. However, intakes of vitamin A and calcium were below recommendations in our female population, which was not the case in the Andersson study. Lourdudoss and co-authors included approximately 700 newly diagnosed patients in their study on vitamin D, folate and omega-3 intake and the association with treatment results (156). They also concluded a markedly low intake of vitamin D, but the folate intake was higher compared to our study. Differences in dietary recommendations over time could be a reason for the discrepancies in the results, but also the dietary assessment methods and the differences in age and disease duration in the different study populations.

Except for the comparisons to the current nutrient recommendations at the time of data collection, ideally we would also compare the nutrient intake in our study population to matched controls from the general Swedish population. Such data was not collected and thus we are only able to compare our results to those from the most recent national survey on dietary habits in the Swedish population – Riksmaten – Adults 2010-11 (238). The median energy intake was similar among the females, but slightly lower among the males than that of the general Swedish population, but the high proportion of energy from SFAs and the low amount of fiber per MJ were similar. The E% of total fat, MUFAs, PUFAs and omega-3 fatty acids was higher in our study population, especially among the males, but within the recommendations. The E% of carbohydrates was lower and even below the recommended intake range, while the E% of protein and alcohol were approximately the same in our study population as it was in Riksmaten. Regarding the micronutrient intake, Riksmaten concluded that the Swedish population in general has an adequate intake, but that intake of vitamin D, folate and iron was low (238). Also in the ADIRA trial the intake of these micronutrients was low. In addition, our participants reported overall lower median intakes compared to the general Swedish population. The relevance of these differences is however uncertain, since most median intakes still were above AR.

A low carbohydrate intake may yield a low intake of whole grain which is the single most important dietary factor responsible for death and overall disease burden – in 2017, 3 million deaths worldwide could be attributed to a low whole grain intake (239). Low carbohydrate intake may also increase the risk for a low intake of fiber (73). An adequate intake of fiber has several positive health effects such as reduced risk for colorectal cancer, CVD, diabetes, and weight gain (73). Due to its possible anti-inflammatory effects through an increase of diversity and production of SCFAs in the microbiota (87, 88), patients with RA may benefit even more from an increased intake. Further, to exchange the excess intake of SFAs to PUFAs or whole grain has been shown to reduce the risk of CVD (73). Merely by having the disease, patients with RA have an increased risk for CVD (36), and thus a diet with less SFAs and more PUFAs may be even more important for this group.

The habitual energy and nutrient intake were estimated using 3-day food records. Weighed food records are the method providing the most precise estimates of intake (167). Still, it is a subjective method and underreporting or misreporting may have biased the results. Misreporting can be more or less conscious. Participants may have wanted to make the reporting easier and thus

either refrained from some foods such as snacks or simply ignored reporting it. If not using a scale, estimation of portion sizes could also have been inaccurate. Further, in an attempt to please the investigator, participants may have reported what they believed would be the "right" way to eat. We carefully instructed the participants on how to perform a food registration with and without a scale, and we went through the performed registrations together with the participants to sort out any uncertainties. Thus, we tried to minimize the risk for misreporting as well as the risk for an inaccurate intake registration by us investigators. Further, the reported energy intake in ADIRA, at least in the females, was similar to that reported in previous studies of Swedish patients with RA as well as in Riksmaten (150, 236, 238).

Further, eating according to specific diets is common in the patients with RA (141, 142, 145, 147, 148). Since the participants in the ADIRA trial had to accept an omnivorous diet and dietary interventions tend to attract individuals with a personal interest in diet, the obtained results regarding habitual nutrient intake may not be transferable to the patient group in general. Likely, the intake in the general patient population is even more insufficient.

The recommendations on nutrient intake are developed for use in the general population. We do not know if these reference values are optimal for patients with RA or if this patient group has increased or reduced needs of certain micronutrients compared to the healthy population. Currently, patients with RA are not referred to any disease-specific nutrient recommendations. Still, the physicians should prescribe folic acid supplementation to reduce side effects of methotrexate and calcium + vitamin D to prevent osteoporosis in patients treated with glucocorticoids (54-56). Although these are in doses not possible to obtain merely by diet, this indicates that the general recommendations may not be optimal for patients with RA. Further, several of the participants included in paper IV also used different kinds of non-prescribed supplements such as multivitamins, omega-3 fatty acids, and iron. Thus, the nutrient status may have been adequate in several of the participants with dietary intakes below RI, AR or even LI. Whether there should be disease-specific nutrient recommendations warrants further research.

Other aspects of dietary treatment in rheumatoid arthritis

Today, patients with RA are recommended to eat according to the general dietary recommendations. The rheumatology societies even recommend against consuming specific diets, except for the Mediterranean diet (58, 59). On the other hand, the Mediterranean diet is similar to the general Swedish dietary

guidelines and the new Nordic nutrition recommendations which emphasize a high intake of healthy fats such as rapeseed and olive oil, fruit, berries, vegetables, and wholegrains, a moderate amount of seafood and lean dairy, and a smaller amount of red meat and added sugars (60, 73). In the U.S., a "Mediterranean-style dietary pattern" is even one of the recommended dietary patterns (240). The recommendation *against* any other diet is due to lack of evidence for reduction of disease symptoms. Still, there is a great potential of the diet to ameliorate RA symptoms due to the anti-inflammatory properties of certain food components. The ADIRA trial contributed to fill in the gap of high-quality dietary interventions in patients with RA.

When investigating or implementing a dietary treatment in RA, it is important to remember that the participants may perceive it more difficult to make a dietary change than to merely add a new medication. Lack of cooking skills, the social and cultural aspects of dietary intake, preferences and the economic situation are all factors that possibly make a change in dietary habits and adherence to a certain diet challenging for the patients (221). Indeed, as earlier described, most of these aspects as well as pain were reported to hinder a transition to a Mediterranean diet among patients with RA (235). The patients would need education on the positive effects and how the dietary change could be implemented, as well as continuous support to promote adherence (221). On the other hand, with serious disease symptoms affecting their quality of life, the patients are probably already highly motivated, and today's possibilities of online grocery shopping and the huge market of ready-to-eat meals (which include also healthy meals) may also simplify a change in dietary intake. Further, it seems that the patients themselves experience a healing effect of certain foods and want to try different diets (141-147, 235).

Patients with RA are encouraged to participate in their own disease management and a change of dietary habits could certainly be categorized as self-management of the disease (211). There are however some negative aspects of following a certain diet. The risk for an inadequate nutrient intake increases with each food group that is being excluded. Further, food is often included in social events: we meet our friends and family over a dinner or fika, and very strict diets may thus negatively affect the patient's social life (59). Rheumatology societies emphasize the role of a dietitian if patients adhere to or wish to follow any exclusion diet (58, 59).

A dietitian may however be important also for patients who do not follow a certain diet. As previous studies have shown and ADIRA confirmed, the

nutrient intake in this patient group is inadequate with a high intake of SFAs (149-154) and low intake of fiber (151, 153-155) as well as several micronutrients (151, 156-161). Also, overweight and obesity is common and patients with obesity are recommended to lose weight in order to reduce inflammation as well as to improve CVD risk factors (59). Further, we know that the diet can reduce the risk of CVD and osteoporosis, both very common comorbidities in these patients. The dietitian also has a role in supporting the patient to navigate through all messages on a healthy diet for patients with inflammatory disease found on the internet and in social media, and to sort out all dietary advice based on non-scientific evidence.

Conclusively, despite the lack of evidence for symptom reduction of specific diets, we should not ignore the patients' dietary intake or avoid giving dietary advice. The patients themselves want to modify their diets and they ask for help from a dietitian. Importantly, the incidence of obesity and CVD but also sarcopenia and osteoporosis in these patients, all disorders where we know that the diet plays an important role in prevention and management, make evidence-based dietary counselling from nutrition educated professionals (i.e., dietitians) important in RA management. The importance of dietitian involvement has also been recognized by both the ACR and EULAR (58, 211).

METHODOLOGICAL CONSIDERATIONS

The crossover design

The ADIRA trial used a crossover design. This means that each participant consumed both study diets (intervention and control diet) with a wash-out period in between. The main advantage of this study design is that it reduces the inter-individual variability. Since each participant is his/her own control, i.e., the differences in treatment effects are compared within the same person, a crossover design reduces many of the possible covariates that usually have confounding effects in dietary interventions. These covariates include, for example, sex, age, height, weight (if weight stable during the study period) and thus BMI, physical activity (if kept stable), and tobacco use. Still, to be sure, we evaluated possible confounding effects of these factors in paper I, but as expected, most did not exhibit any confounding effects and thus were not included in the statistical models. However, since we saw alterations in inflammation and blood lipids during the trial (218, 219), we evaluated confounding effects of this in paper III, because these factors are known to affect

plasma/serum levels of alkylresorcinols and/or carotenoids. Further, since the crossover design reduce inter-individual variations, not as many participants are needed.

There are also some negative aspects of using a crossover design. It could be so that if the participant is feeling better during the first study period, he/she may not be compliant to the second study period. In ADIRA, this means that if the participants experienced symptom relief during the first diet period, regardless of which diet period it was, they may not have been as compliant during the second diet period. Also, they may not have gone back to their regular diet during the wash-out period as intended. We tried to avoid these possible biases by clearly communicating to the participants that we were investigating the effects of both diets. Also, when comparing the median intake of energy and nutrients considered important for the ADIRA diets and the median intake of whole grain, fruit, berries, vegetables, seafood and red meat at visit 1 (before the first study period) to visit 3 (in the end of the wash-out period), only selenium was significantly different ($P = 0.013$) between the visits with a slightly lower intake during wash-out (data not shown). Thus, participants seemed to have consumed their regular diet during the wash-out period, at least regarding the most important nutrients and foods included in the ADIRA trial.

For the validity of our results, it is also important that the wash-out period was long enough to reduce possible carryover effects (241). The ADIRA trial had a pre-determined wash-out period of three months, which in the end became a median of four months (min-max 2-5 months). If it was a pharmacological study, the half-life of the investigated drug would have determined the length of the wash-out (241). For a whole diet intervention study, including several possible potent components, it is more difficult to estimate an appropriate length. An appropriate wash-out period also depends on the outcomes investigated. Four months is a long wash-out period, and we believe this to have been sufficient.

A crossover design yields a longer study period for the participant compared to a parallel design. This could also impact compliance to the second diet period, patients may not be as motivated as in the beginning of participation, or even increase the risk for dropouts. To minimize the possible risk of loss of motivation affecting our results, participants were randomized to which diet period to begin with. The dropout rate in ADIRA was very low and thus not a major problem.

Finally, the different treatments being obtained during different time periods may induce effects which are not attributed to the treatment, but instead are due to a change in outcome with time (241). Also, specific for studies including patients with RA (or certain other diseases), the characteristic disease flares may be problematic in crossover designs. It could be so that improvements, no change or even deterioration could not be attributed to the diet but rather that they had either a "good period" or a flare during one of the diet periods while it was the opposite during the other period. However, since participants were randomized to which diet to begin with, and we included study period as a covariate in the statistical model, this likely did not affect our results. Also, some participants experience that weather affects their symptoms (242). Here, ADIRA being performed in two batches is an advantage in that we managed to cover the whole year.

The study diets

In the previously described RCT by Adam and co-authors, they evaluated the effect of the anti-inflammatory diet both with and without the addition of fish oil supplementation and compared it to the participants' regular diet with and without fish oil supplementation. The effects were most pronounced in the anti-inflammatory diet group when fish oil supplements were added compared to when they were not and compared to the regular diet + fish oil as well. They concluded that the fish oil and the low content of AA in the diet had synergistic effects, possibly through an increase in the EPA:AA ratio in erythrocyte lipids and higher absorption of EPA when AA intakes are low (122). The term *food synergy* can be described as the effects on the human body of food, i.e., natural food components put together forming the concept of what most of us sees as *food,* being greater than the sum of the effects of the individual food components (140). Whole foods may induce other and more pronounced effects on health compared to what isolated food components in the form of supplements do. This was also the theory when designing the ADIRA trial; that the food components with previously reported effects on RA symptoms: omega-3 fatty acids, prebiotics, probiotics, and antioxidants, would potentiate each other in their anti-inflammatory effects. Since we do not eat individual food components but rather a whole diet, a portfolio diet including these food components was designed.

When incorporated into the diet through foods, the dose of food components and nutrients, like omega-3 fatty acids and probiotics, are often lower than those used in supplementation studies. For omega-3 fatty acids, supplemental

doses of 2-3 g/day, preferable from fish oil and for at least three months, have been proposed for effects on several aspects of RA disease activity (128, 243). The daily amount of EPA, DHA and DPA in the ADIRA intervention diet, which was consumed for 10 weeks, was estimated to be 2.3 g/day. However, the reported median intake during the intervention diet period (i.e., including also the days and meals of food not provided by the study) was only 1.7 g/day. Thus, we can conclude that the intake of marine omega-3 fatty acids was below the proposed effective dose, which, together with a study duration of <3 months, could also be an explanation for the only modest and mostly non-significant effects on RA symptoms in our study.

In our intervention diet, probiotics was provided primarily in the form of *L. plantarum 299v* added to a juice shot (5 times/week), but also as *L. acidophilus LA-5*, *B. lactis BB-12* and *L. casei F19* added to sour milk (1.5 portions/week). Bacteria from the genus Lactobacillus and Bifidobacterium are some of the most used probiotics (244). Each genera contains several different species, and each specie contains several different strains, but not all strains are probiotic. To be acknowledged as a probiotic, the health effects, which are strain-specific, must be scientifically proven. Probiotics are currently not recommended to patients with RA due to lack of evidence for an effect on disease symptoms. Still, individual studies on supplemental *L. casei*, *L. acidophilus* and *B. lactis* have resulted in reduced DAS28 (89). Our study population was provided the probiotic enriched sour milk for breakfast only 5 days/week and only for three of the ten weeks during the intervention diet period. In addition, we do not know how much of these probiotic strains that was added to the sour milk. Possibly the participants consumed a too small amount of these probiotics to obtain the symptom reducing effects seen in other studies. *L. plantarum 299v* seems to have immunomodulatory properties and yield beneficial effects in, for example, patients with irritable bowel syndrome (245) but, to my knowledge, there are no previous studies on this specific strain in patients with RA.

The analyses of nutrient content of the ADIRA diets as well as the actual consumption reported by the participants are based on nutrient information from the Swedish Food Database (246). The database is developed by the Swedish Food Agency which has analyzed different foods in-house, used reported nutrient contents from other sources and made own estimates (247). Although they have accounted for certain factors affecting the nutrient content of a food item such as nutrient and weight losses during cooking, there will always be several uncertainties in the final value. For example, the nutrient content of a

food item may vary between both species, individuals, place of cultivation and farming, and season. Thus, nutrient calculations using databases will always be just estimates which means that we cannot guarantee the exact dose of, for example, omega-3 fatty acids in our study diets or from the reported intake.

The control diet was designed to mimic the general Swedish nutrient intake and as mentioned previously, we did not expect a large difference from their usual intake during this diet period. When evaluating and comparing the nutrient and food intake as well as the plasma biomarkers before and after the control diet period, it however seemed like the diet quality was lower during the control diet period compared to their usual intake. On the other hand, the control diet was very structured. Participants received all foods and a menu including three meals each day. The meals were thus pre-planned and easy to prepare. We did not aim to study changes in meal patterns or eating frequency and therefore we do not have such data in the ADIRA study but perhaps the control diet induced a more structured dietary intake during the day compared to usual intake. Possibly these decent meals consumed regularly over the day increased the overall well-being also during the control diet period and thus diminished the differences in effects of the diets. There are not much data on meal patterns and different health outcomes such as obesity and CVD, and thus, NNR does not provide any recommendations to the general population regarding this (73). Yet, meal patterns or eating frequency during the day and their effect on disease activity, quality of life or other aspects of well-being in patients with RA seem to be an unexplored area of research.

An important aspect of dietary treatment in RA is that the diet must be feasible for the participants. This means that the diet and its food components should be affordable, accessible, easily prepared and suit the patients' preferences. Ideally the diet should also be sustainable. The ADIRA diet only included foods that can be bought in regular stores, all year round. Further, due to fatigue, pain and deformed joints of the hands, cooking could be difficult for patients suffering from RA. The upright position when cooking, the chopping and opening of jars – things that comes with food preparation that people usually do not think of as something difficult to perform – could possibly be exhausting or even impossible for these patients. For this reason, the main meals were either ready-to-eat meals or easy to prepare. In addition, the foods were delivered to the participants' homes. Finally, it is challenging to set a menu that suits the preferences of all individual patients, but as previously mentioned, we chose to include Nordic/Swedish foods such as apples and pears,

blueberries, salmon, rapeseed oil and oats, all familiar foods for many people living in Sweden.

Food production and consumption have a huge impact on the climate and environment, and to achieve the global sustainability goals we need to make a transformation towards a diet consisting of much more plant-foods and much less foods of animal origin (248). In 2023, the Nordic nutrition recommendations integrated not only health aspects, but, for the first time, also environmental aspects in their nutrient and dietary recommendations for the Nordic and Baltic population (73). These recommendations include an increased intake of whole grain cereals, vegetables, fruits, berries, nuts, and sustainable fish, and a reduced intake of red meat, all due to positive effects on both health and environment. Further, an increased intake of potatoes and legumes is recommended, primarily due to its positive effects on the environment. Although dairy is considered to have a negative impact on the climate, a *moderate* intake of low-fat dairy is still recommended due to nutrient aspects. Poultry intake is recommended to be low because of the environmental aspects. Consequently, the ADIRA diet is both a healthy and moderately sustainable diet with its high content of fruit, berries and vegetables, whole grain cereals, potatoes, and legumes, and low content of red meat. The fish provided to the participants was mainly farmed salmon which, according to the World Wide Fund For Nature (WWF), from environmental aspects should be consumed with caution (249). However, the marine omega-3 fatty acids could possibly be obtained from other fatty fishes from more sustainably managed stocks.

In conclusion, all these factors and the high compliance during the study period indicate that the ADIRA intervention diet is a feasible diet for Swedish patients with RA. Still, an effectiveness study would be needed to confirm the feasibility in real-world conditions.

The study participants

We recruited participants mainly through the SRQ which is a Swedish register of 121 000 patients with more than a hundred different rheumatologic diseases, with RA being the most common. All eligible patients in this register were invited to participate. However, eligible were only those with an RA diagnosis residing in the food delivery area. This means that only patients residing in the Gothenburg region were invited. In addition, only 15% of invited patients responded. Participation in a dietary intervention like ADIRA likely attracts patients with a personal interest of diet and its effects on disease symptoms and thus induce selection bias. The dietary quality at baseline was considered fair.

Other studies on patients with RA have concluded the same (147, 154) but whether this is representative for the patient group in general is uncertain. It is possible that patients participating in dietary interventions are more health conscious and thus have a healthier dietary pattern compared to those not interested in participating in such studies. Also, we did only include patients with an omnivorous diet which further affects the generalizability since consuming other specific diets is common in this patient group (141, 142, 145, 147). The possible dietary interest may also affect the outcomes. Although we believed that our attempt of blinding the diets was successful, some participants may already have had predetermined opinions on the effects of certain food items which possibly influenced their responses.

Further, at baseline, the study participants had a median DAS28-ESR of 3.7 which corresponds to a moderate disease activity. Data on the average DAS28 of all Swedish patients does not exist (224) but in the 2022 report from SRQ, the average DAS28 of patients one year after diagnosis was reported to be around 2.5-3 in all regions of Sweden (228). Since the report only includes participants with a short-term disease duration, it is not representative for the whole Swedish population with RA and as the median disease duration in ADIRA was considerably longer (19 years), we cannot really compare the disease activity of our study population to that of the included patients in the SRQ report. It is not surprising that we did not manage to recruit participants with even higher disease activity since severely ill patients may feel that participation in a rather intense dietary intervention is too demanding.

According to the same report, the mean HAQ is around 0.3-0.4 for Swedish patients one year after RA diagnosis (228), while the participants in AIDRA had a median baseline score of 0.5 and thus slightly lower physical ability. SRQ also reported pain measured on a VAS. According to the report, one year after diagnosis the average pain corresponded to around 20-30 mm on the scale while our population had over 40 mm. Once again, comparisons between ADIRA and the SRQ report should be made with caution since the differences in disease duration were large. However, in the search of a complementary treatment, severe pain could be one reason to participate in the ADIRA trial (250). Thus, it does not seem unlikely that our participants had more severe pain than the average patient has.

Finally, few males were interested in participating in ADIRA and only eleven males (22%) were finally included. Due to this, our results may not apply to

the male population of patients with RA. On the other hand, the sex distribution was similar to that of the general patient population (22).

The assessments

To measure disease activity, we used the established disease activity instrument DAS28 as well as EULAR response criteria, which are both recommended for use in clinical trials by EULAR and the ACR (251). EULAR/ACR further recommend using DAS28 both as a continuous measure as well as a categorical outcome (the different disease levels), which we did. Due to RA being a chronic disease with life-long pharmacological treatment, HrQoL is an utterly important factor to consider and using patient-reported outcomes when evaluating disease symptoms could be a part of the patient-centered care recommended by EULAR (211, 252). To measure HrQoL may however be difficult since there are many different instruments to choose from and since perceived well-being is highly individual. We also need to consider a potential response shift changing the individuals' perceived HrQoL over time (196). Two individuals could feel the same amount of pain/fatigue/et cetera but its effect on the perceived quality of life may differ between the two individuals. For example, coping may result in one patient getting used to the pain and thus rate the importance of social functioning for a high quality of life much higher than absence of pain. Another patient, maybe newly diagnosed, may feel the opposite. However, the crossover design of the ADIRA trial minimizes between-individual variations since all participants are their own control and hopefully the perception of well-being did not change much during the months participating in ADIRA.

We used a combination of disease-specific and generic instruments to measure HrQoL, covering several different domains. HAQ is an established, validated, disease-specific (although some consider it to be generic (203)) measurement of physical disability while SF-36 is a generic instrument measuring more aspects than just physical functioning but still validated for use also in populations with RA (198, 215, 216). Both instruments are commonly used in RA research and thus we can easily compare our results to other studies. Further, we also investigated pain and fatigue separately using two different VAS. Morning stiffness was measured through VAS as well but for this outcome we also used a scale for minutes of stiffness after waking up. This scale was developed specifically for the ADIRA trial but has not been validated and interpretation of the results should be made with caution. However, measuring morning stiffness in minutes is commonly done in RA research. VAS for pain

and fatigue is frequently used in research and VAS in general is an established instrument for assessment of patient-reported outcomes (194). It is measured in exact mm on a 100 mm long line and thus provide precise results compared to a question with response categories. However, that high precision is probably only theoretical since a respondent may not distinguish one mm from another mm (194). We could have used multi-item questionnaires for both pain and fatigue instead or as a complement. These have the advantage of including questions on different dimensions of the symptoms such as what kind of pain (sharp, tiring, sickening, et cetera) and both general, mental, and physical fatigue (11, 253). On the other hand, it would have been difficult to compare our results to other research since such instruments have not been commonly used in dietary intervention studies in RA. Also, because of HAQ and SF-36 being rather extensive questionnaires demanding much from both participants and investigators, VAS was considered appropriate. Further, EULAR/ACR state in their recommendations that fatigue should be investigated in clinical trials, but they do not recommend a certain instrument (251). Pain is included in the recommended ACR response, but it is not included in the disease activity measures we used (251, 254). Many patients who reach the goal of a low disease activity through pharmacological treatment still suffer from pain and fatigue which make the possible effects of complementary treatment even more important (67-70). As discussed, there are moderate evidence for pain reduction consuming a Mediterranean dietary pattern (58, 59) but further research is needed to confirm dietary effects on fatigue. Hence, these are important outcomes to include in dietary interventions.

Limitations of the patient-reported outcomes used in the ADIRA trial include the individual perception of quality of life and the difficulty interpreting the results as previously discussed but the main limitation of using patient-reported outcomes in dietary interventions would be the lack of blinding. Dietary interventions can seldom be fully blinded. In ADIRA, we tried to blind the participants to which diet was the intervention diet, but since these outcomes are subjective and participants of course could see what they ate, a belief of dietary effects may have affected their responses.

To further interpret results of both disease activity and HrQoL we must be assured that the patients followed the prescribed dietary treatment. By using the biomarkers plasma omega-3 fatty acids, plasma alkylresorcinols and carotenoids we were able to objectively investigate compliance to the study diets regarding provisions of and instructions on seafood, whole grain and fruit, berries, and vegetables, respectively. Although they all have some shortcomings,

these are three established groups of dietary biomarkers (184, 188, 189, 231). By investigating plasma fatty acids through OPLS-analyses we could also explore the overall fatty acid pattern in plasma in the different diet periods and conclude whether the intended differences in fat quality were achieved. However, there is a lack of an established biomarker for red meat intake. Most proposed meat intake biomarkers, such as urine creatine, anserine and 1-methylhistidine, are not specific and could also be used as a biomarker for poultry or fish (255). Using the subjective 3-day food records as a measure of compliance to meat intake was considered more accurate than using objective but unspecific biomarkers. Further, alkylresorcinols only correspond to whole grain wheat, rye, and barley intake. An established biomarker for oat intake does not yet exist, but avenanthramides and avenacosides are under investigation (256). Since there were specific instructions on red meat intake and the participants were expected to have an almost daily intake of oats (oatmeal or granola/muesli for breakfast for at least five days/week), 3-day food records were considered an important complement to evaluate compliance. In addition, also the serum carotenoids needed to be complemented with the food records, as has already been discussed.

Except for compliance measurement, the 3-day food records were also used for evaluation of habitual energy and nutrient intake. As previously discussed, the main problem of this subjective method is the common underreporting (172). It has been reported that highly motivated individuals, which we believed the participants in the ADIRA trial was, can report accurate intakes through weighed food records (168). On the other hand, higher BMI increases the likelihood of underreporting (168), and since a substantial proportion of the ADIRA participants had overweight or obesity, underreporting was likely common. Although encouraging the participants to use a scale when reporting their food and drink consumption, this was sometimes not possible. Therefore, motivated or not, estimation of portion sizes may also have led to underreporting (257). Pictures of portion sizes were often used instead but perhaps providing all participants with a household scale would have yielded more weighed meals and thus more accurate results.

The statistics

The statistical method used for the main analyses in the ADIRA trial, the linear mixed ANCOVA model, is considered appropriate to use in studies with repeated measurements and where the data is non independent, such as in cross-over studies (258). To use such a model requires continuous data with a normal

distribution. For this reason, we transformed some of the variables and used a generalized logistic mixed model for the tender and swollen joints. However, for all the HrQoL-outcomes we used the main model – the linear mixed model. This may not have been the most appropriate approach since it is doubtful that data from questionnaires could be considered continuous. On the other hand, handling these outcomes as continuous variables seem to be the most common approach, thus making it easier for us to make comparisons to previous research. Also, we performed a sensitivity analysis where the data were dichotomized and analyzed using a generalized logistic mixed model, yielding similar conclusions.

When interpreting the few significant results we obtained in ADIRA, it is important to remember that we performed many statistical tests but no correction for these multiple comparisons, such as using the Bonferroni correction test (259), was made. For example, paper II included main analyses on HAQ, all three VAS scales, duration of morning stiffness and each of the eight domains and summary scores of SF-36, within-period-analyses, and also several sensitivity analyses of all these outcomes. Thus, the very few significant results could have been obtained merely by chance. However, the power calculation for the ADIRA study was not based on the HrQoL-outcomes since DAS28 was the primary outcome. A larger study population may have yielded more statistically significant results.

Conclusion

The results of this thesis indicate that a diet rich in whole grain, seafood, fruit, berries, vegetables, and probiotics, and low in red meat, (thus a diet having a healthy fat quality including a high amount of omega-3 fatty acids and containing much fiber/prebiotics and antioxidants) has modest beneficial effects on disease activity and physical functioning in RA, primarily in patients with stable anti-rheumatic treatment. Further, through use of a combination of objective plasma/serum biomarkers and subjective food records and interviews, compliance to the study diets was deemed to be high. This further validate the results and indicate feasibility of the diet. However, an effectiveness study would be needed to confirm this indication. Also, research in other populations with RA as well as long-term studies are needed to draw firm conclusions about the possible symptom alleviating effects of this diet.

The results also showed that patients with RA residing in Southwestern Sweden have a high habitual intake of saturated fatty acids, low intake of fiber and very low intake of vitamin D, which is similar to the results of the latest national dietary survey in the general adult Swedish population. However, many of the patients with RA also seem to consume an inadequate amount of vitamin A, thiamin, riboflavin, and iron. This indicates a need for professional dietary consultations to be included in the standard RA treatment.

Future perspectives

During the last decades, the pharmacological treatment of RA has become highly effective, especially regarding the inflammation reduction. Still, existing treatment does not manage to reduce all symptoms to satisfying levels for the patients. Thus, the patients seek further symptom relief from complementary treatment such as dietary modifications. Despite the potential for anti-inflammatory effects of diet, no firm conclusions on symptom alleviating effects of nutrients or other food components, whole food items or whole diets can be drawn. Except for the Mediterranean diet, which has well-known positive effects on cardiovascular health and seems to reduce pain in patients with RA, the American and European rheumatology societies call on the health professionals to recommend patients to abstain from specific diets and instead follow the general dietary guidelines. The results of this thesis do not change these current dietary recommendations but add to the knowledge of dietary modification as a potential complementary treatment. Modest but uncertain beneficial effects in disease activity, physical functioning and inflammation was obtained and blood lipid profile was improved, and the diet seemed to be feasible for the patients. More research, both short- and long-term, on this specific dietary pattern – a Nordic version of the Mediterranean diet with the addition of probiotics – in other populations; in deprived areas, other countries, with a more severe RA, etc., and with a more intense approach, are needed to draw firm conclusions regarding the effects on disease activity and health-related quality of life. Yet, this diet seems to have the potential to be an effective complement to standard treatment. The economic aspects of eating according to a specific dietary pattern as well as the possible interference with the patient's social life and the risk of social isolation must also be taken into consideration when investigating possible dietary treatments. An effectiveness study would be needed to ensure the feasibility of this diet in real-world conditions.

This thesis confirmed results of previously research regarding the nutrient intake in patients with RA. In the case of any exclusion diets, the patient should be referred to a dietitian. However, also for those not consuming specific diets, future studies should preferably investigate the effects of professional dietary consultations on improvement of nutrient intake in these patients. Also, the possible effects of such consultations on health outcomes such as obesity which seems to negatively affect treatment outcome, as well as

cardiometabolic diseases and osteoporosis, both common comorbidities in RA and which risk factors are modifiable through dietary changes, should be investigated.

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