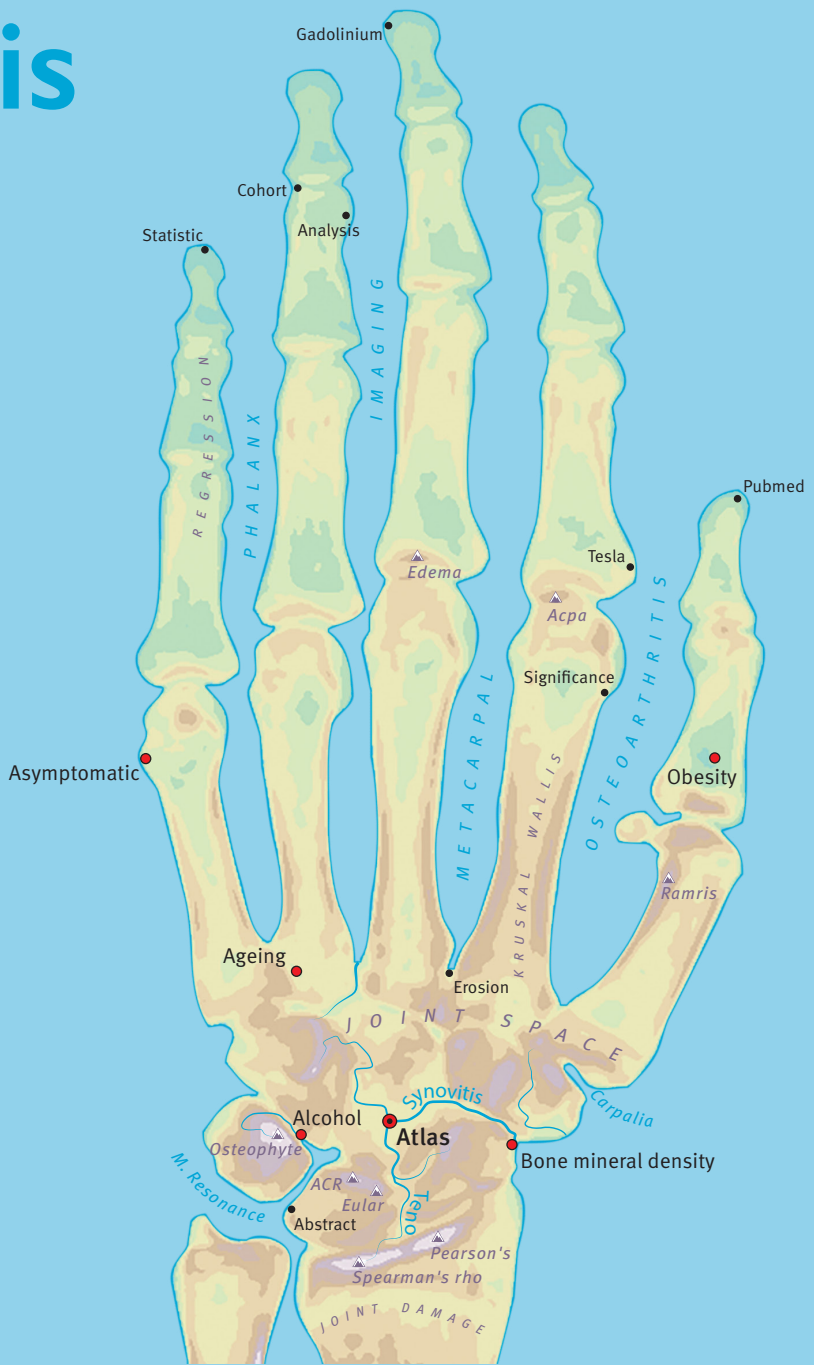
MRI in the earliest phases of rheumatoid arthritis



MRI in the earliest phases of rheumatoid arthritis

Lukas Mangnus

MRI in the earliest phases of rheumatoid arthritis
978-94-6233-739-8

The studies described in this thesis were performed at the Department of Rheumatology of the Leiden University Medical Centre, Leiden, the Netherlands

Cover design and thesis layout: Willem van den Goorbergh

Printing: Gildeprint - Enschede

MRI in the earliest phases of rheumatoid arthritis

PROEFSCHRIFT

Ter verkrijging van
de graad van doctor aan de Universiteit Leiden
op gezag van de Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 26 oktober 2017
klokke 11:15 uur

Door Lukas Mangnus

geboren te Venlo

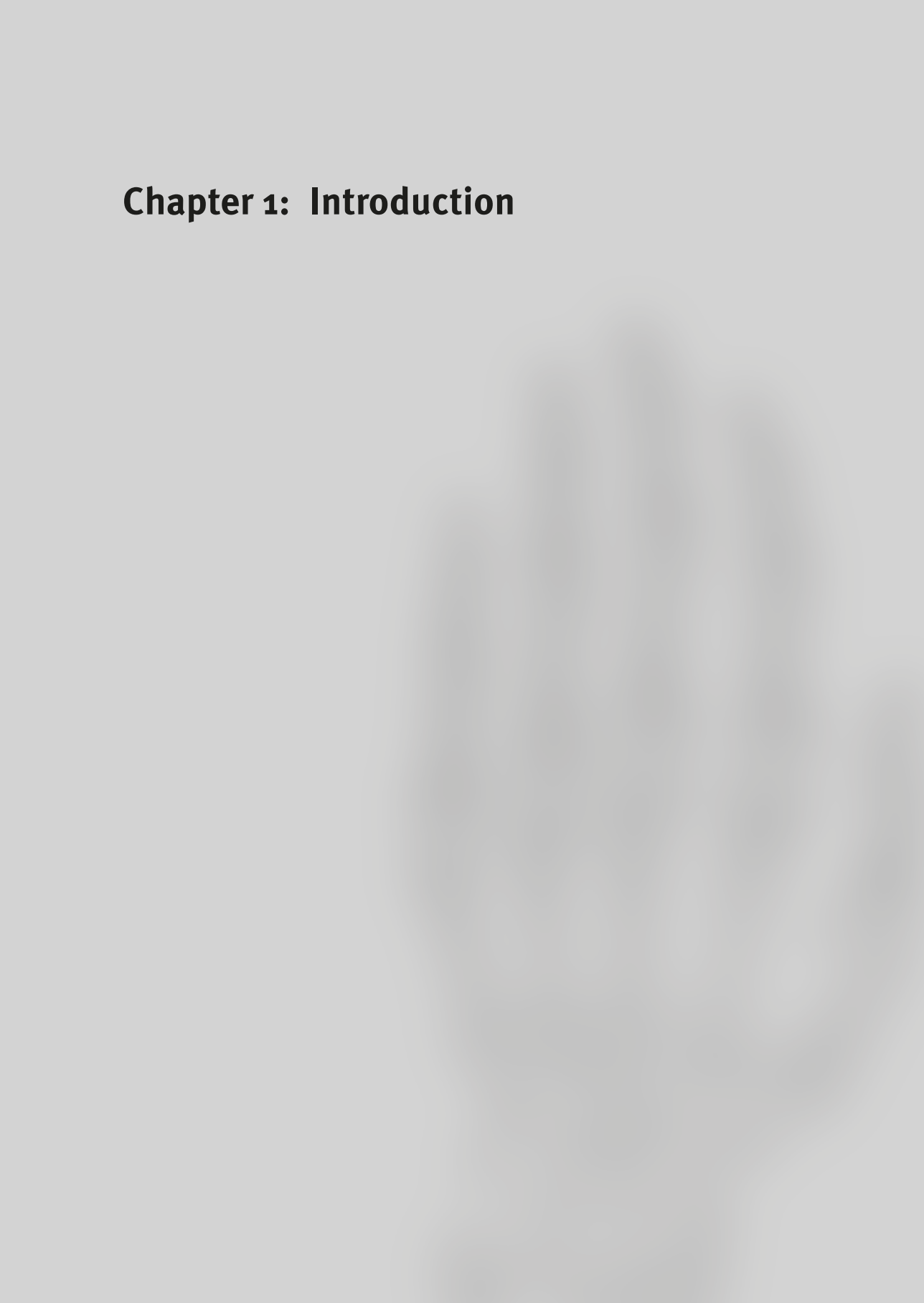
in 1985

Promotiecommissie

Promotores:	Prof. dr. A.H.M. van der Helm-Van Mil
	Prof. dr. T.W.J. Huizinga
Leden promotiecommissie:	Prof. dr. R.B.M. Landewé (AMC)
	Prof. dr. J. L. Bloem
	Dr. J van der Laken (VUmc)

Table of contents

Chapter 1: Introduction



Rheumatoid arthritis (RA) is a common condition affecting 0.5-1.0% of the population.[1] An EULAR study group assessing risk factors for rheumatoid arthritis defined several phases before RA is clinically evident.[2] In the first two phases individuals are at risk of RA on the basis of genetic and environmental risk factors. In the third phase individuals have systemic auto-immunity associated with RA. In the fourth phase, individuals have symptoms without clinically detectable arthritis (soft tissue swelling). Lastly, patients have clinically apparent arthritis but do not full fill the classification criteria for RA (unclassified arthritis (UA)). An individual does not necessarily have to pass all of these phases in the development of RA. Additionally, not all patients in the symptomatic phase before arthritis is clinically evident, actually progress to clinical arthritis or RA, and similarly not all UA patients develop RA.[2]

The earliest phase in which a rheumatologist can identify patients at risk for RA at their outpatient clinic is the fourth phase, in this phase patients have symptoms without a clinically detectable arthritis.[2] In order to explore the biological processes involved in the earliest clinical phase of RA, individuals that are at risk for RA have to be identified. In general two approached exist. One approach is to include individuals with arthralgia and positive auto-antibodies (rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA)).[3] Another method is to include individuals with higher risk on RA-development based on the clinical expertise of the rheumatologist.[4] This latter method is used to include individuals in the Leiden Clinically Suspect Arthralgia (CSA) cohort. In this cohort, individuals are included and followed until clinical arthritis is present, or else for a maximum of two years.[5]

Identification of patients in stages preceding that of clinical arthritis and RA might also be important from a clinical perspective, since the detection and treatment of RA in a very early stage has been associated with better outcomes.[6] It has been convincingly shown that early initiation of treatment of RA is associated less severe radiographic joint damage, lower disease activity scores (DAS) and a higher chance to achieve disease-modifying anti-rheumatic drug (DMARD)-free sustained remis-

sion.[6,7] An even earlier treatment, that in the phase of CSA, requires accurate prediction of progression from CSA to RA.

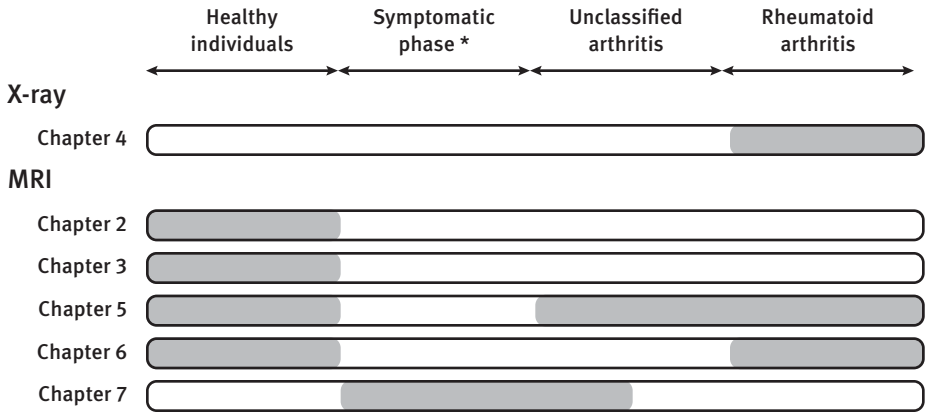
In previous studies, the prevalence of auto-antibodies is assessed before RA is clinically evident. In these studies it is shown that 46-60% of patients that will develop arthritis are RF positive and 43-57% are ACPA positive, depending on inclusion criteria (8-10). Furthermore, the specificity of these auto-antibodies is 78-87% for RF positivity and 86-98% for ACPA positivity.[8-10] Thus, auto-antibodies have an additional value in identifying patients at risk for arthritis development. However, auto-antibody status alone is not sufficient as up to 33-41% of individuals who are auto-antibody positive do not develop RA and auto-antibody negative patients could not be identified.[11,10] Therefore, there is a need for other methods to predict RA-development. Imaging might be useful here.
There are several imaging modalities which could have a predictive value for the development of RA. In current clinical practice, conventional radiographs are widely used. However, conventional radiographs can only depict radiographic joint damage (e.g. erosions and joint space narrowing) which is mostly present in later stages of RA-development.[12] Therefore, when using conventional radiographs for the diagnosis of RA, a window of early treatment could be missed.[6] Ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) can detect erosions in an earlier phase compared to conventional radiographs.[12] Ultrasound, positron emission tomography (PET), single photon emission computed tomography (SPECT) and MRI might play an important role in detecting inflammatory processes as an early sign of RA.[12] Of these imaging modalities, MRI is of particular interest as MRI does not involve radiation and can detect erosions, synovitis, tenosynovitis as well as bone marrow edema (BME). Therefore, MRI is well suited to study joint damage and inflammation in the very early phases of RA and might therefore attribute to the earlier detection of RA. Especially as currently inflammation is measured using C-reactive protein (CRP) levels and the number of involved joints with physical examination. These are not sensitive and, with regard to physical examination, also evaluator dependent.[13,14] Thus, in the (early) detection of patients with (imminent) RA, imaging modalities evaluating inflam-

mation, such as MRI, may play an important role. MRI could be of value as it is a very sensitive technique that can detect local joint inflammation before clinically detectable arthritis occurs.[14] The information obtained by MRI might not only be useful in the diagnostic process of RA, the information obtained by MRI may also improve the understanding of processes which are active within early RA and in the phases preceding RA. In this light this thesis explores the value of MRI-detected inflammation and erosions in early phases of RA.

Outline of this thesis

This thesis is divided in 2 parts. In the first part we explored to what extend MRI-detected features of inflammation and erosions occur in symptom-free persons from the general population. In the second part of the thesis we will discuss factors which could be associated with radiographic joint damage or local inflammation as

Figure 1 Outline of RA-development and studies depicted in relation to disease phase and imaging modality



Schematic overview of this thesis. The grey bars indicate in which phases the studies were performed subdivided in imaging modalities. For example, in chapter 6 MRI was used and healthy individuals and RA-patients were included.

detected on MRI, trying to improve the understanding of the processes which play a role in the early phases of RA. See figure 1 for an overview of disease phase in which studies were performed.

Part I: MRI-detected inflammation and erosions in the general population

MRI has increasingly been used in the clinical practice of RA. Recent recommendations of the European League Against Rheumatism (EULAR) suggest that MRI can be used to improve the certainty of a RA diagnosis in case of doubt. Furthermore, they state that MRI can detect structural damage at an earlier time point compared to radiographs.[15] However, these recommendations are mostly based on studies that included RA-patients. Since it is unknown to what extent MRI-features occur in the general (asymptomatic) population, the role of MRI in the early detection of RA is undetermined. We therefore wanted to evaluate the specificity of MRI-detected features by assessing the prevalence of MRI-features in asymptomatic persons.

As a start, we systematically reviewed the medical literature for asymptomatic persons with MRI-data of joints commonly affect by RA in **chapter 2**. In the literature, a large scale study evaluating MRI-features in a healthy population was lacking. Therefore, it was still largely unknown what the occurrence of MRI-detected erosions and inflammation in asymptomatic persons was.

In **chapter 3** we therefore assessed the prevalence of MRI-detected erosions and inflammation in a large group of asymptomatic volunteers. We also assessed whether the frequency of these MRI-features was dependent on factors such as age and gender.

Part II: Association with MRI-detected inflammation and radiographic joint damage

The processes that are active in the (very) early phases of RA are incompletely unraveled. Local inflammation in joints may be influenced by factors such as age, alcohol consumption or BMI. In subsequent studies, we therefore addressed the associations of age, BMI, alcohol consumption and joint inflammation detected on

MRI or with radiographic joint damage. The extent to which bone mineral density is decreased in the transition from CSA to RA was studied as well.

The western population is ageing and previous studies suggested that RA-patients that are diagnosed at an older age have more radiographic joint damage compared to patients diagnosed at younger age.[16-23] We verified in a multi-cohort study whether radiographic joint damage is indeed age related and assessed this in more detail in **chapter 4**. Furthermore, we explored factors underlying this association based on the general knowledge of risk factors for progressive joint damage. Among others, we assumed that older patients present at a later point in time, and therefore have more severe radiographic joint damage. Similarly other hypotheses were explored including auto-antibody status, clinical measures of joint inflammation, serological measures of inflammation, and MRI-detected inflammation.

Next to the ageing of the western population, the prevalence of obesity is increasing worldwide.[24] A higher BMI is associated with higher systemic inflammatory markers in the general population (25), but also with a higher risk to develop RA.[26,27] Counterintuitively, a higher BMI is associated with less joint damage in RA-patients, on conventional radiographs.[28-31] As MRI-detected inflammation is a precursor of radiographic joint damage, we assessed in **chapter 5** whether MRI-detected inflammation is also inversely associated with BMI in RA-patients. Furthermore, we assessed whether this association differs between patients which have an arthritis other than RA and asymptomatic volunteers.

Previous studies suggest that moderate alcohol consumption is associated with lower inflammatory markers both in the general population and in RA-patients. [32,33] Furthermore, moderate alcohol consumption seems to be protective against RA-development.[34,35] Thus, we hypothesized that moderate alcohol consumption is associated with lower MRI-detected inflammation in RA-patients and in asymptomatic volunteers. This was explored in **chapter 6**.

In **chapter 7** we evaluated bone mineral density (BMD) loss in patients with CSA. BMD-loss is seen as an early sign of RA. Furthermore, BMD-loss is associated with progression of radiographic joint damage and predicts development of RA in the UA phase.[36,37] Additionally, in the symptomatic phase before arthritis is clinically evident, some biomarkers of bone metabolism are already altered.[38,39] Therefore, BMD-loss could be present in the symptomatic phase before arthritis is clinically evident, this was assessed in chapter 7. Furthermore, as MRI-detected inflammation is associated with the development of bone erosions in RA (8), we hypothesized that MRI-detected inflammation was associated with a decrease of BMD. Finally, we explored if patients with higher BMD-loss have a higher risk on development of arthritis.

Chapter 8 consists of a summary and general conclusions of the studies performed in this thesis. In **chapter 9** the summary and general conclusions are provided in Dutch.

References

1 Scott DL, Wolfe F, Huizinga TW. *Rheumatoid arthritis*. The Lancet. 2010 Oct 1;376(9746):1094-108.

2 Gerlag DM, Raza K, van Baarsen LGM, Brouwer E, Buckley CD, Burmester GR, et al. *EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis.* Ann Rheum Dis. 2012 Mar 2;71(5):638-41.

3 Stadt LA van de, Witte BI, Bos WH, Schaardenburg D van. *A prediction rule for the development of arthritis in seropositive arthralgia patients.* Ann Rheum Dis. 2013 Dec 1;72(12):1920-6.

4 Steenbergen HW van, Mil AHM van der H. *Clinical expertise and its accuracy in differentiating arthralgia patients at risk for rheumatoid arthritis from other patients presenting with joint symptoms.* Rheumatology. 2016 Jan 7;kev431.

5 Steenbergen HW van, Nies JAB van, Huizinga TWJ, Bloem JL, Reijnierse M, Mil AHM van der H. *Characterising arthralgia in the preclinical phase of rheumatoid arthritis using MRI.* Ann Rheum Dis. 2015 Jun 1;74(6):1225-32.

6 Nies JAB van, Krabben A, Schoones JW, Huizinga TWJ, Kloppenburg M, Mil AHM van der H. *What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review.* Ann Rheum Dis. 2014 May 1;73(5):861-70.

7 Jayakumar K, Norton S, Dixey J, James D, Gough A, Williams P, et al. *Sustained clinical remission in rheumatoid arthritis: prevalence and prognostic factors in an inception cohort of patients treated with conventional DMARDS*. Rheumatol Oxf Engl. 2012 Jan;51(1):169-75.

8 Steenbergen HW van, Mangnus L, Reijnierse M, Huizinga TWJ, Mil AHM van der H. *Clinical factors, anticitrullinated peptide antibodies and MRI-detected subclinical inflammation in relation to progression from clinically suspect arthralgia to arthritis.* Ann Rheum Dis. 2015 Nov 27;annrheumdis-2015-208138.

9 Nam JL, Hunt L, Hensor EMA, Emery P. *Enriching case selection for imminent RA: the use of anti-CCP antibodies in individuals with new non-specific musculoskeletal symptoms – a cohort study.* Ann Rheum Dis. 2016 Aug 1;75(8):1452-6.

10 Gao IK, Haas-Wöhrle A, Mueller KG, Lorenz H-M, Fiehn C. *Determination of anti-CCP antibodies in patients with suspected rheumatoid arthritis: does it help to predict the diagnosis before referral to a rheumatologist?* Ann Rheum Dis. 2005 Oct 1;64(10):1516-7.

11 ten Brinck R, van Steenbergen H, Verheul M, Trouw L, van der Helm - van Mil A. *The Prognostic Value of Different Auto-Antibodies for Arthritis Development in Patients with Clinically Suspect Arthralgia* [abstract]. Arthritis Rheumatol. 2016;68 (suppl 10).

12 McQueen FM. *Imaging in early rheumatoid arthritis.* Best Pract Res Clin Rheumatol. 2013 Aug;27(4):499-522.

13 Cheung PP, Gossec L, Mak A, March L. *Reliability of joint count assessment in rheumatoid arthritis: A systematic literature review.* Semin Arthritis Rheum. 2014 Jun;43(6):721-9.

14 Krabben A, Stomp W, Huizinga TWJ, Heijde D van der, Bloem JL, Reijnierse M, et al. *Concordance between inflammation at physical examination and on MRI in patients with early arthritis.* Ann Rheum Dis. 2015 Mar 1;74(3):506-12.

15 Colebatch AN, Edwards CJ, Østergaard M, van der Heijde D, Balint PV, D'Agostino M-A, et al. *EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis.* Ann Rheum Dis. 2013 Jun;72(6):804-14.

16 Rasch EK, Hirsch R, Paulose-Ram R, Hochberg MC. *Prevalence of rheumatoid arthritis in persons 60 years of age and older in the United States: Effect of different methods of case classification.* Arthritis Rheum. 2003 Apr 1;48(4):917-26.

17 Woolf AD, Pfleger B. *Burden of major musculoskeletal conditions.* Bull World Health Organ. 2003;81(9):646-56.

18 Innala L, Berglin E, Möller B, Ljung L, Smedby T, Södergren A, et al. *Age at onset determines severity and choice of treatment in early rheumatoid arthritis: a prospective study.* Arthritis Res Ther. 2014 Apr 14;16(2):R94.

19 Bukhari M, Lunt M, Barton A, Bunn D, Silman A, Symmons D. *Increasing age at symptom onset is associated with worse radiological damage at presentation in patients with early inflammatory polyarthritis.* Ann Rheum Dis. 2007 Mar 1;66(3):389-93.

20 Calvo-Alén J, Corrales A, Sánchez-Andrada S, Fernández-Echevarría MA, Peña JL, Rodríguez-Valverde V. *Outcome of late-onset rheumatoid arthritis.* Clin Rheumatol. 2005 Oct 1;24(5):485-9.

21 Khanna D, Ranganath VK, FitzGerald J, Park GS, Altman RD, Elashoff D, et al. *Increased radiographic damage scores at the onset of seropositive rheumatoid arthritis in older patients are associated with osteoarthritis of the hands, but not with more rapid progression of damage.* Arthritis Rheum. 2005 Aug 1;52(8):2284-92.

22 Kuiper S, Gestel AM van, Swinkels HL, Boo TM de, Silva JA da, Riel PL van. *Influence of sex, age, and menopausal state on the course of early rheumatoid arthritis.* J Rheumatol. 2001 Aug 1;28(8):1809-16.

23 van der Heijde DM, van Riel PL, van Leeuwen MA, van 't Hof MA, van Rijswijk MH, van de Putte LB. *Older versus younger onset rheumatoid arthritis: results at onset and after 2 years of a prospective followup study of early rheumatoid arthritis.* J Rheumatol. 1991 Sep;18(9):1285-9.

24 Nguyen DM, El-Serag HB. *The Epidemiology of Obesity.* Gastroenterol Clin North Am. 2010 Mar;39(1):1-7.

25 Tilg H, Moschen AR. *Adipocytokines: mediators linking adipose tissue, inflammation and immunity.* Nat Rev Immunol. 2006 Oct;6(10):772-83.

26 Wesley A, Bengtsson C, Elkan A-C, Klareskog L, Alfredsson L, Wedrén S, et al. *Association between body mass index and anti-citrullinated protein antibody-positive and anti-citrullinated protein antibody-negative rheumatoid arthritis: Results from a population-based case-control study.* Arthritis Care Res. 2013 Jan 1;65(1):107-12.

27 Pedersen M, Jacobsen S, Klarlund M, Pedersen BV, Wiik A, Wohlfahrt J, et al. *Environmental risk factors differ between rheumatoid arthritis with and without auto-antibodies against cyclic citrullinated peptides.* Arthritis Res Ther. 2006;8(4):R133.

28 van der Helm-van Mil AHM, Kooij SM van der, Allaart CF, Toes REM, Huizinga TWJ. *A high body mass index has a protective effect on the amount of joint destruction in small joints in early rheumatoid arthritis.* Ann Rheum Dis. 2008 Jun 1;67(6):769-74.

29 Westhoff G, Rau R, Zink A. *Radiographic joint damage in early rheumatoid arthritis is highly dependent on body mass index.* Arthritis Rheum. 2007 Nov 1;56(11):3575-82.

30 Kaufmann J, Kielstein V, Kilian S, Stein G, Hein G. *Relation between body mass index and radiological progression in patients with rheumatoid arthritis.* J Rheumatol. 2003 Nov 1;30(11):2350-5.
31 Baker JF, Østergaard M, George M, Shults J, Emery P, Baker DG, et al. *Greater body mass independently predicts less radiographic progression on X-ray and MRI over 1-2 years.* Ann Rheum Dis. 2014 Nov 1;73(11):1923-8.
32 Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W. *Effect of alcohol consumption on systemic markers of inflammation.* The Lancet. 2001 Mar 10;357(9258):763-7.
33 Albert MA, Glynn RJ, Ridker PM. *Alcohol Consumption and Plasma Concentration of C-Reactive Protein.* Circulation. 2003 Jan 28;107(3):443-7.
34 Jin Z, Xiang C, Cai Q, Wei X, He J. *Alcohol consumption as a preventive factor for developing rheumatoid arthritis: a dose-response meta-analysis of prospective studies.* Ann Rheum Dis. 2014 Nov 1;73(11):1962-7.
35 Scott IC, Tan R, Stahl D, Steer S, Lewis CM, Cope AP. *The protective effect of alcohol on developing rheumatoid arthritis: a systematic review and meta-analysis.* Rheumatology. 2013 May 1;52(5):856-67.
36 Rooy DPC de, Kälvesten J, Huizinga TWJ, Mil AHM van der H. *Loss of metacarpal bone density predicts RA-development in recent-onset arthritis.* Rheumatology. 2012 Jun 1;51(6):1037-41.
37 Güler-Yüksel M, Bijsterbosch J, Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Ronday HK, Peeters AJ, et al. *Bone mineral density in patients with recently diagnosed, active rheumatoid arthritis.* Ann Rheum Dis. 2007 Nov;66(11):1508-12.
38 Turesson C, Bergström U, Jacobsson LTH, Truedsson L, Berglund G, Saxne T. *Increased cartilage turnover and circulating autoantibodies in different subsets before the clinical onset of rheumatoid arthritis.* Ann Rheum Dis. 2011 Mar 1;70(3):520-2.
39 Schaardenburg D van, Nielen MMJ, Lems WF, Twisk JWR, Reesink HW, Stadt RJ van de, et al. *Bone metabolism is altered in preclinical rheumatoid arthritis.* Ann Rheum Dis. 2011 Jun 1;70(6):1173-4.

Part I
MRI-detected inflammation and erosions in the general population

Chapter 2: What is the prevalence of MRI-detected inflammation and erosions in small joints in the general population? A collation and analysis of published data

L. Mangnus

J.W. Schoones

A.H.M. van der Helm-van Mil

RMD Open 2015

Abstract

Introduction: MRI sensitively depicts erosions, bone marrow edema (BME) and synovitis in rheumatoid arthritis (RA). Recently developed European League Against Rheumatism (EULAR) recommendations stated that MRI is valuable to improve the certainty of a considered diagnosis and to detect structural damage at an early time point. However, these recommendations were mainly based on the data of patients with RA; prevalences of MRI-features in the general population were not extensively explored. We reviewed the literature on MRI-studies including symptom-free persons to assess the occurrence of MRI-features.

Methods: Medical literature databases up to September 2013 were systematically reviewed for symptom-free persons with MRI-data on metacarpophalangeal, wrist and metatarsophalangeal joints. Data were extracted and summarised. When allowed because of comparable scanning and scoring protocols, a mean frequency of features was calculated.

Results: Of the 338 articles screened, 31 studies evaluated MRI-findings in symptom-free persons (n = 516 in total). Both the imaging techniques (< 1/≥ 1 T, with/without contrast enhancement) and the scoring methods (non-validated or RA MRI score (RAMRIS)) varied widely, prohibiting direct comparisons of the results of many studies. 15 studies scored data according to RAMRIS; combining data of similar joint regions showed that erosions (RAMRIS ≥ 1) were present in 33-52% of symptom-free persons. Similarly, synovitis was present in 27% and BME in 0-16% of symptom-free persons. The prevalence of MRI-detected erosions increased with age.

Conclusions: MRI-features, erosions in particular, occur frequently in symptom-free persons. Before MRI can be implemented in the diagnostic process, larger studies should be conducted determining the degree and combination of MRI-features that are disease specific.

Introduction

Early treatment initiation in rheumatoid arthritis (RA) is associated with less radiographic progression and a higher chance to achieve disease-modifying antirheumatic drug-free sustained remission, illustrating the relevance of early diagnosis.[1-6] To what extent MRI is valuable for early detection of RA is undetermined. However, the recently formulated European League Against Rheumatism (EULAR) recommendations for the use of imaging in the management of RA suggest that MRI can improve the certainty of the diagnosis of RA and detect structural damage at an earlier time point than radiographs.[7] Additionally, an imaging task force of the American College of Rheumatology recently concluded that, of all imaging modalities, MRI serves best to ascertain structural damage in trials.[8] These recommendations were mainly based on MRI-data of patients with RA; MRI-features that are present in the general population were scarcely considered.[7-8]

Furthermore, many studies in RA are currently investigating the preclinical phases of the disease because the processes occurring in these phases may influence the long-term course of the disease. Potentially very early detection of RA may allow intervention in an asymptomatic preclinical disease phase. Indeed, several recent studies reported that MRI may play a role in the identification of joint inflammation in the phase before it becomes clinically detectable.[9-10] More studies are needed to determine the value of novel imaging modalities in the early detection of RA and their ability to differentiate patients with the disease from the normal situation.

Thus, to arrive at an evidence-based evaluation on the role of MRI in the diagnostic process in the early clinical and preclinical phases of RA, it is necessary to investigate the occurrence of MRI-features in the general population. In case certain MRI-features (to a certain degree) are also present in persons without joint symptoms, these lesions are presumably not indicative for RA. No large-scale studies have been performed to investigate the prevalence of these features in the general population. However, several MRI-studies included symptom-free persons as controls.[10-41] We aimed to (1) evaluate the prevalence of MRI-features in symptom-free persons and (2), based on these observations, to make recommendations for future studies. To this end, we systematically reviewed the literature.

Method

The databases PubMed, EMBASE and Web of Science up until September 2013 were searched with the assistance of a medical librarian (JWS). Central terms in our search were MRI, healthy volunteers, wrist, metacarpal, metatarsal and RA (complete details of the search strategy can be obtained by the author). Titles and abstracts were screened on whether data on symptom-free persons and MRI of hands or feet were available. Subsequently, full-text articles were read and additional articles were identified through hand searching of reference lists. Articles were included when the studies contained (1) symptom-free persons and (2) information on MRI-detected erosions, bone marrow edema (BME), synovitis or tenosynovitis of hands or feet. Since the symptom-free persons were generally used as the control group, the quality of the overall study design was not valued. Further, in order to get a comprehensive overview, we decided to include all studies fulfilling these two criteria and not to exclude studies based on the quality of the scanner, the scan protocol or scoring protocol that was used.

A standardised form was used to extract the following data: (1) study population (population size, age, recruitment method, description of study population, MRI-scanner, MRI-sequences, joint region scanned and scoring method), (2) MRI-features (erosions, BME, synovitis and tenosynovitis) and quantitative aspects (number of patients affected, number of joints/bones affected and grading of the MRI-features) and (3) relevant characteristics (location of MRI-features, dominant or non-dominant hands, age and sex of symptom-free participants). MRI-features were present ('positive') when recorded as such; studies using the RA MRI score (RAMRIS) generally considered a score of≥1 for that feature as positive.[10,27-40] Data were extracted and reported such as done by the authors: either by presenting the prevalence of a feature or by presenting summary measures of continuous RAMRIS. According to RAMRIS, the range per bone/joint of erosion, BME and synovitis scores are 0-10, 0-3 and 0-3, respectively; scoring of the metacarpophalangeal (MCP) region and wrist region involved evaluation of 8 and 15 bones and 4 and 3 joints (radioulnar joint, radiocarpal joint and intercarpal-carpometacarpal joint), respectively, evaluation of the 5 metatarsophalangeal (MTP) joints involved eval-

uation of 10 bones. In case the same joint regions were assessed using similar scan protocols (ie, either with or without use of contrast enhancement) and similar scoring methodology (RAMRIS), it was considered acceptable to combine the results of different studies. Then mean frequencies (with 95% CIs) were calculated. Since it is known that contrast enhancement increases the reliability of assessment of synovitis,[42] studies evaluating synovitis and tenosynovitis with and without contrast enhancement were not combined but analysed separately.

Results

Selection of studies

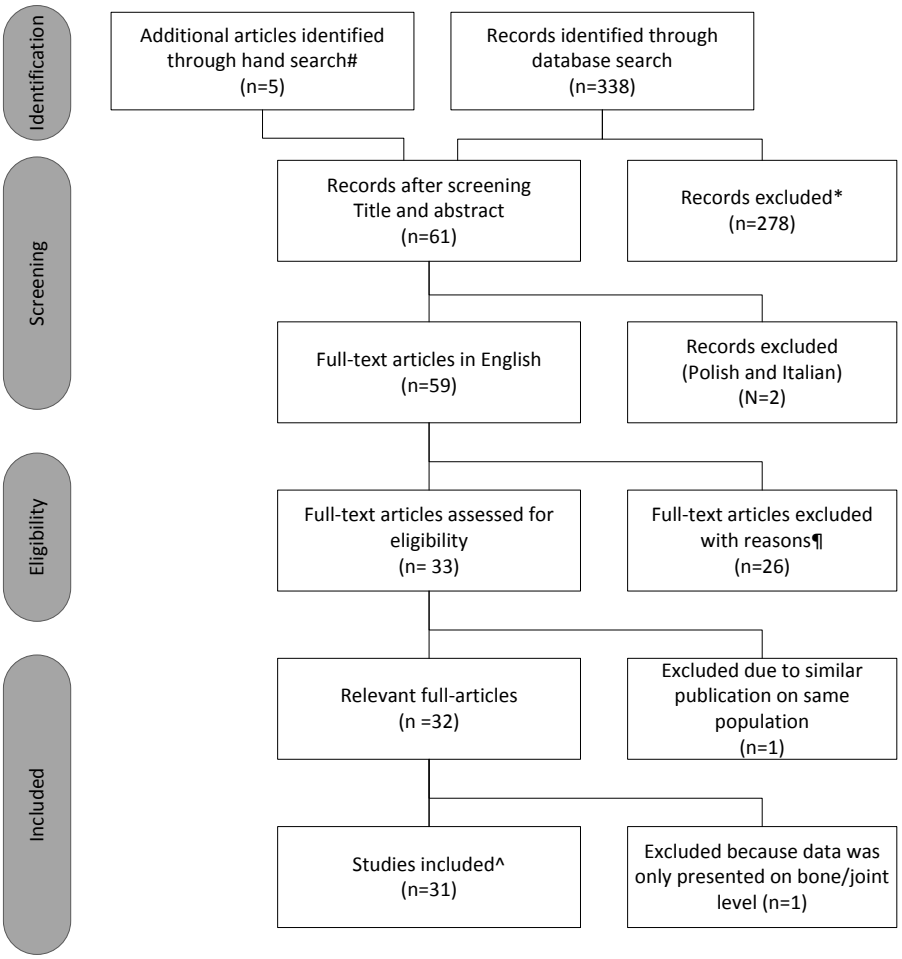
The literature search yielded 338 studies; five additional articles were found by hand searching of reference lists (figure 1). After screening, 61 articles were selected. Two studies were excluded because of a language other than English. Of the remaining articles, 33 were eligible for inclusion. One article was excluded as it concerned a population that was used in two articles. Consequently, data were extracted of 32 articles. Whereas 31 studies provided data on patient level (joint region), one study analysed the data only on individual bone/joint level; therefore, this study was only used when analyzing results on bone/joint level.[41]

Study description

The 31 included studies contained information on 3-42 (range) symptom-free persons per study; in total, 516 symptom-free persons were studied (table 1). Descriptions of the recruitment method is given in only seven studies. [12,23,24,26,31,32,36] Most of these studies are reported to have studied hospital staff. Methods to exclude the target disease were described in 26 articles; four studies did not include this information and described their symptom-free persons as ‘healthy volunteers’[11] or ‘healthy controls’[14,37,38] and one study was described to have performed MRIs of ‘healthy volunteers’ and persons with wrist instability.[26] The methods of excluding target disease differed. Thirteen studies described that there was no history of joint disease, arthritis or joint symptoms.

[15-17,19-22,24,28-30,36,39] Twenty studies mentioned that there were no current musculoskeletal/ joint symptoms.[10,12,13,18,20,21,23-25,27-34,36,39] In four

Figure 1 Overview of literature research



Articles identified by hand searching of reference lists.

* Articles were excluded when no data on symptom-free persons or MRI-features of hands or feet were described.

¶ Articles were excluded when no data were presented on erosions, BME, synovitis or tenosynovitis in symptom-free persons.

^ The data of the 31 included studies provided data on patient level.

studies, persons underwent clinical assessment by a rheumatologist,[24,27,29,36] and in two studies laboratory investigations were done and persons were excluded in case they were rheumatoid factor positive or had increased C reactive protein levels.[32,33]

Of the 31 included studies, 19 used an MRI with ≥ 1 T, 11 with an < 1 T MRI and one study used two different scanners (one with 1 T and one with 0.6 T).[34] Contrast enhancement was used in 17 of the 31 studies.

Sixteen studies did not use a validated scoring method; evaluations were done by experienced radiologists (in 12 studies), an experienced rheumatologist (1 study) and an 'observer' (2 studies), and in one study no information was provided. In 15 studies, MRIs were scored according to RAMRIS.[43] MRI-scoring was done blinded for clinical status in 18 of the 31 studies. In seven studies, scoring of patients and controls was not performed blindly [10,15,20,23,27,34,40] and in six studies (140 symptom-free persons) only symptom-free persons were evaluated. [22,23,28,30,32,36]

Prevalence of erosions

The studies that did not use a validated scoring method reported a lower prevalence of erosions than did the studies using RAMRIS (table 2). A wrist was scanned on one or both sides and assessed using RAMRIS in 69 and 44 persons, respectively. When combining data of the wrist, a total RAMRIS erosion score ≥ 1 was reported in 52.2% (mean, 95% CI 40.6 to 63.5, unilateral wrist) [27,34,37] and 40.9% (95% CI 27.7% to 55.6%, both wrists) [35,36] of symptom-free persons, respectively. Unilateral MCP joints were evaluated in 97 persons and revealed erosions in 33% (95% CI 24.4% to 42.9%).[27,34,38,39] No studies described the prevalence of erosions when using higher cut-offs for positivity for instance, a total RAMRIS erosion score of ≥ 2).

Prevalence of BME

The recorded prevalence of BME was higher in the studies using RAMRIS than in the studies using other methods. Combining the data of the 63 persons in whom unilateral wrists were scanned yielded a mean frequency of BME (RAMRIS BME-

score ≥ 1) of 15.9% (95% CI 8.7% to 27.0%).[27,34] Similarly, BME was present in 9.5% (95% CI 4.1% to 19.6%) [27,34] of persons in whom unilateral MCPs were evaluated. Combining studies assessing unilateral wrist and MCPs showed a mean frequency of BME of 0.0% (95% CI 0.0% to 6.8%).[29,30] No studies categoried BME features with higher cut-off values.

Prevalence of synovitis and tenosynovitis

Synovitis was assessed without contrast enhancement in 8 studies and with contrast in 13 studies. In the studies that used no validated scoring method, synovitis was present in 0-4.8% (range) of persons when no contrast was used13-15 20 and 0-44.4% (range) when contrast was used.[11,16-19,22,26] In the studies that were scanned with contrast enhancement and scored according to RAMRIS, synovitis was present (total synovitis score ≥ 1) in 26.7% (95% CI 15.8% to 41.2%); these studies assessed wrist and MCP joints together.[29,30] Data on the studies that provided results of wrist or MCP joints separately were not combined due to differences in scanning or scoring protocols. Tenosynovitis was assessed infrequently (table 2).

Continuous RAMRIS-scores

Three studies did not report categorised data but reported continuous RAMRIS, incorporating a semi-quantitative evaluation of the severity of the features.[10,27,28] The mean RAMRIS for erosions and BME were low (≤ 3.2 and 0.9, respectively, table 3). For synovitis, contrast enhancement was used in one study;[28] this study revealed higher mean RAMRIS synovitis scores than did the two studies without contrast (mean synovitis scores > 3 vs < 1, respectively; table 3).[10,27]

Prevalence of lesions at the bone and joint level

In the aforementioned studies, total scores per joint region were evaluated. Several studies evaluated the prevalence of MRI-features on the level of individual bones and/or joints, all defining a RAMRIS of ≥ 1 as positive.[24,29-32,36,39,41] Erosions were analysed in six studies; among the 4696 bones evaluated, 161 showed erosions 3.4% (95% CI 2.9% to 4.0%).[30-32,36,39,41] BME was analysed in only two studies; among the 1182 bones evaluated, five were positive for BME 0.4% (95% CI

0.2% to 1.0%).[24,32] Three studies analysed 471 joints on synovitis and reported the prevalence of synovitis in 42 joints 8.9% (95% CI 6.6% to 11.9%).[29,30,41]
The severity of the individual lesions was scarcely reported. Three studies contained information on the severity of erosions and reported that 80.8% (mean, 95% CI 72.8% to 86.9%) of the recorded erosions had a score of 1.[31,32,36] None of the studies reported on the severity of BME or tenosynovitis at the local level. Two studies described the synovitis scores in more detail; 21 joints had a RAMRIS of 1 (95.5%), a RAMRIS synovitis score of 2 was seen in 1 joint (4.5%) and no joints had a RAMRIS of 3.[29,30]
With regard to the location of the MRI-features, erosions and synovitis were more often observed in the wrist than in the MCP joints.[20,31,32] The locations of erosions were evaluated in seven studies at the bone level; most erosions were observed in the carpal bones; however, there was no clear agreement on which carpal bones showed erosions most frequently.[30,32,35,36,41] Erosions were rarely scored on the metacarpal-1 and trapezium (bones that might also be affected by osteoarthritis).[30-32,35,36] Locations of BME and synovitis were not clearly reported.

Relevant characteristics

We next evaluated to what extent differences in the scanner or differences in persons' characteristics influenced the results. No different prevalences were observed when comparing extremity-MRI [10,12,13,27,31-33,35] with whole-body MRI.[11,14-26,28-30,36-40] When comparing the prevalence of MRI-features in studies that used MRI-scanners with ‹1 Tesla (T) [12,13,16,20,31-33,35-38] and those with ›1 T, [10,11,15,17,18,23,24,26,28,29,39,40] a higher prevalence of erosions was detected with ‹1 T scanners (mean 38% vs 24%). Owing to the heterogeneity between studies, no summary results can be provided with regard to the prevalence of MRI inflammatory features in relation to the field strength of the MRI. When comparing the studies that evaluated the MRIs blindly versus those that scored the MRIs knowing that the persons were symptom-free, no differences in the prevalences of the different MRI-features were observed.[11-14,16-19,23-26,29,31,33,35,37-39]

The dominant and non-dominant hands were evaluated in two studies and no significant differences were observed.[31,36] Differences in the frequency of features between sexes were also not detected.[32] Four studies compared the prevalence of MRI-features between age categories and showed a non-significant tendency to [27,32] or a significant [31,36] higher prevalence of MRI erosions in older persons. Synovitis and BME were less frequently studied in relation to age, although a significant difference in two studies was observed with higher prevalences at older age. [31,36] No information was provided on the location or the grading of the erosions and the inflammatory features observed in symptom-free persons of different age categories.

Discussion

MRI is an imaging method that is very sensitive in detecting inflammation and also bone erosions. This makes MRI an interesting tool to measure the course of the disease in randomised clinical trials and this suggests that MRI may also be useful in the diagnostic process. When MRI would be implemented in practice in the diagnostic workup of joint symptoms, it is crucial to consider the prevalence of MRI-features in the general population to prevent false-positive findings due to positive labelling of features that are (also) present in the normal situation. We reviewed the literature systematically to get an overview of the reported prevalence of features in symptom-free persons. The large majority of these studies were not designed to determine the frequencies of MRI-features in the general population but used symptom-free persons as the control group. In addition, there were considerable differences in methodology of the selection of volunteers, MRI-protocols and MRI-scoring. This resulted in heterogeneous data. Indeed, considerable differences in the frequencies of MRI-features in symptom-free persons were observed in the different studies. We combined the data of the studies that had similar scanning and scoring protocols and, based on the data available, we observed that all MRI-features studied were present regularly and that MRI-detected erosions were present most frequently (in 33-52% of symptom-free persons).

Most studies described their findings at the patient/ joint region level and not at the level of individual bones or joints. However, studies that did include evaluation at the bone level showed that most lesions were mild (RAMRIS of 1). Furthermore, we noted a lower prevalence of all MRI-features (erosions in particular) in studies not using RAMRIS than in those using the RAMRIS method. This may possibly reflect that the RAMRIS method is sensitive and that radiologists evaluating the MRIs using clinical experience may more often report an MRI as normal. Additionally, most of the studies that did not use the RAMRIS method were done when MRI-techniques were less developed.[11,12,14-22,24,25,44]

Of all MRI-features, the prevalence of synovitis varied the most between studies. This cannot be explained only by the absence or presence of contrast enhancement that may increase the sensitivity and specificity of identifying MRI-detected synovitis as both types of studies were evaluated separately.[42,45,46] The reasons for these differences between studies are unclear to us.

The most important limitation of this review is the heterogeneity of the data collected, which is a result of the methods with which data were collected in the individual studies. For instance, in many studies the symptom-free persons were used as the control-group and information on how the symptom-free persons were recruited was missing. Some studies included symptom-free persons only and did not use the symptom-free persons as controls.[22,23,28,30,32,36] A consequence of this latter approach is that the evaluators per definition were aware that they had evaluated scans of symptom-free persons. Hypothetically, awareness of the clinical status may affect the scoring with lower scores being given to symptom-free individuals. In addition, the methodology to rule out rheumatic diseases differed between the studies. A difficult issue is to what extent osteoarthritis was ruled out; joint space narrowing or other osteoarthritic features were not assessed in these studies, so no definite conclusions can be drawn as to what extent the presence of asymptomatic osteoarthritis has affected the results. Furthermore, recent studies indicated that ACPA can affect the bone in the absence of clinically apparent arthritis and that subclinical inflammation may precede clinical arthritis.[9,10] In two studies, the symptom-free persons underwent laboratory testing and in three

studies the symptom-free persons were even followed (for 1-5 years); none of these persons developed RA.

Another important limitation relates to the issue when it is allowed to combine the results of different studies. We combined results of studies that used similar scan protocols (same joints and uniformity in contrast enhancement) and similar scoring protocols. Still, the summary measures that we provided should be interpreted with care as the readers of the different studies were not trained together and inter-reader differences and other causes of heterogeneity most likely exist. Nevertheless, this review gives a first impression of the MRI-features present in the general population. It can be argued that more stringent quality criteria should be applied before it is acceptable to combine the results of different studies. For instance, the following quality criteria might be reasonable: (1) the recruitment method was described, (2) appropriate methodology was used to exclude persons with joint symptoms or joint disease, (3) the field strength of the MRI was ≥ 1 T and (4) scans were scored according to the RAMRIS method. None of the 32 studies included in this review fulfilled all these four criteria. This underlines that large,

Box 1 Recommendations for high-quality studies, formulated based on the findings of this review

Recommendations for future studies
Include a large number of symptom-free persons
Include persons of different age categories
Apply population based recruitment methods
Describe the recruitment methodology
Apply thorough anamnesis and physical examination to exclude the presence of joint symptoms or signs of joint disorders.
Perform similar MRI-scans in all persons
MRI strength of ≥ 1 Tesla
Use contrast-enhancement
Score the MRIs according to RAMRIS
Include also MRIs of persons with joint diseases (eg RA) and score the MRIs blinded to the clinical status
Preform analyses stratified for age

high quality studies on this subject are needed. Recommendations for the set-up of such studies are proposed in box 1.

Furthermore, several questions still have to be answered. More detailed studies are needed on the prevalence of MRI-detected erosions, BME, synovitis and tenosynovitis in the symptom-free persons in relation to age. Furthermore, the location and the co-occurrence of erosions and inflammation (BME, synovitis or tenosynovitis) could be important for differentiation. In none of the studies was it reported whether the erosions were accompanied by inflammatory lesions, which may also be relevant to differentiate early disease from normal variants, as disease-specific erosions might presumably more often be accompanied by measures of inflammation. Also the extent or severity of the lesions may be useful to take into account. Ultimately, comparing a large number of MRI-scans of healthy persons and early RA-patients will reveal which combination of features are disease specific and will allow MRI criteria specific for early disease to be defined.

In conclusion, MRI-features, erosions in particular, occur frequently in symptom-free persons and are more prevalent with increasing age. Before MRI can be implemented in the diagnostic process of arthritis, further evaluation of these features in symptom-free persons is required. Preferentially, this is done in large studies, ensuring homogeneity in the scan-protocol and scoring method, by evaluating scans of symptom-free persons as well as early arthritis patients blinded to the clinical status.

References

1 Nell VPK, Machold KP, Eberl G, et al. *Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis.* Rheumatology 2004;43:906-14.

2 Van der Linden MPM, le Cessie S, Raza K, et al. *Long-term impact of delay in assessment of patients with early arthritis.* Arthritis Rheum 2010;62:3537-46.

3 Finckh A, Liang MH, van Herckenrode CM, et al. *Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: a meta-analysis.* Arthritis Care Res 2006;55:864-72.

4 Green M, Marzo-Ortega H, McGonagle D, et al. *Persistence of mild, early inflammatory arthritis: the importance of disease duration, rheumatoid factor, and the shared epitope.* Arthritis Rheum 1999;42:2184-8.

5 Bosello S, Fedele AL, Peluso G, et al. *Very early rheumatoid arthritis is the major predictor of major outcomes: clinical ACR remission and radiographic non-progression.* Ann Rheum Dis 2011;70:1292-5.

6 Quinn MA, Emery P. *Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early intervention.* Clin Exp Rheumatol 2003;21:S154-7.

7 Colebatch AN, Edwards CJ, Østergaard M, et al. *EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis.* Ann Rheum Dis 2013;72:804-14.

8 Group AC of RRACTTFI, Group OM in RMRIIAW. *Review: the utility of magnetic resonance imaging for assessing structural damage in randomized controlled trials in rheumatoid arthritis.* Arthritis Rheum 2013;65:2513-23.

9 Steenbergen HW van, Nies JAB van, Huizinga TWJ, et al. *Characterising arthralgia in the preclinical phase of rheumatoid arthritis using MRI.* Ann Rheum Dis 2014. Published Online First: 9 Apr 2014. doi:10.1136/annrheumdis-2014-205522

10 Krabben A, Stomp W, Heijde DMFM van der, et al. *MRI of hand and foot joints of patients with anticitrullinated peptide antibody positive arthralgia without clinical arthritis.* Ann Rheum Dis 2013;72:1540-4.

11 Nakahara N, Uetani M, Hayashi K, et al. *Gadolinium-enhanced MR imaging of the wrist in rheumatoid arthritis: value of fat suppression pulse sequences.* Skeletal Radiol 1996;25:639-47.

12 Lindegaard H, Vallo J, Horslev-Petersen K, et al. *Low field dedicated magnetic resonance imaging in untreated rheumatoid arthritis of recent onset.* Ann Rheum Dis 2001;60:770-6.

13 Yoshioka H, Ito S, Handa S, et al. *Low-field compact magnetic resonance imaging system for the hand and wrist in rheumatoid arthritis.* J Magn Reson Imaging 2006;23:370-6.

14 Offidani A, Cellini A, Valeri G, et al. *Subclinical joint involvement in psoriasis: magnetic resonance imaging and X-ray findings.* Acta Derm Venereol 1998;78:463-5.

15 Beltran J, Caudill JL, Herman LA, et al. *Rheumatoid arthritis: MR imaging manifestations.* Radiology 1987;165:153-7.

16 Jorgensen C, Cyteval C, Anaya JM, et al. *Sensitivity of magnetic resonance imaging of the wrist in very early rheumatoid arthritis.* Clin Exp Rheumatol 1993;11:163-8.

17 Yanagawa A, Takano K, Nishioka K, et al. *Clinical staging and gadolinium-DTPA enhanced images of the wrist in rheumatoid arthritis.* J Rheumatol 1993;20:781-4.

18 Ostergaard M, Gideon P, Sorensen K, et al. *Scoring of synovial membrane hypertrophy and bone erosions by MR imaging in clinically active and inactive rheumatoid arthritis of the wrist.* Scand J Rheumatol 1995;24:212-8.
19 Tonolli-Serabian I, Poet JL, Dufour M, et al. *Magnetic resonance imaging of the wrist in rheumatoid arthritis: comparison with other inflammatory joint diseases and control subjects.* Clin Rheumatol 1996;15:137-42.
20 Pierre-Jerome C, Bekkelund SI, Mellgren SI, et al. *The rheumatoid wrist: bilateral MR analysis of the distribution of rheumatoid lesions in axial plan in a female population.* Clin Rheumatol 1997;16:80-6.
21 Valeri G, Ferrara C, Ercolani P, et al. T*endon involvement in rheumatoid arthritis of the wrist: MRI-findings.* Skeletal Radiol 2001;30:138-43.
22 Partik B, Rand T, Pretterklieber ML, et al. *Patterns of gadopentetate-enhanced MR Imaging of radiocarpal joints of healthy subjects.* Am J Roentgenol 2002;179:193-7.
23 Robertson PL, Page PJ, McColl GJ. *Inflammatory arthritis-like and other MR findings in wrists of asymptomatic subjects.* Skeletal Radiol 2006;35:754-64.
24 McGonagle D, Conaghan PG, O'Connor P, et al. *The relationship between synovitis and bone changes in early untreated rheumatoid arthritis: a controlled magnetic resonance imaging study.* Arthritis Rheum 1999;42:1706-11.
25 Klarlund M, Ostergaard M, Gideon P, et al. *Wrist and finger joint MR imaging in rheumatoid arthritis.* Acta Radiol 1999;40:400-9.
26 Vlychou M, Koutroumpas A, Alexiou I, et al. *High-resolution ultrasonography and 3.0 T magnetic resonance imaging in erosive and nodal hand osteoarthritis: high frequency of erosions in nodal osteoarthritis.* Clin Rheumatol 2013;32:755-62.
27 Xie X, Webber CE, Adachi JD, et al. *Quantitative, small bore, 1 Tesla, magnetic resonance imaging of the hands of patients with rheumatoid arthritis.* Clin Exp Rheumatol 2008;26:860-5.
28 Rastogi A, Kubassova O, Krasnosselskaia LV, et al. *Evaluating automated dynamic contrast enhanced wrist 3 T MRI in healthy volunteers: One-year longitudinal observational study.* Eur J Radiol 2013;82:1286-91.
29 Brown AK, Quinn MA, Karim Z, et al. *Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: Evidence from an imaging study may explain structural progression.* Arthritis Rheum 2006;54:3761-73.
30 Ejbjerg B, Narvestad E, Rostrup E, et al. *Magnetic resonance imaging of wrist and finger joints in healthy subjects occasionally shows changes resembling erosions and synovitis as seen in rheumatoid arthritis.* Arthritis Rheum 2004;50:1097-106.
31 Olech E, Crues JV, Yocum DE, et al. *Bone marrow edema is the most specific finding for Rheumatoid Arthritis (RA) on noncontrast magnetic resonance imaging of the hands and wrists: a comparison of patients with RA and healthy controls.* J Rheumatol 2010;37:265-74.
32 Parodi M, Silvestri E, Garlaschi G, et al. *How normal are the hands of normal controls? A study with dedicated magnetic resonance imaging.* Clin Exp Rheumatol 2006;24:134-41.

33 Ejbjerg BJ, Vestergaard A, Jacobsen S, et al. *The smallest detectable difference and sensitivity to change of magnetic resonance imaging and radiographic scoring of structural joint damage in rheumatoid arthritis finger, wrist, and toe joints: a comparison of the omeract rheumatoid arthritis magnetic resonance imaging score applied to different joint combinations and the sharp/van der heijde radiographic score.* Arthritis Rheum 2005;52:2300-6.
34 Duer-Jensen A, Hørslev-Petersen K, Hetland ML, et al. *Bone edema on magnetic resonance imaging is an independent predictor of rheumatoid arthritis development in patients with early undifferentiated arthritis.* Arthritis Rheum 2011;63:2192-202.
35 Cimmino MA, Parodi M, Zampogna G, et al. *Polymyalgia rheumatica is associated with extensor tendon tenosynovitis but not with synovitis of the hands: a magnetic resonance imaging study.* Rheumatology 2011;50:494-9.
36 Palosaari K, Vuotila J, Soini I, et al. *Small bone lesions resembling erosions can frequently be found in bilateral wrist MRI of healthy individuals.* Scand J Rheumatol 2009;38:450-4.
37 Døhn UM, Ejbjerg BJ, Hasselquist M, et al. *Detection of bone erosions in rheumatoid arthritis wrist joints with magnetic resonance imaging, computed tomography and radiography.* Arthritis Res Ther 2008;10:R25.
38 Døhn UM, Ejbjerg BJ, Court-Payen M, et al. *Are bone erosions detected by magnetic resonance imaging and ultrasonography true erosions? A comparison with computed tomography in rheumatoid arthritis metacarpophalangeal joints.* Arthritis Res Ther 2006;8:R110.
39 Tan AL, Tanner SF, Conaghan PG, et al. R*ole of metacarpophalangeal joint anatomic factors in the distribution of synovitis and bone erosion in early rheumatoid arthritis.* Arthritis Rheum 2003;48:1214-22.
40 Miese F, Buchbender C, Scherer A, et al. *Molecular imaging of cartilage damage of finger joints in early rheumatoid arthritis with delayed gadolinium-enhanced magnetic resonance imaging.* Arthritis Rheum 2012;64:394-9.
41 Szkudlarek M, Klarlund M, Narvestad E, et al. *Ultrasonography of the metacarpophalangeal and proximal interphalangeal joints in rheumatoid arthritis: a comparison with magnetic resonance imaging, conventional radiography and clinical examination.* Arthritis Res Ther 2006;8:R52.
42 Østergaard M, Conaghan PG, O'connor P, et al. *Reducing invasiveness, duration, and cost of magnetic resonance imaging in rheumatoid arthritis by omitting intravenous contrast injection — does it change the assessment of inflammatory and destructive joint changes by the OMERACT RAMRIS?* J Rheumatol 2009;36:1806-10.
43 Brown AK, Conaghan PG, Karim Z, et al. *An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis.* Arthritis Rheum 2008;58:2958-67.
44 Ai T, Morelli JN, Hu X, et al. *A historical overview of magnetic resonance imaging, focusing on technological innovations.* Investig Radiol 2012;47:725-41.
45 Tamai M, Kawakami A, Uetani M, et al. *Magnetic resonance imaging (MRI) detection of synovitis and bone lesions of the wrists and finger joints in early-stage rheumatoid arthritis: comparison of the accuracy of plain MRI-based findings and gadolinium-diethylenetriamine pentaacetic acid-enhanced MRI-based findings.* Mod Rheumatol 2012;22:654-8.
46 Tehranzadeh J, Ashikyan O, Anavim A, et al. *Enhanced MR imaging of tenosynovitis of hand and wrist in inflammatory arthritis.* Skeletal Radiol 2006;35:814-22.

Table 1-a Characteristics of the 31 selected studies

First author, year of publication	N	Recruitment method *	Age	Female/ Male
Scored without a validated method				
Wrist+MCP summed				
Nakahara et al, 1996 [11]	10	NP	NP	5/5
Lindegaard et al, 2001 [12]	3	Hospital staff	46 (34-55)	1/2
Yoshioka et al, 2006 [13]	13	NP	34.1 (22-48)	5/8
Offidani et al, 1998 [14]	12	NP	NP	NP
Wrist				
Beltran et al, 1987 [15]	6	NP	NP	NP
Jorgensen et al, 1993 [16]	4	NP	30	2/2
Yanagawa et al, 1993 [17]	10	NP	NP	7/3
Østergaard et al, 1995 [18]	3	NP	30 (28-31)	NP
Tonolli-Serabian et al, 1996 [19]	10	NP	59 (46-71)	5/5
Pierre-Jerome et al, 1997 [20]	42	NP	42.1	42/0
Valeri et al, 2001 [21]	12	NP	31	8/4
Partik et al, 2002 [22]	18	NP	30,8 (24-34)	9/9
Robertson et al, 2006 [23]	30	Hospital staff & contacts	31 (22-49)	17/13
MCP				
McGonagle et al, 1999 [24]	31	Hospital staff	48 (28-62)	18/13
Klarlund et al, 1999 [25]	3	NP	31 (24-33)	NP
Vlychou et al, 2013 [26]	5	2 volunteers & with 3 wrist instability	41.2 ± 3.2	3/2
Scored according to RAMRIS (see table 1-b on the next pages)				

* Description of recruitment of symptom-free persons.

† Scoring was done blind for the status (patient/symptom-free person) described, articles that do describe their scoring method but not according to the RAMRIS method;

DIP, distal interphalangeal joint;

Gd, gadolinium;

IP, interphalangeal joint;

MCP, metacarpophalangeal joints;

MTP, metatarsophalangeal;

NP, Not provided;

PIP, proximal interphalangeal joint;

T, tesla.

MRI	Contrast	Area scanned	Uni/bilateral	Score Method	Blinded †
1.5T	Gd +	Wrist+MCP	NP	Described	+
0.2T	Gd +	Wrist+MCP	Unilateral	Described	+
0.21T	Gd -	Wrist+MCP+PIP	Bilateral	NP	+
1.0T	Gd -	Wrist+MCP+IP	NP	Described	+
1.5T	Gd -	Wrist	NP	Described	NP
0.5T	Gd +	Wrist	NP	NP	+
1.5T	Gd +	Wrist	NP	NP	+
1.5T	Gd +	Wrist	NP	NP	+
1.0T	Gd +	Wrist	Bilateral	Described	+
0.5T	Gd -	Wrist	Bilateral	Described	NP
1.0T	Gd -	Wrist	Bilateral	Described	NP
1.0T	Gd +	Wrist	NP	NP	NP
1.5T	Gd +	Wrist	Unilateral	Described	NP
1.5T	Gd -	MCP	Unilateral	Described	+
1.0T	Gd +	MCP	Unilateral	Described	+
3.0T	Gd +	MCP+PIP+DIP	Unilateral	Described	+

Table 1-b Characteristics of the 31 selected studies

First author, year of publication	N	Recruitment method*	Age	Female/ Male
Scored without a validated method (see table 1-a on the previous pages)				
Scored according to RAMRIS				
Wrist+MCP data				
Brown et al, 2006 [29]	17	NP	38	12/5
Ejbjerg et al, 2004 [30]	8	NP	47 (24-67)	20/8
Olech et al, 2010 [31]	40	Hospital staff	36.7 (20-64)	29/11
Parodi et al, 2006 [32]	23	Healthy relatives	59 (25-86)	16/7
Ejbjerg et al, 2005 [33]	9	NP	NP	NP
Duer-Jensen et al, 2011 [34]	24	NP	46 (21-71)	17/7
Wrist				
Cimmino et al, 2011 [35]	13	NP	71 (57-86)	NP
Palosaari et al, 2009 [36]	31	Hospital staff	49 (32-64)	18/13
Døhn et al, 2008 [37]	4	NP	36 (34-57)	3/1
MCP				
Døhn et al, 2006 [38]	4	NP	35.5 (34-57)	3/1
Tan et al, 2003 [39]	28	NP	40	19/9
Miese et al, 2012 [40]	13	NP	51 ± 12 (25-66)	10/3
Mean grading (Wrist+MCP)				
Xie et al, 2008 [27]	14	NP	25 ± 5 (19-33)	4/10
Xie et al, 2008 [27]	27	NP	62 ± 7 (49-74)	22/5
Krabben et al, 2013 [10]	19	NP	46.2 ± 11.8	15/4
Rastogi et al, 2013 [28]	10	NP	(24-40)	7/3

* Description of recruitment of symptom-free persons.

† Scoring was done blind for the status (patient/symptom-free person) described, articles that do describe their scoring method but not according to the RAMRIS method;

DIP, distal interphalangeal joint;

Gd, gadolinium;

IP, interphalangeal joint;

MCP, metacarpophalangeal joints;

MTP, metatarsophalangeal;

NP, Not provided;

PIP, proximal interphalangeal joint;

T, tesla.

MRI	Contrast	Area scanned	Uni/bilateral	Score Method	Blinded †
1.5T	Gd +	Wrist+MCP	Unilateral	RAMRIS	+
1.0T	Gd +	Wrist+MCP	Unilateral	RAMRIS	NP
0.2T	Gd -	Wrist+MCP	Bilateral	RAMRIS	+
0.2T	Gd -	Wrist+MCP+PIP	Bilateral	RAMRIS	NP
0.2T	Gd -	Wrist+MCP+MTP	Bilateral	RAMRIS	+
0.6T(12), 1.0T(12)	Gd +	Wrist+MCP+PIP	Unilateral	RAMRIS	NP
0.2T	Gd -	Wrist	Bilateral	RAMRIS	+
0.23T	Gd+ (10/31)	Wrist	Bilateral	RAMRIS	NP
0.6T	Gd -	Wrist	Unilateral	RAMRIS	+
0.6T	Gd -	MCP	Unilateral	RAMRIS	+
1.5T	Gd + (8/28)	MCP	Unilateral	RAMRIS	+
3T	Gd +	MCP (dig 2&3)	Unilateral	RAMRIS	NP
1.0T	Gd -	Wrist+MCP	Bilateral	RAMRIS	NP
1.0T	Gd -	Wrist+MCP	24/27 Bilateral	RAMRIS	NP
1,5T	Gd -	Wrist+MCP+MTP	Unilateral	RAMRIS	NP
3T	Gd+	Wrist	Unilateral	RAMRIS	NP

Table 2-a Frequency of erosions, BME, synovitis and tenosynovitis in symptom-free persons

First author, year of publication	N = healthy	Uni/bilateral	Erosions
Scored without a validated method			
Wrist+MCP			
Nakahara et al, 1996 [11]	10	NP	NP
Lindegaard et al, 2001 [12]	3	Unilateral	0.0%
Yoshioka et al, 2006 [13]	13 (+PIP)	Bilateral	0.0%
Offidani et al, 1998 [14]	12 (+IP)	NP	0.0%
Wrist			
Beltran et al, 1987 [15]	6	NP	0.0%
Jorgensen et al, 1993 [16]	4	NP	0.0%
Yanagawa et al, 1993 [17]	10	NP	NP
Østergaard et al, 1995 [18]	3	NP	NP
Tonolli-Serabian et al, 1996[19]	10	Bilateral	0.0%
Pierre-Jerome et al, 1997 [20]	42	Bilateral	35.7% *
Valeri et al, 2001 [21]	12	Bilateral	NP
Partik et al, 2002 [22]	18	NP	NP
Robertson et al, 2006 [23]	30	Unilateral	NP
MCP			
McGonagle et al, 1999 [24]	31	Unilateral	25.8%
Klarlund et al, 1999 [25]	3	Unilateral	0.0%
Vlychou et al, 2013 [26]	5 (+PIP, DIP)	Unilateral	0.0%
Scored according to RAMRIS (see table 2-b on the next pages)			

0% is noted when no erosions are found or an abnormality is described in the patient group and the healthy control group is only described as 'no abnormalities' with no further specification.
Italics: studies in which contrast was used to score synovitis and tenosynovitis.
* Contradicting data in original article, with 35.7% erosions in the table and 14.3% erosions in the text.

	BME	Synovitis	Tenosynovitis
	0.0%	0.0%	0.0%
	NP	NP	NP
	NP	0.0%	0.0%
	NP	0.0%	0.0%
	NP	0.0%	0.0%
	NP	0.0%	0.0%
	NP	0.0%	NP
	NP	0.0%	NP
	NP	0.0%	NP
	0.0%	4.8%	Fl: 9.5% Ext: 7.1%
	NP	NP	0.0%
	0.0%	44.4%	NP
	13.3%	NP	NP
	9.7%	NP	NP
	NP	NP	NP
	0.0%	0.0%	0.0%

DIP, distal interphalangeal joint;
Ext, extensor tendons;
Fl, flexor tendons;
IP, interphalangeal joint;
MCP, metacarpophalangeal joints;
MTP, metatarsophalangeal;
NP, Not provided;
PIP, proximal interphalangeal joint.

Table 2-b Frequency of erosions, BME, synovitis and tenosynovitis in symptom-free persons

First author, year of publication	N = healthy	Uni/bilateral	Erosions
Scored without a validated method (see table 1-a on the previous pages)			
Scored according to RAMRIS			
Wrist+MCP (2-5)			
Brown et al, 2006 [29]	17	Unilateral	NP
Ejbjerg et al, 2004 [30]	28	Unilateral	NP
Olech et al, 2010[31]	40	Bilateral	65.0%
Parodi et al, 2006 [32]	23 (+PIP)	Bilateral	26.0%
Ejbjerg et al, 2005 [33]	9 (+MTP)	Bilateral	55.6%
Combined data [29,30]	0/45	Unilateral	
Combined data [29,30]	12/45	Unilateral	
Wrist			
Cimmino et al, 2011 [35]	13	Bilateral	30.8%
Palosaari et al, 2009 [36]	31	Bilateral	45.2%
Døhn et al, 2008 [37]	4	Unilateral	25.0%
Duer-Jensen et al, 2011† [34]	24	Unilateral	45.8%
Xie et al,2008 ‡ [27]	14 Age 25 ± 5	Unilateral	0.0%
	27 Age 62 ± 7	Unilateral	88.9%
Combined data [35,36]	18/44	Bilateral	
Combined data [27,34,37]	36/69	Unilateral	
Combined data [27,34]	10/63 §	Unilateral	
MCP (2-5)			
Døhn et al, 2006 [38]	4	Unilateral	0.0%
Tan et al, 2003 [39]	28	Unilateral	32.1%
Miese et al, 2012 [40]	13 MCP 2&3	Unilateral	NP
Duer-Jensen et al, 2011† [34]	24	Unilateral	45.8%
Xie et al,2008 ‡ [27]	14 Age 25 ± 5	Unilateral	0.0%
	27 Age 62 ± 7	Unilateral	44.4%
Combined data [27,34,38,39]	32/97	Unilateral	
Combined data [27,34]	6/63 §	Unilateral	

o% is noted when no erosions are found or an abnormality is described in the patient group and the healthy control group is only described as 'no abnormalities' with no further specification.
Italics: studies in which contrast was used to score synovitis and tenosynovitis.
† Same study.
‡ Same study.

	BME	Synovitis	Tenosynovitis
	0.0%	17.6%	5.9%
	0.0%	32.1%	NP
	17.5%	42.5%	NP
	8.7%	NP	Fl: 17.4% xt: 4.3%
	NP	NP	NP
		BME mean 0% (95% CI 0.0-6.8)	
		Synovitis mean 26.7% (95% CI 15.8-41.2)	
	30.8%	0.0%	30.8%
	NP	60.0%	NP
	NP	NP	NP
	4.5%	81.8%	0.0%
	0.0	0.0%	NP
	33.3%	3.7%	NP
		Erosions mean 40.9% (95% CI 27.7-55.6)	
		Erosions mean 52.2% (95% CI 40.6-63.5)	
		BME mean 15.9% (95% CI 8.7-27.0)	
	NP	NP	NP
	NP	NP	NP
	0.0%	0.0%	NP
	4.5%	45.5%	0.0%
	14.3%	0.0%	NP
	11.1%	14.8%	NP
		Erosions mean 33.0% (95% CI 24.4-42.9)	
		BME mean 9.5% (95% CI 4.1-19.6)	

§ Duer-Jensen only assessed 22 patients for BME.

DIP, distal interphalangeal joint; Ext, extensor tendons; Fl, flexor tendons; IP, interphalangeal joint; MCP, metacarpophalangeal joints; MTP, metatarsophalangeal; NP, Not provided; PIP, proximal interphalangeal joint.

Table 3 Mean RAMRIS score in symptom-free persons

First author, year of publication	N = healthy	Uni/ bilateral	Erosions	BME	Synovitis	Teno-synovitis
Xie et al, 2008 [27]	14 Age 25 ± 5	Bilateral	0 Pt	Dom MCP: 0.14	0 Pt	NP
	27 Age 62 ± 7	24/27 Bilateral	Dom MCP: 1.51 Dom Wr: 3.11	Dom MCP: 0.29 Dom Wr: 0.85	Dom MCP: 0.29 Dom Wr: 0.03	NP
Krabben et al, 2013 [10]	19 (+MTP)	Unilateral	MCP/PIP: 0.1 Wrist: 0.7	MCP/PIP: 0.1 # Wrist: 0.9		NP
*Rastogi et al, 2013 * [28]*	10	Unilateral	T0: 0.8 ± 1.3 T12: 0.4 ± 0.7 T24: 0.4 ± 0.7 T52: 1.4 ± 1.9	T0: 0.6 ± 0.7 T12: 0.2 ± 0.5 T24: 0.2 ± 0.4 T52: 0.3 ± 0.6	T0: 3.5 ± 2.6 T12: 3.3 ± 1.6 T24: 3.7 ± 2.0 T52: 4.5 ± 1.7	NP

Italics: studies in which contrast was used to score synovitis and tenosynovitis.

Erosions were scored on a scale from 0-10 for each location; BME and synovitis were scored from 0-3 for each location.

Erosions and BME were scored in 23 locations in the hand and 10 in the foot; synovitis was scored in 7 locations in the hand and 5 in the foot.

† Krabben summed the BME and the synovitis into an inflammation score.

* Is a longitudinal study with To as baseline, T12 after 12 weeks, T24 after 24 weeks, T52 after 52 weeks.

Dom, dominant hand;

MCP, metacarpophalangeal joints;

MTP, metatarsophalangeal;

NP, Not provided;

Wr, wrist.

Chapter 3:
Magnetic Resonance Imaging-detected features of inflammation and erosions in symptom-free persons from the general population

L. Mangnus

H. W. van Steenbergen

M. Reijnierse

A. H. M. van der Helm-van Mil

Arthritis Rheumatology 2016

Abstract

Introduction. The use of magnetic resonance imaging (MRI)-detected inflammation and joint damage in the diagnosis of rheumatoid arthritis is recommended by a European League Against Rheumatism imaging task force. This recommendation is based on the sensitivity of MRI and not on specificity. Knowledge of the prevalence of MRI-detected features in symptom-free persons, however, is pivotal when considering MRI for diagnostic purposes.

Methods. From November 2013 to December 2014, 196 symptom-free persons of different ages were recruited from the general population. Inclusion criteria were no history of inflammatory arthritis, no joint symptoms during the previous month, and no clinically detectable arthritis on physical examination. Contrast-enhanced MRIs of the dominant metacarpophalangeal (MCP), wrist, and metatarsophalangeal (MTP) joints were obtained using a 1.5T scanner and scored by 2 readers for synovitis, bone marrow edema, tenosynovitis, and erosions. For analyses at the joint level, MRI-detected inflammation was considered present if both readers scored the image as positive.

Results. Of 193 persons scanned (ages 19-89 years), only 28% had no single inflammatory feature and 22% had no erosions. Primarily low-grade features were observed. All MRI-features were positively correlated with age ($P < 0.001$). Preferential locations for synovitis were MCP2, MCP3, the wrists, and MTP1. Bone marrow edema was frequently present in MCP3, the scaphoid, and MTP1. Tenosynovitis was infrequent, except for in the extensor carpi ulnaris. Preferential locations for erosions were MCP2, MCP3, MCP5, the distal ulna, MTP1, and MTP5. Tables with age-, location-, and inflammation type-dependent frequencies were constructed. Simultaneous colocalized presence of synovitis, bone marrow edema, tenosynovitis, or erosions occurred.

Conclusion. MRI-detected inflammation and erosions are prevalent in symptom-free persons from the general population, especially at older ages and at preferential locations.

Introduction

Magnetic resonance imaging (MRI) findings are increasingly used as outcome measures in clinical trials in rheumatoid arthritis (RA). According to a European League Against Rheumatism (EULAR) imaging task force, MRI is also helpful in the diagnosis of RA.[1] The first recommendation of this task force states that MRI can be used to improve the certainty of a diagnosis when there is doubt. This recommendation is largely based on the fact that MRI is more sensitive than physical examination for detecting local inflammation.[1-3] As such, MRI may increase the ability to identify arthritis or RA very early.

Computed tomography may be more sensitive than MRI for the detection of erosions,[4] but if MRIs are obtained to evaluate local inflammation, erosive lesions can also be detected. An imaging task force of the American College of Rheumatology concluded that MRI assesses structural damage more sensitively than other imaging modalities.[5] The EULAR imaging task force also recommended that MRI be considered for detecting local damage at an earlier time point if conventional radiographs do not show damage.[1] Similar to the recommendation regarding using MRI for the detection of inflammation, this recommendation is based on MRI-studies of RA-patients, which thus assessed the sensitivity of the method.

The specificity of MRI-findings has not yet been determined, because the prevalence of MRI-detected inflammation and erosions in the general population has not been explored extensively. Recently, we reviewed the literature for studies of MRI in healthy subjects.[6-12] Taken together, the findings of those studies suggested that erosions, synovitis, and bone marrow edema occur regularly in the general population. However, the available studies had some limitations. They included few symptom-free persons, recruitment methods were often not reported or not entirely population based, and age was not taken into account. Furthermore, specific locations were not assessed because analyses were mostly done at the level of the person but not at the level of individual bones.

Currently available data, therefore, do not allow a description of the prevalence of MRI-detected inflammation and erosions in the general population. Before MRI-findings can be used for diagnostic purposes in clinical practice, information

on their specificity is required. In this light, we aimed to address the following questions: 1) What is the occurrence of different MRI-features (synovitis, bone marrow edema, tenosynovitis, and erosions) in symptom-free persons? 2) Is the frequency of these MRI-features dependent on anatomic location, sex, or age? 3) Do different MRI-features occur simultaneously at the same joint in symptom-free persons?

Subjects and methods

Participants

This cross-sectional study was performed between November 2013 and December 2014 in Leiden, The Netherlands. Symptom-free individuals were recruited via advertisements in local newspapers and web sites. Inclusion criteria were: age 18 years or older, no history of RA or other inflammatory rheumatic diseases, no joint symptoms during the previous month, and no clinically detectable arthritis on physical examination. Persons who volunteered were screened for these criteria by telephone and a subsequent visit at the outpatient clinic. At inclusion, information was collected on age, sex, weight, height, dominant hand, smoking history, alcohol consumption, comorbidity, and medical history. Physical examinations of the hands and feet were performed to exclude the presence of arthritis and to evaluate the presence of asymptomatic Heberden's nodes or Bouchard's nodes or hallux valgus. We decided not to exclude persons with these asymptomatic signs of osteoarthritis (OA), since prior exclusion would result in a "too healthy" study population.

The presence of these signs was recorded, allowing subanalyses excluding these individuals. At the second visit, MRI was performed. After the 2 visits, participants received a voucher for e20 as compensation for their time and travel costs. Participants did not receive a report of their MRI-findings. The study was approved by the local medical ethics committee, and written informed consent was obtained from all subjects.

MRI-protocol and scoring

MRI of the metacarpophalangeal (MCP) joints, wrist joints, and metatarsophalangeal (MTP) joints on the dominant side was performed within 15 days after the screening visit. Sequences acquired were coronal precontrast T1-weighted fast spin-echo (FSE) and coronal and axial postcontrast T1-weighted FSE with frequency-selective fat suppression. Further details on the scan protocol are provided in the Supplementary Methods, available on the Arthritis & Rheumatology website.

MRI-scoring was done independently by 2 trained readers (LM and HWvS). In an attempt to exclude observer bias introduced by knowing that persons had no symptoms, the MRIs of symptom-free individuals were mixed with MRIs of RA-patients and patients with arthralgia without clinical synovitis (total n = 99).[13,14] The readers were blinded with regard to any personal or clinical data. Scoring of synovitis, bone marrow edema, and erosions was performed following the Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) method (see Supplementary Methods). Tenosynovitis in the MCP and wrist was scored according to the method described by Haavardsholm et al.[15,16] The total MRI inflammation score was calculated by summing the scores for all inflammatory features, including the synovitis, bone marrow edema, and tenosynovitis scores in the MCP and wrist joints and the synovitis and bone marrow edema scores in the MTP joints.

The within-reader intraclass correlation coefficient (ICC), based on 40 MRI-scans, was 0.99 for reader 1 and 0.98 for reader 2, and the interreader ICC, based on 193 MRI-scans, was 0.96. When evaluating the inflammation or erosion scores at the subject level, the mean scores of both readers were studied. When performing analyses at the joint level evaluating MRI-features at specific locations, the data were categorized. In the case of disagreement between the 2 readers, the lower score was used. For instance, when 1 reader scored a feature as 1 and the other reader scored the same feature as 0, the final score for that feature at that location was 0. Differences between readers in scores at individual locations of >1 did not occur. Hence, a conservative method for categorization was used.

Statistical analysis

Frequencies were assessed. Comparisons between sexes were conducted using the Mann-Whitney U test. Correlations of MRI-findings with age were determined using Pearson's correlation coefficient. SPSS V20.0.0 was used.

Results

Characteristics of the participants

Of 199 volunteers screened between November 2013 and December 2014, 196 fulfilled the inclusion criteria. Three individuals were excluded because of hand symptoms. After inclusion, 3 others did not undergo MRI and were excluded because of personal problems, vasovagal response to intravenous puncture, and anxiety, respectively. Consequently, MRIs for 193 persons (ages 19-89 years) were obtained. Baseline characteristics of the subjects are presented in Table 1. On clinical examination, signs of OA (e.g., Heberden's nodes, Bouchard's nodes, and hallux valgus) were observed in 68 persons (33 participants ages 40-59 years and 35 participants older than 60 years). No clinically relevant incidental findings were observed.

Presence of MRI-detected inflammation and erosions

The median total MRI inflammation score was 2 (interquartile range (IQR] 0.5-4.5). For synovitis, bone marrow edema, tenosynovitis, and erosions, the median total scores were 0.5 (IQR 0.0-2.0), 1.0 (IQR 0.0-2.0), 0.0 (IQR 0.0-0.0), and 2.0 (IQR 1.0-4.0), respectively. Forty-two participants (22%) had no erosions, and 54 participants (28.0%) had a total MRI inflammation score of 0 (see Supplementary Table 1, available on the Arthritis & Rheumatology website). A total synovitis score of≥1 was recorded for 48.2% of the subjects, a total bone marrow edema score of≥1 for 57.5%, and a total tenosynovitis score of≥1 for 16.6%. Hence, tenosynovitis was less prevalent than the other features.

Location of MRI-detected inflammation and erosions

Next, we assessed the 3 different joint regions (MCPs, wrist, and MTPs). The highest total inflammation score was obtained in the wrist (median 1.0 [IQR 0.0-2.5]). The median total inflammation score at the MCP and MTP joints was 0.0 (IQR 0.0-1.0) and 0.0 (IQR 0.0-1.0). Synovitis, bone marrow edema, tenosynovitis, and erosion scores of≥1 in the wrist were present in 33.2%, 45.1%, 9.3%, and 68.4% of the participants, respectively; these percentages were higher than those for the MCP and MTP joints (Supplementary Table 1).

We next assessed the MRI-features at the individual joint level. At the level of the MCP joints, synovitis, bone marrow edema, and erosions were most frequently present in MCP3 (in 11.4%, 3.6%, and 14.5% of the subjects, respectively) and MCP2 (in 8.8%, 2.6%, and 17.1% of the subjects, respectively). Flexor tenosynovitis was most frequently present in MCP3 (in 4.7% of the subjects) (see Supplementary Table 2, available on the Arthritis & Rheumatology website).

In the 3 wrist joints, synovitis was frequently observed (in the distal radioulnar joint in 8.3%, in the radiocarpal joint in 17.1%, and in the intercarpal carpometacarpal [CMC] joint in 15.5% of the subjects). In the carpal bones, bone marrow edema was most frequently present in the lunate, scaphoid, and distal ulna (in 19.2%, 8.8%, and 5.2% of the subjects, respectively). Erosions were frequently found in the capitate (in 23.3% of the subjects), lunate (in 21.8% of the subjects), and distal ulna (in 11.9% of the subjects). Tenosynovitis was almost absent in the wrist, with the exception of the extensor carpi ulnaris tendon (extensor compartment VI), which showed tenosynovitis in 7.3% of the subjects (Supplementary Table 2).

At the level of the MTP joints, inflammation preferentially occurred in MTP1, with synovitis in 10.4% of the subjects and bone marrow edema in 17.1% of the subjects; erosions were present in MTP1 in 18.1% of the subjects. Erosions were also frequently present in MTP5 (in 7.8% of the subjects) (Supplementary Table 2).

The anatomic location of the MRI-detected erosion and the cortical break was studied in detail for several bones that were frequently affected (Figures 1A-D). The erosions were more frequently seen in the proximal side of the joint than in the distal part of the joint, and the erosions were not located centrally but at the bone margins.

Figure 1 **(Next page) Schematic overview of observed RAMRIS defined erosions. Schematically depicted are the locations of cortical breaks in MCP-2 and MCP-3 (A), MCP-5 (B), distal ulna (C), and MTP-1 (D) in coronal and axial plane, and an MRI example of erosions (arrows) at these locations. MR sequences include coronal T1 FSE and axial T1 FSE with fat suppression after contrast enhancement.**

Association between sex and MRI-features

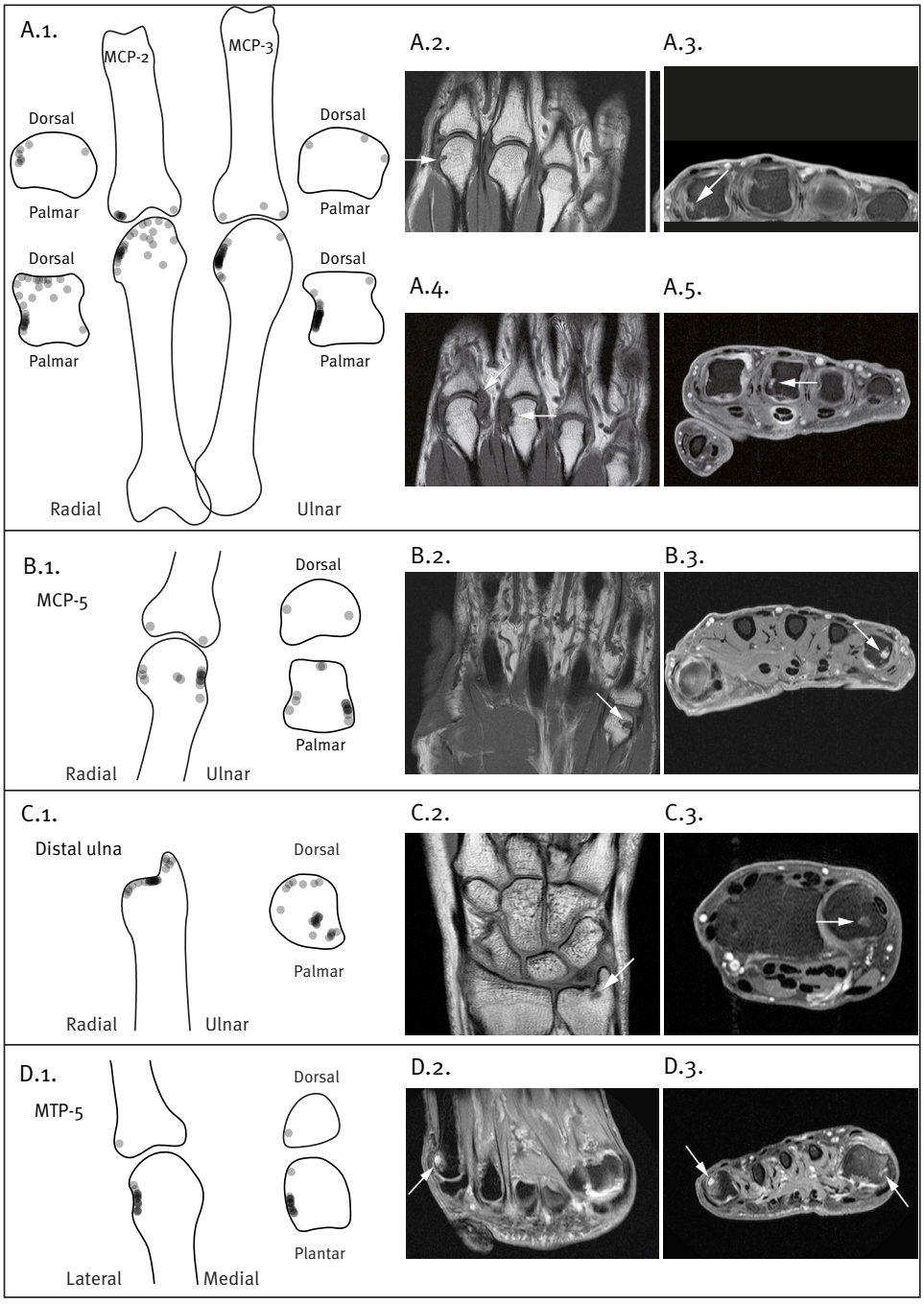
We next investigated whether men and women had different MRI scores. The median total inflammation score for men was 2.0 (IQR 1.0-4.5) and that for women was 2.0 (IQR 0.5-4.4), showing no difference between the sexes ($P = 0.36$). Similarly, the total synovitis, bone marrow edema, tenosynovitis, and erosion scores were compared and showed no differences ($P = 0.79$, $P = 0.14$, $P = 0.41$, and $P = 0.11$, respectively).

Association between age and MRI-features

We next investigated whether age was correlated with MRI-detected inflammation. We observed that older age was positively correlated with a higher total inflammation score ($r = 0.57$, $P < 0.001$) (Figure 2A). This positive correlation with older age was also found for synovitis, bone marrow edema, tenosynovitis, and erosions separately ($r = 0.55$, $r = 0.51$, $r = 0.28$, and $r = 0.69$, respectively) (all $P < 0.001$) (Figures 2B-E).

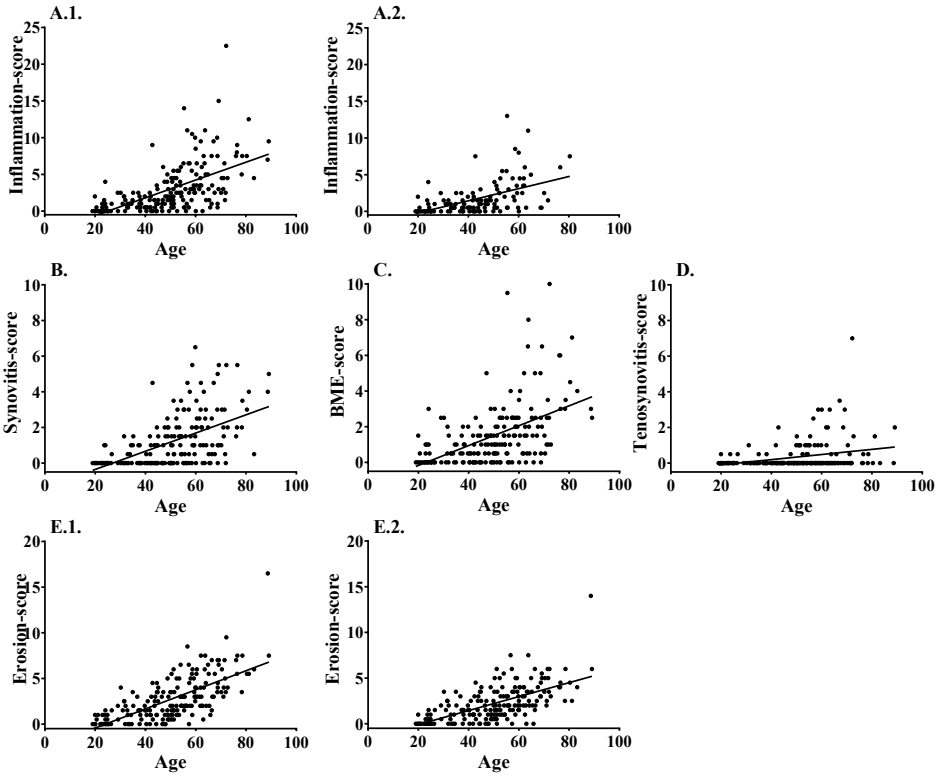
To explore the possibility that these correlations were caused by the presence of asymptomatic OA, the prevalence of which also increases with age, we performed subanalyses. First, subjects with any sign of (asymptomatic) OA at physical examination were excluded. The correlations between age and the total inflammation score and between age and the erosion score remained similar to those obtained

Figure 1: (Next page) The grey dots present the location of the cortical breaks; when more cortical breaks are present at the same location the dots have a darker shade of grey.


A.1.
MCP-2
MCP-3
Dorsal
Palmar
Dorsal
Palmar
Dorsal
Palmar
Dorsal
Palmar
Radial
Ulnar
A.2.
A.3.
A.4.
A.5.
B.1.
MCP-5
Dorsal
Palmar
Radial
Ulnar
B.2.
B.3.
C.1.
Distal ulna
Dorsal
Palmar
Radial
Ulnar
C.2.
C.3.
D.1.
MTP-5
Dorsal
Plantar
Lateral
Medial
D.2.
D.3.

before exclusion of these subjects (r = 0.53, P < 0.001 and r = 0.66, P < 0.001, respectively). When anatomic locations that are included in the RAMRIS method but also

Figure 2 **Correlations between age and total inflammation-score(A.1.), total synovitis-score(B.), total BME-score(C.), total tenosynovitis-score(D.) and total erosions-score(E.1.) in all 193 symptom-free persons, and correlations between age and total inflammation and total erosion-scores after exclusion of persons with Heberden's nodes, Bouchards nodes, or hallux valgus (n = 68) and CMC-1 and MTP-1 joints (A.2., E.2.)**



Correlation coefficient of age with (A.1.) inflammation-score was r = 0.57, (A.2.) inflammation-score r = 0.52, (B.) synovitis-score was r = 0.55, (C.) BME-score was r = 0.51, (D.) tenosynovitis-score was r = 0.28, (E.1.) erosion-score r = 0.69, and (E.2.) erosion-score r = 061, all p < 0.001.

are known to be predilection sites for OA (CMC1 and MTP1) were removed from the analysis, the correlation coefficient for the association of inflammation with age was r = 0.55 (P < 0.001), and the correlation coefficient for the association of erosions with age was r = 0.62 (P < 0.001). Finally, these individuals and anatomic locations were both excluded from the data set, after which the correlation of inflammation score with age was still observed (r = 0.52, P < 0.001) (Figure 2A). Similarly, age remained correlated with the erosion score (r = 0.61, P < 0.001) (Figure 2E).

Generation of tables with age-, location-, and feature-dependent prevalence of MRI-detected inflammation and erosions.

The data presented thus far indicate that the prevalence of MRI-findings in the symptom-free population is dependent on the age of the individual, the anatomic location, and the feature assessed. Therefore, we constructed tables that incorporate these 3 characteristics. These tables present the frequency of synovitis, bone marrow edema, tenosynovitis, and erosions per joint per age category (< 40, 40-59, and ≥ 60 years) and per grade of severity (Tables 2-4). As Tables 2-4 show, in general MRI-detected inflammation was rare in individuals younger than 40 years. Furthermore, features were very rarely assigned scores of 2 or 3.

At the MCP joints, synovitis was present in MCP2 in 8% and in MCP3 in 14% of the participants ages 40-59 years and in MCP2 in 19% and in MCP3 in 17% of the participants age 60 years or older (Table 2). Flexor tenosynovitis at MCP2-4 was present in 6-12% of the participants age 60 years or older.

At the wrist, grade 1 synovitis of the distal radioulnar, radiocarpal, and intercarpal CMC joints was frequent in persons age 40 years or older (Table 3). Bone marrow edema was prevalent in the scaphoid and lunate, and the prevalence increased with older age. In the bones forming the CMC1 joint (proximal metacarpal 1 and trapezium), inflammation occurred more frequently at older ages. (The frequencies of bone marrow edema at proximal metacarpal 1 in the 3 age categories were 0%, 3%, and 8%.) Tenosynovitis seldom occurred in the wrist, with the exception of the extensor carpi ulnaris tendon in persons age 40 years or older (9% and 12% in the groups ages 40-59 years and 60 years or older, respectively) (Table 3).

At the MTP joints, the highest prevalence of MRI-detected inflammation was seen at MTP1. For instance, 23% of the subjects age 60 years or older had bone marrow edema of grade 1 in MTP1. Bone marrow edema and synovitis each occurred in MTP5 in 4% of the symptom-free persons age 60 years or older (Table 4).

When MRI-detected erosions were evaluated, similar patterns were seen. The prevalence of erosions at joints that are known as predilection sites for OA (CMC1 and MTP1) increased with age, but the same was observed for locations that are not considered typical for OA, such as MCP2 and MCP3 (Tables 2-4). Examples of MRI-detected inflammation and erosions observed in the symptom-free participants are shown in Supplementary Figure 1, available on the Arthritis & Rheumatology website.

Co-occurrence of several MRI-detected inflammatory features at the same joint

It is known that simultaneous occurrence of synovitis, bone marrow edema, and/or tenosynovitis is frequent in arthritis and RA (2). If different inflammatory features do not occur simultaneously at the same joint in symptom-free persons, this might be a characteristic differentiating patients from age-matched controls.

At the MCP joints, bone marrow edema, synovitis, and tenosynovitis were studied. Although predominantly only one inflammatory feature was present, synovitis and bone marrow edema or synovitis and tenosynovitis were also regularly simultaneously present. Of 29 persons with any sign of inflammation in MCP3, 10 had colocalization of ≥ 2 features. Similarly, of 22 persons with inflammation in MCP2, 3 had ≥ 2 inflammatory features at this joint (see Supplementary Table 3A, available on the Arthritis & Rheumatology website). At the wrist, synovitis in the radiocarpal joint was evaluated in relation to bone marrow edema in the surrounding bones (scaphoid, lunate, triquetrum, pisiform, distal ulna, and distal radius). Likewise, synovitis of the intercarpal CMC joint was studied in relation to bone marrow edema of the proximal metacarpals 2-5 and all carpals. Both analyses showed that in almost one-third of the participants with any type of inflammation in these wrist joints, synovitis and bone marrow edema were both present (Supplementary Table 3B).

At the level of the MTP joints, bone marrow edema and synovitis frequently occurred together in MTP1 (Supplementary Table 3C). Taken together, these data show that MRI-detected synovitis, bone marrow edema, and tenosynovitis can be present simultaneously in the same joint in symptom-free persons.

Co-occurrence of MRI-detected inflammation and erosions

Similarly, we investigated to what extent MRI-detected erosions were seen at locations that also showed inflammation. These analyses revealed that the parts of the joints with erosions also showed inflammation. For example, of the 33 MCP2 joints with an erosion, 9 also showed inflammation, and of these 9 joints, 3 joints even had ≥ 2 inflammatory features. Of the 23 symptom-free persons with erosions at the distal ulna, 6 also had bone marrow edema (see Supplementary Table 4, available on the Arthritis & Rheumatology website).

Number of joints or bones affected

Finally, the prevalence of MRI-features in ≥ 2 joints was studied. Twenty-two % of the subjects had synovitis in ≥ 2 joints, 23% had bone marrow edema in ≥ 2 bones, 4% had tenosynovitis in ≥ 2 tendons, and 50% had erosions in ≥ 2 bones. This shows that inflammation or erosions can occur at several locations within the same symptom-free person.

Discussion

MRI is a promising tool because of its high sensitivity for the detection of local inflammation of Joints.[1,2] In addition, MRI depicts erosions. When using MRI for diagnostic purposes, the specificity of the findings should be considered. This study revealed that MRI-detected inflammation and erosions are prevalent in symptom-free persons, especially at specific joints or bones and at older ages. We also observed the simultaneous occurrence of different inflammatory features in the same joint in symptom-free persons. Apparently, this might not always indicate

abnormality since the persons studied had no arthritis, no joint symptoms, and no previous inflammatory rheumatic disease.

This is the first large-scale study of MRI in symptom-free persons. Even after stratifying for age, the 3 different strata each contained more than the total number of healthy controls in previous MRI-studies.[6-12] Furthermore, the use of contrast-enhanced MRI obtained using a 1.5T scanner allowed sensitive assessment of MRI-features. Another strength is that our recruitment method is different from previous studies that mostly evaluated hospital staff, which harbors a risk of a "too healthy" population.[6] We recruited volunteers via advertisements in local newspapers and web sites; hence, people could in no way feel forced to participate. To prevent selection bias due to inclusion of persons who would personally benefit from participating, participants did not receive MRI-results and were only partly compensated for travel costs. A completely random selection would entail actively approaching (randomly selected) individuals; we did not have ethics permission for such recruitment. We have not followed up the persons who were studied.

In our view, knowledge of clinical status (being healthy) might result in underscoring. To avoid this, the scans of the symptom-free persons were blinded and mixed with scans of patients. Hence, the readers were unaware of clinical status.

According to the scoring method used, imaging artifacts and normal structures should not be scored. The MRIs were scored accordingly.[17,18] We acknowledge that at several carpalia (e.g., the capitate and lunate) it can be difficult to differentiate erosions from physiologic indentations due to enlarged insertion areas of interosseous ligaments or vascular channels. The availability of serial MRIs might make this differentiation easier, but in the present study persons were scanned once. Differentiation of erosions from anatomic variants was performed by experienced readers (each reader had read >500 scans), and readers were instructed not to score an erosion in case of doubt. Furthermore, we used 2 readers and applied a very conservative method for analysis when categorizing the data. A joint could only be scored as 1 if both readers had scored it as 1. When readers disagreed, erosions were not considered to be present. If a different method had been used (e.g., a third adjudicator), it is likely that more erosions and inflammatory features would have been found.

The RAMRIS method was developed to sensitively follow the level of inflammation in RA-patients in clinical trials and was not designed for diagnostic purposes. If MRI is to be used for diagnostics, data on symptom-free persons are relevant to consider. Evaluation methods other than RAMRIS may be more accurate or more feasible, but this was beyond the scope of the present study.

A challenging question is what processes underlie the occurrence of MRI-detected inflammation and erosions in symptom-free persons. First, the MRI-findings observed could be degenerative in nature. Persons with symptomatic OA were not studied. To prevent recruiting a "too healthy" study population, symptom-free persons with Heberden's nodes, Bouchard's nodes, or hallux valgus were not excluded beforehand. Excluding these persons gave similar results. MRI-features were also present at locations that are not specific to OA (such as MCP2 and the distal ulna). Erosions were located marginally at the joint surface, which is unlike OA. In sum, the observation of more MRI-detected inflammation and erosions at older ages is not solely caused by the inclusion of persons with asymptomatic OA (as identified by physical examination), but it is possible that degenerative processes have contributed. Some observed preferential locations (MCP2, MCP3, and the distal ulna) are also known as preferential locations for arthritis and destruction in RA.[19] This might suggest that findings at these locations are partly mediated by mechanical strains. Furthermore, immunosenescence may also play a role, resulting in asymptomatic subclinical inflammation at older ages. Further studies are needed to identify the underlying mechanisms. Of note for bone marrow edema, it is possible that bone marrow edema in symptom-free persons relates to biologic processes that are different from those in RA-patients.

This observational study does not allow interpretation regarding the biologic nature of the findings. This limitation is inherent to imaging/MRI. However, this does not diminish the value of having a good reference when using MRI for diagnostic purposes.

The findings may be relevant if MRI is used to identify subclinical inflammation in patients with arthralgia without clinical arthritis who are presumed to be at risk for RA. In this setting it is relevant to prevent false-positive findings. If MRI is used for diagnosis and the RAMRIS method is used for MRI evaluation, the data presented

in Tables 2-4 could be used as a reference. For instance, a prevalence of<5% in the general population could be used as a cutoff to define a joint with abnormal MRI-detected inflammation.

In conclusion, this study showed that MRI-detected inflammation and erosions are prevalent in symptom-free persons, especially at older ages. The prevalence differed for the different MRI-features and also depended on the joint, bone, or tendon studied. Individual lesions were all assigned low grades. Interestingly, the joints that had the highest prevalence of MRI-features in symptom-free persons are similar to the joints that are frequently affected in RA.

Supplementary material

Supplementary material is published on the website of arthritis and rheumatology.

References

1 Colebatch AN, Edwards CJ, Østergaard M, van der Heijde D, Balint PV, D'Agostino MA, et al. *EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis*. Ann Rheum Dis 2013;72:804-14.

2 Krabben A, Stomp W, Huizinga TW, van der Heijde D, Bloem JL, Reijnierse M, et al. *Concordance between inflammation at physical examination and on MRI in patients with early arthritis*. Ann Rheum Dis 2015;74:506-12.

3 Krabben A, Stomp W, van Nies JA, Huizinga TW, van der Heijde D, Bloem JL, et al. *MRI-detected subclinical joint inflammation is associated with radiographic progression*. Ann Rheum Dis 2014;73:2034-7.

4 Perry D, Stewart N, Benton N, Robinson E, Yeoman S, Crabbe J, et al. *Detection of erosions in the rheumatoid hand; a comparative study of multidetector computerized tomography versus magnetic resonance scanning*. J Rheumatol 2005;32:256-67.

5 American College of Rheumatology Rheumatoid Arthritis Clinical Trials Task Force Imaging Group and Outcome Measures in Rheumatology Magnetic Resonance Imaging Inflammatory Arthritis Working Group. *The utility of magnetic resonance imaging for assessing structural damage in randomized controlled trials in rheumatoid arthritis [review]*. Arthritis Rheum 2013;65:2513-23.

6 Mangnus L, Schoones JW, van der Helm-van Mil AH. *What is the prevalence of MRI-detected inflammation and erosions in small joints in the general population? A collation and analysis of published data*. RMD Open 2015;1:e000005.

7 Duer-Jensen A, Hørslev-Petersen K, Hetland ML, Bak L, Ejbjerg BJ, Hansen MS, et al. *Bone edema on magnetic resonance imaging is an independent predictor of rheumatoid arthritis development in patients with early undifferentiated arthritis*. Arthritis Rheum 2011;63:2192-202.

8 Ejbjerg B, Narvestad E, Rostrup E, Szkudlarek M, Jacobsen S,Thomsen HS, et al. *Magnetic resonance imaging of wrist and finger joints in healthy subjects occasionally shows changes resembling erosions and synovitis as seen in rheumatoid arthritis*. Arthritis Rheum 2004;50:1097-106.

9 Parodi M, Silvestri E, Garlaschi G, Cimmino MA. *How normal are the hands of normal controls? A study with dedicated magnetic resonance imaging*. Clin Exp Rheumatol 2006;24:134-41.

10 Tan AL, Tanner SF, Conaghan PG, Radjenovic A, O'Connor P, Brown AK, et al. *Role of metacarpophalangeal joint anatomic factors in the distribution of synovitis and bone erosion in early rheumatoid arthritis*. Arthritis Rheum 2003;48:1214-22.

11 Olech E, Crues JV, Yocum DE, Merrill JT. *Bone marrow edema is the most specific finding for rheumatoid arthritis (RA) on noncontrast magnetic resonance imaging of the hands and wrists: a comparison of patients with RA and healthy controls*. J Rheumatol 2010;37:265-74.

12 Palosaari K, Vuotila J, Soini I, Kaarela K, Kautiainen H, Hakala M. *Small bone lesions resembling erosions can frequently be found in bilateral wrist MRI of healthy individuals*. Scand J Rheumatol 2009;38:450-4.

13 Stomp W, Krabben A, van der Heijde D, Huizinga TW, Bloem JL, van der Helm-van Mil AH, et al. *Are rheumatoid arthritis patients discernible from other early arthritis patients using 1.5T extremity magnetic resonance imaging? A large cross-sectional study*. J Rheumatol 2014;41:1630-7.

14 Van Steenbergen HW, van Nies JA, Huizinga TW, Bloem JL, Reijnierse M, van der Helm-van Mil AH. *Characterising arthralgia in the preclinical phase of rheumatoid arthritis using MRI.* Ann Rheum Dis 2015;74:1225-32.
15 Østergaard M, Edmonds J, McQueen F, Peterfy C, Lassere M, Ejbjerg B, et al. A*n introduction to the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas*. Ann Rheum Dis 2005;64 Suppl 1:i3-7.
16 Haavardsholm EA, Østergaard M, Ejbjerg BJ, Kvan NP, Kvien TK. *Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study.* Ann Rheum Dis 2007;66:1216-20.
17 McQueen F, Østergaard M, Peterfy C, Lassere M, Ejbjerg B, Bird P, et al. *Pitfalls in scoring MR images of rheumatoid arthritis wrist and metacarpophalangeal joints*. Ann Rheum Dis 2005;64 Suppl:i48-55.
18 Pfirrmann CW, Zanetti M. *Variants, pitfalls and asymptomatic findings in wrist and hand imaging*. Eur J Radiol 2005;56:286-95.
19 Landewe RB, Strand V, Conaghan PG, van der Heijde D. *Damage and progression on radiographs in individual joints: data from pivotal randomized controlled trials*. J Rheumatol 2011;38:2018-22.
20 Dillon CF, Hirsch R, Rasch EK, Gu Q. *Symptomatic hand osteoarthritis in the United States: prevalence and functional impairment estimates from the third U.S. National Health and Nutrition Examination Survey, 1991-1994*. Am J Phys Med Rehabil 2007;86:12-21.

Table 1 Characteristics of the 193 symptom-free participants

Total n = 193	
Age in years, mean (sd)	49.8 (15.8)
‹40 years, n (%)	51 (26.4)
40-60 years, n (%)	90 (46.6)
≥60 years, n (%)	52 (26.9)
Female, n (%)	136 (70.5)
Weight (kg), median (IQR)	71 (64-82)
Smoking	
Yes, present, n (%)	17 (8.8)
Yes, in past, n (%)	70 (36.3)
No, n (%)	106 (54.9)
Alcohol use †, n (%)	135 (69.9)
If yes, units per week, median (IQR)	7 (4-14)
Recent (less than 1 year) trauma ‡, n (%)	0 (0)
Comorbidity	
Hypertension, n (%)	13 (6.7)
Ischemic heart/cerebral disease, n (%)	4 (2.1)
Thyroid disease (current or past), n (%)	8 (4.1)
Diabetes mellitus, n (%)	1 (0.5)
Patient reported migraine, n (%)	6 (3.1)
Mood disorders (current or past), n (%)	10 (5.2)
Malignancies (current or past), n (%)	4 (2.1)
Other diagnoses, n (%)	53 (27.5)
Any sign of osteoarthritis of small joints at physical examination §, n (%)	68 (35.2)
Heberden nodes DIP, n (%)	55 (28.5)
Bouchard nodes PIP, n (%)	7 (3.6)
CMC-1 osteoarthritis, n (%)	2 (1.0)
Hallux valgus, n (%)	25 (13.0)

IQR = interquartile range; CMC-1 = carpometacarpal joint 1.

† Information on alcohol consumption was missing for 1 person.

‡ Trauma occurring ,1 year prior to magnetic resonance imaging.

§ The percentage of participants with signs of asymptomatic osteoarthritis in this study was similar to the prevalence observed in a large health survey in the US (20).

Table 2 Frequencies of synovitis, bone marrow edema (BME), tenosynovitis, and erosions in the MCP joints of symptom-free participants

	< 40 years n = 51 Grade 1/Grade 2	40-59 years n = 90 Grade 1/Grade 2	≥ 60 years n = 52 Grade 1/Grade 2
Synovitis			
MCP-2	0 / 0	8 / 0	19 / 0
MCP-3	0 / 0	14 / 0	17 / 0
MCP-4	0 / 0	2 / 0	4 / 0
MCP-5	0 / 0	1 / 0	6 / 0
BME*			
MCP-2	2 / 0	2 / 0	4 / 0
MCP-3	2 / 0	3 / 0	6 / 0
MCP-4	0 / 0	0 / 0	0 / 0
MCP-5	0 / 0	2 / 0	0 / 0
Tenosynovitis			
Extensor MCP-2	0 / 0	0 / 0	0 / 0
Extensor MCP-3	0 / 0	1 / 0	0 / 0
Extensor MCP-4	0 / 0	0 / 0	0 / 0
Extensor MCP-5	0 / 0	0 / 0	0 / 0
Flexor MCP-2	0 / 0	1 / 0	6 / 0
Flexor MCP-3	0 / 0	3 / 0	12 / 0
Flexor MCP-4	0 / 0	3 / 0	6 / 0
Flexor MCP-5	0 / 0	1 / 0	2 / 0
Erosions*			
MCP2	6 / 0	13 / 0	33 / 2
MCP3	8 / 0	12 / 0	17 / 6
MCP4	0 / 0	2 / 0	8 / 0
MCP5	2 / 0	6 / 0	21 / 0

Values are the percent of participants with Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) grade 1 or grade 2 features in the indicated joints. RAMRIS grade 3 features rarely occurred; only 1% of participants ages 40-59 had a grade 3 erosion in metacarpophalangeal joint 3 (MCP3).

* Bone marrow edema and erosions were scored in the proximal and distal MCP bones separately. The scores for the 2 bones are summed into 1 score; therefore, the possible range of scores is 0-6 and 0-20, respectively. For MCP2, 1 bone had an erosion score of 2 (scores of 1 in both the proximal and distal bone); for MCP3, 4 bones had an erosion score of ≥ 2 (3 participants had a score of 2 or 3 in the proximal bone and 1 had a score of 1 in both the proximal and distal bone).

Table 3-a Frequencies of synovitis, bone marrow edema (BME), tenosynovitis, and erosions in the wrist joints of symptom-free participants

	< 40 years n = 51 Grade 1/Grade 2	40-59 years n = 90 Grade 1/Grade 2	≥ 60 years n = 52 Grade 1/Grade 2
Synovitis			
Intercarpal-CMC joint	4 / 0	16 / 0	27 / 0
Radio-carpal joints	0 / 0	17 / 0	35 / 0
Distal radio-ulnar joint	0 / 0	8 / 0	17 / 0
BME			
Metacarpal-1 basis	0 / 0	3 / 0	8 / 2
Metacarpal-2 basis	4 / 0	1 / 0	2 / 0
Metacarpal-3 basis	0 / 0	0 / 0	2 / 0
Metacarpal-4 basis	0 / 0	0 / 0	2 / 0
Metacarpal-5 basis	0 / 0	0 / 0	0 / 0
Trapezium	0 / 0	0 / 0	4 / 4
Trapezoid	2 / 0	1 / 0	6 / 0
Capitate	6 / 2	3 / 0	4 / 0
Hamate	0 / 0	3 / 0	8 / 0
Scaphoid	2 / 0	7 / 0	19 / 0
Lunate	6 / 0	19 / 1	27 / 4
Triquetrum	2 / 0	6 / 0	2 / 0
Pisiform	0 / 0	0 / 0	0 / 0
Distal radius	0 / 0	0 / 0	0 / 0
Distal ulna	0 / 0	7 / 0	8 / 0

Frequencies of Tenosynovitis and Erosions see table 3-b on the next page

Values are the percent of participants with Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) grade 1 or grade 2 features in the indicated joints. RAMRIS grade 3 features rarely occurred; only 4% of participants ages ≥ 60 had grade 3 bone marrow edema in the metacarpal 1 base and in the trapezium.

Table 3-b Frequencies of synovitis, bone marrow edema (BME), tenosynovitis, and erosions in the wrist joints of symptom-free participants

	‹ 40 years n = 51 Grade 1/Grade 2	40-59 years n = 90 Grade 1/Grade 2	≥ 60 years n = 52 Grade 1/Grade 2
Frequencies of Synovitis and BME see table 3-a on the previous page			
Tenosynovitis			
I extensor	0 / 0	0 / 0	0 / 2
II extensor	0 / 0	0 / 0	0 / 0
III extensor	0 / 0	0 / 0	0 / 0
IV extensor	0 / 0	0 / 0	2 / 0
V extensor	0 / 0	0 / 0	0 / 0
VI extensor	0 / 0	9 /0	12 / 0
1 flexor	0 / 0	0 / 0	0 / 0
2 flexor	0 / 0	0 / 0	0 / 0
3 flexor	0 / 0	0 / 0	0 / 0
4 flexor	2 / 0	0 / 0	2 / 0
Erosions			
Metacarpal-1 basis	0 / 0	8 / 0	23 / 2
Metacarpal-2 basis	0 / 0	2 / 0	2 / 0
Metacarpal-3 basis	0 / 0	1 / 0	4 / 0
Metacarpal-4 basis	0 / 0	0 / 0	2 / 0
Metacarpal-5 basis	0 / 0	1 / 0	0 / 0
Trapezium	2 / 0	2 / 0	31 / 0
Trapezoid	4 / 0	11 / 0	17 / 0
Capitate	18 / 0	24 / 0	27 / 0
Hamate	0 / 0	4 / 0	13 / 0
Scaphoid	4 / 0	18 / 0	37 / 0
Lunate	8 / 0	19 / 0	40 / 0
Triquetrum	2 / 0	19 / 0	23 / 0
Pisiform	0 / 0	0 / 0	6 / 0
Distal radius	0 / 0	2 / 0	2 / 0
Distal ulna	6 / 0	9 / 0	23 / 0

Values are the percent of participants with Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) grade 1 or grade 2 features in the indicated joints. RAMRIS grade 3 features did not occur.

Table 4 Frequencies of synovitis, bone marrow edema (BME), tenosynovitis, and erosions in the MTP joints of symptom-free participants

	< 40 years n = 51 Grade 1/Grade 2	40-59 years n = 90 Grade 1/Grade 2	≥ 60 years n = 52 Grade 1/Grade 2
Synovitis			
MTP-1	4 / 0	11 / 0	13 / 2
MTP-2	0 / 0	1 / 0	0 / 0
MTP-3	0 / 0	1 / 0	0 / 0
MTP-4	0 / 0	0 / 0	0 / 0
MTP-5	0 / 0	0 / 0	4 / 0
BME *			
MTP-1	10 / 0	12 / 1	23 / 8
MTP-2	2 / 0	0 / 1	0 / 0
MTP-3	0 / 0	1 / 0	0 / 0
MTP-4	0 / 0	1 / 0	0 / 0
MTP-5	0 / 0	1 / 0	4 / 0
Erosions *			
MTP1	2 / 0	14 / 0	37 / 4
MTP2	0 / 0	1 / 0	0 / 0
MTP3	0 / 0	0 / 0	2 / 0
MTP4	0 / 0	0 / 0	0 / 0
MTP5	2 / 0	10 / 0	10 / 0

Values are the percent of participants with Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) grade 1 or grade 2 features in the indicated joints. RAMRIS grade 3 features rarely occurred; only 1% of the participants ages 40-59 years had bone marrow edema in metatarsophalangeal joint 3 (MTP3).

* Bone marrow edema and erosions were scored in the proximal and distal MTP bones separately. The scores for the 2 bones are summed into 1 score; therefore, the possible range of scores is 0-6 and 0-20, respectively. For MTP1, 5 bones had a bone marrow edema score of 2 (4 participants had a score of 1 in both the proximal and distal bone and 1 participant had a score of 2 in the proximal bone). For MTP2 and MTP3, 2 bones had a bone marrow edema score of ≥ 2 (both had a bone marrow edema score of 2 or 3 in the proximal bone). For MTP1, 2 bones had an erosion score of 2 (2 persons with an erosion score of 1 in both the proximal and the distal bone).

Part II
Understanding early RA; what factors influence radiographic joint damage, bone mineral density or local joint inflammation detected on MRI

Chapter 4: Studies on ageing and the severity of radiographic joint damage in rheumatoid arthritis

L. Mangnus

H.W. van Steenbergen

E. Lindqvist

E. Brouwer

M. Reijnierse

T.W.J. Huizinga

P.K. Gregersen

E. Berglin

S. Rantapää-Dahlqvist

D. van der Heijde

A.H.M. van der Helm-van Mil

Arthritis research therapy, 2015

Abstract

Introduction: The western population is ageing. It is unknown whether age at diagnosis affects the severity of Rheumatoid Arthritis (RA), we therefore performed the present study.

Method: 1,875 RA-patients (7,219 radiographs) included in five European and North-American cohorts (Leiden-EAC, Wichita, Umeå, Groningen and Lund) were studied on associations between age at diagnosis and joint damage severity. In 698 Leiden RA-patients with 7-years follow-up it was explored if symptom duration, anti-citrullinatedpeptide- antibodies (ACPA), swollen joint count (SJC) and C-reactive-protein (CRP) mediated the association of age with joint damage. Fifty-six other RA-patients of the EAC-cohort underwent baseline MRIs of wrist, MCP and MTP-joints; MRI-inflammation (RAMRIS-synovitis plus bone marrow edema) was also evaluated in mediation analyses. Linear regression and multivariate normal regression models were used.

Results: Analysis on the five cohorts and the Leiden-EAC separately revealed 1.026-fold and 1.034-fold increase of radiographic joint damage per year increase in age ($\beta = 1.026$, 1.034, both $p < 0.001$); this effect was present at baseline and persisted over time. Age correlated stronger with baseline erosion-scores compared to joint space narrowing (JSN)-scores ($r = 0.38$ versus 0.29). Symptom duration, ACPA, SJC and CRP did not mediate the association of age with joint damage severity. Age was significantly associated with the MRI-inflammation-score after adjusting for CRP and SJC ($\beta = 1.018$, $p = 0.027$). The association of age with joint damage ($\beta = 1.032$, $p = 0.004$) decreased after also including the MRI-inflammation-score ($\beta = 1.025$, $p = 0.021$), suggesting partial mediation.

Conclusion: RA-patients presenting at higher age have more severe joint damage; this might be partially explained by more severe MRI-detected inflammation at higher age.

Introduction

The western population is ageing. Consequently, the number of patients with rheumatoid arthritis (RA) presenting at an older age is increasing.[1, 2] Ageing is associated with alterations and remodelling of the innate and adaptive immune system immunosenescence).[3-5]

It is unclear to what extent ageing or age-associated changes in function of immune cells influence the severity of RA. If RA-severity differs for patients diagnosed at different age categories, this is relevant for clinical practice. Some previous studies suggest that older patients with RA have more joint damage [6-11], whereas other studies observed no difference [12, 13] or observed less joint damage in older patients with RA.[14] Most studies performed analyses at a single time point [7-10, 13, 14] and all studied patients categorized as younger or older.[6-14] The first aim of the present study was to explore the association between age and severity of joint damage in more detail. Patients with RA included in one North-American and four European longitudinal cohorts were studied for severity of joint damage at disease presentation and during the course of the disease. We analysed age as a continuous variable to obtain optimal insight into the effects of age.

Second, no studies have explored processes underlying the association between age at disease onset and radiographic joint damage. First, because joint damage measures such as the Sharp-van der Heijde (SHS)-score assess bone erosions and joint space narrowing (JSN),

JSN may occur not only due to RA but also reflect degeneration. An increase in total SHS-severity at older age could therefore be due to a disproportional increase in JSN. Additionally, based on general knowledge of risk factors for progressive joint damage in RA (longer symptom duration, presence of RA-related auto-antibodies, higher numbers of swollen joints and elevated acute-phase reactants are all associated with more severe damage), we made several other hypotheses. We assumed that older patients present at a later point in time, and therefore have more severe joint damage. In addition, as the prevalence of RA-related auto-antibodies in the general population increases with increasing age, we hypothesized that patients with RA presenting at older age are more often rheumatoid factor (RF)-positive

or anti-citrullinated peptide antibodies (ACPA)-positive and therefore have more severe disease.[8, 11-13, 15-20] Likewise we postulated that inflammation at diagnosis is more severe at older age resulting in more joint damage. Inflammation was evaluated using traditional measures (swollen joint count (SJC), C-reactive protein (CRP)) and using magnetic resonance imaging (MRI), which is more sensitive in detecting local inflammation.[21, 22] We also aimed to explore these hypotheses. Thus the first aim of this study was to explore the association of age with joint damage severity in more detail and, second, we aimed to increase the understanding of the processes underlying the association between age of disease onset and the severity of the disease course.

Methods

Study population

To determine the association between age at diagnosis and severity of joint damage, patients with RA included in five longitudinal inception cohorts were studied. In total this comprised 1,875 patients with 7,219 sets of radiographs made at baseline and during follow up. Patients were included in cohorts of the Leiden early arthritis clinic (EAC), Groningen (both the Netherlands), Wichita (USA), Umeå and Lund (both Sweden). All patients with RA fulfilled the 1987 criteria for RA except for the Lund cohort where the 1958 criteria were used. The age at diagnosis was recorded in all cohorts. For all studies the regional ethics committee approved the study and all participants gave their written informed consent. Extensive descriptions of these cohorts are presented elsewhere [23-26], short descriptions are provided below.

Leiden early arthritis clinic (EAC) cohort

Patients with early RA (n = 698) between 1993 and 2006 were included.[23] From these patients 3,643 sets of radiographs of the hands and feet were obtained during 7 years of follow up. Follow-up visits, including radiographs, were done yearly. All radiographs were chronologically scored by an experienced reader, blinded to the

clinical data, according to the SHS-method. The intra-reader intra-class correlation coefficient (ICC) was 0.91. The applied treatment strategies changed over time, as described elsewhere [27]; the inclusion periods were used to adjust for differences in applied treatments. The data for these patients were used for the mediation analyses as they contained most radiographs and extensive data on clinical and serologic variables. A second study population of patients with RA was included in the EAC in 2010-2012. In addition to the general EAC-protocol including radiographs, these consecutively included patients had contrast-enhanced 1.5 T MRI of unilateral metacarpophalangeal (MCP), wrist and metatarsophalangeal (MTP) joints at baseline. Patients who had 1-year follow up, including radiographs, were selected (n = 56). The MRI (ONI-MSK-Extreme 1.5 T MRI (GE, WI, USA)) was performed at inclusion, on the most symptomatic side or the dominant side in the case of equally severe symptoms. Scanning was done according to the RA MRI score (RAMRIS), with contrast enhancement. The scan protocol is described in Additional file 1. MRI-scoring was done by two trained readers blinded to any clinical data. [28-30] The within-reader ICCs were 0.98 and 0.83, and the inter-reader ICC 0.82. The mean score of both readers was studied.

Wichita

This North-American cohort consisted of 293 patients that were diagnosed between 1963 and 1999.[24] In this cohort 1,062 radiographs were made during 15 years of follow up. All radiographs were chronologically scored by an experienced reader using the SHS (ICC 0.98).[31]

Umeå

The third cohort consisted of 459 patients included between 1995 and 2010.[6] These patients had radiographs at baseline and 2 years: 868 radiographs were obtained and were scored by two trained rheumatologists according to the Larsen score.[32, 33] Treatment strategies differed between 1995 and 1999, 2000 and 2005, and 2006 and 2010, with less severe radiographic progression in the subsequent treatment periods.

Groningen

This dataset included 278 patients with RA who were diagnosed between 1945 and 2001. During 14 years of follow up 865 radiographs were obtained that were chronologically scored according to the SHS by one of two readers (intra-reader ICC›0.90 inter-reader ICC 0.96).[34] Joint destruction was less severe after 1990, which coincides with the introduction of treatment with disease-modifying anti-rheumatic drugs (DMARDs).

Lund

This cohort consist of 147 patients recruited from primary care units in the area of Lund from 1985-1989 [26]: 781 radiographs were obtained during 5 years of follow up. These radiographs were scored according to the Larsen score (ICC 0.94).[32, 35] All results for age in all datasets in this study represent the age of the patient at the time of diagnosis. At the baseline visit, the date of birth or age itself was recorded.

Analyses

First, the associations between age at diagnosis and the severity of joint damage were evaluated for each cohort separately. A multivariate normal regression model for longitudinal data [27] was used with radiographic scores as the outcome and age as the continuous independent variable. The radiographic scores were log10-transformed (log10 (score+1)) to approximate a normal distribution. In all cohorts the residuals of the models were normally distributed around zero, indicating a good fit of the models (Additional file 2: Figure S1). This repeated measurement analysis takes the correlation between repeated measurements within patients into account. A heterogeneous first-order autoregressive (ARH1) correlation structure was used, assuming a stronger correlation for measurements taken in a shorter period of time than for those over a longer period. As described elsewhere in detail [27] this model is able to test for two effects: first the model can be used to analyse whether patients with a risk factor have more severe joint damage at any point in time; this reflects a constant effect size over time.

Second, the model can be used to analyse whether patients have more severe radiographic progression over time; this present the steepness of the curve of joint

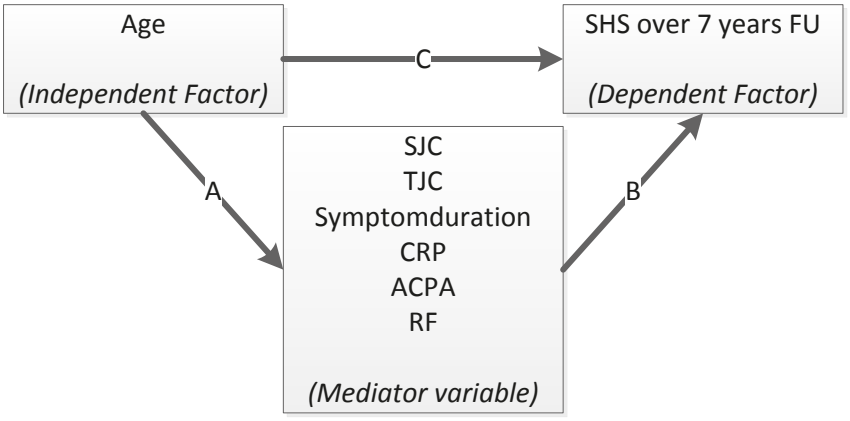
damage over time (risk factor*time). In the evaluated cohorts, the radiographic data were plotted (before starting with statistical analysis); this suggested an effect that is constant over time and not a progression effect. Therefore analyses were focussed on the constant effect and all results presented (effect sizes, p-values) were those of a constant effect, thus, this concerns a difference in joint destruction that was equally present at every time point. In all datasets, analyses were adjusted for gender. In the cohorts that included patients in periods with different treatments strategies (EAC, Umeå and Groningen) an additional adjustment was made for the inclusion period (as proxy for treatment strategy) as radiographic joint damage varied between different inclusion periods. As the analyses were performed on the log-scale, the resulting effect estimates were back-transformed to the normal scale and indicated the fold increase in joint damage per year of increase in age at diagnosis. Thus, this outcome indicates a relative increase in joint damage and is unit-free. This allowed us to enter the effects of the five different cohorts in an inverse-weighted meta-analysis. This method weights the results with a low standard error stronger than results with a higher standard error, preventing over-representation of the less precise data on the overall outcome. A random-effect model was used.

To explore whether the increase in total SHS at increasing age was explained by a disproportionate increase in JSN, possibly reflecting age-related degenerative changes, the total SHS at baseline of the 698 Leiden RA-patients was split into erosion score and JSN-score. Pearson's correlation coefficients were determined and equality/ inequality of the two correlation coefficients was assessed using the corcor command. Similarly, the total SHS was split for separate locations; predilection locations for primary osteoarthritis (proximal interphalangeal (PIP)- joints, carpometacarpal-1 (CMC-1)-joints and MTP-1 plus interphalangeal-1 joints were compared to other joints.

Mediation analyses were used to identify potential mechanisms underlying the association between age at disease onset and radiographic joint damage. Mediation analyses were performed according to Baron and Kenny (Fig. 1).[36] First (step 1), the mediator variables were regressed on the independent variable (age); the independent variable should significantly affect the mediator variables.

Second (step 2), regression analysis of the dependent variable (radiographic joint damage) on the independent variable (age) was done. In this analysis the independent variable must significantly affect the dependent variable. Third (step 3), the dependent variable was regressed on the independent and mediator variable. When mediation occurs, the mediator variable significantly affects the dependent variable and the effect of the independent variable on the dependent variable decreases (partial mediation) or disappears completely (full mediation). Symptom

Figure 1 Schematic overview of the causal paths that were studied using mediation models as described by Baron and Kenny



The figure illustrates two causal paths that lead to an outcome. A direct path from independent to dependent variable (B) and an indirect path from an independent to a dependent variable through a mediator variable (A,C). To test mediation 3 test have to be performed according to Baron and Kenny. [36] First, the mediator variables were regressed on the independent variable (A), the independent variable should significantly affect the mediator variables. Secondly, regression analysis of the dependent variable on the independent variable was done,(B) in this analysis the independent variable must significantly affect the dependent variable. Thirdly, the dependent variable was regressed on the independent and mediator variable (B and C). When mediation occurs the mediator variable significantly affects the dependent variable and the effect of the independent variable on the dependent variable is closer to zero. In this study we tested whether different mediators could influence the effect of age on radiographic joint damage. The tested mediators were symptom duration at diagnosis, swollen joint count (SJC), tender joint count (TJC), C-reactive protein (CRP), anti-citrullinated protein antibody (ACPA), rheumatoid factor (RF), and inflammation detected on MRI. SHS = Sharp-van der Heijde score.

duration at baseline, ACPA (anti-CCP2), IgM-RF, CRP, SJC and TJC were assessed as mediators. Linear or logistic regression was used as appropriate for step 1. For steps 2 and 3 the multivariate normal regression model was used as described. Analyses were performed with SPSS V20.0.0; the meta-analysis and the equality of the correlation test were performed using STATA/SE V12.1.

Results

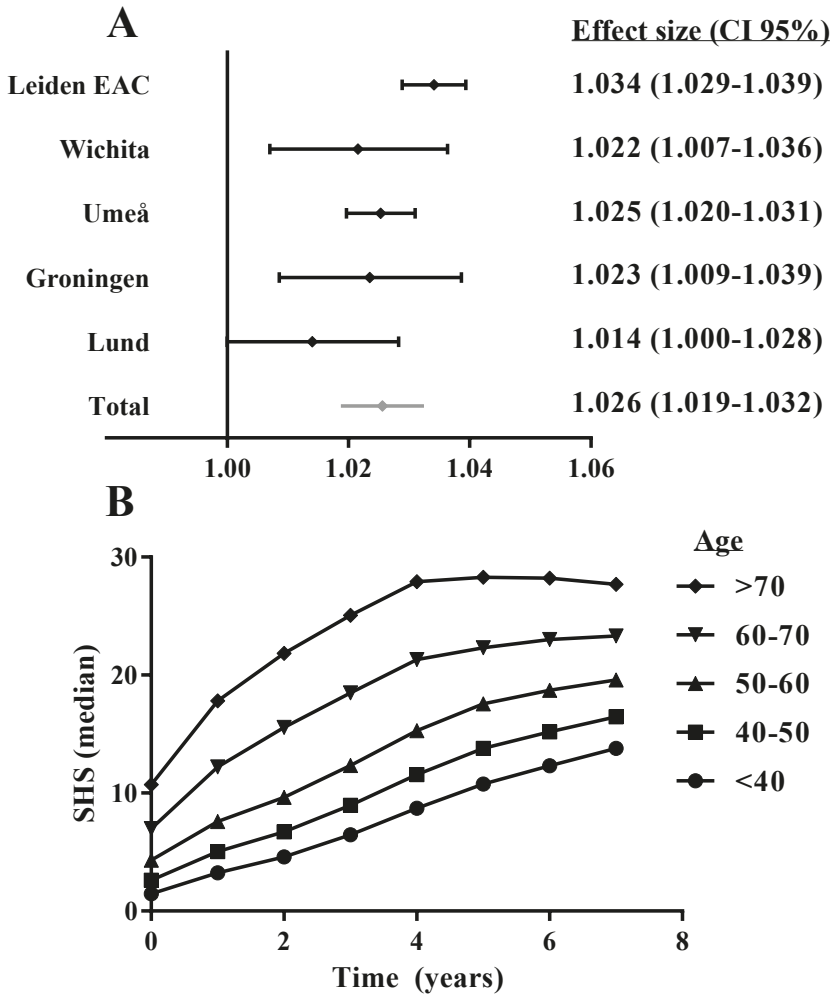
Age at diagnosis and severity of radiographic joint damage

First, the association between age and severity of joint damage observed on radiographs was explored separately in each cohort. Baseline characteristics of these patients are presented in Table 1. In all cohorts an increase in age at diagnosis was associated with more severe joint damage at baseline and this effect persisted over time. Combining all five cohorts in a meta-analysis revealed that patients had 1.026-fold more joint damage observed on radiographs per year increase in age at any point during the disease course ($\beta = 1.026$, $p < 0.001$, Fig. 2a). For illustration, the predicted severity of joint damage per group of patients according to different age categories is depicted in Fig. 2b, based on 698 patients with RA included in the Leiden-EAC. Data for the other cohorts are depicted in Additional file 3: Figure S2. Here joint damage increased 1.034-fold per year increase in age; this effect was constant over time ($\beta = 1.034$, $p < 0.001$).

Correlation of age with erosion score and JSN-score

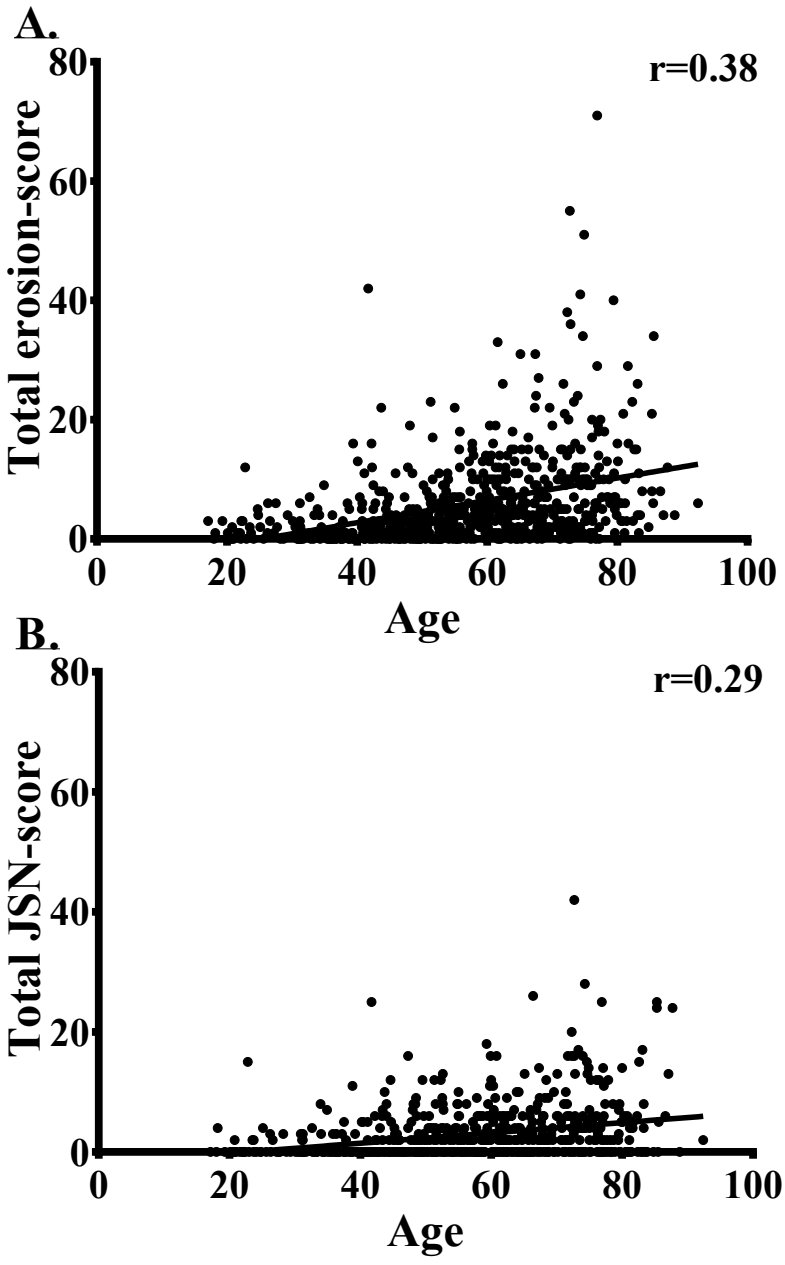
The SHS at disease onset in patients with RA included in the Leiden EAC were split into total erosion scores and total JSN-scores to explore whether age-related degenerative changes explain the association between age and total SHS score, and we assessed whether the correlation between age and JSN-score was stronger than the correlation between age and the erosion score. Age at diagnosis was significantly correlated with both the erosion and JSN-scores ($r = 0.38$, $p < 0.001$ and $r = 0.29$, $p < 0.001$ respectively, Fig. 3) at baseline. The correlation coefficient of the erosion score was significantly higher than that of the JSN-score ($p = 0.006$). The

Figure 2 Association of age at diagnosis with joint damage severity in five longitudinal cohorts summarized in a meta-analysis (A) and depicted for RA-patients included in the Leiden EAC for different age categories (B)



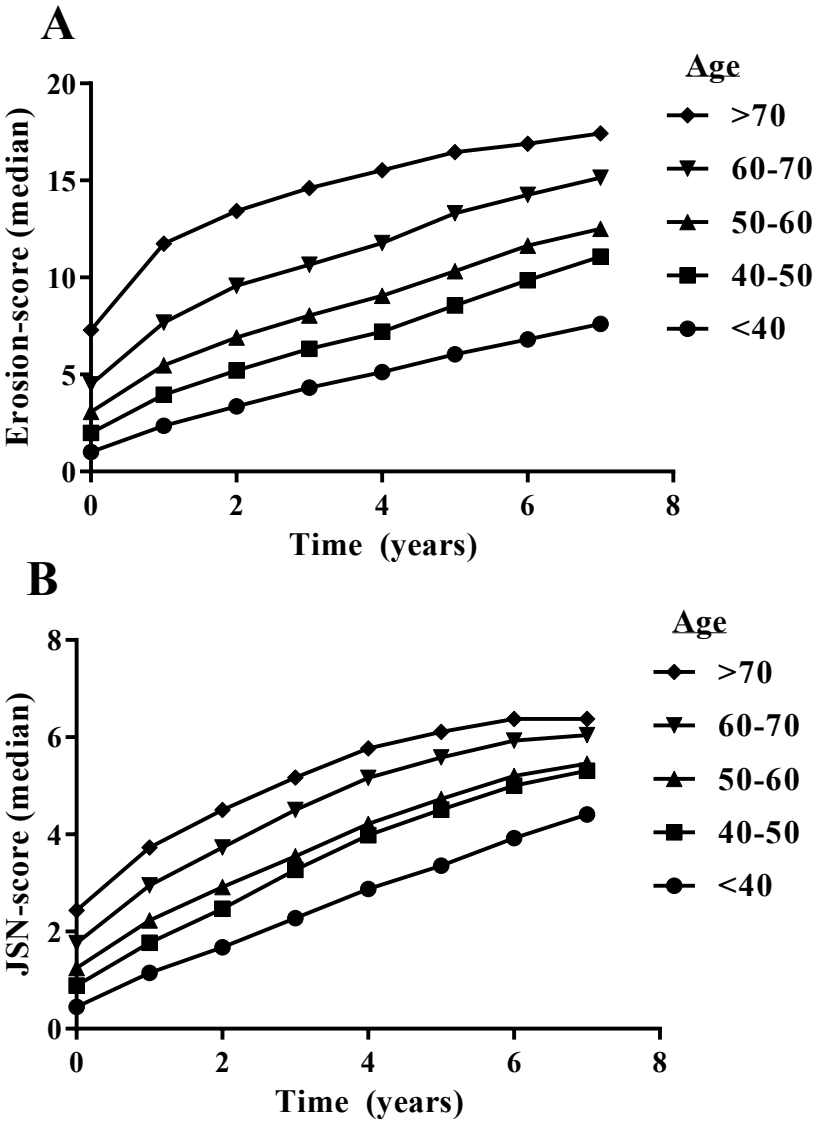
(A) Age was entered as continuous variable in the multivariate normal regression analysis, because the plots of the raw data suggested no interaction of age with time. The meta-analysis (inverse weighted meta-analysis with a random-effect model) summarizes the effects of age of the different cohorts. An effect size of 1.034 represents a 1.034-fold increase in joint damage per year increase in age. Because these effect sizes were unit-free they could be compared in meta-analysis. (B) Although age was analyzed as continuous variable, in order to illustrate the data the predicted SHS per age-categories were plotted. Presented are the SHS predicted by the multivariate normal regression analysis. SHS = predicted Sharp van der Heijde score.

Figure 3 Correlation between age and Sharp-van der Heijde erosion (A) and joint-space narrowing scores (B) at baseline



JSN = Joint space narrowing,
SHS = Sharp-van der Heijde score

Figure 4 'Sharp-van der Heijde erosion score (A) and joint space narrowing score (B) over time for patients with rheumatoid arthritis from the Early Arthritis Clinic, categorized by age at diagnosis'



association between age and erosion and JSN-score over time was also assessed, and older age was associated with higher erosion scores and higher JSN-scores at all points in time (β = 1.030, p < 0.001, and β = 1.020, p < 0.001, respectively) (Fig. 4). The total SHS score is also the sum of the scores of different joints. We hypothesized that some joints (predilection locations for primary osteoarthritis in particular, such as CMC-1) are more frequently affected by age-related degeneration. Therefore the total SHS score at baseline was split for several regions and correlations between the SHS score per region and age were determined. This revealed that the correlation of CMC-1 was comparable to that of the wrist (r = 0.26 and r = 0.23, both p < 0.001). The correlation of the other locations was also comparable (r = 0.20, 0.31 and 0.39 for MTP + IP-1, MCP joints and PIP joints, all p < 0.001), only in the MTP2–5 joints the correlation of the SHS score with age was lower (r = 0.08, p = 0.03, Additional file 4: Figure S3). Together these results suggest that degenerative changes at older age may contribute to more severe joint damage in patients presenting at older age but are clearly insufficient to explain the total effect.

Age and symptom duration at first presentation

Because it is known that prolonged symptom duration at first presentation is associated with more severe radiographic progression [37, 38], we hypothesized that older persons present with a longer symptom duration, hence mediating the association with joint damage. Although longer symptom duration was associated with more joint damage (β = 1.003, p < 0.001), symptom duration was inversely associated with age, (β = 0.99, p < 0.001), hence older age was associated with shorter symptom duration. Therefore, symptom duration did not mediate the effect of age on joint damage (Table 2).

Age and RA-related auto-antibodies

The presence of ACPA and RF were strong risk factors for radiographic progression (β = 1.37, p < 0.001 and β = 1.30, p < 0.001, respectively). These auto-antibodies can mediate the association between age and joint destruction if age is associated with a higher prevalence of these auto-antibodies. We observed no significant association between age at onset and presence of RF (odds ratio (OR) = 0.99,

p = 0.09). The prevalence of ACPA was lower when RA was diagnosed at an older age (OR = 0.98, p < 0.001). Therefore, these auto-antibodies did not mediate the association between age and joint damage (Table 2).

Age and clinical measures of joint inflammation

Next we explored whether the extent of joint inflammation, measured using the SJC and TJC at baseline, was a mediator. Age at diagnosis was not associated with the number of joints involved (β = 1.00, p = 0.11 and β = 1.00, p = 0.55 for SJC and TJC, respectively). The SJC and TJC were also not associated with radiographic joint damage (β = 1.00, p = 0.23 and β = 1.00, p = 0.76); therefore these clinical measures of local inflammation were not mediators (Table 2).

Age and serological measures of inflammation

Subsequently it was explored whether CRP, a measure of systemic inflammation, was a mediator. CRP-levels increased significantly with age (β = 1.016, p < 0.001), indicating that with every year increase in age the CRP increased by 1.6%. CRP-levels were also associated with severity of joint damage (β = 1.003, p = 0.003). In the third step of the mediation analysis, the association between age and joint damage was studied after adjustment for CRP. This revealed a very slight decrease in effect size, from 1.034 to 1.033 (Table 2), based on which it was concluded that also CRP was not a mediator. Similar results were seen when erythrocyte sedimentation rate (ESR) was studied (data not shown).

Age and local inflammation measured by MRI

It is known that MRI of the extremities measures local inflammation more sensitively than physical examination and CRP.[21, 22, 39] To explore local inflammation in more detail, additional mediation analysis was performed in another group of patients with RA who underwent MRI of the extremities at baseline (Table 3). The MRI synovitis and bone marrow edema (BME) scores were summed, yielding the MRI inflammation scores. Also in this group of patients, an increase in age was associated with more joint damage at baseline; also here the effect was constant over time. (β = 1.032 p = 0.004). All subsequent analyses were adjusted for SJC and

CRP to ensure that the results for MRI-detected inflammation were not explained by these traditional measures of inflammation. It was observed that patients presenting at older age had higher MRI inflammation scores (β = 1.018, p = 0.027) and that higher MRI inflammation scores were associated with radiographic joint damage at any point in time evaluated (β = 1.026, p = 0.018). Then in step 3 of the mediation analysis there was a decreased effect size of age with structural damage when additionally adjusting for the MRI inflammation score (β = 1.032 p = 0.004 to β = 1.025 p = 0.02), suggesting that MRI-detected inflammation is a partial mediator for the effect of age on radiographic joint damage.

Discussion

The western population is ageing. Consequently the number of patients with RA diagnosed at an older age is rising.[1, 2] It is generally hoped that the additional years of life are spent in good health. RA, however, is associated with decreased functioning and quality of life. Previous studies on age and RA-severity have contrasting results.[6, 7, 9, 40, 41] The present study of patients with RA, which included five longitudinal cohorts, showed that older patients had more severe joint damage at diagnosis and this effect remained present during the disease course. We evaluated several hypotheses to increase the understanding of the processes driving the observations of the influence of age. We observed that the effect was partially and modestly mediated by MRI-detected inflammation with increasing age.

Longitudinal data from five cohorts were studied on the effect of age on the severity of joint damage. Because of the presence of serial radiographic measurements multivariate normal regression analysis was used (this model is similar to a linear mixed model, only no random effect is added). For reasons of consistency this model was also used in the mediation analysis in the second part of the manuscript. However, the effect of joint damage was already present at baseline and the mediation analyses could also be done with joint damage at baseline as the

outcome. Repeating the mediation analysis with baseline SHS as the outcome indeed revealed similar results (data not shown).

Interestingly, some variables assessed in the mediation analyses were inversely correlated with age. The symptom duration at the time of diagnosis was shorter at older age, indicating that older patients had less delay in getting access to rheumatologic care. Thus, although we hypothesized that older patients presented with more severe damage due to having longer duration of disease, older patients had a shorter period of symptoms at first presentation, hence arguing against this hypothesis. Also the prevalence of ACPA decreased at older age in 1,987-criteria-positive patients with RA, which is in contrast to the prevalence of ACPA in the general population [15], but a lower frequency of ACPA amongst older patients with RA has been described before.[6] Several studies have observed higher CRP-levels in older patients with RA [11, 16, 17], and we also observed this. However, the effect size of the association between age and severity of joint damage decreased very little after adjusting for CRP, therefore CRP was not considered an evident mediator. MRI of the extremities is sensitive in detecting local inflammation and subclinical inflammation observed on MRI has been found to be relevant for radiographic progression of RA.[21, 22] The present data showed that patients with RA presenting at an older age have more MRI-detected inflammation. Ageing is associated with an increase in pro-inflammatory status and a decline in both T cell and B cell function.[3-5] Potentially, changes in the immune system are underlying the current observation of more severe inflammation on MRI at an older age. Earlier studies have shown that the severity of MRI-detected inflammation is associated with the severity of radiographic joint damage and that this effect is independent of the effects of CRP and SJC on radiographic progression.[22, 39] The present data also show that MRI-detected inflammation is associated with severity of joint damage, independent of other measures of inflammation. Hence in the last two steps of the mediation analysis, adjustments for CRP and SJC were made. The finding that the effect size of age decreased after additional adjustment for MRI-detected inflammation suggests that the effect of more severe joint damage at higher age is partly mediated by the presence of more severe MRI-detected inflammation at an older

age. In other words, it suggests that MRI-inflammation acts in the so-called causal path.[36]

Interestingly, some recent evidence suggested that older age might also be associated with presence of more MRI-detected inflammation in symptom-free persons.[42] More studies are needed to determine the validity of these results, and to differentiate disease-related inflammation on MRI from variations that are present in the general population. Nonetheless, in our view this does not affect the validity of the present results. If MRI-detected inflammation also occurs at an older age in people without RA, this most likely does not affect the mediation analyses in RA and does not influence the decrease in the beta value for age between steps 2 and 3.

We explored whether the higher SHS scores at older age were due to age-related degeneration. We have tried to detangle these effects by evaluating JSN-scores and erosion scores separately and predilection locations for degenerative changes separately. Although these comparisons do not allow us to make conclusions about the causality, degenerative changes at an older age appear insufficient to explain the observed association between age and severity of joint damage.

Similarly, it can be questioned whether more severe MRI-detected inflammation is RA-specific or age-specific. This is even more difficult to discriminate as the RAMRIS was derived for RA; degenerative features such as JSN and osteophytes were not included; also the locations assessed by RAMRIS are specific for RA. The CMC-1 joint is included but is known to be affected by degeneration as well. When we evaluated the BME-scores in the base of metacarpal-1 and trapezium (the two bones together forming CMC-1), the correlation with age was not significant ($\rho = 0.24$, $p = 0.07$) whilst the BME-score obtained in other bones in the wrist was positively correlated with age ($\rho = 0.41$, $p = 0.002$). This suggests that the higher MRI scores seen in patients with RA at higher age were not primarily due to degeneration (in the process of osteoarthritis).

Degeneration in the light of osteoarthritis may be different from the more global effects of wear and tear. We cannot exclude that part of the effect of greater MRI-detected inflammation at an older age is due to wear and tear. Part of the observation of more radiographic erosions at older ages can, in the same path, also be due

to wear and tear. If this is true, hand and foot radiographs of healthy people at older ages would also show erosions according to the SHS method. To the best of our knowledge, radiographic studies on the hands and feet of healthy persons of different age categories have not been done.

It has been suggested that older patients are treated differently in comparison to younger patients [43-46], but others have argued against this.[47] The majority of patients studied here were included in periods when early, tailored, treatment and use of biologic agents were uncommon. Importantly, treatment most likely does not affect the results of our study as differences in radiographic joint damage were already present at baseline. The differences were already present before the start of treatment, so treatment was not a likely mediator.

Analyses were adjusted for gender to account for differences in male/female ratios at different ages. Additionally, women have hormonal changes during their lifetime. When repeating the mediation analyses in men only, no differences were observed (data not shown), suggesting that gender was not a confounder.

The strength of this study is that five cohorts with longitudinal data were studied. The cohorts used different inclusion criteria, but despite these differences, all cohorts had more radiographic joint damage with older age at disease onset. This replication supported the validity of the association between age and severity of joint damage. A limitation is that the mediation analyses were performed using data from one cohort only. However, data on the complete set of potential mediators were not available for the other datasets. Another limitation is the relatively small number of patients with RA with baseline MRI-data and 1-year follow up in relation to the large cohorts of patients with radiographic data. This is due to the fact that in our setting MRI was not available until a few years ago. Notably, the effect size of age on radiographic joint damage in this small patient group of patients with RA was almost similar to that of the larger RA datasets.

Conclusions

The present study convincingly showed that patients with RA diagnosed at an older age already have more joint damage on disease presentation, and this effect remains during the disease course. This effect might be partially explained by more severe local inflammation at an older age. Future studies are needed to elucidate the biological mechanisms determining inflammation severity and RA-severity and changes during the patient's lifetime.

Supplementary material
Supplementary material is published on the website of arthritis research and therapy

References

1 Rasch EK, Hirsch R, Paulose-Ram R, Hochberg MC. *Prevalence of rheumatoid arthritis in persons 60 years of age and older in the United States: Effect of different methods of case classification.* Arthritis Rheum. 2003;48:917-26.

2 Woolf AD, Pfleger B. *Burden of major musculoskeletal conditions.* Bull World Health Organ. 2003;81:646-56.

3 Mishto M, Santoro A, Bellavista E, Bonafé M, Monti D, Franceschi C. *Immunoproteasomes and immunosenescence.* Ageing Res Rev. 2003;2:419-32 [Proteolysis in Ageing and Age Related Disease].

4 Johnson SA, Cambier JC. *Ageing, autoimmunity and arthritis: Senescence of the B cell compartment – implications for humoral immunity.* Arthritis Res Ther. 2004;6:131-9.

5 Alberti S, Cevenini E, Ostan R, Capri M, Salvioli S, Bucci L, et al. *Age-dependent modifications of Type 1 and Type 2 cytokines within virgin and memory CD4+ T cells in humans.* Mech Ageing Dev. 2006;127:560-6.

6 Innala L, Berglin E, Möller B, Ljung L, Smedby T, Södergren A, et al. *Age at onset determines severity and choice of treatment in early rheumatoid arthritis: a prospective study.* Arthritis Res Ther. 2014;16:R94.

7 Bukhari M, Lunt M, Barton A, Bunn D, Silman A, Symmons D. *Increasing age at symptom onset is associated with worse radiological damage at presentation in patients with early inflammatory polyarthritis.* Ann Rheum Dis. 2007;66:389-93.

8 Calvo-Alén J, Corrales A, Sánchez-Andrada S, Fernández-Echevarría MA, Peña JL, Rodríguez-Valverde V. *Outcome of late-onset rheumatoid arthritis.* Clin Rheumatol. 2005;24:485-9.

9 Khanna D, Ranganath VK, FitzGerald J, Park GS, Altman RD, Elashoff D, et al. *Increased radiographic damage scores at the onset of seropositive rheumatoid arthritis in older patients are associated with osteoarthritis of the hands, but not with more rapid progression of damage.* Arthritis Rheum. 2005;52:2284-92.

10 Kuiper S, van Gestel AM, Swinkels HL, de Boo TM, da Silva JA, van Riel PL. *Influence of sex, age, and menopausal state on the course of early rheumatoid arthritis.* J Rheumatol. 2001;28:1809-16.

11 Van der Heijde DM, van Riel PL, van Leeuwen MA, van't Hof MA, van Rijswijk MH, van de Putte LB. *Older versus younger onset rheumatoid arthritis: results at onset and after 2 years of a prospective follow up study of early rheumatoid arthritis.* J Rheumatol. 1991;18:1285-9.

12 Pease CT, Bhakta BB, Devlin J, Emery P. *Does the age of onset of rheumatoid arthritis influence phenotype? A prospective study of outcome and prognostic factors.* Rheumatology. 1999;38:228-34.

13 Hellier J-P, Eliaou J-F, Daurès J-P, Sany J, Combe B. *HLA-DRB1 genes and patients with late onset rheumatoid arthritis.* Ann Rheum Dis. 2001;60:531-3.

14 El-Labban AS, Omar HASA, EL-Shereif RR, Ali F, El-Mansoury TM. *Pattern of young and old onset rheumatoid arthritis (YORA and EORA) among a group of Egyptian patients with rheumatoid arthritis.* Clin Med Insights Arthritis Musculoskelet Disord. 2010;3:25-31.

15 Terao C, Ohmura K, Ikari K, Kawaguchi T, Takahashi M, Setoh K, et al. T*he effects of smoking and shared epitope on the production of ACPA and RF in a Japanese adult population: The Nagahama Study.* Arthritis Care Res. 2014;66:1818-27.
16 Tamas M-M, Felea I, Rednic S. *How much difference does the age at onset make in early arthritis patients? Comparison between the ACR 1987 and the ACR/EULAR 2010 classification criteria for rheumatoid arthritis at the time of diagnosis.* Rheumatol Int. 2013;33:2881-4.
17 Chen D-Y, Hsieh T-Y, Chen Y-M, Hsieh C-W, Lan J-L, Lin F-J. *Proinflammatory cytokine profiles of patients with elderly-onset rheumatoid arthritis: a comparison with younger-onset disease.* Gerontology. 2009;55:250-8.
18 Radovits BJ, Fransen J, van Riel PLCM, Laan RFJM. *Influence of age and gender on the 28-joint Disease Activity Score (DAS28) in rheumatoid arthritis.* Ann Rheum Dis. 2008;67:1127-31.
19 Cho S-K, Sung Y-K, Choi C-B, Cha H-S, Choe J-Y, Chung WT, et al. *Do patients with elderly-onset rheumatoid arthritis have severe functional disability?* Semin Arthritis Rheum. 2012;42:23-31.
20 Turkcapar N, Demir O, Atli T, Kopuk M, Turgay M, Kinikli G, et al. *Late onset rheumatoid arthritis: clinical and laboratory comparisons with younger onset patients.* Arch Gerontol Geriatr. 2006;42:225-31.
21 Krabben A, Stomp W, Huizinga TWJ, Heijde D van der, Bloem JL, Reijnierse M et al. *Concordance between inflammation at physical examination and on MRI in patients with early arthritis.* Ann Rheum Dis. 2015:74:506-12. doi: 10/1136/ annrheumdis-2013-204005.
22 Krabben A, Stomp W, van Nies JAB, Huizinga TWJ, van der Heijde D, Bloem JL, et al. *MRI-detected subclinical joint inflammation is associated with radiographic progression.* Ann Rheum Dis. 2014;73:2034-7.
23 de Rooy DPC, van der Linden MPM, Knevel R, Huizinga TWJ, van der Helm Mil AHM. *Predicting arthritis outcomes–what can be learned from the Leiden Early Arthritis Clinic?* Rheumatology. 2011;50:93-100.
24 Sharp JT, Wolfe F, Mitchell DM, Bloch DA. *The progression of erosion and joint space narrowing scores in rheumatoid arthritis during the first twenty-five years of disease.* Arthritis Rheum. 1991;34:660-8.
25 Innala L, Kokkonen H, Eriksson C, Jidell E, Berglin E, Rantapää-Dahlqvist S. *Antibodies against mutated citrullinated vimentin are a better predictor of disease activity at 24 months in early rheumatoid arthritis than antibodies against cyclic citrullinated peptides.* J Rheumatol. 2008;35:1002-8.
26 Fex E, Jonsson K, Johnson U, Eberhardt K. *Development of radiographic damage during the first 5-6 yr of rheumatoid arthritis. A prospective follow-up study of a Swedish cohort.* Rheumatology. 1996;35:1106-15.
27 Knevel R, Tsonaka R, le Cessie S, van der Linden M, Huizinga T, van der Heijde D, et al. *Comparison of methodologies for analysing the progression of joint destruction in rheumatoid arthritis.* Scand J Rheumatol. 2013;42:182-9.
28 Østergaard M, Peterfy C, Conaghan P, McQueen F, Bird P, Ejbjerg B, et al. *OMERACT rheumatoid arthritis magnetic resonance imaging studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI-scoring system.* J Rheumatol. 2003;30:1385-6.

29 Haavardsholm EA, Østergaard M, Ejbjerg BJ, Kvan NP, Kvien TK. *Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study.* Ann Rheum Dis. 2007;66:1216-20.
30 Baan H, Bezooijen R, Avenarius JKA, Dubbeldam R, Drossaers-Bakker WK, van de Laar MAFJ. *Magnetic resonance imaging of the rheumatic foot according to the RAMRIS system is reliable.* J Rheumatol. 2011;38:1003-8.
31 Knevel R, de Rooy DPC, Zhernakova A, Gröndal G, Krabben A, Steinsson K, et al. *Association of variants in IL2RA with progression of joint destruction in rheumatoid arthritis.* Arthritis Rheum. 2013;65:1684-93.
32 Larsen A, Dale K, Eek M. *Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films.* Acta Radiol Diagn (Stockh). 1977;18:481-91.
33 Larsen A. *How to apply Larsen score in evaluating radiographs of rheumatoid arthritis in long-term studies.* J Rheumatol. 1995;22:1974-5.
34 Knevel R, Krabben A, Brouwer E, Posthumus MD, Wilson AG, Lindqvist E, et al. *Genetic variants in IL15 associate with progression of joint destruction in rheumatoid arthritis: a multicohort study.* Ann Rheum Dis. 2012;71:1651-7.
35 Rau R, Herborn G. *A modified version of Larsen's scoring method to assess radiologic changes in rheumatoid arthritis.* J Rheumatol. 1995;22:1976-82.
36 Baron RM, Kenny DA. T*he moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations.* J Pers Soc Psychol. 1986;51:1173-82.
37 Van der Linden MPM, le Cessie S, Raza K, van der Woude D, Knevel R, Huizinga TWJ, et al. *Long-term impact of delay in assessment of patients with early arthritis.* Arthritis Rheum. 2010;62:3537-46.
38 Nies JAB van, Krabben A, Schoones JW, Huizinga TWJ, Kloppenburg M, Mil AHM van der H. *What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review.* Ann Rheum Dis 2014;73:861-70. doi: 10.1136/annrheumdis-2012-203130.
39 Haavardsholm EA, Bøyesen P, Østergaard M, Schildvold A, Kvien TK. *Magnetic resonance imaging findings in 84 patients with early rheumatoid arthritis: bone marrow oedema predicts erosive progression.* Ann Rheum Dis. 2008;67:794-800.
40 Kuijper TM, Luime JJ, Alves C, Barendregt PJ, van Zeben J, Bindels PJE, et al. *Quality of life and health care use in patients with arthralgias without synovitis compared with patients diagnosed with early rheumatoid arthritis: data from an early arthritis cohort.* Arthritis Care Res. 2014;66:379-86.
41 Salaffi F, Carotti M, Gasparini S, Intorcia M, Grassi W. *The health-related quality of life in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis: a comparison with a selected sample of healthy people.* Health Qual Life Outcomes. 2009;7:25.
42 Mangnus L, Schoones JW, van der Helm-van Mil AHM. FRI0210 *What is the prevalence of MRI-detected features in small joints in the general population? A literature review.* Ann Rheum Dis. 2014;73:458-8.
43 Fraenkel L, Rabidou N, Dhar R. *Are rheumatologists' treatment decisions influenced by patients' age?* Rheumatol Oxf Engl. 2006;45:1555-7.

44 Radovits BJ, Fransen J, Eijsbouts A, van Riel PLCM, Laan RFJM. *Missed opportunities in the treatment of elderly patients with rheumatoid arthritis.* Rheumatology. 2009;48:906-10.
45 Mueller RB, Kaegi T, Finckh A, Haile SR, Schulze-Koops H, von Kempis J. *Is radiographic progression of late-onset rheumatoid arthritis different from young-onset rheumatoid arthritis? Results from the Swiss prospective observational cohort.* Rheumatology. 2014;53:671-7.
46 Huscher D, Sengler C, Gromnica-Ihle E, Bischoff S, Eidner T, Ochs W, et al. *Clinical presentation, burden of disease and treatment in young-onset and late-onset rheumatoid arthritis: a matched-pairs analysis taking age and disease duration into account.* Clin Exp Rheumatol. 2013;31:256-62.
47 Harrison MJ, Kim CA, Silverberg M, Paget SA. *Does age bias the aggressive treatment of elderly patients with rheumatoid arthritis?* J Rheumatol. 2005;32:1243-8.

Table 1 Characteristics of patients with rheumatoid arthritis included in the longitudinal cohorts studied

	EAC Part 1	EAC Part 2 (MRI)	Wichita	Umeå	Groningen	Lund
Total n of patients	698	56	293	459	278	147
Total n of radiographs	3.643	105	1.062	868	865	781
Mean n of radiographs per patient (SD)	5.2 (2.1)	1.9 (0.3)	3.6 (2.0)	1.9 (0.3)	3.1 (1.4)	5.3 (0.8)
Year of diagnosis	1993-2006	2010-2012	1963-1999	1995-2010	1945-2001	1985-1989
Radiographic follow-up in years	7	1	15	2	14	5
Method of scoring	SHS	SHS	SHS	Larsen	SHS	Larsen
Age						
Mean (SD)	56.6 (15.6)	55.9 (14.2)	48.8 (14.2)	53.9 (14.5)	49.3 (12.6)	50.7 (11.5)
Median (IQR)	58 (46-68)	59 (46-65)	49(39-60)	56 (45-64)	50 (40-59)	51 (43-59)
Range	17.1-92.4	21.5-77.8	16.0-83.0	17.0-83.0	18.3-76.3	18.0-78.0
Female sex (%)	474 (67.8)	31 (55.4)	226 (77.1)	321 (69.2)	196 (70.5)	98 (66.7)
Symptom duration in weeks (IQR)	19 (11-37)	18 (11-32)	NA	NA	NA	43 (29-62)
TJC (IQR)	8(5.0-12.0)	7(4.-10.5)	NA	NA	NA	NA
SJC (IQR)	8(4.0-14.0)	5(3.5-10.0)	NA	NA	NA	NA
BSE (IQR)	33(19-54)	25(10-41)	NA	NA	NA	NA
CRP (IQR)	17(8.0-40.0)	11(3.0-20.5)	NA	NA	NA	NA
ACPA positivity (%)	365(53.7)	33 (63.5)	238 (82.1)	339 (73.1)	162 (79.4)	114 (80.3)
RF positivity (%)	405 (58.2)	36 (64.3)	NA	NA	259 (93.8)	115 (80.3)

Age, symptom duration, TJC, SJC, ESR, CRP, ACPA and RF were assessed at baseline.
EAC, Early Arthritis Clinic;
MRI, magnetic resonance imaging;
TJC, tender joint count;
SJC, swollen joint count; CRP, C-reactive protein;
ESR, erythrocyte sedimentation rate;
ACPA, anti-citrullinated peptide antibodies;
RF, rheumatoid factor;
SHS, Sharp-van der Heijde.

Table 2 Mediation analysis in 698 patients with rheumatoid arthritis from the Leiden Early Arthritis Clinic, with radiographic severity of joint damage over 7 years as the outcome variable

	Effect (β)1	95% CI	p-value
Step 1: Effect of age on possible mediators			
SJC	1.00	1.00-1.01	0.11
TJC	1.00	1.00-1.01	0.55
Symptom duration	0.992	0.988-0.996	‹0.001
CRP	1.016	1.011-1021	‹0.001
RF	0.99	0.98-1.00	0.09
ACPA	0.98	0.97-0.99	‹0.001
Step 2: Effect of age on radiographic joint damage			
Ageing	1.034	1.029-1.040	‹0.001
Step 3: Effect of age and possible mediator on radiographic joint damage			
SJC	1.00	0.99-1.00	0.23
Ageing	1.035	1.029-1.040	‹0.001
TJC	1.00	0.98-1.01	0.76
Ageing	1.037	1.030-1.044	‹0.001
Symptom duration	1.003	1.002-1.005	‹0.001
Ageing	1.035	1.029-1.040	‹0.001
CRP	1.003	1.001-1.005	0.003
Ageing	1.033	1.027-1.038	‹0.001
ACPA	1.37	1.16-1.60	‹0.001
Ageing	1.035	1.030-1.040	‹0.001
RF	1.30	1.10-1.52	0.002
Ageing	1.034	1.029-1.039	‹0.001

The effect size (β) of swollen joint count (SJC), tender joint count (TJC), symptom duration and C-reactive protein (CRP) reflect the increase per year increase of age. For example, the β for CRP is 1.016 this means that for every year increase in age there is 1.016-fold increase in CRP. A β of 0.992 indicates an increase 0.992- fold, hence actually a decrease. The effect size of anticitrullinated protein antibody (ACPA) and rheumatoid factor (RF) reflect the odds ratio. Step 1, 2 and 3 of the mediation analyses are explained in Fig. 1. In step 1 a linear or logistic regression was used, in step 2 and 3 a multivariate normal regression analysis was used.[27] Also here the effects are per unit. For example, the β for age on joint damage is 1.034/year this means that for every year increase in age there is an increase of 3.4% this is equal to an increase of 95.2% every 20 years (1.034^20). All features (SJC, TJC, ACPA, RF, symptom duration, and age) were assessed at baseline.

Table 3 Mediation analysis in 56 patients with rheumatoid arthritis from the Leiden Early Arthritis Clinic, with radiographic severity of joint damage as the outcome variable

	Effect (β)	95% CI	p-value
Step 1: Effect of age on possible mediators			
MRI inflammation	1.018	1.002-1.034	0.027
Synovitis	1.011	1.00-1.024	0.092
BME	1.021	1.00-1.043	0.052
Step 2: Effect of age on radiographic joint damage			
Ageing	1.032	1.010-1.055	0.004
Step 3: Effect of age and possible mediator on radiographic joint damage			
MRI inflammation	1.026	1.004-1.047	0.018
Ageing	1.025	1.004-1.047	0.021
Synovitis	1.069	0.97-1.17	0.15
Ageing	1.029	1.007-1.051	0.011
BME	1.039	1.011-1.067	0.007
Ageing	1.026	1.005-1.047	0.014

Step 1, 2 and 3 are explained in Fig. 1.

In step 1 a linear regression is used, in step 2 and 3 a multivariate normal regression analysis is used.[27] The effects are per unit increase, for example per point increase in rheumatoid arthritis magnetic resonance imaging score (RAMRIS) and per year increase in age; for further explanation see legend of Table 2.

MRI, magnetic resonance imaging;

BME bone marrow edema

Chapter 5: Body mass index and extent of MRI-detected inflammation: opposite effects in rheumatoid arthritis versus other arthritides and asymptomatic persons

L. Mangnus

W.P. Nieuwenhuis

H.W. van Steenbergen

T.W.J. Huizinga

M. Reijnierse

A.H.M. van der Helm-van Mil

Arthritis research therapy, 2016

Abstract

Introduction: In the population a high body mass index (BMI) has been associated with slightly increased inflammatory markers. Within rheumatoid arthritis (RA), however, a high BMI has been associated with less radiographic progression; this phenomenon is unexplained. We hypothesized that the phenomenon is caused by an inverse relationship between BMI and inflammation in hand and foot joints with RA. To explore this hypothesis, local inflammation was measured using magnetic resonance imaging (MRI) in early arthritis patients presenting with RA or other arthritides and in asymptomatic volunteers.

Methods: A total of 195 RA-patients, 159 patients with other inflammatory arthritides included in the Leiden Early Arthritis Clinic, and 193 asymptomatic volunteers underwent a unilateral contrast-enhanced 1.5 T MRI-scan of metacarpophalangeal, wrist, and metatarsophalangeal joints. Each MRI-scan was scored by two readers on synovitis, bone marrow edema (BME), and tenosynovitis; the sum yielded the total MRI inflammation score. Linear regression on log-transformed MRI-data was used.

Results: A higher BMI was associated with higher MRI inflammation scores in arthritides other than RA ($\beta = 1.082$, $p < 0.001$) and in asymptomatic volunteers ($\beta = 1.029$, $p = 0.040$), whereas it was associated with lower MRI inflammation scores in RA ($\beta = 0.97$, $p = 0.005$). Evaluating the different types of inflammation, a higher BMI was associated with higher synovitis, BME, and tenosynovitis scores in arthritides other than RA (respectively $\beta = 1.084$, $p < 0.001$, $\beta = 1.021$, $p = 0.24$, and $\beta = 1.054$, $p = 0.003$), but with lower synovitis and BME-scores in RA (respectively $\beta = 0.98$, $p = 0.047$ and $\beta = 0.95$, $p = 0.002$).

Conclusions: Increased BMI is correlated with less severe MRI-detected synovitis and BME in RA. This might explain the paradox in RA where obesity correlates with less severe radiographic progression.

Background

The prevalence of obesity is increasing worldwide. It has become evident that adipose tissue is an active organ, producing proinflammatory cytokines and adipocytokines. A population-based study has shown that a high body mass index (BMI) is associated with increased inflammatory markers, such as C-reactive protein (CRP).[1] Obesity is also associated with an increased risk for several diseases, among which is cardiovascular disease, in which low-grade inflammation is part of the pathogenesis. Furthermore, recent data have revealed that obesity is also associated with an increased risk for rheumatoid arthritis (RA).[2]

Interestingly, however, although obese persons have a higher risk to develop RA, the presence of obesity within RA has been shown advantageous. Several studies have observed and replicated that a higher BMI is associated with less severe radiographic joint progression in RA.[3-6] The mechanisms underlying this observation are unknown. Data from a recent clinical trial in RA, evaluating drug efficacy with magnetic resonance imaging (MRI) to measure the disease outcome, suggested that patients with a higher BMI have less severe bone marrow edema (BME) on MRI.[3] BME is strongly associated with erosive progression [7], which may explain the finding of BMI and radiographic progression in RA. Together these observations prompted us to study the association between BMI and MRI-detected joint inflammation in more detail.

This cross-sectional study investigated the association between BMI and inflammation in hand and foot joints detected by MRI at disease presentation; we hypothesized that a higher BMI is associated with less severe local inflammation in RA. Because an advantageous effect of BMI has only been observed thus far in RA, we also evaluated the association between BMI and MRI-detected inflammation differed in RA-patients compared with patients with other inflammatory arthritides or with asymptomatic volunteers.

Methods

Participants

Three groups were studied. Firstly, RA-patients who were consecutively included in the Leiden Early Arthritis Clinic (EAC) cohort between August 2010 and October 2014. Secondly, early arthritis patients with other inflammatory diagnoses who were included in the same cohort in the same time period. Thirdly, asymptomatic volunteers who were recruited from the general population.

The EAC-cohort is an inception cohort of early arthritis patients presenting with clinically detected arthritis of ≥ 1 joint and symptom duration < 2 years.[8] At baseline, questionnaires were filled, physical examination was performed (including weight and height), blood samples were obtained, and MRI was performed. RA was defined as fulfilling the 1987 ACR criteria during the first year of follow-up.

The asymptomatic volunteers were recruited between November 2013 and December 2014.[9] Volunteers were recruited via advertisements in local newspapers and websites. The volunteers had no history of RA or other inflammatory rheumatic diseases, no joint symptoms during the last month, and no clinically detectable arthritis at physical examination. Participants received a voucher of €20 to compensate for their time and travel costs and did not receive a report of the MRI-results. Therefore, volunteers had no/limited benefit from participating.

MRI-protocol and scoring

On an ONI-MSK-extreme 1.5 T extremity MRI machine (General Electric, WI, USA), imaging was performed of the unilateral metacarpophalangeal (MCP) 2-5 joints, wrist joints, and metatarsophalangeal (MTP) 1-5 joints. In patients the most painful side was scanned or, in case of equally severe symptoms on both sides, the dominant side. In asymptomatic volunteers, the dominant side was scanned. According to the protocol, the MRI-scan was performed before the 2-week visit in which patients receive their diagnosis, and the median time between the first visit and the MRI-scan was 8 days. Furthermore, patients were asked to stop NSAIDS 24 hours prior to the MRI-scan. The following sequences were acquired: T1 fast-spin echo (T1), T2-weighted fat saturated (T2), and, after intravenous contrast administration

(gadoteric acid, 0.1 mmol/kg; Guerbet, Paris, France), T1 fast-spin echo with fat saturation (T1 Gd). A detailed scan protocol is provided in Additional file 1. Scoring was carried out according to the RAMRIS for synovitis and BME in the MCP, wrist, and MTP joints and according to Haavardsholm et al. for tenosynovitis in the MCP and wrist.[10, 11] The total MRI inflammation score was calculated by summing the synovitis, BME, and tenosynovitis scores. MRI-scoring of the arthritis patients was done independently by two trained readers (WPN and ECN) and the asymptomatic volunteers were scored independently by two trained readers (HWvS and LM). All readers were trained before the start of this project. Readers were blinded for any clinical data. MRI images of asymptomatic volunteers were blinded and mixed with MRI images of RA-patients and patients with arthralgia without clinical synovitis (n = 99), to exclude observer bias scoring introduced by knowledge that persons had no symptoms. The within-reader intraclass correlation coefficients (ICC) for the readers who scored the arthritis patients were 0.98 and 0.93, and for the readers who scored the asymptomatic volunteers these were 0.98 and 0.99. The between-reader ICC of the four readers were all above 0.91 (Additional file 2). The mean scores of two readers were used for the analyses.

Analyses

Associations between MRI-detected inflammation and BMI were assessed using univariable and multivariable linear regression analyses. The MRI inflammation scores were log10-transformed (log10(score + 1)) to approximate a normal distribution. Thereafter, BMI was divided into three categories according to the World Health Organization (WHO) definition: low-normal weight (< 25 kg/m^2), overweight (≥ 25 to < 30 kg/m^2), and obese (≥ 30 kg/m^2). The Kruskal-Wallis test, Mann-Whitney U test, linear regression models, and Spearman rank correlation coefficient were used as appropriate. SPSS V23.0.0 was used.

In RA-patients treated in a trial, an association between BMI and BME was observed [3]. We sought to compare our findings in an unselected RA population at disease presentation with these results. In order to do so, we performed a multivariable ordinal logistic regression model in which BME was categorized into quintiles, similar to that done in the trial.[3]

Results

Participants

In total, 202 RA-patients and 170 early arthritis patients with other inflammatory diagnoses were consecutively included in the Leiden EAC. Five RA-patients and eight other arthritis patients had no information on height or weight and, respectively, two and three patients had an MRI-scan without contrast enhancement and were excluded. Therefore, 195 RA-patients and 159 arthritis patients with other inflammatory diagnoses were evaluated.In addition, 196 asymptomatic volunteers were recruited, as already described, three of whom did not receive an MRI-scan due to personal problems (n = 1), vasovagal collapse at intravenous puncture (n = 1), and anxiety (n = 1).

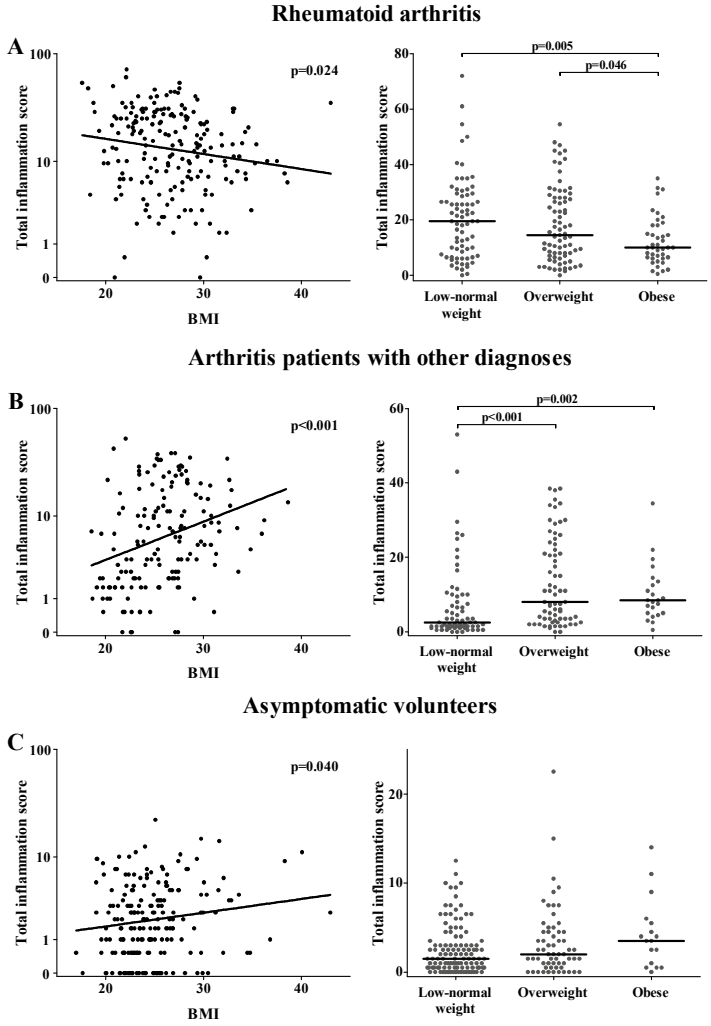
Baseline characteristics of all participants are presented in Table 1. Seventy-nine (41%) RA-patients were overweight (BMI > 25 to < 30 kg/m^2) and 41 (21%) were obese (≥ 30 kg/m^2); in other arthritis patients these percentages were respectively 44% (n = 70) and 14% (n = 23), and in asymptomatic volunteers these percentages were 32% (n = 61) and 9% (n = 17) respectively.

BMI and MRI-detected inflammation

The median MRI inflammation score in RA-patients was 14.5 (IQR = 7.0-26.5), in other arthritis patients the median was 6.0 (IQR = 2.0-15.0), and in asymptomatic volunteers the median was 2.0 (IQR = 0.5-4.5, p < 0.001), showing that RA-patients had the highest MRI inflammation scores.

In RA-patients, a higher BMI was associated with lower MRI inflammation scores (β = 0.97, p = 0.024). A β value of 0.97 indicates that for every point increase in BMI there is a 0.97-fold increase in MRI inflammation score; thus higher BMI was associated with less severe MRI inflammation. In contrast, in other arthritis patients and in asymptomatic volunteers, a higher BMI was associated with higher MRI inflammation scores (respectively β = 1.082, p < 0.001 and β = 1.029, p = 0.040; Fig. 1). When BMI was categorized into three groups (low-normal weight, overweight, and obese), similar results were obtained. Obese RA-patients had significantly lower MRI inflammation scores (median = 10.0, IQR = 6.5- 18.0) compared with low-nor-

Figure 1 The association between BMI (both when presented on a continuous scale or categorized) and MRI-detected inflammation is different in early RA-patients (A) compared to early arthritis patients with other diagnoses (B) and asymptomatic volunteers (C)



Total inflammation score were log transformed for regressions. Regression coefficients presented are back-transformed (10^β and 10^95%CI). In RA-patients the back-transformed regression coefficient is 0.97 (95%CI 0.94-1.00; A.1.). In arthritis patients with other diagnoses the coefficients is 1.082 (95%CI 1.041-1.13; B.1.) and in asymptomatic volunteers it was 1.029 (95%CI 1.001-1.057; C.1.), The lines presented in figure A.2., B.2., and C.2. represent median values.

mal weight RA-patients (median = 19.5, IQR = 7.5-29.0, p = 0.005) and overweight RA-patients (median = 14.5, IQR = 7.0-28.0, p = 0.046). Within the group of other early arthritis patients, obese patients had higher total MRI inflammation scores (median = 8.5, IQR = 5.0-13.5) compared with patients with a low-normal weight (median = 2.5, IQR = 0.5-9.5, p = 0.002). Similarly, overweight was also associated with higher total MRI inflammation scores (median = 8.0, IQR = 3.5-22.0, p < 0.001). Within asymptomatic volunteers a tendency towards higher inflammation scores was seen in obese persons (median = 3.5, IQR = 1.0-5.5) compared with low-normal weight persons (median = 1.5, IQR = 0.5-3.5, p = 0.064) and overweight persons (median = 2.0, IQR = 1.0-4.5, p = 0.24; Fig. 1).

Thereafter, the association between BMI (measured continuously) and MRI-detected inflammation was adjusted for age and gender, also showing that a higher BMI was associated with higher inflammation scores in other early arthritis patients (β = 1.036, p = 0.054) and asymptomatic volunteers (β = 1.022, p = 0.040) but with lower inflammation scores in RA-patients (β = 0.96, p = 0.005; Table 2 (for nonback-transformed β values, see Additional file 3)). After additional adjustments for CRP and anti-citrullinated protein antibody (ACPA) the results remained similar (β = 0.96, p = 0.003 for RA-patients and β = 1.039, p = 0.043 for other early arthritis patients).

The group of early arthritis patients with diagnoses other than RA was divided into the following six subgroups: inflammatory osteoarthritis (n = 38), spondyloarthritis with peripheral arthritis and psoriatic arthritis (n = 40), systemic lupus erythematosus/mixed connective tissue disease and other systemic disease (n = 20), reactive arthritis and lyme arthritis (n = 17), gout and pseudogout (n = 19), and other diseases (n = 25). These subgroups were studied to assess whether the association was more pronounced in a particular disease group. However, the directionality of the effect was similar in all subgroups (Additional file 4).

BMI and different types of MRI inflammation

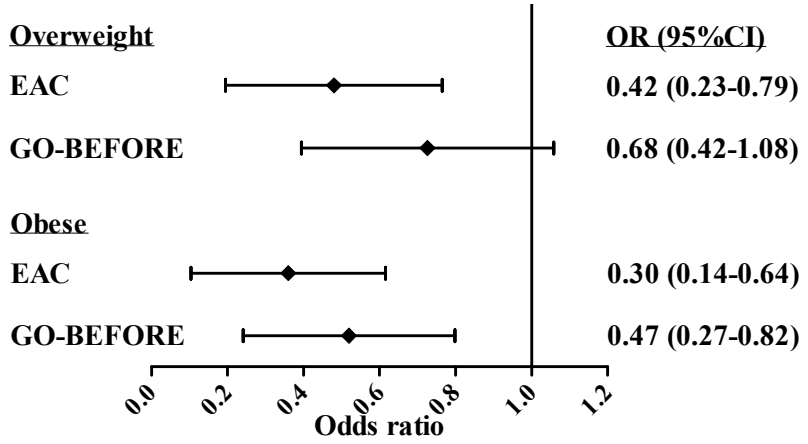
The total MRI inflammation score is composed of the synovitis, tenosynovitis, and BME-scores. To assess whether synovitis, BME, and tenosynovitis have different associations with BMI, these types of inflammation were assessed separately. The

synovitis score showed a negative association with BMI in RA-patients (β = 0.98, p = 0.047) and a positive association in other arthritis patients and in asymptomatic volunteers (β = 1.084, p < 0.001 and β = 1.031, p = 0.006 respectively). A higher BMI was associated with lower BME in RA-patients (β = 0.95, p = 0.002). In other arthritis patients and in asymptomatic volunteers, BMI was not associated with BME-scores (respectively β = 1.021, p = 0.24 and β = 1.003, p = 0.79). Within other arthritis patients and in asymptomatic volunteers there was a positive association between BMI and the tenosynovitis score (β = 1.054, p = 0.003 and β = 1.021, p = 0.003 respectively), whereas BMI was not associated with tenosynovitis in RA (β = 0.98, p = 0.21; Additional file 5).

Further analyses in BMI and BME

Recently, an inverse association between BMI and BME was shown in RA-patients who were treated in a trial.[3] The median BME-scores of patients included in this trial and who were low-normal weight, overweight, and obese patients were

Figure 2 Association of overweight and obesity with BME compared to low-normal weight in RA-patients included the EAC-cohort and the GO-BEFORE trial[3] summarized.



BMI was categorized in three groups, low-normal weight (< 25 kg/m²), overweight (≥ 25 to < 30 kg/m²) and obese (≥ 30 kg/m²). Odds ratios were calculated with low/normal weight as the reference category.

respectively 9 (IQR 2.5-19), 6.3 (IQR 2.5-13), and 4.8 (IQR 1.5-9.8).[3] We wished to compare these recent results with our findings obtained in an unselected set of RA-patients at the time of disease onset. The median scores observed in our cohort showed a similar tendency but were lower; the median scores in the three groups were respectively 5.0 (IQR 2.0-11.0), 3.0 (IQR 1.0-9.0), and 2.0 (IQR 1.0-4.5). The trial data showed that, after adjusting for race, ACPA, disease duration, DAS, age, and sex, overweight patients had an odds ratio (OR) of 0.68 (95% CI 0.42- 1.08, p = 0.1) and obese patients an OR of 0.47 (95% CI 0.27-0.82, p = 0.008) for being in a higher BME quintile (Fig. 2). We performed the same analyses without adjusting for race because our study population consisted of 96% Caucasians, and without disease duration because all of our early arthritis patients were evaluated at their first presentation to the rheumatologic outpatient clinics. In our data, overweight patients had an OR of 0.42 (95% CI 0.23-0.79, p = 0.007) and obese patients had an OR of 0.30 (95% CI 0.14-0.64, p = 0.002) compared with low-normal weight patients (Fig. 2). Analyses of both data sets thus showed an inverse association between BMI and BME-scores.

BMI and regular measures of inflammation

The association of BMI with regular measures of inflammation was assessed in RA-patients and other arthritis patients. In RA-patients the median swollen joint count (SJC) in low-normal weight patients was 5 (IQR = 3-10), in overweight patients the median was 6 (IQR = 2-10), and in obese patients the median was 8 (IQR = 3-10; p = 0.69). The median CRP-levels in low-normal weight, overweight, and obese RA-patients were respectively 7 mg/L (IQR = 3-23 mg/L), 12 mg/L (IQR = 4-23 mg/L), and 10 mg/L (IQR = 4-24 mg/L; p = 0.39). In other arthritis patients the median of SJC in low-normal weight, overweight, and obese patients were respectively 3 (IQR = 1-5), 3 (IQR = 2-5), and 4 (IQR = 3-7; p = 0.074). Lastly, the median CRP-level in the three groups were respectively 4 mg/L (IQR = 3-18 mg/L), 4 mg/L (IQR = 3-12 mg/L), and 5 mg/L (IQR = 3-13 mg/L; p = 0.65). Therefore, in RA-patients and in other arthritis patients, BMI was neither associated with swollen SJC nor with CRP-levels.

BMI and ACPA in RA-patients

The influence of BMI on MRI-detected inflammation in ACPA-positive or ACPA-negative RA-patients was assessed separately. Although the subgroups became small (n = 107 and n = 88 respectively), the effect size of the association between BMI and MRI-detected inflammation remained unchanged (respectively $\beta = 0.97$, $p = 0.071$ and $\beta = 0.97$, $p = 0.12$ for ACPA-positive RA and ACPA-negative RA in the univariable analyses and respectively $\beta = 0.97$, $p = 0.097$ and $\beta = 0.96$, $p = 0.011$ for the analyses adjusted for age and gender).

Furthermore, the association between ACPA level and BMI was assessed with the Spearman rank test in all RA-patients. ACPA levels were not correlated with BMI ($\rho = -0.33$, $p = 0.65$) and did not differ between the three BMI categories ($p = 0.38$; Additional file 6).

Discussion

An increased BMI is associated with higher inflammatory markers in the general population [1], and a higher risk for RA-development.[2] A high BMI within RA, however, is associated with less severe radiographic joint damage.[3-6] Because joint destruction is the result of persistent inflammation, the present cross-sectional study assessed the association between BMI and MRI-detected inflammation and showed that RA-patients with a high BMI had less MRI-detected inflammation. More specifically, patients had less severe synovitis and BME. This inverse association was not observed in early arthritis patients with other inflammatory diagnoses and in asymptomatic volunteers. This suggests that the inverse association between BMI and local joint inflammation is confined to RA and may explain the previously reported observation of less severe radiographic progression in obese RA-patients. The mechanism underlying this inverse association is unknown. It can be speculated that adipocytokines play a role. It could be that the composition of the adipocytokines is different between various diseases; for example, the balance between low molecular weight versus high molecular weight adiponectin might be different. Another possibility is that the interaction between adipocytokines and immune

cells is different within RA compared with other diseases. However, we have no data to support these speculations and further studies are needed to unravel the biologic mechanism underlying our observation.

To the best of our knowledge RA is the only disease in which obese patients have less severe inflammation and progression. Also, the effect of obesity for RA is two-fold. Despite the association with less severe MRI-detected inflammation and less severe radiographic progression, obesity has been associated with a higher risk for developing RA and a lower risk for reaching persistent remission.[2, 12] Furthermore, a lower chance to achieve a low disease activity has also been observed in RA-patients that use synthetic DMARDs and biological DMARDs.[13-15] Of note, when evaluating the components of the disease activity score, the effect was only present for subjective measures (tender joint count and patient global assessment) and not for objective measures of inflammation (CRP, erythrocyte sedimentation rate, and swollen joint count).[13]

Also in the present study we observed no association between BMI and either the CRP-levels or the number of swollen joints. This illustrates that local inflammation is different from systemic inflammation and also underlines that MRI is a more sensitive method to detect local inflammation than physical examination of joints. Apparently the less severe radiographic progression in RA is paralleled by less severe local inflammation, which is detected when local inflammation is measured using a sensitive method. As such, the results of the present study suggest that MRI is not only valuable as an outcome measure in clinical trials but that MRI-studies may also help to increase our pathophysiological understanding of RA.

In line with recommendations of the ESSR [16], BME was evaluated on T1 Gd, which is different from the RAMRIS methodology using T2. Our scan protocol omitted T2 because previous studies have shown that these sequences perform equally well in the depiction of BME [17, 18] and the T1 Gd sequence allows a shorter imaging time for the patients. The present finding of similar effects of BMI in BME as observed in two different studies in which BME was assessed on different sequences (Baker et al.[3] used short tau inversion recovery (or T2 precontrast) sequences) support the notion that the findings are not influenced by the sequence used to depict BME.

This study has limitations. The BMI was used as an estimate of the adipose tissue, but differences in BMI are not only caused by differences in adipose tissue but also by differences in, for instance, muscle mass. There are methods that could make more accurate estimations in this respect, such as waist circumference, bioelectrical impedance, or computed tomography. Another important limitation is that long-term follow-up was not yet available for the RA-patients who had undergone MRI. Therefore we could not assess whether our findings at disease presentation might explain the association of BMI with less severe radiographic joint progression. In addition we could not determine the association of BMI with other disease outcomes, such as persistent remission.

Conclusions

The association between BMI and MRI-detected inflammation differs in patients with RA compared with patients with other inflammatory diagnoses and with asymptomatic controls. Within RA a higher BMI is associated with less severe MRI-detected inflammation, and this may explain the finding that obese RA-patients have less severe radiographic progression.

Supplementary material
Supplementary material is published on the website of arthritis research and therapy.

References

1 Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. *ELevated Creactive protein levels in overweight and obese adults*. JAMA. 1999;282: 2131-5.

2 Qin B, Yang M, Fu H, Ma N, Wei T, Tang Q, et al. *Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis*. Arthritis Res Ther. 2015;17:86.

3 Baker JF, Østergaard M, George M, Shults J, Emery P, Baker DG, et al. *Greater body mass independently predicts less radiographic progression on X-ray and MRI over 1-2 years*. Ann Rheum Dis. 2014;73:1923-8.

4 van der Helm-van Mil AHM, van der Kooij SM, Allaart CF, Toes REM, Huizinga TWJ. *A high body mass index has a protective effect on the amount of joint destruction in small joints in early rheumatoid arthritis*. Ann Rheum Dis. 2008;67:769-74.

5 Westhoff G, Rau R, Zink A. *Radiographic joint damage in early rheumatoid arthritis is highly dependent on body mass index*. Arthritis Rheum. 2007;56: 3575-82.

6 Kaufmann J, Kielstein V, Kilian S, Stein G, Hein G. *Relation between body mass index and radiological progression in patients with rheumatoid arthritis*. J Rheumatol. 2003;30:2350-5.

7 Nieuwenhuis WP, van Steenbergen HW, Stomp W, Stijnen T, Huizinga TWJ, Bloem JL, et al. *The course of bone marrow edema in early undifferentiated and rheumatoid arthritis; a longitudinal MRI-study on bone level*. Arthritis Rheumatol. 2016;68:1080-8.

8 de Rooy DPC, van der Linden MPM, Knevel R, Huizinga TWJ, Mil AHM van der H. *Predicting arthritis outcomes—what can be learned from the Leiden Early Arthritis Clinic?* Rheumatology. 2011;50:93-100.

9 Mangnus L, van Steenbergen HW, Reijnierse M, van der Helm-van Mil AHM. *MR-detected features of inflammation and erosions occur in symptom-free persons from the general population*. Arthritis Rheumatol. 2016. doi:10.1002/art.39749.

10 Østergaard M, Edmonds J, McQueen F, Peterfy C, Lassere M, Ejbjerg B, et al. *An introduction to the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas*. Ann Rheum Dis. 2005;64 Suppl 1:i3-7.

11 Haavardsholm EA, Østergaard M, Ejbjerg BJ, Kvan NP, Kvien TK. *Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study*. Ann Rheum Dis. 2007; 66:1216-20.

12 Ajeganova S, Andersson ML, Hafström I, for the BARFOT Study Group. *Association of obesity with worse disease severity in rheumatoid arthritis as well as with comorbidities: a long-term followup from disease onset*. Arthritis Care Res. 2013;65:78-87.

13 Sandberg MEC, Bengtsson C, Källberg H, Wesley A, Klareskog L, Alfredsson L, et al. *Overweight decreases the chance of achieving good response and low disease activity in early rheumatoid arthritis*. Ann Rheum Dis. 2014;73: 2029-33.

14 Gremese E, Carletto A, Padovan M, Atzeni F, Raffeiner B, Giardina AR, et al. *Obesity and reduction of the response rate to anti-tumor necrosis factor a in rheumatoid arthritis: an approach to a personalized medicine*. Arthritis Care Res. 2013;65:94-100.

15 Heimans L, van den Broek M, le Cessie S, Siegerink B, Riyazi N, Han KH, et al. *Association of high body mass index with decreased treatment response to combination therapy in recent-onset rheumatoid arthritis patients.* Arthritis Care Res. 2013;65:1235-42.
16 Sudoł-Szopińska I, Jurik AG, Eshed I, Lennart J, Grainger A, Østergaard M, et al. *Recommendations of the ESSR Arthritis Subcommittee for the use of magnetic resonance imaging in musculoskeletal rheumatic diseases.* Semin Musculoskelet Radiol. 2015;19:396-411.
17 Stomp W, Krabben A, van der Heijde D, Huizinga TWJ, Bloem JL, Mil AHM van der H, et al. *Aiming for a shorter rheumatoid arthritis MRI-protocol: can contrast-enhanced MRI replace T2 for the detection of bone marrow oedema?* Eur Radiol. 2014;24:2614-22.
18 Mayerhoefer ME, Breitenseher MJ, Kramer J, Aigner N, Norden C, Hofmann S. *STIR vs. T1-weighted fat-suppressed gadolinium-enhanced MRI of bone marrow edema of the knee: computer-assisted quantitative comparison and influence of injected contrast media volume and acquisition parameters.* J Magn Reson Imaging. 2005;22:788-93.

Table 1 Characteristics of early rheumatoid arthritis patients, early arthritis patients with other arthritides, and asymptomatic volunteers

	Rheumatoid arthritis (n = 195)	Arthritis patients with other arthritides (n = 159)	Asymptomatic volunteers (n = 193)
Female, N (%)	119 (66)	80 (52)	136 (70)
Age, mean (SD)	55.9 (14.6)	54.3 (17.2)	50.7 (z)
Symptom duration (months), median (IQR)	3.2 (1.8-6.8)	3.0 (1.0-6.2)	-
Current smokers, N (%)	38 (24)	29 (23)	17 (9)
BMI (kg/m^2), median (IQR)	26.4 (23.7-29.4)	25.5 (22.9-27.9)	24.1 (22.3-26.3)
WHO BMI classification, N (%)			
Low-normal weight (BMI 18.5-24.9) (%)	75 (38)	66 (42)	115 (60)
Overweight (BMI 25.0-29.9) (%)	79 (41)	70 (44)	61 (32)
Obesity (BMI ≥ 30) (%)	41 (21)	23 (14)	17 (9)
CRP (mg/L), median (IQR)	9.8 (3.7-23.0)	4.0 (3.0-15.1)	NA
ACPA positivity, N (%)	107 (55)	6 (4)	NA
RF positivity, N (%)	120 (62)	27 (17)	NA

Three (2%) RA-patients had a low weight (BMI < 18.5 kg/m^2), no patients with other arthritides had a low weight, and two (1%) asymptomatic volunteers had a low weight.
Gender was missing in 11 RA-patients; within early arthritis patients with other arthritides, gender, ACPA positivity and RF positivity was missing in respectively six, two, and three patients.
NA, not assessed;
WHO, World Health Organization;
BMI, body mass index;
CRP, C-reactive protein;
ACPA, anti-citrullinated protein antibody;
RF, rheumatoid factor;
RA, rheumatoid arthritis.

Table 2 Association of BMI with MRI-detected inflammation in patients with RA, early arthritis patients with other arthritides, and asymptomatic volunteers

	Rheumatoid arthritis (n = 195)		Other arthritides (n = 159)		Asymptomatic volunteers (n = 193)	
	β (95%CI)	p	β (95%CI)	p	β (95%CI)	p
Univariable						
BMI	0.97 (0.94-1.00)	0.024	1.082 (1.041-1.13)	‹0.001	1.029 (1.001-1.057)	0.040
Multivariable						
Model 1						
BMI	0.96 (0.94-0.99)	0.005	1.036 (1.00-1.075)	0.054	1.022 (1.001-1.044)	0.040
Age	1.025 (1.017-1.033)	‹0.001	1.033 (1.024-1.041)	‹0.001	1.031 (1.025-1.036)	‹0.001
Gender	1.13 (0.89-1.44)	0.30	0.88 (0.67-1.15)	0.34	1.010 (0.84-1.21)	0.92
Model 2						
BMI	0.96 (0.94-0.99)	0.003	1.039 (1.001-1.078)	0.043	NA	
Age	1.022 (1.014-1.030)	‹0.001	1.030 (1.021-1.039)	‹0.001	NA	
Gender	1.12 (0.89-1.41)	0.35	0.93 (0.71-1.23)	0.62	NA	
CRP	1.007 (1.003-1.012)	0.001	1.002 (0.998-1.006)	0.29	NA	
ACPA positivity	0.96 (0.77-1.20)	0.72	1.55 (0.75-3.20)	0.24	NA	

Total inflammation scores were log-transformed for regressions.
Regression coefficients presented are back-transformed (10β and 1095% CI). Therefore, the effect size (β) can be interpreted as the fold increase in MRI-detected inflammation per point increase in BMI. Thus, an effect size of ‹1 means a decrease in MRI-detected inflammation per unit increase in BMI and an effect size of ›1 means an increase in MRI-detected inflammation per unit increase in BMI. The raw beta coefficients are presented in Additional file 3.
BMI, body mass index;
MRI, magnetic resonance imaging;
RA, rheumatoid arthritis;
NA, not assessed;
CRP, C-reactive protein;
ACPA, anti-citrullinated protein antibody.

Chapter 6: Moderate use of alcohol is associated with lower levels of C-reactive protein but not with less severe joint inflammation; a cross-sectional study in early RA and healthy volunteers

L. Mangnus

H.W. van Steenbergen

W.P. Nieuwenhuis

M. Reijnierse

A.H.M. van der Helm-van Mil

Submitted

Abstract

Introduction: Moderate alcohol consumption is protective against rheumatoid arthritis (RA)-development and associated with lower levels of systemic inflammation in RA and in the general population. We therefore hypothesized that moderate alcohol consumption is associated with less severe local inflammation in joints in RA, detected by MRI. Since asymptomatic persons can have low-grade MRI-detected inflammation [1,2], we also hypothesized that alcohol consumption is associated with the extent of MRI-inflammation in asymptomatic volunteers.

Methods: 188 newly presenting RA-patients and192 asymptomatic volunteers underwent a unilateral contrast-enhanced 1.5T MRI of MCP, wrist and MTP-joints. The MRIs were scored on synovitis, bone marrow edema and tenosynovitis; the sum of these yielded the MRI-inflammation score. MRI-data was evaluated in relation to current alcohol consumption, categorized: non-drinkers, consuming 1-7 drinks/week, 8-14 drinks/week, and›14 drinks/week. Association between C-reactive protein-level and alcohol was studied in 1070 newly presenting RA-patients.

Results: Alcohol consumption was not associated with the severity of MRI-detected inflammation in hand and foot joints of RA-patients ($p = 0.55$) and asymptomatic volunteers ($p = 0.33$). A J-shaped curve was observed in the association between alcohol consumption and CRP-level, with the lowest levels in patients consuming 1-7 drinks/week ($p = 0.037$).

Conclusion: Despite the fact that moderate alcohol consumption has been shown protective against RA, and our data confirm a J-shaped association of alcohol consumption with CRP-levels in RA, alcohol was not associated with the severity of joint inflammation. The present data suggest that the pathophysiological mechanism underlying the effect of alcohol consists of a systemic effect that might not involve joints.

Introduction

In the general population moderate alcohol consumption has been associated with lower levels of systemic inflammation, as several studies have shown that alcohol consumption is associated with levels of C-reactive protein (CRP) in a J-shaped or U-shaped manner.[1,2] Individuals with an alcohol consumption of 1-2 drinks daily had the lowest CRP-levels.

In rheumatoid arthritis (RA), the influence of alcohol consumption on the risk of developing RA has been studied extensively. Moderate alcohol consumption has been associated with a decreased risk on developing RA.[3-5] The risk of developing RA was lowest in persons who consumed approximately 1 unit of alcohol per day.[3] In RA-patients, alcohol consumption was associated with lower levels of inflammatory markers (e.g., CRP and erythrocyte sedimentation rate (ESR) soluble tumor necrosis factor receptor II, Interleukin-6 (IL-6)).[6-8] For IL-6 levels a U-shaped association was also observed, with the lowest IL-6 levels in RA-patients that consumed 1 unit of alcohol per day.[6]

Within RA the effect of alcohol on local inflammation in joints has been studied once using the swollen joint count (SJC) and no evident association between alcohol consumption and the number of swollen joints was observed in 1238 RA-patients.[9] Because magnetic resonance imaging (MRI) is more sensitive than the swollen joint count to detect local inflammation [10], we anticipated that MRI is useful to detect an effect of alcohol on the severity of local inflammation in RA.

Furthermore, as the effect of alcohol on markers of systemic inflammation is also present in the general population [1] and since some asymptomatic persons of the general population also have low-graded MRI-detected inflammation [11,12], an association between alcohol and joint inflammation might not be confined to RA-patients, but even be present in asymptomatic volunteers.

Therefore, we hypothesized that moderate alcohol consumption is associated with less inflammation in hand and foot joints, visualized by MRI, both in patients with RA and in asymptomatic volunteers. The present study evaluated these two hypotheses.

Methods

Participants

The RA-patients studied were consecutively included in the Leiden Early Arthritis Clinic (EAC). This is an inception cohort that includes patients with ≥ 1 swollen joint and a symptom duration of < 2 years. When patients presented at the outpatient clinic, questionnaires were obtained that included a self-reported average number of alcohol consumptions per week (current consumption). Furthermore, physical examination was performed and blood samples were obtained.[13] RA was defined as fulfilling the 1987 ACR-criteria during the first year of follow-up. From 1993 to 2016 1244 RA-patients were included in the EAC cohort. The association between alcohol consumption and CRP was assessed in all RA-patients of whom alcohol consumption was available (1070 RA-patients). From 2010 onwards MRI was added to the study protocol [10] and the association between alcohol and MRI-detected inflammation was assessed in 188 consecutive RA-patients who underwent an MRI at baseline (See Supplementary Figure 1 for a flowchart).

The asymptomatic volunteers were recruited between November 2013 and December 2014, and were described earlier.[12] Volunteers were recruited via advertisements in local newspapers and websites. Volunteers had no history of RA or other inflammatory rheumatic diseases, no joint symptoms during the last month and no clinically detectable arthritis at physical examination. Questionnaires were obtained, including self-reported alcohol consumption. CRP-levels were not assessed in these volunteers. 193 volunteers underwent an MRI; in one of these persons no data on alcohol consumption was obtained. The volunteers received a voucher of 20€ to compensate for their time and travel costs and did not receive a report of the MRI. Therefore, volunteers had no/limited benefit from participating. The medical ethics committee of the Leiden University Medical Center approved this study and all participants have given a written informed consent.

MRI-protocol and scoring

A contrast-enhanced MRI was performed of the unilateral metacarpophalangeal (MCP) 2-5 joints, wrist joints and metatarsophalangeal (MTP) 1-5 joints. In the EAC

the most painful side was scanned or in case of equally severe symptoms at both sides the dominant side was scanned. In asymptomatic volunteers the dominant side was scanned. An ONI-MSK-extreme 1.5T extremity MRI-scanner (GE, Wisconsin, USA) was used. The scan protocol is described in more detail in the Supplementary methods. Briefly, T1-weighted sequences (T1) were acquired. After intravenous contrast administration (gadoteric acid, Guerbet, Paris, 0.1 mmol/kg) T1-weighted sequences with fat saturation (T1Gd) were performed. The foot was scanned with T2-weighted fat saturated (T2) and T1 sequences in the first 106 RA-patients and with T1Gd in the last 82 RA-patients. Scoring of synovitis and bone marrow edema (BME) was done according to the RA MRI score (RAMRIS) method in the MCP, wrist and MTP joints.[14] Tenosynovitis was scored according to Haarvardsholm et al. in the MCP and wrist.[15] The total MRI-inflammation score was calculated by summing the synovitis, BME and tenosynovitis scores, and ranged between 0 and 189. MRI-scoring was done independently by trained readers, the RA-patients were scored by two readers (WPN and ECN) and the asymptomatic volunteers were scored by two readers (HWvS and LM). Readers were blinded for any clinical data. Furthermore, to exclude observer bias introduced by knowledge that persons had no symptoms, MRI images of asymptomatic volunteers were mixed with MRI images of RA-patients and patients with arthralgia without clinical synovitis (n = 99). The within-reader intraclass correlation coefficients (ICC) of the readers were all greater than 0.93 and the between reader ICCs of the four readers were all above 0.91. The mean scores of two readers were used for the analyses.

Analyses

Alcohol consumption was categorized into 4 groups: non-drinkers, participants that consume 1-7 drinks/week, 8-14 drinks/week and >14 drinks/week, this corresponded to no, 1, 2 and more drinks daily as used is some previous studies.[3-6] Groups were compared with the Kruskal Wallis test and the Mann-Whitney U-test when appropriate. The association of alcohol consumption with MRI-detected inflammation was analysed using univariable and multivariable linear regressions adjusted for age, gender, smoking status, and anti-citrullinated protein antibody (ACPA). ACPA was not assessed in asymptomatic volunteers and the multivariable

linear regression in the asymptomatic volunteers was adjusted for age, gender, and smoking status. In the linear regression analyses MRI inflammation scores were log10-transformed (log10(score+1)) to approximate a normal distribution. To analyse whether a J-shape existed in the association between alcohol consumption and CRP-levels, a linear regression with a piecewise linear spline on 1 alcohol consumption per week was used as this fitted the data best. SPSS V23.0.0 was used for analysis.

Results

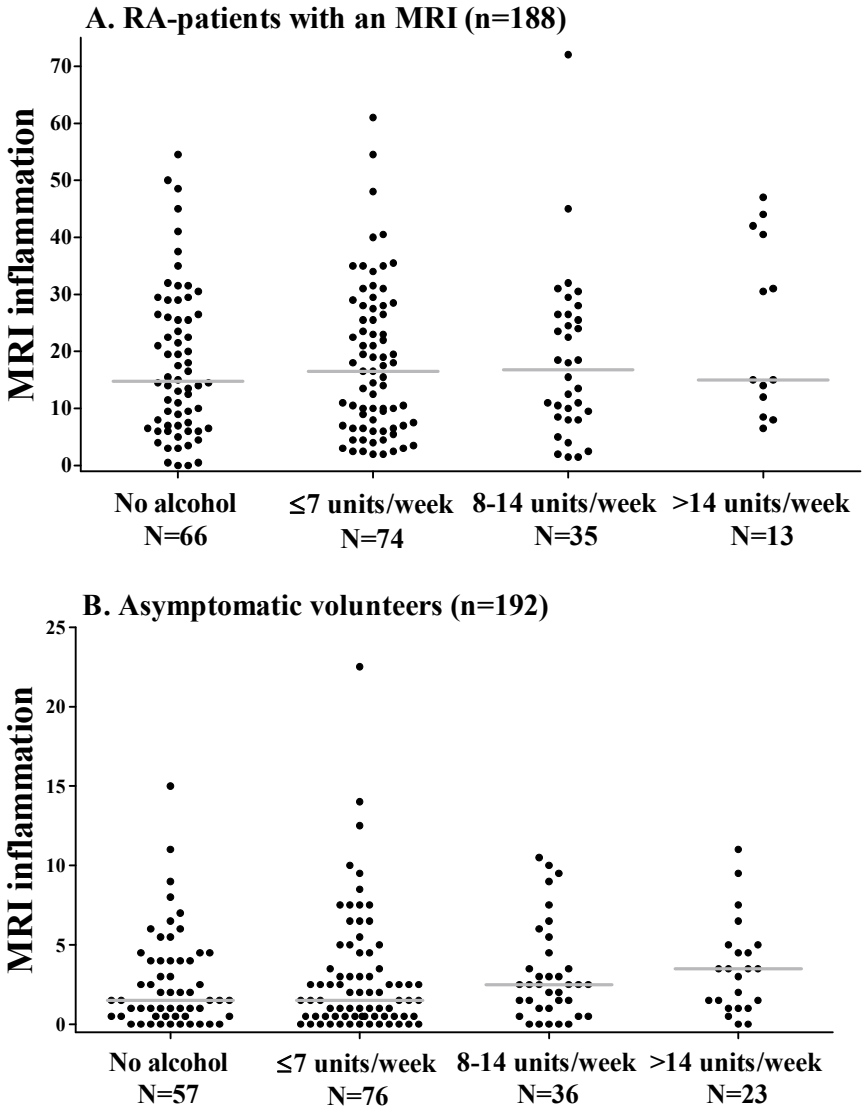
Patients

Baseline characteristics are presented in table 1. Sixty-four % (n = 121) of the RA-patients that underwent MRI (See Supplementary Figure 1 for a flowchart), consumed alcohol at baseline, with a median consumption of 6 drinks/week (IQR 3-11). Of the asymptomatic volunteers, 70% (n = 135) consumed alcohol with a median consumption of 7 drinks/week (IQR 4-14). The RA-patients consumed on average one alcohol consumption less than the asymptomatic volunteers, this difference did not reach statistical significance (p = 0.14).

The association of MRI-detected inflammation with alcohol consumption in RA-patients

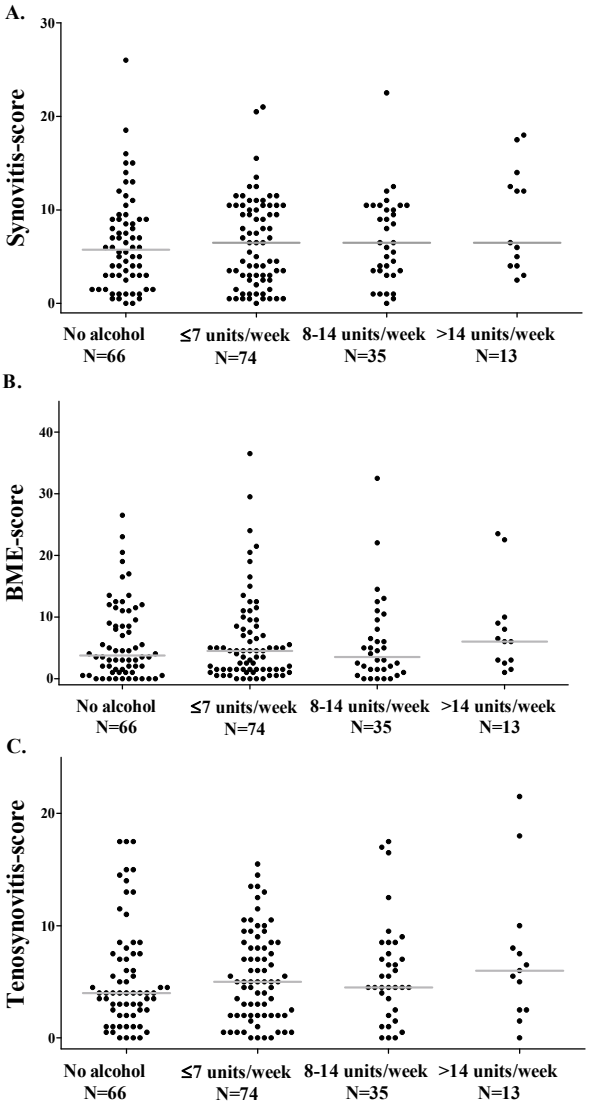
The extent of MRI-detected inflammation was first compared in 4 categories of alcohol consumption. The median MRI-detected inflammation in RA-patients did not significantly differ between the 4 categories; RA-patients who did not drink alcohol had a median MRI inflammation score of 14.8 (IQR = 7.0-26.5), RA-patients consuming ≤ 7 drinks/week had a median of 16.5 (IQR = 7.0-27.5), RA-patients consuming 8-14 drinks/week had a median of 16.8 (IQR = 8.5-26.5),and RA-patients consuming › 14 drinks/week median of median of 15.0 (IQR = 12.0-40.5), p = 0.53 (Figure 1A). When analysing BME, synovitis, and tenosynovitis separately similar results were seen (see Figure 2).

Figure 1 The association between alcohol consumption and the severity of MRI-detected inflammation in hand and foot joints of RA-patients (A), asymptomatic volunteers (B)



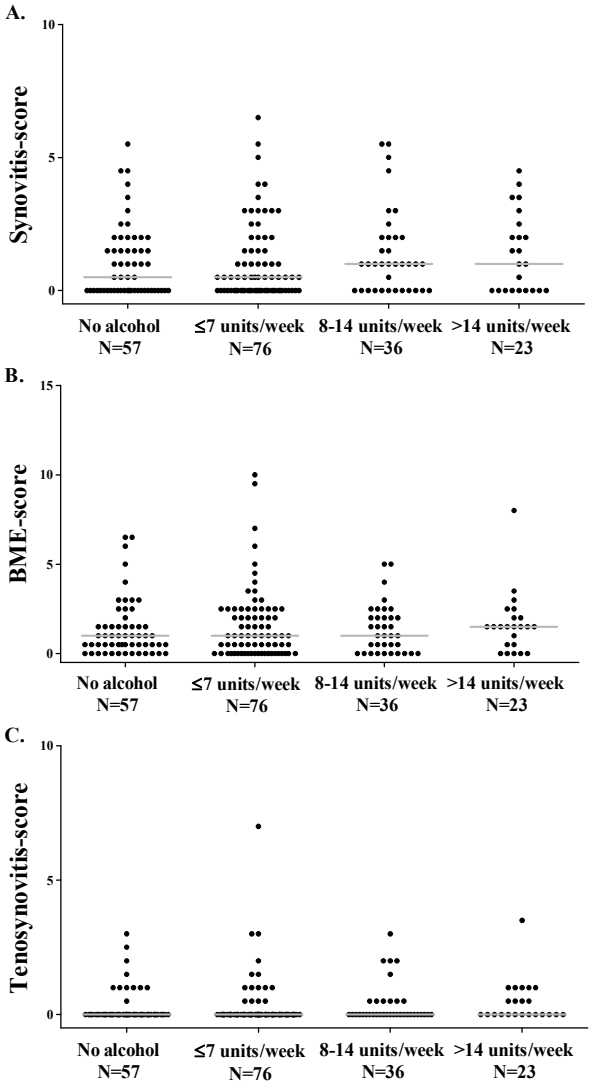
The lines presented in the figure represent median values. MRI-detected inflammation does not differ significantly between the 4 groups in RA-patients and asymptomatic volunteers (respectively $p = 0.53$ and $p = 0.33$)

Figure 2 The association between alcohol consumption and the severity of synovitis (A), BME (B) and tenosynovitis (C) in RA-patients



The lines presented in the figure represent median values. Synovitis, BME, and tenosynovitis scores did not differ significantly between the 4 groups in RA-patients (respectively p = 0.60, p = 0.47 and p = 0.85).

Figure 3 The association between alcohol consumption and the severity of synovitis (A), BME (B) and tenosynovitis (C) in asymptomatic volunteers



The lines presented in the figure represent median values. Synovitis, BME, and tenosynovitis scores did not differ significantly between the 4 groups in asymptomatic volunteers (respectively $p = 0.81$, $p = 0.44$ and $p = 0.15$).

The association between alcohol and MRI-detected inflammation was also evaluated with the number of alcohol consumptions on a continuous scale, also showing no association (β = 1.011, 95%CI = 0.992-1.030, p = 0.36). To exclude the possibility of non-significance due to the presence of confounders, the analysis was subsequently adjusted for age, gender, smoking, and ACPA. Also this showed no association between alcohol and inflammation in hand and foot joints. (β = 0.994, 95%CI = 0.975-1.013, p = 0.53).

The association of MRI-detected inflammation with alcohol consumption in asymptomatic volunteers

In asymptomatic volunteers, the extent of MRI-detected inflammation was also compared in 4 categories of alcohol consumption. The median MRI-detected inflammation did not significantly differ between the 4 categories; asymptomatic volunteers who did not drink alcohol had a median MRI inflammation score of 1.5 (IQR = 0.5-4.0), ≤ 7 drinks/week 1.5 (IQR = 0.5-4.0), 8-14 drinks/week 2.5 (IQR = 1.0-4.0), > 14 drinks/week 3.5 (IQR = 1.0-5.0), p = 0.33 (Figure 1B). Analysing BME, synovitis, and tenosynovitis separately revealed similar results (see Figure 3).

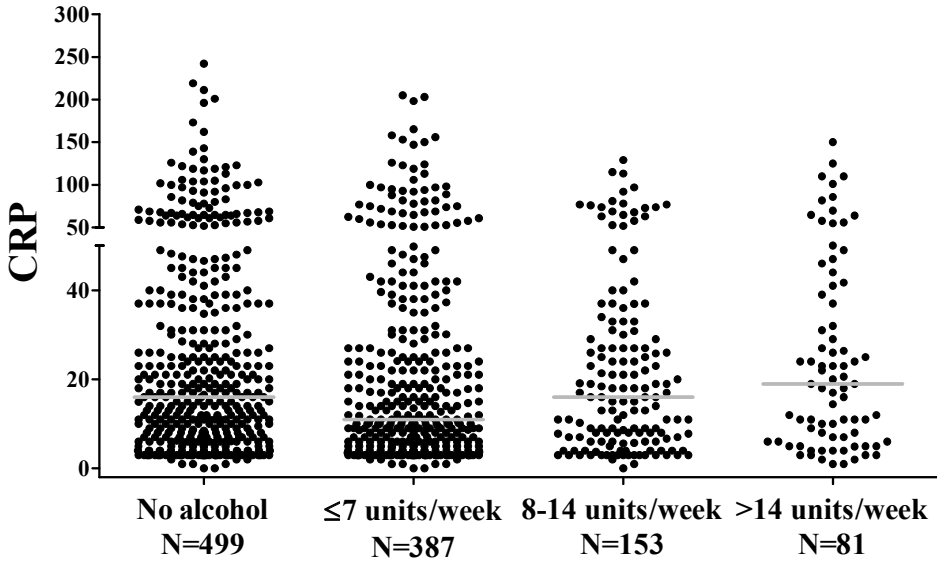
Assessing alcohol consumption on a continuous scale an association was observed in univariable analysis (β = 1.018, 95%CI = 1.002-1.034, p = 0.025). However, after adjusting for age, the association disappeared (β = 1.003, 95%CI = 0.99-1.016, p = 0.62), and also after adjusting for age, gender, and smoking status no association was observed (β = 1.002, 95%CI = 0.99-1.015, p = 0.76).

Association of alcohol consumption and CRP in RA-patients

Because of the negative findings done thus far, we searched for a positive control and we wished to verify if the previously observed association between alcohol consumption and CRP was present in our cohort of RA-patients. In a total of 1070 RA-patients 58% consumed alcohol with a median consumption of 6 drinks/week (IQR 2-11). The median CRP-level in nondrinkers was 16 mg/L (interquartile range (IQR) = 6-37 mg/L), in patients that consume ≤ 7 drinks/week the median was 11 mg/L (IQR = 5-29 mg/L), in patients that consume 8-14 drinks/week the median was 16 mg/L (IQR = 6-31 mg/L), and in patients that consume > 14 drinks/week the

median was 19 mg/L (IQR = 6-41 mg/L). The median CRP-levels between these four groups differed significantly (p = 0.043). Evaluation by eye suggested the presence of a J-shaped effect with the lowest CRP in the group that consumes ≤ 7 drinks/week. Indeed comparing this group with the non-drinkers revealed a significant difference (p = 0.011, Figure 4). To further confirm this J-shape, a piecewise linear spline regression was used. The regression was divided into 2 regression coefficients of the J-curve (e.g. the left decreasing part and the right increasing part with the lowest CRP-level on 1 drink/week). CRP-level decreased significantly with increasing alcohol consumption up until a maximum of 1 drink/week (β = 0.80, 95%CI = 0.68-0.93, p = 0.003). In patients consuming > 1 drink/week, CRP-levels increased significantly (β = 1.015, 95%CI = 1.004-1.025, p = 0.006). Hereby, the J-shaped association was confirmed. In a multivariable analyse adjusting for

Figure 4 The association between alcohol consumption and the association between alcohol consumption and CRP-levels in RA-patients



The lines presented in the figure represent median values. CRP does not differ significantly between the groups (p = 0.043).

age, gender, smoking and ACPA status, the downward part of the J-curve was still present (β = 0.85, 95%CI = 0.73-0.99, p = 0.039) but the upward part of the J-curve lost its significance (β = 1.007, 95%CI = 1.00-1.017, p = 0.214). A beta of 1.007 indicates that for every drink/week increase in alcohol consumption there is an 1.007-fold increase in CRP-level, thus in patients consuming > 1 drink/week higher alcohol consumption was associated with a higher CRP-level.

Discussion

Moderate alcohol consumption has been associated with less severe systemic inflammation (generally measured using CRP-levels), in the general population. [1,2] Also within RA-patients, it has been shown repeatedly that moderate alcohol consumption lowers the risk of developing RA and is associated with less severe systemic inflammation [3,4] Because of these findings, we hypothesized that moderate alcohol consumption might also be associated with less severe inflammation in joints, which can be sensitively detected with MRI. The current data revealed no association between alcohol consumption and the severity of local inflammation in hand and foot joints on MRI. Thus, though moderate alcohol consumption is associated with lower levels of systemic inflammation and a lower risk to develop RA, based on the present findings it is not associated with less severe inflammation in joints.

The pathophysiological mechanism underlying the association between alcohol consumption and inflammation is unknown. Different studies explored the immunoregulatory effects of alcohol and various results have been observed. High alcohol consumption has been reported to be associated with depleted cell-mediated and humoral immune responses [16], whereas other data suggest that low alcohol consumption has a stimulatory effect on the cellular immune response.[17]

Distinguishing high alcohol consumption from moderate alcohol consumption has several pitfalls. In this study, assessment of alcohol consumption is based on questionnaires and could therefore deviate from the true alcohol consumption. Also, the concentration of alcohol in plasma might significantly differ, depending on the

size and type of the alcohol consumption and variability in the period in which alcohol is used. Nonetheless, the fact that the association of alcohol consumption and CRP-levels in this study resemble the associations found in the literature [1] supports the validity of the data on alcohol consumption.

Alcohol consumption is part of a lifestyle and might therefore be a proxy for other factors associated with lifestyle. So, the association of alcohol on joint inflammation might have been influenced by other factors. Multivariate analyses were performed to adjust for some of these factors (amongst others age, smoking), but this did not majorly influence the study results.

The lack of association between alcohol consumption and the extent of local joint inflammation on MRI found in this study might have been caused by an inadequate power to detect an effect of alcohol on joint inflammation on MRI, especially as the previously observed effect of alcohol on systemic inflammatory markers, such as CRP-levels, was generally observed in very large studies.[1] MRI is more time-consuming and more expensive to perform than e.g. CRP-level measurements; making an MRI-study within thousands of RA-patients infeasible. In our view there was not even a trend towards an association between alcohol and local inflammation, this makes it unlikely that the present finding is falsely negative.

The present study in early RA had a cross-sectional study design. This allowed to perform the measurements before disease modifying treatment was initiated. A longitudinal study is needed to evaluate the association between alcohol and long-term outcome of RA, but current treatments and treat-to-target strategies may mask an effect of alcohol (if it is present) on the course of RA.

According to the European Society of musculoSkeletal Radiology (ESSR) recommendations, BME was evaluated on T1Gd. The RAMRIS method suggest to use T2, but a T2 was omitted from our scan protocol since previous studies have shown that these sequences preform equally well to depict BME [18,19] and a T1Gd has already been used to assess synovitis and tenosynovitis. This allowed a shorter imaging time for the participants.

Healthy, asymptomatic volunteers can also have some subclinical inflammation in hand and foot joints, especially at higher age. The nature of this inflammation is incompletely clear. Immunosenescence or degeneration may play a role. Although

the origin is incompletely known, we speculated that a potential effect of alcohol on joint inflammation might also be present in persons without RA. But similar as to within RA, alcohol did not influence the severity of subclinical inflammation in hand and foot joints of asymptomatic volunteers.

Conclusions

Moderate alcohol consumption has been shown to have a beneficial effect on the risk of RA-development and inflammatory markers, and the present study confirmed a J-shaped association between alcohol and CRP, we observed no association between alcohol and the extent of local inflammation in joints. Therefore the present data suggest that the pathophysiological mechanism underlying the effect of alcohol consists of a systemic effect that might not involve joints.

Supplementary material
Supplementary material is available from the author on request.

References

1 Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W. *Effect of alcohol consumption on systemic markers of inflammation.* The Lancet. 2001;357:763-7.

2 Albert MA, Glynn RJ, Ridker PM. *Alcohol Consumption and Plasma Concentration of C-Reactive Protein.* Circulation. 2003;107:443-7.

3 Jin Z, Xiang C, Cai Q, Wei X, He J. *Alcohol consumption as a preventive factor for developing rheumatoid arthritis: a dose-response meta-analysis of prospective studies.* Ann. Rheum. Dis. 2014;73:1962-7.

4 Scott IC, Tan R, Stahl D, Steer S, Lewis CM, Cope AP. *The protective effect of alcohol on developing rheumatoid arthritis: a systematic review and meta-analysis.* Rheumatology. 2013;52:856-67.

5 Källberg H, Jacobsen S, Bengtsson C, Pedersen M, Padyukov L, Garred P, et al. *Alcohol consumption is associated with decreased risk of rheumatoid arthritis: results from two Scandinavian case-control studies.* Ann Rheum Dis. 2009;68:222-7.

6 Lu B, Solomon DH, Costenbader KH, Keenan BT, Chibnik LB, Karlson EW. *Alcohol Consumption and Markers of Inflammation in Women with Pre-clinical Rheumatoid Arthritis.* Arthritis Rheum. 2010;62:3554-9.

7 Huidekoper AL, Woude D van der, Knevel R, van der Helm-van Mil AHM, Cannegieter SC, Rosendaal FR, et al. *Patients with early arthritis consume less alcohol than controls, regardless of the type of arthritis.* Rheumatology. 2013;52:1701-7.

8 Maxwell JR, Gowers IR, Moore DJ, Wilson AG. *Alcohol consumption is inversely associated with risk and severity of rheumatoid arthritis.* Rheumatology. 2010;49:2140-6.

9 Bergman S, Symeonidou S, Andersson ML, Söderlin MK. *Alcohol consumption is associated with lower self-reported disease activity and better health-related quality of life in female rheumatoid arthritis patients in Sweden: data from BARFOT, a multicenter study on early RA.* BMC Musculoskelet. Disord. 2013;14:218.

10 Krabben A, Stomp W, Huizinga TWJ, Heijde D van der, Bloem JL, Reijnierse M, et al. *Concordance between inflammation at physical examination and on MRI in patients with early arthritis.* Ann. Rheum. Dis. 2015;74:506-12.

11 Mangnus L, Schoones JW, van der Helm-van Mil AHM. *What is the prevalence of MRI-detected inflammation and erosions in small joints in the general population? A collation and analysis of published data.* RMD Open [Internet]. 2015 [cited 2016 Aug 11];1. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4613156/

12 Mangnus L, van Steenbergen HW, Reijnierse M, van der Helm-van Mil AHM. *Magnetic Resonance Imaging–Detected Features of Inflammation and Erosions in Symptom-Free Persons From the General Population.* Arthritis Rheumatol. 2016;n/a-n/a.

13 Rooy DPC de, Linden MPM van der, Knevel R, Huizinga TWJ, Mil AHM van der H. *Predicting arthritis outcomes—what can be learned from the Leiden Early Arthritis Clinic?* Rheumatology. 2011;50:93-100.

14 Østergaard M, Edmonds J, McQueen F, Peterfy C, Lassere M, Ejbjerg B, et al. *An introduction to the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas.* Ann. Rheum. Dis. 2005;64 Suppl 1:i3-7.

15 Haavardsholm EA, Østergaard M, Ejbjerg BJ, Kvan NP, Kvien TK. *Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study.* Ann. Rheum. Dis. 2007;66:1216-20.
16 MacGregor R. *Alcohol and immune defense.* JAMA. 1986;256:1474-9.
17 Romeo J, Wärnberg J, Nova E, Díaz LE, González-Gross M, Marcos A. *Changes in the immune system after moderate beer consumption.* Ann. Nutr. Metab. 2007;51:359-66.
18 Stomp W, Krabben A, Heijde D van der, Huizinga TWJ, Bloem JL, Mil AHM van der H, et al. *Aiming for a shorter rheumatoid arthritis MRI-protocol: can contrast-enhanced MRI replace T2 for the detection of bone marrow oedema?* Eur. Radiol. 2014;24:2614-22.
19 Mayerhoefer ME, Breitenseher MJ, Kramer J, Aigner N, Norden C, Hofmann S. *STIR vs. T1-weighted fat-suppressed gadolinium-enhanced MRI of bone marrow edema of the knee: Computer-assisted quantitative comparison and influence of injected contrast media volume and acquisition parameters.* J. Magn. Reson. Imaging. 2005;22:788-93.

Table 1 Baseline characteristics of RA-patients and asymptomatic volunteers in which hand and foot MRIs were performed and RA-patients in which CRP was analysed

	RA-patients with an MRI n = 188	Asymptomatic volunteers n = 192	RA-patients with CRP measurement n = 1070
Age in years, mean (SD)	56 (14)	50 (16)	56 (15)
Female, n (%)	121 (64.4)	NA	717 (67.0)
Symptom duration in weeks, median (IQR)	15.4 (7.9-29.6)	NA	18.4 (9.1-35.6)
CRP in mg/L, median (IQR)	10.0 (3.8-23.5)	NA	14.0 (6.0-33.0)
ACPA positivity, n (%)	102 (54.3)	NA	550 (52.6)
RF positivity, n (%)	116 (61.7)	NA	604 (56.9)
Curernt smokers, n (%)	50 (28.4)	17 (8.8)	271 (25.7)
Patients consuming alcohol, n (%)	121 (64.4)	135 (69.9)	621 (58.0)
Units/week, median (IQR)	6.0 (3.0-10.5)	7.0 (4.0-14.0)	6.0 (2.0-10.5)

Of RA-patients with an MRI smoking status was missing in 12 RA.
In RA-patients with a CRP measurement smoking status, RF and ACPA status was missing in respectively 17, 9, and 24 RA-patients.
NA, not assessed.

Chapter 7: Bone mineral density loss in clinically suspect arthralgia is associated with subclinical inflammation and progression to clinical arthritis

L. Mangnus

H.W. van Steenbergen

M. Reijnierse

J. Kälvesten

A.H.M. van der Helm-van Mil

Scandinavian journal of rheumatology, accepted

Abstract

Introduction: Peripheral bone mineral density (BMD) can be decreased in early rheumatoid arthritis but it is unknown if BMD-loss emerges already before arthritis is clinically apparent. We aimed to study if BMD-loss occurs in patients with clinically suspect arthralgia (CSA), if it is associated with progression to clinical arthritis and if it is associated with MRI-detected subclinical inflammation.

Methods: Patients with CSA had arthralgia for < 1 year and were suspect to progress to RA according to their rheumatologists. At baseline a 1.5T MRI was performed of unilateral MCP, wrist and MTP-joints and scored on synovitis, bone marrow edema and tenosynovitis;. summing these features yielded the MRI-inflammation score. Digital X-ray radiogrammetry (DXR) was used to estimate BMD on two sequential conventional hand radiographs (mean interval between radiographs 4.4 months). The change in BMD was studied; BMD-loss was defined as decrease of ≥ 2.5 mg/cm^2/month. Patients were followed on arthritis development for median 18.4 months.

Results: In CSA-patients (n = 108) change in BMD was negatively associated with age (β = -0.03, p = 0.007). Within CSA-patients BMD-loss was associated with arthritis development (adjusted for age HR = 6.1, 95%CI = 1.7;21.4) and was most frequently estimated in the months before clinical arthritis development. The MRI-inflammation scores were associated with the change in BMD (adjusted for age β = -0.05, p = 0.047). The MRI-inflammation score and BMD-loss were both independently associated with arthritis development (HR = 1.1 95%CI = 1.1;1.2 and HR = 4.6 95%CI = 1.2;17.2 respectively).

Conclusion: In CSA-patients BMD-loss is associated with MRI-detectable subclinical inflammation and with progression to clinical arthritis.

Introduction

Processes that underlie the development of rheumatoid arthritis (RA) are already active in the symptomatic phase before arthritis is clinically evident. In this phase pro-inflammatory cytokines can be elevated, and auto-antibodies and subclinical inflammation can be present.[1,2] Whether bone metabolism is changed in the phase preceding clinical arthritis is less clear, but it has previously been reported that several biomarkers of bone and cartilage metabolism (cartilage oligomeric matrix protein, N-terminal telopeptide of type I procollagen and osteoprotegerin) were altered.[3,4]

BMD-loss of the hands (metacarpal bones II-IV) can be estimated with digital X-ray radiogammetry (DXR).[5] Previous studies revealed that the association with radiographic progression of BMD estimated by DXR is stronger than that of BMD measured by dual energy X-ray absorptiometry (DEXA) of periarticular metacarpal bones.[6] BMD-loss has not only been associated with radiographic progression in early RA (7), but also with RA-development in patients presenting with undifferentiated arthritis.[8]

Clinically Suspect Arthralgia (CSA) patients have no clinical arthritis and are prone to progress towards RA.[2,10] This study aimed to address if BMD-loss is present in CSA and if so, whether BMD-loss is preferentially present in CSA-patients that progress to clinically detectable arthritis. Second, as MRI-detected subclinical inflammation in CSA has been strongly associated with progression to RA (2,11), it was explored whether subclinical inflammation is associated with a decrease in BMD.

Patients and Methods

Patients

Patients were included in the Leiden Clinically Suspect Arthralgia (CSA)-cohort between April 2012-Augustus 2014. As described previously (10) this inception cohort was set up to study the symptomatic phase of RA before clinical arthritis

emerges. Inclusion criteria were the presence of arthralgia of small joints for < 1-year and an increased risk to progress to RA according to the clinical expertise of the rheumatologists.[2,10] Patients were not included when clinically detectable arthritis was present or when another explanation for arthralgia was more likely. Patients had a visit at baseline and after 4, 12 and 24 months. If indicated, patients were seen in between visits to evaluate arthritis development. At all scheduled visits physical examination was performed, radiographs were made and blood samples obtained. MRI was performed at the baseline visit. Follow-up ended at 24 months or earlier when clinical arthritis had developed. This outcome was evaluated in medical files until December 24, 2014. The medical ethics committee of the Leiden University Medical Center approved this study. All patients provided written informed consent.

Digital X-ray radiogrammetry

Radiographs of both hands, performed in posteroanterior position (baseline and the first consecutive visit), were used to estimate BMD with DXR. Briefly, DXR is an automated analysis of the cortical bone at the centres of metacarpal bones II-IV, this technique is described in detail previously.[5] The mean BMD change of both hands was calculated as the difference per month between 2 radiographs (mg/cm^2/month) as described previously.[8,9] BMD change was analysed as a continuous measure and was dichotomized; with a change of BMD of ≤ -2.5 mg/cm^2/month defined as BMD-loss.[8,9]

MR imaging and scoring

At baseline contrast-enhanced MRIs was made of unilateral metacarpophalangeal (MCP)2-5 joints, wrist joints and metatarsophalangeal (MTP)1-5 joints as described earlier.[10] A detailed scan protocol is provided in the Supplementary methods. The most painful side was scanned or, in case of equally severe symptoms at both sides, the dominant side. An ONI-MSK-extreme 1.5T extremity-MRI-scanner (GE, Wisconsin, USA) was used.

Scoring of inflammation (synovitis, bone marrow edema (BME) and tenosynovitis) was done according to the RA MRI-scoring system (RAMRIS).[13,14] Synovitis and

BME were scored in MCP, wrist, and MTP-joints and tenosynovitis in the MCP and wrist-joints. The total MRI-inflammation score was calculated by summing the BME, synovitis and tenosynovitis-scores of all scored joints. The mean MRI-scores, performed by 2 trained independent readers (HWvS and LM) blinded for any clinical data, were used. For the total MRI-inflammation score the within-reader intraclass correlation coefficient (ICC) was 0.98 and 0.99, and the between-reader ICC 0.96.

Analyses

Unpaired t-test, Mann-Whitney U test and the chi-squared test were used as appropriate. Univariable and multivariable linear regression models were used to study associations of inflammation with BMD change. Univariable and multivariable Cox proportional hazard regression analyses were used to determine associations with arthritis development. To prevent overfitting of the data the multivariable Cox regression contained only age as an adjustment factor. Data were analyzed using IBM SPSS statistics version 20.

Results

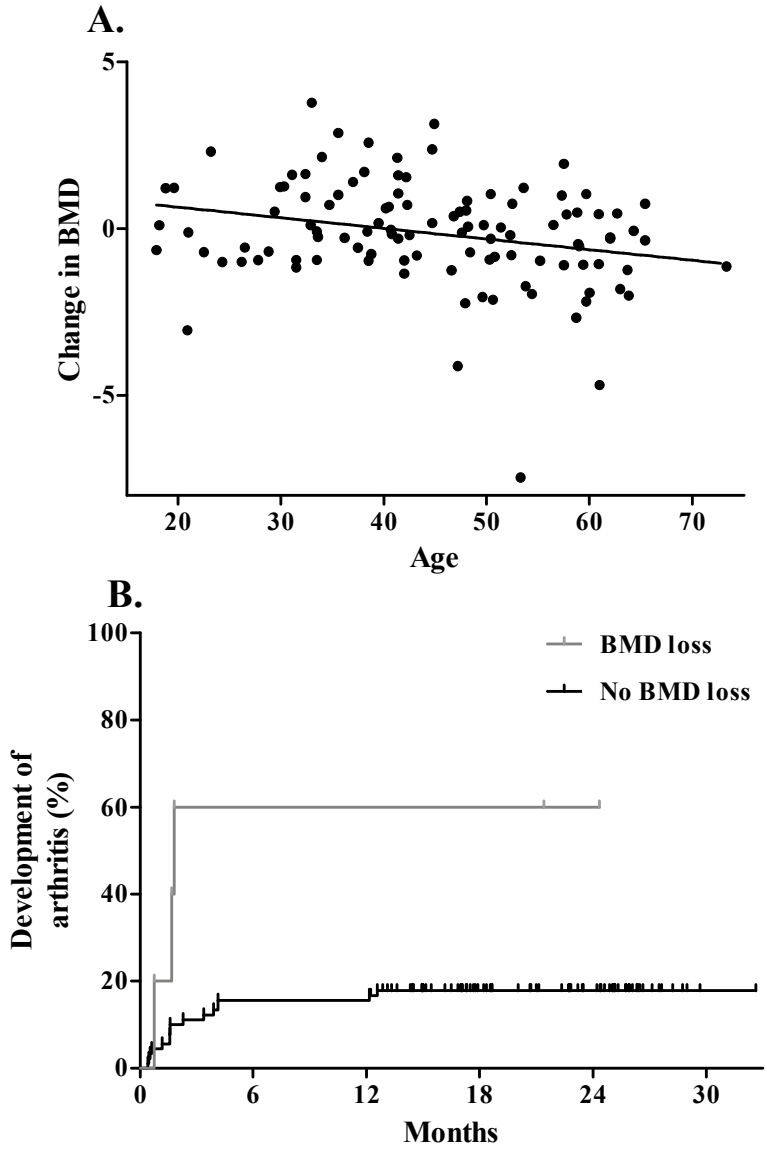
Patients

162 patients were consecutively included in the CSA-cohort. Of these, 116 patients had conventional radiograph at baseline and follow-up (mean time interval 4.4 months (SD 1.3)). Radiographs of 8 patients could not be studied by DXR due to settings when acquiring the images. Therefore, DXR results were obtained from 108 CSA-patients in total. The 108 CSA-patients that were studied and the 54 CSA-patients that were excluded did not differ in baseline characteristics (Table 1). Median follow-up of the studied patients was 18.6 months (IQR = 15.6-21.6).

BMD change and age

A higher age was associated with a larger decrease in BMD ($\beta = -0.03$, $p = 0.007$, Figure 1A). No statistically significant difference in BMD change was observed between gender (mean females = -0.18, males = 0.003, $p = 0.60$), RF-status (mean

Figure 1 Association between age and change in BMD (A) and the development of clinical arthritis in CSA-patients with and without increased BMD-loss (B)



Ad Figure 1A.The correlation coefficient of age with BMD-loss was -0.03 (p = 0.007).
Ad Figure 1B. BMD-loss was defined as a decrease in BMD of ≥ 2.5 mg/cm^2/month.

RF-positive = -0.89, RF-negative = -0.079, p = 0.06) and ACPA-status (median ACPA-positive = -0.23, ACPA-negative = -0.09 p = 0.58).

MRI-detected inflammation and BMD change

The total MRI-inflammation score at baseline was associated with BMD change during the first months of follow-up (β = -0.07, p = 0.018, Table 2); β = -0.07 indicates that per point increase in total MRI-inflammation, the BMD decreased with 0.07 mg/cm^2/month. After adjustment for age, the association remained present (β = -0.05, p = 0.047). Studying the MRI-detected inflammatory features separately revealed that synovitis and tenosynovitis-scores were associated with BMD-loss (β = -0.18, p = 0.008 and β = -0.19, p = 0.006 respectively), in contrast to the BME-score (β = -0.03, p = 0.63).

In a sub-analysis, the association between BMD-loss in one hand and MRI-inflammation of metacarpal bones of the same metacarpals was studied (See supplementary figure 1). This analysis revealed similar results as presented above (see Supplementary table 1).

BMD-loss and progression to clinical arthritis

Twenty (19%) CSA-patients developed clinically apparent arthritis after a median interval of 1.7 months (range = 0.4-15.0) and15 fulfilled the 1987-criteria for RA. BMD-loss was present in 4.6% (n = 5) of the CSA-patients, out of which 3 developed arthritis. BMD-loss was more often present in CSA-patients that progressed to clinically apparent arthritis than in CSA-patients that did not progress (hazard ratio (HR) = 4.94, 95%CI = 1.44;16.97, Figure 1B). After adjustment for age, the HR of BMD-loss was 6.01 (95%CI = 1.72;21.38, Table 3). Furthermore, the association of BMD-loss and arthritis development was independent of MRI-inflammation (HR = 4.62, 95%CI = 1.24-17.20, Table 3).

Six patients converted to clinical arthritis one month after inclusion in the CSA-cohort and these patients had the second radiograph made 2-3 months after arthritis development. In a sensitivity analysis, these patients were excluded; this revealed similar results (Supplementary Table 2).

Discussion

Studying patients with arthralgia at risk for RA can increase the understanding of the processes that are active in the earliest symptomatic phase of RA. In this light, this study evaluated BMD-loss, estimated at the metacarpals using DXR. We observed that BMD-loss was present in CSA, that BMD-loss was more often present in the CSA-patients that progressed to arthritis than in patients that did not progress, and that MRI-detected subclinical inflammation was associated with a decrease in BMD.

BMD-loss was mostly estimated using radiographs taken in the months preceding the development of clinical arthritis. Therefore, our study mainly evaluated the last preclinical phase and does now allow conclusions on the presence of bone loss in earlier, asymptomatic, preclinical phases.

We showed that MRI-detected subclinical inflammation was associated with a decrease in BMD and that BMD-loss was associated with arthritis development. A multivariable analysis showed that MRI-detected inflammation and BMD-loss were both independently associated with progression to clinical arthritis, suggesting that both are markers of processes that are active in a very early phase of RA.

This study is the first assessing BMD-loss in CSA-patients. Only a part of the CSA-patients progressed to arthritis and most patients did not progress. This explains why the average decrease in BMD observed in this study is lower than previously reported in RA.[8,9]

The cut-off value for BMD-loss that we used was suggested by the manufacturer and based on data from studies in RA; age was not included in this cut-off. A very recent study assessed variation in BMD in the general population and established age and sex-adjusted reference values.[14] Applying these cut-off values revealed that 46% (n = 50) of the CSA-patients had BMD-loss, but that BMD-loss was equally present in CSA-patients that did not progress to arthritis and in those that did progress (HR 0.99 (95%CI = 0.41-2.38, p = 0.98). Hence this did not increase the discriminative ability in the present population.

The most important limitation of this study is the sample size. A small part of patients progressed to clinical arthritis during the follow-up period and BMD-loss was also infrequent. Further studies are therefore needed to confirm the present findings.

In conclusion, BMD-loss is increased in CSA-patients progressing to clinical arthritis and is associated with MRI-detectable subclinical inflammation in CSA.

Supplementary material

Supplementary material is available from the author on request

References

1 van Steenbergen HW, Huizinga TWJ, van der Helm-van Mil AHM. *Review: The Preclinical Phase of Rheumatoid Arthritis: What Is Acknowledged and What Needs to be Assessed?* Arthritis Rheum. 2013;65:2219-2232.

2 Steenbergen HW van, Mangnus L, Reijnierse M, Huizinga TWJ, Mil AHM van der H. *Clinical factors, anticitrullinated peptide antibodies and MRI-detected subclinical inflammation in relation to progression from clinically suspect arthralgia to arthritis.* Ann Rheum Dis. 2016;75:1824-30.

3 Turesson C, Bergström U, Jacobsson LTH, Truedsson L, Berglund G, Saxne T. *Increased cartilage turnover and circulating autoantibodies in different subsets before the clinical onset of rheumatoid arthritis.* Ann Rheum Dis. 2011;70:520-2.

4 Schaardenburg D van, Nielen MMJ, Lems WF, Twisk JWR, Reesink HW, Stadt RJ van de, et al. *Bone metabolism is altered in preclinical rheumatoid arthritis.* Ann Rheum Dis. 2011;70:1173-4.

5 Rosholm A, Hyldstrup L, Bæksgaard L, Grunkin M, Thodberg HH. *Estimation of Bone Mineral Density by Digital X-ray Radiogrammetry: Theoretical Background and Clinical Testing.* Osteoporos Int. 2001;12:961-9.

6 Jensen T, Hansen M, Jensen KE, Pødenphant J, Hansen TM, Hyldstrup L. *Comparison of dual X-ray absorptiometry (DXA), digital X-ray radiogrammetry (DXR), and conventional radiographs in the evaluation of osteoporosis and bone erosions in patients with rheumatoid arthritis.* Scand J Rheumatol. 2005;34:27-33.

7 Forslind K, Kälvesten J, Hafström I, Svensson B. *Does digital X-ray radiogrammetry have a role in identifying patients at increased risk for joint destruction in early rheumatoid arthritis?* Arthritis Res Ther. 2012;14:R219.

8 Rooy DPC de, Kälvesten J, Huizinga TWJ, Mil AHM van der H. *Loss of metacarpal bone density predicts RA-development in recent-onset arthritis.* Rheumatology. 2012;51:1037-41.

9 Steenbergen HW van, Nies JAB van, Huizinga TWJ, Bloem JL, Reijnierse M, Mil AHM van der H. *Characterising arthralgia in the preclinical phase of rheumatoid arthritis using MRI.* Ann Rheum Dis. 2015;74:1225-32.

10 Steenbergen HW van, Mil AHM van der H. *Clinical expertise and its accuracy in differentiating arthralgia patients at risk for rheumatoid arthritis from other patients presenting with joint symptoms.* Rheumatology. 2016;56:1140-1.

11 Østergaard M, Edmonds J, McQueen F, Peterfy C, Lassere M, Ejbjerg B, et al. *An introduction to the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas.* Ann Rheum Dis. 2005;64(suppl 1):i3-7.

12 Haavardsholm EA, Østergaard M, Ejbjerg BJ, Kvan NP, Kvien TK. *Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study.* Ann Rheum Dis. 2007;66:1216-20.

13 Bøyesen P, Hoff M, Ødegård S, Haugeberg G, Syversen SW, Gaarder PI, et al. *Antibodies to cyclic citrullinated protein and erythrocyte sedimentation rate predict hand bone loss in patients with rheumatoid arthritis of short duration: a longitudinal study.* Arthritis Res Ther. 2009;11:R103.

14 Ørnbjerg LM, Østergaard M, Jensen T, Hyldstrup L, Bach-Mortensen P, Bøyesen P, et al.
Establishment of age- and sex-adjusted reference data for hand bone mass and investigation of hand bone loss in patients with rheumatoid arthritis treated in clinical practice: an observational study from the DANBIO registry and the Copenhagen Osteoarthritis Study.
Arthritis Res Ther. 2016;18:53.

Table 1 Baseline characteristics of included and excluded CSA-patients

	CSA-patients analyzed (n = 108)	CSA-patients excluded (n = 54)	p-value
Age (years), mean (SD)	44.5 (12.9)	40.4 (12.3)	0.057
Female, N (%)	81 (75)	39 (72)	0.70
TJC, median (IQR)	5.0 (3.0-10.0)	5.5 (3.0-8.0)	0.92
CRP, median (IQR)	0.0 (0.0-4.6)	0.0 (0.0-4.3)	0.98
RF positive, N (%)	24 (22)	13 (24)	0.79
ACPA positive, N (%)	14 (13)	12 (22)	0.13
Total MRI-inflammation, median (IQR)	2.0 (1.0-5.5)	2.0 (0.5-4.9)	0.43
Total synovitis score, median (IQR)	1.0 (0.0-2.5)	1.0 (0.0-2.8)	0.67
Total BME-score, median (IQR)	0.5 (0.0-1.5)	1.0 (0.0-1.5)	0.81
Total tenosynovitis score, median (IQR)	0.0 (0.0-2.0)	0.0 (0.0-1.0)	0.33

TJC, tender joint count;
CRP, C-reactive protein;
RF, rheumatoid factor;
ACPA, Anti-citrullinated protein antibody.

Table 2 Association between MRI-detected inflammation at baseline and change in BMD

BMD	β (95%CI)	p
Univariable		
Total MRI-inflammation score	-0.07 (-0.12;-0.01)	0.018
Total BME-score	-0.03 (-0.16;0.10)	0.63
Total synovitis score	-0.18 (-0.32;-0.05)	0.008
Total tenosynovitis score	-0.19 (-0.32;-0.05)	0.006
Multivariable		
Age	-0.03 (-0.05;-0.01)	0.015
Total MRI-inflammation score	-0.05 (-0.11;0.00)	0.047

BME, Bone marrow edema;
Total MRI-inflammation is the sum of all scored synovitis, BME and tenosynovitis in one hand and foot.

Table 3 The association of BMD-loss and progression from CSA to clinical arthritis in univariable and multivariable Cox regression analyses

	HR (95%CI)	p
Univariable		
BMD-loss *	4.94 (1.44;16.97)	0.011
Multivariable		
Model A		
BMD-loss *	6.07 (1.72;21.38)	0.005
Age	0.97 (0.94;1.00)	0.076
Model B		
BMD-loss *	4.62 (1.24;17.20)	0.023
Age	0.96 (0.93;0.99)	0.016
Total MRI-inflammation score	1.12 (1.05;1.19)	‹0.001

* BMD-loss is defined as decrease of≥ 2.5 mg/cm^2/month.

Chapter 8:
Summary and general conclusion

This thesis focussed on inflammation observed on magnetic resonance imaging (MRI) in the early phases of rheumatoid arthritis (RA) and was divided into two parts. In the first part we explored the prevalence of inflammation and erosions detected on MRI in the general population. In the second part, we studied the early phases of RA and assessed factors which could be associated with radiographic joint damage or local inflammation detected on MRI.

Part I: Inflammation and erosions detected on MRI in the general population

In **chapter 2**, a systematic literature search, we summarized the prevalence of MRI-detected inflammation and erosions in an asymptomatic population. Though MRI is generally considered to be of value in the diagnostic process of RA and is also sensitive in the early detection of structural damage (1), the prevalence of inflammation and erosions detected on MRI in the general population (e.g. the specificity of MRI in the diagnostics of RA) was unknown. MRI-findings in asymptomatic volunteers were evaluated in 31 studies. Both inflammation and erosions detected on MRI were present in asymptomatic volunteers. However, the frequency of MRI-detected findings varied widely between the different studies. This was most likely caused by the fact that the data were heterogeneous. Most of the studies were not designed to determine MRI-findings in asymptomatic volunteers and they were mainly used as a control population; consequently the number of included healthy subjects was small. Furthermore, methodologies differed between studies and the healthy control groups were not well described. Often, baseline characteristics as age, body mass index (BMI), or medical history were lacking and in- and exclusion criteria were poorly described, if described at all. Therefore, we concluded that the data summarized in the review suggested that inflammation and erosions were present in an asymptomatic population, but that a large scale study with the main goal to assess the prevalence of MRI-detected findings in the general (asymptomatic) population was lacking.

In **chapter 3** we assessed the prevalence of inflammation and erosions detected on MRI in a study population of 193 volunteers, recruited from the general (asymptomatic) population. We aimed to include volunteers without joint symptoms. Therefore inclusion criteria were: age 18 years or older, no history of RA or other inflammatory rheumatic diseases, no joint symptoms during the previous month, and no clinically detectable arthritis on physical examination. All volunteers underwent a contrast enhanced MRI of the dominant metacarpophalangeal (MCP), wrist, and metatarsophalangeal (MTP) joints on a 1.5T extremity scanner. Scoring was done independently by 2 readers and, to prevent observer bias, MRIs of symptom-free individuals were mixed with MRIs of RA-patients and patients with arthralgia without clinical synovitis.[2,3] Scoring was done according to the RA MRI-scoring (RAMRIS) method for synovitis and bone marrow edema (BME) in the MCP, wrist, and MTP joints (4) and tenosynovitis was scored according to Haavardsholm et al in the MCP and wrist.[5] Synovitis, BME and tenosynovitis was summed into an inflammation-score.

Inflammation and erosions detected on MRI were frequently observed. An inflammation score of ≥ 1 was present in 72% of volunteers and an erosion score of ≥ 1 was present in 78% of the volunteers. These findings were primarily low-grade according to RAMRIS (a score of 1), and severe findings were very rare. BME and synovitis were more often observed compared to tenosynovitis. The prevalence of detected inflammation and erosions increased with a higher age. Therefore, the findings observed could be degenerative in nature, even though we did exclude volunteers with symptomatic osteoarthritis.

To evaluate if asymptomatic osteoarthritis caused the observation of more severe inflammation at higher age, we performed a sub-analysis in which we excluded both volunteers with any sign of asymptomatic osteoarthritis but also locations known to be predilection sites for osteoarthritis. Also in this analysis, we found a positive association with the prevalence of MRI-detected findings and age. Although it cannot be excluded that degenerative processes underlie the observation on age, the findings of this study are not solely explained by asymptomatic osteoarthritis as identified by clinical examination.

The locations in which MRI-detected findings were most frequently seen in the asymptomatic volunteers were MCP II, MCP III, wrist and the MTP I joint. Interestingly, these locations are remarkably similar to the locations in which RA is regularly presented and where the most radiographic joint damage is seen during RA.[6] Therefore, it can be hypothesised that in these locations certain stressors, for instance mechanical stress, are more abundant compared to other joints and thereby could elicit processes which eventually lead to inflammation and/or erosions. Future research should assess whether indeed the minor MRI-findings detected in an asymptomatic population are due to certain stressors (e.g. mechanical) and whether these minor findings could elucidate the appearance of RA in these joints.

In the last decades, MRI is increasingly used in RA-research. Along with the increased use of MRI, there was a need to increase the comparability between studies. Therefore, a scorings methodology on MRI was developed, the RA MRI score (RAMRIS).[4] Erosions, BME and synovitis were incorporated in this method, and later a scorings method for tenosynovitis was developed and added.[5] Even though the comparability between studies increased by the use of one scorings method, the use of RAMRIS has several disadvantages. The scorings method was developed for the follow-up of patients in clinical trials and was therefore not developed for a single time point measurement. The RAMRIS method therefore may be suboptimal for use as a diagnostic instrument.

Thus in conclusion, the prevalence of inflammation and erosions in asymptomatic volunteers is higher than anticipated. This has consequences for the use of MRI in the early detection of RA since ignorance of the observations done in a control population could lead to false positive test results.

Part II: Association with MRI-detected inflammation and radiographic joint damage

In chapter 4-7 we studied the early phases of RA, both with regards to the severity of MRI-detected inflammation at disease onset and the severity of radiographic damage over time.

In **chapter 4** we first assessed the association between age of onset and radiographic joint damage progression. This was done in 5 cohorts including 1,875 RA-patients. We observed that a higher age of onset was associated with more severe radiographic joint damage. This association was seen on baseline and the effect remained similar during 7 years follow-up.
In the second part of this article we tried to improve the understanding of the mechanisms which may have been involved in this association. These analyses were performed in the Leiden early arthritis cohort (EAC) in which 698 RA-patients were included with 7 years of follow-up. As MRI was added to the EAC-cohort protocol 56 RA-patients had an MRI performed and had a minimum of 1 year of follow-up, including conventional radiographs. Firstly, we tried to assess whether the increase of radiographic joint damage with an increase in age was due to degeneration. Therefore, we assessed whether the increase in the radiographic joint damage was due to a disproportional increase in the joint space narrowing (JSN) score, reflecting degenerative changes. We observed an increase in both the erosion score as well as the JSN-score with age. Furthermore, we analysed bones and joints that are known to be predilection sites for osteoarthritis separately from other scored joints and bones. In this analyse we also observed an increase in all sites analysed. These findings suggest that degeneration insufficiently explains the association between age and radiographic joint damage.
Secondly, mediation analyses were performed in which we assessed whether age has an indirect relationship with radiographic joint damage. In this cohort we explored whether symptom duration, anti-citrullinated-peptide-antibodies (ACPA), rheumatoid factor (RF), swollen joint count (SJC), C-reactive-protein (CRP),

and inflammation detected on MRI had an effect on the association between age and radiographic joint damage. We hypothesized that older persons with joint complaints present at a later point in time and therefore have more severe radiographic joint damage. However, symptom duration, ACPA, RF, SJC and CRP did not mediate the association between age and radiographic joint damage. We observed that older patients have more MRI-detected inflammation and that MRI-detected inflammation partially explains the association between age and radiographic joint damage. Thus, we observed partial mediation of MRI-detected inflammation. In sum, a higher age at inclusion was associated with more severe radiographic joint damage, and this could be partially explained by MRI-detected inflammation. However, this last conclusion should be replicated within a larger cohort since our analysis was only performed in a small subgroup of patients.

In **chapter 5** we assessed the association of BMI with inflammation detected on MRI. Previously it has been observed, in a population based study, that BMI is associated with increased inflammatory markers (7). Intriguingly, several studies within RA had shown that a high BMI is associated with less progression of radiographic joint damage.[8-11] We assessed whether there was an association between BMI and MRI-detected inflammation in 195 RA-patients, 159 patient with other inflammatory arthritides and in 193 asymptomatic volunteers. When assessing the association between BMI and MRI-detected inflammation in patients with other inflammatory arthritides and in asymptomatic volunteers, a higher BMI is associated with more severe MRI-detected inflammation. This is in line with the previously observed association between increased inflammatory markers and BMI in the general population.[7] However, within the RA-patients, a higher BMI was associated with less inflammation detected on MRI, this is in line with the association between BMI and radiographic joint damage which was previously observed. These findings are intriguing as a higher BMI is generally associated with a worse outcome in RA-patients (e.g. function and disease activity).[12] Similarly, RA-patients with a higher BMI seems to have a decreased treatment response (13), and have a decreased chance on reaching remission.[14] This might be caused by the fact that functional ability, and partially disease activity and clinical remission

are dependent on subjective measurements as well as objective measurements. Indeed a high BMI has been shown to be associated with higher subjective measurements (e.g. tender joint count, patient global assessment) but with similar objective measurements (e.g. C-reactive protein, erythrocyte sedimentation rate and 28-swollen joint count) compared to RA-patients with a low BMI.[15]
Altogether a high BMI is associated with lower MRI-detected inflammation but with higher subjective measurements. Whether this latter issue has consequences for the clinical practise has to be investigated (e.g. differences in medication due to differences in DAS-scores).
In sum this study illustrated the paradox of BMI in RA compared to patients with other inflammatory arthritides and in asymptomatic volunteers. A high BMI is associated with less severe local inflammation and less severe joint destruction. A paradoxical effect of BMI has also been observed in relation to mortality; RA-patients with a high BMI had a lower mortality than thinner patients.[16]

In **chapter 6** we assessed whether there was an association between alcohol consumption and inflammation detected on MRI in RA-patients. Moderate alcohol consumption has been shown to be beneficial as it is associated with a decrease in inflammatory markers and a decreased risk of RA-development.[17-20] Therefore, we first assessed whether we could replicate the association between moderate alcohol consumption and C-reactive protein (CRP-) level as a marker for inflammation in 1070 RA-patients. We indeed observed that moderate alcohol consumption (1 consumption per week) is associated with the lowest CRP-level. Subsequently we wanted to assess whether moderate alcohol consumption was also beneficial for MRI-detected inflammation. We therefore assessed the association between alcohol consumption and MRI-detected inflammation in 188 RA-patients and in 192 asymptomatic volunteers. Unexpectedly, we did not observe an association between alcohol consumption and MRI-detected inflammation in RA-patients or asymptomatic volunteers.
In conclusion, moderate alcohol consumption is associated with a lower systemic inflammation but there was no association between alcohol consumption and joint inflammation detected on MRI.

A decreased BMD can be observed in patients with early RA.[21-23] In RA-patients, BMD-loss has been associated with more radiographic joint damage. Also, in patients with UA (22), BMD-loss is a predictor for the development of RA.[23] However, it is unknown to what extent BMD changes are present in the phase before arthritis is clinically evident. Therefore, in **chapter 7** we assessed BMD in the clinically suspect arthralgia (CSA) cohort consisting out of 108 CSA-patients. An MRI was performed at baseline and digital X-ray radiogrammetry on two sequential conventional hand radiographs was used to estimate BMD. This change was standardized by calculating the mean difference per month. We observed that BMD-loss (defined as a decrease of ≥ 2.5 mg/cm^2/month) was seen in a small proportion of CSA-patients. Furthermore, we observed that with more severe inflammation detected on MRI at baseline, a higher decrease in BMD was seen in the months following the MRI. Together with the previous findings on changed bone markers in the preclinical phase of RA[24,25], the data suggest that the bone metabolism is altered in some patients in the symptomatic phase preceding clinical arthritis.

Conclusions and future perspectives

In the current thesis it was shown that the prevalence of inflammation and erosions in the general, asymptomatic population, are highly dependent on age and location. The RAMRIS method does not take into account these factors. In clinical practice, radiologists that assess an MRI for diagnostic purposes already take into account the age of the patient and the location of the lesion(s). But apart from these factors, radiologists also take into account other factors such as the pattern of inflammation. These differences between the RAMRIS method and the assessment by a radiologist in clinical practise highlights the disadvantages of the use of the RAMRIS score in the diagnostics of RA. This illustrates the need for the development of another scorings methodology which incorporates factors such as age, location, pattern, and the level of inflammation in the general population. The value of this scorings method in the diagnostic process of RA has still to be derived and validated in longitudinal cohorts of patients.

In addition, if MRI-data of asymptomatic volunteers would be used as a reference, even larger data-sets of controls might be required to ensure that sufficient patients are available in the different age categories.

Apart from MRI, several other imaging techniques could be helpful to assess joint inflammation in the clinical practise such as ultrasonography, positron emission tomography (PET), and single photon emission computed tomography (SPECT).[26] In clinical practise ultrasound is more easily available and is often performed by the treating rheumatologist. However, ultrasound cannot detect BME and is operator dependent.[26] In the future the additional value to ultrasound above MRI or vice versa should be assessed in a head to head comparison, as a diagnostic tool for the clinical practise of RA. Similarly, the value of SPECT and PET in the detection of early inflammation during RA should be assessed. In all of these studies the specificity of findings will be important. A first study on ultrasonography findings in symptom-free persons was published recently (27), but more effort is needed here as well.

Apart from accurate prognostication, it remains to be determined how early RA should be treated. The early detection of RA is very important as starting treatment in an early, clinically apparent, phase of the disease improves the clinical outcome.[28] Imaging techniques may contribute to the detection of inflammation at an earlier time point as compared to the current diagnostics resulting in the possibility to start treatment at even earlier time points (thus in pre-arthritis phases). At present it is unknown whether starting treatment this early is indeed beneficial and results in better outcomes than when treatment is started in the early clinical phase.

In the literature, a higher age of onset of RA is associated with more severe radiographic joint damage.[29-34] Likewise, in chapter 3 we have observed a higher prevalence of MRI-detected erosions at higher age. Although these MRI-detected erosions are asymptomatic and mostly small, these erosions could be prone for the development of radiographic joint damage. Indeed, previous studies showed that bones with MRI-detected erosions are more prone to develop erosions on conventional radiographs (HR 4.1, 95%CI 2.2-7.5).[35] Therefore, as older persons

have more MRI-detected erosions, radiographic joint damage might develop more easily in older RA-patients. This hypothesis should be addressed in future studies. With respect to the findings on BMI and the severity of joint inflammation in RA, further studies are needed to determine the biological mechanisms that underlie this effect. A recent study in mice suggested that arthritis has an earlier onset in obesity, amongst others due to an increased neutrophil recruitment, but also that when arthritis was evident obesity had no influence anymore as leucocytes, T-cell population and chemoattractants did not differ between lean and obese mice.[36] The severity of joint damage was not assessed here. In conclusion, the mechanisms underlying the obesity paradox in RA is not yet elucidated.

There has been a lot of debate about the pros or cons of drinking 1 or 2 alcohol beverages a day. The preventive effects of moderate alcohol consumption have been advocated for several diseases (e.g. cardiovascular disease). However the data presented in this thesis may imply that moderate alcohol consumption has no beneficial effect on the joints of RA-patients. However, we only evaluated the association on the local level of joints, which is presumably different from systemic effects.

All studies investigating bone metabolism in the preclinical phase of RA performed so far have a small sample size. To validate the altered bone metabolism in the symptomatic phase preceding clinical arthritis, larger studies are needed. At the moment, cohorts of arthralgia patients are still increasing in size and therefore, these studies could be started in the nearby future.

RA is considered to be a multifactorial disease, resulting from genetic and environmental factors.[37,38] The best known environmental factor, smoking, has been studied extensively in the past.[39] The relation of RA-development with other factors, such as BMI and alcohol consumption, is less clear.[19,20,40] In this thesis, we addressed two of these factors, namely BMI and alcohol. We tried to elucidate whether these factors were associated with inflammation detected on MRI. A limitation of our studies is the cross-sectional study design. Even though we found BMI to be associated with inflammation on MRI, longitudinal studies are needed to confirm that lower inflammation in obese patients is indeed associated with less radiographic progression.

Furthermore longitudinal studies following symptomatic patients without clinically detectable arthritis are of particular interest. In these cohorts patients could be followed and the sequence of these events can be assessed in relation to environmental factors. Thereby the influence of different factors can be assessed on the development of RA. For example, it can be assessed whether losing weight has any effect on MRI-detected inflammation and may prevent progression to RA. In addition, it can be explored if alcohol consumption in the symptomatic phase is still of influence on further progression to clinical arthritis. Finally, longitudinal studies may also increase the understanding on the biological mechanisms underlying some of the associations assessed in part II of this thesis. To better understand the pathophysiology in the earliest phases of RA future research is needed to elucidate biologic mechanisms underlying the associations assessed in this thesis (e.g. immunosenescence, inflammatory properties of adipose tissue, bone metabolism).

In conclusion, the current thesis showed that inflammation detected on MRI is frequently seen in an asymptomatic population. This is essential to take into account during the assessment of MRIs for diagnostic purposes or for determining remission of RA. Furthermore, age, BMI and BMD are associated with inflammation detected on MRI. These factors, amongst others, should be subject of future research to elucidate processes that are active in the earliest phases of RA.

References

1 Colebatch AN, Edwards CJ, Østergaard M, van der Heijde D, Balint PV, D'Agostino M-A, et al. *EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis.* Ann Rheum Dis. 2013 Jun;72(6):804-14.

2 Nieuwenhuis W, Mangnus L, van Steenbergen H, Newsum E, Huizinga T, van der Helm - van Mil A. *Older age is associated with more MRI-detected inflammation in hand and foot joints.* Rheumatology (Oxford). in press.

3 Steenbergen HW van, Nies JAB van, Huizinga TWJ, Bloem JL, Reijnierse M, Mil AHM van der H. *Characterising arthralgia in the preclinical phase of rheumatoid arthritis using MRI.* Ann Rheum Dis. 2015 Jun 1;74(6):1225-32.

4 Østergaard M, Edmonds J, McQueen F, Peterfy C, Lassere M, Ejbjerg B, et al. *An introduction to the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas.* Ann Rheum Dis. 2005 Feb;64 Suppl 1:i3-7.

5 Haavardsholm EA, Ostergaard M, Ejbjerg BJ, Kvan NP, Kvien TK. *Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study.* Ann Rheum Dis. 2007 Mar 15;66(9):1216-20.

6 Landewé RBM, Strand V, Conaghan PG, Heijde D van der. *Damage and Progression on Radiographs in Individual Joints: Data from Pivotal Randomized Controlled Trials.* J Rheumatol. 2011 Sep 1;38(9):2018-22.

7 Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. *Elevated c-reactive protein levels in overweight and obese adults.* JAMA. 1999 Dec 8;282(22):2131-5.

8 van der Helm-van Mil AHM, Kooij SM van der, Allaart CF, Toes REM, Huizinga TWJ. *A high body mass index has a protective effect on the amount of joint destruction in small joints in early rheumatoid arthritis.* Ann Rheum Dis. 2008 Jun 1;67(6):769-74.

9 Baker JF, Østergaard M, George M, Shults J, Emery P, Baker DG, et al. *Greater body mass independently predicts less radiographic progression on X-ray and MRI over 1-2 years.* Ann Rheum Dis. 2014 Nov 1;73(11):1923-8.

10 Westhoff G, Rau R, Zink A. *Radiographic joint damage in early rheumatoid arthritis is highly dependent on body mass index.* Arthritis Rheum. 2007 Nov 1;56(11):3575-82.

11 Kaufmann J, Kielstein V, Kilian S, Stein G, Hein G. *Relation between body mass index and radiological progression in patients with rheumatoid arthritis.* J Rheumatol. 2003 Nov 1;30(11):2350-5.

12 Ajeganova S, Andersson ML, Hafström I, for the BARFOT Study Group. *Association of obesity with worse disease severity in rheumatoid arthritis as well as with comorbidities: A long-term followup from disease onset.* Arthritis Care Res. 2013 Jan 1;65(1):78-87.

13 Heimans L, van den Broek M, le Cessie S, Siegerink B, Riyazi N, Han KH, et al. *Association of High Body Mass Index With Decreased Treatment Response to Combination Therapy in Recent-Onset Rheumatoid Arthritis Patients.* Arthritis Care Res. 2013 Aug 1;65(8):1235-42.

14 Gremese E, Carletto A, Padovan M, Atzeni F, Raffeiner B, Giardina AR, et al. *Obesity and reduction of the response rate to anti-tumor necrosis factor a in rheumatoid arthritis: An approach to a personalized medicine.* Arthritis Care Res. 2013 Jan 1;65(1):94-100.

15 Sandberg MEC, Bengtsson C, Källberg H, Wesley A, Klareskog L, Alfredsson L, et al. *Overweight decreases the chance of achieving good response and low disease activity in early rheumatoid arthritis.* Ann Rheum Dis. 2014 Nov 1;73(11):2029-33.
16 Escalante A, Haas RW, del Rincón I. *Paradoxical effect of body mass index on survival in rheumatoid arthritis: Role of comorbidity and systemic inflammation.* Arch Intern Med. 2005 Jul 25;165(14):1624-9
17 Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W. *Effect of alcohol consumption on systemic markers of inflammation.* The Lancet. 2001 Mar 10;357(9258):763-7.
18 Albert MA, Glynn RJ, Ridker PM. *Alcohol Consumption and Plasma Concentration of C-Reactive Protein.* Circulation. 2003 Jan 28;107(3):443-7.
19 Jin Z, Xiang C, Cai Q, Wei X, He J. *Alcohol consumption as a preventive factor for developing rheumatoid arthritis: a dose-response meta-analysis of prospective studies.* Ann Rheum Dis. 2014 Nov 1;73(11):1962-7.
20 Scott IC, Tan R, Stahl D, Steer S, Lewis CM, Cope AP. *The protective effect of alcohol on developing rheumatoid arthritis: a systematic review and meta-analysis.* Rheumatology. 2013 May 1;52(5):856-67.
21 Green MJ, Deodhar AA. *Bone changes in early rheumatoid arthritis.* Best Pract Res Clin Rheumatol. 2001 Mar;15(1):105-23.
22 Guler H, Turhanoglu AD, Ozer B, Ozer C, Balci A. *The relationship between anti-cyclic citrullinated peptide and bone mineral density and radiographic damage in patients with rheumatoid arthritis.* Scand J Rheumatol. 2008 Jan 1;37(5):337-42.
23 Rooy DPC de, Kälvesten J, Huizinga TWJ, Mil AHM van der H. *Loss of metacarpal bone density predicts RA-development in recent-onset arthritis.* Rheumatology. 2012 Jun 1;51(6):1037-41.
24 Turesson C, Bergström U, Jacobsson LTH, Truedsson L, Berglund G, Saxne T. *Increased cartilage turnover and circulating autoantibodies in different subsets before the clinical onset of rheumatoid arthritis.* Ann Rheum Dis. 2011 Mar 1;70(3):520-2.
25 Schaardenburg D van, Nielen MMJ, Lems WF, Twisk JWR, Reesink HW, Stadt RJ van de, et al. *Bone metabolism is altered in preclinical rheumatoid arthritis.* Ann Rheum Dis. 2011 Jun 1;70(6):1173-4.
26 McQueen FM. *Imaging in early rheumatoid arthritis.* Best Pract Res Clin Rheumatol. 2013 Aug;27(4):499-522.
27 Padovano I, Costantino F, Breban M, D'Agostino MA. *Prevalence of ultrasound synovial inflammatory findings in healthy subjects.* Ann Rheum Dis. 2016 Oct;75(10):1819-23.
28 Nies JAB van, Krabben A, Schoones JW, Huizinga TWJ, Kloppenburg M, Mil AHM van der H. *What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review.* Ann Rheum Dis. 2014 May 1;73(5):861-70.
29 Khanna D, Ranganath VK, FitzGerald J, Park GS, Altman RD, Elashoff D, et al. *Increased radiographic damage scores at the onset of seropositive rheumatoid arthritis in older patients are associated with osteoarthritis of the hands, but not with more rapid progression of damage.* Arthritis Rheum. 2005 Aug 1;52(8):2284-92.
30 van der Heijde DM, van Riel PL, van Leeuwen MA, van 't Hof MA, van Rijswijk MH, van de Putte LB. *Older versus younger onset rheumatoid arthritis: results at onset and after 2 years of a prospective followup study of early rheumatoid arthritis.* J Rheumatol. 1991 Sep;18(9):1285-9.

31 Innala L, Berglin E, Möller B, Ljung L, Smedby T, Södergren A, et al. *Age at onset determines severity and choice of treatment in early rheumatoid arthritis: a prospective study.* Arthritis Res Ther. 2014 Apr 14;16(2):R94.
32 Kuiper S, Gestel AM van, Swinkels HL, Boo TM de, Silva JA da, Riel PL van. *Influence of sex, age, and menopausal state on the course of early rheumatoid arthritis.* J Rheumatol. 2001 Aug 1;28(8):1809-16.
33 Calvo-Alén J, Corrales A, Sánchez-Andrada S, Fernández-Echevarría MA, Peña JL, Rodríguez-Valverde V. *Outcome of late-onset rheumatoid arthritis.* Clin Rheumatol. 2005 Oct 1;24(5):485-9.
34 Bukhari M, Lunt M, Barton A, Bunn D, Silman A, Symmons D. *Increasing age at symptom onset is associated with worse radiological damage at presentation in patients with early inflammatory polyarthritis.* Ann Rheum Dis. 2007 Mar 1;66(3):389-93.
35 Østergaard M, Hansen M, Stoltenberg M, Jensen KE, Szkudlarek M, Pedersen-Zbinden B, et al. *New radiographic bone erosions in the wrists of patients with rheumatoid arthritis are detectable with magnetic resonance imaging a median of two years earlier.* Arthritis Rheum. 2003 Aug 1;48(8):2128-31.
36 Kim S-J, Chen Z, Essani AB, Elshabrawy HA, Volin MV, Fantuzzi G, et al. *Differential impact of obesity on the pathogenesis of RA or preclinical models is contingent on the disease status.* Ann Rheum Dis. 2016 Oct 18;
37 Karlson EW, Chibnik LB, Tworoger SS, Lee I-M, Buring JE, Shadick NA, et al. *Biomarkers of Inflammation and Development of Rheumatoid Arthritis in Women From Two Prospective Cohort Studies.* Arthritis Rheum. 2009 Mar;60(3):641-52.
38 Alamanos Y, Drosos AA. *Epidemiology of adult rheumatoid arthritis.* Autoimmun Rev. 2005 Mar;4(3):130-6.
39 Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al. *Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies.* Ann Rheum Dis. 2010 Jan;69(1):70-81.
40 Qin B, Yang M, Fu H, Ma N, Wei T, Tang Q, et al. *Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis.* Arthritis Res Ther [Internet]. 2015 [cited 2016 Jul 4];17(1). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4422605/

Chapter 9: Samenvatting en conclusies

In dit proefschrift hebben we ontsteking, gevonden op magnetic resonance imaging (MRI) in de vroege fases van reumatoïde artritis (RA), bestudeerd. Dit proefschrift bestaat uit twee delen. In het eerste deel is de prevalentie van lokale ontstekingen in de algemene bevolking bestudeerd. In het tweede deel hebben we bekeken of verschillende factoren een associatie vertoonden met radiografische gewrichtsschade of lokale ontsteking. In dit proefschrift hebben we lokale ontsteking afgebeeld en onderzocht middels MRI.

Deel I: Ontsteking en erosies, gevonden op MRI in de algemene bevolking

Hoofdstuk 2 is een systematisch literatuuronderzoek waarin we de prevalentie van ontsteking en erosies, gevonden op MRI, in een bevolkingsgroep zonder gewrichtsklachten hebben beschreven. MRI wordt beschouwd als een belangrijke modaliteit in het diagnostische proces van RA en is sensitief bij het vroeg-detecteren van structurele gewrichtsschade.[1] De prevalentie van ontsteking en erosies, gevonden middels MRI, in de algemene bevolking (de specificiteit van MRI in de diagnostiek van RA) is echter onbekend. Bevindingen op MRI in asymptomatische vrijwilligers zijn onderzocht in 31 studies. Hieruit kwam naar voren dat zowel ontsteking als erosies aanwezig waren op MRI bij asymptomatische vrijwilligers. Echter, de frequentie van de bevindingen op MRI varieerden vrij veel tussen verschillende studies. Dit kan hoogstwaarschijnlijk toegeschreven worden aan het feit dat de data heel heterogeen was. De meeste studies hadden niet als doel om MRI-bevindingen in asymptomatische vrijwilligers op te sporen. De vrijwilligers waren vooral bedoeld als een controlepopulatie waardoor het aantal geïncludeerde gezonde vrijwilligers erg laag was. Daarnaast verschilde de methodologie tussen de studies en waren de controlegroepen over het algemeen niet goed omschreven. Zo ontbraken vaak meerdere persoonskarakteristieken zoals leeftijd, body mass index (BMI) of medische voorgeschiedenis maar waren ook in- en exclusiecriteria slecht beschreven – als ze al beschreven waren. Hierop concludeerden wij dat zowel ont-

steking als erosies aanwezig zijn in een asymptomatische populatie. Echter, een groot opgezet onderzoek met als hoofddoel om de prevalentie van bevindingen op MRI in de algehele (asymptomatische) populatie te onderzoeken ontbrak.

In **hoofdstuk 3** hebben we hierom de prevalentie van ontsteking en erosies op MRI bekeken in de algehele (asymptomatische) bevolking. Hiervoor hebben we 193 vrijwilligers geïncludeerd. Deze vrijwilligers werden geïncludeerd als ze voldeden aan de inclusiecriteria (ouder dan 18 jaar, geen voorgeschiedenis van RA of andere inflammatoire reumatische ziekten, geen gewrichtsklachten in de maand voorafgaand aan het onderzoek en geen klinisch aanwezige gewrichtsontsteking (artritis) bij lichamelijk onderzoek). Vrijwilligers mochten dus wel een medische voorgeschiedenis hebben, als deze maar vrij was van reumatologische en aanverwante ziekten.
Alle vrijwilligers kregen een MRI met contrast van de dominante metacarpophalangeale (MCP), pols en metatarsophalangeale (MTP) gewrichten. De MRI's werden door twee onafhankelijke beoordelaars gescoord. De MRI's van asymptomatische vrijwilligers werden gemengd met MRI's van patiënten met RA en patiënten met gewrichtsklachten zonder klinische synovitis (ontsteking van het gewrichtskapsel) om beïnvloeding van de beoordeling te voorkomen.[2,3] Voor het scoren werd de RA MRI (RAMRIS) methode (bedoeld voor het scoren van synovitis en beenmergontsteking (BME)) gebruikt in de MCP, pols en MTP gewrichten.[4] Tenosynovitis (ontsteking van peesschedes) in de MCP en polsgewrichten werd gescoord volgens de methode beschreven door Haavardsholm et al.[5] De scores van de synovitis, BME en tenosynovitis werden opgeteld tot een totale ontstekingsscore.
Ontsteking en erosies werden frequent gevonden op de MRIs. Een ontstekingsscore van ≥ 1 werd gevonden bij 72% van de vrijwilligers, voor erosies had 78% van de vrijwilligers een score van ≥ 1. De meeste van deze bevindingen waren klein en hadden een RAMRIS score van 1. Ernstige bevindingen waren zeldzaam. BME en synovitis werden vaker gezien dan tenosynovitis. De prevalentie van ontsteking en erosies nam toe met de leeftijd. Daarom zouden deze bevindingen ook wel degeneratief van aard kunnen zijn, ook al hadden we vrijwilligers met symptomatische artrose niet meegenomen in dit onderzoek.

We hebben een sub-analyse uitgevoerd om te kijken of asymptomatische artrose een verklaring van dit leeftijdsverschil kan zijn. Hierbij hebben we niet alleen vrijwilligers met enige aanwijzingen voor een asymptomatische artrose uit de analyses gelaten, maar ook alle locaties die vaak aangedaan zijn bij artrose. Ook in deze analyse vonden we een positieve associatie tussen de prevalentie van bevindingen op MRI en leeftijd. Hoewel niet uitgesloten kan worden dat het degeneratieve processen zijn die hieraan ten grondslag liggen, kunnen de bevindingen van deze studie niet enkel verklaard worden door degeneratie gevonden middels anamnese en lichamelijk onderzoek.

In asymptomatische vrijwilligers werden vooral MRI afwijkingen gevonden in MCP II, MCP III, de pols en het MTP I gewricht. Opmerkelijk genoeg zijn deze locaties nagenoeg gelijk aan de locaties waarin RA zich normaal presenteert en waarin tevens de meeste radiografische schade wordt gevonden bij RA-patiënten.[6] Het zou kunnen dat op deze locaties bepaalde stressoren (bijvoorbeeld mechanische stress) meer aanwezig zijn in vergelijking met andere gewrichten. Hierdoor zouden deze gewrichten vatbaarder kunnen zijn voor processen die uiteindelijk leiden tot ontsteking en/of erosies. Toekomstig onderzoek moet uitwijzen of deze MRI afwijkingen bij asymptomatische vrijwilligers inderdaad veroorzaakt worden door bepaalde stressoren en of deze vervolgens de ontwikkeling van RA kunnen uitlokken.

In de laatste decennia wordt MRI in toenemende mate gebruikt voor het onderzoek naar RA. Tegelijk met de toename van het gebruik van de MRI was er ook een toenemende behoefte om deze onderzoeken met elkaar te kunnen vergelijken. Hiervoor werd een scoringsmethode voor de MRI ontworpen, de RA MRI score (RAMRIS).[4] Deze scoringsmethode omvatte in eerste instantie erosies, BME en synovitis, later werd er nog een scoringsmethode voor tenosynovitis aan toegevoegd.[5] Hoewel de vergelijkbaarheid tussen de studies inderdaad toenam door het gebruik van de RAMRIS, heeft het ook enkele nadelen. De scoringsmethode is van oorsprong ontwikkeld om ontsteking en erosie te vervolgen in de tijd, maar niet voor een enkele meting. Het gebruik van de RAMRIS voor een enkel scoringsmoment of als diagnostische methode, zou dus sub-optimaal kunnen zijn.

Concluderend is er een hogere prevalentie van ontsteking en erosies in asymptomatische vrijwilligers dan verwacht. Dit heeft consequenties voor het gebruik van de MRI bij de vroege detectie van RA, omdat het kan leiden tot vals-positieve beoordelingen.

Deel II: Associaties met ontsteking gevonden op MRI en radiografische gewrichtsschade

In hoofdstukken 4 t/m 7 hebben we gekeken naar associaties tussen factoren (leeftijd, BMI, alcohol, botdichtheid (BMD) in de vroege fases van RA en in de symptomatische fase voordat artritis klinisch evident is) en radiografische gewrichtsschade of bevindingen op MRI.

In **hoofdstuk 4** hebben we de invloed van leeftijd op radiografische gewrichtsschade onderzocht. We hebben dit gedaan in 5 cohorten waarin in totaal 1875 RA-patiënten zaten. Hierin vonden we dat een hogere leeftijd geassocieerd was met meer radiografische gewrichtsschade. Deze associatie werd gevonden op baseline, maar het effect bleef gelijk gedurende de 7 jaar follow-up.
In het tweede deel van dit artikel hebben we geprobeerd om meer te begrijpen van de mechanismen die ten grondslag zouden kunnen liggen aan deze associatie. Deze analyses werden uitgevoerd in het Leiden early arthritis cohort (EAC), dat 698 RA-patiënten bevat met een follow-up van 7 jaar. MRI werd pas later toegevoegd aan het EAC-cohort protocol. Hierdoor hadden 56 RA-patiënten een MRI met een minimum van 1 jaar follow-up waarin tevens conventionele röntgenfoto's gemaakt werden.
Als eerste hebben we onderzocht of de toename van radiografische gewrichtsschade met het toenemen van de leeftijd het gevolg van degeneratie was. Hiervoor hebben we gekeken of de toename in radiografische gewrichtsschade geassocieerd was met een disproportionele toename in de gewrichtsspleetsvernauwings-score (joint space narrowing (JSN)score), als een maat van degeneratieve verandering.

We vonden een toename in zowel de erosiescore als in de JSN-score. Verder hebben we botten en gewrichten, die bekend staan als locaties waar osteoartritis zich ontwikkelt, apart onderzocht van de andere botten en gewrichten. Ook in deze analyse vonden we een toename met de leeftijd op alle onderzochte locaties. Deze bevindingen suggereren dat degeneratie alléén een onvoldoende verklaring is voor de associatie tussen leeftijd en een radiografische gewrichtsschade.
Vervolgens hebben we een mediatie-analyse uitgevoerd waarin we onderzochten of leeftijd een indirecte relatie heeft met radiografische gewrichtsschade. In dit cohort onderzochten we of symptoomduur, anti-citrullinated-peptide-antibodies (ACPA), reumafactor (RF), het aantal gezwollen gewrichten (SJC), C-reactive-protein (CRP) en ontsteking gevonden op MRI, een effect hadden op de associatie tussen leeftijd een radiografische gewrichtsschade. Een van onze hypotheses was dat oudere personen met gewrichtsklachten zich later melden en daarom ernstigere radiografische schade hebben bij binnenkomst. Echter, symptoomduur, ACPA, RF, SJC en CRP hadden geen invloed op de associatie tussen leeftijd en radiografische gewrichtsschade. We vonden dat oudere patiënten meer MRI-gedetecteerde ontsteking hebben en dat MRI-gedetecteerde ontsteking deels de associatie tussen leeftijd en radiografische gewrichtsschade verklaart. MRI-gedetecteerde ontsteking verklaart dus voor een deel de associatie tussen leeftijd en radiografische gewrichtsschade.
Een hogere leeftijd bij inclusie is dus geassocieerd met ernstigere radiografische gewrichtsschade, en dit kan deels verklaard worden door MRI-gedetecteerde ontsteking. Echter, deze laatste conclusie zal herhaald moeten worden in een groter cohort, aangezien onze analyse slechts uitgevoerd is in een kleine subgroep patiënten.

In **hoofdstuk 5** hebben we de associatie tussen body mass index (BMI) en MRI-gedetecteerde ontsteking onderzocht. Een toename van BMI is geassocieerd met toegenomen ontstekingsmarkers.[7] Bijzonder genoeg zijn er verschillende studies waarin een hoger BMI geassocieerd is met minder progressie van radiografische gewrichtsschade in RA.[8-11] Wij hebben derhalve onderzocht of er een associatie was tussen BMI en MRI-gedetecteerde ontsteking in 195 RA-patiënten, 159 patiën-

ten met andere inflammatoire artritiden en in 193 asymptomatische vrijwilligers. Een hoger BMI was inderdaad geassocieerd met ernstigere MRI-gedetecteerde ontsteking bij patiënten met andere inflammatoire artritiden en in asymptomatische vrijwilligers. Dit is conform de eerder gevonden associatie van toegenomen ontstekingsmarkers en BMI in de algehele populatie.[7] Echter, bij RA-patiënten is een hogere BMI geassocieerd met minder ernstigere MRI-gedetecteerde ontsteking. Dit is conform de eerder gevonden associatie tussen BMI en radiografische gewrichtsschade. Deze bevindingen zijn intrigerend, aangezien een hoger BMI over het algemeen geassocieerd is met een slechtere uitkomst bij RA-patiënten (functie en ziekte-activiteit).[12] Ook hebben RA-patiënten met een hogere BMI een verminderde respons op behandeling,[13] en hebben ze een verminderde kans dat ze weer klachtenvrij worden.[14] Dit zou veroorzaakt kunnen worden door het feit dat functioneel vermogen – en voor een deel ook ziekte-activiteit – afhankelijk zijn van zowel subjectieve als objectieve maten. Inderdaad blijkt een hoger BMI geassocieerd te zijn met hogere subjectieve maten (aantal pijnlijke gewrichten, patient global assessment) maar met gelijke objectieve maten (CRP, bezinking en aantal gezwollen gewrichten) in vergelijking met RA-patiënten met een lagere BMI.[15] Dus, een hogere BMI is geassocieerd met lagere MRI-gedetecteerde ontsteking en andere objectieve maten, maar met hogere subjectieve maten. Of dit consequenties heeft voor de kliniek moet nog onderzocht worden (bijvoorbeeld andere behandeling middels medicatie, andere of meer fysieke activiteiten).
Concluderend laat deze studie de BMI-paradox zien bij RA-patiënten in vergelijking met patiënten met andere inflammatoire artritiden en asymptomatische vrijwilligers. Een hoge BMI is geassocieerd met minder ernstige lokale ontsteking en minder ernstige gewrichtsdestructie. Een paradoxaal effect van BMI wordt ook gezien in het kader van mortaliteit; RA-patiënten met een hoge BMI hebben een lagere mortaliteit dan patiënten met een lagere BMI.[16]

In **hoofdstuk 6** onderzochten we de associatie tussen alcoholconsumptie en MRI-gedetecteerde ontsteking in patiënten met RA. Matige consumptie van alcohol lijkt een positief effect te hebben en is geassocieerd met een afname van ontstekingsmarkers en een verminderd risico op het krijgen van RA.[17-20] Ten eerste wilden

we bekijken of we de associatie tussen matige alcoholconsumptie en CRP-concentraties (als maat voor ontsteking) konden repliceren in 1070 RA-patiënten. We vonden inderdaad dat matige alcoholconsumptie (1 glas per week) geassocieerd was met de laagste CRP-concentraties. Vervolgens wilden we bekijken of matige alcoholconsumptie eveneens een positief effect had op MRI-gedetecteerde ontsteking, dit deden we in 188 RA-patiënten en 192 asymptomatische vrijwilligers. Tegen de verwachtingen in, vonden we geen associatie tussen alcohol en MRI-gedetecteerde ontsteking in zowel de RA-patiënten als de asymptomatische vrijwilligers. Matige alcoholconsumptie is dus positief geassocieerd met een lagere systemische ontsteking maar niet met MRI-gedetecteerde ontsteking.

Een afname in botdichtheid (BMD) wordt gezien bij patiënten die net gediagnosticeerd zijn met RA.[21-23] Bij patiënten met RA is BMD-verlies ook wel geassocieerd met ernstigere radiografische gewrichtsschade. In patiënten met UA[ref 23] is BMD-verlies een voorspeller voor de ontwikkeling van RA (23). Echter, het is onbekend in welke mate BMD veranderingen aanwezig zijn in de fase voordat artritis klinisch aanwezig is. Dit hebben wij onderzocht in **hoofdstuk 7**, in het Clinically Suspect Arthralgia (CSA) cohort, bestaande uit 108 CSA-patiënten. In deze groep werd een MRI gemaakt bij aanvang en digitale X-ray radiogrammetry op twee opeenvolgende conventionele röntgenfoto's van de handen werd gebruikt om de BMD te bepalen. Deze BMD-veranderingen werd gestandaardiseerd naar BMD-verlies per maand. We zagen dat BMD-verlies (gedefinieerd als een verlies van ≥ 2.5 mg/cm^2/maand), gevonden werd in een klein deel van de CSA-patiënten. Tevens zagen we dat bij een ernstigere MRI-gedetecteerde ontsteking bij aanvang, een groter BMD-verlies werd gevonden in de maanden volgend op de MRI. Samen met de bevindingen van veranderde botmakers in de preklinische fase van RA,[24,25] suggereren deze data dat het botmetabolisme veranderd is bij sommige patiënten in de symptomatische fase voorafgaande aan klinisch evidente artritis.

Conclusies en toekomstperspectieven

In deze thesis hebben we aangetoond dat de prevalentie van ontsteking en erosies in de algehele, asymptomatische bevolking, erg afhankelijk is van leeftijd en de locatie van de laesie(s). De RAMRIS-methode houdt geen rekening met deze factoren. In de praktijk nemen radiologen, bij de beoordeling van een diagnostische MRI, al verschillende factoren mee in de beoordeling (leeftijd, locatie van de laesie(s)). Maar naast deze factoren neemt een radioloog ook nog andere factoren mee, zoals het patroon van de ontsteking. Het verschil tussen de RAMRIS-methode en de daadwerkelijke beoordeling van een radioloog benadrukt de nadelen van het gebruik van de RAMRIS-methode in de diagnostiek van RA. Er is dus behoefte aan een andere scoringsmethode die deze verschillende factoren (bijvoorbeeld leeftijd, locatie, patroon, mate van afwijkingen in de algehele populatie) wel meeneemt in de beoordeling. De waarde van deze scoringsmethode voor de diagnostiek van RA moet uiteraard nog wel gevalideerd worden in longitudinale cohorten van patiënten.

Tevens, als MRI-data van asymptomatische vrijwilligers gebruikt gaat worden als een referentie, dan zullen controles met grotere groepen nodig zijn om er zeker van te zijn dat er voldoende personen zijn in de verschillende leeftijdscategorieën. Naast MRI zijn er ook nog andere beeldende technieken die een toevoeging kunnen zijn bij de beoordeling van ontsteking in gewrichten in de kliniek. Je kan hierbij denken aan echografie, positron emission tomografie (PET) en single photon emission computed tomografie (SPECT).[26] In de kliniek is echografie goed beschikbaar. Echter, echografie kan bijvoorbeeld geen BME detecteren en de beoordeling is erg afhankelijk van degene die de echografie uitvoert.[26] De additionele waarde van echografie of MRI als een diagnostisch middel bij de beoordeling van RA zal derhalve onderzocht moeten worden in een directe vergelijking tussen deze twee methoden. Tevens zou de waarde van SPECT en PET bij de detectie van vroege ontsteking bij RA moeten worden onderzocht. Bij al deze studies is het van belang om te kijken naar de specificiteit. Hoewel er recent een onderzoek is gepubliceerd waarin gekeken is naar bevindingen op echografie in asymptomatische vrijwilligers,[27] is ook hier nog extra onderzoek nodig.

Afgezien van een accurate prognose, is het nog onbekend hoe vroeg het nuttig is om RA te behandelen. De vroeg-detectie van RA is erg belangrijk, aangezien behandeling in een vroege klinische fase van de ziekte de klinische uitkomst aanzienlijk verbetert.[28] Beeldende technieken zouden aanzienlijk kunnen bijdragen aan de vroege detectie van ontsteking op een eerder tijdspunt in vergelijking met de huidige diagnostische middelen. Hierdoor zou behandeling eerder, zo mogelijk zelfs in een pre-artritis fase, gestart kunnen worden. Echter, het is onbekend of de behandeling in zó'n vroege fase daadwerkelijk leidt tot betere klinische uitkomsten in vergelijking met het starten van de behandeling bij de eerste klinisch detecteerbare artritis.

In de literatuur is een hogere leeftijd geassocieerd met ernstigere radiografische gewrichtsschade.[29-34] Ook wij vonden in hoofdstuk 3 een hogere prevalentie van MRI-gedetecteerde erosies op een hogere leeftijd. Hoewel deze laesies asymptomatisch en vaak klein waren, kunnen dit wel plekken zijn waar zich radiografische gewrichtsschade ontwikkelt. Eerdere studies wijzen inderdaad uit dat botten met MRI-gedetecteerde erosies vatbaarder zijn voor de ontwikkeling van erosies op conventionele röntgenfoto's.[35] Dus, omdat oudere personen meer MRI-gedetecteerde erosies hebben in vergelijking met jongere personen, zou radiografische gewrichtsschade zich sneller kunnen ontwikkelen in oudere RA-patiënten. Deze hypothese zou getoetst moeten worden in toekomstig onderzoek.

In het kader van de bevindingen van de invloed van BMI op de ernst van gewrichtsschade bij RA-patiënten, zijn er aanvullende onderzoeken nodig om de achterliggende biologische processen te ontrafelen. De uitkomsten uit een recente studie bij muizen suggereren dat artritis eerder begint bij overgewicht door neutrofiele rekrutering. Echter, zodra RA evident aanwezig is, blijkt overgewicht geen invloed meer te hebben omdat op dat punt er geen verschil meer is in leukocyten, T-cel populatie en chemoattractanten tussen slanke muizen en muizen met overgewicht.[36] De ernst van de gewrichtsschade is niet onderzocht in deze studie.

Er is veel discussie over de voor- en nadelen van het drinken van een tot twee alcoholische consumpties op een dag. De positieve effecten van matige alcoholconsumptie worden wel vaker genoemd bij verschillende ziekten (bijvoorbeeld

hart- en vaatziekten). Echter, onze data laten zien dat matige alcoholconsumptie geen positieve invloeden heeft op de gewrichten van RA-patiënten.
Alle studies die tot dusverre onderzoek hebben gedaan naar botmetabolisme in de preklinische fase van RA, bestonden slechts uit kleine aantallen deelnemers. Om het veranderde botmetabolisme daadwerkelijk te valideren in de symptomatische fase voorafgaand aan klinisch evidente artritis, zijn groter opgezette studies nodig. De cohorten met artralgie-patiënten groeien echter gestaag en daarom zal dit onderzoek in de nabije toekomst al mogelijk zijn.
RA is een multifactoriële ziekte, waarbij genetische en omgevingsfactoren van invloed zijn.[37-38] De best bekende omgevingsfactor, roken, is uitgebreid onderzocht in het verleden.[39] De relatie tussen de ontwikkeling van RA en andere factoren zoals BMI en alcoholconsumptie is echter minder bekend.[19,20,40] In dit proefschrift hebben we twee van deze factoren nader onderzocht, (BMI en alcoholconsumptie). We hebben onderzocht of deze factoren van invloed waren op MRI-gedetecteerde ontsteking. Een limitatie van deze onderzoeken is de cross-sectionele opzet van de studie. Hoewel hieruit naar voren kwam dat BMI geassocieerd was met MRI-gedetecteerde ontsteking, zijn longitudinale studies nodig om inderdaad te bevestigen dat een lagere ontsteking bij patiënten met overgewicht inderdaad geassocieerd is met minder radiografische progressie.
De follow-up van symptomatische patiënten zonder klinisch detecteerbare artritis in longitudinale studies zou zeer waardevol kunnen zijn. In deze cohorten zouden de patiënten opgevolgd kunnen worden waardoor de volgorde van gebeurtenissen gevolgd kan worden in relatie tot omgevingsfactoren. Hierbij kan de invloed van deze omgevingsfactoren op de ontwikkeling van RA nader onderzocht worden. Zo zou bijvoorbeeld onderzocht kunnen worden of gewichtsverlies enig effect zou kunnen hebben op MRI-gedetecteerde ontsteking en of dit mogelijk zelfs de progressie naar RA zou kunnen afremmen. Tevens zou de invloed van alcohol beter onderzocht kunnen worden. De longitudinale studies zouden ons begrip over de biologische mechanismen, die ten grondslag liggen aan een aantal associaties die we onderzocht hebben in deel II van dit proefschrift, doen toenemen. Om de pathofysiologie in de vroege fasen van RA beter te begrijpen is toekomstig onderzoek nodig. In dit onderzoek moet in meer detail gekeken worden naar de biologi-

sche mechanismen (bijvoorbeeld immunosenescence, inflammatoire eigenschappen van vetweefsel of botweefsel) die ten grondslag liggen aan, onder andere, de associaties gevonden in dit proefschrift.
Concluderend laten de onderzoeken uit dit proefschrift zien dat MRI-gedetecteerde ontsteking vaak gezien wordt in een asymptomatische populatie. Dit is van belang om mee te nemen bij de beoordeling van diagnostische MRI's of voor het bepalen van het al dan niet in remissie zijn van RA. Verder is aangetoond dat leeftijd, BMI en BMD geassocieerd zijn met MRI-gedetecteerde ontsteking. Deze, en andere beïnvloedende factoren, zouden het onderwerp moeten zijn van toekomstig onderzoek, om processen op te helderen die actief zijn in de vroege fasen van RA.

Bronnen

1 Colebatch AN, Edwards CJ, Østergaard M, van der Heijde D, Balint PV, D'Agostino M-A, et al. *EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis.* Ann Rheum Dis. 2013 Jun;72(6):804-14.

2 Nieuwenhuis W, Mangnus L, van Steenbergen H, Newsum E, Huizinga T, van der Helm - van Mil A. *Older age is associated with more MRI-detected inflammation in hand and foot joints.* Rheumatology (Oxford). in press.

3 Steenbergen HW van, Nies JAB van, Huizinga TWJ, Bloem JL, Reijnierse M, Mil AHM van der H. *Characterising arthralgia in the preclinical phase of rheumatoid arthritis using MRI.* Ann Rheum Dis. 2015 Jun 1;74(6):1225-32.

4 Østergaard M, Edmonds J, McQueen F, Peterfy C, Lassere M, Ejbjerg B, et al. *An introduction to the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas.* Ann Rheum Dis. 2005 Feb;64 Suppl 1:i3-7.

5 Haavardsholm EA, Ostergaard M, Ejbjerg BJ, Kvan NP, Kvien TK. *Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study.* Ann Rheum Dis. 2007 Mar 15;66(9):1216-20.

6 Landewé RBM, Strand V, Conaghan PG, Heijde D van der. *Damage and Progression on Radiographs in Individual Joints: Data from Pivotal Randomized Controlled Trials.* J Rheumatol. 2011 Sep 1;38(9):2018-22.

7 Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. *Elevated c-reactive protein levels in overweight and obese adults.* JAMA. 1999 Dec 8;282(22):2131-5.

8 van der Helm-van Mil AHM, Kooij SM van der, Allaart CF, Toes REM, Huizinga TWJ. *A high body mass index has a protective effect on the amount of joint destruction in small joints in early rheumatoid arthritis.* Ann Rheum Dis. 2008 Jun 1;67(6):769-74.

9 Baker JF, Østergaard M, George M, Shults J, Emery P, Baker DG, et al. *Greater body mass independently predicts less radiographic progression on X-ray and MRI over 1-2 years.* Ann Rheum Dis. 2014 Nov 1;73(11):1923-8.

10 Westhoff G, Rau R, Zink A. *Radiographic joint damage in early rheumatoid arthritis is highly dependent on body mass index.* Arthritis Rheum. 2007 Nov 1;56(11):3575-82.

11 Kaufmann J, Kielstein V, Kilian S, Stein G, Hein G. *Relation between body mass index and radiological progression in patients with rheumatoid arthritis.* J Rheumatol. 2003 Nov 1;30(11):2350-5.

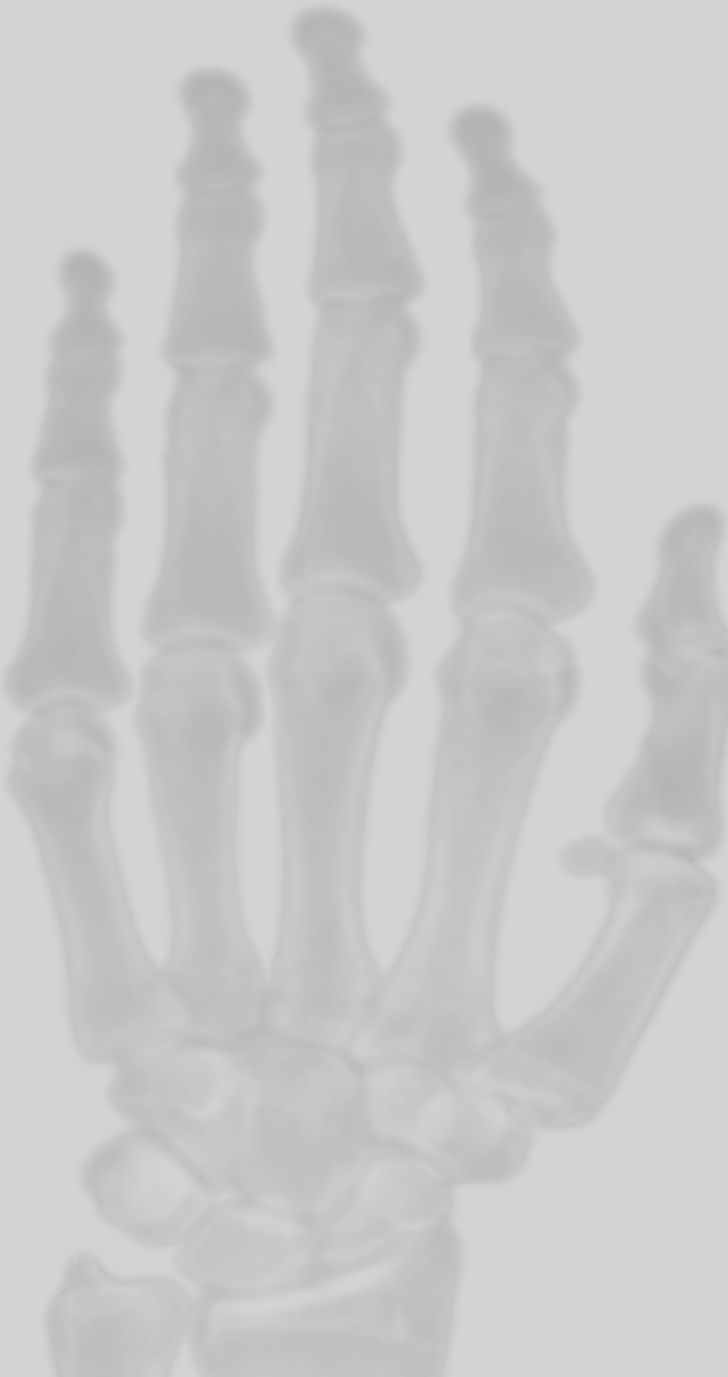
12 Ajeganova S, Andersson ML, Hafström I, for the BARFOT Study Group. *Association of obesity with worse disease severity in rheumatoid arthritis as well as with comorbidities: A long-term followup from disease onset.* Arthritis Care Res. 2013 Jan 1;65(1):78-87.

13 Heimans L, van den Broek M, le Cessie S, Siegerink B, Riyazi N, Han KH, et al. *Association of High Body Mass Index With Decreased Treatment Response to Combination Therapy in Recent-Onset Rheumatoid Arthritis Patients.* Arthritis Care Res. 2013 Aug 1;65(8):1235-42.

14 Gremese E, Carletto A, Padovan M, Atzeni F, Raffeiner B, Giardina AR, et al. *Obesity and reduction of the response rate to anti-tumor necrosis factor a in rheumatoid arthritis: An approach to a personalized medicine.* Arthritis Care Res. 2013 Jan 1;65(1):94-100.

15 Sandberg MEC, Bengtsson C, Källberg H, Wesley A, Klareskog L, Alfredsson L, et al. *Overweight decreases the chance of achieving good response and low disease activity in early rheumatoid arthritis.* Ann Rheum Dis. 2014 Nov 1;73(11):2029-33.
16 Escalante A, Haas RW, del Rincón I. *Paradoxical effect of body mass index on survival in rheumatoid arthritis: Role of comorbidity and systemic inflammation.* Arch Intern Med. 2005 Jul 25;165(14):1624-9
17 Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W. *Effect of alcohol consumption on systemic markers of inflammation.* The Lancet. 2001 Mar 10;357(9258):763-7.
18 Albert MA, Glynn RJ, Ridker PM. *Alcohol Consumption and Plasma Concentration of C-Reactive Protein.* Circulation. 2003 Jan 28;107(3):443-7.
19 Jin Z, Xiang C, Cai Q, Wei X, He J. *Alcohol consumption as a preventive factor for developing rheumatoid arthritis: a dose-response meta-analysis of prospective studies.* Ann Rheum Dis. 2014 Nov 1;73(11):1962-7.
20 Scott IC, Tan R, Stahl D, Steer S, Lewis CM, Cope AP. *The protective effect of alcohol on developing rheumatoid arthritis: a systematic review and meta-analysis.* Rheumatology. 2013 May 1;52(5):856-67.
21 Green MJ, Deodhar AA. *Bone changes in early rheumatoid arthritis.* Best Pract Res Clin Rheumatol. 2001 Mar;15(1):105-23.
22 Guler H, Turhanoglu AD, Ozer B, Ozer C, Balci A. *The relationship between anti-cyclic citrullinated peptide and bone mineral density and radiographic damage in patients with rheumatoid arthritis.* Scand J Rheumatol. 2008 Jan 1;37(5):337-42.
23 Rooy DPC de, Kälvesten J, Huizinga TWJ, Mil AHM van der H. *Loss of metacarpal bone density predicts RA-development in recent-onset arthritis.* Rheumatology. 2012 Jun 1;51(6):1037-41.
24 Turesson C, Bergström U, Jacobsson LTH, Truedsson L, Berglund G, Saxne T. *Increased cartilage turnover and circulating autoantibodies in different subsets before the clinical onset of rheumatoid arthritis.* Ann Rheum Dis. 2011 Mar 1;70(3):520-2.
25 Schaardenburg D van, Nielen MMJ, Lems WF, Twisk JWR, Reesink HW, Stadt RJ van de, et al. *Bone metabolism is altered in preclinical rheumatoid arthritis.* Ann Rheum Dis. 2011 Jun 1;70(6):1173-4.
26 McQueen FM. *Imaging in early rheumatoid arthritis.* Best Pract Res Clin Rheumatol. 2013 Aug;27(4):499-522.
27 Padovano I, Costantino F, Breban M, D'Agostino MA. *Prevalence of ultrasound synovial inflammatory findings in healthy subjects.* Ann Rheum Dis. 2016 Oct;75(10):1819-23.
28 Nies JAB van, Krabben A, Schoones JW, Huizinga TWJ, Kloppenburg M, Mil AHM van der H. *What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review.* Ann Rheum Dis. 2014 May 1;73(5):861-70.
29 Khanna D, Ranganath VK, FitzGerald J, Park GS, Altman RD, Elashoff D, et al. *Increased radiographic damage scores at the onset of seropositive rheumatoid arthritis in older patients are associated with osteoarthritis of the hands, but not with more rapid progression of damage.* Arthritis Rheum. 2005 Aug 1;52(8):2284-92.
30 van der Heijde DM, van Riel PL, van Leeuwen MA, van 't Hof MA, van Rijswijk MH, van de Putte LB. *Older versus younger onset rheumatoid arthritis: results at onset and after 2 years of a prospective followup study of early rheumatoid arthritis.* J Rheumatol. 1991 Sep;18(9):1285-9.

31 Innala L, Berglin E, Möller B, Ljung L, Smedby T, Södergren A, et al. *Age at onset determines severity and choice of treatment in early rheumatoid arthritis: a prospective study.* Arthritis Res Ther. 2014 Apr 14;16(2):R94.
32 Kuiper S, Gestel AM van, Swinkels HL, Boo TM de, Silva JA da, Riel PL van. *Influence of sex, age, and menopausal state on the course of early rheumatoid arthritis.* J Rheumatol. 2001 Aug 1;28(8):1809-16.
33 Calvo-Alén J, Corrales A, Sánchez-Andrada S, Fernández-Echevarría MA, Peña JL, Rodríguez-Valverde V. *Outcome of late-onset rheumatoid arthritis.* Clin Rheumatol. 2005 Oct 1;24(5):485-9.
34 Bukhari M, Lunt M, Barton A, Bunn D, Silman A, Symmons D. *Increasing age at symptom onset is associated with worse radiological damage at presentation in patients with early inflammatory polyarthritis.* Ann Rheum Dis. 2007 Mar 1;66(3):389-93.
35 Østergaard M, Hansen M, Stoltenberg M, Jensen KE, Szkudlarek M, Pedersen-Zbinden B, et al. *New radiographic bone erosions in the wrists of patients with rheumatoid arthritis are detectable with magnetic resonance imaging a median of two years earlier.* Arthritis Rheum. 2003 Aug 1;48(8):2128-31.
36 Kim S-J, Chen Z, Essani AB, Elshabrawy HA, Volin MV, Fantuzzi G, et al. *Differential impact of obesity on the pathogenesis of RA or preclinical models is contingent on the disease status.* Ann Rheum Dis. 2016 Oct 18;
37 Karlson EW, Chibnik LB, Tworoger SS, Lee I-M, Buring JE, Shadick NA, et al. *Biomarkers of Inflammation and Development of Rheumatoid Arthritis in Women From Two Prospective Cohort Studies.* Arthritis Rheum. 2009 Mar;60(3):641-52.
38 Alamanos Y, Drosos AA. *Epidemiology of adult rheumatoid arthritis.* Autoimmun Rev. 2005 Mar;4(3):130-6.
39 Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al. *Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies.* Ann Rheum Dis. 2010 Jan;69(1):70-81.
40 Qin B, Yang M, Fu H, Ma N, Wei T, Tang Q, et al. *Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis.* Arthritis Res Ther [Internet]. 2015 [cited 2016 Jul 4];17(1). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4422605/



List of publications

- Mangnus L,van Steenbergen HW, Reijnierse M, Kälvesten J, van der Helm-van Mil AHM, *Studying bone mineral density loss in clinically suspect arthralgia, associations with subclinical inflammation and progression to clinical arthritis*. Scan J Rheumatol. 2017 Jun;5:1-5

- Boeters DM, Mangnus L, Ajeganova S, Lindqvist E, Svensson B, Toes REM, Trouw LA, Huizinga TWJ, Berenbaum F, Morel J, Rantapää-Dahlqvist S, van der Helm-van Mil AHM. T*he prevalence of ACPA is lower in rheumatoid arthritis patients with an older age of onset but the composition of the ACPA response appears identical*. Arthritis Res Ther. 2017 May 31; 19(1):115

- Aizenberg E, Roex EAH, Nieuwenhuis WP, Mangnus L, van der Helm-van Mil AHM, Reijnierse M, Bloem JL, Lelieveldt BPF, Stoel BC. *Automatic quantification of bone marrow edema on MRI of the wrist in patients with early arthritis: A feasibility study*. Magn Reson Med. 2017 May 7

- Nieuwenhuis WP, van Steenbergen HW, Mangnus L, Newsum EC, Bloem JL, Huizinga TWJ, le Cessie S, Reijnierse M, van der Helm-van Mil AHM. *Evaluation of the diagnostic accuracy of hand and foot MRI for early Rheumatoid Arthritis*. Rheumatology(Oxford). 2017 apr 27

- Mangnus L, van Steenbergen HW, Reijnierse M and van der Helm-van Mil AHM, *Magnetic Resonance Imaging-Detected Features of Inflammation and Erosions in Symptom-Free Persons From the General Population*. Arthritis Rheumatol. 2016 Nov;68(11):2593-2602

- Mangnus L, Nieuwenhuis WP, van Steenbergen HW, Reijnierse M, van der Helm-van Mil AHM, *Body mass index and extent of MRI-detected inflammation: opposite effects in rheumatoid arthritis versus other arthritides and asymptomatic persons*. Arthritis Res Ther. 2016 Oct 22;18(1):245.

- Nieuwenhuis WP, Mangnus L, van Steenbergen HW, Newsum EC, Huizinga TW, Reijnierse M, van der Helm-van Mil AHM, *Older age is associated with more MRI-detected inflammation in hand and foot joints*. Rheumatology (Oxford). 2016 Dec;55(12):2212-2219

- Van Steenbergen HW, Mangnus L, Reijnierse M, Huizinga TWJ, van der Helm-van Mil AHM, *Clinical factors, anticitrullinated peptide antibodies and MRI-detected subclinical inflammation in relation to progression from clinically suspect arthralgia to arthritis*. Ann Rheum Dis. 2015 Nov 27.

- Mangnus L, van Steenbergen HW, Lindqvist E, Brouwer E, Reijnierse M, Huizinga TWJ, Gregersen PK, Berglin E, Rantapää-Dahlqvist S, van der Heijde D and van der Helm-van Mil AHM, *Studies on ageing and the severity of radiographic joint damage in rheumatoid arthritis*. Arthritis Research & Therapy 2015, 17:222

- Mangnus L, van den Bosch WB and A.H.M. van der Helm-van Mil, *Is the Squeeze test predictive for arthritis in the Metacarpophalangeal and Metatarsophalphalangeal joints?*. Ann Rheum Dis. 2015 Apr 24

- Mangnus L, Schoones JW and van der Helm-van Mil AHM, *What is the prevalence of MRI-detected inflammation and erosions in small joints in the general population? A collation and analysis of published data*. RMD Open 2015;1:e000005

- Mangnus L, Meijer DT, Stufkens SA, Mellema JJ, Steller EP, Kerkhoffs GM, Doornberg JN, *Posterior Malleolar Fracture Patterns*. J Orthop Trauma 2015 Sep;29(9):428-35

- Mangnus L, Bähler L, Nederkoorn PJ, *Inflammatie van de carotis-plaque als voorspeller voor een recidiefberoerte*. Ned Tijdschr Geneeskd, in het kort; 2012;156:A5334

Curriculum vitae

Lukas Mangnus werd op 2 Juli 1985 geboren als jongste zoon van Jeannette Mangnus-v.d. Elsen en Theo Mangnus. Hij groeide op in Tegelen. In 2002 deed hij zijn eindexamen havo aan het Valuascollege te Venlo. Direct aansluitend is hij begonnen met zijn opleiding Medisch Beeldvormde en Radiotherapeutische Technieken (MBRT) aan de Fontys in Eindhoven. Tijdens het laatste jaar van de MBRT studie begon hij op het Erasmus college te Eindhoven, om certificaten te halen zodat hij aansluitend aan de MBRT de studie Geneeskunde kon gaan doen. In 2006 rondde hij zijn MBRT-studie af en behaalde ook zijn examens scheikunde, biologie, natuurkunde en wiskunde op vwo-niveau. Na de decentrale selectie op de Vrije Universiteit in Amsterdam gedaan te hebben, begon hij daar in 2006 aan zijn studie Geneeskunde. Naast de geneeskundestudie bracht hij een groot deel van zijn tijd door op A.A.S.R. Skøll met voornamelijk wedstrijdroeien. Hier leerde hij ook Lonneke Bähler kennen. In 2013 rondde hij zijn geneeskundestudie af en aansluitend begon hij aan zijn promotietraject bij Reumatologie, waar hij onderzoek deed naar MRI in de vroege fases van reumatoïde artritis onder begeleiding van prof. dr. A.H.M. van der Helm-van Mil en prof. dr. T.W.J Huizinga. Tijdens zijn promotietraject trouwde Lukas met Lonneke Bähler en kregen zij 2 kinderen, Fiene en Tijn. Na zijn promotietraject is hij begonnen als arts-assistent niet in opleiding bij de afdeling cardiologie van het Spaarne Gasthuis te Haarlem, alvorens hij met zijn opleiding tot nucleair radioloog in het Academisch Medisch Centrum te Amsterdam begon.

Dankwoord

Graag wil ik hierbij de gelegenheid nemen om iedereen te bedanken die meegewerkt heeft aan de totstandkoming van dit proefschrift.
Allereerst wil ik alle vrijwilligers bedanken die hebben deelgenomen aan de verschillende studies en de research nurses en artsen die voor de inclusies en follow-up gezorgd hebben. Graag wil ik mijn promotores bedanken, prof. Dr. T.W.J. Huizinga en prof. dr. A.H.M. van der Helm-van Mil. Beste Tom, dank voor je oneindig enthousiasme en je motivatie richting het onderzoek en de hele afdeling. Annette, wat heb jij mij veel geleerd. Toen ik begon als promovendus had ik nog weinig echte onderzoekservaring. Je hebt me bij de hand genomen en me zelf laten ontdekken wanneer dit nodig was. Dr. Reijnierse, beste Monique bedankt voor de frisse kijk op mijn data en manuscripten.
De afgelopen jaren heb ik met veel plezier gewerkt op de afdeling reumatologie dankzij al mijn collega promovendi. Maar in het bijzonder wil ik Hanna, Elize, Leonie, Robin en Debbie bedanken voor de fijne samenwerking en de kritische blik op mijn data en manuscripten. In het bijzonder wil ik Wouter bedanken voor zijn eeuwige verbeterpunten en de precieze gedachte daarachter, gevraagd of ongevraagd. Ik zou geen andere collega als paranimf kunnen bedenken.
Jozé, Cedric, Nancy, Joyce en Hughine bedankt voor het openstaan voor vragen en de vrolijkheid die dit altijd met zich mee bracht.
Vanuit de radiologie-afdeling heb ik veel hulp gehad. In het bijzonder wil ik Tina en Hettie bedanken voor al het geregel van de roosters. En natuurlijk ook alle studenten die de MRI's hebben gemaakt.
Tijdens mijn promotie heb ik Wytse en Kay mogen begeleiden in hun wetenschappelijke stage. Tijdens het begeleiden heb ik veel van jullie geleerd en ik vond het leuk om te doen.
Lieve vrienden en vriendinnen, jullie wil ik bedanken voor al jullie broodnodige steun en gezelligheid in de afgelopen jaren.
Natuurlijk wil ik ook mijn schoonfamilie bedanken. Bedankt voor alle warmte die jullie mij hebben geboden en alle hulp die jullie ons door de jaren heen hebben gegeven. Daarin wil ik in het bijzonder Karlien bedanken die altijd voor ons klaar

staat om te helpen en Willem voor al het werk dat je doet aan het verwerken van dit manuscript tot een boek om trots op te zijn.
Lieve mam, Maarten, Lucie, Irene en Ellen. Ik wil jullie bedanken voor de interesse in mijn onderzoek, ook al was het af en toe wat abstract. Als gezin hebben we in de afgelopen jaren enorm veel meegemaakt. Ik wil jullie bedanken voor het gezamenlijk vieren van hoogtepunten en voor de steun, hulp en liefde tijdens het verwerken van de dieptepunten. René en pap we zullen jullie enorm missen. Pap ik wil je bedanken voor het meedenken bij mijn onderzoek, je enorme oprechte interesse en trots. Ik zal jullie altijd missen maar bij hoogtepunten zoals deze net nog dat beetje extra.
Lieve Lon, hoe kan ik jou bedanken voor alles wat je voor mij hebt gedaan en betekend. Zonder jou had ik nooit het zelfvertrouwen gehad om überhaupt aan een promotietraject te beginnen. Nooit hadden we van tevoren kunnen bedenken wat een roerige tijd het zou worden. Wat ben ik blij dat ik met jou alle momenten heb mogen delen, van de vele hoogtepunten zoals onze trouwdag, de geboorte van Fiene en van Tijn tot de vele dieptepunten. Zonder jouw liefde en steun had ik het nooit zo kunnen doorstaan. Lieve Fiene, Tijn en verwachte dochter, jullie vervullen mij van een trots en plezier welke ik voor jullie komst nog niet kende. Ik ben zo enorm benieuwd naar wat jullie de toekomst zullen brengen.