RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

# Rheumatoid arthritis, disease-modifying antirheumatic drugs and risk of major osteoporotic fracture: prospective data from the HUNT Study, Norway

Ingebjørg Tronstad ,[1,2] Mari Hoff,[3,4] Julie Horn,[1,5] Sigrid Anna Aalberg Vikjord,[1,6] Vibeke Videm ,[7,8] Jonas Johansson,[9] Tom Ivar Lund Nilsen,[10] Arnulf Langhammer[1,11]

**To cite:** Tronstad I, Hoff M, Horn J, *et al*. Rheumatoid arthritis, disease-modifying antirheumatic drugs and risk of major osteoporotic fracture: prospective data from the HUNT Study, Norway. *RMD Open* 2024;**10**:e003919. doi:10.1136/rmdopen-2023-003919

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/rmdopen-2023-003919).

Received 17 November 2023
Accepted 31 January 2024



For numbered affiliations see end of article.

**Correspondence to**
Dr Ingebjørg Tronstad; ingebjorg.tronstad@ntnu.no

## ABSTRACT

**Objectives** Rheumatoid arthritis has been associated with increased fracture risk. New treatments have improved the course of the disease substantially, but it is not clear if this influences fracture risk. We examined if rheumatoid arthritis, overall and according to disease-modifying antirheumatic drugs (DMARDs), is associated with a risk of major osteoporotic fractures.

**Methods** Overall, 92 285 participants in the population-based Nord-Trndelag Health Study (HUNT), Norway were included and linked with hospital records for a validated rheumatoid arthritis diagnosis (n=605), type of DMARD treatment and fracture diagnosis. Participants were followed up until the first major osteoporotic fracture, death, emigration or end of follow-up. Cox regression was used to estimate HRs for fractures among individuals with rheumatoid arthritis, overall and by DMARD treatment, compared with participants without rheumatoid arthritis.

**Results** A total of 9670 fractures were observed during follow-up, of which 88 were among those with rheumatoid arthritis. Compared with the reference group of participants without rheumatoid arthritis, those with the disease had an HR of fracture of 1.41 (95% CI 1.13 to 1.74). The association was largely similar for users of csDMARDs (HR 1.44; 95% CI 1.15 to 1.81), whereas the association for bDMARD users was weaker and less precise (HR 1.19; 95% CI 0.64 to 2.21).

**Conclusion** Participants with rheumatoid arthritis had a 40% higher risk of fracture than participants without the disease. A similar fracture risk was observed for conventional synthetic DMARD use, whereas there was weak evidence that the use of biological DMARDs may be associated with a somewhat lower fracture risk.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The increased risk of fragility fractures in rheumatoid arthritis is well documented. Over the last decades, new treatments and treatment strategies have been implemented into clinical practice, improving the outcomes of rheumatoid arthritis substantially.

⇒ However, so far, most studies have failed to show any difference in fracture preventive abilities between conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARDs) and biological (b) DMARDs in rheumatoid arthritis, and little is known when it comes to the influence of different DMARD treatment regimens on fracture risk in rheumatoid arthritis compared with the general population.

⇒ We aimed to investigate whether rheumatoid arthritis overall and by DMARD treatment are at risk of major osteoporotic fractures compared with individuals without rheumatoid arthritis.

### WHAT THIS STUDY ADDS

⇒ Overall, individuals with rheumatoid arthritis had a 40% increased risk of major osteoporotic fractures compared with participants without rheumatoid arthritis.

⇒ A similar fracture risk was seen in participants with rheumatoid arthritis assigned csDMARDs. We found, however, weak evidence that bDMARD use may be associated with a somewhat lower fracture risk, that is, more comparable to those without rheumatoid arthritis.

## INTRODUCTION

Osteoporotic fractures are common extra-articular comorbidities reported in rheumatoid arthritis,[1] an autoimmune disease characterised by chronic inflammation in joints as well as systemic organ involvement of the skeleton, lungs, cardiovascular system and nervous system.[2 3] It is well documented that individuals with rheumatoid arthritis are at increased risk of fractures compared with those without rheumatoid arthritis, and a meta-analysis reported a relative risk of 1.52.[1] The negative effect on the bone structure

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

⇒ Our findings suggest that individuals treated with bDMARDs might have the same fracture risk as individuals without rheumatoid arthritis. This finding could indicate that aggressive anti-inflammatory treatment is also favourable for preventing fractures.

⇒ Our findings might support the earlier introduction of bDMARDs in high-risk patients for osteoporosis and fractures, in addition to targeted antiosteoporotic treatment.

⇒ Further research over the years to come is needed to confirm our findings when longer follow-up periods for individuals initiating bDMARDs according to the treatment-to-target principle are available.

may involve several mechanisms, such as inflammation, inactivity and the use of glucocorticoids.[4]

Previous studies have reported that cytokines stimulate the receptor activator of nuclear factor kappa-B ligand (RANKL) pathway, with a net result of bone resorption over bone formation.[5] There has been significant improvement in the management of rheumatoid arthritis over the past two decades, especially with the introduction of biological disease-modifying antirheumatic drugs (bDMARDs) and the adoption of an early, aggressive anti-inflammatory treatment approach known as 'treat to target' (t2t).[6 7] Biological and targeted synthetic (ts) DMARDs directly influence inflammatory cytokines and signalling molecules, and studies have shown that bDMARDs inhibit both RANKL and osteoclasts, thereby preventing joint erosion and general bone loss.[8–10] Furthermore, studies on bDMARDs have demonstrated protective effects against generalised bone loss and favourable effects on bone resorptive markers.[8 10] Use of bDMARDs may therefore offer superior fracture prevention compared with conventional synthetic (cs) DMARDs alone. However, previous studies have mainly focused on bDMARD or tsDMARD treatment compared with csDMARDs, and most studies report no difference in fracture risk between the two groups.[11 12] There is limited knowledge on fracture risk in individuals with rheumatoid arthritis undergoing various DMARD treatments compared with the general population.

The aim of this study was therefore to investigate the risk of major osteoporotic fractures in participants with rheumatoid arthritis compared with participants without the disease and also examine fracture risk according to different DMARD treatment regimens.

## MATERIALS AND METHODS

### Study population

The Nord-Trøndelag Health Study (HUNT) is a population-based cohort study conducted in the geographical region of Nord-Trøndelag in central Norway and consists of four main surveys: HUNT1 (1984–1986), HUNT2 (1995–1997), HUNT3 (2006–2008) and HUNT4 (2017–2019). All inhabitants in the region aged ≥20 years were invited to participate in each survey. In HUNT 2, HUNT3 and HUNT4, 65 228 (69.5% of those invited), 50 800 (54.1%) and 56 042 (54%) chose to participate, respectively. Details of the HUNT Study have been described previously.[13] All participants in the HUNT Study are recorded with their unique 11-digit personal identification number. This allowed linkage to the Norwegian arthroplasty registry, which holds information on all joint and arthroplasties since 1987,[14] as well as hospital records in the catchment area for validated rheumatoid arthritis and fracture diagnoses since 1988.

For the purpose of the current study, a total of 96 433 participants who attended at least one of the HUNT2 to HUNT4 surveys were included. Among the included participants, 605 had rheumatoid arthritis (53 were diagnosed before the time of inclusion and 552 were diagnosed during follow-up), and 91 680 participants were never diagnosed with rheumatoid arthritis. Of all eligible participants, we excluded 4148 who were diagnosed with rheumatoid arthritis, experienced a fracture, emigrated or died before 1 January 2000, when bDMARDs were introduced in Norway. Individuals with rheumatoid arthritis never treated with DMARDs were excluded from the analyses (n=40) due to uncertainty around the underlying reasons for not being prescribed such treatment. The final study sample comprised 92 245 participants available for statistical analyses (figure 1).

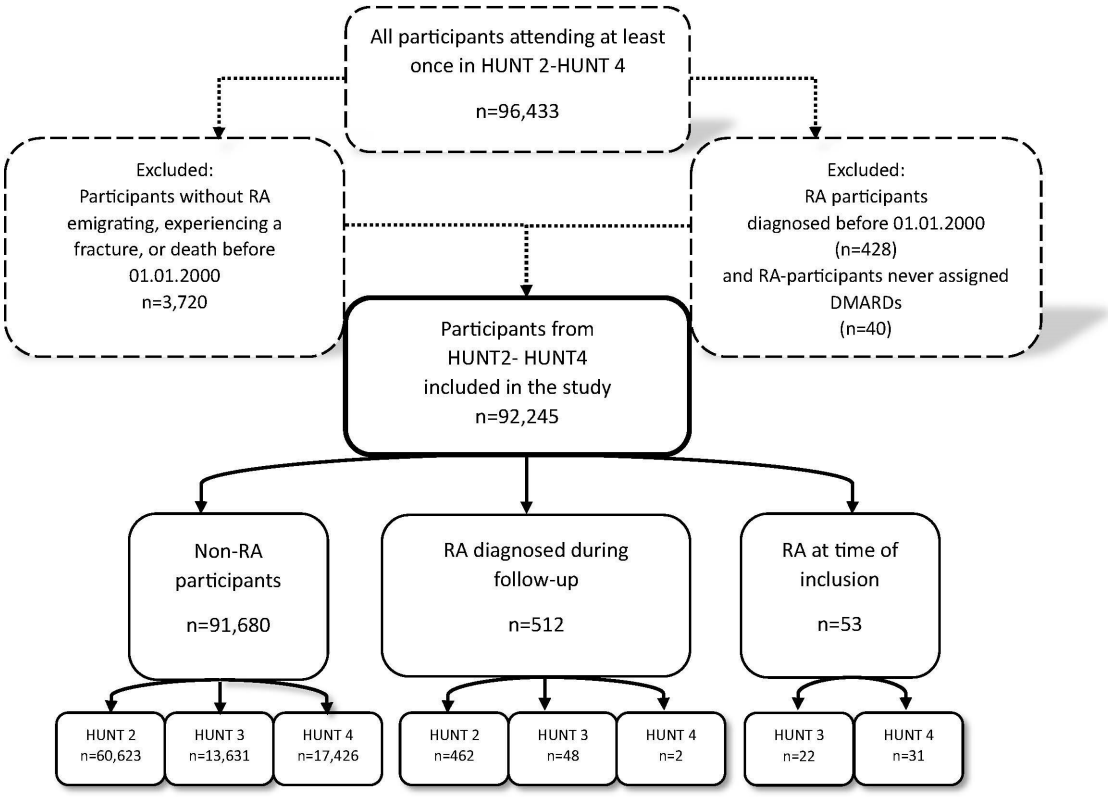
### Rheumatoid arthritis and medication

Due to the low validity of self-reported rheumatoid arthritis in the HUNT questionnaires, hospital records have been evaluated and only valid diagnoses, according to the American College of Rheumatology/(EULAR) 2010 criteria, were included.[15] Information regarding the use of DMARDs, date of diagnosis and serological status (seropositive or seronegative) was obtained by medical record review by the first author (IT). Date of initiation and type of DMARD prescription(s) by a rheumatologist were registered, as well as the DMARDsprescription duration and use of glucocorticoids and antiosteoporotic drugs. The use of medication was registered during the whole follow-up period.

Available DMARD treatments in Norway at the end of observation included: bDMARDs (tumour necrosis factor-alpha inhibitors (TNFi) (infliximab, golimumab, certolizumab, adalimumab and etanercept), T-cell inhibitors (abatacept), antibodies against B-lymphocytes (rituximab), interleukin (IL)-1 (anakinra), IL-6 inhibitors (tocilizumab) and Janus-kinase inhibitors (tofacitinib and baricitinib)) and csDMARDs (methotrexate, sulfasalazine, leflunomide and hydroxychloroquine). Participants using DMARDs were divided into categories of never users of any DMARDs, ever users of csDMARDs only and ever users of bDMARDs with or without previous or concomitant csDMARD use.

### Outcome

We used the following International Classification of Disease (ICD) codes, V.9 or V.10, to identify relevant




Abbreviations: RA= rheumatoid arthritis; Non-RA participants = participants without rheumatoid arthritis

**Figure 1** Inclusion of study participants by exposure status and time of inclusion. *RA, rheumatoid arthritis; **non-RA participants, participants without RA; ***excluded, n=40 never assigned disease-modifying antirheumatic drugs, all with first participation HUNT2; ****RA diagnosis before first HUNT-survey participation (diagnosed after 1 January 2000).

major osteoporotic fractures: the proximal humerus (812.0–812.3 and S42.2–S42.31), distal forearm (813.4, 813.5 and S52.5–S52.61), hip (820.0–820.3 and S72.0–S72.21) and spine (805.2–805.5, 806.0–806.5, S12.0–S12.21, S22.0–S22.1, S32.0–S32.01, T08 and T08.90). Whenever available, we also used the NOMESCO Classification of Surgical Procedure codes or 'classification of surgeries' codes from hospitals in the catchment area for fracture identification.

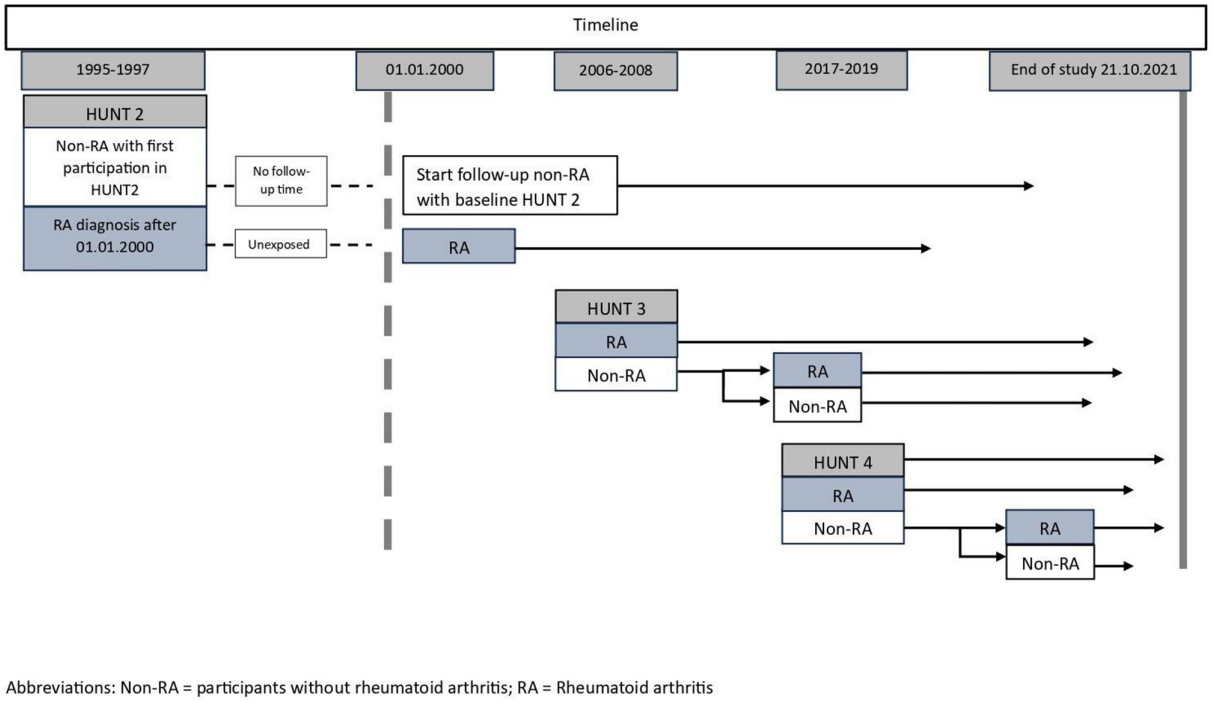
A fracture was defined as one of the following: (1) two identical ICD codes within 3 months, (2) one or more ICD codes for spinal fracture and (3) one ICD code in addition to a relevant surgical procedure code within 1 month prior to the ICD code or 2 months after the ICD code. Fractures were recorded from 1988 (the start of electronic recording) through 21 October 2021 and included fractures from outpatient clinics and hospital admission. Since bDMARDs were introduced as a treatment option for rheumatoid arthritis in Norway shortly before the year 2000, participants in the HUNT2 survey entered the study on 1 January 2000. Participants contributed person time as unexposed until the data of diagnoses of rheumatoid arthritis and then contributed person time as exposed until the date of an event (ie, fracture) or until censoring (figure 2). Similarly, participants with rheumatoid arthritis who were treated with csDMARDs contributed person time in this category and shifted exposure status to bDMARDs at the date of the change to the new treatment and contributed person time in this category thereafter.

## Other variables

Potential confounders were identified using directed acyclic graphs (DAGs) and included sex, baseline age (divided into 10-year age groups from age 20 to 100) and smoking status (categorised into never, current and previous smokers). Information on sex and age was obtained from the Central Person Registry upon participation in the HUNT Study. Information on smoking status was assessed from participants' first available HUNT questionnaire and not updated during follow-up. The final DAG is included in online supplemental figure 1.

## Statistical analyses

Incidence ratios (IRs) of fracture were calculated for participants with rheumatoid arthritis, both overall and according to the DMARD treatment group, and for




Abbreviations: Non-RA = participants without rheumatoid arthritis; RA = Rheumatoid arthritis

**Figure 2** Illustration of time of inclusion and follow-up. *Non-RA participants, participants without RA; **RA, rheumatoid arthritis.

participants without rheumatoid arthritis. Cox proportional hazards regression was used to estimate the crude and adjusted HRs of fractures associated with rheumatoid arthritis status and with the different DMARD treatments. All covariates were included as categorical variables in the model to allow for non-linear relationships with fracture risk. The precision of the estimated rates and HRs was assessed by a 95% CI. Violations of the proportional hazards assumption were evaluated by tests of Schoenfeld residuals and by visual inspection of log-log plots. The proportional hazards assumption was not met for age, and we, therefore, used a stratified Cox procedure based on 10-year age strata to control for potential confounding by age. Rheumatoid arthritis is more common in women and in advanced age; therefore, we evaluated a product term of rheumatoid arthritis and sex and rheumatoid arthritis and age (±45 years) in likelihood ratio tests to assess possible effect modification by these factors. Missing data on smoking status (n=1646) and DMARD treatment (n=1) were imputed using 20 imputations from a multinominal logistic regression including sex, HUNT survey, age, fractures and the Nelson-Aalen estimate of the cumulative baseline hazard. In sensitivity analyses, we also conducted analyses with delayed entry of 6 months, 1 year and 2 years in the csDMARD group after changing treatment status from csDMARDs to bDMARDs, since fractures occurring shortly after changing DMARDs may not be biologically related to bDMARD initiation. We also excluded individuals with fractures and rheumatoid arthritis diagnoses before baseline, with the aim of investigating the potential influence on the estimated fracture risk. Hip prosthesis surgery is common and might be a protective factor for hip fractures.[16] Analyses, including the date of hip prosthesis surgery as a competing risk for all fractures and hip fractures in rheumatoid arthritis compared with participants without rheumatoid arthritis, were performed using competing risk regression (stcrreg) in Stata. Statistical analyses were performed using Stata V.17.0 (StataCorp LCC, College Station, Texas, USA).

### Patients and public involvement

The HUNT Study collaborates with representatives from patient associations, the political and administrative bodies of municipalities and the country council through an advisory board. Furthermore, the leader of the regional osteoporosis association is involved in osteoporosis research.

## RESULTS

In total, 9670 fractures were observed during follow-up; 9582 fractures were registered in participants without rheumatoid arthritis (IR 6.4/1000 per person-year (PY)), and 88 (IR 16.2/1000 PY) fractures were registered in participants with rheumatoid arthritis. In the csDMARD group and bDMARD treatment group, 78 fractures (IR 17.4/1000 PY) and 10 fractures were registered (IR 10.5/1000 PY), respectively.

Participants with rheumatoid arthritis at the time of inclusion were on average diagnosed 5.4 years prior to inclusion (median 5 years). They had overall higher C reactive protein (CRP) levels, a lower estimated glomerular filtration rate (eGFR), worse self-reported health and older age at baseline compared with participants

**Table 1** Baseline characteristics of the study population according to RA status

| Baseline characteristics | Without rheumatoid arthritis, n=91 680 | With rheumatoid arthritis, n=605 | |
|---|---|---|---|
| | | Diagnosis at the time of inclusion, n=53 | Diagnosed during follow-up, n=552 |
| Women, n (%) | 48 634 (53.0) | 32 (60.4) | 350 (63.4) |
| Age, years, mean, (SD) | 45.7 (16.8) | 57.9 (16.5) | 51.5 (13.4) |
| Body mass index, kg/m², mean (SD) | 26.4 (4.4) | 27.4 (4.6) | 26.9 (4.2) |
| CRP, mg/L, mean (SD)* | 2.6 (5.2) | 5.2 (9.2) | 2.5 (3.1) |
| eGFR, mL/min/1.73 m², mean (SD)† | 101.7 (18.8) | 93.0 (22.1) | 97.3 (16.6) |
| Baseline survey, n (%) | | | |
| HUNT2 | 60 623 (66.1) | 0 (0) | 502 (90.9) |
| HUNT3 | 13 631 (14.9) | 22 (41.5) | 48 (8.7) |
| HUNT4 | 17 426 (19.0) | 31 (58.5) | 2 (0.4) |
| How is your health at the moment? n (%) | | | |
| Poor or not so good | 21 386 (23.3) | 28 (52.8) | 167 (30.3) |
| Good or very good | 69 233 (75.5) | 22 (41.5) | 378 (68.5) |
| Missing | 1061 (1.2) | 3 (5.7) | 7 (1.2) |
| Do you suffer from any longstanding illness? That impairs your function in everyday life? n (%) | | | |
| Yes | 29 956 (32.7) | 46 (86.8) | 192 (34.8) |
| No | 58 839 (64.2) | 6 (11.3) | 344 (62.3) |
| Missing | 2885 (3.1) | 1 (1.9) | 16 (2.9) |
| Smoking status, n (%)‡ | | | |
| Never | 40 476 (44.2) | 14 (26.4) | 165 (29.9) |
| Previous | 26 344 (28.7) | 21 (39.6) | 149 (27.0) |
| Current | 23 214 (25.3) | 18 (34.0) | 220 (39.8) |
| Missing | 1646 (1.8) | 0 (0) | 18 (3.3) |
| Major osteoporotic fracture, n (%) | 1795 (2.0) | 2 (3.8) | 5 (0.9) |
| Hip prosthesis at baseline, n (%)§ | 937 (1.0) | 1 (1.9) | 6 (1.1) |
| Years with RA diagnosis, mean (SD) | – | 5.4 (3.6) | – |

*CRP (n=38 981 in non-RA, n=50 in RA diagnosis at the time of inclusion and n=116 in RA diagnosis after inclusion).
†eGFR using CKD-EPI formula.[34]
‡Cigarette smoking categorised into never, previous and current smoker.
§Information on hip prosthesis of any cause (hip fracture, RA, cox arthrosis hip osteoarthritis and other) from 1987 were included from the Norwegian Arthroplasty register.[14]
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation ; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; HUNT, Nord-Trøndelag Health Study; RA, rheumatoid arthritis.

diagnosed with rheumatoid arthritis during follow-up and participants without rheumatoid arthritis (table 1).

Individuals treated with bDMARDs were younger at baseline and had higher CRP levels. They were also more likely to be female, current smokers, seropositive and use antiosteoporotic drugs and prednisolone compared with csDMARD users (table 2). Participants in the bDMARD group were followed up for an average of 6.0 years and had received treatment with csDMARDs for an average of 4.1 years (SD 4.2) before initiating bDMARDs. Participants in the csDMARD group had a mean follow-up of 7.8 years and csDMARDstreatment was initiated 0.3 (SD 1.4) years after inclusion (data not shown).

Participants in the bDMARDs group were followed up for an average of 6.0 years and had received treatment with csDMARDs for an average of 4.1 years (SD 4.2) before initiating bDMARDs (data not shown). Participants in the csDMARDs group had a mean follow-up of 7.8 years and csDMARDs treatment was initiated 0.3 (SD 1.4) years after inclusion (data not shown).

### Rheumatoid arthritis and DMARD association with fractures

Participants with rheumatoid arthritis had an HR of 1.41 (95% CI 1.13 to 1.74) for fractures compared with those without rheumatoid arthritis. Estimates remained nearly unchanged after excluding fractures and rheumatoid arthritis diagnoses before the time of inclusion (online supplemental table 1). No meaningful interaction between rheumatoid arthritis and age (p=0.34) or rheumatoid arthritis and sex (p=0.89) was observed.

Table 2 Descriptive characteristics of participants with rheumatoid arthritis by DMARD group

| | Participants with rheumatoid arthritis, n=605* | | |
|---|---|---|---|
| | Never DMARDs, n=40 | csDMARDs, n=418 | bDMARDs, n= 146 |
| Age, years, mean (SD) | 64.7 (11.8) | 53.3 (13.3) | 44.6 (11.7) |
| Women, n (%) | 21 (52.5) | 257 (61.5) | 103 (70.6) |
| Seropositive rheumatoid arthritis, n (%) | 19 (47.5) | 301 (72.0) | 126 (86.3) |
| CRP, mg/L, mean (SD)† | 4.1 (6.3) | 3.9 (7.3) | 7.5 (11.8) |
| Smoking status at baseline, n (%) | | | |
| Never | 17 (43.6) | 124 (30.8) | 37 (25.7) |
| Previous | 10 (25.6) | 125 (31.0) | 35 (24.3) |
| Current | 12 (30.8) | 155 (38.2) | 72 (50.0) |
| Use of antiosteoporotic drugs and/or calcium and vitamin D supplements, yes, n (%)‡ | 31 (52.5) | 307 (73.4) | 117 (80.1) |
| ≥5 mg prednisolone for ≥3 months, yes, n (%) | 32 (80.0) | 364 (87.1) | 138 (94.5) |
| Years with RA at the time of inclusion, mean (SD) | 0 | 4.6 (3.2) | 6.6 (3.9) |
| Mean duration of follow-up, years (SD)§ | 7.1 (6.6) | 7.8 (5.5) | 6.0 (5.0) |
| Type of initial bDMARD treatment | | | |
| TNFi | – | – | 125 (85.6) |
| Rituximab | – | – | 10 (6.8) |
| Other¶ | – | – | 11 (7.5) |

*One individual is missing DMARD status.
†Mean CRP values are presented for individuals with RA diagnosis at the time of inclusion in conventional synthetic DMARD and biological DMARD users. In never DMARDs, mean CRP is calculated based on CRP levels for all participants with RA (RA diagnosis at the time of inclusion and RA diagnosis during follow-up) due to few registered CRP measurements in participants with RA at the time of inclusion never assigned DMARD treatment.
‡Including tablets with calcium and vitamin D.
§Mean follow-up non-RA 15.6 years (SD 8.9), median 15.
¶Other: in total, five individuals were treated with targeted synthetic DMARDs, one individual treated with abatacept and five individuals treated with IL-6 inhibitor.
DMARDs, disease-modifying antirheumatic drugs; IL-6, interleukin 6; non-RA, participants without rheumatoid arthritis diagnosis; RA, rheumatoid arthritis; TNFi, tumour necrosis factor-alpha inhibitor.

Participants treated with csDMARDs had an HR of 1.44 (95% CI 1.15 to 1.81), whereas participants treated with bDMARDs had an HR of 1.19 (95% CI 0.64 to 2.21) for fractures, both compared with participants without rheumatoid arthritis (table 3).

The sensitivity analyses with 6-month, 1-year and 2-year delayed entry showed that the HR of fractures in bDMARD users compared with participants without rheumatoid arthritis remained largely similar to the main results (online supplemental table 2). Moreover, including analysis of competing risk by hip prosthesis surgery did not influence the effect of rheumatoid arthritis on fracture risk (online supplemental table 3).

## DISCUSSION

In this study, individuals with rheumatoid arthritis overall had an increased risk of fractures compared with participants without rheumatoid arthritis. csDMARD users had a comparable fracture risk with participants with rheumatoid arthritis overall, and bDMARD users had a somewhat lower fracture risk, closer to participants without rheumatoid arthritis.

The increased risk of fractures related to rheumatoid arthritis is in line with the previously reported HR (1.37–1.78).[17–19] Higher CRP levels, in general,[20] disease duration and disease severity in rheumatoid arthritis participants at baseline are factors associated with fractures and might explain some of the difference in fracture risk observed between the two groups.[21 22] The observed incidence rate of fractures among persons with rheumatoid arthritis was comparable to the incidence rate published in a meta-analysis in 2018.[1] The substantial difference in the incidence rate between participants with rheumatoid arthritis and those without rheumatoid arthritis in our study might be due to differences in age and gender that were not accounted for in the crude estimates. This is also supported by the attenuation of the HRs in the multiadjusted analysis.

Table 3 Risk of fractures according to RA and treatment status

| | Number of fractures | Person years | Incidence ratio (95% CI) | Crude HR (95% CI) | Adjusted HR (95% CI) |
|---|---|---|---|---|---|
| Exposure status | | | | | |
| Non-RA | 9582 | 1 488 387 | 6.4 (6.3 to 6.6) | Ref. | Ref. |
| RA | 88 | 5442 | 16.2 (13.1 to 20.0) | 1.96 (1.59 to 2.42) | 1.41 (1.13 to 1.74) |
| RA by DMARD treatment | | | | | |
| Conventional synthetic DMARDs only | 78 | 4491 | 17.4 (13.9 to 21.7) | 2.11 (1.69 to 2.64) | 1.44 (1.15 to 1.81) |
| Ever biological DMARDs | 10 | 950 | 10.5 (5.7 to 19.5) | 1.27 (0.69 to 2.37) | 1.19 (0.64 to 2.21) |

Adjusted for: sex (female/male), age (divided into 10-year age groups from age 20–100) and smoking status (never, previous and current smokers).
DMARDs, disease-modifying antirheumatic drugs; RA, rheumatoid arthritis.

Chronic inflammation drives bone homeostasis towards bone resorption through cytokines, resulting in an elevated RANKL/osteoprotegerin (OPG) ratio as well as inhibition of the Wnt signalling pathway, with a net result of increased osteoclast activity and a reduction in osteoblast activity.[5 8] In studies on fracture risk in rheumatoid arthritis overall, different treatment regimens and disease activity most often have not been taken into consideration.[23] From our data, it is not known if patients had well-controlled disease since we are lacking data on disease activity. A study from Norway, with the enrolment of newly diagnosed patients with rheumatoid arthritis from 1999 to 2001 and a 10-year follow-up, found that almost 60% had high disease activity at baseline, with a decline to 9.7% with high disease activity after 2 years of treatment. After 5 and 10 years, 42.0% and 27.4% had moderate disease activity, respectively, and the rest had low disease activity or clinical remission.[24] If we assume that our population with rheumatoid arthritis had the same development in disease activity after treatment initiation, the majority should have achieved a reduction in disease activity over the first years of treatment. Still, a non-negligible proportion had moderate disease activity after 5 and 10 years, indicating that not all individuals with rheumatoid arthritis are sufficiently treated. Individuals with rheumatoid arthritis who do not achieve low disease activity or remission are reported to have an increased risk of future fractures.[22]

Since the introduction of bDMARD or tsDMARD, studies have investigated these treatments' effects on bone mineral density (BMD),[8 25] bone resorptive markers[10] and fracture risk.[11 12] Several studies comparing the fracture risk in bDMARD users to csDMARD have concluded with no favourable effect of bDMARDs.[11 12] However, some studies have reported bDMARDs to have superior bone-sparing properties compared with csDMARDs alone,[25] as well as a positive effect on bone resorptive markers.[10] In the existing literature, little is known when it comes to the influence of different DMARD treatment regimens on fracture risk in rheumatoid arthritis compared with participants without rheumatoid arthritis.

Prescription of bDMARDs increased steadily from the year 2000 until the end of follow-up. Thus, in our study population, a higher percentage of included participants were assigned bDMARD treatment over the last years of the study. A Norwegian multicentre study from 2013 found that disease activity and inflammation in patients prescribed TNFi in combination with methotrexate (MTX) and MTX monotherapy for the first time decreased from high to moderate from the year 2000–2010. They also reported a reduction in time from diagnosis to initiation of csDMARDs and bDMARDs, as well as a twofold increase in 6-month remission rates over the same time period.[26] Individuals treated with bDMARDs initiated in early 2000 seem to be a stricter selected group, which does not necessarily provide the 'correct' picture of bDMARDs' efficiency in preventing fractures. We might first, in a few years, get a good picture of bDMARDs' influence on fracture risk in the rheumatoid arthritis population, with longer follow-up times for the increasing numbers of patients receiving bDMARDs after the t2t principle.

Antiosteoporotic drugs are important medications for the prevention of bone loss and fractures.[27] In our study, the percentage of individuals with rheumatoid arthritis registered with antiosteoporotic drug use was higher compared with a previous publication of antiosteoporotic drug use in the HUNT3 population.[28] This might be explained by differences in the registration of included medication between the two studies, as we registered calcium supplements with or without vitamin D as an antiosteoporotic treatment. If ever another antiosteoporotic treatment was assigned after the first registered treatment, this was not updated during our registration, making it impossible to compare the numbers with the previously published study without calcium or vitamin D medication. The favourable effect of antiosteoporotic treatment in rheumatoid arthritis, independently

of DMARD treatment, is reported in a study by Chen *et al*,[25] and the potentially favourable effect of bDMARD reported in our study might partly be due to a synergistic effect of bDMARD and antiosteoporotic drug use.

Investigating different medical treatments' effects on endpoints in observational studies is challenging and prone to several biases.[29] One concern is confounding by indication.[30] Due to the current and previous EULAR treatment recommendations, bDMARDs are indicated if csDMARDs have failed to acheive clinical remission or are not tolerated.[31] Years with rheumatoid arthritis, lack of clinical remission or achievement of low disease activity during the first 2 years after treatment initiation are shown to increase the risk of fractures.[21 22 32] In contrast to individuals with rheumatoid arthritis not achieving clinical remission, individuals with rheumatoid arthritis who achieved clinical remission showed no difference in BMD levels to the general population, supporting that t2t strategy contributes positively to bone health.[33] In our study, all evaluations of indications for DMARDs were made by rheumatologists. Individuals treated by bDMARDs most probably failed to achieve clinical remission or had higher disease activity at the time of changing treatment status, and therefore might have had a higher fracture risk compared with participants only on csDMARDs. This could mask the beneficial effect of bDMARD treatment on bone. We found that bDMARD users had a lower HR for fractures than csDMARD users when compared with participants without rheumatoid arthritis, despite expected higher disease activity or more severe disease in bDMARD users. This might indicate that bDMARD treatment has superior bone-sparing properties compared with csDMARDs, but this finding must be confirmed in larger studies.

Theoretically, it will take some time from the initiation of bDMARDs until the treatment is effective and could have any bone-sparing effect. Thus, fractures occurring shortly after initiating bDMARDs could be less related to the bDMARD treatment, and registration of fractures in the bDMARD group right after treatment change might lead to an overestimation of the fracture risk among participants treated with bDMARDs. The duration of a potential latency period is, however, uncertain. Treatment with bDMARDs has shown rapid changes in bone metabolism markers, with an increase in bone formation markers and a decrease in bone resorptive markers already after 14 weeks of treatment.[10] Several studies have reported favourable BMD levels in bDMARD users,[8] but the minimum duration of treatment that is needed to see changes in bone architecture is not well established. We included three different timespans for delayed entry after changing DMARD treatment (online supplemental table 2) with results supporting our main findings, but due to the low number of cases and short follow-up time, the findings are difficult to interpret in further detail.

The strengths of our study include the population-based design with long follow-up and the high validity of exposure and outcome data. We included validated diagnoses of rheumatoid arthritis,[15] outcomes and prescribed medication in rheumatoid arthritis participants were obtained from local hospital data, and DMARDs were only prescribed by rheumatologists. Detailed information provided precise temporality between the time of diagnosis and treatment initiation. Immortal time bias is a concern in studies on treatment effects on outcomes.[29] We tried to minimise this type of misclassification by letting participants with rheumatoid arthritis contribute to follow-up time in different treatment groups during follow-up, depending on which treatments they were assigned, allowing continuous censoring during the whole follow-up period.

One limitation is that our data did not provide information on disease activity or bone metabolism markers at the time of inclusion or during follow-up, leaving us unable to evaluate whether participants on different treatment regimens achieved remission during follow-up. Despite having over 600 participants with rheumatoid arthritis, we had a limited number of cases per treatment group, providing some uncertainty in our estimates. A direct comparison of fracture risk between csDMARD and bDMARD users would be of interest but was not included in our manuscript due to low statistical power. We had no information on antiosteoporotic drugs in participants without rheumatoid arthritis, and a comparison of antiosteoporotic treatment between participants with rheumatoid arthritis and participants without rheumatoid arthritis was not possible. Our population was recruited from a population-based health survey, and there is always a possibility of 'healthy cohort selection', not including participants more severely affected by rheumatoid arthritis. However, most of our participants with rheumatoid arthritis were included prior to diagnosis. Some participants might have experienced a fracture outside Trøndelag County, but this is likely to have had a minor influence on the results since most fracture controls are performed and registered at local hospitals.

## CONCLUSION

Overall, individuals with rheumatoid arthritis were at increased risk of fractures compared with the general population. An increased fracture risk was also seen in csDMARD users compared with individuals without rheumatoid arthritis. However, our findings showed weak evidence that the fracture risk in bDMARDs might be comparable to participants without rheumatoid arthritis, indicating that anti-inflammatory treatment and/or antiosteoporotic treatment are important for fracture prevention in this patient group. This finding may be of importance not only for individuals with rheumatoid arthritis but also for society when considering the substantial economic burden associated with fractures.

**Author affiliations**
[1]HUNT Research Centre, Department of Public Health and Nursing, Norwegian University of Science and Technology, Faculty of Medicine and Health Sciences, Levanger, Trøndelag, Norway

[2]Department of Medicine and Rehabilitation, Nord-Trøndelag Hospital Trust, Levanger Hospital, Levanger, Trøndelag, Norway
[3]Department of Rheumatology, St Olavs Hospital Trondheim University Hospital, Trondheim, Trøndelag, Norway
[4]Neuromedicine and Movement Science, Norwegian University of Science and Technology, Faculty of Medicine and Health Sciences, Trondheim, Trøndelag, Norway
[5]Department of Obstetrics and Gynecology, Nord-Trøndelag Hospital Trust, Levanger Hospital, Levanger, Trøndelag, Norway
[6]Clinic of Thoracic and Occupational Medicine, St Olavs Hospital Trondheim University Hospital, Trondheim, Trøndelag, Norway
[7]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Faculty of Medicine and Health Sciences, Trondheim, Trøndelag, Norway
[8]Department of Immunology and Transfusion Medicine, St Olavs Hospital Trondheim University Hospital, Trondheim, Trøndelag, Norway
[9]Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Troms, Norway
[10]Department of Public Health and Nursing, Norwegian University of Science and Technology, Faculty of Medicine and Health Sciences, Trondheim, Trøndelag, Norway
[11]Nord-Trøndelag Hospital Trust, Levanger, Norway, Levanger Hospital, Levanger, Trøndelag, Norway

**Acknowledgements** The Trøndelag Health Study (HUNT) is a collaboration between the HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), Trøndelag County Council, Central Norway Regional Health Authority and the Norwegian Institute of Public Health. We want to thank clinicians and other employees at Nord-Trøndelag Hospital Trust for their support and for contributing to data collection. The authors thank the Norwegian orthopaedic surgeons for conscientiously reporting to the Norwegian Arthroplasty Register (NAR) and the staff at the NAR for entering the data and providing statistical advice. A poster of this work was presented at the 2023 European League Against Rheumatic Disease (EULAR) Congress, and the congress abstract is published in the EULAR Congress Abstract Book.

**Contributors** IT ran the main analyses with guidance from TILN, SAAV, JH, MH and AL and also wrote the main draft of the manuscript. All authors participated in the design, critical revision of the manuscript and approved the final manuscript. VV and MH have previously validated rheumatoid arthritis diagnoses in the HUNT material. AL is responsible for the overall content as the guarantor.

**Funding** The study was founded by the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU), grant number 19/3888.

**Competing interests** JH: grants or contracts from any entity; grant from the Liaison Committee for education, research and innovation in Central Norway, grant number 17/38297; payment made to NTNU; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events and paid activity as speaker for the Norwegian Physiotherapist Association, presentation March 2023. SAAV: payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events; paid activity for meeting presentations for Astra Zeneca and GSK; congress participation by Astra Zeneca; participation on a Data Safety Monitoring Board or Advisory Board; participation in advisory boards for Astra Zeneca; leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid and member of the Young Researcher's Society, Norway.

**Patient consent for publication** Not applicable.

**Ethics approval** The Regional Committee for Medical and Health Research Ethics Central Norway approved the study (project number 246732). HUNT Study participants have given written consent for using the data in clinical research as well as to linking data to registries.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. To protect participants' privacy, HUNT Research Centre aims to limit storage of data outside HUNT databank and cannot deposit data in open repositories. HUNT databank has precise information on all data exported to different projects and are able to reproduce these on request. There are no restrictions regarding data export given approval of applications to HUNT Research Centre. For more information see: http://www.ntnu.edu/hunt/data.



**ORCID iDs**
Ingebjørg Tronstad http://orcid.org/0009-0003-5603-9529
Vibeke Videm http://orcid.org/0000-0002-1042-3889

## REFERENCES

1 Jin S, Hsieh E, Peng L, *et al*. Incidence of fractures among patients with rheumatoid arthritis: a systematic review and meta-analysis. *Osteoporos Int* 2018;29:1263–75.
2 Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet* 2016;388:2023–38.
3 Kim JW, Suh CH. Systemic manifestations and complications in patients with rheumatoid arthritis. *J Clin Med* 2020;9:2008.
4 Pietschmann P, Butylina M, Kerschan-Schindl K, *et al*. Mechanisms of systemic osteoporosis in rheumatoid arthritis. *IJMS* 2022;23:8740.
5 Epsley S, Tadros S, Farid A, *et al*. The effect of inflammation on bone. *Front Physiol* 2020;11:511799.
6 Smolen JS, Aletaha D, Bijlsma JWJ, *et al*. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010;69:631–7.
7 Stoffer MA, Schoels MM, Smolen JS, *et al*. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. *Ann Rheum Dis* 2016;75:16–22.
8 Zerbini CAF, Clark P, Mendez-Sanchez L, *et al*. Biologic therapies and bone loss in rheumatoid arthritis. *Osteoporos Int* 2017;28:429–46.
9 Schett G. Effects of inflammatory and anti-inflammatory cytokines on the bone. *Eur J Clin Invest* 2011;41:1361–6.
10 Vis M, Havaardsholm EA, Haugeberg G, *et al*. Evaluation of bone mineral density, bone metabolism, osteoprotegerin and receptor activator of the NFkappaB ligand serum levels during treatment with infliximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2006;65:1495–9.
11 Shao F, Li H-C, Wang M-J, *et al*. Impact of biologic disease-modifying antirheumatic drugs on fracture risk in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci* 2021;25:3416–24.
12 Abtahi S, Cordtz R, Dreyer L, *et al*. Biological disease-modifying antirheumatic drugs and osteoporotic fracture risk in patients with rheumatoid arthritis: a Danish Cohort Study. *Am J Med* 2022;135:879–88.
13 Åsvold BO, Langhammer A, Rehn TA, *et al*. Cohort profile update: the HUNT Study, Norway. *Int J Epidemiol* 2023;52:e80–91.
14 Helse Bergen. Norwegian national advisory unit on arthroplasty and hip fractures. 2023. Available: https://helse-bergen.no/nasjonal-kompetansetjeneste-for-leddproteser-og-hoftebrudd/norwegian-national-advisory-unit-on-arthroplasty-and-hip-fractures
15 Videm V, Thomas R, Brown MA, *et al*. Self-reported diagnosis of rheumatoid arthritis or ankylosing spondylitis has low accuracy: data from the Nord-Trøndelag Health Study. *J Rheumatol* 2017;44:1134–41.
16 Kjeldgaard HK, Meyer HE, O'Flaherty M, *et al*. Impact of total hip replacements on the incidence of hip fractures in norway during 1999-2019. A Norwegian Epidemiologic Osteoporosis Studies (NOREPOS) Study. *J Bone Miner Res* 2022;37:1936–43.
17 Erwin J, Enki DG, Woolf AD. Younger people with rheumatoid arthritis are at increased risk of fracture even before age 50 years: a population-based cohort study. *Osteoporos Int* 2021;32:1651–9.
18 Nyhäll-Wåhlin BM, Ajeganova S, Petersson IF, *et al*. Increased risk of osteoporotic fractures in Swedish patients with rheumatoid arthritis despite early treatment with potent disease-modifying anti-rheumatic drugs: a prospective general population-matched cohort study. *Scand J Rheumatol* 2019;48:431–8.

19 Amin S, Gabriel SE, Achenbach SJ, *et al*. Are young women and men with rheumatoid arthritis at risk for fragility fractures? A population-based study. *J Rheumatol* 2013;40:1669–76.
20 Schett G, Kiechl S, Weger S, *et al*. High-sensitivity C-reactive protein and risk of nontraumatic fractures in the Bruneck study. *Arch Intern Med* 2006;166:2495–501.
21 Choi S, Kwon S-R, Jung J-Y, *et al*. Prevalence and fracture risk of osteoporosis in patients with rheumatoid arthritis: a multicenter comparative study of the FRAX and WHO criteria. *JCM* 2018;7:507.
22 Ajeganova S, Andersson M, Forslind K, *et al*. Long-term fracture risk in rheumatoid arthritis: impact of early sustained DAS28-remission and restored function, progressive erosive disease, body mass index, autoantibody positivity and glucocorticoids. A cohort study over 10 years. *BMC Rheumatol* 2023;7:23.
23 Xue A-L, Wu S-Y, Jiang L, *et al*. Bone fracture risk in patients with rheumatoid arthritis: a meta-analysis. *Medicine (Baltimore)* 2017;96:e6983.
24 Haugeberg G, Bøyesen P, Helgetveit K, *et al*. Clinical and radiographic outcomes in patients diagnosed with early rheumatoid arthritis in the first years of the biologic treatment era: a 10-year prospective observational study. *J Rheumatol* 2015;42:2279–87.
25 Chen J-F, Hsu C-Y, Yu S-F, *et al*. The impact of long-term biologics/target therapy on bone mineral density in rheumatoid arthritis: a propensity score-matched analysis. *Rheumatology* 2020;59:2471–80.
26 Aga A-B, Lie E, Uhlig T, *et al*. Time trends in disease activity, response and remission rates in rheumatoid arthritis during the past decade: results from the NOR-DMARD study 2000-2010. *Ann Rheum Dis* 2015;74:381–8.
27 van der Burgh AC, de Keyser CE, Zillikens MC, *et al*. The effects of osteoporotic and non-osteoporotic medications on fracture risk and bone mineral density. *Drugs* 2021;81:1831–58.
28 Hoff M, Skurtveit S, Meyer HE, *et al*. Anti-osteoporosis drug use: too little, too much, or just right? The HUNT study, Norway. *Osteoporos Int* 2018;29:1875–85.
29 Suissa S, Dell'Aniello S. Time-related biases in pharmacoepidemiology. *Pharmacoepidemiol Drug Saf* 2020;29:1101–10.
30 Catalog of Bias. Confounding by indication. 2018. Available: https://catalogofbias.org/biases/confounding-by-indication/
31 Smolen JS, Landewé RBM, Bijlsma JWJ, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020;79:685–99.
32 van Staa TP, Geusens P, Bijlsma JWJ, *et al*. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. *Arthritis Rheum* 2006;54:3104–12.
33 Yoshii I, Chijiwa T, Sawada N. Rheumatoid arthritis in tight disease control is no longer risk of bone mineral density loss. *Osteoporos Sarcopenia* 2020;6:75–81.
34 Levey AS, Stevens LA, Schmid CH, *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–12.
35 Tronstad I, Hoff M, Horn J, *et al*. Pos0175 "Do disease modifying antirheumatic drugs influence the fracture risk in rheumatoid arthritis?" the hunt study, Norway. EULAR 2023 European Congress of Rheumatology, 31 May - 3 June. Milan, Italy; 2023:311–2