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Male patients with inflammatory joint diseases are less likely than controls to be childless: results from a Norwegian population-based cohort study of 10 865 patients

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ABSTRACT

Objectives To investigate the number of children per man and the proportion of childless men as a proxy of fertility in a national cohort of men with inflammatory joint diseases (IJDs), compared with matched controls from the general population.

Methods This is a nationwide, population-based retrospective cohort study. Male patients with IJDs (n = 10 865) in the Norwegian Arthritis Registry were individually matched 1:5 on birth year and county of residence with men without IJDs obtained from the National Population Register (n = 54 325). Birth data were obtained from the Medical Birth Registry of Norway. We compared the mean number of children per man and the proportion of childless men and analysed the impact of age and year of diagnosis.

Results The mean number of children per man in the patient group was 1.80 versus 1.69 in the comparison group (p <0.001), and 21% of the patients in the patient group were childless versus 27% in the comparison group (p <0.001). The finding of less childlessness and higher number of children per man remained consistent across age at diagnosis, except for those diagnosed at age 0–19 years. The difference in childlessness was most pronounced for men diagnosed after year 2000, especially when diagnosed at 30–39 years of age (22% vs 32%, p<0.001).

Conclusion In this large cohort study we found that patients with IJD have a higher number of children and are less likely to be childless compared with controls. Factors associated with developing or having an IJD might influence fertility and this requires further investigation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There are limited data regarding fertility in male patients with inflammatory joint diseases (IJDs) but an association between inflammatory arthritis and reduced male fertility has been suggested, underlining the need for a large-scale study.

WHAT THIS STUDY ADDS

⇒ In this well-powered nationwide study, we show that male patients with IJDs have more children and are less likely to be childless compared with an age-matched and residence-matched control population.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Male patients with IJD may be reassured that no impairment of fertility is expected. However, substudies according to specific diagnoses should be performed to offer more targeted patient information.

⇒ Our finding of less childlessness and a higher number of children per man in patients with IJD is novel and generates new hypotheses regarding associations between fertility, inflammatory rheumatic diseases and immune-modulating drugs. This ought to be investigated further.

INTRODUCTION

Autoimmune diseases are on the rise in the western world,[1–3] and several studies have found an association between certain autoimmune diseases[4–7] and male infertility. Factors associated with the autoimmune disease itself, as well as medication used to treat the disease, could potentially all affect fertility.[8]

In the field of rheumatology, impaired fertility has been reported in Norwegian women with inflammatory joint diseases (IJDs).[9–11] However, there is a lack of large studies regarding male fertility, a problem well summarised in several systematic reviews.[12–14] The British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding was the first international guideline to produce recommendations regarding prescription of antirheumatic drugs in male subjects wishing to father. In the 2022 update it is stated that 'Although the evidence is weak, men who take rheumatological medicine should be reassured about the safety of conceiving'.[15] Still, like the European and American guidelines they emphasise that there are limited data on medication effects in men with rheumatic diseases. In the European Alliance of Associations for Rheumatology (EULAR) publication dealing with points to consider for use of antirheumatic drugs before pregnancy and during pregnancy and

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lactation, men were not included in the recommendations owing to lack of data.[16] Furthermore, the 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases stated that the evidence of recommendations for medical treatment in men was either not graded, or there was no, or low, strength of evidence.[17]

In the clinic, there is a low awareness of reproductive health in male patients with rheumatic disease.[18] Increased knowledge on this topic is of importance to reduce anxiety and prevent patients from stopping treatment when not necessary, as well as to identify those who need close follow-up during the period when they are trying to become fathers. So far, owing to the limited knowledge in this field, recommendations for male patients have been extrapolated from the literature on female reproduction and fertility. The 'iFAME-fertility' study published in 2021 found that inflammatory arthritis can impair male fertility,[19] underlining the need for more research to further address this association.

Although several factors apart from the direct influence of the IJD could also influence fertility in men, a high proportion of childless men can be considered a proxy of reduced fertility. Based on the observed impaired fertility in women with IJD, the aim of this study was to investigate the number of children per man and the proportion of childless men in a national cohort of 10 865 Norwegian men with IJD, compared with matched controls from the general population.

MATERIAL AND METHODS

Setting

This is a nationwide, population-based, retrospective cohort study, in which the number of children per man and the proportion of childless men is measured in male patients with IJDs and compared with a matched comparison group from the general population. Our data were extracted in August 2021 from the three following databases:

- The Norwegian Arthritis Registry (NAR), which is a national quality registry established in 2014. All rheumatology departments in Norway report to the registry and so far, more than 30 000 patients have been included, among whom 41% are men. Patients are enrolled at the time of diagnosis, although those who were diagnosed before NAR was established have been included retrospectively by the treating rheumatologist, based on data from the patient records. To be included, a relevant clinical diagnosis must be established by a specialist of rheumatology. Patients and physicians report data to the NAR at each visit. The national completeness of NAR was 64% in 2021. Some centres started enrolling patients in 2014 and have a high completeness (>80%), whereas others just recently began inclusion.[20]
- The Medical Birth Registry of Norway (MBRN), which contains information about all births in Norway since 1967 and holds complete identification of the mother and the father by a unique national identification number. This makes it possible to link patient records and other national registries to the MBRN. The completeness of MBRN is close to 100%; hence we register men without match in MBRN as childless (figure 1).
- The National Population Register (NPR), which is a registry of all inhabitants in Norway, and forms the basis for the tax register, the electoral register and population statistics. NPR contains information concerning the following: date of birth, name, address, civil status and date of death, when relevant.

Study population

Our study population is described in figure 1. Men, aged 18 years or older, included in the NAR between 2014 and 2021 with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or spondyloarthritis (SpA) constitute the patient cohort (n=10 865). Patients with juvenile idiopathic arthritis are not registered in the NAR and were thus not included in our study. Of the included patients, 37% had a diagnosis of RA, 33% PsA and 30% SpA. For each patient, five male subjects matched by age and county of residence were randomly selected from the NPR, yielding a comparison cohort of 54 325 subjects.

Data from the MBRN were linked to the patient and comparison cohort data files to identify children fathered by the subjects. This gave us a total of 111 246 children born between 1967 and August 2021.

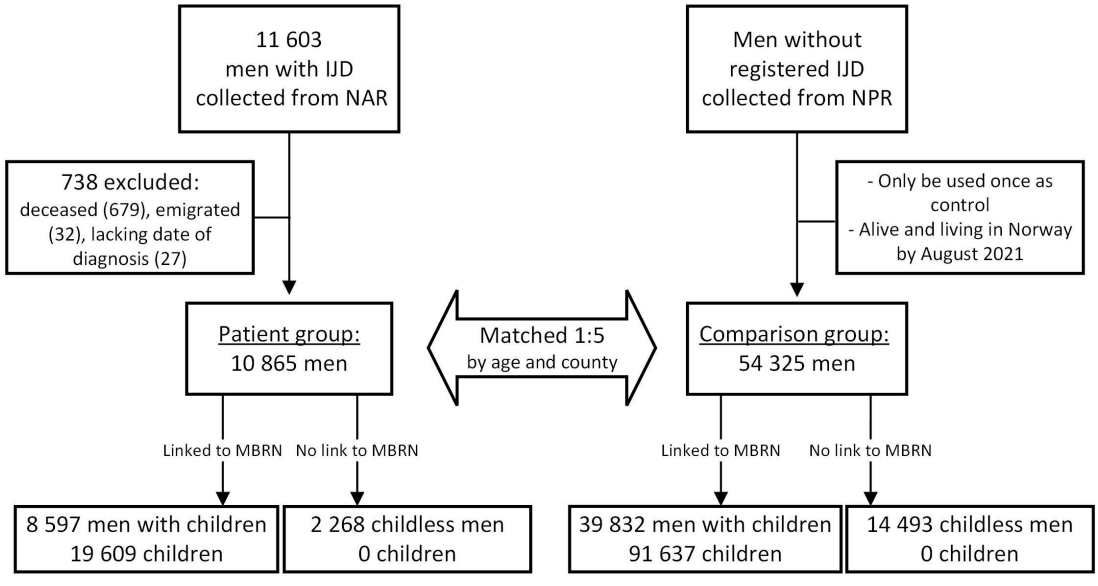

Figure 1 Selection process for the study population. IJD, inflammatory joint diseases; MBRN, Medical Birth Registry of Norway; NAR, Norwegian Arthritis Registry; NPR, National Population Register.

Table 1 Mean number of children and proportion of childless men in 2021 according to age at diagnosis

Age at diagnosis*	No of patients	Mean No of children per man			Percentage childless men		
		Patients	Comparisons	P value†	Patients	Comparisons	P value‡
All	10865	**1.80**	**1.69**	**<0.001**	**21**	**27**	**<0.001**
0–19	537	1.22	1.24	0.59	42	44	0.49
20–29	1946	1.41	1.31	<0.001	34	39	<0.001
30–39	2276	1.79	1.61	<0.001	20	28	<0.001
40–49	2344	1.94	1.80	<0.001	17	23	<0.001
50–59	2024	2.05	1.95	<0.001	15	19	<0.001
60–69	1257	2.03	1.98	0.16	13	17	<0.001
70–79	444	1.88	1.70	0.003	15	21	0.004
80–89	37	0.84	0.81	0.85	41	48	0.54

*The Medical Birth Registry of Norway contains information about births since 1967, and children born before this are not registered. This gives a lower mean number of children per man and higher percentage childless men in the elderly part of our study group.
†P values based on paired t-tests.
‡P values based on Cochran–Mantel–Haenszel χ^2 tests.

MBRN contains information about all births in Norway since 1967, and children born before this were not post-registered. This particularly affects the older part of the population, who were of reproductive age before 1967, and the apparent number of children in this age group will be lower than the actual number. For this reason, men over 70 years of age at data extraction are not included in figure 3A,B. The mean number of children per man as well as the percentage of childless men are shown according to age at diagnosis in table 1. Deceased patients and comparisons were excluded, rendering a low number of subjects in the oldest age category. Age at the date of data extraction in 2021 is not shown but ranges from 18 to 92 years. Patients of reproductive age at the time of data extraction might thus have become fathers after this date. However, the same also applies to the comparison group.

We looked at childlessness and the number of children born in three different time eras, reflecting major changes in drug treatment for IJDs: 1967–1985 (pre-methotrexate era, n=575), 1986–1999 (methotrexate era, n=1360), and 2000–2021 (biologic era, n=8930).

Outcome

The primary outcome of the present study was to investigate the number of children per man and the proportion of childless men (at the end of follow-up), as a proxy of fertility, in the patient versus the comparison cohort. In the patient group, all children were counted, regardless of the timing of the IJD diagnosis.

Ethics

All included patients signed written consent before inclusion in the NAR. In the consent form, they specifically agreed to the use of data in research and to the use of linkage to the Medical Birth Registry of Norway. The use and linkage of data files were approved by the regional ethics committee South-East Norway (no 147849). Possible impacts of the data handling for the included subjects were evaluated through the preparation of a data protection impact assessment.

Statistical analysis

We compared the mean number of children per man in the patient and comparison groups using paired t-tests, where the average number of children for the five controls served as the outcome for the comparison group. We compared the proportion of childless men using the Cochran–Mantel–Haenszel X^2 tests, with each patient–control group (six subjects) forming a strata. The results are reported as conditional (within-strata) ORs. The same statistical analyses were used when analysing subgroups according to era of diagnosis and age at diagnosis. In our analyses, we did not adjust for the father's age as the patients and comparisons are already matched by year of birth.

Estimates are given with 95% confidence intervals. A two-sided p value <0.05 was set as the level of significance, and all data were analysed using R version 4.2.2.

Before the study, we performed a power analysis based on the paired t-test. For each age group, data from Statistics Norway indicate that the SD of the number of children is usually ≤1.3 (and much smaller for younger men). Based on this and a patient population of 11000 men with 55000 matched controls, the probability of detecting a mean difference of at least 0.1 children per male subject exceeds 99%.

Patient and public involvement

A patient who is a member of the Norwegian patient organisation 'Norsk Revmatikerforbund' was involved in the planning of the project and read and approved the study protocol. Later on, 'Norsk Revmatikerforbund' will be involved in disseminating new knowledge from the project to patients.

RESULTS

The mean number of children per man in the patient group was 1.80 versus 1.69 in the comparison group (mean difference 0.12, 95% CI 0.09 to 0.14, p < 0.001), and 21% of the patients were childless versus 27% in the comparison group (conditional OR=0.69, 95% CI 0.66 to 0.73, p < 0.001). The number of children in the patient and comparison groups, respectively, was as following: no children: 21% vs 27%; one child: 15% vs 14%; two children: 36% vs 33%; three children: 20% vs 19%; four or more children: 7% vs 7%. The observed difference was thus largely driven by the difference in childless men. The father's average age at first child was 27.6 years in the patient group and 28.2 in the comparison group, and the average age at diagnosis was 44 years.

The difference in childlessness and number of children between patients and comparisons was seen in all age groups, except the youngest one (figure 2A,B). Similarly, the proportion of childless men remained significantly lower in the patient group than in the comparison group for patients diagnosed between 20 and 79 years of age (table 1 and figure 2B).

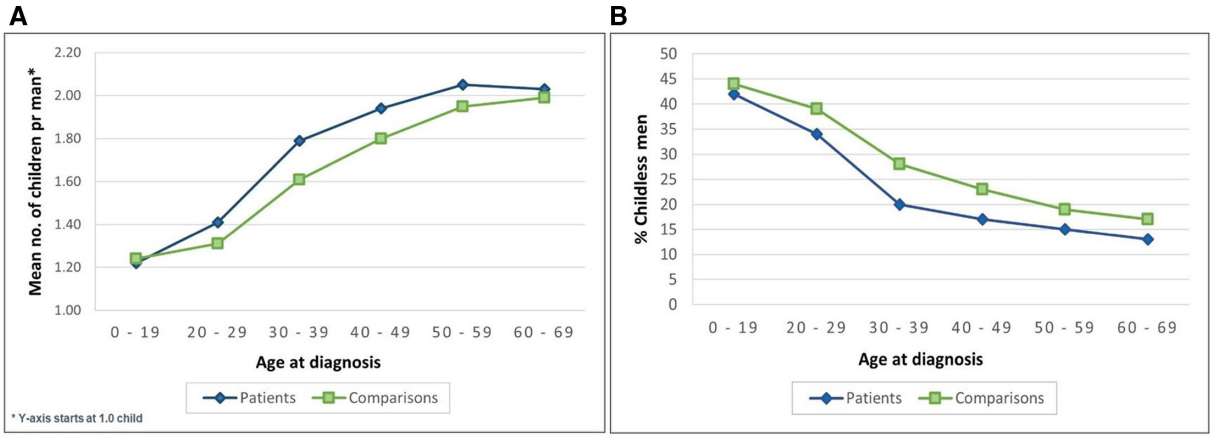

Figure 2 (A) Mean number of children per man in 2021 according to age of diagnosis. (B) Proportion of childless men in 2021 according to age at diagnosis.

The percentage of childless men and mean number of children per man according to time period of diagnosis are shown in figure 3A,B, and the difference in number of children was numerically highest for those diagnosed after year 2000 (figure 3A), with mean number of children 1.79 and 1.65, respectively. These patients also had the comparatively lowest risk of being childless (22% vs 28%) (figure 3B). These differences were less prominent for those diagnosed before 2000 (table 2).

Table 2 presents subanalyses for age at diagnosis in groups within each treatment era. In the 2000–2021 era, the largest absolute difference was seen in patients diagnosed at 30–39 years of age, where 22% of the patients versus 32% of the comparisons were childless ($p<0.001$). In the 1967–1985 and 1986–1999 eras, differences were also present, but less evident (table 2). Also, in these two eras, no statistically significant differences were found in the average number of children between patients and comparisons, although the patients generally tended to have more children.

DISCUSSION

In this large population-based retrospective cohort study, we examined childlessness and number of children as a proxy of fertility and showed that male patients with IJDs have more children and are less likely to be childless compared with controls. Although the finding was consistent over time, the greatest difference was seen in those diagnosed after year 2000.

Fertility is commonly defined as the number of children born to a woman.[21] A high proportion of childless men could therefore be considered a proxy of reduced fertility, but several factors aside from the direct influence of the IJD could also influence fertility in men, including psychological factors, socioeconomic factors, etc. Few studies have examined number of children and childlessness in men, but rather focused on other aspects of male fertility, such as production of healthy spermatozoa, the level of reproductive hormones and sexual function. Available literature on male fertility is based on small patient cohorts and inconsistent methodology,[12–14] with a general conclusion that fertility is compromised in several rheumatic diseases. Tengstrand *et al*[22] followed up 41 male patients with RA for 2 years and found lower testosterone levels at disease onset than in controls, but a significantly increasing level of testosterone when disease activity decreased. On the other hand, both Almeida *et al* and Micu *et al* reported no difference in semen quality between patients with SpA and a control group,[23 24] and Almeida *et al* found normal sex hormone levels in both groups. Impaired male sexual function has been reported as a more frequent problem in both patients with RA and those with SpA than in the general population. The reasons are presumably complex and caused by both disease activity, fatigue, reduced joint mobility and pain.[13]

In a cross-sectional study of more than 600 male patients with inflammatory arthritis (IA) (iFAME-fertility),[19] Perez-Garcia *et al* observed an association between IA and reduced male fertility when IA was diagnosed before and during peak reproductive years, while fertility rates remained normal when diagnosed after 40 years of age. No control group was included, and the response rate of the study was 34%. Both factors might have

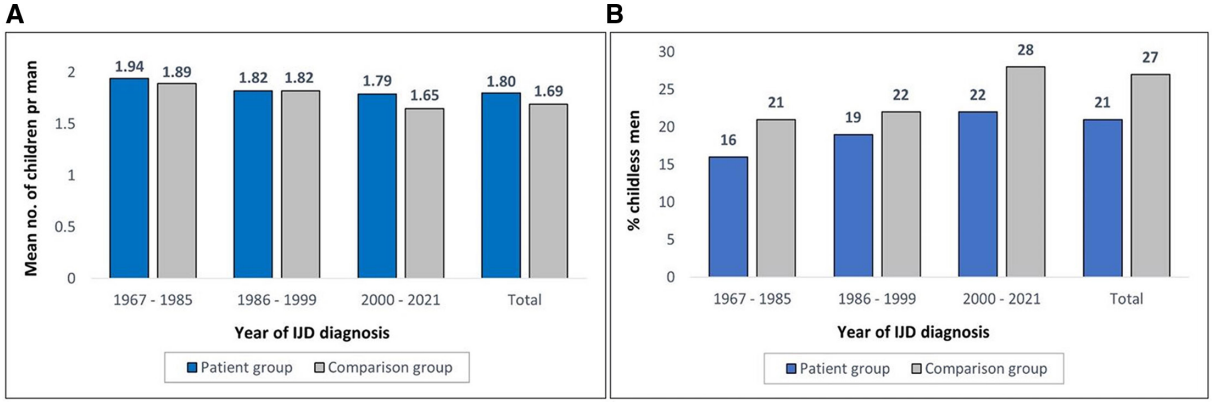

Figure 3 (A) Mean number of children per man in 2021 according to year of diagnosis. (B) Proportion of childless men in 2021 according to year of diagnosis.

Table 2 Mean number of children and proportion of childless men in 2021 according to year and age at diagnosis

Year of diagnosis*	Age (years) at diagnosis	No. of patients	Mean no. of children per man			Percentage childless men		
			Patients	Comparisons	P value†	Patients	Comparisons	P value‡
1967–1985		690	1.94	1.89	0.30	16	21	0.01
	0–19	194	1.76	1.85	0.38	20	22	0.53
	20–29	330	2.02	1.94	0.26	14	19	0.04
	30–39	130	2.12	1.93	0.09	13	19	0.15
	40–49	35	1.46	1.43	0.90	29	33	0.71
1986–1999		1561	1.82	1.82	0.87	19	22	0.01
	0–19	146	1.50	1.49	0.93	30	32	0.65
	20–29	495	1.70	1.72	0.72	23	26	0.18
	30–39	431	1.99	1.96	0.63	16	19	0.08
	40–49	356	1.99	1.96	0.70	14	17	0.23
	50–59	117	1.79	1.85	0.58	15	17	0.67
2000–2021		8614	1.79	1.65	<0.001	22	28	<0.001
	0–19	197	0.47	0.46	0.95	74	74	0.97
	20–29	1121	1.11	0.95	<0.001	45	51	<0.001
	30–39	1715	1.72	1.50	<0.001	22	32	<0.001
	40–49	1953	1.94	1.78	<0.001	17	24	<0.001
	50–59	1906	2.07	1.96	<0.001	15	19	<0.001
	60–69	1241	2.04	1.99	0.17	12	17	<0.001
	70–79	444	1.88	1.70	0.003	15	21	0.004

*The Medical Birth Registry of Norway contains information about births since 1967, and children born before this are not registered. This gives a lower mean number of children per man and higher percentage of childless men in the elderly part of our study group, and hence we have excluded the following categories from this table; diagnosis age 50–89 in era 1967–1985 (n=1), diagnosis age 60–89 in era 1986–1999 (n=16), diagnosis age 80–89 in era 2000–2021 (n=37).
†P values based on paired t-tests.
‡P values based on Cochran–Mantel–Haenszel χ^2 tests.

influenced the results and could explain the discrepancy between their findings and ours. Other reasons for our contrary findings might be the difference in socioeconomic conditions between The Netherlands and Norway. In Norway there are good economical compensations for people with chronic diseases and work difficulties, which could reduce a possible negative impact of having IJD.

Treatment for IJDs has vastly improved in recent decades owing to the introduction of potent immune-modulating drugs, new treatment strategies such as the 'treat to target' and new diagnostic tools—for example, ultrasound and MRI. Consequently, patients tend to have lower disease activity throughout the disease course, and they are generally less affected by their disease than previously.[25] To address this, we performed subanalyses in which the patients were divided into three groups, based on time era of disease onset, reflecting major changes in treatment strategy for the IJDs—methotrexate from the late 1980s and biological treatment from the early 2000s. Interestingly, our findings of fewer childless men and higher mean number of children were seen in all eras, but more pronounced and highly significant in the latest disease-onset era.

Whether the onset of the disease occurs before or after the reproductive age is likely to have an impact on fertility.[9 19] For this reason, we performed subanalyses according to age at diagnosis within the different treatment eras. For those diagnosed before 20 years of age, no differences in childlessness or number of children were seen between patients and controls. This group was small, however, partly because patients with juvenile idiopathic arthritis were not included, making it difficult to interpret this finding any further. Interestingly, when diagnosed during reproductive age, IJD did not influence the number of children fathered in a negative way, as described for women[9] and suggested in the iFAME-fertility study.[19] The finding of less childlessness was consistent also in patients diagnosed at older ages. The reason for this is not known but might indicate that factors other than the disease itself are also of relevance.

The question of whether drug treatment itself affects fertility is still debated.[26] The most commonly used drugs for treating IJDs are prednisolone, methotrexate (MTX) and tumour necrosis factor α (TNF-α) inhibitors. The use of TNF inhibitors in patients with SpA seems to improve sperm quality, probably as a result of reduced disease activity,[27] less sperm abnormalities[27 28] or as a direct effect on sperm function.[29] For low doses of MTX to treat rheumatic diseases, it has been unclear whether the drug affects fertility,[26] but a new iFAME-MTX study[30] did not show any testicular toxicity. In the present study, the most pronounced difference in number of children was seen in the group diagnosed at age 30–39 in the biological treatment era, where the percentage of childless men was 10% lower in the patients than in the comparison group. Whether this finding is related to the use of biological disease-modifying antirheumatic drugs might not be answered in the present study but should be addressed in future research.

Our study has some limitations. The data regarding diagnosis and date of diagnosis were collected from the NAR, which has a completeness of 64%. Despite incomplete coverage, the register is assumed to be representative, as patients are included at the time of diagnosis or at follow-ups, and lack of inclusion is mainly related to the fact that some centres only recently started to include patients and not all patients have yet been post-registered. Consequently, we believe that this does not represent a significant selection bias.

Fertility might be affected by several factors. Age and county of residence[31] are known to be of importance, since socioeconomic factors and cultural tradition can differ within Norway, and we adjusted for these variables by matching. The use of a comparison

group matched by birth year will also adjust for other time-dependent factors, such as environmental and cultural ones. Nevertheless, possible confounding factors like civil status, work participation, smoking and education might affect men's fertility and could be unevenly distributed between patients and the comparison group. Unfortunately, we did not have data regarding these factors and thus were unable to evaluate their possible effects on the risk of being childless in our patients compared with the general population. To investigate some plausible factors that could affect fertility, further studies are warranted—for example, regarding fertility according to the different IJD diseases, disease activity and patient-reported outcome measures, such as quality of life or fatigue, education and work disability.

In conclusion, in this large nationwide study, we observed that our patients with IJD had a significantly higher average number of children compared with the age-matched and residence-matched comparison group. This was largely driven by the lower proportion of childless men. The finding was consistent over time, even when studying subgroups according to era of diagnosis and age at diagnosis and was found for all but the youngest age group. Based on the large study population, matched population subjects and methods of analysis, we have little reason to doubt our findings. Factors associated with developing or having an IJD might influence fertility and need to be further investigated.

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Contributors All authors meet the authorship criteria. GDS, SH, MW, GB and B-TSF all contributed to the design of the work. GDS, SH and B-TSF carried out the acquisition of data for the work. KOH, GDS, SH and B-TSF contributed to the analysis of the data, and all authors were substantial contributors to interpretation of the data. All authors have also been significant contributors to critical revision of the article for important intellectual content and gave final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. GDS, SH and B-TSF are all guarantors and accept full responsibility for the work and the conduct of the study, had access to the data and controlled the decision to publish.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by all included patients who signed written consent prior to inclusion in the Norwegian Arthritis Registry. In the consent form, they specifically agreed to the use of data in research and to the use of linkage to Medical Birth Registry of Norway. The use and linkage of data files were approved by the regional ethics committee South-East Norway (no 147849). Possible impacts of the data handling for the included subjects were evaluated through the preparation of a data protection impact assessment. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The data that support the findings of this study are available in the Medical Birth Registry of Norway and the Norwegian Arthritis Registry:The Norwegian Arthritis Registry - NorArthritis - Helse Bergen (helse-bergen.no) Medical Birth Registry of Norway - NIPH (fhi.no).

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