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Original Article

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Clinical science

Patterns of reproductive health in inflammatory rheumatic diseases and other immune-mediated diseases: a nationwide registry study

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Abstract

Objectives: Rheumatic diseases may impair reproductive success and pregnancy outcomes, but systematic evaluations across diseases are lacking. We conducted a nationwide cohort study to examine the impact of rheumatic diseases on reproductive health measures, comparing the impacts with those of other immune-mediated diseases (IMDs).

Methods: Out of all of the 5 339 804 Finnish citizens, individuals born 1964–1984 and diagnosed with any of the 19 IMDs before age 30 (women) or 35 (men) were matched with 20 controls by birth year, sex, and education. We used data from nationwide health registers to study the impact of IMDs on reproductive health measures, such as reproductive success and, for women, ever having experienced adverse maternal and perinatal outcomes.

Results: Several of the rheumatic diseases, particularly SLE, JIA, and seropositive RA, were associated with higher rates of childlessness and fewer children. The risks for pre-eclampsia, newborns being small for gestational age, preterm delivery, non-elective Caesarean sections, and need of neonatal intensive care were increased in many IMDs. Particularly, SLE, SS, type 1 diabetes, and Addison's disease showed >2-fold risks for some of these outcomes. In most rheumatic diseases, moderate (1.1–1.5-fold) risk increases were observed for diverse adverse pregnancy outcomes, with similar effects in IBD, celiac disease, asthma, ITP, and psoriasis.

Conclusion: Rheumatic diseases have a broad impact on reproductive health, with effects comparable with that of several other IMDs. Of the rheumatic diseases, SLE and SS conferred the largest risk increases on perinatal adverse event outcomes.

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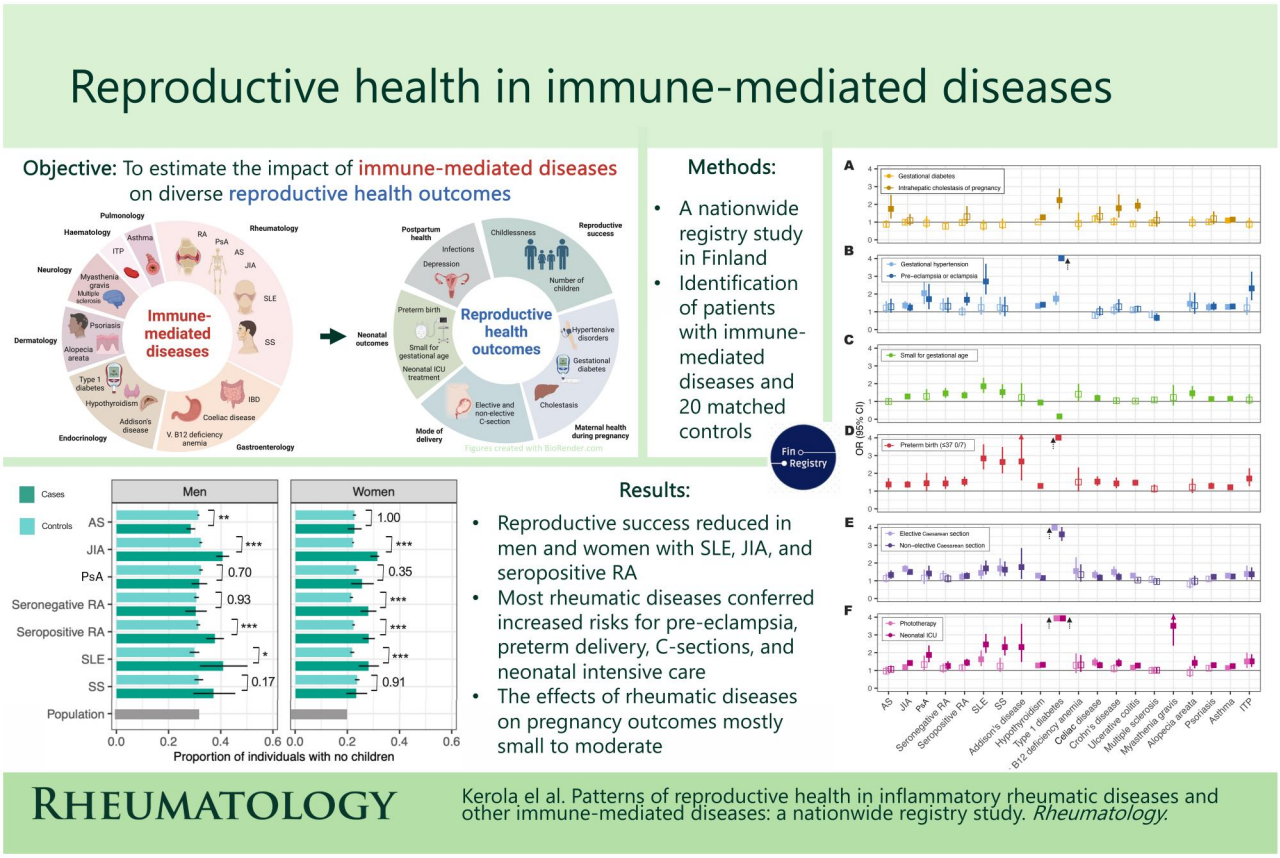
Graphical abstract



Keywords: autoimmune diseases, inflammatory rheumatic diseases, reproductive health, maternal health, male reproductive health.

Rheumatology key messages

- Reproductive success was impaired in men and women with seropositive RA, JIA and SLE.
- Most rheumatic diseases conferred increased risks for pre-eclampsia, preterm delivery, caesarean sections, and neonatal intensive care
- The effects of rheumatic diseases on pregnancy outcomes were mostly small to moderate.

Introduction

Immune-mediated diseases (IMDs) are a heterogeneous group of diseases with varying etiologies but each displaying an aberrant activity of the immune system as a common feature. Some IMDs, such as JIA and type 1 diabetes (T1D) are mostly diagnosed before the early reproductive years, and many other IMDs can also affect persons of reproductive age. Especially SLE has been actively studied regarding its impact on reproductive health, and it increases the risk for several adverse pregnancy outcomes, such as pre-eclampsia, preterm delivery, caesarean sections (C-sections), and infants classified as small for gestational age (SGA) [1, 2]. However, for many other rheumatic diseases and other IMDs, such as for the spondyloarthritides, psoriasis, and alopecia areata, data regarding fertility and pregnancy are more scarce or characterized by inconsistent results [3–6].

Many studies on reproductive health in IMDs are characterized by small sample sizes, with less systematic data available on unselected patient populations, few comparative studies across different IMDs, and even fewer looking at both women and men [7, 8]. Family planning and pregnancy represent a clinical challenge for health-care professionals treating patients with IMDs, but lack of high-quality data has limited the availability of evidence-based recommendations in the guidelines [9–11]. Moreover, with substantial therapeutic advances, such as earlier diagnosis and the use of biologics in inflammatory rheumatic diseases, updated estimates on reproductive health are warranted.

Using nationwide registry data comprising the entire Finnish population, including comprehensive data on all births within the country for 32 years, we set out to assess the impact of six rheumatic diseases on reproductive health, including impact on reproductive success, maternal and perinatal conditions, and postpartum health. The effects are compared with those of 13 IMDs across different specialties, including endocrinology, gastroenterology, neurology, dermatology and pulmonology, offering a broad perspective on

reproductive health in autoimmune and inflammatory diseases.

Methods

Study population

We studied all individuals in the FinRegistry ($N = 5\,339\,804$) alive on 1 January 2010 [12]. Individuals with any of the 19 IMDs were identified through the Care Register for Health Care (available 1969–) and the drug reimbursement registry (1968–), harmonizing diagnoses over International Classification of Diseases (ICD) revisions 8, 9 and 10 (Supplementary Table S1, available at *Rheumatology* online). Cases were identified from individuals born between 1964 and 1984, who had a first disease record before age 30 (women) or age 35 (men), and who were either alive at the end of follow-up on 31 December 2019, or had died at earliest at age 35 (flow chart in Supplementary Fig. S1, available at *Rheumatology* online). For each case, we identified 20 sex-, birth-year–, and education level–matched controls. All analyses were performed by sex (based on social security number).

Outcomes

The number of children was obtained from the Population Register. Since 1987, the Medical Birth Register includes data on live births and on stillbirths of fetuses (birth weight >500 g or gestational age >22 weeks), and data on mothers. From the Medical Birth Register, we obtained information on the mother's age at each delivery, and pregnancy-related characteristics and outcomes [number of prenatal visits, smoking status, oral glucose tolerance test (OGTT), use of insulin, gestational age at birth, birth weight, mode of delivery, admission to neonatal intensive care unit (NICU), need of phototherapy, length of hospital stay]. See Supplementary Methods, available at *Rheumatology* online for definitions of fertility treatments, gestational diabetes, gestational hypertension, and pre-eclampsia or eclampsia, and the postpartum outcomes (uterine infection, puerperal sepsis, postpartum depression, and mastitis). We analysed the use of the child home-care allowance by the parent (mean weeks per child; allowance used by 90.7% of women and by 3.7% of men in our dataset, analyses therefore performed only for women).

All variables were classified as ever/never having the outcome, unless otherwise specified. Details on the outcome definitions are found in the Supplementary Methods, available at *Rheumatology* online.

Statistical analysis

Analyses were performed for outcomes with at least 20 IMD cases with the outcome. The follow-up ended on 31 December 2019 or at the time of death. Effect sizes with 95% CIs were estimated with logistic regression (for binary outcomes) and linear regression (continuous outcomes; after model assumption evaluation), adjusting for birth year and mother's age at delivery (mean across her deliveries). For gestational diabetes and pre-eclampsia or eclampsia, sensitivity analyses were performed adjusting for pre-pregnancy BMI (mean of each woman's measurements, obtained from the Medical Birth Registry). Due to the explorative nature of the project, no multiple testing adjustments were performed, with $P < 0.05$ being the threshold for statistical significance. All tests were two-sided. Analyses were performed with R version 4.1.1.

Ethics statement

FinRegistry is a joint project of the Finnish Institute for Health and Welfare (THL) and the Data Science Genetic Epidemiology research group at the Institute for Molecular Medicine Finland (FIMM), the University of Helsinki. The FinRegistry project has received the following approvals for data access: the National Institute of Health and Welfare (THL/1776/6.02.00/2019 and subsequent amendments), the Digital and Population Data Services Agency DVV (VRK/5722/2019–2), the Finnish Center for Pension (ETK/SUTI 22003) and Statistics Finland (TK-53–1451-19). The FinRegistry project has received institutional review board approval from the National Institute of Health and Welfare (meeting 7/2019). The study is based on registry data, and therefore no individual patient consents were required. The data is pseudonymized.

Results

Identified from the full dataset of 5 339 804 individuals, the cases of reproductive age diagnosed with any of the 19 diseases are described in Table 1. In women, the case count ranged from 147 in myasthenia gravis to 21 878 in asthma and in men, from 65 in myasthenia gravis to 28 441 in asthma. The cases showed low overlap (Supplementary Table S2, available at *Rheumatology* online). Of all the individuals born 1964–1984, 7.9% of the women and 7.8% of the men had an autoimmune disease fulfilling the case criteria.

Number of children and reproductive window in women

Overall, we observed high variability in the prevalence of childlessness and the number of children between diseases, as well as high variability in the impact of individual diseases for the different outcomes (Fig. 1, Supplementary Table S3, available at *Rheumatology* online). On average, women with IMDs experienced a higher prevalence of childlessness than controls (mean difference 3.6%), with the top three diseases with largest differences being Addison's disease (23.9% more childlessness), JIA (9.3%) and vitamin B12 deficiency anaemia (presumably mostly autoimmune atrophic gastritis and Crohn's disease with small bowel resection, 8.6%) (Fig. 1A). Of the inflammatory rheumatic diseases, women with RA, JIA and SLE had more childlessness than controls. However, many other IMDs had little or no impact on the prevalence of childlessness.

Women with an IMD also had fewer children than controls (mean difference 0.2 fewer), with the top three diseases with the largest differences being observed for Addison's disease (0.8 fewer children), T1D (0.4 fewer), and multiple sclerosis (0.3 fewer) (Fig. 1B). Again, most IMDs had little or no impact on the number of children. Of the inflammatory rheumatic diseases, RA, JIA and SLE were characterized by fewer children than controls. For many of the diseases in which we observed fewer children, fewer pregnancies were also observed (Supplementary Table S4, available at *Rheumatology* online).

Overall, only a few IMDs had associations with risk of miscarriage; diagnoses of hypothyroidism [odds ratio (OR) 1.12, 1.07–1.17] and asthma (OR 1.11, 1.08–1.15) were associated with slightly elevated risk, and diagnosis of multiple sclerosis (OR 0.80, 0.69–0.93) and seronegative RA (OR

Table 1. Study characteristics

	Women			Men		
	No. cases	No. controls	AAO, mean (S.D.)	No. cases	No. controls	AAO, mean (S.D.)
AS	982	19 640	25.7 (3.2)	2790	55 800	28.5 (4.4)
JIA	2895	55 640	13.5 (8.4)	1548	30 360	14.0 (8.6)
PsA	412	8240	25.5 (3.5)	959	19 180	29.7 (4.2)
Seronegative RA	871	17 420	25.1 (3.4)	501	10 020	28.0 (4.9)
Seropositive RA	1487	29 740	25.2 (3.4)	812	16 240	28.6 (4.8)
SLE	543	10 860	24.3 (3.8)	120	2400	27.0 (5.2)
SS	451	9020	25.5 (3.7)	148	2960	28.4 (5.9)
Addison's disease	170	3400	17.9 (10.0)	204	4080	19.7 (10.9)
Hypothyroidism	14 192	283 840	25.6 (4.0)	4994	99 880	28.7 (5.4)
Type 1 diabetes	2064	41 280	17.1 (6.7)	3762	75 240	20.3 (8.0)
Vitamin B12 deficiency anaemia	256	5120	24.2 (5.8)	196	3920	26.7 (8.4)
Celiac disease	1439	28 780	22.8 (5.9)	1069	21 380	25.6 (7.7)
Crohn's disease	1103	22 060	23.1 (4.5)	1520	30 400	25.8 (6.0)
Ulcerative colitis	3842	76 840	22.2 (6.8)	6300	126 000	25.6 (7.6)
Multiple sclerosis	1499	29 980	25.5 (3.3)	1118	22 360	28.4 (4.7)
Myasthenia gravis	147	2940	21.2 (6.6)	65	1300	21.4 (9.3)
Alopecia areata	460	9200	22.4 (6.2)	381	7620	24.7 (7.5)
Psoriasis	2428	48 560	22.7 (6.0)	4500	90 000	27.1 (6.1)
Asthma	21 878	437 560	18.3 (8.3)	28 441	568 820	17.5 (9.8)
ITP	486	9720	19.5 (7.9)	424	8480	18.7 (10.1)

Cases were identified from individuals born between 1964 and 1984, who had a first disease record before age 30 (women) or age 35 (men). For each case, we identified 20 sex-, birth-year–, and education level–matched controls.
AAO: age at onset.

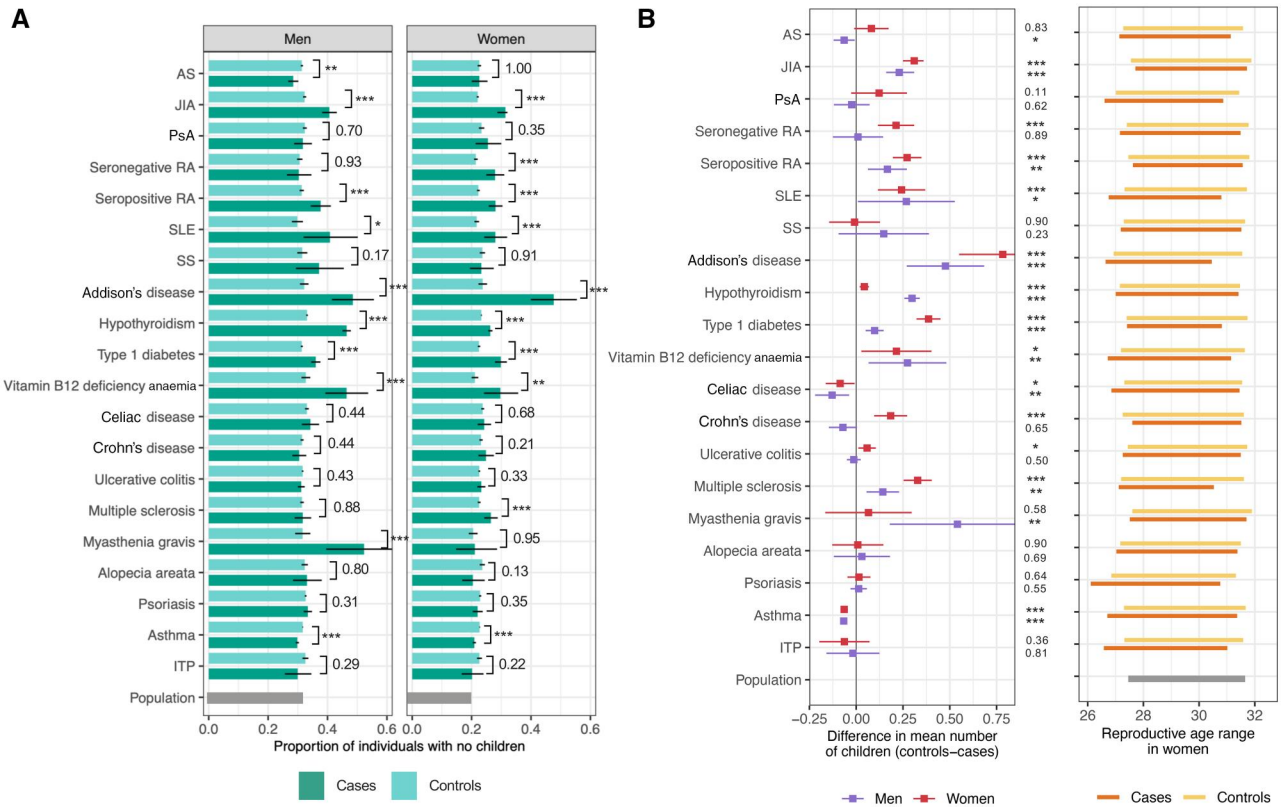


Figure 1. Number of children and reproductive window. (**A**) Prevalence of childlessness in men and women. In the population, the prevalence was 21.3% in women and 30.7% in men. (**B**) Difference in the mean number of children by sex, and reproductive age range in women. For the reproductive age range, the bar represents mean age at first child to mean age at last child. For the reproductive age range, the population mean for age at first child was 27.4 years and for the last child 31.8 years. The whiskers represent 95% CIs. *P*-value categories: ***: <0.001, **: 0.001–0.01, *: 0.01–0.05. Detailed numbers and exact *P*-values for the plot are shown in Supplementary Table S3, available at *Rheumatology* online. The population datasets represent individuals born 1964–1984, in line with the study cohort

0.76, 0.62–0.92) were associated with a decreased risk (Supplementary Table S5, available at *Rheumatology* online).

On average, both the ages of having the first and the last child were slightly shifted towards an earlier age in women with rheumatic diseases and other IMDs compared with controls (Fig. 1B). On average, women with an IMD had their first child 0.2 years younger than the controls, and their last child 0.4 years younger. The largest shifts in age at delivery of the first child were observed for ITP and psoriasis (0.7 years earlier in both). The largest shifts in age at delivery of the last child were observed for Addison's disease and multiple sclerosis (1.1 years earlier), and for T1D and SLE (0.9 years earlier). Across all diseases, controls had on average 0.2 years longer reproductive age range, with a similar difference across the rheumatic diseases (Supplementary Fig. S2, available at *Rheumatology* online).

Number of children in men

Similarly, men with an IMD had a higher prevalence of childlessness than controls (mean difference 4.7%), with most diseases showing no difference but some diseases having much higher prevalence of childlessness, and the top three diseases being myasthenia gravis (20.1% more childlessness), Addison's disease (16.4% more childlessness), and vitamin B12 deficiency anaemia (13.7% more childlessness) (Fig. 1, Supplementary Table S3, available at *Rheumatology* online). For men, most IMDs were associated with little or no difference in the number of children compared with controls (mean difference 0.1 fewer); the top three diseases with largest differences were myasthenia gravis and Addison's disease (both with 0.5 fewer children), and JIA (0.2 fewer children). Of the rheumatic diseases, seropositive RA, SLE and JIA were characterized by increased prevalence of childlessness and fewer children also being observed in men.

Use of assisted reproductive technology

Only a few IMDs were associated with increased use of assisted reproductive technologies. The only disease associated with all three evaluated treatments was hypothyroidism (OR 1.34, 95% CI 1.17–1.52 for ovulation induction, OR 1.40, 1.20–1.64 for insemination, and OR 1.45, 1.20–1.73, for *in vitro* fertilization/intracytoplasmic sperm injection), with associations of similar magnitude being observed for ulcerative colitis (UC) for ovulation induction, for asthma and psoriasis for insemination, and for UC and seropositive RA for *in vitro* fertilization/intracytoplasmic sperm injection (Supplementary Table S6, available at *Rheumatology* online).

Maternal and perinatal outcomes

The mean number of prenatal visits was 16.1 for controls and 17.7 for IMD cases, with the largest differences being observed in T1D (6.4 more visits), SLE (3.4 more visits) and SS (3.2 more visits) (Supplementary Table S7, available at *Rheumatology* online). No large systematic differences across the IMDs were observed for smoking during pregnancy, but two IMDs showed much a higher prevalence of smoking (37.0% in psoriasis *vs* 23.4% in their matched controls; 33.4% in alopecia areata *vs* 22.2% in controls; Supplementary Fig. S3, available at *Rheumatology* online).

Associations and respective prevalences for maternal and perinatal outcomes are shown in Figs 2 and 3. After adjusting for BMI, only asthma was weakly associated with gestational diabetes (Fig. 2A). Six diseases were associated with intrahepatic cholestasis of pregnancy, with the largest associations being observed for T1D (OR 2.24, 1.74–2.88), UC (OR 1.92, 1.60–2.32) and Crohn's disease (OR 1.79, 1.25–2.56) (Fig. 2A). Eleven IMDs were associated with hypertensive disorders of pregnancy, with 1.3–4.9-fold elevated risks (Fig. 2B). The largest associations were detected for pre-eclampsia or eclampsia for T1D, SLE and ITP. In addition to SLE, it was observed that, of the rheumatic diseases, RA, JIA and PsA were also associated with pre-eclampsia. PsA showed a particularly high risk for gestational hypertension. The detailed results for all maternal and perinatal outcomes are shown in Supplementary Table S8 (available at *Rheumatology* online).

Most rheumatic diseases conferred increased risks for preterm delivery, SGA newborns, C-sections, and need for NICU treatment, with particularly high risks in SLE and SS. Across the 19 IMDs, the largest difference in gestational age at birth between cases and controls was observed for T1D (18.1 days earlier). Excluding T1D, the mean difference was 2.4 days lower in IMD cases (range 7.3 days lower in Addison's disease to 0.8 lower in asthma). The risk of SGA was elevated in several diseases, with the highest effect sizes for SLE (OR 1.86, 95% CI 1.48–2.34), SS (1.52, 1.18–1.97) and alopecia areata (1.46, 1.15–1.87) (Fig. 2C). Most IMDs increased the risk of preterm delivery ($\leq 37^{0/7}$ weeks of gestation), with over 2-fold risks observed for T1D (OR 8.47, 7.59–9.45), SLE (OR 2.84, 2.22–3.64), Addison's disease (2.84, 2.22–3.64) and SS (OR 2.67, 1.60–4.45) (Fig. 2D). We also observed widespread associations with both elective and non-elective C-section (Fig. 2E), with generally 1.3–1.8-fold elevated risks. After T1D, the three diseases with the highest effect sizes for non-elective C-section were Addison's disease (OR 1.77, 1.10–2.84), SLE (1.70, 1.34–2.14), and SS (1.62, 1.26–2.09). None of the IMDs increased the risk for instrumental vaginal delivery.

All IMDs, except multiple sclerosis, AS, and vitamin B12 deficiency anaemia were associated with elevated risk of needing care in the NICU (Fig. 2F). In addition to the diseases with the highest effect sizes for C-section, the highest effect sizes for NICU care were observed for myasthenia gravis (OR 3.51, 2.39–5.16; insufficient sample size for analyses on C-section), PsA (1.87, 1.45–2.41) and ITP (1.51, 1.20–1.91). Many of the diseases associated with risk of C-section and NICU care were also associated with the need for phototherapy.

For AS, JIA, PsA and RA cases, we analysed the association of ever having used biologic or targeted synthetic DMARDs (a proxy for disease activity or disease severity) and maternal and perinatal outcomes (Supplementary Fig. S4, available at *Rheumatology* online). The only associations were observed for JIA for SGA (OR 1.54, 1.21–1.97), gestational hypertension (OR 1.96, 1.38–2.77) and elective C-section (OR 1.63, 1.25–2.13).

Looking at full-term pregnancies ($\geq 39^{0/7}$), the mother's and child's hospital stay durations were on average only marginally longer in patients with IMDs compared with controls (mean 0.3 days longer and mean 0.2 days longer, respectively; Supplementary Table S9, available at *Rheumatology* online).

Postpartum health complications

Looking at risk of mastitis, puerperal sepsis, postpartum endometritis, and postpartum depression (Supplementary Table S10, available at *Rheumatology* online), we observed a

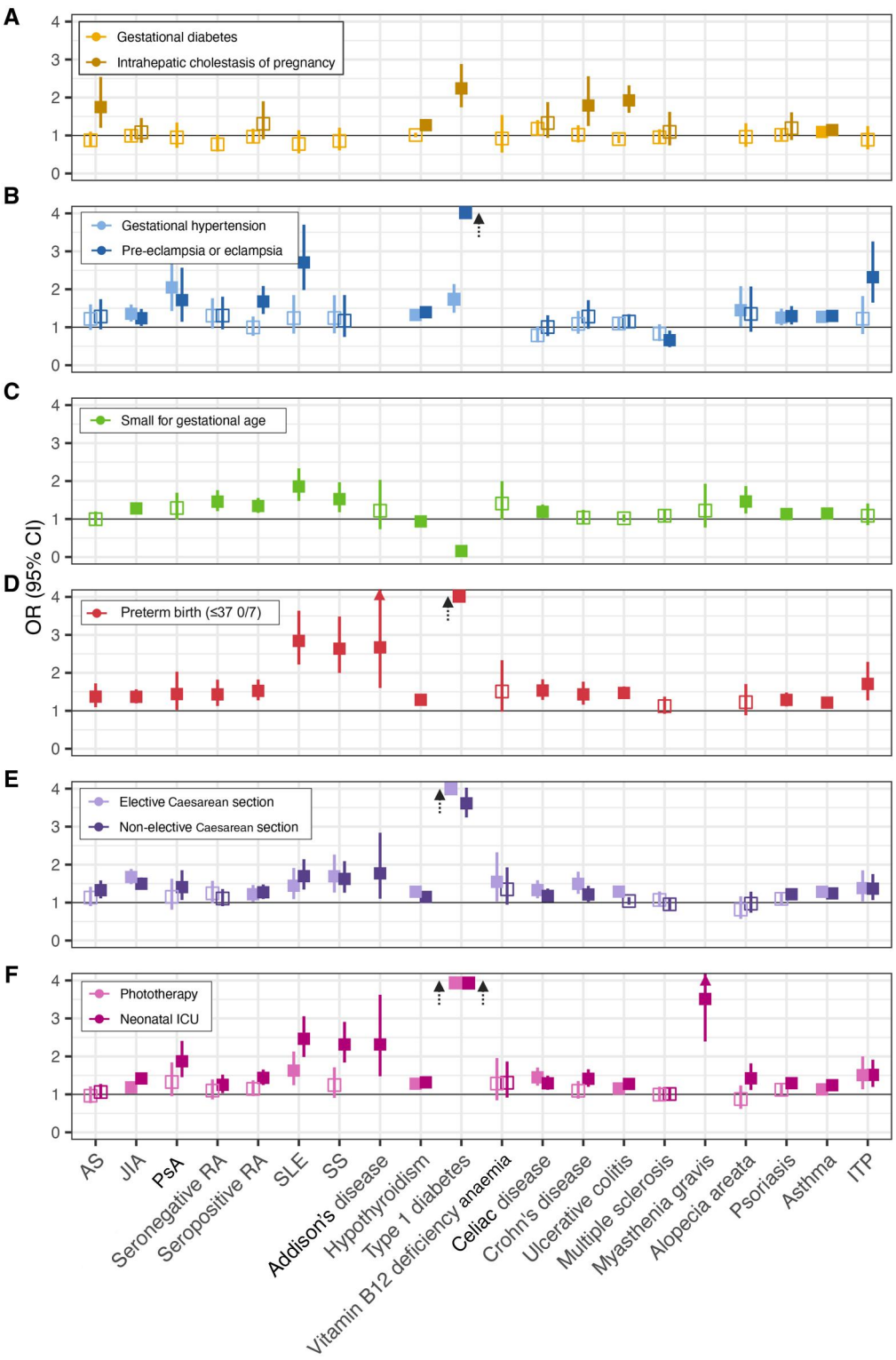


Figure 2. Associations with maternal and perinatal outcomes. (**A**) Gestational diabetes, adjusted for BMI, and intrahepatic cholestasis of pregnancy. (**B**) Hypertensive disorders of pregnancy. (**C**) Child small for gestational age (weight below the 10th percentile for gestational age) at birth. (**D**) Preterm birth ($\leq 37\ ^{0/7}$ weeks). (**E**) Elective and non-elective caesarean section. (**F**) Phototherapy and neonatal intensive care unit (ICU). Outcomes with no association ($P > 0.05$) are displayed with a hollow box, and results are shown for diseases with over 20 cases for the outcome. The outcomes are defined as ever having experienced the outcome, compared with individuals who have never had the outcome. Analyses on gestational diabetes were not performed for T1D. In panels A–C, in analyses for other IMDs than T1D the individuals with comorbid T1D were excluded. In panels D–F, analyses for IMDs other than T1D were adjusted for comorbid T1D. The detailed association results are shown in Supplementary Table S8, available at *Rheumatology* online. T1D: type 1 diabetes

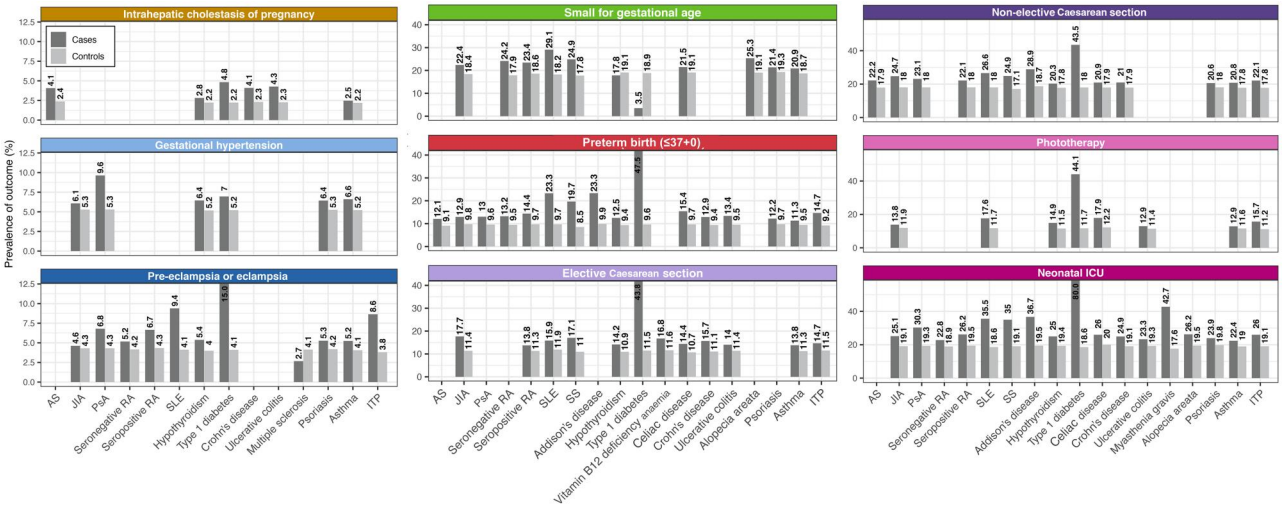


Figure 3. Prevalence of maternal and perinatal outcomes. Prevalences are shown for diseases with an association *P*-value below 0.05 in Fig. 2. The outcomes are defined as ever having experienced the outcome, compared with individuals who have never had the outcome. The detailed counts for the prevalences are in Supplementary Table S8, available at *Rheumatology* online

prevalence of <3% for all outcomes across IMDs, limiting the power for association analysis. We observed associations with several outcomes for both asthma and hypothyroidism (the most well-powered IMDs), with the largest associations being for uterine infection after C-section (OR 1.69, 1.31–2.18 for hypothyroidism; OR 1.62, 1.31–2.00 for asthma). Despite the impacts of IMDs on diverse aspects of reproductive health, they did not impact the time of returning to the workforce after having a child (Supplementary Table S11, available at *Rheumatology* online).

Discussion

Using nationwide registry data, we show that inflammatory rheumatic diseases and other IMDs have a widespread impact on reproductive success, maternal health, and pregnancy outcomes. Variability in effect sizes was observed between individual rheumatic diseases, with largest effects on reproductive success being observed in RA, JIA and SLE, and on pregnancy outcomes in SLE and SS. Across all IMDs, even larger variability was observed, with T1D showing the largest effect sizes for many adverse pregnancy outcomes, followed by SLE, SS and Addison's disease. Our study replicates some well-documented associations of adverse maternal and perinatal outcomes with diseases such as T1D and SLE, and we extend prior studies with respect to the wide range of diseases and outcomes evaluated and compared [2, 7, 13]. Our findings offer important insights into reproductive health outcomes for IMDs that are not typically considered high-risk maternal conditions, such as spondyloarthropathies and autoimmune diseases of the skin. While recommendations for monitoring and treatment of pregnant women with some IMDs exist [9–11, 14, 15], they are lacking for others. Therefore, awareness of the risks, even if small, may help in the development of such recommendations. Finally, we provide a broad view on reproductive success in males with IMDs.

Reproductive success

Of the rheumatic diseases, SLE, JIA and RA were associated with a higher prevalence of childlessness and lower number of children in both men and women. In non-rheumatic IMDs, this held true for Addison's disease, hypothyroidism, T1D, and vitamin B12 deficiency anaemia. Myasthenia gravis reduced reproductive success especially in men. The results are consistent with the findings of previous studies for most of these diseases in women [16–19].

IMDs such as psoriatic disease, asthma, alopecia areata, coeliac disease, and ITP, were not associated with an increased prevalence of childlessness or reduced number of children in either sex, although some had higher use of assisted reproductive technology. IBD was not, in contrast to the findings of previous studies [20], associated with an increased risk of childlessness, suggesting that treatment improvements may have positively impacted the reproductive health of these patients.

Prior studies on fertility in men with IMDs are scarce [21]. Men with inflammatory arthritis, diagnosed before or during reproductive age, have higher infertility rates, more involuntary childlessness, and more medical evaluations for fertility problems than those diagnosed later in life [8]. Several rheumatic diseases can impair sexual function and sperm quality, and potentially cause clinically relevant reproductive hormone abnormalities [22], with similar changes in T1D [23]. Our study also highlights the need for improved screening and care of hypothyroidism in men—thyroid dysfunction leads to multiple alterations of semen quality [24]. In addition to reduced fertility, patient choices may be contributing to our findings in both men and women, possibly related to concerns about the impact of the IMD on offspring and family life [25, 26].

Maternal conditions during pregnancy

The risk of hypertensive disorders of pregnancy was increased across a wide range of IMDs, beyond the well-known associations of pre-eclampsia and SLE or T1D [27]. The risk of gestational hypertension was increased especially in PsA, which may be related to the overall cardiometabolic burden in PsA (more obesity, and more pregestational hypertension and diabetes has been observed in pregnant women with PsA) [28]. Pre-eclampsia is primarily considered a placental disorder, in which the immune system also plays a role [27].

IMDs associated with pre-eclampsia included a variety of inflammatory rheumatic diseases, psoriasis, hypothyroidism, ITP and asthma. Previous studies have reported similar results in subclinical hypothyroidism, asthma, psoriasis, PsA, RA and JIA, and have suggested a link to rheumatic disease activity [29–33]. Additionally, the risk of RA may be increased in women with a history of gestational hypertension or pre-eclampsia, which may suggest a shared predisposition or that the subclinical phase of RA can affect pregnancy outcomes [34].

In contrast, the risk of gestational diabetes was not generally increased in patients with rheumatic diseases or other IMDs. The risk of intrahepatic cholestasis of pregnancy was increased especially in AS, IBD and T1D. One possible explanation for the association with IBD is misdiagnosis: undiagnosed primary sclerosing cholangitis may worsen during pregnancy and be erroneously interpreted as intrahepatic cholestasis of pregnancy [35].

Adverse perinatal outcomes

Most maternal rheumatic diseases as well as other IMDs were associated with some adverse perinatal outcomes, including preterm delivery, SGA, non-elective C-section, and NICU treatment. Furthermore, these outcomes were highly linked. The highest risks for NICU and preterm delivery were observed for pregnant women with T1D, SLE, SS and Addison's disease. The mechanisms and impacts on reproductive health for the first two are well documented, and management recommendations are available [1, 9, 14, 15, 36]. Surprisingly, the relative risks for preterm delivery, C-sections and NICU treatment were as high in SS as in SLE, and the reasons remain largely unclear. Of 451 patients with SS, only 50 (11.0%) had an overlapping diagnosis of SLE and 27 (6.0%) had a diagnosis of seropositive RA, making it unlikely that the risks were driven solely by other rheumatic diseases. Both patients with SLE and SS commonly carry anti-Ro/SSA and/or anti-La/SSB antibodies, which are highly linked to the risk of neonatal lupus and fetal congenital heart block, which may partly explain our results [9]. For Addison's disease, previous large registry-based studies from the USA and Sweden have also shown elevated risks of adverse pregnancy outcomes, including preterm delivery and delivery by C-section [19, 37].

Consistent with previous studies, the effects of IBD and inflammatory rheumatic diseases other than SS and SLE on adverse pregnancy outcomes were small to moderate [7, 38, 39]. Increased risk of pre-eclampsia may partly mediate the effects of IMDs on preterm deliveries and excess C-sections [40]. Overall, the effect sizes of IBD and inflammatory arthritides on adverse pregnancy outcomes were rather small compared with some previous evaluations [38, 41], and advances in antirheumatic treatments may have contributed to improved pregnancy outcomes [42]. Of note, the risks of postpartum infections and depression were overall low, with no increased risk detected in rheumatic diseases, and increased risk only in the most well-powered IMDs.

Moderately increased risks for adverse pregnancy outcomes were observed for many IMDs not traditionally regarded as high-risk maternal conditions. Prior studies on psoriasis have been inconsistent, without clear links to adverse pregnancy outcomes [3]. In our study, psoriasis and PsA were associated with somewhat increased risk of hypertensive disorders of pregnancy, preterm delivery, non-elective C-section, and NICU treatment. Similarly, asthma and celiac disease conveyed a small increase in the risk of several maternal and perinatal outcomes. Poorly controlled asthma, and undiagnosed or untreated celiac disease have been linked to adverse pregnancy outcomes [33, 43]. Alopecia areata was associated with increased risk of NICU treatment and SGA, without any other associations. Smoking during pregnancy was especially common in autoimmune diseases of the skin, which may contribute to some of the observed associations.

Disease activity and reproductive health

Risk factors for adverse pregnancy outcomes and decreased fertility vary among IMDs, including disease severity, disease activity, autoantibodies, and drug therapy [44]. Disease activity in rheumatic diseases and IBD may be a risk factor for pre-eclampsia, preterm delivery and SGA [29, 38, 39]. Glucocorticoid use during pregnancy may also be a risk factor for adverse pregnancy outcomes [39, 45]. In AS, JIA, PsA and RA, we used biologic or targeted synthetic DMARDs as a proxy for disease activity and severity. The only associations for these were observed for JIA, where use of these medications was associated with a 2-fold risk increase for gestational hypertension, a 1.5-fold risk increase for SGA infant, and a 1.6-fold risk increase for elective C-section. These results should be interpreted with caution due to the fairly low numbers of individuals with biologic/targeted synthetic DMARD use and experiencing each outcome. Pregnancy is advised preferably during quiescent or low disease activity in women with rheumatic diseases or IBD, and selected medications for these diseases decrease fertility (e.g. CYC), are not compatible with pregnancy (e.g. MTX), or have the potential to increase the risk for adverse maternal and fetal outcomes (e.g. continuous high-dose glucocorticoids) [9, 11]. Therefore, disease-specific factors should be considered when interpreting our results. Pregnancy can impact the course of IMDs. For instance, RA and multiple sclerosis may show decrease in disease activity during pregnancy, whereas SLE exacerbations are common [46]. In addition to SLE and SS, IMDs such as ITP and myasthenia gravis may cause fetal manifestations of disease, requiring NICU treatment [46].

Strengths and limitations

A strength to our study is that it utilizes nationwide registry data from the entire Finnish population, which reduces recall and selection bias, and makes the findings generalizable to countries with similar health-care systems. We matched controls by education level to account for the impact of education and socio-economic status on family planning and pregnancy outcomes. An important limitation is that we were unable to account for disease-specific factors, such as autoantibodies and disease activity indices. Second, we used an ever–never approach for pregnancy outcomes, but this enabled us to examine less common reproductive health outcomes, even for IMDs that are rare during reproductive age. The case definition for IMDs relied on ICD codes, medication reimbursement codes, and medication purchases (Supplementary Table S1, available at *Rheumatology* online), which always involves problems such as erroneous or unspecific coding. For example, the underlying cause of vitamin B12 deficiency anaemia diagnosis could be pernicious anaemia, atrophic gastritis due to *Helicobacter pylori* or small bowel resection in Crohn's disease, and the impacts of these conditions on reproductive health outcomes are likely to vary. The age criteria used in the case definition (<30 years in

women and <35 years in men) may have resulted in some pregnancies occurring prior to the diagnosis of IMD in some patients, although it also accommodates diagnostic delays. Finally, it is important to interpret the results with an exploratory perspective, given the conventional significance threshold ($P < 0.05$).

Conclusion

Rheumatic diseases and other IMDs have wide-ranging effects on maternal health and pregnancy outcomes, with the largest effect sizes for many of the outcomes in T1D, followed by SLE, SS and Addison's disease, but small to moderate effect sizes across other rheumatic diseases. Reproductive success is preserved in many rheumatic diseases, but SLE, JIA, and seropositive RA were associated with a higher incidence of childlessness in both men and women. Considering the widespread impact of rheumatic diseases on reproductive health, our results emphasize the recommendation to discuss family planning early and often in women of reproductive age who have rheumatic diseases [9, 14], and may aid in forming recommendations for pregnancy monitoring in women with rheumatic diseases. Future research is warranted on male reproductive health in IMDs, and determinants and prevention of adverse pregnancy outcomes in each IMD.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Access to FinRegistry data can be obtained by submitting a data permit application for individual-level data to the Finnish social and health data permit authority Findata (https://asiointi.findata.fi/). The requests are evaluated on a case-by-case basis. Once approved, the data are sent to a secure computing environment Kapseli and can be accessed within the European Economic Area (EEA) and within countries with an adequacy decision from the European Commission. Data dictionaries for the FinRegistry are publicly available on the FinRegistry website (www.finregistry.fi/finnish-registry-data).

Contribution statement

N.M. designed and directed the project. A.M.K. and A.P. were involved in the initial conception, and A.M.K., A.P. and J.V.L were involved in the planning of the analyses. A.G. and M.P. were responsible for acquisition of the data and founding of the FinRegistry framework. N.M. performed all statistical analyses, with support from J.V.L. N.M. and A.M.K. drafted the manuscript. All authors were involved in designing the study, interpretation of the data, and critical revision of the manuscript for important intellectual content, and all authors approved the final version of the manuscript.

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