EPIDEMIOLOGICAL SCIENCE

Outcomes of SARS-CoV-2 infection among children and young people with pre-existing rheumatic and musculoskeletal diseases

Lianne Kearsley-Fleet [1], Min-Lee Chang [2], Saskia Lawson-Tovey [3,4] Ruth Costello [1], Šárka Fingerhutová [5], Natálie Švestková,[5] Alexandre Belot [6] Florence A Aeschlimann [7], Isabelle Melki [7,8] Isabelle Koné-Paut [9] Sascha Eulert [10], Tilmann Kallinich [11], Yackov Berkun [12,13] Yosef Uziel [14,15], Bernd Raffeiner [16], Filipa Oliveira Ramos,[17] Daniel Clemente [18], Christina Dackhammar [19], Nico M Wulffraat [20,21] Helen Waite [22], Anja Strangfeld [10], Elsa F Mateus [23,24] Pedro M Machado [25,26], CARRA Registry Investigators, COVID-19 Global Pediatric Rheumatology Database Investigators, Marc Natter [2], Kimme L Hyrich [1,27]

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ABSTRACT

Objectives Some adults with rheumatic and musculoskeletal diseases (RMDs) are at increased risk of COVID-19-related death. Excluding post-COVID-19 multisystem inflammatory syndrome of children, children and young people (CYP) are overall less prone to severe COVID-19 and most experience a mild or asymptomatic course. However, it is unknown if CYP with RMDs are more likely to have more severe COVID-19. This analysis aims to describe outcomes among CYP with underlying RMDs with COVID-19.

Methods Using the European Alliance of Associations for Rheumatology COVID-19 Registry, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry, and the CARRA-sponsored COVID-19 Global Paediatric Rheumatology Database, we obtained data on CYP with RMDs who reported SARS-CoV-2 infection (presumptive or confirmed). Patient characteristics and illness severity were described, and factors associated with COVID-19 hospitalisation were investigated.

Results 607 CYP with RMDs <19 years old from 25 different countries with SARS-CoV-2 infection were included, the majority with juvenile idiopathic arthritis (JIA; n=378; 62%). Forty-three (7%) patients were hospitalised; three of these patients died. Compared with JIA, diagnosis of systemic lupus erythematosus, mixed connective tissue disease, vasculitis, or other RMD (OR 4.3; 95% CI 1.7 to 11) or autoinflammatory syndrome (OR 3.0; 95% CI 1.1 to 8.6) was associated with hospitalisation, as was obesity (OR 4.0; 95% CI 1.3 to 12).

Conclusions This is the most significant investigation to date of COVID-19 in CYP with RMDs. It is important to note that the majority of CYP were not hospitalised, although those with severe systemic RMDs and obesity were more likely to be hospitalised.

BACKGROUND

Worldwide, as of 11 January 2022, there were over 308 million confirmed cases of COVID-19,

Key messages

What is already known about this subject?
► Some adults with rheumatic and musculoskeletal diseases (RMDs) are at increased risk of COVID-19-related death.

What does this study add?
► Hospitalisation for COVID-19 among children and young people with underlying RMDs were rare in this study with the majority having mild affects only.
► Treatment with biologics, such as tumour necrosis factor inhibitors, did not appear to be associated with more severe COVID-19 in children and young people with RMDs.

How might this impact on clinical practice or future developments?
► While protective measures, as indicated by local policy, are important to follow with respect to minimising risk of acquiring SARS-CoV-2 infection, parents and families can be reassured that these data do not support a high probability of severe COVID-19 in the majority of children and young people with underlying RMDs.

including over 5.4 million deaths.[1] The collective experience is that children, especially younger children, seem less susceptible to symptomatic SARS-CoV-2 illness and reports of death are rare.[2][3] However, less is known about the impact of comorbidity and especially immunosuppression on the risk of severe COVID-19 in the paediatric population.

Data from one analysis of adults with rheumatic and musculoskeletal diseases (RMDs) have shown that presence of rheumatoid arthritis, lupus or psoriasis (as a group) is associated with increased risk of COVID-19-related death compared with

those without comorbid RMDs.[4] However, this analysis did not account for the effects of treatments or disease activity. In another analysis of almost 4000 adults with RMDs, moderate to high RMD disease activity and certain types of therapies (eg, B-cell depletion, alkylating agents) were associated with COVID-19-related death.[5] A recent systematic literature review suggested that the increased risk of severe COVID-19 cannot be generalised to all patients with RMDs and it is probably restricted to very specific subgroups of patients with RMDs.[6]

According to data from seven countries, as of January/February 2021, approximately 1.7 deaths per 1 000 000 population attributable to COVID-19 have occurred in individuals up to 19 years old, contributing 0.48% of estimated total all-cause mortality.[7] In a recent (preprint) systematic review of children and young people with COVID-19, those with comorbid conditions were at increased risk of hospital admissions to critical care, although only eight patients in this review were considered to have an RMD.[8]

It remains unknown whether children and young people with RMDs who acquire COVID-19 have a more severe COVID-19 course and if there is additional risk attributable to either underlying disease or its therapy. It is important to understand the impact of COVID-19 on these individuals to inform national guidelines on protective measures (ie, recommendations to stay home and avoid face-to-face contact), vaccination guidance and address individual decisions regarding heightened social distancing measures for paediatric RMD patients and their families. Critically for this age group is the need to ensure they continue to have full and appropriate access to school and education, with in-person attendance if safe to do so.

Around the recognised outset of the COVID-19 pandemic, individual national and international efforts to collect, analyse, and disseminate data about COVID-19 in patients with paediatric RMDs were rapidly established. In collaboration with the COVID-19 Global Rheumatology Alliance,[9] there were three organised cooperative efforts for COVID-19 in paediatric RMDs internationally: (1) the European Alliance of Associations for Rheumatology (EULAR)/Paediatric Rheumatology European Society sponsored COVID-19 Registry, consisting of >10 000 clinician-entered reports of individuals with RMDs with COVID-19[10] including children, collecting cases from across Europe; (2) inclusion of SARS-CoV-2 infection reporting for the United States Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry; (3) the CARRA-sponsored COVID-19 Global Paediatric Rheumatology Database (COVID-19 GPRD) for international reporting of subjects not covered by either of the other two efforts. Data collection was designed to align between efforts and this collaboration has yielded the largest collection of COVID-19-related data for patients with paediatric onset RMDs to date.

The aims of this global analysis are: (1) to describe characteristics of those children and young people with pre-existing RMDs with COVID-19, (2) to describe outcomes following COVID-19 and (3) to identify characteristics that are associated with more severe COVID-19 outcomes.

METHODS
Databases
The data analysed comprise cases reported to the EULAR COVID-19 Registry, the CARRA Registry, and the COVID-19 GPRD. Data were entered by the treating rheumatologist or their designee directly into data entry websites. For some countries in Europe (France, Germany, Greece, Italy, Portugal and

Sweden), under an existing agreement, cases were transferred from other national COVID-19 registries into the EULAR COVID-19 Registry. It was not possible for patients or families to report directly into any of the registries, but mild or asymptomatic cases of COVID-19 reported to a rheumatologist could be entered subsequently by a physician. The EULAR COVID-19 Registry data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at The University of Manchester, United Kingdom.[11] REDCap is a secure, web-based application designed to support data capture for research studies, providing: (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources. The COVID-19 GPRD study is operated by Boston Children's Hospital (USA) and utilises REDCap Cloud (nPhase, USA) for data entry from the USA, Canada, and international sites not participating in the EULAR COVID-19 Registry. For patients with RMDs enrolled in the CARRA Registry (prospective observational cohort) and who also tested positive for SARS-CoV-2 infection, data are collected in Rave (Medidata Solutions Inc., USA). Data reported in the EULAR COVID-19 Registry and the COVID-19 GPRD are collected on an ad hoc basis. CARRA Registry investigators were instructed to report all SARS-CoV-2 infections in registry subjects as a safety event of special interest (ESI). Complete CARRA Registry ESI reports were validated, abstracted, and combined with data from the COVID-19 GPRD; these data elements were then mapped to and harmonised with the EULAR COVID-19 Registry dataset for combined data analyses.

Data collection
The data collected across the registries include patient demographic information (age, sex at birth, country of residence), primary RMD diagnosis, RMD disease activity (tick box: remission, low, moderate, high or unknown), RMD treatments including glucocorticoid use and which disease modifying antirheumatic drug (DMARD) the patient was on at the time of COVID-19, and comorbidities (tick box: none, ocular inflammation, interstitial lung disease, asthma, diabetes, obesity, hypertension, cerebrovascular accident, renal disease, inflammatory bowel disease, heart disease). Information on COVID-19 include diagnosis date, whether the case was presumptive or confirmed (via PCR, antigen test, antibody test, or other laboratory assay), clinical symptoms (tick box), hospitalisation and/or death due to COVID-19, and whether the patient stopped rheumatic therapies.

Inclusion criteria
All children and young people <19 years of age at the time of detection of SARS-CoV-2 infection or the development of COVID-19 illness (presumptive or confirmed) were included in the primary analyses. Individuals with juvenile idiopathic arthritis (JIA) aged 19 and over were included for additional descriptive analyses. The CARRA Registry required documentation of positive SARS-CoV-2 testing (PCR, antigen or antibody) in order to be validated as a COVID-19 ESI. These cases underwent validation by two independent reviewers.

Cases for this analysis were included from initial COVID-19 date (EULAR COVID-19 Registry: 27 March 2020; CARRA Registry: 1 March 2020; COVID-19 GPRD: 13 April 2020) until a cut-off date of 20 July 2021 for the EULAR COVID-

Registry, 25 May 2021 for the CARRA Registry and 23 June 2021 for the COVID-19 GPRD.

Statistical analysis

Demographic characteristics of all children and young people aged <19 years were described using relevant categorical and continuous variables and patients who died were further characterised. Rheumatology diagnosis was categorised into four groups: (1) JIA, (2) systemic lupus erythematosus (SLE), mixed-connective tissue disease (MCTD), vasculitis or other RMD (including Behcet's disease, inflammatory myopathy, systemic sclerosis, localised scleroderma), (3) autoinflammatory syndromes (including tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), cryopyrin-associated autoinflammatory syndromes (CAPS), and familial Mediterranean fever (FMF)), (4) other (including chronic recurrent multifocal osteomyelitis, sarcoidosis, ocular inflammation, 'other' or was left blank).

Logistic regression (complete case) was used to assess factors associated with COVID-19 hospitalisation, including: age, sex, rheumatology diagnosis (four categories as above), obesity (body mass index, BMI ≥30; tick box (EULAR) or combination of BMI and tick box (CARRA Registry and CARRA GPRD)), glucocorticoid use, and DMARD use (none, conventional-synthetic DMARD only, biologic or targeted-synthetic DMARD only, combination therapy). OR and 95% CI are presented for each variable individually (univariable logistic regression). For the multivariable logistic regression, all variables in the univariable analysis were included as it was believed that each was an important factor to be accounted for. Disease activity was also included in the multivariable analysis with unknown (ie, missing) included as an indicator variable (categories: remission, low, moderate to high, or unknown). Finally, dataset (EULAR or CARRA (CARRA Registry and CARRA GPRD)) was included in the multivariable model to account for differences between data collection. One patient with unknown sex was dropped from this analysis.

Two sensitivity analyses of the logistic regression were conducted. The first without inclusion of two patients retrospectively diagnosed with SLE after presentation with COVID-19 (both of whom died), given uncertainties regarding the possibility of COVID-19-induced autoimmune disease and the small number of deaths and serious illness reported in the data. The second excluded disease activity from the model due to the large amount of missing data.

Patients with JIA over 19 years old were included in a further descriptive analysis regarding age, sex, rheumatology diagnosis, hospitalisations and deaths.

RESULTS

Children and young people

There were a total of 607 children and young people under the age of 19 years old included from 25 different countries; 464 from the EULAR COVID-19 Registry and 143 from the CARRA datasets (CARRA Registry and CARRA GPRD) (table 1). Of these, 499 (82%) were confirmed SARS-CoV-2 cases (majority with PCR; n=425), 399 (66%) were female, and median age was 14 years old (IQR 9–16). The majority of children and young people had JIA (n=378; 62%); 140 with polyarticular (37% of JIA), 112 with oligoarticular (30% of JIA), 44 with enthesitis-related JIA (12% of JIA), 34 with systemic JIA (9% of JIA), 16 psoriatic (4% of JIA), and 33 other or unknown (9% of JIA). There were also 78 (13%) patients with auto-inflammatory syndromes, 47 (8%) with SLE or MCTD, 16 (3%) with vasculitis and 15 (2%) with inflammatory myopathy.

The majority of patients did not report any comorbidities (83%), although 38 (6%) had ocular inflammation (largely uveitis in association with JIA), and 34 (6%) were reported to be obese. Less than 1% reported comorbid inflammatory bowel disease, diabetes mellitus, or renal disease. Twelve (2%) patients reported more than one comorbidity.

Of these 607 children and young people, 43 (7%) were admitted to hospital. A higher proportion were reported as hospitalised in CARRA data vs the EULAR registry (11% vs 6%), as well as those with SLE/MCTD (16%) and systemic JIA (15%) compared with other JIA patients (4%). One hundred and forty (23%) patients had asymptomatic COVID-19. The most common symptoms overall were fever (n=236; 39% of all patients) and cough (n=181; 30% of all patients), with hospitalised patients reporting fever more frequently (77% vs 36%).

Most patients (n=423; 70%) were on DMARD therapy at the time of COVID-19. There were 267 (44%) patients on a conventional-synthetic DMARD (predominantly methotrexate, n=198), 143 of those as monotherapy and 124 in combination with biologic DMARDs. No patients were on combination therapies of conventional-synthetic DMARDs with targeted-synthetic DMARDs. There were 280 (46%) patients on biologic or targeted-synthetic DMARDs (predominantly anti-TNF therapy, n=200), 156 of those as monotherapy. There were a similar proportion of hospitalised and non-hospitalised patients discontinuing either their conventional-synthetic, or biologic or targeted-synthetic DMARD therapy at the time of COVID-19 diagnosis (approximately one third). Eleven percent (n=66) of patients were receiving glucocorticoid treatment at the time of COVID-19; of these, 36 patients reported dosage with median dose 6.5 mg/kg (IQR 3.8–12.3).

Among those for whom disease activity at the time of COVID-19 had been recorded, the majority were in remission (n=194; 49% of those with data) or had low disease activity (n=159; 40% of those with data). Disease activity at the time of COVID-19 was unavailable for 208 (34%) patients, primarily from the CARRA datasets and the EULAR French data subset (non-recorded at all in the French data subset). Hospitalised patients more often had moderate (9% vs 6%) or high (7% vs <1%) disease activity than non-hospitalised patients.

Three patients died with PCR confirmed SARS-CoV-2 (table 2). One death in a female <5 years old with a pre-existing auto-inflammatory syndrome (unknown disease activity status), on low-dose glucocorticoids and methotrexate (described in further detail elsewhere[12]). Two deaths occurred in subjects from lower-resource areas who were diagnosed with SLE around the same time as they developed COVID-19 (one with SLE manifestations recognised at the time of COVID-19 presentation, another with preceding SLE manifestations but not yet diagnosed).

Factors associated with hospitalisation in children and young people with COVID-19 (table 3) included diagnosis of SLE/MCTD, vasculitis or other RMD (OR 4.3; 95% CI 1.7 to 11) or autoinflammatory syndromes (OR 3.0; 95% CI 1.1 to 8.6) compared with JIA, and obesity (OR 4.0; 95% CI 1.3 to 12). When the analysis was repeated (1) excluding the two patients who died who were retrospectively diagnosed with SLE after presentation with COVID-19 (online supplemental table 1) and (2) excluding disease activity as a confounder (online supplemental table 2), the estimates did not change substantially.

Adults

There were 99 adults with JIA, 82 from the EULAR COVID-19 Registry and 17 from the CARRA dataset, with a median age of

Table 1 Patient characteristics, rheumatic disease information, and main COVID-19 outcomes of 607 children and young people under the age of 19 years with COVID-19

		All patients	Not hospitalised	Hospitalised
N		607	564 (93%*)	43 (7%*)
Dataset	EULAR COVID-19 Registry	464 (76%)	437 (77%)	27 (63%)
	CARRA Datasets (CARRA Registry and CARRA COVID-19 GPRD)	143 (24%)	127 (23%)	16 (37%)
Sex	Female	399 (66%)	369 (65%)	30 (70%)
	Male	207 (34%)	194 (34%)	13 (30%)
	Unknown	1 (<1%)	1 (<1%)	0
Age, years	Median (IQR)	14 (9, 16)	14 (10, 16)	14 (8, 17)
	Range	one to 18.9	one to 18.9	two to 18
Primary rheumatology diagnoses	Juvenile Idiopathic Arthritis	378 (62%)	360 (64%)	18 (42%)
	Polyarticular	*139 (23%)*	*137 (24%)*	*2 (5%)*
	Oligoarticular	*112 (18%)*	*108 (19%)*	*4 (9%)*
	Systemic	*34 (6%)*	*29 (5%)*	*5 (12%)*
	Psoriatic	*16 (3%)*	*16 (3%)*	*0*
	Enthesitis-related	*44 (7%)*	*39 (7%)*	*5 (12%)*
	Other/Unknown	*33 (5%)*	*31 (6%)*	*2 (5%)*
	SLE/MCTD/Vasculitis/Other RMD†	87 (14%)	73 (13%)	14 (33%)
	Auto-inflammatory syndromes (eg, TRAPS, CAPS, FMF)	78 (13%)	71 (13%)	7 (16%)
	Other‡	64 (11%)	60 (11%)	4 (9%)
Comorbidities	None stated	505 (83%)	472 (84%)	33 (77%)
	Ocular inflammation	38 (6%)	36 (6%)	2 (5%)
	Obesity (BMI ≥30)	34 (6%)	28 (5%)	6 (14%)
	Asthma	7 (1%)	7 (1%)	0
Disease activity	Remission	194 (32%)	178 (32%)	16 (37%)
	Low	159 (26%)	152 (27%)	7 (16%)
	Moderate	40 (7%)	36 (6%)	4 (9%)
	High	6 (1%)	3 (<1%)	3 (7%)
	Unknown§	208 (34%)	195 (35%)	13 (30%)
Confirmed or suspected	Confirmed	499 (82%)	465 (82%)	34 (79%)
	Suspected	108 (18%)	99 (18%)	9 (21%)
Most frequently reported symptoms	Asymptomatic	140 (23%)	137 (24%)	3 (7%)
	Fever	236 (39%)	203 (36%)	33 (77%)
	Cough	181 (30%)	163 (29%)	18 (42%)
	Rhinorrhoea	111 (18%)	105 (19%)	6 (14%)
	Headache	107 (18%)	96 (17%)	11 (26%)
	Anosmia	105 (17%)	104 (18%)	1 (2%)
Treatment at onset of COVID-19 infection	Any DMARD	423 (70%)	395 (70%)	28 (65%)
	csDMARD monotherapy	143 (24%)	132 (23%)	11 (26%)
	b/tsDMARD monotherapy	156 (26%)	144 (26%)	12 (28%)
	Combination therapy (cs and bDMARD)	124 (20%)	119 (21%)	5 (12%)
	Any csDMARD	267 (44%)	251 (45%)	16 (37%)
	Methotrexate	*198 (33%)*	*189 (34%)*	*9 (21%)*
	Antimalarials	*48 (8%)*	*40 (7%)*	*8 (19%)*
	Mycophenolate	*28 (5%)*	*24 (4%)*	*4 (9%)*
	Cyclophosphamide	*0*	*0*	*0*
	Any b/tsDMARD	280 (46%)	263 (47%)	17 (40%)
	Anti-TNF inhibitor	*200 (33%)*	*193 (34%)*	*7 (16%)*
	IL-6 inhibitor	*30 (5%)*	*27 (5%)*	*3 (7%)*
	IL-1 inhibitor	*19 (3%)*	*15 (3%)*	*4 (9%)*
	Rituximab	*11 (2%)*	*9 (2%)*	*2 (5%)*
	JAK inhibitor	*6 (1%)*	*6 (1%)*	*0*
	Glucocorticoids	66 (11%)	56 (10%)	10 (24%)
	In combination with cs/btsDMARD	*56 (9%)*	*49 (9%)*	*7 (16%)*
Required hospitalisation	Yes	43 (7%)	0	43 (100%)
	Required oxygen/ventilation	*8 (1%)*	*–*	*8 (19%)*
	None needed	*35 (6%)*	*–*	*35 (81%)*
Deaths due to COVID-19¶		3 (<1%)	0	3 (7%)

*Row percentage.
†Other RMD includes: Behcet's disease, inflammatory myopathy, systemic sclerosis, localised scleroderma.
‡Other includes: chronic recurrent multifocal osteomyelitis, sarcoidosis, ocular, 'other', or was left blank.
§94% of which are from the CARRA dataset and the EULAR French data subset.
¶Two deaths occurred in subjects who were diagnosed with SLE around the same time as COVID-19: one with SLE manifestations recognised at the time of COVID-19 presentation, one with SLE manifestations in the preceding 2 months.
BMI, body mass index; b/tsDMARD, biologic or targeted-synthetic DMARD; CAPS, cryopyrin-associated auto-inflammatory syndromes; CARRA, Childhood Arthritis and Rheumatology Research Alliance; csDMARDs, conventional-synthetic disease modifying anti-rheumatic drug; EULAR, European Alliance of Associations for Rheumatology; FMF, familial Mediterranean fever; GPRD, Global Paediatric Rheumatology Database; JAK, Janus-kinase; MCTD, mixed-connective tissue disease; RMD, rheumatic and musculoskeletal disease; SLE, systemic lupus erythematosus; TRAPS, tumour necrosis factor receptor-associated periodic syndrome.

Table 2 Description of the three fatalities in children and young people with COVID-19

Patient	Age	Sex	Rheumatology diagnosis	Comorbidities	Glucocorticoids	Rheumatology treatment	Disease activity	Time from COVID-19 onset to death
1	<15 years	Female	Systemic lupus erythematosus	None	None	Antimalarials Intravenous Immunoglobulin	High	8 days
2	<10 years	Female	Systemic lupus erythematosus	None	Yes (dose unknown)	None	High	9 days
3	<5 years	Female	Auto-inflammatory syndrome	None	Yes (low dose)	Methotrexate	Unknown	7 days

Table 3 Factors associated with hospitalisation in children and young people with COVID-19 (N=606)

	Univariable OR (95% CIs)	Multivariable OR* (95% CIs)
Female (vs male)	1.2 (0.6 to 3.8)	1.1 (0.6 to 2.4)
Age (years)	1.0 (0.9 to 1.1)	1.0 (0.9 to 1.0)
Rheumatic disease		
JIA	(comparator)	(comparator)
SLE/MCTD, Vasculitis	3.8 (1.8 to 8.1)†	4.3 (1.7 to 11)†
Auto-inflammatory syndromes	2.0 (0.8 to 4.9)	3.0 (1.1 to 8.6)†
Other	1.3 (0.4 to 4.1)	1.7 (0.5 to 5.5)
Obesity	3.1 (1.2 to 8.0)†	4.0 (1.3 to 12)†
Glucocorticoid use	2.7 (1.3 to 5.9)†	2.1 (0.8 to 5.6)
DMARD use		
None stated	(comparator)	(comparator)
csDMARD only	0.9 (0.4 to 2.1)	0.6 (0.2 to 1.7)
b/tsDMARD only	0.9 (0.4 to 2.1)	1.5 (0.6 to 3.6)
Combination therapy	0.5 (0.2 to 1.3)	0.4 (0.1 to 1.5)

*Adjusted for disease activity (remission, low, moderate to high, or unknown) and dataset (EULAR COVID-19 Registry or CARRA (CARRA Registry and CARRA COVID-19 GPRD)).
†P<0.05.
b/tsDMARD, biologic or targeted-synthetic DMARD; CARRA, Childhood Arthritis and Rheumatology Research Alliance; csDMARD, conventional-synthetic DMARD; DMARD, disease modifying anti-rheumatic drug; EULAR, European Alliance of Associations for Rheumatology; GPRD, Global Paediatric Rheumatology Database; JIA, juvenile idiopathic arthritis; MCTD, mixed-connective tissue disease; SLE, systemic lupus erythematosus.

26 years (IQR 20–34, range 19–72 years old). Of these adults, 76 (77%) were confirmed cases (majority with PCR; n=66), 9 were hospitalised, and two died. The two deaths were in females with oligoarticular JIA with PCR confirmed SARS-CoV-2. One was 31–40 years old with moderate disease activity receiving glucocorticoid (dose 10 mg) and combination conventional-synthetic DMARD with anti-TNF therapy at the time of COVID-19 diagnosis, with concomitant inflammatory bowel disease. The other was 61–70 years old in remission receiving no glucocorticoid or DMARD therapy, with asthma, diabetes and hypertension.

DISCUSSION

This is the most significant global investigation to date of short-term COVID-19 outcomes in children and young people with RMDs. Of the 607 cases reported, 7% were hospitalised, although less than one-in-five of these needed oxygen or ventilation, and three patients died. There were no associations between DMARD treatment (conventional-synthetic, biologic/targeted-synthetic or combination therapy, compared with no DMARD treatment), or glucocorticoid use, with hospitalisation. However, children and young people with SLE/MCTD, vasculitis, other RMDs or autoinflammatory syndromes were more likely to be hospitalised compared with those with JIA. As in multiple other reports in non-disease-specific populations, obesity represented a risk factor for more severe COVID-19 outcome.

These initial results are reassuring against the occurrence of severe COVID-19 illness (excluding multisystem inflammatory syndrome in children (MIS-C)) in the majority of individuals with paediatric RMDs, with only 1-in-15 children and young people with RMDs with COVID-19 reporting hospitalisation. Using the same database structure, almost half of the cases reported in adults with RMDs were fatal cases, likely representing a significant bias in reporting.[5] If this same bias is present in the paediatric reports, it is possible that outcomes are even

more favourable in this younger population, with many children and young people with RMDs experiencing milder COVID-19 not reporting the case to their physician, who in turn cannot report to the registries. The ad hoc nature of voluntary reporting to these data sources prevents a population-based analysis.

Nonetheless, although uncommon in all children and young people, those with RMDs other than JIA (predominantly SLE/MCTD, vasculitis or autoinflammatory syndromes) were more likely to have serious outcomes, which is not surprising given the typically greater systemic involvement and need for more aggressive immunosuppressive therapy than the majority of individuals with JIA. In addition, patients with more severe JIA are often treated with anti-TNF DMARD therapies, which have been associated with less severe COVID-19 disease in some adult reports compared with other therapies.[13–15] In adults with RMDs, those with SLE were at increased risk of COVID-19-related hospitalisation, and those with comorbidities such as hypertension, cardiovascular disease, chronic lung disease, chronic kidney disease, and diabetes, have been identified as being at increased risk of COVID-19-related hospitalisation and death.[5 13] Regarding obesity as a risk factor for more severe COVID-19, our data is in agreement with other studies evidencing poorer COVID-19 outcomes with obesity in the adult general population.[4 16] That obesity is also associated with severe COVID-19 in children is a new finding.

This analysis is the largest investigation of COVID-19 in children and young people with RMDs globally. However, it was not without limitations. SARS-CoV-2 infection reported to the combined registries included both presumptively diagnosed and confirmed cases, introducing possible misclassification bias. The authors believe this is not likely to have substantially confounded our results as the majority of severe COVID-19 cases would have been reported. In the treatment of COVID-19 deaths, we noted no significant difference in results of serious COVID-19 illness when excluding the two subjects without RMD diagnoses established prior to their presentation with COVID-19. Several limitations in data collection so far precluded drawing conclusions regarding other factors that have been shown to be associated with poor outcomes: (1) approximately one-third of the combined dataset had missing RMD disease activity, preventing meaningful exploration of this factor on short-term outcomes; (2) substantial differences in reporting of race and ethnicity between data sources prevented cross-mapping between efforts and we were unable to analyse whether black, Asian and minority ethnic groups with paediatric RMDs are at higher risk of COVID-19-related death compared with those of white ethnicity, as has been reported for the general population[4 17] and (3) we did not have access to data on SARS-CoV-2 variant types although all the data were collected prior to the emergence of the Omicron variant.[18] Our registries did not capture vaccination status at the time of data collection (although most cases occurred prior to approval of vaccination for the relevant age groups) and we do not capture long-term or late outcomes such as 'long COVID-19'[19 20] or MIS-C. Finally, our data sources received very limited reporting from low-resource healthcare areas internationally.

In conclusion, understanding the impact of COVID-19 infection on children and young people with RMDs is important to inform national protection, education (such as school attendance) and vaccination guidance. We report the most significant investigation to date of short-term outcomes of COVID-19 in over 600 children and young people with RMDs. The majority of children and young people with RMDs appear to do well and experience mild COVID-19 disease. However, where hospitalisations did occur, they were more likely among those with SLE/MCTD, vasculitis, autoinflammatory syndromes, and other paediatric RMDs compared with their peers with JIA. The data also showed for the first time that obesity is a relevant comorbidity also in children with RMDs, supporting that protection measures in those children should be strictly followed. While mortality has been reported, it appears to occur rarely in high-resource healthcare areas.

Author affiliations
[1]Centre for Epidemiology Versus Arthritis, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK
[2]Computational Health Informatics Program, Boston Children's Hospital, Boston, Massachusetts, USA
[3]Centre for Genetics and Genomics Versus Arthritis, The University of Manchester, Manchester, UK
[4]National Institute of Health Research Manchester Biomedical Research Centre, Centre for Musculoskeletal Research, Manchester University NHS Foundation Trust, Manchester, UK
[5]Department of Pediatrics and Adolescent Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic
[6]Pediatric Nephrology, Rheumatology & Dermatology Department, HFME, Université Lyon-1, Hospices Civils de Lyon, Lyon, France
[7]Pediatric Hematology-Immunology and Rheumatology Department, AP-HP, Hôpital universitaire Necker-Enfants malades, Paris, France
[8]General Pediatrics, Infectious Disease and Internal Medicine Department, AP-HP, Hôpital Robert Debré, Reims, France
[9]Service de Rhumatologie Pédiatrique, Centre de Référence des Maladies Auto-Inflammatoires de l'enfant, Centre Hospitalier Universitaire de Bicêtre, Paris, France
[10]Epidemiology Unit, German Rheumatism Research Center Berlin, Berlin, Germany
[11]Department of Pediatrics, Division of Pneumonology and Immunology with intensive Medicine, Charité Universitätsmedizin Berlin, Berlin, Germany
[12]Department of Pediatrics, Hadassah-Hebrew University Medical Center, Jerusalem, Mount Scopus, Israel
[13]Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel
[14]Paediatric Rheumatology Unit, Department of Paediatrics, Sackler School of Medicine, Tel-Aviv University, Meir Medical Center, Tel-Aviv, Israel
[15]Clinical Affairs Committee, Pediatric Rheumatology European Society (PReS), Geneva, Switzerland
[16]Department of Rheumatology, Central Hospital of Bolzano, Bolzano, Italy
[17]Rheumatology Department, Centro Hospitalar Universitário Lisboa Norte EPE, Lisboa, Portugal
[18]Paediatric Rheumatology Unit, Hospital Infantil Universitario Niño Jesús, Madrid, Spain
[19]Department of Rheumatology, Sahlgrenska University Hospital, Goteborg, Sweden
[20]Pediatrics, University Medical Center Utrecht, Utrecht, The Netherlands
[21]European Reference Network RITA, Utrecht, Netherlands
[22]Atrius Health Inc, Newton, Massachusetts, USA
[23]Portuguese League Against Rheumatic Diseases (LPCDR), Lisbon, Portugal
[24]Standing Committee of People with Arthritis/Rheumatism in Europe (PARE), European Alliance of Associations for Rheumatology (EULAR), Kilchberg, Switzerland
[25]Centre for Rheumatology & Department of Neuromuscular Diseases, University College London, London, UK
[26]National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre, University College London Hospitals NHS Foundation Trust, London, UK
[27]National Institute of Health Research Manchester Biomedical Research Centre, Manchester Academic Health Science Centre, Manchester University NHS Foundation Trust, Manchester, UK

ORCID iDs
Lianne Kearsley-Fleet http://orcid.org/0000-0003-0377-1575
Min-Lee Chang http://orcid.org/0000-0001-9868-4030
Saskia Lawson-Tovey http://orcid.org/0000-0002-8611-162X
Ruth Costello http://orcid.org/0000-0003-2709-6666
Šárka Fingerhutová http://orcid.org/0000-0003-2170-2688
Alexandre Belot http://orcid.org/0000-0003-4902-5332
Florence A Aeschlimann http://orcid.org/0000-0001-7212-9151
Isabelle Melki http://orcid.org/0000-0002-8057-333X
Isabelle Koné-Paut http://orcid.org/0000-0001-8939-5763
Sascha Eulert http://orcid.org/0000-0002-7921-708X
Tilmann Kallinich http://orcid.org/0000-0003-2404-9397
Yackov Berkun http://orcid.org/0000-0001-9823-4750
Yosef Uziel http://orcid.org/0000-0003-4655-1652
Bernd Raffeiner http://orcid.org/0000-0002-7719-1736
Daniel Clemente http://orcid.org/0000-0002-1605-7488
Christina Dackhammar http://orcid.org/0000-0001-9389-4282
Nico M Wulffraat http://orcid.org/0000-0001-9548-5562
Helen Waite http://orcid.org/0000-0002-8435-9496
Anja Strangfeld http://orcid.org/0000-0002-6233-022X
Elsa F Mateus http://orcid.org/0000-0003-0059-2141
Pedro M Machado http://orcid.org/0000-0002-8411-7972
Marc Natter http://orcid.org/0000-0003-0748-2674
Kimme L Hyrich http://orcid.org/0000-0001-8242-9262

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