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Investigating the association between SARS-CoV-2 infection, COVID-19 vaccination, and autoimmune diseases in a pediatric population: a comprehensive analysis

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Abstract

Background During the COVID-19 pandemic there were reports of an increased association between COVID 19 and various autoimmune diseases (AID) in adults. This study aims to investigate the incidence of AIDs in children before and during the pandemic and explores potential links to SARS-CoV-2 vaccination.

Methods We analyzed 493,705 anonymized medical records from Maccabi Healthcare Services, Israel's second-largest healthcare provider, to study AID incidence during 2014–2022. The study period was divided into three phases: two pre-pandemic phases of equal duration (A and B) and a pandemic phase (C).

Results Of 4,596 (0.9%) patients diagnosed with an AID in the cohort, incidence rates were 0.9% for Group A (2014–2016), 1.0% for Group B (2017–2019), and 0.9% for Group C (2020–2022) ($p=0.13$). Logistic regression showed no significant differences in overall autoimmune disease incidence between the pre-COVID and COVID periods. Notably, specific conditions like celiac disease showed reduced incidence in Group A (OR 0.8309, $p=0.0071$) while arthritis was significantly more common in Groups A and B. Additionally, COVID-19 diagnosis was not significantly associated with increased autoimmune disease risk (HR 1.092, $p=0.491$); however, receiving at least one COVID vaccine was linked to higher risk (HR 1.2323, $p=0.0033$).

Conclusion Our findings suggest that the overall incidence of new-onset autoimmune diseases in children remained relatively stable during the COVID-19 pandemic. The study indicates a potential association between COVID-19 vaccination and an increased risk of developing autoimmune diseases, necessitating further research to elucidate long-term effects in the pediatric population.

Keywords COVID-19 infection, COVID1-19 vaccination, Autoimmune diseases, Pediatric rheumatology, Epidemiology

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Introduction

The COVID-19 pandemic, officially declared by the World Health Association in early 2020 and caused by the SARS-CoV-2 virus, had a profound impact on human health worldwide [1]. While children generally experience a milder form of illness as compared to adults, they remain at risk for severe conditions such as Multisystem inflammatory syndrome (MIS-C) and other complications resulting from COVID-19 infection [2].

The pathophysiology of autoimmune disease is complex. Though not fully understood, autoimmune disease pathophysiology involves interplay between genetic and environmental factors. Viral infections are well-known contributors to autoimmune diseases, with hepatitis C, hepatitis B, Chikungunya, parvovirus B19, and herpes viruses identified as potential causes [3, 4]. The ongoing challenges related to the COVID-19 pandemic, when millions were infected by the SARS-CoV-2 virus, underscores the importance of this research. In this context, several hypotheses have been put forward regarding the mechanisms by which SARS-CoV-2 infection can trigger autoimmune responses including molecular mimicry, bystander activation, and epitope spreading [5–7]. Moreover, autoantibodies have been detected in patients with COVID-19 [8].

A broad spectrum of autoimmune phenomena were extensively reported as complications of COVID-19 [9, 10]. For instance, MIS-C is a rare but serious condition that can develop in children weeks after they being infected with COVID-19. The pathogenesis of MIS-C remains enigmatic with a suspected link to postinfectious immune dysregulation, potentially involving a cytokine storm. Initially mistaken for Kawasaki syndrome, MIS-C has since been established as a distinct entity specifically associated with COVID-19 [11].

Growing evidence indicates a rise in new autoimmune diseases in adults following COVID-19 infection, including conditions such as Guillain-Barré syndrome, systemic lupus erythematosus, arthritis, psoriasis, type 1 diabetes, and vasculitis [12–14]. However, the overall risk of autoimmune diseases post-COVID-19 infection in children has not been extensively studied.

To address this gap, we conducted a retrospective study using large-scale data to determine if the incidence of new-onset autoimmune diseases in the pediatric population has changed since the COVID-19 pandemic.

Furthermore, while COVID-19 vaccines have significantly reduced the spread of the pandemic [15], ongoing research is exploring potential long-term side effects. Recent studies have highlighted concerns about the emergence of new autoimmune diseases following COVID-19 vaccinations, including autoimmune glomerulonephritis, autoimmune rheumatic diseases, and autoimmune hepatitis [16]. This study also aims to investigate a potential link between SARS-CoV-2 vaccination in children and the development of new-onset autoimmune diseases.

Patients and methods

This was a retrospective and population-based cohort study based on anonymized data from electronic medical records of the Maccabi Healthcare Services (MHS) centralized computerized database. MHS, Israel's second-largest healthcare organization, serves approximately 2.6 million insured patients and offers access to electronic medical records across its extensive healthcare network, including diagnoses, medications, lab results, and hospitalization data. MHS has tracked COVID-19 results since February 23, 2020, when the first positive case in Israel was detected on February 27, 2020 [17]. MHS recorded data for all patients vaccinated with COVID -19 vaccine as soon as the vaccine was available. In this study, we investigated a cohort of 493,705 insured patients. The research was initiated and data retrieved after obtaining Institutional Review Board (IRB) approval (0103-23-MHS).

In the first instance, we investigated trends in new diagnoses of select autoimmune diseases across three consecutive 3-year periods. Periods A and B, representing the pre-COVID-19 pandemic periods, spanned from early 2014 to late 2016 and from early 2017 to late 2019, respectively. Period C, encompassing the COVID-19 pandemic era, extended from early 2020 to the end of 2022. The pre-COVID-19 period was divided into two sub-periods to assess whether the incidence of autoimmune diseases had increased over time, independently of COVID-19 infection.

Building upon previous research suggesting a link between COVID-19 infection and the onset or exacerbation of certain autoimmune diseases, we established a list of diagnoses investigated in this study, diseases we considered relevant to the pediatric population (Table 1).

We evaluated the occurrence of newly diagnosed autoimmune diseases across three randomly selected groups (A-C) of equal size and matched for age, gender, and social status. Included were persons not documented as having any of the autoimmune diseases under investigation prior to the onset of the study. Participant age ranged from 1 to 21 years at the start of each study period. We identified diagnoses of the investigated diseases in the MHS database using ICD-9 [18] codes and Maccabi Health Services specific codes to capture all disease subtypes.

Subsequently, we focused on the COVID-19 pandemic period to examine the prevalence of autoimmune diseases amongst patients with evidence of COVID-9

Table 1 Demographic data stratified by groups

Characteristic	Overall, *N* = 493,705	2020–2022 (Group C), *N* = 166,480	2014–2016 (Group A), *N* = 162,650	2017–2019 (Group B), *N* = 164,575	*P*-value
Autoimmune Disease	4,596 (0.9%)	1,503 (0.9%)	1,499 (0.9%)	1,594 (1.0%)	0.13
Sex					0.3
Female	242,366 (49%)	82,001 (49%)	79,569 (49%)	80,796 (49%)	
Male	251,053 (51%)	84,479 (51%)	82,909 (51%)	83,665 (51%)	
Age, years					0.5
Mean (SD)	10.6 (5.3)	10.6 (5.3)	10.6 (5.3)	10.6 (5.3)	
Median (IQR)	11.0 (6.0, 15.0)	11.0 (6.0, 15.0)	11.0 (6.0, 15.0)	11.0 (6.0, 15.0)	
Age category, years					0.8
< 5	111,420 (23%)	37,513 (23%)	36,816 (23%)	37,091 (23%)	
6 to 10	129,333 (26%)	43,527 (26%)	42,641 (26%)	43,165 (26%)	
11 to 15	136,096 (28%)	46,101 (28%)	44,743 (28%)	45,252 (28%)	
> 15	116,570 (24%)	39,339 (24%)	38,278 (24%)	38,953 (24%)	
Sector					< 0.0001
Jewish	123,145 (25%)	44,703 (27%)	39,570 (24%)	38,872 (24%)	
Not Known	319,370 (65%)	105,276 (63%)	105,159 (65%)	108,635 (66%)	
Arab	51,204 (10%)	16,501 (9.9%)	17,749 (11%)	16,954 (10%)	
Unknown	286	0	172	114	
SES					< 0.0001
Mean (SD)	6 (2)	6 (2)	6 (2)	6 (2)	
Median (IQR)	6 (4, 8)	6 (4, 8)	6 (4, 8)	6 (4, 8)	
Unknown	286	0	172	114	
SES category					< 0.0001
1 to 3	85,456 (17%)	29,810 (18%)	28,407 (17%)	27,239 (17%)	
4 to 7	251,168 (51%)	84,621 (51%)	81,941 (50%)	84,606 (51%)	
8 to 10	156,795 (32%)	52,049 (31%)	52,130 (32%)	52,616 (32%)	
Unknown	286	0	172	114	

Group A (first pre-pandemic period): 2014–2016, Group B (second pre-pandemic period): 2017–2019, Group C (COVID- 19 pandemic period): 2020–2022

Abbreviations: *SES* Socio-economic status

infection before or after vaccination. At the beginning of the pandemic in the early 2020 s, the reliability of COVID-19 case data was strong, as MHS recorded all polymerase chain reaction (PCR) tests conducted on its insured patients. At that time, other testing methods to detect COVID-19 were not yet available, making PCR the primary tool for case evaluation. However, during the later phase of the pandemic (from July 2021), data on infections became less reliable due to reliance on self-reported antigen testing. Given the declining accuracy of COVID-19 infection reports following the change in testing policy, we limited that part of our study to the period from January 2020 to June 2021.

We collected information on COVID-19 vaccination status, including the number of doses administered, and then calculated the incidence of new autoimmune disease diagnoses in relation to vaccination status. Israel's COVID-19 vaccination program was rolled out in phases. It began with individuals aged 16 and above in December 2020, expanded to 12-year-olds in June 2021, 5-year-olds in November 2021, and finally to infants in June 2022 as reported on the Israeli Ministry of Health's COVID-19 dashboard [19].

Statistical analysis

Descriptive statistics

Baseline characteristics of the study population were comprehensively summarized using descriptive statistics. Continuous variables were assessed for normality while those conforming to a normal distribution were described using means and standard deviations (SDs). Variables with non-normal distributions were characterized using medians and interquartile ranges (IQRs). For univariate analyses, t-tests were applied to normally distributed variables and the Mann–Whitney U test was used for variables not meeting normality criteria. Categorical variables were reported as frequencies and percentages, and associations were analyzed using the Chi-square test. In our analyses, we categorized age and socio-economic status (SES) into defined ranges—age

into four groups: 1–5, 6–10, 11–15, and over 15 years; SES into three groups: 1–3, 4–7, and 8–10—because the effects of these variables on the outcome, AI disease diagnosis, were not linear.

Logistic regression analysis

Logistic regression analyses were conducted to evaluate the impact of various factors on the overall risk of developing autoimmune diseases as well as risk associated with each specific diagnosis. For the overall analysis, adjustments were made for sex, SES group, and age group. The models produced adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for each predictor. Findings were stratified and presented in two separate forest plots: one compared the odds of developing an autoimmune disease in Group A versus Group C, and the other compared Group B versus Group C. For analyses specific to each diagnosis, initial attempts to adjust for age and SES were unsuccessful due to the low frequency of autoimmune disease events. Consequently, adjustments were restricted only to sex ensured the stability and reliability of the estimates. By limiting the number of covariates, we avoided overfitting and reduced variability in the estimates, which is essential when dealing with rare events.

Cox proportional hazards regression analysis

Cox proportional hazards regression model was used to assess the risk of autoimmune disease development. We executed a 1:10 exact case–control matching based on socio-economic variables, such as age and sex, specifically within Group C. This group comprised individuals diagnosed with autoimmune diseases and their matched controls without these conditions. The analysis covered the period from January 1, 2020, to December 31, 2022. Key covariates included in the model were any prior COVID-19 diagnosis up to July 1, 2021. Vaccination status was considered only if it occurred within the follow-up period; any vaccinations administered after the onset of an autoimmune disease or outside the follow-up were excluded from the analysis. The model adjustments provided hazard ratios (HRs) with 95% CIs.

Statistical significance and software used

Statistical significance was established at a two-sided alpha level of 0.05, with *p*-values below this threshold denoting statistically significant differences. All statistical analyses were performed using R, version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio, version 2020 (RStudio Team, Boston, MA, USA).

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Institutional review board statement

This study was approved by the MHS Institutional Review Board, approval number MHS-0103-23.

Results

The study involved a total of 493,705 patients, with demographic data for the entire group provided in Table 1. The whole cohort was divided into three groups based on 3-year intervals: Group A (2014–2016), Group B (2017–2019), and Group C (2020–2022). Group A comprised 162,650 patients, Group B 164,575 patients, and Group C 166,480 patients. The patients in each group were matched for age, sex, and socio-economic status at the beginning of each period. Across the entire cohort, 4,596 (0.9%) patients were diagnosed with an autoimmune disease. When stratified by time period, 1,499 (0.9%) patients in Group A, 1,594 (1.0%) patients in Group B, and 1,503 (0.9%) patients in Group C had a documented autoimmune disease ($p = 0.13$) (Table 2).

The detailed breakdown of autoimmune disease prevalence, including the exact case counts and corresponding percentages for each group, is outlined in Table 2.

The results of the multivariable logistic regression analysis, adjusted for sex, age, and SES, using Group C as the reference category, revealed that Group A (OR 1.0192, 95% CI 0.9485–1.0952, $p = 0.6036$) and Group B (OR 1.0689, 95% CI 0.9958–1.1474, $p = 0.0651$) did not demonstrate statistically significant differences in the odds of developing an autoimmune disease as compared to Group C (Table 3).

A series of logistic regression analyses conducted separately for each autoimmune disease, with adjustments made for sex, found that celiac disease was significantly less likely to occur in Group A as compared to the reference group, Group C (OR 0.8309, 95% CI 0.7261–0.9508, $p = 0.0071$). Arthritis showed a significantly increased likelihood in both Group A (OR 1.2438, 95% CI 1.0452–1.4458, $p = 0.0045$) and Group B (OR 1.2154, 95% CI 1.0452–1.4134, $p = 0.0113$) as compared to Group C. Psoriasis was more likely to occur in Group A (OR 1.4112, 95% CI 1.0051–1.9625, $p = 0.0406$) relative to Group C. Raynaud's Syndrome was significantly less likely to occur in Group A as compared to Group C (OR 0.7199, 95% CI 0.5255–0.9863, $p = 0.0407$). Lastly, IGA Vasculitis had a significantly higher likelihood to occur in Group B as compared to Group C (OR 1.5432, 95% CI 1.1718–2.0394, $p = 0.002$). All other autoimmune

Table 2 Names of the assessed autoimmune diseases and their incidence rates during periods A-C

Characteristic	Overall AID, *N* = 4,591	2020–2022 (Group C), *N* = 1,502	2014–2016 (Group A), *N* = 1,497	2017–2019 (Group B), *N* = 1,592
Ankylosing spondylitis	82 (1.8%)	22 (1.5%)	28 (1.9%)	32 (2.0%)
APLA syndrome	342 (7.4%)	117 (7.8%)	121 (8.1%)	104 (6.5%)
Arthritis	1,056 (23%)	310 (21%)	375 (23%)	371 (23%)
Bechet disease	23 (0.5%)	5 (0.3%)	11 (0.7%)	7 (0.4%)
Celiac disease	1,305 (28%)	474 (32%)	524 (32%)	307 (19%)
Juvenile dermatomyositis, polymyositis	5 (0.1%)	1 (< 0.1%)	1 (< 0.1%)	3 (0.2%)
Diabetes mellitus type 1	267 (5.8%)	63 (6.1%)	92 (5.8%)	112 (6.8%)
Familial mediterranean fever	19 (0.4%)	6 (0.4%)	5 (0.3%)	8 (0.5%)
Guillain–barre syndrome	28 (0.6%)	7 (0.5%)	14 (0.9%)	7 (0.4%)
IgA vasculitis	305 (6.6%)	84 (6.6%)	93 (6.8%)	128 (8.0%)
Inflammatory bowel disease	442 (9.6%)	143 (9.6%)	148 (9.8%)	151 (9.5%)
ITP	21 (0.5%)	9 (0.6%)	9 (0.6%)	3 (0.2%)
Kawasaki disease	52 (1.1%)	19 (1.3%)	17 (1.0%)	16 (1.0%)
Morphea	102 (2.2%)	35 (2.3%)	35 (2.2%)	32 (2.2%)
Multiple sclerosis	33 (0.7%)	7 (0.5%)	13 (0.8%)	13 (0.8%)
Psoriasis	225 (4.9%)	61 (4.1%)	84 (5.4%)	80 (5.0%)
Raynaud	245 (5.3%)	94 (6.3%)	66 (4.4%)	85 (5.3%)
Sarcoidosis	3 (< 0.1%)	1 (< 0.1%)	1 (< 0.1%)	4 (< 0.1%)
Systemic lupus erythematosus	21 (0.5%)	9 (0.6%)	9 (0.6%)	3 (0.2%)
Systemic sclerosis	5 (0.1%)	3 (0.2%)	0 (0%)	2 (0.1%)
Uveitis, panuveitis	8 (0.2%)	4 (0.2%)	1 (< 0.1%)	3 (0.2%)
Vasculitis[a]	2 (< 0.1%)	0 (0%)	0 (0%)	2 (< 0.1%)

Acronyms: *APLA syndrome* Antiphospholipid syndrome, *ITP* Idiopathic Thrombocytopenic Purpura, *AID* autoimmune diseases

[a] Vasculitis include Takayasu disease, ANCA-associated vasculitis, Granulomatosis with polyangiitis, microscopic polyangiitis

Table 3 Multivariable logistic regression for autoimmune disease onset in follow-up

Characteristic	OR	Lower 95% CI	Upper 95% CI	*P*-value
Group A	1.0192	0.9485	1.0952	0.6036
Group B	1.0689	0.9958	1.1474	0.0651
SES cat 4–7	1.315	1.1975	1.444	< 0.0001
SES cat 8–10	1.8626	1.6939	2.0481	< 0.0001
Sex Male	0.7391	0.697	0.7837	< 0.0001
Age at Start cat 6 - 10y	0.8494	0.7804	0.9245	0.0002
Age at Start cat 11 - 15y	0.9628	0.8878	1.0441	0.3591
Age at Start cat > 15y	1.0192	0.9377	1.1077	0.6552

OR odds ratio, *SES cat* Socioeconomic status category, *cat* category, *y* years

diseases were not found to differ significantly amongst the groups (Fig. 1).

In a case–control analysis within Group C, patients with and without autoimmune diseases were matched for sex, age, and SES to evaluate the impact of COVID-19 and COVID vaccination on the development of autoimmune diseases (Table 3). The analysis revealed that being diagnosed with COVID-19 until June 2021 was not significantly associated with an increased risk of developing an autoimmune disease (HR 1.092, 95% CI 0.8501–1.4026, $p = 0.491$). However, receiving at least one COVID vaccine was associated with a statistically significant increase in risk of developing an autoimmune disease (HR 1.2323, 95% CI 1.0721–1.4165, $p = 0.0033$) (Table 4).

Based on a baseline risk of 0.9%, the hazard ratio of 1.2323 translates to an absolute risk increase of 0.21%. The mean time interval between vaccination and the onset of autoimmune disease was 8.74 months (IQR: 4.73–13.11).

Discussion

The present retrospective study shows pioneering research investigating the potential association between COVID-19 infection, vaccination, and the development of new-onset autoimmune diseases in a large pediatric population.

The main purpose of this study was to investigate the temporal trends in the prevalence of autoimmune

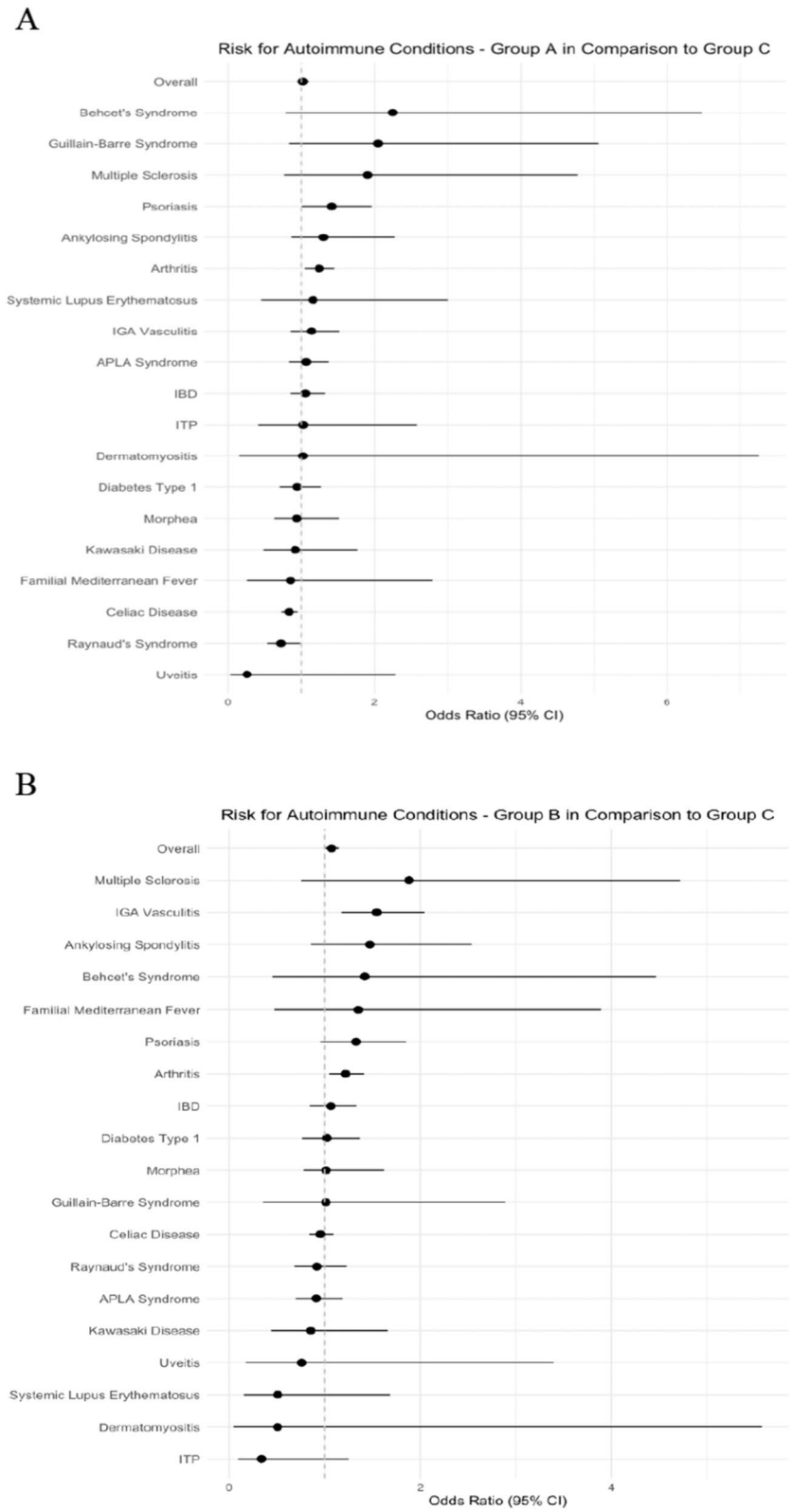

Fig. 1 **A** and **B** Multivariable logistic regression analysis comparing the incidence of autoimmune diseases between Group C (pandemic period) and Groups A and B (pre-pandemic periods)

Table 4 Cox regression analysis of autoimmune disease onset in association with COVID-19 infection and vaccination during pandemic period, period C (2020–2022)

Characteristic	HR	Lower 95% CI	Upper 95% CI	*P*-value
COVID until June 2021	1.092	0.8501	1.4026	0.491
COVID vaccine	1.2323	1.0721	1.4165	0.0033

diseases before and after onset of the COVID-19 pandemic.

By examining scientific literature released since the pandemic started, it is evident that COVID-19 infection is associated with new autoimmune disease diagnoses. For instance, in a recent systematic review by Ramos et al. [9], 14 studies were analyzed from PubMed and Scopus databases (December 2019 to September 2021), comprising a total of 99 patients ranged in age from 37.3 to 64.8 years. The findings suggest a potential association between SARS-CoV-2 infection and a spectrum of systemic and rheumatic autoimmune diseases, particularly vasculitis and arthritis but also a limited number of cases of idiopathic inflammatory myopathies, systemic lupus erythematosus, sarcoidosis, systemic sclerosis, and Still's disease. Similarly, in a more recent study, Hileman et al. [10] presented a retrospective study based on data from 74 healthcare organizations that included a large population of over 3 million adults diagnosed with new autoimmune disease diagnoses between January 1, 2020, and March 3, 2023. They showed that individuals who had COVID-19 were at a significantly increased risk of developing an autoimmune disease within a year of diagnosis as compared to matched controls (adjusted risk ratio: 1.09, 95% CI: 1.07–1.12). Of the 24 assessed diseases, eight were found to be associated with increased risk following infection with COVID-19. Additionally, interest in investigating the impact of COVID-19 on the development of autoimmune diseases in children was further stimulated by the intriguing phenomenon known as MIS-C, which is unique to COVID-19. MIS-C, is a rare but severe complication of COVID-19 that can affect multiple organs and shares some similarities with Kawasaki disease [20].

In the Italian province of Bergamo, Verdoni et al. reported a 30-fold surge in monthly Kawasaki disease cases during the peak of the COVID-19 pandemic (February to April 2020) [21]. Given this, we hypothesized that a similar increase might have occurred in other regions of Israel. Unfortunately, our analysis of the odds ratio for Kawasaki disease incidence before and after the onset of the COVID-19 pandemic did not yield statistically significant results. This discrepancy could stem from the fact that MIS-C cases, which often involve rapid deterioration and systemic shock, were treated directly in hospitals and may not have been recorded in the MHS database. It is important to note that the MHS database primarily captures data from community clinics and primary care physicians within the organization. Therefore, it may not fully reflect cases requiring hospitalization, such as those involving severe MIS-C. This exclusion of hospital-managed MIS-C cases could potentially bias our results, as it might have led to an underestimation of the overall incidence of severe inflammatory conditions during the COVID-19 pandemic. Another possible explanation for this discrepancy is that at the onset of the COVID pandemic, some MIS-C cases were mistakenly diagnosed as Kawasaki disease, leading to increased early reporting of Kawasaki disease incidence during that time. The reduced exposure to other infectious agents, especially viruses, during social confinement may have inadvertently protected the population from developing autoimmune diseases such as Kawasaki disease, which are potentially linked to viral infections [22]. Lastly, as our study focused solely on Kawasaki diagnoses and not on MIS-C, it is conceivable that while incidence of Kawasaki cases remained stable, there might have been a surge in cases meeting the clinical criteria for MIS-C during the COVID-19 pandemic. We acknowledge that future research incorporating hospital records or national registries of MIS-C cases would provide a more comprehensive understanding of the impact of the COVID-19 pandemic on both Kawasaki disease and MIS-C incidence.

In contrast to findings in existing literature, our study did not reveal any statistically significant changes in the overall incidence of autoimmune diseases amongst pediatric populations, either prior to or following onset of the COVID-19 pandemic. One potential explanation for this discrepancy is that previous studies have not focused on pediatric populations, and these diseases are even rarer in younger age groups. Furthermore, children were less likely than adults to develop severe illness from COVID-19, suggesting that the immune response to COVID-19 infection differs between adults and the pediatric population. This difference may also have influenced the development of AI diseases [23].

However, our study shows that certain specific diseases, such as celiac disease, were indeed diagnosed more frequently during the pandemic as compared to during the pre-pandemic periods. Celiac disease is an autoimmune disorder triggered by gluten, a protein found in wheat, barley, and rye. It damages the small intestine, causing symptoms including abdominal pain, bloating, diarrhea, fatigue, and weight loss. A retrospective study at a tertiary Turkish hospital by Cakir et al. yielded comparable findings [24]. Specifically, they

found a significant increase in new-onset celiac disease cases in children during the COVID-19 pandemic as compared to the pre-pandemic period. It's important to note that their study did not find direct evidence of COVID-19 infection in patients diagnosed with celiac disease during the pandemic. Building on previous research, Cakir et al. proposed that prolonged exposure to SARS-CoV-2 in the gastrointestinal tract can disrupt gut integrity and contribute to the development of celiac disease. The researchers suggest that this can lead to dysbiosis and increased intestinal permeability, allowing harmful antigens to enter the bloodstream and trigger an inflammatory response that may contribute to the development of celiac disease.

Additionally, our study shows an increased diagnosis of Raynaud's phenomenon during the COVID-19 pandemic. Raynaud's phenomenon (RP), affecting about 5% of people, is often primary but can be secondary to other conditions [25]. There is evidence in the literature linking both COVID-19 infection and vaccination to cases of Systemic Sclerosis and RP [9, 26, 27]. Interestingly, pediatric patients have shown a temporal link between chilblains and COVID-19, similar as in RP, with acro-ischemic lesions in the fingers and toes [28]. Our findings reinforce the evidence linking the onset of the pandemic to RP. However, the underlying mechanism by which the virus causes these acro-ischemic lesions remains unclear.

In contrast, there was a decrease in diagnosis rates for a subset of diseases during the pandemic, such as arthritis. Arthritis diseases were diagnosed approximately 20% more frequently in the pre-pandemic period as compared to the pandemic. Conversely, recent studies investigating the relationship between COVID-19 and adult inflammatory arthritis have shown the opposite to be true. A retrospective analysis of over 2 million Colombian health insurance records by Marin et al. revealed a notable rise in rheumatoid arthritis diagnoses post-pandemic, especially amongst women aged 51–60. In contrast, the incidence of rheumatoid arthritis remained relatively stable among younger adults aged 18–30 [29]. Moreover, in the previously cited study by Hileman et al., the rate of new cases of reactive arthritis and rheumatoid arthritis were not affected by COVID-19 infection [10]. The high incidence of reactive arthritis following viral infections in the pediatric population suggests that the protective effect of social confinement during the pandemic, by limiting exposure to contagious infections, may have contributed to the decrease in cases. Further research in pediatric populations is needed to better understand this issue [30].

In the second phase, our study examined the COVID-19 pandemic period, starting from January 2020, to explore potential correlations between COVID-19 infection or vaccination and the development of autoimmune diseases. However, as mentioned previously, this investigation was restricted to the period before July 2021 due to concerns regarding the accuracy of COVID-19 testing and record-keeping. The limited duration of data collection posed certain limitations to later results.

It is also important to acknowledge that for rare outcomes, such as juvenile dermatomyositis ($n = 5$), our results related to COVID-19 infection may be underpowered. Therefore, findings related to these specific conditions should be interpreted as exploratory. Larger studies are needed to confirm these observations and to provide more robust evidence regarding the association between COVID-19 infection and these rare autoimmune diseases.

If COVID-19 infection did not increase the risk of autoimmune diseases, vaccinations did show a significantly heightened risk of developing autoimmune conditions by over 23%.

Regarding the potential link with the COVID-19 vaccine, these results are in alignment with the current literature, which establishes a causal link between the vaccine and the development of long-term adverse effects, particularly autoimmune diseases [31]. The primary mechanisms proposed for vaccine-induced autoimmunity following SARS-CoV-2 vaccination include molecular mimicry, generation of autoantibodies, and the role of vaccine adjuvants [32].

Case reports and research on adult populations are increasingly numerous and demonstrate a link between autoimmune phenomena and the COVID-19 vaccine [16, 31–33]. In contrast, research on pediatric populations is less abundant, but emerging reports also show an increase in autoimmune phenomena in children following the COVID-19 vaccine, such as MIS-C [33], transverse myelitis [34], myasthenia gravis [35], systemic lupus erythematosus [36], and IgA vasculitis [37]. Similarly, our study revealed a considerably higher incidence of new autoimmune disease diagnoses among vaccinated pediatric subjects as compared to their unvaccinated counterparts, representing a nearly 40% increased risk during the study period from January 2020 to December 2023.

We acknowledge that the observed increase in autoimmune diseases diagnoses among vaccinated children could be influenced by factors such as increased healthcare utilization and heightened parental health-seeking behavior. Vaccinated children may have more frequent medical encounters, and parents who choose vaccination may be more vigilant in seeking medical attention for their children. Adjusting for these potential confounders in a retrospective database study is challenging. While we did not have direct measures of these behaviors, it is

important to note that the incidence of autoimmune diseases in children is low. Future prospective studies are warranted to more accurately assess the causal relationship between COVID-19 vaccination and AI diseases development, while controlling for these potential biases.

The temporal relationship between COVID-19 vaccination and the onset of autoimmune diseases is an important aspect of understanding potential associations. In our cohort, we observed a median time interval of 8.74 months (IQR: 4.73–13.11) between vaccination and autoimmune diseases onset. This relatively long interval contrasts noticeably with findings from other studies. For example, Rodríguez et al., in a systematic review of 928 adult cases, reported a median period of eight days (IQR: 3 to 14) between COVID-19 vaccination and the onset of autoimmune or autoinflammatory conditions, highlighting a much shorter interval compared to our cohort [38]. Similarly, Yang et al. found that the median onset time for antineutrophil cytoplasmic antibody-associated vasculitis (AAV) post-vaccination was 12 days (range: 1–77 days) after the first dose and 14 days (range: 1–60 days) after the second dose, further indicating a shorter interval than our findings [39]. These studies indicate that the onset of autoimmune conditions post-COVID-19 vaccination can vary widely, with many cases occurring within days to weeks, contrasting with the longer median interval observed in our cohort. However, it should be noted that our study encompassed a broader spectrum of autoimmune diseases, including rare and less-studied conditions in the pediatric population, which may also contribute to the observed variability in latency compared to studies focusing on specific, more common autoimmune conditions. Specifically, further research is critically needed to understand the factors contributing to these differences in pediatric populations, including variations in study populations, specific autoimmune conditions, and potential underlying mechanisms.

Moreover, while our study found a statistically significant hazard ratio of 1.23 for autoimmune diseases following vaccination, it is crucial to consider the absolute risk difference. Based on a baseline risk of 0.9% in the unvaccinated group, the hazard ratio of 1.23 translates to an increased risk of 1.1% in the vaccinated group. This results in an absolute risk difference of 0.21%. This absolute risk difference, while statistically significant, represents a relatively modest increase. It is important to consider the clinical implications of this finding. While a 0.21% increase may be statistically notable in a large population, it is crucial to balance this risk against the well-established benefits of COVID-19 vaccination.

COVID-19 vaccination in children has demonstrated significant benefits, particularly in reducing the incidence of severe COVID-19-related outcomes. A systematic review and meta-analysis published in JAMA Pediatrics found that two-dose mRNA COVID-19 vaccination in children aged 5 to 11 years was associated with lower risks of SARS-CoV-2 infections, symptomatic infections, hospitalizations, and multisystem inflammatory syndrome in children (MIS-C) [40].

Additionally, a study in Nature Communications involving 5.1 million children in England reported a favorable safety profile for COVID-19 vaccines, with no increased risks of adverse events in 5-11-year-olds and only a small number of additional cases of myocarditis in 12-17-year-olds following vaccination [41].

Furthermore, research published in JAMA Network Open indicated that COVID-19 vaccination was associated with reduced odds of post-COVID-19 condition symptoms in children, suggesting benefits beyond protection against acute infection [42].

Overall, the evidence supports the efficacy and safety of COVID-19 vaccination in children, highlighting its role in preventing severe disease, reducing hospitalizations, and mitigating long-term complications associated with SARS-CoV-2 infection.

The low incidence of autoimmune diseases in children further emphasizes the need for careful consideration of the risk–benefit ratio. Further studies are warranted to elucidate the mechanisms through which the vaccine might trigger autoimmune responses.

Conclusion

This retrospective study provides valuable insights into the potential association between COVID-19 infection, vaccination, and the development of new-onset autoimmune diseases in a pediatric population. Although we did not observe an overall increase in the incidence of autoimmune diseases during the COVID-19 pandemic, our analysis revealed a concerning elevated association of autoimmune disease development following COVID-19 vaccination. While no significant association was found between COVID-19 infection and the development of autoimmune diseases, the potential association with vaccination warrants further investigation.

The findings of this study align with emerging evidence suggesting a potential association between COVID-19 and autoimmune diseases, particularly with regard to vaccination. However, further research is needed to elucidate the underlying mechanisms and determine the long-term implications of these findings.

While our study identifies a potential association between vaccination and autoimmune disease development, it is crucial to emphasize that the absolute risk remains low. This low absolute risk must be carefully balanced against the well-established and significant

benefits of COVID-19 vaccination in preventing severe COVID-19 outcomes, including MIS-C, hospitalization, and death. Given the potential severity of COVID-19 infection, particularly in vulnerable populations, the benefits of vaccination generally outweigh the potential, albeit low, risk of autoimmune disease development. Future studies should focus on identifying factors that may increase or decrease the association of autoimmune diseases following COVID-19 infection or vaccination, as well as developing strategies for early detection and management of these conditions.

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Authors' contributions
Conceptualization: C.F, Y.A.B; methodology: C.F, Y.A.B; formal analysis: A.D; funding acquisition: C.F; Y.A.B; supervision: C.F, Y.A.B; writing—original draft: C.F, D.A, A.D, Y.A.B; writing—review and editing: C.F, D.A, A.D, Y.A.B; validation: C.F, D.A, A.D, Y.A.B. All authors have read and agreed to the published version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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