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REVIEW

Autoimmune Diseases following COVID-19 Infection: How Solid is the Evidence?

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Many COVID-19 survivors report protracted symptoms, sometimes lasting 3 years or more. These are collectively called post-acute sequelae of SARS-CoV-2 infection (PASC), or long Covid.[1–4] In addition, several common diseases appear to be diagnosed more frequently following COVID-19 infection. Amongst these, cardiopulmonary disorders predominate, but diseases of many organ systems have been reported. Case reports of de novo autoimmune disorders appeared early during the pandemic. In 2023, 5 large international cohort studies provided further evidence that autoimmune disorders may be more common.

INCIDENCE OF AUTOIMMUNE DISEASES

Dysregulated immune responses have been a consistent feature of SARS-CoV-2 infection. One of the first examples was multi-inflammatory syndrome in children (MIS-C), first described in early 2020. It was characterized by cardiovascular, gastrointestinal, and mucocutaneous symptoms that appeared in the first 6 weeks following infection. Markers of inflammation, such as C-reactive protein, ferritin, and interleukin-6 were increased, at times dramatically, and levels appeared to correlate with disease severity. Typically, symptoms improved, and markers normalized with time. As the pandemic evolved sustained dysfunction of the immune system was recorded and case reports of de novo autoimmune disorders began to appear. A 2021 review reported 90 cases of new-onset rheumatic autoimmune disorders in Europe, Asia, and North America.[5] Arthritis and vasculitis predominated; systemic lupus, antiphospholipid syndrome and inflammatory myopathies were also recorded. The authors suggested that SARS-CoV-2 infection might precipitate autoimmune disorders.

In 2023, a large cohort study that included patients from 48 global health care organizations, compared 880,000 SARS-CoV-2 polymerase chain reaction (PCR) positive, unvaccinated individuals to a similar number of propensity score-matched controls.[6] After 6 months of follow-up, there was an increased risk of 14 different autoimmune conditions, including rheumatoid arthritis (aHR 2.98, 95% CI:2.78–3.20), ankylosing spondylitis (aHR 3.21, 95% CI:2.50–4.13), systemic lupus erythematosus (aHR 2.99, 95% CI:2.68–3.34), dermatopolymyositis (aHR 1.96, 95% CI:1.47–2.61), systemic sclerosis (aHR 2.58, 95% CI:2.02–3.28), Sjogren's syndrome (aHR 2.62, 95% CI:2.29–3.00), mixed connective tissue disease (aHR 3.14, 95% CI:2.26–4.36), Bechet's disease (aHR 2.32, 95% CI:1.38–3.89), polymyalgia rheumatica (aHR 2.90, 95% CI:2.36–3.57), vasculitis (aHR 1.96, 95% CI:1.74–2.20), psoriasis (aHR 2.91, 95% CI:2.67–3.17), inflammatory bowel disease (aHR 1.78, 95%CI:1.72–1.84), celiac disease (aHR 2.68, 95% CI:2.51–2.85) and type 1 diabetes mellitus (aHR 2.68, 95%CI:2.51–2.85). When adjusted for competing risks, the hazard ratios were reduced but remained elevated (HR 1.19 to HR 1.47). The risk of most autoimmune diseases was similar in men and women and was age independent. Surprisingly, in contrast to reports of other diseases following COVID-19 infection, hospitalization did not confer additional risk. Of further interest, a sub-analysis of European, Middle Eastern and African cohorts in the same database failed to show similar results.

A 2023 analysis of a German general practice database compared 640,000 SARS-CoV-2 PCR-positive individuals to 1.8 million unvaccinated controls, with a 3-to-15-month follow-up.[7] Overall, there was a 43% increased risk of developing a new autoimmune disease. The most common diagnoses were Hashimoto thyroiditis (IRR 1.42, 95% CI:1.33–1.52), Graves' disease (IRR 1.41, 95% CI:1.31–1.51), psoriasis (IRR 1.17, 95% CI:1.09–1.26), rheumatoid arthritis (IRR 1.42, 95% CI:1.30–1.56), and Sjogren's syndrome (IRR 1.44, 95% CI:1.27–1.63). The highest risks were recorded for Granulomatosis with Polyangiitis (GPA, formerly known as Wegener's disease) (IRR 2.51, 95% CI:1.42–4.46), Behcet's disease (IRR 2.42, 95% CI:1.10–5.35), sarcoidosis (IRR 2.14, 95% CI:1.73–2.65), and temporal arteritis (IRR 1.63, 95% CI:1.05–2.53). In contrast to the previous study, the risk of autoimmune disease was higher among women, higher at older ages and higher following hospitalization. Among individuals with pre-existing autoimmune conditions, the risk of a new autoimmune diagnosis was increased by 23%.

A 2023 UK study of 458,000 adults with 1.8 million controls, drawn from a large general practice database and followed for 4 months, reported an increased risk for 11 autoimmune disorders (aHR 1.22, 95% CI:1.12-1.33), following adjustment for important risk factors.[8] The crude incidence rate of autoimmune disorder was 4.59 per 1000-person years in the study group and 3.65 per 1000 person-years in the control group. Risk was increased for type 1 diabetes mellitus (aHR 1.56, 95% CI:1.09–1.23), psoriasis (HR 1.23, 95% CI:1.05–1.42) and inflammatory bowel disease (1.36, 95% CI:1.18-1.56) but was not increased for the remaining 8 disorders.

A 2023 study of 1.02 million COVID-19 cases and 3.1 million controls, drawn from a Hong Kong database and followed for up to 8 months, evaluated the incidence of 22 autoimmune diseases following COVID-19 infection.[9] It showed an increased risk of pernicious anemia (aHR 1.72; 95% CI: 1.12–2.64), spondyloarthritis (aHR 1.32, 95% CI:1.03–1.69), rheumatoid arthritis (aHR 1.29, 95% CI: 1.09–1.54), psoriasis (aHR 1.42, 95% CI:1.13–1.78), pemphigoid (aHR 2.39, 95% CI:1.83–3.11), Graves' disease (aHR: 1.30, 95% CI: 1.10–1.54), antiphospholipid syndrome (aHR 2.12, 95% CI: 1.47–3.05), immune thrombocytopenia (aHR 2.1, 95% CI: 1.82–2.43), multiple sclerosis (aHR 2.66, 95% CI:1.17–6.05) and vasculitis (aHR 1.46, 95% CI:1.04–2.04). Following vaccination, the risk of some but not all conditions decreased.

Lastly a 2023 Korean study of 354,000 COVID-19 cases and 6.1 million controls

recorded an increase incidence of alopecia areata (aHR 1.12; 95% CI: 1.05-1.19), alopecia totalis (aHR 1.74; 95% CI 1.39-2.17), ANCA-vasculitis (aHR 2.76; 95% CI 1.64-4.65), Crohǹs disease (aHR 1.68; 95% CI 1.31-2.15) and sarcoidosis (aHR 1.59 95% CI: 1.00-2.52).[10] For a further 11 autoimmune conditions, incidence was not increased. Interestingly, the incidence of systemic lupus erythematosus was reduced by 50% compared to controls.

HOW STRONG IS THIS EVIDENCE?

At first flush, the evidence for increased incidence of autoimmune diseases provided by these studies appears consistent, both in frequency and magnitude. Combined with the evidence that SARS-CoV-2 infection can cause widespread immune disruption, with many features of autoimmunity, such a result might not seem surprising. However, caution is required. The 5 studies were retrospective analyses of electronic health records; such analyses have limitations. First, reliance on diagnostic codes, prescription records and laboratory results to establish disease incidence is intrinsically error-prone, capable of both overdiagnosing and underdiagnosing a condition of interest. Second, the control groups may have included individuals who, despite negative PCR testing, had contracted SARS-CoV-2 infection, creating misclassification bias. Additionally, healthcare visits for COVID-19 infection may have prompted earlier diagnoses, thereby artificially increasing disease incidence. Two further problems deserve mention: The incidence of individual diseases is not consistently elevated across all 5 studies. For example, rheumatoid arthritis, a common autoimmune condition, was increased in 3 of the 5 studies. Systemic lupus, another common entity, was increased in 1 of 4 studies and significantly reduced in the fifth. Second, the impact of age, sex and hospitalization is not consistent across all studies, a rather surprising finding. Autoimmune diseases disproportionately affect women and hospitalization has been consistently associated with worse COVID-19 related outcomes. One might have expected that both observations be replicated in these 5 cohorts. Lastly, the follow-up periods in 4 of the 5 studies, all conducted in the pre-Omicron years, were relatively short, raising the question of whether the reported increased incidences were sustained. Interestingly, a large US study reported the resolution of rheumatological symptoms 2 years after COVID-19 infection, particularly in non-hospitalized individuals.[11]

ARE THESE FINDINGS RELEVANT TO INSURED COHORTS?

Unlikely. Insured individuals, being healthier and with fewer co-morbidities, are unlikely to be at the same risk as the general population cohorts included in these studies. They are also more likely to be vaccinated, which appears to be protective.[9] Coupled with the problems and inconsistencies noted above, the relevance to insured populations is questionable.

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