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COVID-19

Associations between COVID-19 and skin conditions identified through epidemiology and genomic studies

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Background: Coronavirus disease 2019 (COVID-19) is commonly associated with skin manifestations, and may also exacerbate existing skin diseases, yet the relationship between COVID-19 and skin diseases remains unclear.

Objective: By investigating this relationship through a multiomics approach, we sought to ascertain whether patients with skin conditions are more susceptible to COVID-19.

Methods: We conducted an epidemiological study and then compared gene expression across 9 different inflammatory skin conditions and severe acute respiratory syndrome coronavirus 2–infected bronchial epithelial cell lines, and then performed a genome-wide association study transdisease meta-analysis between COVID-19 susceptibility and 2 skin diseases (psoriasis and atopic dermatitis).

Results: Skin conditions, including psoriasis and atopic dermatitis, increase the risk of COVID-19 (odds ratio, 1.55; \( P = 1.4 \times 10^{-5} \)) but decrease the risk of mechanical ventilation (odds ratio, 0.22; \( P = 8.5 \times 10^{-5} \)). We observed significant overlap in gene expression between the infected normal bronchial epithelial cells and inflammatory skin diseases, such as psoriasis and atopic dermatitis. For genes that are commonly induced in both the severe acute respiratory syndrome coronavirus 2 infection and skin diseases, there are 4 S100 family members located in the epidermal differentiation complex, and we also identified the “IL-17 signaling pathway” (\( P = 4.9 \times 10^{-77} \)) as one of the most significantly enriched pathways. Furthermore, a shared genome-wide significant locus in the epidermal differentiation complex was identified between psoriasis and severe acute respiratory syndrome coronavirus 2 infection, with the lead marker being a significant expression quantitative trait locus for \( S100A12 \) (\( P = 3.3 \times 10^{-7} \)).

Conclusions: Together our findings suggest association between inflammatory skin conditions and higher risk of COVID-19, but with less severe course, and highlight shared components involved in anti–COVID-19 immune response. (Allergy Clin Immunol 2021;147:857–69.)

Key words: COVID-19. SARS-CoV-2, skin conditions, psoriasis, atopic dermatitis, epidemiology, genetics, gene expression

Coronavirus disease 2019 (COVID-19) is an emerging and rapidly growing pandemic, with more than 23 million confirmed cases worldwide as of August 23, 2020,1 including 5.6 million cases and more than 170,000 deaths in the United States alone. COVID-19 is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has an estimated basic reproduction number between 1.4 and 6.49.2,3 The Centers for Disease Control and Prevention (CDC) report that symptoms can appear 2 to 14 days after exposure, and may include cough,
fever, chills, muscle pain, shortness of breath, sore throat, and new loss of taste or smell. Cutaneous manifestations have also been described, with prevalence between 7.8% and 20.4%. A detailed study of 375 COVID-19 skin-affected patients in Spain found maculopapular rashes to be the most common manifestation (47% of skin-affected patients). Other manifestations include pseudo-chilblains, urticarial lesions, and vesicular eruptions. Histopathology reports describe lymphocyte infiltration (including of CD4/CD8 T cells) with or without evidence of vasculitis, colocalization of SARS-CoV-2 spike proteins with signs of complement activation, and antibodies for SARS-CoV-2 in the upper dermis and epithelial cells of eccrine glands.

It is currently unclear whether patients with inflammatory skin conditions are at greater risk of COVID-19 than the general population. Although no skin conditions are included on the CDC list of COVID-19 risk factors, many of the diseases listed by the CDC as risk factors have been found to co-occur more frequently with skin diseases, for example, type 2 diabetes and psoriasis, cardiovascular diseases and eczema, or chronic kidney disease and lupus. Notably, patients suffering from inflammatory skin conditions can have different susceptibility to infection, potentially due to their defective skin barrier or systemic impact on the immune system. For instance, patients with psoriasis are more susceptible to pneumonia and serious infections in general, while skin and systemic infections are also more common in patients suffering from atopic dermatitis. Staphylococcus aureus skin colonization, subclinical Chlamydia psittaci infection of PBMCs, and skin/hair colonization with β-papillomaviruses have all been found to occur more frequently among patients with psoriasis than among the general population, while other infections, including streptococcal pharyngitis and periodontitis, are associated with triggering or exacerbating psoriasis. Preliminary case reports from Turkey and the United States suggest that COVID-19 risk may be higher in patients with psoriasis, and that it may exacerbate or trigger psoriasis. One epidemiological study grouped psoriasis with systemic lupus erythematosus (SLE) and rheumatoid arthritis and found that together they had an elevated rate of COVID-19 in-hospital death (1.19 adjusted hazard ratio).

Many skin conditions have dysregulated immune responses, and thus could potentially alter the risk of COVID-19 susceptibility and manifestation through their interaction with host immunology, either directly or through various immunosuppressant treatments. Although previous work has illustrated the binding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2), a cell entry receptor, in lung epithelia, ACE2 is also present in skin, particularly in the epidermal layer, and thus could act as a reservoir for indirect transmission. SARS-CoV-2 has at least 10 times higher binding affinity with ACE2 compared with severe acute respiratory syndrome coronavirus 1, but it induces less interferon response in the early stages of infection, thus allowing accumulation of the viral load and making it difficult to detect and clear. Elderly patients and those with imbalanced immune systems can particularly have a delayed response on the viral infection, and if the virus is not cleared quickly this may lead to a sudden immune overreaction, which could be further exacerbated in patients with preexisting immune-mediated diseases.

The mechanisms linking COVID-19 with skin conditions remain unclear. Registries are being established to record the details of cases with psoriasis as well as other dermatologic and inflammatory conditions, yet because these registries only include cases, they cannot be used to test for prevalence. We therefore performed an epidemiological study of the link between psoriasis and COVID-19 in a large hospital-wide health system, and investigated the relationship further through genomic analysis.

METHODS
Epidemiology

We conducted an epidemiological study of 435,019 patients in Michigan Medicine who had at least 1 health system encounter between January 1, 2019, and June 20, 2020, with recorded race, age, sex, body mass index (BMI), and socioeconomic status (for use as covariates). There were 1115 (0.26%) patients identified as having COVID-19, from a detected, presumptive positive or positive SARS-CoV-2 laboratory test result or a diagnosis code of U07.1 or U07.2 tested elsewhere, of which 150 (13.5%) required mechanical ventilation between March 1 and June 20, 2020 (see Table E1 in this article’s Online Repository at www.jacionline.org). A total of 24 different disease conditions were considered in the comorbidity association analysis, including COVID-19 risk factors reported by the CDC (chronic kidney disease, chronic obstructive pulmonary disease [COPD], coronary artery disease, and type 2 diabetes), inflammatory diseases (such as rheumatoid arthritis, SLE, and multiple sclerosis), and skin conditions (including psoriasis, atopic dermatitis, and cutaneous lupus).

Data on patients with COVID-19, their medical conditions, and covariates were extracted using the University of Michigan’s DataDirect. A patient was determined as having a condition if they have at least 1 International Classification of Diseases, Ninth Revision or International Classification of Diseases, Tenth Revision code for the condition (Table E1). Covariates were extracted using the various views available through DataDirect. In particular, social disadvantage was extracted using a DataDirect filter designed to estimate disadvantage by comparing census tract location to data from the 2013-2017 American Community Survey. The mean of 4 different indicators (pfhfam: proportion of families female headed; ppubas: proportion of households with public assistance income; pnumemp: proportion 16+ unemployed; ppov: proportion of people with income below poverty level) is taken and divided into 4 quartiles. The highest quartile (Disadvantage 3) included 60,299 individuals from our study. Obesity was graded into 3 categories, following the same procedure as a recent large-scale epidemiological study.
The risk of COVID-19 among all patients and mechanical ventilation among patients with COVID-19 was modeled using logistic regression and correcting for multiple testing (false detection rate [FDR] ≤ 0.05), conditioning on all the covariates and applying each of the 24 comorbidities 1 at a time. For the risk of COVID-19 among all patients, we used the following model: COVID-19 ~ Race + Age + Obese + Social Disadvantage + Comorbidity. For the risk of requiring mechanical ventilation among patients with COVID-19, we used the following model: Ventilation ~ Race + Age + Obese + Social Disadvantage + Comorbidity. To ensure a sufficient sample size for accurate risk factor estimation, we included only those traits that have more than 5 cases, and otherwise aggregated the traits together.

Transcriptome

Expression data for SARS-CoV-2-infected human bronchial epithelial cells were extracted from 2 previous studies: normal bronchial epithelial cells (NHBE) and 2 lung cancer epithelial cell lines (A549 and Calu-3) were RNA-sequenced with and without SARS-CoV-2 infection, in a separate study, human bronchial organoids (hBO) were prepared from normal bronchial epithelial cells and RNA-sequenced with and without SARS-CoV-2 infection. We compared the differentially expressed genes from these studies with those from 8 skin conditions: acne (6 lesional and 6 control, microarray), alopecia areata (60 lesional and 36 control, microarray), atopic dermatitis (21 lesional and 38 control, RNA-seq), burn injury (57 lesional and 63 control, microarray), discoid lupus (7 lesional and 3 control, microarray), hidradenitis suppurativa (22 lesional and 10 control), nonneoplastic nevi (18 lesional and 7 control, microarray), psoriasis (28 lesional and 38 control, RNA-seq), and rosacea (19 lesional and 10 control, microarray); we also included an nonskin inflammatory disease, rheumatoid arthritis (10 cases and 10 control from synovial tissue), for comparison. Details of each study are provided in Table E2 in this article’s Online Repository at www.jacionline.org.

Genes were considered to be significantly upregulated in the cases if they have FDR less than or equal to 0.05 and log2fold change (FC) greater than or equal to 1 in the differential expression analysis when compared with the controls. Kyoto Encyclopedia of Genes and Genomes Pathway enrichment was performed on the upregulated genes from each data set using a web-based pathway analysis tool Enrichr. Pathways were compared between data sets, using Association analysis based on SubSETs (ASSET) to detect the most significant subset, and also the data sets belonging to each significant pathway. To avoid biasing the results toward any 1 data set, we adopted an equally weighted combination of the effect sizes (\( \beta_{\text{ASSET}} = \frac{\beta_{\text{NHBE}} + \beta_{\text{hBO}}}{2} \)) and variances (\( \sigma^2_{\text{ASSET}} = \frac{\sigma^2_{\text{NHBE}} + \sigma^2_{\text{hBO}}}{2} \)), to avoid biasing the results toward the disease with the largest sample size (psoriasis). Loci were considered significant if the lead marker from TDMA is genome-wide significant (\( P \leq 5 \times 10^{-8} \)) in TDMA, as well as suggestive significant in both psoriasis and COVID-19 (\( P \leq 1 \times 10^{-5} \)) and more significant in TDMA than in either disease.

RESULTS

Epidemiology of COVID-19 in Michigan Medicine

Confirming previous research, we found blacks to be at a substantially higher risk of COVID-19 than whites (odds ratio [OR], 4.86; \( P = 4.1 \times 10^{-5} \)), with other ethnic groups also having significantly elevated risk compared with whites (Table I). We observed an increased risk with age and obesity: OR, 21.04, \( P = 1.6 \times 10^{-38} \) for age 80 years or more compared with the youngest group; OR, 2.06, \( P = 6.2 \times 10^{-15} \) for BMI greater than or equal to 40 kg/m² (ie, “Obese 3”) compared with nonobese. Social disadvantage was significant only for the highest compared with the lowest quartile (OR, 1.67; \( P = 2.3 \times 10^{-8} \)). Chronic kidney disease (OR, 1.96; \( P = 5.3 \times 10^{-17} \)), type 2 diabetes (OR, 1.77; \( P = 7.8 \times 10^{-16} \)), coronary artery disease (OR, 1.56; \( P = 2.3 \times 10^{-7} \)), and COPD (OR, 1.40; \( P = 8.4 \times 10^{-4} \)) were all significant risk factors as per the CDC’s guidance. Interestingly, we further confirmed 3 comorbidities indicated as having limited information by the CDC: type 1 diabetes (OR, 1.55; \( P = 9.4 \times 10^{-4} \)), hypertension (OR, 1.39; \( P = 5.1 \times 10^{-6} \)), and asthma (OR, 1.24; \( P = 2.3 \times 10^{-3} \)); some of these findings are consistent with results from a recent study using the University of Michigan Michigan Medicine data.

Several skin conditions, including burn injury (OR, 1.59; \( P = .011 \)), acne (OR, 1.53; \( P = 5.9 \times 10^{-7} \)), psoriasis (OR, 1.48; \( P = .022 \)), and atopic dermatitis (OR, 1.48; \( P = .020 \)), were significantly associated with an increased risk of COVID-19, conditioning on all covariates and testing comorbidities 1 at a time, using FDR less than or equal to 0.05 to correct for multiple testing and declare statistical significance. Interestingly, cutaneous lupus (including discoid lupus and subacute cutaneous lupus erythematosus) was nominally significant (OR, 1.67; \( P = .038 \)), whereas SLE had substantially lower effect size and was not significant (OR, 1.19; \( P = .372 \)). Significantly, we found having at least 1 of the skin conditions (including the skin conditions above as well as alopecia areata, cutaneous lupus, hidradenitis suppurativa, rosacea, and nonneoplastic nevi) to be a significant risk factor for COVID-19 (OR, 1.55, \( P = 1.4 \times 10^{-8} \)), as is having an inflammatory skin disease (ie, excluding burn injury and nonneoplastic nevi) (OR, 1.59; \( P = 2.1 \times 10^{-9} \)). The use of disinfectant and personal protective equipment (including gloves and masks) may exacerbate certain preexisting skin conditions, such as acne and atopic dermatitis. We therefore repeated the model with the same covariates, but only included cases with diagnoses from encounters before 2020, and found comparable effect size for acne (OR, 1.45), atopic dermatitis (OR, 1.43), burn injury (OR, 1.59), and psoriasis (OR, 1.41), indicating that individuals with preexisting skin conditions have elevated risk for COVID-19. We also applied Cox proportional hazard regression on the risk of patients with a diagnosis of burn injury, acne, atopic dermatitis, or psoriasis before 2020 contracting COVID-19. The regression was significant for these diseases (\( P = 2.3 \times 10^{-21} \)), hazard ratio, 1.78), whereas for rheumatoid arthritis by comparison it was not significant (\( P = .23 \), hazard ratio, 1.18).

Previous researchers have considered whether immunosuppressive treatments such as biologics used for certain skin diseases (such as psoriasis) may increase the risk of COVID-19 by modulating immune response. We tested the effect of 31 immunosuppressive agents (see Table E3 in this article’s Online Repository at www.jacionline.org), using the same logistic model and covariates, but the result was not significant, neither was being prescribed a biologic from a subset used to treat psoriasis. Non-COVID-19 respiratory tract infections have previously been observed to occur more frequently in patients with psoriasis on IL-17 inhibitors (brodalumab, which targets IL-17RA; ixekizumab and secukinumab, which target IL-17 directly). Analysis of patients treated with these drugs came close to achieving nominal significance (OR, 3.13; \( P = .050 \), providing some limited
TABLE I. Logistic regression for risk of COVID-19 infection

| Covariates | N   | OR   | P value | Traits | N     | OR   | P value |
|------------|-----|------|---------|--------|-------|------|---------|
| Black      | 422 | 4.86 (4.18-5.66) | 4.1 × 10^-93 | Myasthenia gravis | 5 | 2.02 (0.83-4.90) | .120 |
| Asian      | 54  | 1.70 (1.28-2.26) | 2.5 × 10^-4 | Chronic kidney disease | 224 | 1.96 (1.67-2.29) | 5.3 × 10^-17 |
| Other race | 52  | 1.77 (1.33-2.36) | 9.9 × 10^-5 | Type 2 diabetes | 345 | 1.77 (1.54-2.04) | 7.8 × 10^-16 |
| Age 18-39 y| 257 | 8.42 (5.53-12.83) | 3.2 × 10^-23 | Sjögren syndrome | 21 | 1.77 (1.42-2.15) | .010 |
| Age 40-59 y| 423 | 14.17 (9.35-21.48) | 8.4 × 10^-36 | Alopecia areata | 7 | 1.71 (0.81-3.62) | .161 |
| Age 60-79 y| 333 | 13.20 (8.68-20.05) | 1.3 × 10^-33 | Cutaneous lupus | 17 | 1.67 (1.03-2.72) | .038 |
| Age 80+    | 78  | 21.04 (13.28-33.33) | 1.6 × 10^-38 | Primary biliary cirrhosis | 5 | 1.62 (0.67-3.93) | .284 |
| Male       | 507 | 1.15 (1.02-1.30) | .021 | Burn injury | 31 | 1.59 (1.11-2.28) | .011 |
| Obese 1 (BMI 30-34.9 kg/m²) | 235 | 1.26 (1.08-1.49) | 3.3 × 10^-3 | Coronary artery disease | 193 | 1.56 (1.32-1.85) | 2.3 × 10^-7 |
| Obese 2 (BMI 35-39.9 kg/m²) | 171 | 1.75 (1.47-2.09) | 4.5 × 10^-10 | Any skin condition* | 251 | 1.55 (1.35-1.79) | 1.4 × 10^-9 |
| Obese 3 (BMI ≥40 kg/m²) | 167 | 2.06 (1.72-2.46) | 6.2 × 10^-15 | Acne | 105 | 1.53 (1.24-1.88) | 5.9 × 10^-8 |
| Disadvantage 1 | 227 | 1.05 (0.88-1.25) | .599 | Psoriasis | 36 | 1.48 (1.06-2.07) | .022 |
| Disadvantage 2 | 216 | 1.17 (0.97-1.40) | .093 | Inflammatory bowel disease | 101 | 1.44 (1.18-1.77) | 4.7 × 10^-4 |
| Disadvantage 3 | 376 | 1.67 (1.40-2.00) | 2.3 × 10^-8 | COPD | 121 | 1.40 (1.15-1.70) | 8.4 × 10^-4 |
|            |     |       |       | Hypertension | 596 | 1.39 (1.21-1.60) | 5.1 × 10^-6 |
|            |     |       |       | Rosacea | 35 | 1.35 (0.96-1.89) | .088 |
|            |     |       |       | Celiac disease | 8 | 1.32 (0.66-2.66) | .435 |
|            |     |       |       | Multiple sclerosis | 9 | 0.77 (0.40-1.50) | .447 |
|            |     |       |       | Asthma | 265 | 1.24 (1.08-1.43) | 2.3 × 10^-3 |
|            |     |       |       | Rheumatoid arthritis | 38 | 0.81 (0.59-1.13) | .219 |
|            |     |       |       | Systemic lupus | 27 | 1.19 (0.81-1.76) | .372 |
|            |     |       |       | Nonneoplastic nevi | 23 | 1.10 (0.72-1.66) | .670 |
|            |     |       |       | Other inflammatory disease† | 84 | 0.95 (0.75-1.19) | .630 |

ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision.

N refers to either (a) the number of patients with COVID-19 or (b) the number of COVID-19 cases requiring ventilation (for more details, see Table E1).

Bold indicates results significant after adjusting for multiple tests (FDR < 0.05). Covariates are evaluated together, without any traits, and then traits are evaluated 1 at a time, conditioning on the covariates. The P values shown are the original unadjusted values.

*Patients are indicated as having “Any Skin Condition” if they have ICD-9/ICD-10 codes for at least 1 of the following conditions: acne, alopecia areata, atopic dermatitis, burn injury, cutaneous lupus, hidradenitis suppurativa, nonneoplastic nevi, psoriasis, rosacea.

†Patients are indicated as having “Other Inflammatory Disease” if they have ICD-9/ICD-10 codes for at least 1 of the following conditions: celiac disease, multiple sclerosis, myasthenia gravis, primary biliary cirrhosis, rheumatoid arthritis, Sjögren syndrome, systemic lupus.

support to the hypothesis of IL-17 involvement. However, conditioning on the IL-17 inhibitors (in addition to the existing covariates) did not have a substantial impact on the effect size for psoriasis (OR, 1.42-1.48) or skin disease in general (same OR, 1.55), suggesting that biologic treatments alone are not sufficient to explain this effect.

To further investigate the role of skin conditions and other diseases with respect to COVID-19, we tested the impact of each comorbidity on the risk of requiring mechanical ventilation among patients with COVID-19 (Table II). Because of the reduced sample size, we merged together some of the covariates to increase their impact. Blacks were not at a significantly higher risk of requiring ventilation, but people who are older (age ≥60 years; OR, 2.45; P = 2.0 × 10^-6), obese (BMI ≥35kg/m²; OR, 1.68; P = 9.2 × 10^-3), or in the highest quartile for social disadvantage (OR, 2.15; P = 5.2 × 10^-5) were at increased risk. Interestingly, although the risk of COVID-19 infection between sexes was only marginally significant (OR, 1.15; P = 0.021), males were at a substantially higher risk of requiring ventilation (OR, 2.99; P = 1.6 × 10^-4).

Of all the comorbidities tested, having a skin condition had the greatest effect size, reducing the risk of requiring mechanical ventilation for all skin conditions (OR, 0.22; P = 8.5 × 10^-3) and for inflammatory skin diseases in particular (OR, 0.16; P = 1.1 × 10^-4). In contrast, the other comorbidities that remained significant after multiple testing correction—type 2 diabetes (OR, 3.53; P = 3.7 × 10^-10), hypertension (OR, 2.95; P = 9.5 × 10^-5), chronic kidney disease (OR, 2.35; P = 3.2 × 10^-3), and coronary artery disease (OR, 1.72; P = 0.013)—all increased the risk of requiring mechanical ventilation. Interestingly, the “Other Inflammatory Disease” category (composed of diseases with fewer than 5 cases of ventilation) also had an OR below 1, although it was not significant. We tested whether the lack of significance may be due to insufficient power by combining it with the other immune-mediated diseases that fell shy of significance (asthma, COPD, inflammatory bowel disease, and type 1 diabetes), but the combination of inflammatory diseases still had no significant impact on the risk of ventilation (OR, 1.06; P = .772), even though it included almost twice as many COVID-19 samples as “Any Skin Condition” (460 compared with 251), suggesting the observation is not due to lack of power.

Because some of the comorbidities of skin diseases are known risk factors of COVID-19, we included all the comorbidities apart from skin diseases that were associated with a significant risk of COVID-19 (chronic kidney disease, type 2 diabetes, Sjögren syndrome, coronary artery disease, type 1 diabetes, inflammatory bowel disease, COPD, hypertension, and asthma) as covariates, in addition to the covariates we have already been using. Having a skin disease was still significantly associated with increased risk of COVID-19 (OR, 1.45; P = 4.1 × 10^-5) among the general population and decreased risk of requiring ventilation (OR,
TABLE II. Logistic regression for risk of requiring mechanical ventilation

| Covariates | N  | OR   | P value | Traits       | N  | OR   | P value |
|------------|----|------|---------|--------------|----|------|---------|
| Black      | 81 | 1.48 | 0.079   | Any skin condition* | 8  | 0.22 | 0.11-0.47 | 8.5 × 10⁶|
| Age 60+ y  | 83 | 2.45 | 2.0 × 10⁻⁶| Type 2 diabetes  | 96 | 3.53 | 2.38-5.24 | 3.7 × 10⁻⁶|
| Male       | 100| 2.99 | 1.6 × 10⁻⁸| Hypertension   | 123| 2.95 | 1.83-4.76 | 9.5 × 10⁻⁶|
| Obese 2/3 (BMI ≥35 kg/m²) | 57 | 1.68 | 9.2 × 10⁻³| Chronic kidney disease | 64 | 2.35 | 1.57-3.52 | 3.2 × 10⁻⁵|
| Disadvantage 3 | 80 | 2.15 | 5.2 × 10⁻⁴| Other inflammatory disease† | 5  | 0.45 | 0.17-1.15 | 0.094|

ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision.

N refers to either (a) the number of patients with COVID-19 or (b) the number of COVID-19 cases requiring ventilation (for more details, see Table E1).

Bold indicates results significant after adjusting for multiple tests (FDR ≤0.05). Covariates are evaluated together, without any traits, and then traits are evaluated 1 at a time, conditioning on the covariates. The P values shown are the original unadjusted values.

*Patients are indicated as having “Any Skin Condition” if they have ICD-9/ICD-10 codes for at least 1 of the following conditions: acne, alopecia areata, atopic dermatitis, burn injury, cutaneous lupus, hidradenitis suppurativa, nonneoplastic nevi, psoriasis, rosacea.

†Patients are indicated as having “Other Inflammatory Disease” if they have ICD-9/ICD-10 codes for at least 1 of the following conditions: celiac disease, multiple sclerosis, myasthenia gravis, primary biliary cirrhosis, rheumatoid arthritis, Sjögren syndrome, systemic lupus, 0.21; P = 6.9 × 10⁻⁵) among patients with COVID-19. Notably, many of the comorbidities became nonsignificant when included in the model together (only type 2 diabetes and chronic kidney disease were significantly associated with COVID-19, and only type 2 diabetes and hypertension were significantly associated with ventilation), suggesting many of the comorbidities share a common basis (eg, metabolic syndrome or autoimmunity), whereas having a skin disease is an independent risk factor.

Previous research indicates that sore throat occurs more frequently in patients with psoriasis than in controls, and by extending our epidemiological study, we revealed sore throat (tonsillitis or pharyngitis) to be significantly associated with the risk of psoriasis (OR, 1.64; P = 1.5 × 10⁻⁶), atop dermatitis (OR, 60.13; P = 1.5 × 10⁻⁸), acne (OR, 64.72; P = 4.9 × 10⁻²⁴), discoid lupus (OR, 34.58; P = 7.1 × 10⁻³⁷), and rosacea (OR, 44.07; P = 1.2 × 10⁻⁴⁷). We investigated the overlap between these 5 skin conditions and the SARS-CoV-2–infected NHBE, including all 94 genes upregulated in NHBE and at least 1 skin condition (Fig 1, B). A total of 14 genes were upregulated in all 5 skin conditions: SI00A7/8/9/12 are located in the epidermal differentiation complex, which regulates the epidermal barrier protecting against infection, and have antiviral activities; SI00A12 activates nuclear factor kappa B through RAGE, which may also be involved in COVID-19 immune responses; KRT6B is a barrier alarmin, signaling injury or infection; BCL2A1, CXCL1, and PI3 are involved in nuclear factor kappa B signaling; TLR2 is essential for viral and bacterial recognition and is the target of a drug under phase 2 trial for the prevention of COVID-19; IL36G, SERPINC4, SLC6A414/15 are involved in protective against infection; TUMP is upregulated by TNF-α, IFN-γ, and IL-17; and CFB is a factor for complement activation, which was found to be involved in microvascular injury and thrombosis of COVID-19 cases. Interestingly, we also found that these genes tend to have tissue-specific expressions when investigating their profiles using the Genotype-Tissue Expression project (GTEx) data.

Gene expression

To evaluate the potential shared mechanisms between skin conditions and COVID-19 infection, we collected transcriptomic expression data from 9 different skin conditions, as well as 4 different SARS-CoV-2–infected bronchial epithelial cell lines (Methods). Fig 1, A, presents the overlap of upregulated genes (log₂ FC ≥ 1, FDR ≤ 0.05) between the skin conditions and SARS-CoV-2–infected cells, using Fisher exact test to calculate the enrichment log ORs, and showing the total number of overlapping genes for each pair. Fig E1 in this article’s Online Repository at www.jacionline.org presents the same plot including SARS-CoV-2–infected bronchial epithelial cancer cell lines (A549 and Calu3) and a nonskin inflammatory disease (rheumatoid arthritis) for comparison. Interestingly, the infected noncancer (hBO and NHBE) epithelial cell lines clustered more closely with the inflammatory skin conditions (except hidradenitis suppurativa), than did the infected cancer (A549 and Calu-3) cell lines, and they had higher overlap with skin diseases than rheumatoid arthritis. In particular, NHBE showed strong overlap with psoriasis (OR, 53.72, P = 1.4 × 10⁻⁶), atop dermatitis (OR, 60.13; P = 1.5 × 10⁻⁸), acne (OR, 64.72; P = 4.9 × 10⁻²⁴), discoid lupus (OR, 34.58; P = 7.1 × 10⁻³⁷), and rosacea (OR, 44.07; P = 1.2 × 10⁻⁴⁷).
FIG 1. Overlap of upregulated genes between COVID-19–infected bronchial epithelial cells and skin conditions. A, Heatmap of enrichment log ORs, with the number of genes overlapped in cyan and the total number of genes for each data set next to the data set names. Bronchial epithelial cells are shown in red. Inset: histogram and color key for enrichment log ORs. B, Circular plot of genes, overlapping NHBE, and the 5 most enriched skin conditions, in red. C, Heatmap of the genes overlapping at least 1 of the 5 most significant pathways from ASSET in red. HS, Hidradenitis suppurativa.
In parallel with the investigation of individual genes, we conducted pathway-level analysis using data from the Kyoto Encyclopedia of Genes and Genomes\textsuperscript{105,106} ASSET\textsuperscript{77} was applied to the summary statistics from Enrichr\textsuperscript{10} (see Fig E2 in this article’s Online Repository at www.jacionline.org). The subsets identified by ASSET for each pathway are indicated using a cyan square. The most significant pathway overall was “Cytokine-cytokine receptor interaction” (P = 7.9 \times 10^{-126}), followed by “Rheumatoid arthritis” (P = 6.3 \times 10^{-93}), “TNF signaling pathway” (P = 1.3 \times 10^{-81}), “IL-17 signaling pathway” (P = 4.9 \times 10^{-77}), and “Staphylococcus aureus infection” (P = 3.3 \times 10^{-70}). The first 4 were indicated for all SARS-CoV-2–infected bronchial epithelial cell lines, as well as the 5 skin conditions with high gene overlap, whereas Staphylococcus aureus infection was indicated only for hBO, in addition to the skin conditions. Interestingly, TNF-signaling pathway and IL-17 signaling pathway are specific to the 5 skin conditions, whereas the other 2 also include hidradenitis suppurativa and alopecia areata. Burn injury and atopic nevi show little involvement in the top 20 pathways, whereas discoid lupus and rosacea clustered together because of their high involvement in all the pathways.

Fig 1, C, presents the genes overlapping NHBE and the 5 skin conditions involved in the 5 most significant pathways from ASSET. The FC for these genes in each condition and SARS-CoV-2–infected bronchial epithelial cell line is provided in Fig E3 in this article’s Online Repository at www.jacionline.org. The pathway with the greatest number of overlapping genes is IL-17 signaling (17 of 26 genes), followed by cytokine-cytokine receptor interaction with 15, TNF signaling with 14, and the rheumatoid arthritis pathway with 12. Of the genes upregulated in all 5 skin conditions, CXCL1 is included in every pathway, except Staphylococcus aureus infection; IL36G is present only in cytokine-cytokine receptor interaction and TLR2 is present only in the rheumatoid arthritis pathway, whereas S100A7, S100A7, and S100A9 are present only in IL-17 signaling. IL-17 is considered a key target for COVID-19 treatment, being involved in cytokine storm and lung damage,\textsuperscript{107} but it is also central to inflammatory skin diseases, such as psoriasis.\textsuperscript{108}

**Genetics**

To investigate whether genetic susceptibility may play a role in the relationship between skin conditions and COVID-19, we took advantage of our recent large meta-analysis of 11,024 psoriasis cases and 16,336 controls,\textsuperscript{78} and compared it against release 2 of the COVID-19 Host Genetics Initiative meta-analysis (May 2020),\textsuperscript{79} using TDMA (Methods). TDMA identified a signal (Fig 2) in the epidermal differentiation complex (chromosome 1) whose lead marker, rs12564811 (previously known as rs151224049), was suggestive significant for psoriasis (OR, 1.17; P = 1.4 \times 10^{-5}) and COVID-19 (OR, 1.33, P = 5.8 \times 10^{-5}), but genome-wide significant in TDMA (OR, 1.25; P = 2.7 \times 10^{-8}). The epidermal differentiation complex is a known locus for psoriasis, and our signal is located near a more significant psoriasis signal (rs6677595), but the 2 signals are not in linkage disequilibrium with each other (r^2 = 0.0464 in 1000 Genomes Europeans). To confirm the signals are indeed distinct, we conditioned on the known psoriasis signal and found that our signal became the most significant in the region (see Fig E4 in this article’s Online Repository at www.jacionline.org).

rs12564811 is a significant eQTL in whole blood\textsuperscript{109} for S100A12 (P = 3.3 \times 10^{-7}), one of the genes that was upregulated in each of the 5 skin conditions and NHBE. It is also an eQTL for LCE1E in GTEx-exposed skin (P = 1.0 \times 10^{-11}) and not exposed skin (P = 7.1 \times 10^{-10}). The transcription start site for LCE1E overlaps cg14792160, which is a significant methylation QTL for rs12564811 in whole blood during pregnancy (P = 1.08 \times 10^{-22}), birth (P = 4.9 \times 10^{-19}), adolescence (P = 2.27 \times 10^{-28}), and middle age (P = 1.26 \times 10^{-16}).\textsuperscript{110} Furthermore, rs12564811 is an eQTL for LCE3A (P = 1.9 \times 10^{-7}) and LCE3C (P = 1.1 \times 10^{-5}) in exposed skin, as well as LCE3D (P = 3.5 \times 10^{-5}) in esophagus mucosa (epithelium).\textsuperscript{39,100} We applied colocalization analysis in GTEx using a colocalization approach (fastENLOC\textsuperscript{111}), which takes advantage of multiple imputation and precomputed signal clusters. In total, the eQTL signals of 9 genes expressing in 14 tissue types were colocalized with the genome-wide association study signals in the same regions, with exposed skin having the highest number of colocalized eQTL signals (7 of 9, including LCE1E). However, none of the colocalizations had a high regional colocalization probability, with LCE4A being the most probable candidate (regional colocalization probability = 0.015), indicating it may be difficult to reach a firm conclusion with regard to the target genes. LCE3 genes have been found to have antibacterial/antimicrobial activity,\textsuperscript{86} and are often upregulated in inflamed tissue.\textsuperscript{112,113} Some of the LCE3 genes exhibit tissue-specific expression patterns (eg, LCE3A/C/D/E are expressed only in the mucosa of the esophagus, skin, and a few other tissues according to GTEx).

**DISCUSSION**

We conducted a large epidemiological study of COVID-19 susceptibility (435,019 patients) and severity (indicated by requiring mechanical ventilation), using a range of covariates (race, age, sex, BMI, and socioeconomic status) to ensure the robustness of our findings. Most notably, having a skin condition or inflammatory skin disease increased the risk of being infected with SARS-CoV-2, but decreased the risk of requiring mechanical ventilation, whereas previously known risk factors (eg, chronic kidney disease or coronary artery disease) increased the risk of both. One potential explanation would be that SARS-CoV-2 can enter through the skin,\textsuperscript{119} or that the skin can act as a reservoir.\textsuperscript{55,56} because this could result in a different rate of disease progression compared with transmission via the respiratory tract. Skin conditions such as psoriasis,\textsuperscript{115} atopic dermatitis,\textsuperscript{116} and burn injuries\textsuperscript{110,118} are associated with defective epidermal barrier, and because the immune system is already activated in lesional sites of the skin, it is possible these infected individuals can have different immunologic rates of viral response. Indeed, previous research has suggested that an early interferon response or decreased viral load can result in a mild form of the disease,\textsuperscript{119} and thus could be associated with the lower rate of requiring ventilation among patients with COVID-19 with skin conditions. Notably, COVID-19 is known to affect multiple organs\textsuperscript{120} and has the potential to cause kidney disease or coronary artery disease) increased the risk of work is needed to determine whether this is also true of the skin.
susceptibility may also be through the oral/respiratory epithelium. Clinically normal tissue (ie, noninvolved skin) of patients with skin diseases, such as psoriasis and atopic dermatitis, has a heightened immune state and can exhibit delayed barrier recovery. Although still unstudied, it would be expected that this also occurs in the oral mucosal and respiratory epithelium, where low-grade inflammation may facilitate entry of the virus, but at the same time the already heightened immune state may help accelerate the immune response against the virus, leading to less severe outcomes. As with epidermal keratinocytes, ACE2 is also

FIG 2. TDMA. Regional association plots for the chromosome 1 epidermal differentiation complex locus in psoriasis and COVID-19 (with the lead marker in purple). The locus is suggestive significant for each disease and genome-wide significant in the TDMA.
expressed in epithelial cells of oral mucosa, serving as a potential entry point for SARS-CoV-2. Of the skin diseases we investigated, ACE2 is upregulated (FDR \leq 0.05, logFC \geq 1) only in psoriasis and discoid lupus, yet barrier dysregulation without upregulation could still make ACE2 more accessible. Interestingly, SARS-CoV-2–specific T cells have been found in a large proportion of unexposed patients, and this is believed to be a result of cross-reactivity with other circulating coronaviruses, such as the common cold. Mucosal barrier disruption facilitates various infections (including with coronaviruses), which in turn weaken the barrier function, potentially increasing susceptibility to COVID-19, while providing some degree of immunity, which might help speed up the initial interferon response, allowing COVID-19 to be more effectively controlled.

An alternative measure of COVID-19 severity used by some researchers is mortality; however, only 4 of the 251 COVID-19 skin condition patients (OR, 0.44; \( P = 0.142 \)) died between March 1 and June 20, 2020. This lack of association may be due to the low sample size, and it is also possible some of the deaths recorded during this period were not related to COVID-19. Case-fatality rates are notoriously difficult to estimate; for example, the United Kingdom substantially reduced its COVID-19 mortality count because it was found patients had died of causes other than COVID-19. Although we found hypertension (OR, 5.0; \( P = 3.4 \times 10^{-8} \)) and coronary artery disease (OR, 2.7; \( P = 9.8 \times 10^{-6} \)) to be associated with mortality among patients with COVID-19, these conditions are known to be associated with mortality in general. It therefore appears we have insufficient power for an analysis of conditions based on mortality, and hence we believe mechanical ventilation is a more accurate metric for COVID-19 severity. It is also worth noting the potential for ascertainment bias, because patients with more severe COVID-19 and other diseases may be more likely to interact with the health system.

Secondary diagnoses are included in the data from Michigan Medicine, whereby a patient is in hospital for something else and a skin condition gets captured too. We believe it is important to include these diagnoses to ensure all the patients’ conditions are taken into account. However, it is conceivable secondary diagnoses may be less likely to be recorded in urgent care settings, such that skin conditions could potentially be underreported in patients with COVID-19 on mechanical ventilation, for example. We therefore repeated our analysis restricting to only those patients who had at least 1 health system encounter in 2019. If the negative association between skin conditions and requirement for ventilation was due to patients who sought urgent care only for COVID-19, we would expect it to disappear given the requirement for patients to also have been seen before the pandemic. In contrast, we still observed a strong negative association in our new analysis (OR, 0.39), albeit with nominal significance (\( P = 0.027 \)) due to reduced sample size.

Furthermore, we tested the hypothesis that patients with a recorded skin diagnosis may be more vigilant with regard to their health, thus increasing the rate of COVID-19 testing (even if they have no symptoms). Specifically, for patients who have received at least 1 test for COVID-19, we evaluated the ratio of patients diagnosed with a skin condition (burn injury, acne, atopic dermatitis, or psoriasis) before 2020 among patients who have been tested positive for COVID-19, and compared that with the ratio for patients who did not have skin conditions. The results showed no significant direction of effect (\( P = 0.90 \); OR, 1.01), in contrast to the same test applied to rheumatoid arthritis (\( P = 0.02 \); OR, 0.73), suggesting that patients with skin disease are not prone to overtesting compared with the general population. The significant result for rheumatoid arthritis could potentially be due to routine testing performed before surgery, for example, joint replacement.

Through the use of TDMA, we identified a shared genome-wide significant locus between psoriasis and COVID-19. The location of this signal, in the epidermal differentiation complex, is consistent with our findings from the gene expression analysis, which showed S100 genes to be upregulated in SARS-CoV-2–infected NHE cells and the 5 most enriched skin diseases. Although we were unable to replicate this locus in the phase 3 release (June 2020) of the Human Genetics Initiative, a substantial difference between this and the version we used is the inclusion of a large meta-analysis of severe COVID-19 infections. Our lead marker is not available in the phase 4 release (October 2020), due to limitations on the 23andMe cohort; however, a nearby variant (rs10888505, \( r^2 = 0.82 \)) had \( P = 1.1 \times 10^{-7} \) in COVID-19, \( P = 9.1 \times 10^{-5} \) in psoriasis, and \( P = 9.0 \times 10^{-7} \) in TDMA (which is substantially more significant than the phase 3 result: \( P = 6.9 \times 10^{-7} \) in COVID-19 and \( P = 8.6 \times 10^{-5} \) in TDMA). It is possible that the inclusion of a large number of patients with severe COVID-19 in phase 3 may cancel out the relationship observed (which could support our epidemiologic finding that patients with skin disease are less susceptible to severe COVID-19 infections than the general population). The phase 4 release also revealed a genome-wide significant locus in chromosome 14 (rs10047949: COVID-19 \( P = 5.9 \times 10^{-3} \), psoriasis \( P = 1.1 \times 10^{-7} \), TDMA \( P = 2.4 \times 10^{-7} \)), in proximity to a known psoriasis locus indicated for NFKBIA. We further applied TDMA (with the phase 4 release) to summary statistics from a genome-wide association study for atopic dermatitis, revealing a different locus in chromosome 14 (rs190850598: COVID-19 \( P = 3.9 \times 10^{-4} \), psoriasis \( P = 7.3 \times 10^{-5} \), TDMA \( P = 1.6 \times 10^{-7} \), although no loci were genome-wide significant for this disease.

We also found cutaneous lupus to have a higher effect size (OR, 1.67) than SLE (OR, 1.19), although it was only nominally significant, providing further evidence for a skin-specific effect. This did not however apply to psoriatic arthritis, which had a higher effect size (OR, 1.88) than psoriasis alone (OR, 1.34), yet it is important to note that most patients with psoriatic arthritis develop skin symptoms first before their joint inflammation, whereas patients with SLE are more likely to develop fatigue, fever, and joint pain first. We also identified differentially expressed genes involved in host defense outside the epidermal differentiation complex (eg, TLR2) common to SARS-CoV-2–infected NHE cells and the skin diseases. Previous researchers have reported that inflammation in COVID-19 does not match the distribution of SARS-CoV-2, and this suggests it is the immune response that causes damage, rather than the direct effect of the virus itself.

We analyzed transcriptome data (RNA-seq and microarray) from multiple different skin diseases because our
epidemiological evidence suggests they may all have effect on COVID-19 susceptibility. Steps were taken to ensure comparability of these results. All the RNA-seq studies were analyzed using Differential Expression analysis for Sequence count data\textsuperscript{2,137} and the microarray studies using limma\textsuperscript{38} (through the R programming language implemented in the Gene Expression Omnibus of National Center for Biotechnology Information\textsuperscript{139}). There were minor differences in the preprocessing steps performed by each RNA-seq study. For example, although most studies used Spliced Transcripts Alignment to a Reference\textsuperscript{140} for the alignment and high-throughput sequencing software library\textsuperscript{141} (or RNA Express,\textsuperscript{142} which is comparable to high-throughput sequencing software library) for gene expression quantification, the COVID-19 study for hBo used Hierarchical Indexing for Spliced Alignment of Transcripts \textsuperscript{2}\textsuperscript{143} for alignment and featureCounts\textsuperscript{144} for counting. By including both hBo and NHBE as normal bronchial epithelial cell lines (with or without infection), we were able to assess the impact of these differences and conclude the particular pipeline used to have minimal effect. It is also important to point out we do not combine the data through meta- or mega-analysis. Instead, we apply multiple testing adjustment (FDR) and separately report the significantly upregulated genes in each study. Although some studies may have more power to detect upregulated genes than others due to differences in sample size, we ameliorate this effect through pathway analysis. The enrichment of a pathway is not affected by the total number of upregulated genes, because it measures the relative proportion of genes in the pathway.

IL-17 signaling was one of the most strongly enriched pathways across the data sets we investigated. In particular, 100 genes are targets of IL-17 signaling\textsuperscript{145-147} and (in addition to being upregulated) were indicated by eQTL analysis of the TDMA locus. IL-17 is believed to have a complex relationship to viral response,\textsuperscript{148} because it can both protect against and promote viral infections. IL-17 stimulation can induce ACE2 expression in bronchial epithelial cells,\textsuperscript{149} and ACE2 has been shown to modulate IL-17–mediated neutrophil infiltration.\textsuperscript{150} A previous study\textsuperscript{151} suggested that IL-17 inhibitors can increase the risk of respiratory tract infections, and our epidemiological analysis indicated that IL-17–targeted biologics may also increase COVID-19 risk (close to nominal significance) with a substantial effect size. Consistent with previous research, treatment with other biologic immunosuppressants was far from significant.\textsuperscript{151,152} For example, no significant association with respiratory tract infections, and our epidemiological analysis indicated that IL-17–targeted biologics can increase the risk of respiratory tract infections, and our epidemiological analysis indicated that IL-17–targeted biologics may also increase COVID-19 risk (close to nominal significance) with a substantial effect size. Consistent with previous research, treatment with other biologic immunosuppressants was far from significant.\textsuperscript{151,152} For example, no significant association with respiratory tract infections was observed for IL-23 inhibitors,\textsuperscript{153} and in a large study of 600 COVID-19 cases with rheumatic disease (including 74 with psoriatic arthritis), TNF inhibitors did not significantly increase COVID-19 hospitalization.\textsuperscript{154}

Conclusions Overall, our study has highlighted the significant link between skin conditions and COVID-19. By further revealing the shared genomic components, this work will serve as an important study to reveal individuals who are more susceptible to infection of SARS-CoV-2, and how their preexisting conditions may affect the course of the disease. The epidemiologic and genetic findings require additional validation and replication, for example, to assess the impact of including presumptive positive patients and confirm the rs12564811 locus. Animal models that have been used to enable the study of SARS-CoV-2 infection,\textsuperscript{155} such as the mouse-adapted version of the virus,\textsuperscript{156} could help validate the suggested pathophysiology mechanisms, including the testing of the hypothesis that animals with lesional skin\textsuperscript{157} or dysregulated epithelium may experience a higher rate of SARS-CoV-2 infection.

Key messages

- Skin conditions are associated with increased COVID-19 risk.
- However, intriguingly they are associated with less severe COVID-19 course.
- There are shared components between skin conditions and COVID-19 immune response.

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FIG E1. Heatmap of enrichment log ORs, with the number of genes overlapped in cyan, and the total number of genes for each data set next to the data set names. Bronchial epithelial cells are shown in red, and a nonskin inflammatory disease (rheumatoid arthritis) is included for comparison in blue. Inset: histogram and color key for enrichment log ORs. HS, Hidradenitis suppurativa.
FIG E2. Heatmap of enrichment $-\log_{10}$ $P$ values from top 20 most significant pathways from analysis in Kyoto Encyclopedia of Genes and Genomes, with expression data sets selected by ASSET for each pathway set indicated in cyan. COVID-19–infected bronchial epithelial cells are shown in red, and the ASSET $P$ value for each pathway is provided next to the pathway names. HS, Hidradenitis suppurativa.
FIG E3. Heatmap of log 2 FC from case vs control differential expression, showing genes that overlap at least 1 of the 5 most significant pathways from ASSET. COVID-19–infected bronchial epithelial cells are shown in red. HS, Hidradenitis suppurativa.
FIG E4. Regional association plot of psoriasis meta-analysis, conditioning on known epidermal differentiation complex signal (rs6677595).
| Characteristic                          | Individuals, n (%               | COVID, n (%) | Ventilation, n (%) |
|----------------------------------------|----------------------------------|--------------|--------------------|
| Race                                    | Individual                     | COVID        | Ventilation        |
| Black                                   | 42,886 (9.9)                    | 422 (0.98)   | 81 (19.19)         |
| Asian                                   | 24,651 (5.7)                    | 54 (0.22)    | 6 (11.11)          |
| White                                   | 347,769 (79.9)                  | 587 (0.17)   | 56 (9.54)          |
| Other                                   | 19,713 (4.5)                    | 52 (0.26)    | 7 (13.46)          |
| Age (y)                                 |                                 |              |                    |
| 0-17                                    | 96,323 (22.1)                   | 24 (0.02)    | 2 (8.33)           |
| 18-39                                   | 108,391 (24.9)                  | 257 (0.24)   | 14 (5.45)          |
| 40-59                                   | 105,854 (24.3)                  | 423 (0.40)   | 51 (12.06)         |
| 60-79                                   | 105,854 (24.3)                  | 333 (0.31)   | 70 (21.02)         |
| 80+                                     | 18,597 (4.3)                    | 78 (0.42)    | 13 (16.67)         |
| Sex                                     |                                 |              |                    |
| Female                                  | 237,863 (54.7)                  | 608 (0.26)   | 50 (8.22)          |
| Male                                    | 197,156 (45.3)                  | 507 (0.26)   | 100 (19.72)        |
| BMI                                     |                                 |              |                    |
| Not obese                               | 305,030 (70.1)                  | 542 (0.18)   | 61 (11.3)          |
| Obese 1 (30-34.9 kg/m²)                 | 69,398 (16.0)                   | 235 (0.34)   | 32 (13.6)          |
| Obese 2 (35-39.9 kg/m²)                 | 34,272 (7.9)                    | 171 (0.50)   | 27 (15.8)          |
| Obese 3 (>40 kg/m²)                     | 26,319 (6.1)                    | 167 (0.63)   | 30 (18.0)          |
| Socioeconomic disadvantage              |                                 |              |                    |
| Not disadvantaged                       | 176,961 (40.7)                  | 296 (0.17)   | 25 (8.45)          |
| Disadvantage 1 (Q1-Q2)                  | 116,265 (26.7)                  | 227 (0.20)   | 25 (11.01)         |
| Disadvantage 2 (Q2-Q3)                  | 81,494 (18.7)                   | 216 (0.27)   | 20 (9.26)          |
| Disadvantage 3 (>Q3)                    | 60,299 (13.9)                   | 376 (0.62)   | 80 (21.3)          |
| Comorbidity                             |                                 |              |                    |
| Acne (L70.*, 706.[0,1])                 | 40,154 (6.9)                    | 105 (0.35)   | 1 (0.95)           |
| Alopecia areata (L63.*, 704.01)         | 1,130 (0.3)                     | 7 (0.62)     | 0 (0.00)           |
| Asthma (J45.*, 493.*)                   | 79,306 (18.2)                   | 265 (0.33)   | 32 (12.08)         |
| Atopic dermatitis (L20*, 691.8)         | 18,360 (4.2)                    | 38 (0.21)    | 1 (2.63)           |
| Burn injury                             | 6,558 (1.5)                     | 31 (0.47)    | 0 (0.00)           |
| Celiac disease (K90.0, 579.0)           | 3,373 (0.8)                     | 8 (0.24)     | 0 (0.00)           |
| Coronary artery disease (I25.*, 414.*)  | 37,105 (8.5)                    | 193 (0.52)   | 50 (25.91)         |
| Chronic kidney disease (N18.*, 585.*)   | 31,212 (7.2)                    | 224 (0.72)   | 64 (28.57)         |
| COPD (J4[2-4].*, 49[1,2].*)             | 23,836 (5.5)                    | 121 (0.51)   | 26 (21.49)         |
| Cutaneous lupus (L93.*, 695.4)          | 2,284 (0.5)                     | 17 (0.74)    | 1 (5.88)           |
| Hidradenitis suppurativa (L73.2, 705.83)| 1,921 (0.4)                     | 17 (0.88)    | 1 (5.88)           |
| Hypertension (I1[0-5].*, 40[1-5].*)     | 132,291 (30.4)                  | 596 (0.45)   | 123 (20.64)        |
| Inflammatory bowel disease              | 26,813 (6.2)                    | 101 (0.38)   | 13 (12.87)         |
| Multiple sclerosis (G35, 340)           | 3,487 (0.8)                     | 9 (0.26)     | 0 (0.00)           |
| Myasthenia gravis (G70.0*, 358.0*)      | 756 (0.2)                       | 5 (0.66)     | 1 (20.00)          |
| Nonneoplastic nevi (I78.1, 448.1)       | 9,685 (2.2)                     | 23 (0.24)    | 4 (17.4)           |
| Primary biliary cirrhosis (K74.3, 571.6)| 1,033 (0.2)                     | 5 (0.48)     | 0 (0.00)           |
| Psoriasis (L40.*, 691.[0,1])            | 8,720 (2.0)                     | 36 (0.41)    | 2 (5.56)           |
| Rheumatoid arthritis                    | 13,506 (3.1)                    | 38 (0.28)    | 3 (7.89)           |
| Rosacea (L71.*, 695.3)                  | 11,253 (2.6)                    | 35 (0.31)    | 0 (0.00)           |
| Sjögren syndrome (M35.0*, 710.2)        | 3,642 (0.8)                     | 21 (0.58)    | 1 (4.76)           |

(Continued)
### TABLE E2. Transcriptome study samples

| Study                  | Test                              | Cases* | Controls* | Technology     | Pipeline                  |
|------------------------|-----------------------------------|--------|-----------|----------------|---------------------------|
| NHBE                   | SARS-CoV-2 vs mock infected       | 3      | 3         | RNA-seq (Illumina NextSeq 500) | STAR/RNA-Express/DESeq2   |
| A549                   | SARS-CoV-2 vs mock infected       | 3      | 3         | RNA-seq (Illumina NextSeq 500) | STAR/RNA-Express/DESeq2   |
| Calu-3                 | SARS-CoV-2 vs mock infected       | 3      | 3         | RNA-seq (Illumina NextSeq 500) | STAR/RNA-Express/DESeq2   |
| hBO                    | SARS-CoV-2 vs mock infected       | 3      | 3         | RNA-seq (Illumina NovaSeq 6000) | HISAT2/featureCounts/DESeq2 |
| Acne                   | SARS-CoV-2 vs mock infected       | 6 (29 y) | 6 (38 y) | Microarray (Affymetrix U133A 2.0) | limma (GEO2R)            |
| Alopecia areata        | Lesional skin vs control          | 60 (41 F, 19 M, 41 y) | 36 (23 F, 13 M, 38 y) | Microarray (Affymetrix U133 Plus 2.0) | limma (GEO2R)            |
| Atopic dermatitis      | Lesional skin vs control          | 21 (10 F, 17 M, 34 y) | 38 (6 F, 4 M, 70 y) | RNA-seq (Illumina HiSeq 2500) | STAR/HTSeq/DESeq2        |
| Burn injury            | Lesional skin vs control          | 57 (12 F, 45 M, 24 y) | 63 (33 F, 30 M, 21 y) | Microarray (Affymetrix U133 Plus 2.0) | limma (GEO2R)            |
| Discoid lupus          | Lesional skin vs control          | 7 (5 F, 2 M) | 3         | Microarray (Affymetrix U133A 2.0) | limma (GEO2R)            |
| Hidradenitis suppurativa | Lesional skin vs control          | 22 (13 F, 13 M, 42 y) | 10 (6 F, 4 M, 70 y) | RNA-seq (Illumina NextSeq 500) | STAR/HTSeq/DESeq2        |
| Nonneoplastic nevi     | Lesional skin vs control          | 18 (9 F, 9 M, 33 y) | 7 (6 F, 1 M) | Microarray (Affymetrix U133A) | limma (GEO2R)            |
| Psoriasis              | Lesional skin vs control          | 28 (14 F, 14 M, 42 y) | 38 (22 F, 16 M, 33 y) | RNA-seq (Illumina HiSeq 2500) | STAR/HTSeq/DESeq2        |
| Rosacea                | Lesional skin vs control          | 19     | 10        | Microarray (Affymetrix U133 Plus 2.0) | limma (GEO2R)            |
| Rheumatoid arthritis   | Synovial tissue cases vs control   | 10     | 10        | Microarray (Affymetrix U133A) | limma (GEO2R)            |

DESeq2, Differential Expression analysis for Sequence count data 2; F, female; GEO2R, Gene Expression Omnibus into the R programming language; HISAT2, Hierarchical Indexing for Spliced Alignment of Transcripts 2; HTseq, high-throughput sequencing software library; M, male; STAR, Spliced Transcripts Alignment to a Reference.

*Number of samples, along with number of males, females, and average age, where available.
| Biologic                | Full set | Psoriasis set | IL-17 set |
|-------------------------|----------|---------------|-----------|
| Abatacept               | Yes      |               |           |
| Adalimumab              | Yes      | Yes           |           |
| Alefacept               | Yes      |               |           |
| Anakinra                | Yes      |               |           |
| Basiliximab             | Yes      |               |           |
| Belatacept              | Yes      |               |           |
| Belimumab               | Yes      |               |           |
| Benralizumab            | Yes      |               |           |
| Brodalumab              | Yes      |               | Yes       |
| Canakinumab             | Yes      |               |           |
| Certolizumab pegol      | Yes      |               |           |
| Daclizumab              | Yes      |               |           |
| Dupilumab               | Yes      |               |           |
| Eculizumab              | Yes      |               |           |
| Efalizumab              | Yes      |               |           |
| Etanercept              | Yes      | Yes           |           |
| Golimumab               | Yes      |               |           |
| Infliximab              | Yes      | Yes           |           |
| Ixekizumab              | Yes      | Yes           | Yes       |
| Mepolizumab             | Yes      |               |           |
| Muromonab-CD3           | Yes      |               |           |
| Natalizumab             | Yes      |               |           |
| Omalizumab              | Yes      |               |           |
| Reslizumab              | Yes      |               |           |
| Rilonacept              | Yes      |               |           |
| Rituximab               | Yes      |               |           |
| Sarilumab               | Yes      |               |           |
| Secukinumab             | Yes      | Yes           | Yes       |
| Tocilizumab             | Yes      |               |           |
| Ustekinumab             | Yes      | Yes           |           |
| Vedolizumab             | Yes      |               |           |