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Deciphering Factors Linked With Reduced Severe Acute Respiratory Syndrome Coronavirus 2 Susceptibility in the Swiss HIV Cohort Study

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Background. Factors influencing susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remain to be resolved. Using data from the Swiss HIV Cohort Study on 6270 people with human immunodeficiency virus (HIV) and serologic assessment for SARS-CoV-2 and circulating human coronavirus (HCoV) antibodies, we investigated the association of HIV-related and general parameters with SARS-CoV-2 infection.

Methods. We analyzed SARS-CoV-2 polymerase chain reaction test results, COVID-19–related hospitalizations, and deaths reported to the Swiss HIV Cohort Study between 1 January 2020 and 31 December 2021. Antibodies to SARS-CoV-2 and HCoVs were determined in prepandemic (2019) and pandemic (2020) biobanked plasma samples and compared with findings in HIV-negative individuals. We applied logistic regression, conditional logistic regression, and bayesian multivariate regression to identify determinants of SARS-CoV-2 infection and antibody responses to SARS-CoV-2 in people with HIV.

Results. No HIV-1–related factors were associated with SARS-CoV-2 acquisition. High prepandemic HCoV antibodies were associated with a lower risk of subsequent SARS-CoV-2 infection and with higher SARS-CoV-2 antibody responses on infection. We observed a robust protective effect of smoking on SARS-CoV-2 infection risk (adjusted odds ratio, 0.46 [95% confidence interval, .38–.56]; $P < .001$), which occurred even in previous smokers and was highest for heavy smokers.

Conclusions. Our findings of 2 independent protective factors, smoking and HCoV antibodies, both affecting the respiratory environment, underscore the importance of the local immune milieu in regulating susceptibility to SARS-CoV-2.

Keywords. SARS-CoV-2; HIV; preexisting immunity; endemic human coronaviruses; smoking.

Identifying factors that influence the acquisition, transmission, severity, prevention, and treatment of SARS-CoV-2 infection relies on comprehensive sources of health, behavioral, epidemiologic, and socioeconomic data. Prospective, large-scale, longitudinal cohort studies can provide this type of data, enabling critical public health research [1–3]. Human immunodeficiency virus (HIV) cohorts provide a unique opportunity in resolving interactions between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), HIV-1, and other comorbid conditions [4–6]. Coronavirus disease 2019 (COVID-19) seriously affects particularly vulnerable populations, including people with advanced age, comorbid conditions, or immunosuppression [7–9]. Accordingly, HIV-1 has been identified as a potential risk factor that may exacerbate COVID-19 disease, especially if HIV-1 infection is not effectively treated [10–13]. Immune responses to infections and vaccines often remain reduced in people with HIV (PWH) even with suppressive antiretroviral treatment (ART) [14–16]. This may also affect the course of SARS-CoV-2 infection in PWH, since decreased antibody responses to

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SARS-CoV-2 infection have been linked with slower clearance of SARS-CoV-2 [17]. Understanding whether and how HIV-1 positivity affects SARS-CoV-2 susceptibility and outcome is therefore important.

Here we report on a comprehensive systematic investigation of the interactions of HIV-1 and SARS-CoV-2 infection within the Swiss HIV Cohort Study (SHCS) [3] during the initial waves of the SARS-CoV-2 pandemic in Switzerland. The SHCS is highly representative of PWH living in Switzerland [3]. With its longitudinal study design, plasma and blood cell biobank, and comprehensive demographic data, including HIV-related as well as general health, behavioral, and epidemiology parameters, the SHCS provides a large data resource with opportunities to address public health concerns beyond HIV infection [18, 19]. While residual immune suppression in antiretroviral-treated PWH is a potential concern, most SHCS participants are fully virologically suppressed, comparatively healthy, and immunologically stable [3]. Accordingly, investigation of determinants of SARS-CoV-2 infection within the SHCS may also provide insights relevant for the general population. In support, the prevalence of SARS-CoV-2 infections in PWH has been found to be similar to the general population [20–23], and virologically suppressed PWH respond well to SARS-CoV-2 vaccines [24, 25]. In the current study, we explored the epidemiology of SARS-CoV-2 waves in Switzerland from 2020–2021 among PWH compared with the general Swiss population and determined the parameters associated with SARS-CoV-2 infection in both populations.

METHODS

Study Population and Ethics

Study Population With HIV

The SHCS is a prospective PWH cohort with semiannual visits and blood collections [3]. Detailed information is available online (http://www.shcs.ch). The SHCS is registered under the Swiss National Science longitudinal platform [26] and has been approved by the ethics committee of the participating institutions (Supplementary Material 1.1). Written informed consent had been obtained from all participants. In March 2020, a SARS-CoV-2 questionnaire was introduced into the SHCS, resulting in 7073 assessments of whether participants had a polymerase chain reaction (PCR) test for SARS-CoV-2, whether that test result was positive, and whether participants were hospitalized for COVID-19 (see flowchart in Supplementary Figure 1).

Study Population Without HIV

We included a population of 382 HIV-uninfected (HU) individuals with PCR-confirmed SARS-CoV-2 infections from 2 prior SARS-CoV-2 studies [17, 27] with published AntiBody COronavirus Assay (ABCORA) serology data (Supplementary Material 1.2; Supplementary Table 1). Published epidemiology data from the Swiss Federal Office of Public Health on the number of SARS-CoV-2 cases, hospitalizations, and deaths were used to compare these outcomes between PWH and the general Swiss population [28].

SARS-CoV-2 Serology

SARS-CoV-2 serology was performed on biobanked SHCS plasma samples with the ABCORA 5 assay [27]. ABCORA 5 determines antibody binding for each of the 3 immunoglobulin (Ig) classes—IgA, IgG, and IgM—as the median fluorescence intensity (MFI) against 4 SARS-CoV-2 antigens (S1 subunit, S2 subunit, nucleocapsid protein [N], and receptor-binding domain [RBD]) and the S1 subunits of the 4 endemic human coronaviruses (HCoVs) (HCoV-OC43, HCoV-NL63, HCoV-HKU1, and HCoV-229E). MFI values were normalized relative to empty bead controls yielding binding strengths quantified as MFI–log-fold over empty (MFI-LFOE). We used the previously calibrated random-forest-based ABCORA 5.4 algorithm to infer SARS-CoV-2 seropositivity based on the SARS-CoV-2 MFI-LFOE values.

HCoV Testing

Routine diagnostic analyses of respiratory samples for the endemic HCoVs (HCoV-OC43, HCoV-NL63, HCoV-HKU1, and HCoV-229E) were performed with multiplex respiratory PCR panels (ePlex RP [Roche] or BioFire RP2.1 [BioMérieux]). Repetitive tests of the same patient within 20 days of the initial positive result were excluded.

Assessing the Impact of Prepandemic HCoV Response in a Matched PWH Case-Control Study

We conducted a 1:2 matched nested case-control study in selected PWH from the SHCS to assess the impact of prior existing HCoV-specific antibodies on the risk of SARS-CoV-2 infection. For this we retrieved prepandemic plasma samples for all SARS-CoV-2–infected case patients and matched controls from 2019 from the SHCS biobank and measured their HCoV antibody levels using ABCORA 5 (Supplementary Figure 2*A* and 2*B*).

Statistical Analysis

To assess risk factors for acquiring SARS-CoV-2, we used logistic regression models with SARS-CoV-2 infection as an outcome (ie, having either a positive PCR or a positive ABCORA serologic result) and included a wide range of demographic, behavioral, and disease variables documented in the SHCS database as explanatory variables (Figure 1, Supplementary Table 2, and Supplementary Material 1.6).

To assess the impact of prepandemic HCoV immunity on the risk of SARS-CoV-2 infection, we conducted a time-

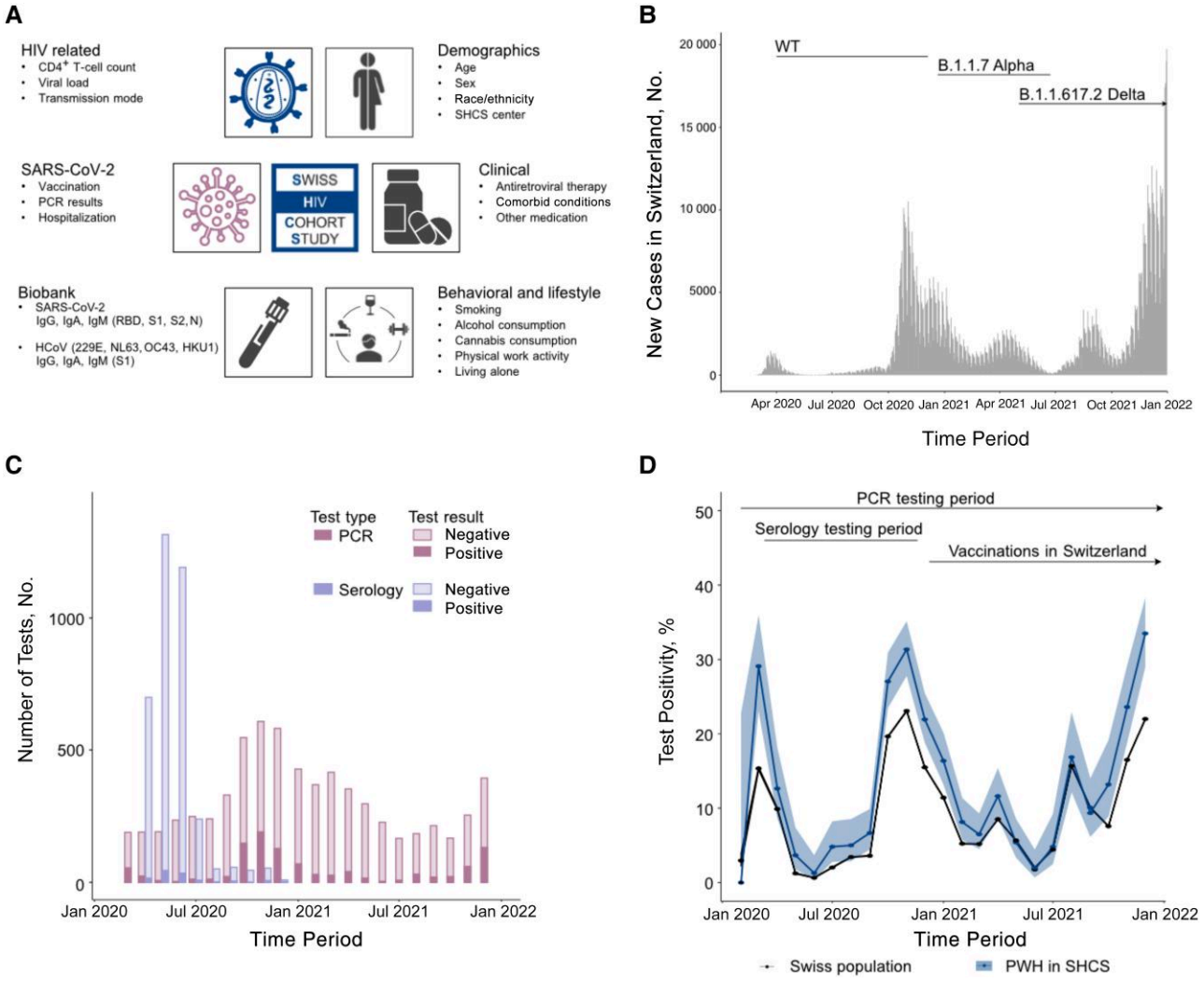

Figure 1. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) surveillance in Swiss HIV Cohort Study (SHCS) and the Swiss population. *A*, Schematic overview of the determinants of SARS-CoV-2 infections recorded in the SHCS. *B*, SARS-CoV-2 cases in Switzerland, as reported by the Swiss Federal Office of Public Health over time and waves of variants of concern. *C*, Numbers of self-reported polymerase chain reaction (PCR) and serologic tests performed in the SHCS, displayed by month and stratified by result. *D*, Test positivity in the SHCS (*blue*) and the Swiss population (*black*), by month. Dots represent the mean estimate, while the shaded area represents the 95% confidence interval, assuming a binomial distribution. Abbreviations: HCoV, human coronavirus; HIV, human immunodeficiency virus; Ig, immunoglobulin; RBD, receptor-binding domain; WT, wild type.

updated survival analysis [29], adjusted for age, sex, center, race/ethnicity, smoking status, and sampling time. We analyzed the data from the matched case-control study using a conditional logistic regression to estimate the risk of SARS-CoV-2 seropositivity. For each HCoV antigen, we defined the exposure variables by first summing the reactivities of IgG, IgA, and IgM and then stratifying these composite reactivities by the median into 2 groups (low vs high reactivity). We used linear univariate and multivariate regression models to compare SARS-CoV-2 antibody responses in PWH (n = 43) and HU individuals (n = 382) with PCR-confirmed SARS-CoV-2 infection and analogously to analyze HCoV antibody responses among the 453 PWH with ABCORA 5 measurements in 2019 (Supplementary Material 1.5). Statistical analysis was conducted using R software, version 4.1.2 [30].

RESULTS

Factors that influence the highly variable susceptibility to SARS-CoV-2 infection and disease severity, particularly those that result in asymptomatic disease, have not been fully elucidated [31, 32]. The SHCS [3], through its prospective, longitudinal design and systematic collection of HIV-specific and general health parameters along with behavioral and socioeconomic factors, provided us with a unique opportunity for systematic investigation of factors associated with SARS-CoV-2

acquisition. By January 2020, the SHCS database comprised >300 parameters that were either self-reported or obtained from clinical records at the semiannual study visits [3]. Here, we investigated the effect of 25 specific parameters on susceptibility to SARS-CoV-2 infection based on their potential significance for the general population, as well as their influence on the interaction between HIV-1 infection and SARS-CoV-2 infection (Figure 1*A* and Supplementary Table 2).

To enable SARS-CoV-2 population studies, the SHCS database included information on SARS-CoV-2 PCR testing from April 2020 onward and information on vaccination following its availability in Switzerland. We focused in the present analysis on the period between 1 February 2020 and 31 December 2021, to cover the initial waves of the SARS-CoV-2 epidemic in Switzerland in a SARS-CoV-2 naive population and later on the onset of vaccination (Figure 1*B*–1*D*). During this period, 10 301 PWH were actively enrolled in the SHCS, and 4241 reported SARS-CoV-2 PCR results, of which 1009 were positive. During the first wave in 2020, PCR testing was not yet widely performed in Switzerland (Figure 1*B* and 1*C*) [33]. To improve SARS-CoV-2 prevalence assessment during this period, we performed SARS-CoV-2 multifactorial seroprofiling [27] of SHCS biobanked plasma samples from 2020 (n = 3633) (Figure 1*C*).

Retrospectively, 120 plasma samples were scored as SARS-CoV-2 positive. Combining SARS-CoV-2–positive PCR results (2020–2021) and seropositive serology results (2020), we obtained information on the SARS-CoV-2 status of 6270 SHCS participants. Of these, 1088 (17%) were rated as SARS-CoV-2 positive (Figure 1*C* and 1*D* and Supplementary Table 1 [demographics of the study cohort], and Supplementary Figure 1 [flowchart]). These 6270 PWH with known SARS-CoV-2 status were used as the full study cohort (Supplementary Figure 1). Importantly, SARS-CoV-2 test positivity in the SHCS reflected the SARS-CoV-2 waves in the Swiss population, as recorded by the Federal Office of Public Health (Figure 1*D*) [28].

No Impact of HIV-Related Factors on the Risk of SARS-CoV-2 Acquisition

We explored factors influencing susceptibility to SARS-CoV-2 infection by analyzing 16 diverse parameters, including variables that apply to the general population as well as HIV-related biomarkers (Figure 2*A*). We found that HIV-1 viral load and $CD4^+$ T-cell levels, were not associated with SARS-CoV-2 infection risk in our well-treated cohort (96% PWH with undetectable HIV RNA in plasma; Supplementary Table 3). Several antiretroviral drugs, including the nucleotide inhibitor tenofovir and the protease inhibitors lopinavir and darunavir, have been controversially discussed to protect against SARS-CoV-2 infection [5, 34, 35]. We observed no evidence for a reduced SARS-CoV-2 infection risk with these antiretrovirals (Figure 2*A*).

Influence of Health and Demographic Factors

SARS-CoV-2 vaccination had a protective effect for SARS-CoV-2 infection for the full study cohort (adjusted odds ratio [aOR], 0.51 [95% confidence interval [CI], .37–.7]) and when restricted to the 2021 subcohort (aOR, 0.49 [95% CI, .36–.68]) when vaccines became widely available (Figure 2*A* and Supplementary Tables 5 and 6). We found no effect of age or sex on acquisition of SARS-CoV-2 (Figure 2 and Supplementary Figures 3 and 4), except for age >65 years, which was associated with a lower risk, likely reflecting increased use of protective measures in this age group. Combined analysis of 6 comorbid conditions showed no effect on SARS-CoV-2 infection (Figure 2*A*), but individual analysis revealed a modest protective trend of drugs for obstructive airway diseases (Supplementary Figure 5). Interestingly, the frequency of SARS-CoV-2 infection differed by race/ethnicity, with a significantly increased infection risk in black participants (aOR, 1.4 [95% CI, 1.1–1.7]) in the full study cohort. The effect was stronger in the 2020 subcohort but faded in 2021 (Figure 2*A*).

Influence of Behavioral Factors

HIV acquisition risk groups did not show differential SARS-CoV-2 risk (Figure 2*A* and Supplementary Table 5). However, we observed a lower risk of infection among people living in single-person households (aOR, 0.77 [95% CI, .66–.9]) in 2021, but not in 2020 (Figure 2*A*). We attribute this to the gradual relaxation of mask wearing and social distancing in 2021, combined with the arrival of the higher-transmissible variants of concern Alpha and Delta in Switzerland (Figure 1 and [28]). It is plausible that living in a single-person household during these periods of higher infection rates reduced the likelihood of transmission.

Cigarette smoking had a significant effect on SARS-CoV-2 infection over all time periods studied (Figure 2*A* and 2*B*) (aOR, 0.49 [95% CI, .41–.59]), even with correction for a range of factors, including the intake of drugs for obstructive airway disease (Supplementary Figure 5), an indirect indicator for ruled underlying chronic lung disease. We therefore rated this finding (and in particular the strength of the effect) as highly unexpected and performed a series of sensitivity analyses. We ruled out confounding effects of a potential differential sensitivity of serology and PCR tests in smokers by stratifying the analyses per test type and test period (Supplementary Figures 3, 6, and 7). A negative association with SARS-CoV-2 infection among smokers persisted regardless of whether the entire study period or individual years were considered, or of whether SARS-CoV-2 infection was diagnosed by means of PCR or serology (Supplementary Figures 6 and 7).

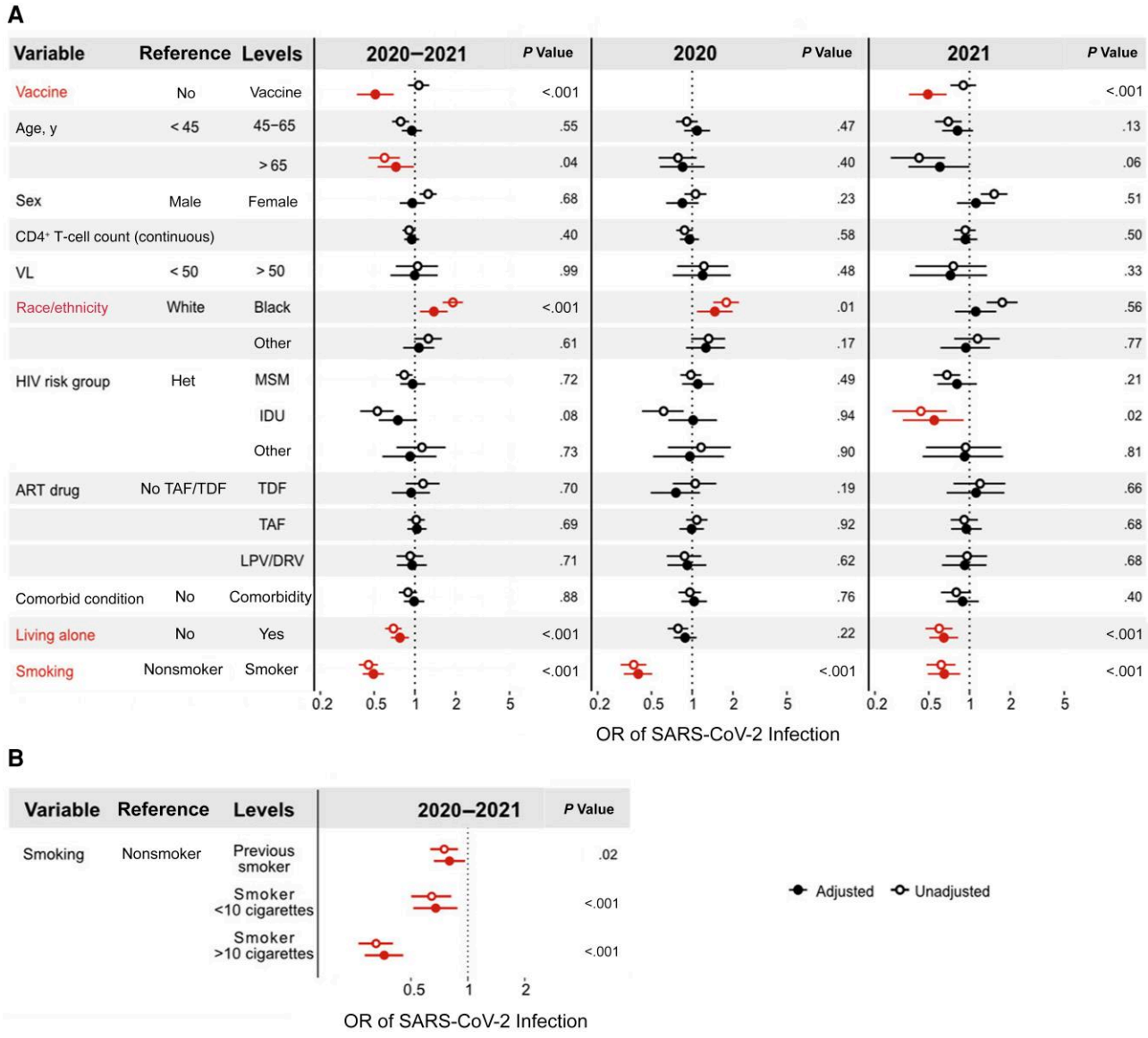

Figure 2. Risk factors for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) acquisition. *A*, Univariate and multivariate analysis of SARS-CoV-2 infection (determined by either polymerase chain reaction [PCR] or serology) risk factors adjusted for the depicted covariables and calendar time (included as cubic spline) and stratified by calendar time. The exposure variable comorbid conditions was defined as reports of either diagnoses (eg, hypertension and diabetes), risk factors (body mass index >35 [calculated as weight in kilograms divided by height in meters squared]), or the use of drugs related to comorbid conditions (immunosuppressive drugs, corticosteroids, or drugs for obstructive airway diseases). Numerical values of the odds ratio (OR; Supplementary Table 5) and a summary of population characteristics (Supplementary Table 6) are displayed in the Supplementary Materials. *B*, Univariate and multivariate analysis of the dose-dependent effect of smoking on the risk SARS-CoV-2 infection (determined by either PCR or serology). Dots correspond to effect sizes; lines, to 95% confidence intervals. Abbreviations: ART, antiretroviral therapy; DRV, darunavir; Het, heterosexual; HIV, human immunodeficiency virus; IDU, injection drug use; LPV, lopinavir; MSM, men who have sex with men; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; VL, viral load (copies/mL).

The effect of smoking also remained robust when additional potential confounders were included, such as alcohol (Supplementary Figure 8) and marijuana use (Supplementary Figure 9), or when behavioral variables were expanded to include heavy physical work, having a stable partner, or having an occasional partner (Supplementary Figure 10). None of these variables had an effect by themselves, with the exception of having occasional partners, which was associated with a higher infection risk (aOR, 1.27 [95% CI, 1.05–1.55]). In support of a direct effect of smoking, stratification by the number of daily cigarettes showed a clear and striking dose-response effect, with smoking more cigarettes per day being associated with a greater reduction in infection risk (Figure 2*B*). Notably, even previous smokers retained some protective effect. Taken

together these findings reveal a puzzling but strikingly clear protective impact of cigarette smoking on SARS-CoV-2 susceptibility that warrants further investigation.

Differential Control of SARS-CoV-2 Infection Susceptibility and Severity

Over the full study period, 73 (6.7%) SARS-CoV-2–infected individuals were hospitalized, and 8 (0.74%) died (Supplementary Table 4). One additional participant was recorded to have likely died because of COVID-19 but could formally not be included in our study population as PCR confirmation was not available. This relatively low frequency of hospitalizations and deaths reflects the age distribution within the SHCS, with only 0.8% of PWH (82 of 10 301) aged ≥80 years. When stratified by age, the SHCS exhibited slightly higher hospitalization and case-fatality ratios compared with the general population (Supplementary Table 4). This modestly increased rate needs to be weighed carefully, as it may partly reflect more accurate monitoring possibilities in the SHCS than in the general population. Given the low number of hospitalized and deceased individuals, further analysis of associated parameters must be cautiously interpreted.

As seen generally in COVID-19, hospitalization in the SHCS was driven by older age and the presence of comorbid conditions (Supplementary Figure 4). We found no effect of HIV-related factors or antiretroviral medication on the risk of hospitalization. Only higher $CD4^+$ T-cell values showed a trend toward a reduced risk of hospitalization (aOR, 0.62 [95% CI, .36–1.03]; $P = .07$). Notably, factors associated with infection risk—namely, living alone, smoking, and being black—had no impact on hospitalization rates. We observed a significantly lower hospitalization rate in 2021 than in 2020 (aOR, 0.48 [95% CI, .22–.95]; Supplementary Figure 4), after accounting for vaccination and other potential confounders. This effect is likely due to several factors as well as immunization, including increased SARS-CoV-2 immunity due to prior infection and the availability of SARS-CoV-2 therapeutics [33] for high-risk individuals in Switzerland in 2021.

Multiple Factors Influencing the SARS-CoV-2 Antibody Response

Because the immune system of PWH, even if successfully treated, remains at least partially impaired [36], in 2020 we included a control group composed of HU individuals with PCR-documented SARS-CoV-2 infection (n = 257) to investigate factors influencing the antibody response to SARS-CoV-2 infection. PWH with SARS-CoV-2 serology sampled after PCR-documented infection in 2020 (n = 42) were compared with HU individuals (Figure 3*A*). Restricting the analysis to PCR-documented infections enabled control of antibody responses for the time since infection (Supplementary Figure 11). Using multivariate regression models deriving the overall effect of potential determinants across all antigens and adjusting for age, sex, and time since PCR positivity, we found that PWH had significantly lower SARS-CoV-2–specific antibody binding levels than HU individuals (Figure 3*A* and 3*B* and Supplementary Figure 11). Reduced antibody levels in PWH were observed across all immunoglobulin classes and antigens (Figure 3*C* and Supplementary Figures 12–14). A sensitivity analysis accounting for hospitalizations in the subgroup of PWH and HU individuals for whom this information was available corroborated the lower SARS-CoV-2 responses in PWH (Supplementary Figure 15).

We observed markedly lower SARS-CoV-2 IgG antibody reactivities among smokers, as also seen in response to vaccination [24, 37] (Figure 3*D* and 3*E*). Interestingly, black PWH had higher IgG antibody binding to all 3 spike antigens (RBD, S1, and S2) but not to the nucleocapsid (N) antigen, compared with white PWH (Figure 3*D* and 3*E* and Supplementary Figures 16–18). This selective up-regulation of spike antibodies is intriguing, as it may indicate a difference in immune recognition of viral antigens, depending on the race/ethnicity of the individual.

Preexisting HCoV Immunity and SARS-CoV-2 Infection

We and others reported modest protective effects of HCoV immunity on SARS-CoV-2 infection [27, 38–41]. We sought to determine the impact of prepandemic HCoV antibody titers on SARS-CoV-2 infection risk. We analyzed the S1 antigen reactivity of all 4 HCoVs in prepandemic plasma samples (collected in 2019 within the SHCS) from SARS-CoV-2–seropositive PWH (n = 92) and control PWH without SARS-CoV-2 infection (n = 182). Controls were matched for age, sex, race/ethnicity, smoking status, SHCS study center, and dates of pandemic and prepandemic plasma sample collection (Figure 4*A* and 4*B* and Supplementary Figure 18). We found that PWH with high prepandemic (2019) levels of antibody to HCoV-229E had a significantly reduced risk of a SARS-CoV-2 infection (aOR, 0.58 [95% CI, .35–.97]), whereas antibodies to the other HCoVs showed no such effect (Figure 4*B*). HCoV-229E was the most frequent HCoV detected in 2019 in our local virus diagnostics unit in Zurich, Switzerland (Figure 4*C*), suggesting that immunity to the most recent HCoV wave had the strongest impact on cross-protectiong against SARS-CoV-2. We next analyzed whether HCoV antibody responses in early 2020 had an impact on subsequent SARS-CoV-2 infection in 2020 or 2021, across the full study cohort. Consistent with the observed peak of HCoV-NL63 diagnoses in early 2020 (Figure 4*C*), we observed a significant protective effect of HCoV-NL63 antibodies (Figure 4*D*).

Notably, prepandemic antibody titers to HCoV (in particular, HCoV-NL63) were positively associated with higher SARS-CoV-2 antibody titers after a PCR-confirmed infection (Figure 5*A* and 5*B*). These effects were robust to adjustment for age, sex, $CD4^+$ T-cell counts, smoking, race/ethnicity, and

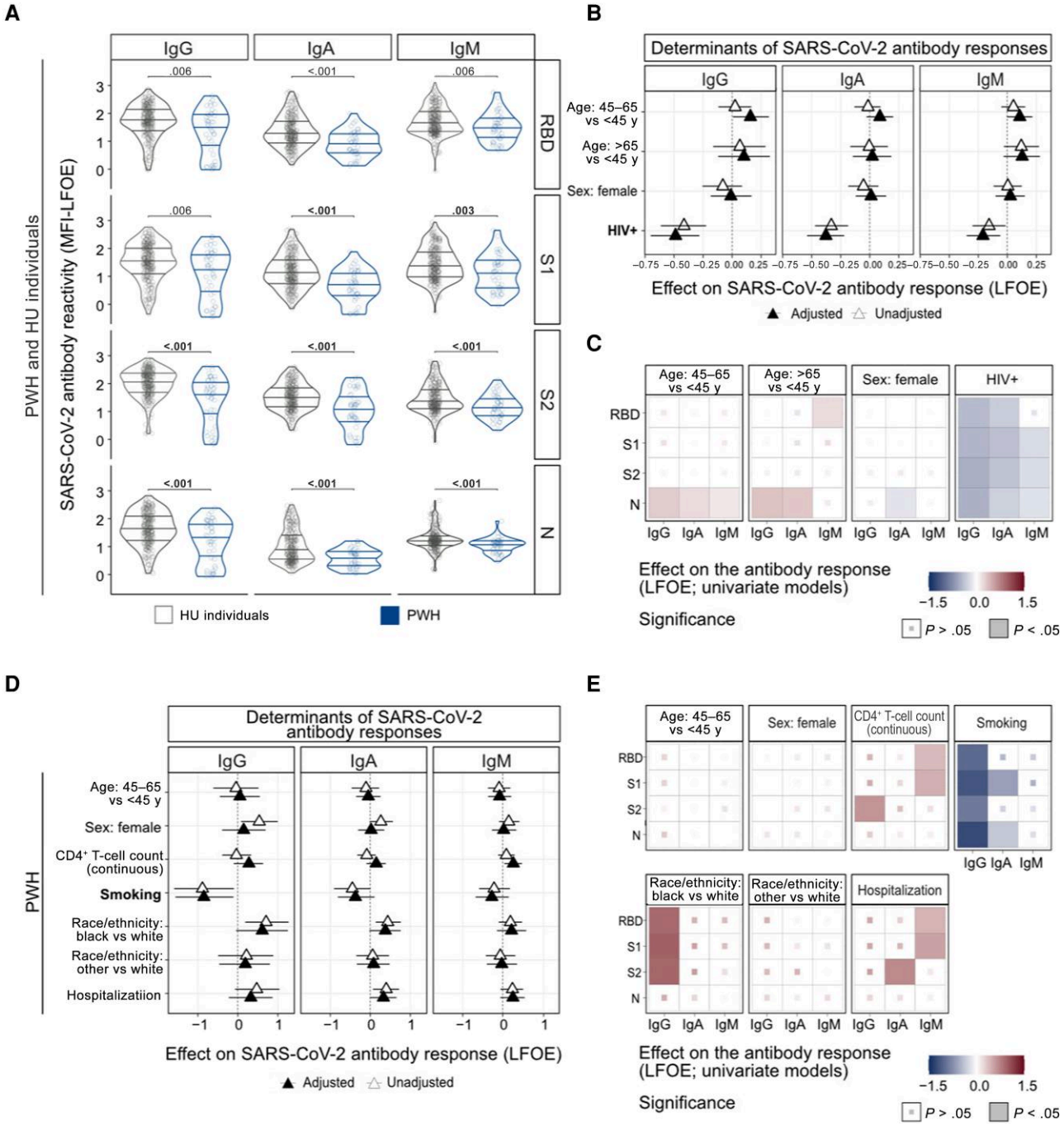

Figure 3. Factors that influence severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody response. *A*, Comparison of AntiBody CORonavirus Assay (ABCORA) 5 reactivity for SARS-CoV-2 in individuals who had a positive SARS-CoV-2 polymerase chain reaction (PCR) result before serology, stratified by human immunodeficiency virus (HIV) status (42 people with HIV [PWH] and 257 HIV-uninfected [HU] individuals). Horizontal lines within violin plots correspond to the first quartile, median, and third quartile. *B*, Determinants of SARS-CoV-2 antibody response, as analyzed by a Bayesian multivariate analyses response in the combined data set consisting of Swiss HIV Cohort Study (SHCS) participants (n = 42) and HU individuals (n = 257). The plots summarize the effects across antigens (receptor-binding domain [RBD], S1, S2, and nucleocapsid [N]) but are stratified by immunoglobulin (Ig) class. Effects are adjusted for age, sex, HIV status, and the time since the positive SARS-CoV-2 PCR result (included as a cubic spline). *C*, Univariate analyses of the determinants of SARS-CoV-2 antibody response in the combined data set of SHCS participants and HU individuals. Effect sizes are calculated using a frequentist linear model adjusted for the shown variables and for the time since the positive SARS-CoV-2 PCR result, which is included as a cubic spline. Colors indicate effect size and direction. Fully covered cells indicate significant effects ($P < .05$), and small internal squares, nonsignificant effects. *D*, Bayesian multivariate analyses of the determinants of SARS-CoV-2 antibody response among SHCS participants, who had a positive SARS-CoV-2 PCR result before serology (n = 42). Plots summarize the effects across antigens (RBD, S1, S2, and N) but are stratified by immunoglobulin class. Effects are adjusted for age, sex, $CD4^+$ T-cell count, smoking status, race/ethnicity, hospitalization, and the time since the positive SARS-CoV-2 PCR result, which is included as a cubic spline. *E*, Univariate analyses of the determinants of SARS-CoV-2 antibody responses in SHCS participants who had a positive SARS-CoV-2 PCR result before serology (n = 42). Effect sizes are calculated using a frequentist linear model adjusting for the shown variables and for. Colors indicate effect size and direction. Fully covered cells indicate significant effects ($P < .05$), and small internal squares, nonsignificant effects. In Panels *B* and *D*, lines correspond to 95% credible intervals. Abbreviations: LFOE, log-fold over empty; MFI, median fluorescence intensity.

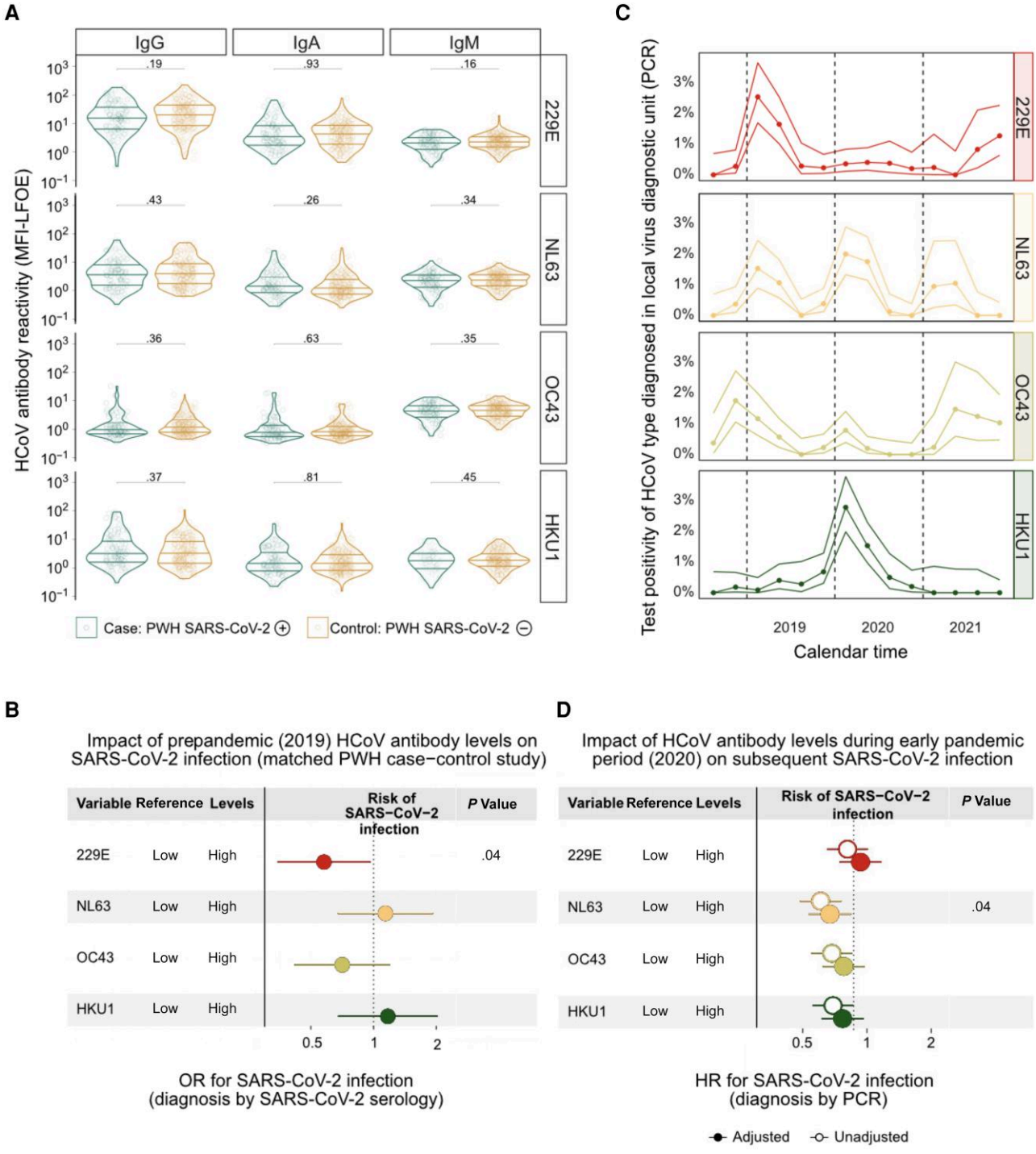

Figure 4. High prepandemic human coronavirus (HCoV) antibody levels are associated with a lower risk of subsequent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. *A*, Prepandemic HCoV S1 antibody responses among case patients (people with human immunodeficiency virus [HIV; PWH] who were polymerase chain reaction [PCR] positive; n = 92; *green*) and controls (PWH who were PCR negative; n = 182; *yellow*). Horizontal lines within violin plots correspond to the first quartile, median, and third quartile. *B*, Test positivity of the 4 HCoVs (229E, NL63, OC43, and HKU1) diagnosed in the local virus diagnostic unit by PCR by quarter year. *C*, Odds ratio (OR) of positive SARS-CoV-2 serologic results according to the level of prepandemic HCoV and SARS-CoV-2 serology, calculated using conditional logistic regression on the matched data comprising case patients and controls (see *A* and *B*). Only significant *P* values ($P < .05$) are displayed. *D*, Hazard ratios (HRs) comparing the time to a positive PCR test according to the prior (prepandemic and/or pandemic) HCoV level, and SARS-CoV-2 serology. The time-updated survival model is adjusted for age, sex, center, race/ethnicity, smoking status, and time of sample collection. Only significant *P* values ($P < .05$) are displayed. Abbreviations: Ig, immunoglobulin; LFOE, log-fold over empty; MFI, median fluorescence intensity.

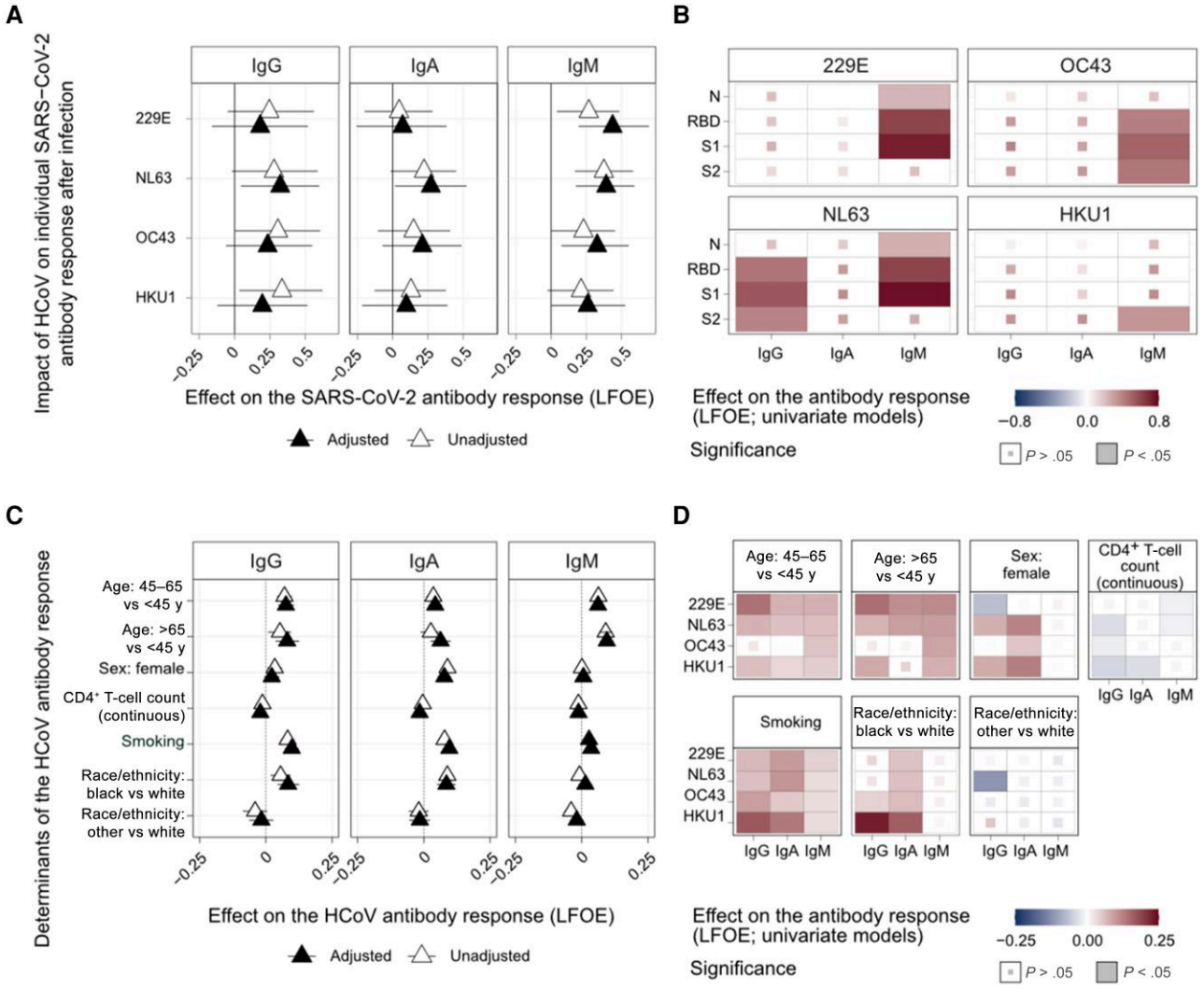

Figure 5. Dissecting the cross-talk between human coronavirus (HCoV) immunity and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responses. *A*, Impact of preexisting HCoV antibody response on individual SARS-CoV-2 antibody response after infection, analyzed using a Bayesian multivariate regression model. The model summarizes the effects across epitopes but is stratified by immunoglobulin class. Effects are adjusted for age, sex, $CD4^+$ T-cell count, smoking status, race/ethnicity, hospitalization, and the time since the positive SARS-CoV-2 polymerase chain (PCR) reaction (included as a cubic spline). *B*, Univariate analyses of the determinants of SARS-CoV-2 antibody response in people with human immunodeficiency virus (HIV; PWH) with PCR-confirmed SARS-CoV-2 infection and prepandemic serologic data available (n = 32). Effect sizes are calculated using a frequentist linear model adjusted for age, sex, $CD4^+$ T-cell count, smoking status, race/ethnicity, hospitalization, and the time since the positive SARS-CoV-2 PCR result (included as a cubic spline). Colors indicate effect size and direction. Fully covered cells indicate significant effects ($P < .05$), and small internal squares, nonsignificant effects. *C*, Bayesian multivariate analyses of the determinants of HCoV antibody responses sampled in 2020 among Swiss HIV Cohort Study (SHCS) participants (n = 3496). Plots summarize the effects across HCoV (HKU-1, OC43, NL63, 229E) but are stratified by immunoglobulin class. Effects are adjusted for age, sex, $CD4^+$ T-cell count, smoking, and race/ethnicity. *D*, Univariate analyses of the determinants of HCoV antibody responses sampled in 2020 among SHCS participants (n = 3496). Effect sizes are calculated using a frequentist linear model. Colors indicate effect size and direction. Fully covered cells indicate significant effects ($P < .05$), and small internal squares, nonsignificant effects. Effects are adjusted for age, sex, $CD4^+$ T-cell count, smoking, and race/ethnicity. Abbreviations: Ig, immunoglobulin; LFOE, log-fold over empty; N, nucleocapsid; RBD, receptor-binding domain.

hospitalization. Thus, irrespective of disease severity (as measured by hospitalization), high preexisting HCoV immunity promoted a higher antibody response to SARS-CoV-2 infection. Exploring factors associated with prepandemic HCoV antibody responses, we found that high $CD4^+$ T-cell values were associated with overall lower HCoV antibody responses among PWH, which may indicate less frequent HCoV infections with increasing immune competence (Figure 5*C* and 5*D* and Supplementary Figures 19 and 20). Consistent with more extended exposure to HCoVs, older age was associated with higher prepandemic HCoV antibody responses. Intriguingly, we found that smoking was associated with higher antibody responses to HCoV, which may be correlated with a potential protective mechanism, considering the observed lower SARS-CoV-2 infection rates among smokers. The fact that smokers mount elevated HCoV antibody levels (Figure 5*D*)

but decreased SARS-CoV-2 antibody responses (Figure 3*E*) highlights fundamental differences between HCoV and SARS-COV-2 infection biology and immune recognition that need to be resolved.

DISCUSSION

Using the potential of a systematic risk-factor screen in a large prospective cohort, our study yields several key observations relevant to understanding factors influencing SARS-CoV-2 infection in PWH and the general population. It provides new insights into the interplay between HCoV and SARS-CoV-2 immunity and supports evidence of the protective effects of preexisting HCoV immune responses [27, 38–40]. Observed lower SARS-CoV-2 antibody responses in PWH are likely attributable to the known residual immune dysfunction despite long-term suppressive ART [36], but they are not associated with increased infection rates or disease severity compared with the general Swiss population. Given the very high proportion of PWH with virologic suppression in the SHCS, this may not apply to settings with lower treatment or suppression rates.

The observed impact of living alone in the initial phases of the pandemic underline the influence of social distancing in limiting SARS-CoV-2 spread. Higher infection rates among black PWH may be due to socioeconomic differences that should be investigated, as they may result in fewer opportunities to protect oneself at the workplace and at home. In turn, fading of the effect in 2021 may be attributable to increased herd immunity [42]. Higher (IgG) spike antibody responses in black PWH may also have an underlying host genomic factor, as our group previously observed stronger and broader HIV-antibody responses among black PWH [43, 44].

An association between smoking and reduced SARS-CoV-2 infection risk has been reported in other studies but has not found wide acceptance [45, 46]. Our results support a potential impact of smoking: The effect is strong and highly robust as demonstrated through several sensitivity analyses. The extent of smoking was associated with the effect size, with heavy smokers being at the lowest risk. Future studies will be needed to unravel whether pathophysiologic effects, such as stimulation of innate defenses or down-regulation of angiotensin-converting enzyme 2 receptors, are involved in lower susceptibility to SARS-CoV-2 [47]. While we observed a protective lower risk of SARS-CoV-2 acquisition in smokers, this should not be read to mean that smoking will prevent against the virus or severe disease. Our study focuses on the initial SARS-CoV-2 waves in the absence of specific SARS-CoV-2 immunity. Later circulating variants are more fit than the initial strains, which also may outweigh the effect of smoking. It also needs to be considered that the reduced ability of smokers to mount SARS-CoV-2 antibody responses may reduce the capacity for virus clearance [17], inflicting more severe disease courses in smokers [48–50].

The current study has several limitations and important strengths. Some analyses remain inconclusive owing to limited power. This was the case for risk factors for hospitalization because of the overall small number of hospitalizations. Limited statistical power may also have hindered our ability to detect a protective effect associated with immunity to HCoVs with lower prevalence before the onset of the SARS-CoV-2 pandemic. As with all observational studies, confounding by unreported factors cannot be excluded. Despite careful data collection, some underreporting of SARS-CoV-2 infection remains possible, and false-negative serologic tests cannot be accounted for. Despite these limitations, our study demonstrates the power of observational cohorts to achieve a comprehensive assessment of the drivers of COVID-19 in PWH and beyond. Our cohort screen confirms that SARS-CoV-2 vaccination has a clear protective effect in PWH on ART.

The depth of our analysis allowed us to identify several factors associated with SARS-CoV-2 infection risk. Overall, we found it most intriguing that 2 unrelated factors affecting the respiratory milieu, namely prior HCoV infection and smoking, had strong protective effects against SARS-CoV-2 acquisition. This warrants future in-depth analyses of the protective mechanisms in the respiratory mucosa to potentially implicate these factors in antiviral defense.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Data sharing. Deidentified individual-level participant data are available on reasonable request. The data sets generated and/or analyzed during the current study are not publicly available, since they are subject to national data protection laws and restrictions imposed by the ethics committee to ensure data privacy of the study participants (http://www.shcs.ch/294-open-data-statement-shcs). The code for the analysis is archived at the University Hospital of Zurich. Requests for data sharing can be directed to the corresponding authors.

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