on number of infections. In addition, contact tracing methods to limit the spread of infection will face considerable challenges.

This study has limitations. Selection bias is likely. The estimated prevalence may be biased due to nonresponse or that symptomatic persons may have been more likely to participate. Prevalence estimates could change with new information on the accuracy of test kits used. Also, the study was limited to 1 county. Serologic testing in other locations is warranted to track the progress of the epidemic.

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Nasal Gene Expression of Angiotensin-Converting Enzyme 2 in Children and Adults

Children account for less than 2% of identified cases of coronavirus disease 2019 (COVID-19).[1,2] It is hypothesized that the lower risk among children is due to differential expression of angiotensin-converting enzyme 2 (ACE2),[3] the receptor that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) uses for host entry.[4] We investigated *ACE2* gene expression in the nasal epithelium of children and adults.

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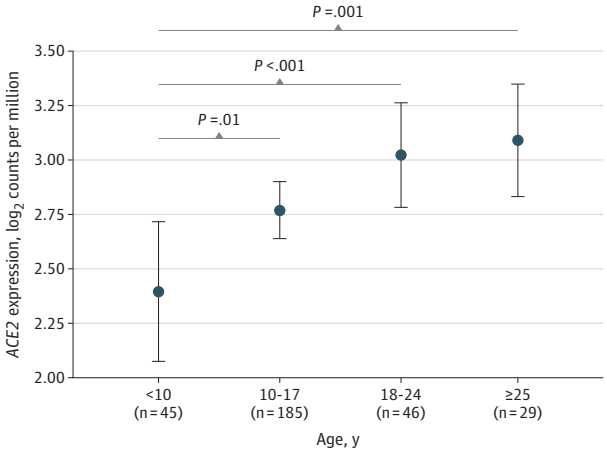
Methods | We conducted a retrospective examination of nasal epithelium from individuals aged 4 to 60 years encountered within the Mount Sinai Health System, New York, New York, during 2015-2018. Samples were collected from individuals with and without asthma for research on nasal biomarkers of asthma. The study was approved by the Mount Sinai institutional review board. Written informed consent was obtained from participants (or their parents for minors). Nasal epithelium was collected using a cytology brush that was immediately placed in RNA stabilization fluid and stored at −80 °C. RNA was isolated within 6 months. RNA samples were checked for quality and sequenced as a single batch in 2018. Sequence data processing included sequence alignment and normalization of gene expression counts across genes and samples.

Given the role of ACE2 in SARS-CoV-2 host entry,[4] *ACE2* gene expression was the focus of this study. Linear regression

Figure. Nasal Gene Expression of *ACE2* in Different Age Groups



Data are means (data points) and 95% confidence intervals (error bars) for angiotensin-converting enzyme 2 (*ACE2*) gene expression in younger children (aged <10 years), older children (aged 10-17 years), young adults (aged 18-24 years), and adults (aged ≥25 years). Gene counts are shown as logarithmic (log_2) counts per million. *P* values are from linear regression modeling in which *ACE2* gene expression in log_2 counts per million was the dependent variable and age group was the independent variable.

Table. β Coefficients for Age Group From Unadjusted and Adjusted Linear Regression Models[a]

	β Coefficient (95% CI)[c]	
Age group, y[b]	Unadjusted model	Adjusted model[d]
10-17	0.37 (0.08-0.67)	0.30 (0.01-0.59)
18-24	0.63 (0.26-1.00)	0.49 (0.13-0.86)
≥25	0.69 (0.27-1.11)	0.52 (0.09-0.94)

[a] Angiotensin-converting enzyme 2 gene expression in log_2 counts per million was the dependent variable and age group was the independent variable.

[b] Children younger than 10 years were the reference age group.

[c] β Coefficients indicate the difference in *ACE2* gene expression (in log_2 counts per million) between a given age group and the group of children younger than 10 years.

[d] Adjusted for sex and asthma.

models with and without adjustment for covariates (sex and asthma) were built with *ACE2* gene expression in log_2 counts per million as the dependent variable and age group as the independent variable using R software, version 3.6.0 (R Foundation). Age was categorized into the following groups reflecting developmental life stages: younger children (aged <10 years), older children (aged 10-17 years), young adults (aged 18-24 years), and adults (aged ≥25 years). Two-sided tests and a significance threshold of $P \leq .05$ were used. Trend pattern was evaluated using polynomial orthogonal contrasts.

Results | The cohort of 305 individuals aged 4 to 60 years was balanced with regard to sex (48.9% male). Because the cohort had been recruited to study biomarkers of asthma, 49.8% had asthma.

We found age-dependent *ACE2* gene expression in nasal epithelium (**Figure**). *ACE2* gene expression was lowest (mean log_2 counts per million, 2.40; 95% CI, 2.07-2.72) in younger children (n = 45) and increased with age, with mean log_2 counts per million of 2.77 (95% CI, 2.64-2.90) for older children (n = 185), 3.02 (95% CI, 2.78-3.26) for young adults (n = 46), and 3.09 (95% CI, 2.83-3.35) for adults (n = 29).

Linear regression with *ACE2* gene expression as the dependent variable and age group as the independent variable showed that compared with younger children, *ACE2* gene expression was significantly higher in older children ($P = .01$), young adults ($P < .001$), and adults ($P = .001$) (Figure). As the distributions of sex and asthma varied among the age groups, a linear regression model adjusted for sex and asthma was built that also showed significant adjusted associations ($P \leq .05$) between *ACE2* expression and age group. Regression (β) coefficients for age groups from the unadjusted and adjusted models are shown in the **Table**. These regression coefficients indicate the difference in *ACE2* expression (in log_2 counts per million) between a given age group and the group of children younger than 10 years. Tests for trend using polynomial orthogonal contrasts indicated a significant linear trend for change in *ACE2* expression with advancing age group ($P \leq .05$).

Discussion | The results from this study show age-dependent expression of *ACE2* in nasal epithelium, the first point of contact for SARS-CoV-2 and the human body. Covariate-adjusted models showed that the positive association between *ACE2* gene expression and age was independent of sex and asthma. Lower *ACE2* expression in children relative to adults may help explain why COVID-19 is less prevalent in children.[3] A limitation of this study is that the sample did not include individuals older than 60 years.

Few studies have examined the relationship between ACE2 in the airway and age. A study of bronchoalveolar lavage fluid from 92 patients with acute respiratory distress syndrome reported no association between ACE2 protein activity and age,[5] but epithelial gene expression was not examined, and ACE2 protein may be variably shed into bronchoalveolar lavage fluid. Furthermore, the lung and nasal environments are distinct, with known differences in gene expression.[6] This study provides novel results on *ACE2* gene expression in nasal epithelium and its relationship with age.

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Effect of Physician Notification Regarding Nonadherence to Colorectal Cancer Screening on Early Cancer Detection

Although screening for colorectal cancer reduces mortality, participation in screening is low. A randomized clinical trial that focused on sending specific reminders to general practitioners resulted in a modest but significant increase in patient participation after 1 year.[1] Data on the second co-primary outcome regarding cancer detection were not available at the time of publication[2] but are reported herein.

Supplemental content

Methods | A cluster randomized clinical trial was conducted in France from July 14, 2015, to July 14, 2016, with medical practice as the unit of randomization. Details have been previously published.[1] The trial protocol (appears in Supplement 1) was approved by the Committee of Protection of Persons in Rennes, France, with a waiver of informed consent.

Briefly, patients eligible for screening (aged 50-74 years; asymptomatic; no family history of colorectal cancer; no personal history of colorectal cancer or adenoma >1 cm in diameter; and no colonoscopy within the past 5 years) are invited by mail to obtain a fecal immunochemical test (FIT) kit from their general practitioner. Patients who do not return a FIT screening within 3 months are defined as nonadherent and receive a new invitation letter.

General practitioners in 801 practices and their nonadherent patients were included. Physicians were assigned to 1 of 3 groups: (1) the patient-specific reminders group, which received a list of nonadherent patients; (2) the generic reminders group, which received general information about regional screening adherence; and (3) the usual care group, which did not receive any reminders. The patient participation rates at 1 year were 24.8% in the patient-specific reminders group, 21.7% in the generic reminders group, and 20.6% in the usual care group, with the difference between the patient-specific reminders group and the other 2 groups reaching statistical significance.

The second co-primary outcome was the rate of colorectal cancer cases detected after 1 year, which was obtained from the regional cancer registry. This rate was calculated in each group as follows: the number of patients with colorectal cancer detected/the number of patients eligible for organized screening. The rates were compared among all 3 groups using a generalized linear mixed model with medical practices as the between-random effects. The same model was used to make pairwise comparisons.

The significance threshold was $P < .05$ and the testing was 2-sided. One of the goals of the study design was to avoid having missing data. The patients were analyzed according to their original allocation. All analyses were performed using R version 3.6.0 (R Foundation for Statistical Computing).

Results | Of 1482 randomized general practitioners, 1446 were included (496 in the patient-specific reminders group, 495 in the generic reminders group, and 455 in the usual care group). Of the 33 044 patients, 31 229 were included in the analysis. Characteristics of the general practitioners and patients have been published.[1]

There were 102 patients (0.97% [95% CI, 0.79%-1.18%]) who underwent a colonoscopy in the patient-specific reminders group (n = 10 476), 81 patients (0.76% [95% CI, 0.61%-0.95%]) in the generic reminders group (n = 10 606), and 66 patients (0.65% [95% CI, 0.50%-0.83%]) in the usual care group (n = 10 147) (**Table 1**).

Ten cases of colorectal cancer (0.10% [95% CI, 0.05%-0.18%]) were detected after 1 year in the patient-specific reminders group, 9 cases (0.08% [95% CI, 0.04%-0.16%]) in the generic reminders group, and 2 cases (0.02% [95% CI, 0.002%-0.07%]) in the usual care group (global effect of the randomization group on cancer detection, $P = .04$). The between-group differences were 0.010% (95% CI, −0.08% to 0.10%) for the patient-specific reminders group vs the generic reminders group ($P = .98$), 0.076% (95% CI, 0%-0.15%) for the patient-specific reminders group vs the usual care group ($P = .049$), and 0.065% (95% CI, −0.01% to 0.14%]) for the generic reminders group vs the usual care group ($P = .08$) (**Table 2**).

Discussion | Providing general practitioners with a list of their nonadherent patients led to a modest increase in the number of cases of colorectal cancer detected after 1 year compared with usual care. There was no significant difference