Discussion | In this study, initial vaccine-elicited neutralizing antibody titers were negatively associated with age, resulting in a diminished ability to neutralize SARS-CoV-2 in vitro. Neutralizing titers against P.1 were reduced across all ages, although the magnitude of the age-dependent difference was smaller. Interim clinical trial data did not identify age as a contributing factor to overall vaccine efficacy.[1] However, recent studies in vaccinated populations have found a measurable increase in COVID-19 cases among vaccinated older adults.[3,4] The data from the current study are consistent with neutralizing antibody levels playing an important role in this observation.

Neutralizing antibody titers are thought to be strongly correlated with protection from infection; however, the threshold of this protection has not yet been precisely determined.[5] Future studies should specifically address whether the reduced antibody levels seen among older vaccinated individuals lead to concomitantly diminished protection. Additionally, the emerging SARS-CoV-2 variants of concern, including P.1, B.1.1.7, and B.1.351, have been widely reported to be less well neutralized by vaccine-induced antibodies and are responsible for a majority of breakthrough infections, according to a May 2021 report.[6] The compounding effects of reduced neutralizing antibody titers due to both age and the variants of concern should be considered when designing policies around booster vaccinations. Limitations of this study include the small sample size and the possibility of unrecognized infection prior to vaccination.

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Long-term Symptoms After SARS-CoV-2 Infection in Children and Adolescents

Children can experience SARS-CoV-2 postviral syndromes, but it is unclear to what extent these individuals are affected by long COVID. Evidence is predominantly limited to select populations without control groups,[1-4] which does not allow estimating the overall prevalence and burden in a general pediatric population. We compared symptoms compatible with long COVID in children and adolescents (hereafter "children") reported within 6 months after SARS-CoV-2 serologic testing.

Supplemental content

Methods | Ciao Corona is a longitudinal cohort study investigating SARS-CoV-2 seroprevalence in 55 randomly selected schools in the canton of Zurich in Switzerland,[5,6] which has a linguistically and ethnically diverse population of 1.5 million

Table. Participant Characteristics, Most Frequently Reported Symptoms After Serologic Testing (October 2020 Through March-April 2021), and Self-rated Health Among Seropositive and Seronegative Children

	No. (%)	
	Seropositive (n = 109)	Seronegative (n = 1246)
Female sex	58 (53)	669 (54)
Age, y		
6-11	66 (61)	703 (56)
12-16	43 (39)	543 (44)
≥1 Symptom lasting >12 wk	4 (4)	28 (2)
Tiredness	3 (3)	10 (1)
Difficulty concentrating	2 (2)	8 (1)
Increased need for sleep	2 (2)	0
Congested or runny nose	1 (1)	3 (<1)
Stomachache	1 (1)	3 (<1)
Chest tightness	1 (1)	0
≥1 Symptom lasting >4 wk	10 (9)	121 (10)
Tiredness	7 (6)	51 (4)
Headache	5 (5)	39 (3)
Congested or runny nose	3 (3)	40 (3)
Stomachache	3 (3)	18 (1)
Sleep disturbances	3 (3)	14 (1)
Cough	2 (2)	15 (1)
Self-rated health[a]		
Excellent	43 (41)	497 (41)
Good	56 (53)	680 (55)
Fair	5 (5)	48 (4)
Poor	2 (2)	2 (<1)

[a] The item self-rated health was assessed with the Health Behavior in School-Aged Children–Survey Instrument (eMethods in the Supplement). Self-rated health was not reported for 3 seropositive and 19 seronegative children.

residents in urban and rural settings. Schools were selected randomly from the 12 cantonal districts, with number of schools proportional to population size. In Switzerland, children attended schools in person (with protective measures) in 2020-2021, except during a 6-week nationwide lockdown (March 16 to May 10, 2020).

Within participating schools, we invited all children of randomly selected classes to participate. Between June 2020 and April 2021, 3 testing phases included collection of venous blood for serologic analysis and online questionnaires for symptoms. For serologic analysis, we used the ABCORA 2.0 test (eMethods in the Supplement).[5]

We compared children who tested positive for SARS-CoV-2 antibodies in October or November 2020 with those who tested negative. We excluded children who were seronegative in October or November 2020 and seroconverted or were not retested by March or April 2021. In March to May 2021, parents reported symptoms of their children occurring since October 2020 and lasting for at least 4 weeks, as well as whether the symptoms persisted for more than 12 weeks. The questionnaire contained a list of predefined symptoms and a free-text field.

Descriptive analysis was performed with R version 4.0.3 (R Foundation). The Ethics Committee of the Canton of Zurich, Switzerland, approved the study and parents provided written informed consent.

Results | Overall, 1355 of 2503 children (54%) (median age, 11 years; interquartile range, 9-13 years; 54% girls) with a serology result in October or November 2020 were included. Two hundred thirty-eight children were not eligible because they seroconverted, 292 because they were not retested, and 618 because they did not provide information on symptoms. Compared with children not included, those included in the analysis were younger (median age, 11 vs 12 years) and more likely to be girls (54% vs 49%), and their parents had a higher proportion of university or college education (77% vs 64%). Age and sex distribution was comparable between seropositive children (n = 109) and seronegative ones (n = 1246) (**Table**).

Between October and November 2020 and March and April 2021, 4 of 109 seropositive children (4%) vs 28 of 1246 seronegative ones (2%) reported at least 1 symptom lasting beyond 12 weeks (see Table for all symptoms lasting beyond 4 and 12 weeks). The most frequently reported symptoms lasting more than 12 weeks among seropositive children were tiredness (3/109 [3%]), difficulty concentrating (2/109 [2%]), and increased need for sleep (2/109 [2%]). None of the seropositive children reported hospitalization after October 2020. Similar proportions of seropositive and seronegative children reported excellent or good health.

Discussion | This study found a low prevalence of symptoms compatible with long COVID in a randomly selected cohort of children assessed 6 months after serologic testing.

Although long COVID exists in children,[1,3,4] estimates of the prevalence of persisting symptoms based on scarce literature range from 0%[2] to 27%.[1] Initial SARS-CoV-2 infection severity, different methodological approaches (clinical assessment vs self-report), definition of cases (diagnosed vs suspected), variable follow-up times, and prevalence of preexisting clinical conditions likely contribute to the variability in prevalence estimates.

This study reports the distribution of symptoms compatible with long COVID on a population level; it did not capture severe SARS-CoV-2 infections because they are rare in children. A strength of this study is the population-based seronegative control group. Limitations include the relatively small number of seropositive children, lack of information on the exact time of SARS-CoV-2 infection, possible misclassification of some children with false seropositive results, potential recall bias, parental report of child's symptoms, lack of information on symptom severity, and noncompletion of the questionnaire. Also, systematic differences existed between children included vs not included in the analysis, possibly affecting the representativeness of the sample.

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Concept and design: All authors.
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COMMENT & RESPONSE

Age at Diabetes Onset and Subsequent Risk of Dementia

To the Editor The article by Dr Barbiellini Amidei and colleagues[1] suggested that younger age at onset of diabetes was significantly associated with a higher risk of subsequent dementia. However, we have some concerns about the strength of this conclusion.

First, the authors did not describe the hearing and visual functioning of the participants in this study. It is essential to know these details because hearing loss has been identified as a critical potential risk factor for dementia, with a population-attributable fraction of 8.2% (relative risk, 1.9; 95% CI, 1.4-2.7).[2] Moreover, recent research has shown that people with both hearing and visual impairments had a higher risk of all-cause dementia (hazard ratio, 1.86; 95% CI, 1.25-2.76).[3] Loss of hearing and vision function can lead to social isolation, which increases the incidence of dementia.[2] Therefore, we suggest that the authors consider hearing and vision levels in their study to avoid these possible confounding factors.

Second, although the authors mentioned that oral diabetes drug data were collected at the clinical examination, no detailed information was provided about the oral glucose-lowing drugs used in the adjusted model. A study by Scherrer et al[4] found that metformin was associated with a lower risk of incident dementia compared with sulfonylurea drugs. Thus, it is necessary to adjust the oral diabetes drug factors in this study,[1] or else it may increase the confounding bias of the result.

Third, young-onset type 2 diabetes (age <40 years) may differ from late-onset type 2 diabetes (age ≥40 years) in aspects of pathogenic mechanisms, risk factors, and complications such as insulin resistance, genetics, and retinopathy, which can affect the occurrence of dementia.[5] We strongly recommend that the authors further discuss or perform a subtype analysis of age to avoid the potential confounding bias.

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In Reply Dr Gao and colleagues raise 3 concerns regarding the conclusions of our article.[1] First, they want us to consider hearing and visual complications of diabetes. Our study examined the role of age at onset of diabetes in determining risk of dementia rather than the complications of diabetes. Gao and colleagues refer to 2 recent articles showing sensory impairment to be a risk factor for dementia.[2,3] The first of these is a report in which the details of the studies used to estimate the risk ratio of 1.9 are not clear.[2] In the second study, people with hearing and visual impairment had a hazard ratio of dementia of 1.86; however, their mean age at baseline was 79.1 years with an 8-year follow-up.[3] The authors of this study noted that "reverse causation from early neurodegenerative stages"[3] of dementia was a possible explanation of their findings.