Universität Zürich[UZH]

Final Report: Zurich Coronavirus School Study 'Ciao Corona'

(Order 142005113)

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The Federal Office of Public Health (FOPH) supported the 'Ciao Corona' study as noted in Order 142005113. We are pleased to present you with the final report and current results. All study results are also available on our website (www.ciao-corona.ch).

To remind you, here are some key details and main objectives of the 'Ciao Corona' study. 'Ciao Corona' is a population-based school study in the Canton of Zurich, conducted from June 2020 to July 2022 over 5 measurement periods of 3-4 weeks each. Approximately 1,900 to 2,600 students aged 6 to 17 from 55 randomly selected schools and classes participated in each period. The studies took place in schools over 3-4 weeks and included blood samples and questionnaires filled out by parents and school principals.

The main goals of the study were:

1. Determining the seroprevalence of participating students over time
2. Determining the spread of the SARS-CoV-2 virus within schools and classes (known as clustering)
3. Recording symptoms and severity of SARS-CoV-2 infections in students under different prevailing variants of the virus
4. Determining the longitudinal progression of anti-Spike (anti-S) and neutralizing antibodies (against all variants relevant for Switzerland) after a SARS-CoV-2 infection, a vaccination, or a combination of infection and vaccination
5. Recording and characterizing long-term symptoms consistent with Long COVID in students with and without SARS-CoV-2 infection
6. Tracking lifestyle and well-being during the pandemic

The following summarizes the key insights from the study, presented in text and illustrations, if no published article is available yet, or with references to publications or preprints if articles are already available.

Figure 1 provides an overview of our school-based cohort study "Ciao Corona." Detailed information about the study design, objectives, and methodology can be found in the design paper.1 The study has been ongoing since June 2020. Between 1,900 and 2,600 children and teenagers, aged 6-17, participated in five measurement periods from June 2020 to July 2022. Of these, 751 participated in at least four out of five rounds. The students were from 55 randomly selected schools in the Zurich canton. Schools were chosen from all districts, with the number of schools in each district being proportional to the population size. Within each school, classes were randomly selected, ensuring equal representation from lower, middle, and upper levels. The green-shaded curve shows the infection trend in the Swiss population.

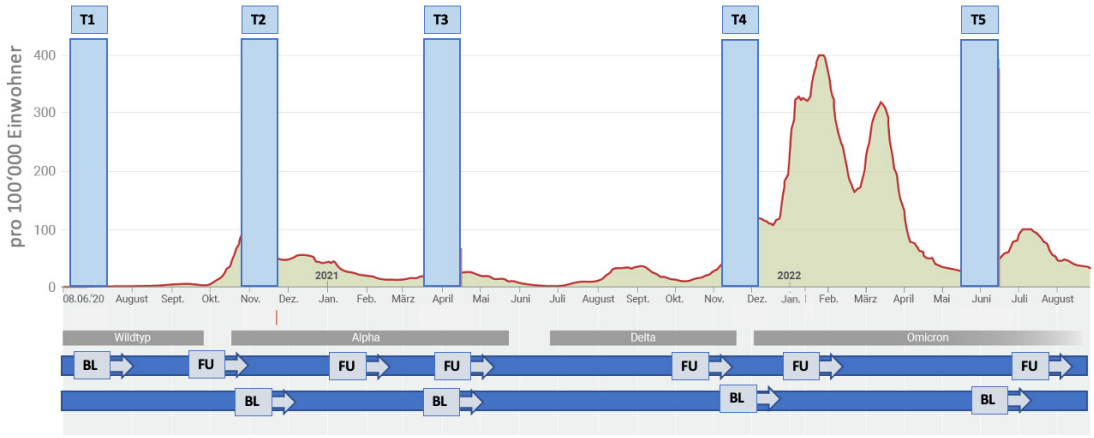


Figure 1: During each test phase of the "Ciao Corona" study, 1,900-2,600 students participated. These students came from randomly selected schools and classes within the Zurich canton. At measurement periods (Timepoints T1-T5), blood samples were taken to determine seroprevalence and immune response. Students and their parents, along with school principals, regularly completed questionnaires (Q). BL=Baseline Questionnaire, FU=Follow-up Questionnaire.

In the following **Table 1** you will find the characteristics of the school cohort at each measurement point.

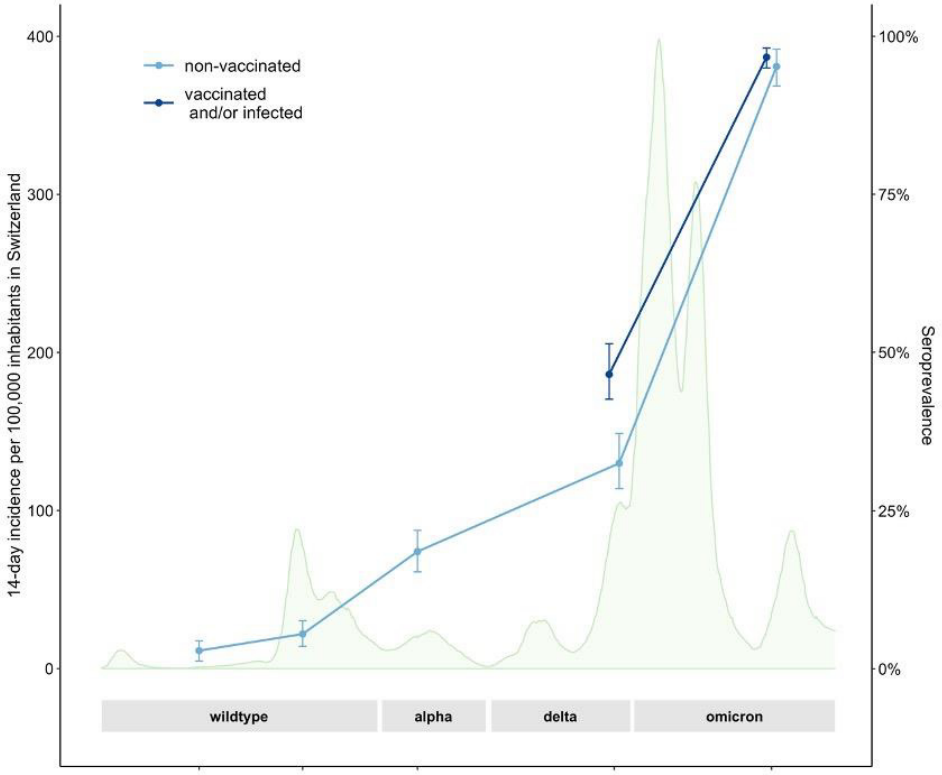
Table 1 Characteristics of schools, classes, and students included in the study

	T1	T2	T3	T4	T5
Testing Phases	Jun/Jul 2020	Oct/Nov 2020	Mar/Apr 2021	Nov/Dec 2021	Jun/Jul 2022
Predominant VOC [a]	wildtype	wildtype	alpha	delta	omicron
CROSS-SECTIONAL COHORT					
n	2473	2500	2453	1876	2125
Age in years (range)	12 (6-17)	12 (7-17)	12 (7-17)	12 (7-17)	12 (7-18)
Gender (n, % male)	1197 (48%)	1211 (48%)	1166 (48%)	883 (47%)	851 (47%)
Age Group					
<12 years	1450 (59%)	1298 (52%)	1144 (47%)	945 (50%)	1015 (48%)
≥12 years	1023 (41%)	1202 (48%)	1306 (53%)	930 (50%)	1110 (52%)
Chronic Condition a	546 (24%)	551 (24%)	536 (24%)	375 (23%)	413 (23%)
Vaccinated					
Total	N/A	N/A	N/A	476/1876 (25%)	922/2125 (43%)
<12 years				N/A 476/930	285/1015 (28%)
≥12 years				(51%)	637/1110 (57%)
Completed Questionnaire	2210 (89%)	2014 (81%)	1898 (77%)	1459 (78%)	1426 (67%)
LONGITUDINAL COHORT					
n Age in years			751		
(range)	10 (6-15)	11 (7-16)	11 (7-16)	12 (8-17)	12 (8-17)
Gender (n, % male)			355 (47%)		
Age Group					
<12 years	496 (71%)	492 (68%)	465 (63%)	377 (52%)	325 (43%)
≥12 years	199 (29%)	233 (32%)	273 (37%)	345 (48%)	426 (56%)
Chronic Condition a			166 (23%)		
Vaccinated					
Total	N/A	N/A	N/A	184/751 (25%)	345/751 (46%)
<12 years				N/A	93/325 (29%)
≥12 years				184/345 (53%)	252/426 (59%)
Completed Questionnaire	678 (90%)	647 (86%)	636 (85%)	610 (81%)	515 (69%)

Values are expressed as number (n) and percentage (%); Predominant VOC: SARS-CoV-2 variant affecting over 50% of new infections, a) Chronic conditions (potentially affecting immunity) such as asthma, hay fever, allergies, chronic bowel diseases.

1. Development of Seroprevalence from June 2020 to July 2022

Figure 2 illustrates the seroprevalence trends among students during two years of the pandemic. Students over the age of 12 were eligible for vaccination starting in June 2021, and those aged 5-11 from December 2021. Looking at all participating students, seroprevalence rose from an initial 2% in summer 2020 to 47% in winter 2021, reaching 97% by summer 2022. Among unvaccinated students, 33% showed SARS-CoV-2 Anti-S IgG antibodies in winter 2021, increasing to 95% by summer 2022. These figures indicate that by the final measurement, nearly all students had either recovered, been vaccinated, or both.



Seroprevalence	T1 Jun/Jul 2020	T2 Oct/Nov 2020	T3 Mar/Apr 2021	T4 Nov/Dec 2021	T5 Jun/Jul 2022
non-vaccinated	2.8%	5.5%	18.5%	32.5%	95.2%
vaccinated and/or infected				46.5%	96.7%

Figure 2: Seroprevalence trends over time among approximately 1900-2600 tested students (cross-sectional data). T1-T5 denote the measurement periods in schools, with seroprevalence and 95% confidence intervals shown in light blue for unvaccinated students and dark blue for all students including those vaccinated. The green shaded area represents the pandemic progression in the Swiss population, showing the number of PCR-positive cases per 100,000 inhabitants.

2. Determining the spread of the SARS-CoV-2 virus within schools and classes through a method called clustering

For insights into clustering, please refer to the publications from the first four measurement periods, which we have included in the final report.2-5 Since nearly all students were seropositive during measurement period T5, this analysis was not necessary.

3. Development of the humoral immune response following infections and vaccinations

Figure 3 illustrates the progression of Anti-Spike-IgG antibodies using a longitudinal cohort (n = 715). Students who tested seronegative in all five test rounds (n = 37) and those who seroconverted between T4 and T5 (n = 328) were excluded. The remaining students (n=350) were categorized into four groups based on their seroconversion timing, such as Group 1 comprising participants who seroconverted before T1, Group 2 those who seroconverted between T1 and T2, and so on. Consequently, the antibody titer trends are shown over 6, 12, and 18 months. **Antibodies were detectable up to 18 months**, and titers increased with each test round. This rise was due to new infections, reinfections, vaccinations, or a combination thereof. A noticeable rise in antibody titers occurred between T3 and T4, coinciding with the start of vaccinations. The most significant color change and highest titer increase happened between T4 and T5, when Omicron became the dominant virus variant. At T5, **99% of all students with previous positive antibody results still had detectable antibodies**. About 5% of students consistently remained seronegative (n=37), and all others were infected, reinfected, vaccinated, or both by June/July 2022.

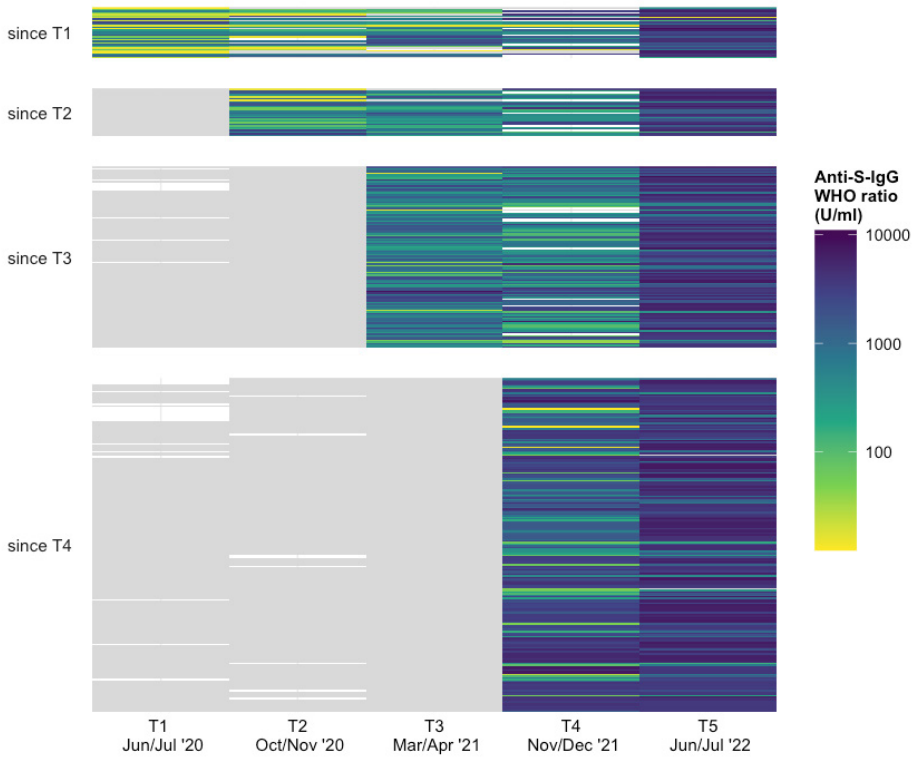


Figure 3: Individual longitudinal courses of SARS-CoV-2 Anti-Spike-IgG titers over time, grouped by the first appearance of a seropositive result (n = 386) at specific times (T1: June/July 2020, T2: October/November 2020, T3: March/April 2021, T4: November/December 2021, T5: June/July 2022). Students who remained consistently seronegative (n=37) and those who seroconverted between T4 and T5 (n=328) were excluded. In gray: seronegative results, seropositive results shown as a color scale from yellow to dark blue based on titer levels in WHO ratios (U/ml).

4. Impact of the Omicron Wave

Figure 4 illustrates the impact of the Omicron wave from winter 2021 to summer 2022 by tracking the development of Anti-S-IgG antibodies between T4 (Nov/Dec 2021) and T5 (June/July 2022). This period marks the start of Omicron as the dominant VOC (variant of concern) until the end of the first major infection peak (see **Figure 1**). Students were grouped based on their infection or vaccination status at T4 and T5 into seronegative (no Anti-S IgG antibodies), infected (Anti-S IgG+, Anti-Nuc IgG-), vaccinated (Anti-S IgG+, Anti-Nuc IgG-), or hybrid (Anti-S IgG+, Anti-Nuc IgG+). The figure shows that vaccinated students and those with hybrid immunity generally had higher titers than infected students during the T4 and T5 measurement periods. It also reveals that under Omicron and vaccination guidelines, almost all students (97%) either seroconverted (meaning newly infected) or experienced a titer increase due to reinfection, vaccination, or both. Furthermore, it is noticeable that titers increased between T4 and T5 across all groups, regardless of new infection, vaccination, or hybrid immunity.

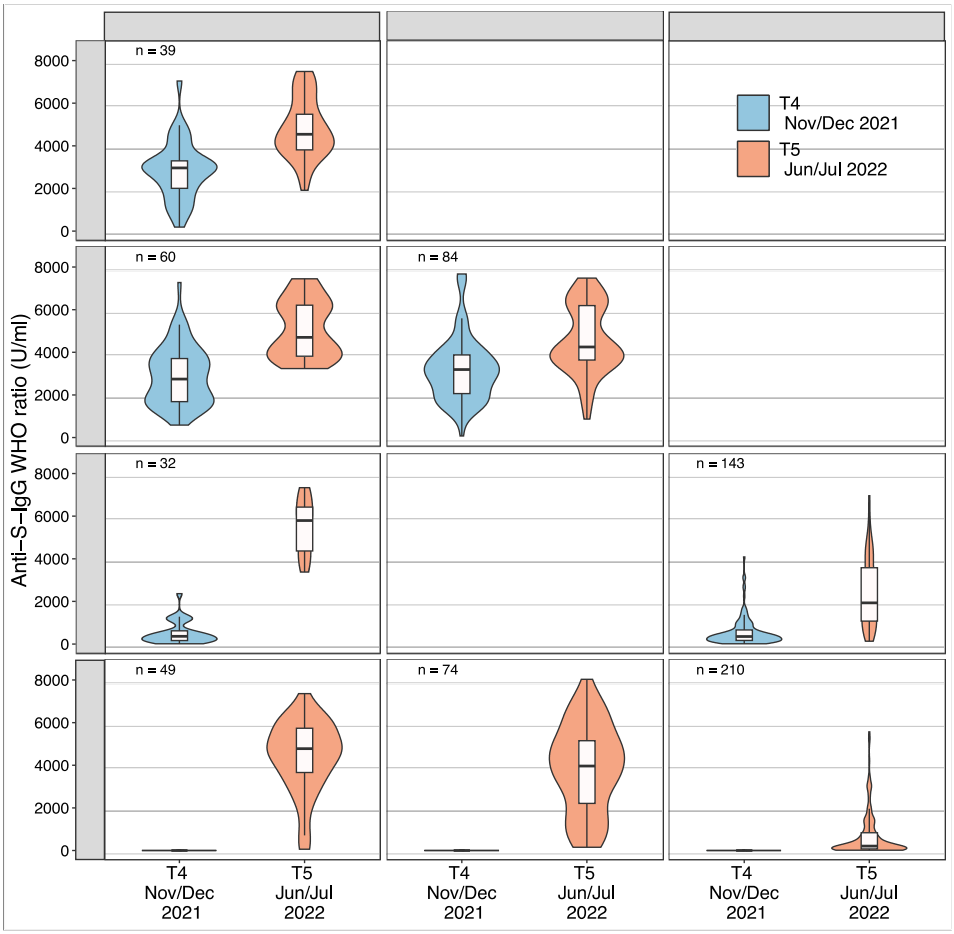


Figure 4: Development of Anti-Spike-IgG titers between T4 (November/Dec. 2021) and T5 (June/July 2022) in primarily seronegative, infected, vaccinated students and those with hybrid immunity at T4. The boxplots show median and interquartile ranges (IQR; Whisker: 1.5 IQR). The violin plots display mirrored density for each titer value (continuous distribution) for Anti-S IgG WHO ratio (U/ml). Reinfections were diagnosed using Anti-Nuc IgG antibodies; hybrid immunity was identified with primary seropositivity followed by vaccination, or vaccination and the presence of Anti-Nuc IgG antibodies. Also presented is the number of tested students (n) in each category a) to l)

5. Symptoms and Severity of SARS-CoV-2 Infections in Students Under Various Predominant Variants of the SARS-CoV-2 Virus

The symptoms observed in students over time remained mild or were absent in every study. Hospitalizations were rare. The most common symptoms included headaches, stuffy nose, sore throat, fatigue, dry cough, or fever/feeling feverish. Taste and smell disturbances were extremely rare. **Figure 5** illustrates the symptoms of seronegative and seropositive students at time point T2 (Oct/Nov 2020). The symptom overlap in both groups was consistently large, making symptoms unhelpful as a diagnostic tool at any point in the study.2-4 Symptoms reported in later studies from winter 2021 and summer 2022 became uninterpretable due to additional symptoms from vaccination, and by summer 2022, there were hardly any seronegative students left.

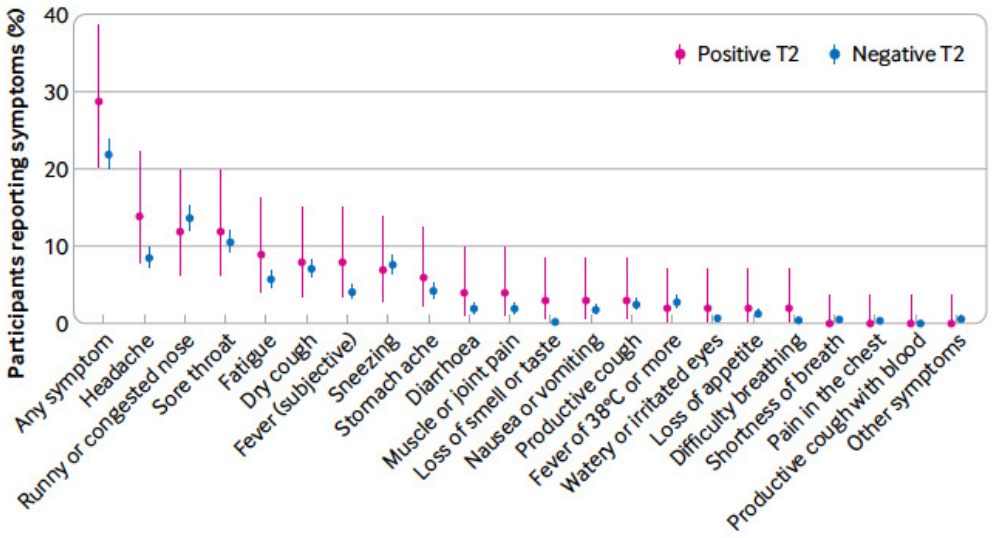


Figure 5 shows the symptoms reported by students or their parents during the 6 months before measurement time point T2 (Oct/Nov 2020) for antibody-positive students in red and antibody-negative students in blue. There was a significant overlap in all symptoms, making it impossible to differentiate between a SARS-CoV-2 infection and another cause for symptom occurrence.

6. Assessment and Characterization of Long-Term Symptoms Compatible with Long COVID in Students With and Without SARS-CoV-2 Infection

Tracking the frequency of Long COVID in children and adolescents is challenging, as many symptoms are non-specific and can occur without prior SARS-CoV-2 infection due to other infections or psychosomatic issues. 'Ciao Corona' was one of the few population-based studies worldwide that allowed comparison of symptoms between antibody-positive and antibody-negative students. This is crucial because many of the aforementioned non-specific symptoms are common in the general population and aren't linked to coronavirus infections. It's important to account for this 'background noise' when evaluating the frequency of long-term symptoms potentially caused by SARS-CoV-2 infection.

Table 2 shows the differences in symptoms among antibody-positive, vaccinated, and antibody-negative students experiencing Long COVID symptoms during the Alpha wave (March/April 2021) and the Delta wave (November/December 2021 to June/July 2022). The difference in the frequency of symptoms between seropositive and seronegative groups and the vaccinated group was consistently around 1-2%. Our data align with reviews of studies on non-hospitalized children and adolescents, which reported a 3% prevalence of Long COVID symptoms in this population. The most common symptoms were fatigue, headaches, stomach aches, and difficulty concentrating. These symptoms were mostly mild and rarely led to hospitalization. The perceived health did not significantly differ among seropositive, vaccinated, or seronegative children and adolescents at any point.

Long COVID in children and adolescents can be considered rare and generally mild until the Delta wave. Evaluations for the Omicron wave are not yet available. These results should be interpreted cautiously due to the small seronegative group. As of now, Long COVID appears in 1-2% of children and adolescents in Switzerland and is mostly mild.

Table 2 Differences in the frequency of Long COVID-related symptoms among antibody-positive, vaccinated, and antibody-negative students during the Alpha wave (Spring - Winter 2021) and the Delta wave (Winter 2021 and Summer 2022)

	T3 –T4 (alpha) Mär/Apr 2021 – Nov/Dez 2021			T4 –T5 (delta) Nov/Dez 2021 – Jun/Jul 2022		
	Seropositiv	**Geimpft**	**Seronegativ**	**Seropositiv**	**Geimpft**	**Seronegativ**
N (Total)	232	169	336	279	261	58
Symptome >4 Wochen (%)	20 (9)	22 (13)	38 (11)	44 (16)	31 (12)	8 (14)
Symptome >12 Wochen (%)	**8 (3)**	**6 (4)**	**8 (2)**	**14 (5)**	**9 (3)**	**2 (3)**
Müdigkeit (%)	5 (2)	4 (2)	2 (1)	7 (3)	3 (1)	0
Kopfschmerzen (%)	3 (1)	0	3 (1)	1 (1)	2 (1)	1 (2)
Bauchschmerzen (%)	3 (1)	0	2 (1)	2 (1)	0	0
Konzentrationsschwierigkeiten (%)	3 (1)	0	2 (1)	3 (1)	2 (1)	0
Empfundene Gesundheit						
Ausgezeichnet (%)	87 (38)	48 (29)	118 (35)	93 (34)	90 (35)	20 (36)
Gut (%)	132 (58)	105 (63)	199 (59)	164 (60)	159 (61)	33 (59)
Einigermassen gut (%)	10 (4)	14 (8)	18 (5)	16 (6)	11 (4)	3 (5)
Schlecht (%)	0	0	0	0	0	0

7. Changes in Lifestyle and Well-being During the Pandemic

Generally, research indicates that the lifestyle and mental health of children and adolescents worsened during the pandemic, sometimes significantly. Most findings are based on the early stages of the pandemic, using small samples and comparison data, with a lack of long-term studies. In the 'Ciao Corona' study, physical activity decreased early on but quickly returned to nearly pre-pandemic levels. However, the increase in screen time persisted and did not recover, especially among secondary school students (Figure 6A). Primary school students generally met recommendations for physical activity and media use more than secondary students. Overall quality of life slightly decreased during the pandemic but was consistently 2-3 points higher among children who met physical activity or screen time recommendations (Figure 6B). The quality of life difference between these groups was small and not clinically significant.

In Switzerland, children and adolescents were mainly affected by reduced social interactions, homeschooling, and closed sports clubs at the start of the pandemic. In many countries, the extent and duration of lockdowns and school closures were much more severe. Our brief 6-week lockdown and subsequent restrictions had little impact on their quality of life, which was hardly influenced by the children's lifestyle. It's important to note that most children in our study came from higher social classes, suggesting a selection bias. Therefore, trends and associations might be less pronounced compared to those in lower socio-economic groups.

Figure 6A

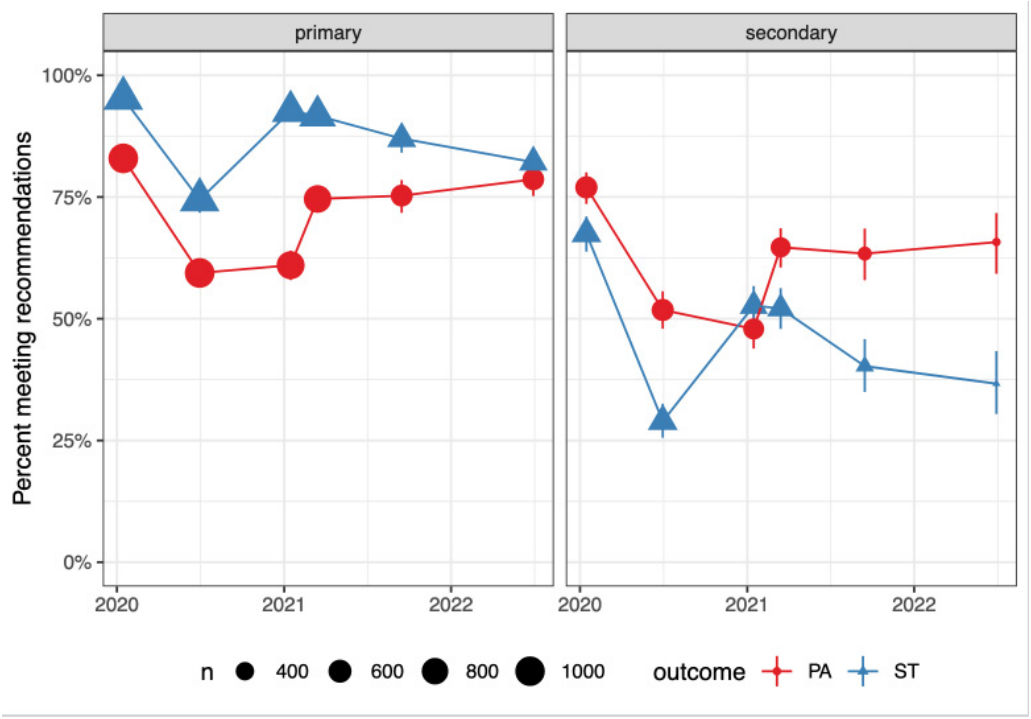


Figure 6B

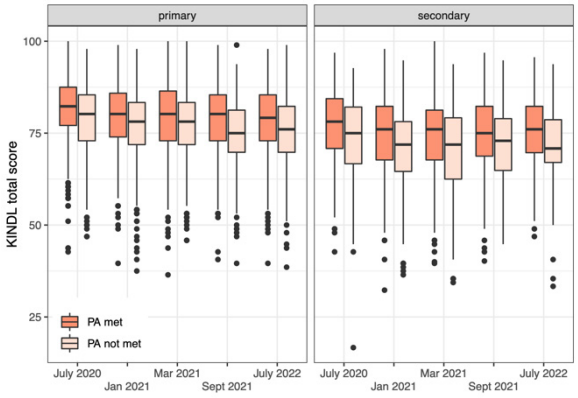


Figure 6C

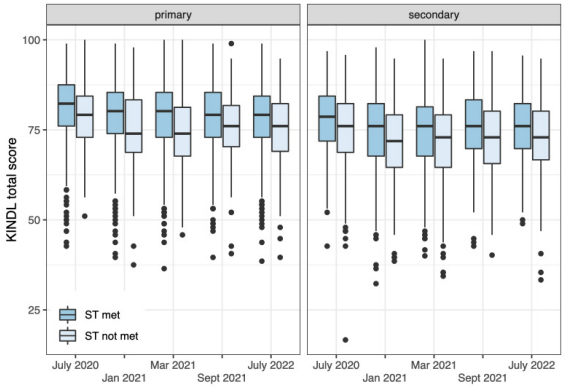


Figure 6 illustrates the number of students who met the official recommendations for physical activity (60 minutes of moderate to intense activity) and sedentary behavior (maximum 120 minutes per day) at each measurement point. The red circles denote physical activity (PA), and the blue triangles represent sedentary time (ST). Figures 6B and 6C depict well-being, assessed using a validated KINDL questionnaire and presented as a total score (scale from 0-100, with higher values indicating better quality of life). At each point, children who adhered to Switzerland's guidelines for physical activity (red) and media consumption (blue) scored 2-3 points higher than those who did not.

Additional publications not specifically mentioned can be found under 9-12

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Publications

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8. Peralta GP, Crameri AL, Haile SR, Kahlert CR, Lorthe E, Marciano L, Nussbaumer A, Radtke T, Ulyte A, Puhan MA, Kriemler S. Lifestyle Behaviours of Children and Adolescents During the First Two Waves of the COVID-19 Pandemic in Switzerland and Their Relation to Well-Being: An Observational Study *Int J Public Health* 2022;67:1604978. doi: 10.3389/ijph.2022.1604978
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10. Blankenberger J, Haile SR, Puhan MA, Berger C, Radtke T, Kriemler S, Ulyte A. Prediction of Past SARS-CoV-2 Infections: A Prospective Cohort Study Among Swiss Schoolchildren. *Front Pediatr* 2021;9:710785. doi: 10.3389/fped.2021.710785
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